CELEBRATING 40 YEARS OF THE ALDRICHIMICA ACTA

Aldrichimica ACTA

VOL. 40, NO. 1 • 2007

Catalytic Azide–Alkyne Cycloaddition

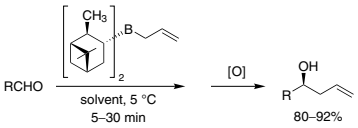
Selecting and Driving Monolayer Structures

New Products from Aldrich R&D

Aldrich Is Pleased to Offer the Latest Asymmetric Allylation Reagents

Stable Ipc$_2$B(allyl) Solutions

The asymmetric allylboration of aldehydes is an extremely important method for the preparation of homoallylic alcohols, as demonstrated in numerous complex natural product syntheses.[1] Although a variety of reagents have been developed to execute this reaction, the most broadly adopted have been Brown's α-pinene-derived (–)- and (+)-*B*-allyldiisopinocampheylboranes.[2] Typically, the allylboration reagents are generated in situ and used immediately at –78 to –100 °C. We recently developed new, salt-free, Ipc$_2$B(allyl) reagents as stable solutions in pentane or dioxane.[3] Under refrigerator storage, no appreciable decreases in selectivity are observed after several months. They exhibit superb reactivity, and reactions can be performed at 5 °C, *even in water.*[4] We are excited to introduce these convenient allylboration reagents to the research community.



Enantiomeric excess, ee (%)

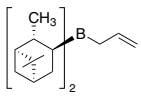
R	Pentane	Dioxane	Water
Ph	94*	92	90
2-BrC$_6$H$_4$	92	90	89
Et	92	90	—

*96% ee at –78 °C

(1) (a) Fürstner, A. et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 5506. (b) Smith, A. B., III et al. *J. Am. Chem. Soc.* **2003**, *125*, 350. (2) For a review of allylborane reagents, see Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23. (3) Patent pending. (4) Josyula, K. V. B. et al., 2006 National ACS meeting, San Francisco, MEDI 545.

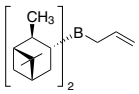
(+)-Ipc$_2$B(allyl) solution, 1 M in pentane
((+)-*B*-Allyldiisopinocampheylborane)

678503 5 mL, 25 mL
[*106356-53-0*]
$C_{23}H_{39}B$
FW: 326.37



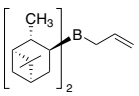
(–)-Ipc$_2$B(allyl) solution, 1 M in pentane
((–)-*B*-Allyldiisopinocampheylborane)

678538 5 mL, 25 mL
[*85116-38-7*]
$C_{23}H_{39}B$
FW: 326.37



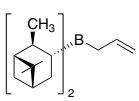
(+)-Ipc$_2$B(allyl) solution, 1 M in dioxane

678511 5 mL, 25 mL
[*106356-53-0*]
$C_{23}H_{39}B$
FW: 326.37



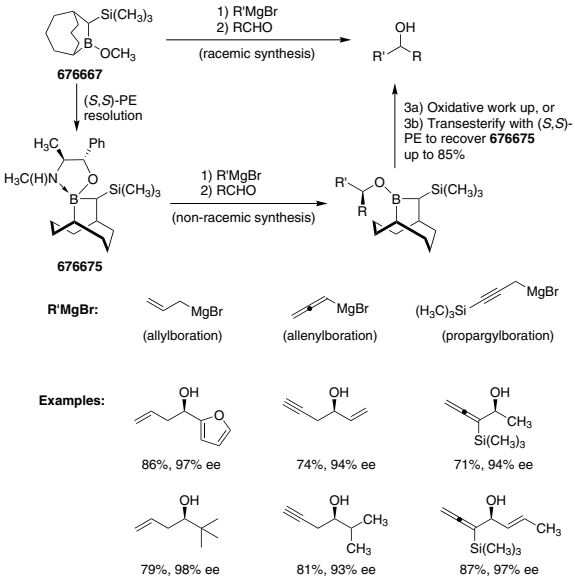
(–)-Ipc$_2$B(allyl) solution, 1 M in dioxane

678546 5 mL, 25 mL
[*85116-38-7*]
$C_{23}H_{39}B$
FW: 326.37



Soderquist Borabicyclodecanes

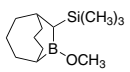
Treatment of these air-stable crystalline pseudoephedrine (PE) borinic acid complexes with the appropriate Grignard reagent is an excellent method for accessing non-racemic homoallylic or homopropargylic alcohols and α-allenyl carbinols via asymmetric allyl-, propargyl-, and allenylboration reactions.[1–3] Allylboration reactions occur rapidly (<3 h), can be performed in the presence of Mg salts, and the degree of asymmetric induction is only minimally affected by temperature. Moreover, the reagent is easily recycled in good yield. The reagents also perform well in asymmetric crotylborations,[1] allylborations of imines,[4] and the alkynylboration of *N*-acylimines to give chiral *N*-propargylamides.[5]



(1) Burgos, C. H. et al. *J. Am. Chem. Soc.* **2005**, *127*, 8044. (2) Lai, C.; Soderquist, J. A. *Org. Lett.* **2005**, *7*, 799. (3) Hernandez, E.; Soderquist, J. A. *Org. Lett.* **2005**, *7*, 5397. (4) Hernandez, E. et al. *Pure Appl. Chem.* **2006**, *78,* 1389. (5) Gonzales, A. Z. et al. *Org. Lett.* **2006**, *8*, 3331.

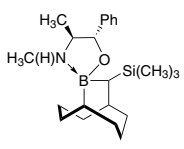
***B*-Methoxy-10-trimethylsilyl-9-borabicyclo[3.3.2]decane, 95%**

676667 5 g, 25 g
$C_{13}H_{27}BOSi$
FW: 238.25



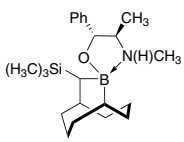
(+)-9-(1*S*,2*S*-Pseudoephedrinyl)-(10*R*)-(trimethylsilyl)-9-borabicyclo[3.3.2]decane

676675 1 g, 5 g
[*848618-13-3*]
$C_{22}H_{38}BNOSi$
FW: 371.44



(–)-9-(1*R*,2*R*-Pseudoephedrinyl)-(10*S*)-(trimethylsilyl)-9-borabicyclo[3.3.2]decane

676683 1 g, 5 g
$C_{22}H_{38}BNOSi$
FW: 371.44



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General Correspondence

Editor: Sharbil J. Firsan, Ph.D.
P.O. Box 355, Milwaukee, WI 53201, USA

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"PLEASE BOTHER US."

Joe Porwoll, President
Aldrich Chemical Co., Inc.

Christopher P. Johnson, III, of the process development department at Boehringer Ingelheim Chemicals, Inc., kindly suggested that we offer boron trichloride as a solution in toluene, in addition to our other solutions of this reagent. Boron trichloride is a versatile Lewis acid and has been used extensively in the selective cleavage of alkyl aryl ethers[1] as well as a variety of C–C and C–O bond-forming reactions.[2]

(1) Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249. (2) For recent examples, see: (a) Zhang, L.; Zhang, J. Y. *J. Comb. Chem.* **2006**, *8*, 361. (b) Kabalka, G. W.; Yao, M.-L.; Borella, S. *J. Am. Chem. Soc.* **2006**, *128*, 11320. (c) Bellur, E.; Langer, P. *J. Org. Chem.* **2005**, *70*, 3819.

678732 Boron trichloride solution, 1.0 M in toluene 100 mL
800 mL

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the inside back cover.

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ABOUT OUR COVER

Photograph © Board of Trustees, National Gallery of Art, Washington.

Winter in the Country (oil on canvas, 66.7 × 92.1 cm) was painted by the American landscape artist, George Henry Durrie (1820–1863), in Connecticut in the winter of 1859. Durrie, the son of a stationer, married a choirmaster's daughter and lived in New Haven, Connecticut, most of his short life. Although he studied painting with a portraitist, landscapes, which first appeared as backgrounds for his portraits, became his primary focus. Durrie did many snow scapes and advertised them in New Haven newspapers, noting, "no collection … is complete without … [a] winter scene." After his death, he was immortalized when the lithographic firm of Currier and Ives successfully reproduced ten of his scenes.

In *Winter in the Country*, Durrie illustrates a number of his most famous compositional conventions. Snow blankets the cold, shadowy landscape, while the ominous sky, reminiscent of Dutch landscapes, covers most of the background. The composition is at eye level, balanced by the centered barn and complementary dark leaf-less trees. Farm workers and animals in the barnyard bring a sense of scale and reality and suggest a waning day. The viewer is invited to explore this everyday 19th-century New England winter scene, pleased to find curling smoke from the farmhouse in the left middle ground, signifying a welcome and warm refuge from the cold, hard day.

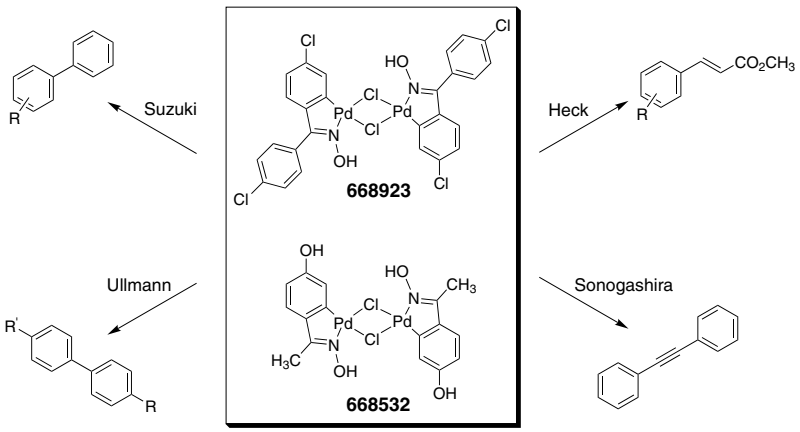
This painting was acquired by the National Gallery of Art, Washington, DC, through the Avalon Fund.

New Products for Cross-Coupling

Highly Robust Oxime Palladacycles

The air- and water-stable palladium complexes shown here are extremely active catalysts for C–C and C–X bond-forming processes, ranging from the Heck to the Sonogashira to the Suzuki reaction.[1] These oxime palladacycles represent novel and powerful tools to mediate an array of industrially useful transformations. Furthermore, the versatility of this family of Pd compounds and their electronic and steric features should ensure their wide application in research and manufacturing.

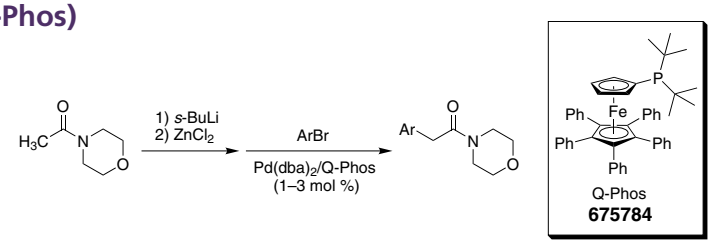
(1) (a) Botella, L.; Najera, C. *J. Org. Chem.* **2005**, *70*, 4360. (b) Alonso, D. A. et al. *Org. Lett.* **2000**, *2*, 1823.



Hindered Ferrocenyl(Dialkyl)phosphine Ligand (Q-Phos)

Developed by the Hartwig group, Q-Phos is a sterically hindered ferrocenylphosphine ligand that has demonstrated broad applicability in a variety of Pd-catalyzed C–C, C–N, and C–O bond-forming reactions including: amination and etherification of aryl chlorides, Suzuki coupling and, most recently, the α arylation of zinc amide enolates.[1]

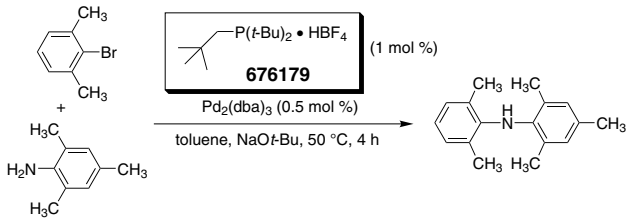
(1) (a) Hama, T. et al. *J. Am. Chem. Soc.* **2006**, *128*, 4976. (b) Kataoka, N. et al. *J. Org. Chem.* **2002**, *67*, 5553.



Bulky Alkylphosphine Ligand for Amination Reactions

Shaughnessy and co-workers have utilized this neopentyl-substituted phosphine with a palladium source to form a highly active catalyst for the amination of a diverse set of aryl halides.[1] The increased steric bulk of this ligand, when compared to tri(*tert*-butyl)phosphine, enhances the effectiveness of this system and allows for the formation of the tetra-*ortho*-substituted product shown here.

(1) Hill, L. L. et al. *J. Org. Chem.* **2006**, *71*, 5117.



For more information on these and other new products from Sigma-Aldrich, visit sigma-aldrich.com/synthesis.

What a Journey It Has Been!

Sharbil J. Firsan
Sigma-Aldrich Corporation
6000 N. Teutonia Ave.
Milwaukee, WI 53209, USA
Email: sfirsan@sial.com

This January, the *Aldrichimica Acta* begins its 40th year of uninterrupted publication. Reaching this milestone is a genuine measure of the high regard in which chemists worldwide have held it for four decades. Their enduring interest has been sustained by the high-quality scientific information they find within its pages—information contributed by their peers from around the world. Without the loyalty and commitment of these two pillars of the *Acta*, its authors and readers, I would not be sharing this significant anniversary with you today. Thank you both! Your interest and support over the years have fostered stimulating scientific exchanges, provided many answers, and inspired further quests. I am enthusiastic about the prospect of continuing this journey with a new generation of *Aldrichimica Acta* authors and readers.

While some readers may be quite familiar with the *Acta*, others have only recently been introduced to it. As we celebrate reaching this milestone, and in the interest of these readers, let me briefly reflect on the past four decades of the *Acta*.

The *Aldrichimica Acta* publishes review articles on innovative chemistry research that are written by leading experts. It is an ideal vehicle for disseminating the accumulated scientific knowledge, research findings, and insights of these experts to chemistry practitioners in academic, industrial, governmental, and nonprofit laboratories around the globe. In this regard, it serves an important function for both our readers and our company. The key to its popularity and longevity has been its unique format and look, which successfully combine high-quality scientific and technical information with an eye-catching cover featuring a beautiful painting and accompanying commentary, and with the latest useful product offerings from the publisher, Sigma-Aldrich Corporation. All of this at no cost to over 130,000 readers worldwide! While its appearance has undergone several modifications over the years, the premise the *Acta* was based on has not changed.

Now for a bit of history. The *Aldrichimica Acta* evolved from the *Kardindex Sheets* that Aldrich used to distribute to its best customers in the 1960s. Dr. Alfred R. Bader, the President of Aldrich Chemical Company at the time, came up with the name, in analogy to the names of such well-known chemistry journals as *Helvetica Chimica Acta* and *Inorganica Chimica Acta*. The name, of course, is a great choice because it combines in its first half the name of the company ("Aldri" from Aldrich) with the type of business it is in ("chimica" for chemical). The second half of the name, *Acta*, is derived from the Latin "Ācta", which means "Proceedings", and was intended to convey the idea that it is a record of scientific proceedings both at Aldrich and the chemistry community at large. The name *Aldrichimica Acta* has been in use since 1967, and is currently highly recognized worldwide.

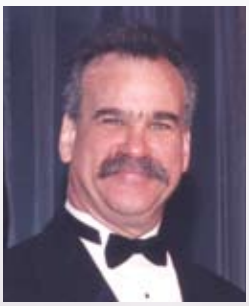
The *Aldrichimica Acta* is treated on a par with other popular chemistry journals and its content is covered by such prominent chemical-abstract publishers as Chemical Abstracts Service® and Thomson ISI®. Collections of *Acta* issues are in practically every academic and industrial science library in the U.S. and many others abroad. In the field of organic chemistry, the Science Edition of Thomson ISI®'s *Journal Citation Reports*® has ranked the *Acta* #1 five times since 1998, out of 45–58 journals compared by Impact Factor. This is no coincidence, since some of the most prestigious names in chemistry have published in the *Acta* over the years, including six Nobel laureates: Derek H. R. Barton (1969), Vladimir Prelog (1975), Herbert C. Brown (1979), Charles J. Pedersen (1987), George A. Olah (1994), and K. Barry Sharpless (2001). On this occasion, I would like to state unequivocally that we owe them, as well as all the authors that have published in the *Acta* since 1967 (cf. table), a debt of gratitude for their outstanding contributions. Without these contributions, we would not be marking this significant milestone today.

I would be remiss if I didn't also acknowledge my debt and gratitude to all the editors that have preceded me, to the dedicated staff past and present, and to the members of Sigma-Aldrich management, past and present, who have believed in the vital role that the *Acta* plays and have shown unwavering support for it through the ups and downs of the often-turbulent world of modern business. I would also like to thank Sean Battles of Sigma-Aldrich for his stimulating questions and comments relating to this write-up.

Mindful of the great legacy of the past 40 years, we strive everyday not only to keep the *Acta* changing with the times, but also to maintain and enhance its appeal, relevance, and usefulness to our readers and to our company.

Here is to another 40 magnificent years of the Aldrichimica Acta!

All Contributors to the *Aldrichimica Acta* from 1967 to the Present[a]



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University of Illinois

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Tomalia, Donald A.
Tour, James M.

Professor David W. C. MacMillan
California Institute of Technology

Toy, Patrick H.
Trost, Barry M.
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Williams, Dudley H.
Williams, Robert M.
Winter, Charles H.
Wiswesser, William J.
Witkop, Bernhard
Wong, Chi-Huey
Wu, Peng
Yamamoto, Yoshinori
Yang, Zhijun
Yau, Eric K.
Zhang, Mianji
Zhao, Hua

[a] Authors with more than one contribution are listed only once.

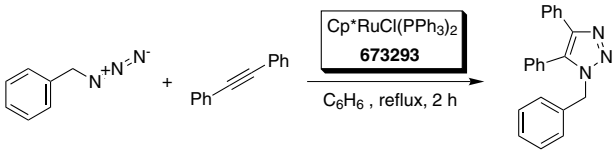
Dr. Firsan is Product Information and Publications Senior Specialist in the Marketing Department at Sigma-Aldrich Corp., and has been Editor of the *Aldrichimica Acta* for the past 11 years.

New Products for Click Chemistry

$Cp^*RuCl(PPh_3)_2$

Although the copper-catalyzed cycloaddition of azides and terminal alkynes to form 1,4-disubstituted 1,2,3-triazoles is well-known, Sharpless and co-workers recently reported the ruthenium-catalyzed counterpart to form the complementary 1,5-disubstituted triazoles.[1] Whereas the Cu(I)-catalyzed reaction is typically limited to terminal alkynes, the Ru(II)-catalyzed one takes place with internal alkynes as well.

673293 Pentamethylcyclopentadienylbis(triphenylphosphine)ruthenium(II) chloride



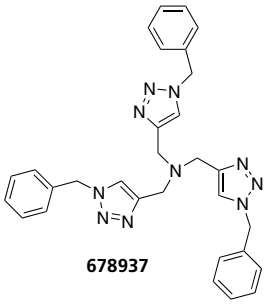
Other Catalysts and Additives for Click Chemistry

C1297 Copper(II) sulfate, *ReagentPlus*®, ≥99%
209198 Copper(II) sulfate pentahydrate, ACS reagent, ≥98.0%
326755 Copper(II) acetate, 98%
A7631 (+)-Sodium L-ascorbate, crystalline, ≥98%
205540 Copper(I) iodide, 98%
212865 Copper(I) bromide, 98%

TBTA

Using Cu(II) salts with ascorbate has been the method of choice for the preparative synthesis of 1,2,3-triazoles, but is problematic in bioconjugation applications. However, tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) has been shown to effectively enhance the copper-catalyzed cycloaddition without damaging biological scaffolds.[2]

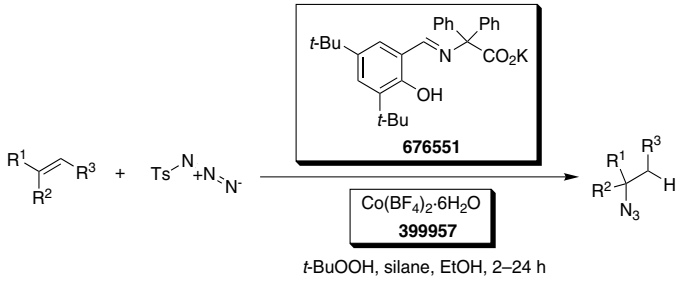
678937 Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine, 97% (TBTA)



Carreira SALDIPAC Ligand

One limitation to click chemistry is that many azides are not commercially available. Carreira recently reported the hydroazidation of unactivated olefins to yield aliphatic azides in the presence of a cobalt catalyst prepared in situ from the SALDIPAC ligand and $Co(BF_4)_2 \cdot 6H_2O$.[3] Additionally, the reaction can be coupled to the copper-catalyzed cycloaddition to yield the 1,4-triazole in a one-pot process.

676551 Potassium 2-(3,5-di-*tert*-butyl-2-hydroxybenzylideneamino)-2,2-diphenylacetate, 95%
399957 Cobalt(II) tetrafluoroborate hexahydrate, 99%



References

(1) Zhang, L. et al. *J. Am. Chem. Soc.* **2005**, *127*, 15998.
(2) Chan, T. R. et al. *Org. Lett.* **2004**, *6*, 2853.
(3) Waser, J. et al. *J. Am. Chem. Soc.* **2005**, *127*, 8294.

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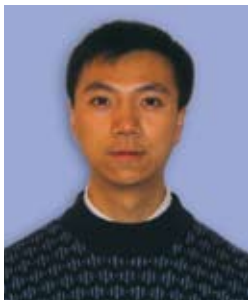
Catalytic Azide–Alkyne Cycloaddition: Reactivity and Applications



Dr. Peng Wu

Professor Valery V. Fokin

*Peng Wu and Valery V. Fokin**
Department of Chemistry
The Scripps Research Institute
10550 North Torrey Pines Road
La Jolla, CA 92037, USA
Email: fokin@scripps.edu

Outline

1. Introduction

Copper(I) acetylides are postulated intermediates in a number of widely used organic transformations. The oxidative homocoupling of terminal acetylenes, discovered by Glaser in 1869,[1,2] is probably the most studied of these transformations. The scope of the reaction was extended in subsequent studies by Baeyer,[3] Straus,[4,5] Reppe,[6] and Eglinton.[7] Heterocoupling reactions of copper(I) acetylides, which do not involve oxygen, have been reported by Castro and Stephens (with aryl halides),[8,9] and Chodkiewicz and Cadiot (with bromoalkynes).[10,11] These copper-mediated cross-coupling reactions of alkynes have been extensively reviewed.[12–14]

1,3-Dipolar cycloaddition reactions have also been the subject of intensive research, most notably by Rolf Huisgen, whose work led to the formulation of the general concepts of 1,3-dipolar cycloadditions.[15] Dipolar cycloaddition chemistry has found widespread applications in organic synthesis and has been the subject of several reviews.

Given the extensive body of literature on the aforementioned topics, it is perhaps surprising that, with the exception of the disclosure of a copper-mediated synthesis of β-lactams from nitrones and alkynes by Kinugasa and Hashimoto in 1972,[16] the paths of copper acetylides and 1,3-dipoles did not cross, and the exceptional reactivity of copper acetylides towards organic azides was not discovered until the 21st century.[17,18] Even though organic azides have been used in synthesis for well over a century, their utility has been limited mostly to a facile introduction of the amino group into organic molecules. Other facets of their uniquely narrow reactivity profile remained largely unexplored until recently. In pioneering work on the development of small-molecule chemical reporters, Bertozzi recognized the nearly bioorthogonal properties of organic azides and the ease of their introduction into biological molecules. She elegantly exploited their reaction with phosphines (the modified Staudinger ligation) in metabolic oligosaccharide engineering studies.[19,20] Around the same time, the concept of "click chemistry" was introduced by Kolb, Finn, and Sharpless.[21] It was defined as an efficient approach to the synthesis of diverse compounds based on a handful of "near-perfect" (very selective, modular, high-yielding, wide in scope) carbon–heteroatom bond-forming reactions. The potential of organic azides as highly energetic, yet very selective, functional groups in organic synthesis was highlighted, and their dipolar cycloaddition with alkynes was placed among the top reactions fulfilling the click criteria. Nevertheless, it was only after the independent discovery of copper catalysis of this reaction by our group and Meldal's in 2002,[17,18] that its applications began to be reported, making it the most useful click reaction discovered so far. However, one should remember that the concept of click chemistry is clearly not limited to a single transformation.

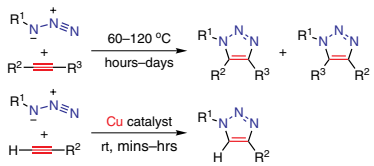
In the few years since its discovery, the **Cu**-catalyzed **a**zide–**a**lkyne 1,3-dipolar **c**ycloaddition (CuAAC) has been established as one of the most reliable means for the covalent assembly of complex molecules. It has enabled a number of applications in synthesis, medicinal chemistry, molecular biology, and materials science.

This review is not intended to be a comprehensive survey of the subject; it will focus instead on the fundamental aspects of the transformation, highlighting the advantages, potential, and limitations of CuAAC by using several representative examples. Additional reviews on this subject have recently been published.[22,23,24]

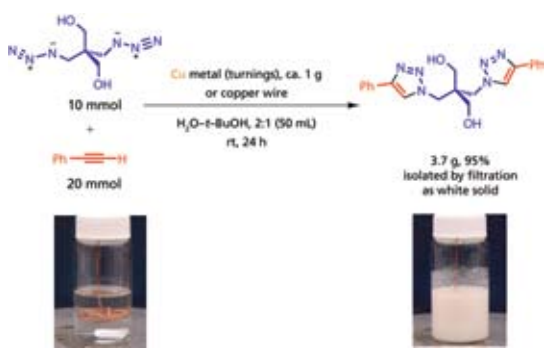
2. Copper-Catalyzed Azide–Alkyne Cycloaddition (CuAAC)

The fundamental thermal reaction, involving terminal or internal alkynes (**Scheme 1**, top), has been known for over a century (to the best of our knowledge, the first 1,2,3-triazole was synthesized by A. Michael from phenyl azide and diethyl acetylenedicarboxylate in 1893),[25] and has been most thoroughly investigated by Rolf Huisgen and co-workers in the 1950s to the 1970s.[26,27] The process is strongly thermodynamically favored (ΔH^o = –45 to –55 kcal/mol) due to the high potential-energy content of the two reaction components, but has a relatively high kinetic-energy barrier (ca. 26 kcal/mol for methyl azide and propyne[28]) that renders the reaction very slow at room temperature for unactivated reactants. Copper(I) catalysis[17,18] dramatically accelerates the reaction of azides with terminal alkynes (**Scheme 1**, bottom) and exhibits several features that make the catalyzed reaction unique among other block-ligation reactions.

1. The reaction is not significantly affected by the steric and electronic properties of the groups attached to the azide and alkyne reactive centers. For example, azides carrying a primary, secondary, or tertiary group; electron-deficient or electron-rich group; and aliphatic, aromatic, or heteroaromatic substituent usually react well with variously substituted terminal alkynes.
2. The reaction is unaffected by water and by most organic and inorganic functional groups; thus, all but eliminating the need for protecting-group chemistry.



Scheme 1. The Uncatalyzed Thermal Cycloaddition of Azides to Alkynes Usually Requires Prolonged Heating and Results in Mixtures of the 1,4- and 1,5-Disubstituted Regioisomers. In Contrast, CuAAC Produces Only 1,4-Disubstituted-1,2,3-Triazoles at Room Temperature in Excellent Yields.



Ref. 17,28

eq 1

3. The rate of the Cu-catalyzed process is approximately 10^7 times that of the uncatalyzed version,[28] making the reaction conveniently fast in the temperature range of 0 to 25 °C. Furthermore, ligand-accelerated-catalysis effects[29] are also significant, resulting in further increases in the reaction rate.
4. The 1,2,3-triazole unit that results from the reaction has several advantageous properties: (i) a high chemical stability (in general, being inert to severe hydrolytic, oxidizing, and reducing conditions, even at high temperature), (ii) a strong dipole moment (5.2–5.6 D), (iii) an aromatic character, and (iv) a good hydrogen-bond-accepting ability.[30,31] Thus, it can interact productively in several ways with biological molecules, and serve as a replacement for the amide linkage in some circumstances.

2.1. Catalysts and Ligands

The robustness of CuAAC and its compatibility with most functional groups, solvents, and additives—regardless of the source of the catalyst—are evidenced by the number of experimental conditions that have been successfully employed for the reaction since its inception. The most commonly used experimental protocols and their advantages and liabilities are discussed below.

2.1.1. The Copper Catalyst

A number of different copper(I) sources can be utilized in the reaction. Copper(I) salts (CuI, CuBr) and coordination complexes (such as $[Cu(CH_3CN)_4]PF_6$,[17] $(EtO)_3P{\bullet}CuI$,[32] $[Cu(PPh_3)_3]Br$[33,34]) can be used directly. The latter have been particularly effective in organic solvents, in which cuprous salts have limited solubility.[35] However, Cu(I) is thermodynamically unstable and can be relatively easily oxidized to catalytically inactive Cu(II). The standard potential of the Cu^{2+}/Cu^{+} couple is 159 mV, but can vary widely with the solvent and the ligand environment of the metal. Cu(II), itself, is an oxidant and can mediate the oxidative alkyne coupling reactions mentioned above, thereby impairing the efficiency of the cycloaddition and resulting in the formation of undesired byproducts. Therefore, when a copper(I) catalyst is used directly, whether by itself or in conjunction with amine ligands, exclusion of oxygen may be required to prevent these complications. As an alternative to oxygen-free conditions, a sacrificial reducing agent, for example ascorbate, can be used. Its combination with a copper(II) salt, such as the readily available and stable copper(II) sulfate pentahydrate or copper(II) acetate, is an economical and practical solution, and is the method of choice for preparative syntheses of 1,2,3-triazoles. Thus, "the aqueous ascorbate" procedure often furnishes triazole products in nearly quantitative yield and over 90% purity.[17]

Catalytic amounts of Cu(I) can also be introduced in the reaction through comproportionation of Cu(II) and Cu(0), thus further simplifying the experimental procedure. A small piece of copper metal (wire or turning) is all that is added to the reaction mixture, followed by shaking or stirring for 12–48 hours (**eq 1**).[17,36] Aqueous alcohols (MeOH, EtOH, *t*-BuOH), THF, and DMSO can be used as solvent. Cu(II) sulfate may be added to accelerate the reaction; however, this is not necessary in most cases, as copper oxides and carbonates (the patina), which are normally present on the surface of the copper metal, are sufficient to initiate the catalytic cycle. Copper nanoclusters, which are easily obtained and are air-stable,[37] and copper/cuprous oxide nanoparticles[38] have also shown excellent catalytic activity.

Although this procedure requires longer reaction times than the aqueous "ascorbate" variant, it usually yields very pure triazole products with low levels of copper contamination. Experimentally very simple, this protocol is particularly convenient for the high-

throughput synthesis of screening libraries. The reaction is very selective, and triazole products are generally isolated in >85–90% yields, and can often be directly submitted for screening (**Figure 1**). When required, trace quantities of copper remaining in the reaction mixture can be removed with an ion-exchange resin or using solid-phase extraction techniques.

2.1.2. Auxiliary Ligands

Chemical transformations used in the synthesis of bioconjugates must be exquisitely chemoselective, biocompatible, and efficient. Despite the experimental simplicity and efficiency of the "ascorbate" procedure, it does not always perform well in its original form in bioconjugation applications. The reaction is not fast enough at very low concentrations of the reagents, and copper- or ascorbate-mediated degradation of the biological scaffolds has been observed. The ligand tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA, **1**; **Figure 2**), discovered soon after the disclosure of CuAAC,[39] significantly accelerates the CuAAC reaction and stabilizes the +1 oxidation state of the copper catalyst. In addition, it appears to sequester copper ions, thereby preventing damage to the biological molecules. After its utility was demonstrated by efficient attachment of 60 alkyne-containing fluorescent dye molecules to the azide-labeled cowpea mosaic virus,[40] it has been used numerous times in bioconjugation studies with nucleic acids, proteins, and cells. The sulfonated bathophenanthroline, **2**, has been identified as a water-soluble and commercially available TBTA alternative.[41] In a recent study by Finn and co-workers, **2** was shown to be superior to TBTA for the efficient covalent attachment of small molecules to cowpea mosaic virus scaffolds,[42] eliminating the requirement for the large excess of a coupling partner (4–6 equivalents was usually sufficient) to achieve reasonable reaction rates and high yields. The drawback of this ligand is the increased sensitivity of the copper catalyst to oxidation, thus requiring the rigorous exclusion of oxygen from the reaction mixture.

2.2. Studies of the Mechanism of CuAAC

The intermediacy of copper(I) acetylides in CuAAC was postulated early on based on the lack of reactivity of internal alkynes. Soon thereafter, a computational study of the elementary steps of the sequence was performed. The initial computations focused on the possible reaction pathways between copper(I) acetylides and organic azides (propyne and methyl azide were chosen for simplicity).[28] The key bond-making steps are shown in **Scheme 2**. The formation of copper acetylide **4** (Step A) was calculated to be exothermic by 11.7 kcal/mol. This is consistent with the well-known facility of this step, which probably occurs through the intermediacy of a π-alkyne–copper complex. The π coordination of an alkyne to copper is calculated to move the pK_a of the alkyne terminal proton down by ca. 10 units, bringing it into the proper range to be deprotonated in an aqueous medium. A concerted 1,3-dipolar cycloaddition of the azide to the copper acetylide has a high calculated potential energy barrier (23.7 kcal/mol), thus the metal must play an additional role. In the proposed sequence, the azide is activated by coordination to copper (Step B), forming the intermediate **5**. This ligand exchange step is nearly thermoneutral computationally (2.0 kcal/mol uphill when L is a water molecule). The key bond-forming event takes place in the next step (Step C), when **5** is converted to the unusual 6-membered copper metallacycle **6**. This step is endothermic by 12.6 kcal/mol with a calculated barrier of 18.7 kcal/mol, which is considerably lower than the barrier for the uncatalyzed reaction (approximately 26.0 kcal/mol), thus accounting for the enormous rate acceleration accomplished by Cu(I). The CuAAC reaction is therefore not a true concerted cycloaddition, and its regiospecificity is explained by the binding of both azide and alkyne to copper prior to the formation of the C–C bond. The energy barrier for the ring contraction of **6**, which leads to the triazolyl–copper derivative **7**, is quite low (3.2 kcal/mol). Proteolysis of **7** releases the triazole product, thereby completing the catalytic cycle.

The density functional theory (DFT) investigation described above was soon followed by an examination of the kinetics of the copper-mediated reaction between benzyl azide and phenylacetylene. This study revealed that, with catalytic Cu(I) concentrations under saturation conditions (rate independent of the alkyne concentration), the reaction was *second-order* in copper.[43]

$$\text{rate} = k[\text{alkyne}]^{0}[\text{azide}]^{0.2\pm0.1}[\text{Cu}]^{2.0\pm0.1}$$

The second-order dependence on Cu(I) is not unreasonable since most copper(I) acetylides are highly aggregated species,[44] and the second copper atom might be present, and in fact required, in the matallacycle-forming step. A recent DFT study suggests that this is indeed the case.[45]

2.3. The Cyclodimerization Phenomenon

The bimetallic requirement of CuAAC has manifested itself most dramatically in the ring closure of peptides prepared on the solid phase with azide and alkyne groups at opposite ends, as reported by Finn and co-workers (**Scheme 3**).[46] The 11-mer and 19-mer peptides,

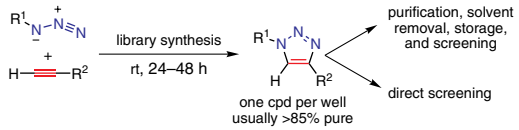
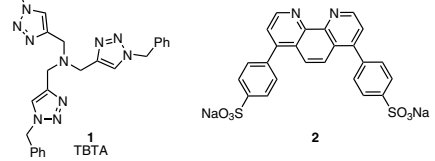
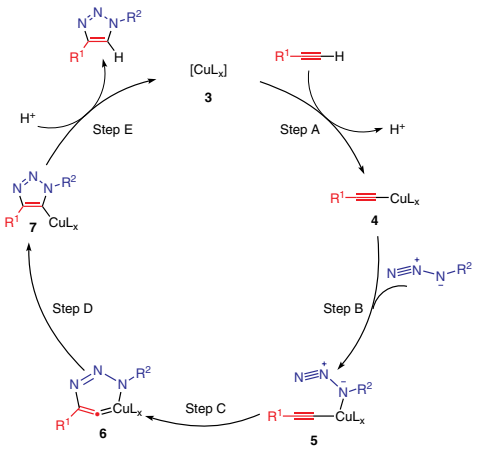


Figure 1. Protocol for the Synthesis and Direct Screening of Compound Libraries Using CuAAC.



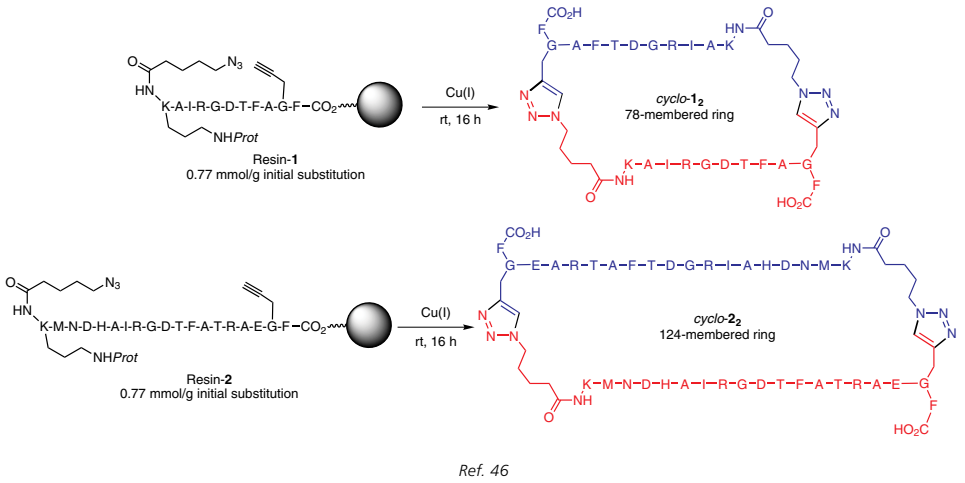
Ref. 39–42

Figure 2. Tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA) and Sulfonated Bathophenanthroline Ligand for CuAAC.



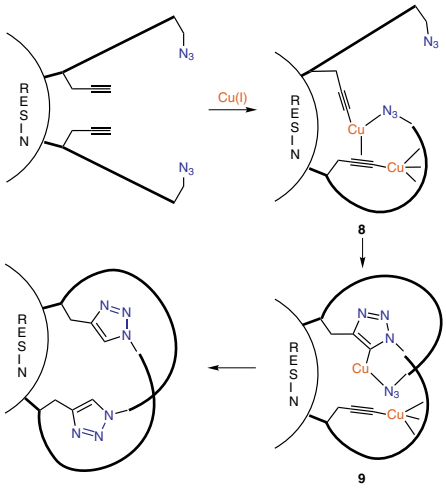
Ref. 17,28

Scheme 2. Proposed Catalytic Cycle for CuAAC.



Ref. 46

Scheme 3. Cyclodimerization of Peptides on Solid Support.

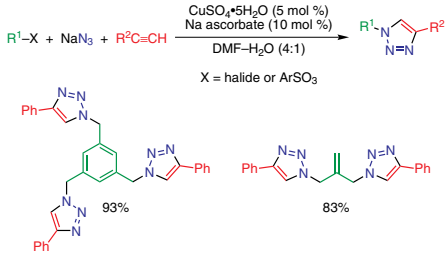


Ref. 46

Scheme 4. Possible Intermediates in the Cyclodimerization of Peptides on Solid Support.

Resin-**1** and Resin-**2**, contained L-propargylglycine as the second residue on one end, and the other end of each chain was capped with 5-azidopentanoic acid. Exposure of each of these resins to Cu(I) for 16 h at room temperature resulted in the consumption of all of the azide groups and the complete disappearance of the linear oligopeptides. However, the single dominant species in each case was the cyclic dimer, *cyclo*-**1**$_2$ and *cyclo*-**2**$_2$, rather than the monomer of the desired sequence; isolated yields were in the 80–90% range, which is excellent for peptides of this size.

An extensive series of experiments established that the cyclodimerization process was dependent on the density of peptides on the resin and did not occur as efficiently off the resin.[46] The cyclodimerization was inhibited by excess copper(I), addition of a copper-binding chelating ligand that normally promotes other AAC reactions, or added phenylacetylene (but not added azide). **Scheme 4** illustrates several possible explanations of these observations. Since the ligand-free system showed a rate order in PhC≡CH of between 1 and 2, a second-order pathway in alkyne is possible, with one alkyne playing a structural role. If, for example, one copper acetylide of associated chains is π-complexed to the other, as shown in structure **8**, the reactivities of the two acetylides



Ref. 48–51

eq 2

toward the azide will be different. Alternatively, interaction of the azide at the terminus with the copper acetylide at its base should be entropically less favorable than interaction with another copper acetylide fragment, as also represented in structure **8**. Furthermore, once the first cycloaddition event takes place (leading to **9**), the organometallic fragment may bind and direct the second azide to engage the remaining acetylide and complete the macrocyclization. Angell and Burgess proposed a similar hypothesis to explain their observation of a strong preference for the formation of cyclic dimers from small peptides in solution.[47]

2.4. One-Pot CuAAC Procedure

Although organic azides are generally safe compounds, those of low molecular weight can be unstable and, therefore, difficult to handle. This is especially true for small molecules with several azide functionalities that would be of much interest for the generation of polyvalent structures. In these cases, CuAAC can be performed as a one-pot two-step sequence, whereby an in situ generated organic azide is immediately consumed in a reaction with a copper acetylide. Alkyl azides can be readily obtained from the corresponding halides or arylsulfonates by reaction with sodium azide (**eq 2**).[48–51] Residual NaN_3, even when used in excess in the alkyl azide forming step, does not interfere with the subsequent cycloaddition reaction.

Similarly, aryl and vinyl azides are available in one step from aryl halides via a copper-catalyzed reaction with sodium azide in the presence of a catalytic amount of L-proline (**eq 3**).[48] Using this approach, a range of 1,4-disubstituted 1,2,3-triazoles were prepared in excellent yields.[49–51] The same reaction sequence can be

performed at elevated temperature under microwave irradiation, reducing the reaction time to 10–30 minutes.[36]

2.5. Reactions of Sulfonyl Azides

The reaction of sulfonyl azides with terminal alkynes under copper catalysis is an interesting exception. Depending on the conditions and reagents, it can result in the formation of different products (**Scheme 5**). As reported by Chang and co-workers, *N*-sulfonyl azides are converted to *N*-sulfonyl amidines when the reaction is conducted in the presence of amines.[52] Under aqueous conditions, *N*-acylsulfonamides are the major products.[53,54]

Although the catalysis initially appears to follow the same pathway as in other CuAAC reactions of azides, the cuprated triazole intermediate **10** (**Scheme 6**)—the *N*-sulfonylated analogue of **7** in Scheme 2—can undergo a ring–chain isomerization to form the cuprated diazoimine **11** which, upon the loss of a molecule of dinitrogen, furnishes the *N*-sulfonylketenimine **12**.[55] Alternatively, copper(I) alkynamide **13** can be generated with a concomitant elimination of dinitrogen and, after protonation, would also generate the same reactive *N*-sulfonylketenimine species **12**. In addition to amines and water, **12** can be trapped with imines, furnishing *N*-sulfonylazetidinimines.[55] However, when the reaction is performed in chloroform in the presence of 2,6-lutidine, *N*-sulfonyltriazoles are obtained in good yields.[56]

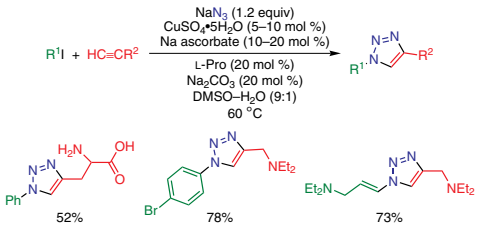
3. Selected Applications of CuAAC

3.1. Synthesis of Small-Molecule Screening Libraries

The CuAAC process performs well in most common laboratory solvents and usually does not require protection from oxygen and water (in fact, aqueous solvents are commonly used and, in many cases, result in cleaner isolated products), making it an ideal tool for the synthesis of libraries for initial screening as well as for structure–activity profiling. The lack of byproducts and high conversions often allow screening of the reaction products without further purification. When necessary, traces of copper and byproducts can be removed by solid-phase extraction utilizing a metal-scavenging resin or by simple filtration through a plug of silica.

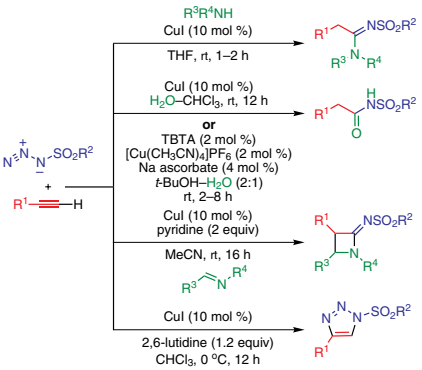
3.1.1. Inhibitors of Fucosyl Transferases

Sialyl Lewis x (sLe^x) and sialyl Lewis a (sLe^a) of the cell-surface glycoproteins and glycolipids play a central role in cell–cell interactions and cell migration in physiological and pathological processes such as fertilization, embryogenesis, inflammation, and cancer metastasis.[57] The terminal step in the biosynthetic pathway of these fucose-containing saccharides is the transfer of L-fucose from guanosine diphosphate β-L-fucose (GDP-fucose) to the corresponding glycoconjugate acceptor by action of fucosyl transferases (FucTs).[58] The selective inhibition of FucTs is an attractive treatment for pathologies associated with the aforementioned glycoconjugates. However, the low substrate (GDP-fucose and sialyl *N*-acetyllactosamine) affinity, combined with the lack of enzyme structural data, make the rational development of potent inhibitors for FucTs difficult. In a study reported by Lee et al., CuAAC was used to link 85 azides to the GDP-derived alkyne **14** with excellent yields (**eq 4**).[59] The absence of offensive byproducts allowed the direct screening of the library, and resulted in the identification of a nanomolar inhibitor, **15**. Testing purified **15** against several glycosyltransferases and nucleotide-binding enzymes revealed that it was up till then the most potent and selective inhibitor of human α-1,3-fucosyltransferase VI .



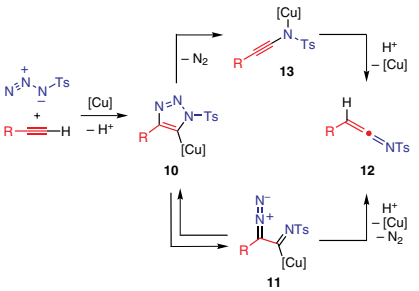
Ref. 48–51

eq 3



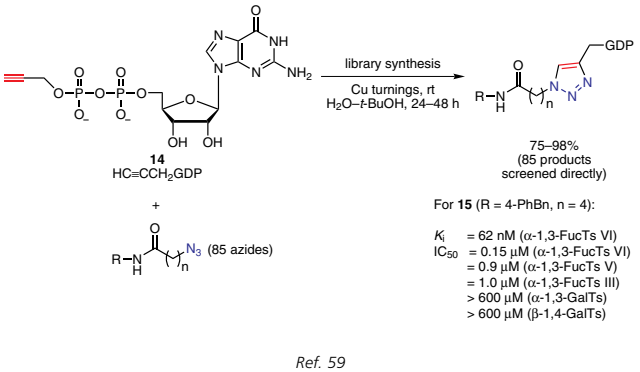
Ref. 52–56

Scheme 5. The Dependence of the Outcome of the Reaction of Sulfonyl Azides with Alkynes on the Reaction Conditions.



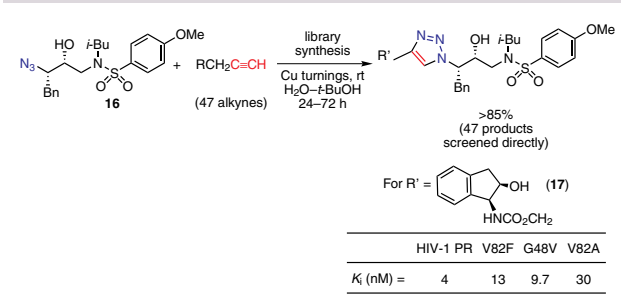
Ref. 55,56

Scheme 6. Postulated Pathways That Lead to a Common Ketenimine Intermediate in the CuAAC Reaction of Sulfonyl Azides with Alkynes.



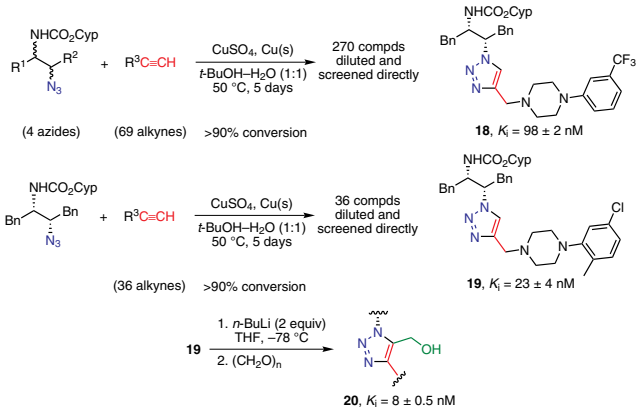
Ref. 59

eq 4



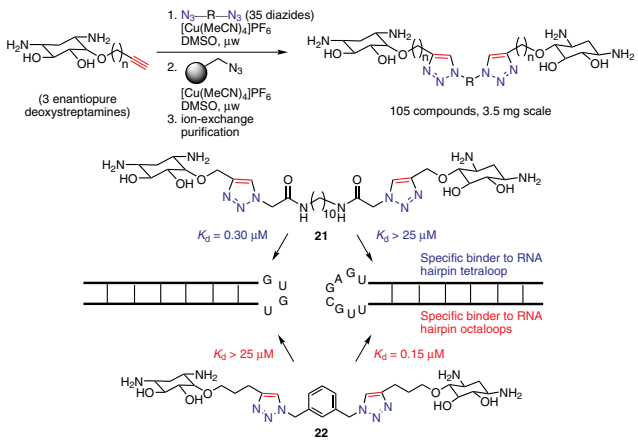
Ref. 60,61

eq 5



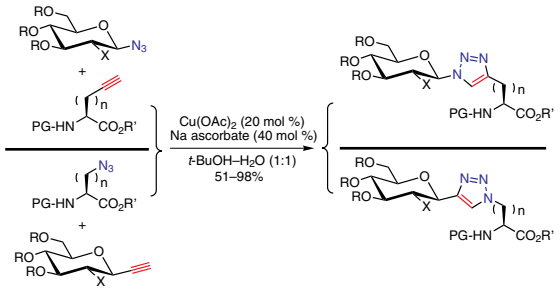
Ref. 62

Scheme 7. Novel Series of Inhibitors of HIV-1 Protease.



Ref. 63

eq 6



Ref. 64

Scheme 8. Synthesis of Triazole-Linked Glycopeptides.

3.1.2. HIV-1 Protease Inhibitors

HIV-1 protease has been recognized as an important target for the inhibition of viral replication. Although seven inhibitors have been approved by the FDA since 1995, and a number more are currently undergoing clinical evaluation, their success has been undermined by the alarmingly rapid mutation of the virus. In one study, a focused library of about 50 compounds was prepared utilizing CuAAC as the last assembly step.[60] The azide-decorated scaffold **16**, inspired by the structure of Amprenavir, and a selection of 47 alkynes, were united through a 1,2,3-triazole unit by simply shaking the reactants with a piece of copper turning for 72 hours. After dilution with water, the compounds were screened, without purification, against the wild type HIV-1 protease and three mutants (G48V, V82F, and V82A). Several hits were identified, and the two most active compounds were resynthesized, and their IC_{50} and K_i values were determined (**eq 5**; only one active, **17**, is shown). Analysis of the crystal structures of the HIV-1 protease with bound inhibitor **17** confirmed that the triazole ring acted as an amide-bond surrogate, retaining all hydrogen bonds in the active site of the enzyme.[61]

Another recent study disclosed a novel series of potent HIV-1 protease inhibitors that have been developed.[62] CuAAC was used to unite a focused library of azide-containing fragments with a diverse array of functionalized alkyne-containing building blocks (**Scheme 7**, top). After the direct screening of the crude reaction products, a lead structure, **18**, with K_i = 98 nM was identified. Optimization of both azide and alkyne fragments proved equally facile (e.g., **19**; K_i = 23 nM). Further functionalization of the triazole at C-5 gave a series of compounds with increased activity, exhibiting K_i values as low as 8 nM (**20**).

3.1.3. Size-Specific Ligands for mRNA Hairpin Loops

The development of ligands that target mRNAs coding for proteins that lack small-molecule binding sites could be a promising approach to drug discovery. To this end, Hergenrother's group reported an approach utilizing CuAAC for the synthesis of a screening library of mRNA hairpin loop binders.[63] A collection of 105 deoxystreptamine dimers from three alkynylated derivatives of enantiopure deoxystreptamines and thirty-five diazides was prepared (**eq 6**). Under microwave heating, the reactions proceeded almost to completion in 40 seconds. After treating the reaction mixture with a resin-supported azide to scavenge unreacted alkyne, the bistriazole products of 91% average purity were isolated and screened for size-specific mRNA hairpin loop binding. Two hits, **21** and **22**, which exhibit complementary specificity (for mRNA tetraloops and octaloops, respectively), were identified.

3.2. Synthesis of Neoglycoconjugates

The importance of glycoconjugates as mediators of complex cellular events has inspired the development of new methodologies for the construction of glycoproteins with well-defined, homogeneous glycoforms. One of the difficulties inherent in the synthesis of *N*- and *O*-linked glycopeptides is the sensitivity of glycosidic linkages toward chemical and enzymatic hydrolysis. This problem could potentially be solved by introducing a chemically and metabolically stable isosteric linkage such as 1,2,3-triazole. Thus, two high-yielding syntheses of triazole-linked glycopeptides have been achieved by Rutjes and co-workers.[64] CuAAC chemistry demonstrated equal efficiency for the coupling of either azidoglycosides with acetylenic oligopeptides or acetylenic glycosides with azide-containing peptides (**Scheme 8**).

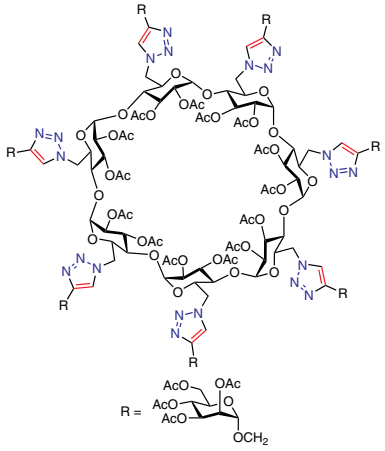
Many cell-surface recognition events, which result in cellular adhesion, inflammation, and immune surveillance are mediated by complex carbohydrate interactions. It is therefore not surprising

that the development of synthetic architectures that bear multiple carbohydrate units has received much attention. CuAAC—utilizing organic-soluble catalysts $[Cu(Ph_3P)_3]Br$ and $(EtO)_3P{\bullet}CuI$ in combination with $Et(i\text{-}Pr)_2N$—have been employed by Santoyo-Gonzalez and co-workers to synthesize a number of poly- (di- to hepta-) mannosylated ligands (**Figure 3**).[32] Under microwave irradiation, the reactions were generally complete in less than 30 minutes, and polyvalent products were isolated in high yields. More recently, *C*-glycoside clusters,[65] neoglycopolymers,[66] and virus-glycopolymer conjugates[67] have been reported utilizing CuAAC alone or in combination with atom-transfer polymerization techniques.

3.3. Modification and Biological Profiling of Natural Products

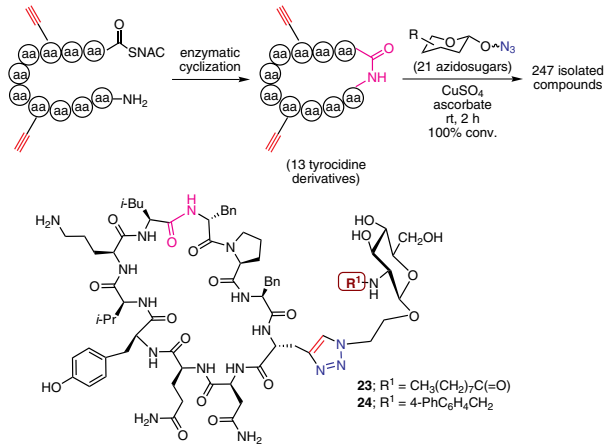
Many bioactive natural products have limited therapeutic potential because of the narrow activity–toxicity window (the minimum therapeutically useful concentration and the concentration at which side effects make treatment impractical). Therefore, the modification of potentially useful bioactive natural products is a viable approach towards improving their therapeutic index. Ideally, such a modification should be accomplished on the molecule itself to avoid protection–deprotection steps. In reality, most chemical transformations are not compatible with a range of functional groups present in the parent compound. The high selectivity and fidelity of the CuAAC make it a good candidate for the last-step derivatization of complex bioactive molecules. This approach was demonstrated by Lin and Walsh, who utilized CuAAC for the preparation of an analogue library of the glycopeptide antibiotic tyrocidine,[68] a nonribosomal peptide which is believed to target the bacterial lipid bilayer. Although a potent antibiotic, it can cause hemolysis at concentrations close to MIC. First, thirteen head-to-tail cyclic tyrocidine derivatives containing one to three propargylglycines were generated from linear *N*-acetylcysteamine peptides by the action of a thioesterase domain excised from tyrocidine synthetase (**Scheme 9**). The resulting cyclic peptides were then conjugated to twenty-one azido sugars at less than 1 mM concentration, resulting in a library of 247 isolated compounds. The two most active of these, **23** and **24**, identified by antibacterial and hemolysis assays, were purified and further profiled, revealing a 6-fold improvement in the therapeutic index when compared to wild-type tyrocidine. The toxicity of different reagents that can be used in the CuAAC step was also examined: neither ascorbate, Cu(II), nor TBTA caused a hemolytic reaction, thus allowing the direct assay of the analogue library.

The biological activity of natural products is often modulated by their glycosylation, and recent studies suggest that novel therapeutics could be generated by altering the glycosylation patterns of their secondary metabolites. To study the effects of such glycosylation, Thorson and co-workers took advantage of CuAAC in a glycorandomization study performed on vancomycin (**eq 7**).[69–71] In the first step, a number of sugar precursors bearing reactive handles were covalently linked to the heptapeptide aglycon regio- and stereospecifically to furnish a library of monoglycosylated vancomycin analogues. This one-pot, three-step process was mediated by three enzymes: a sugar kinase, a nucleotidyltransferase, and a glycosyltransferase. Monoglycosylated derivative **25**, containing an azide handle, was further diversified using CuAAC with a selection of alkynes to create a small library of vancomycin analogues. Antibacterial screens of the resulting library identified carboxylic acid derivative **26** as having twice the activity of vancomycin against both *S. aureus and E. faecium*.



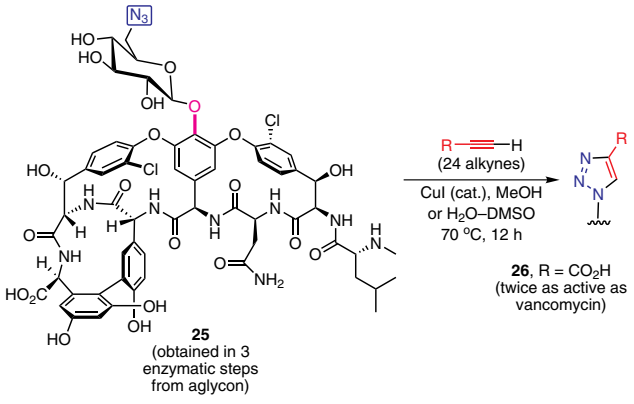
Ref. 32

Figure 3. Heptamannosylated Cyclodextrin Derivative Synthesized by CuAAC in One Step.



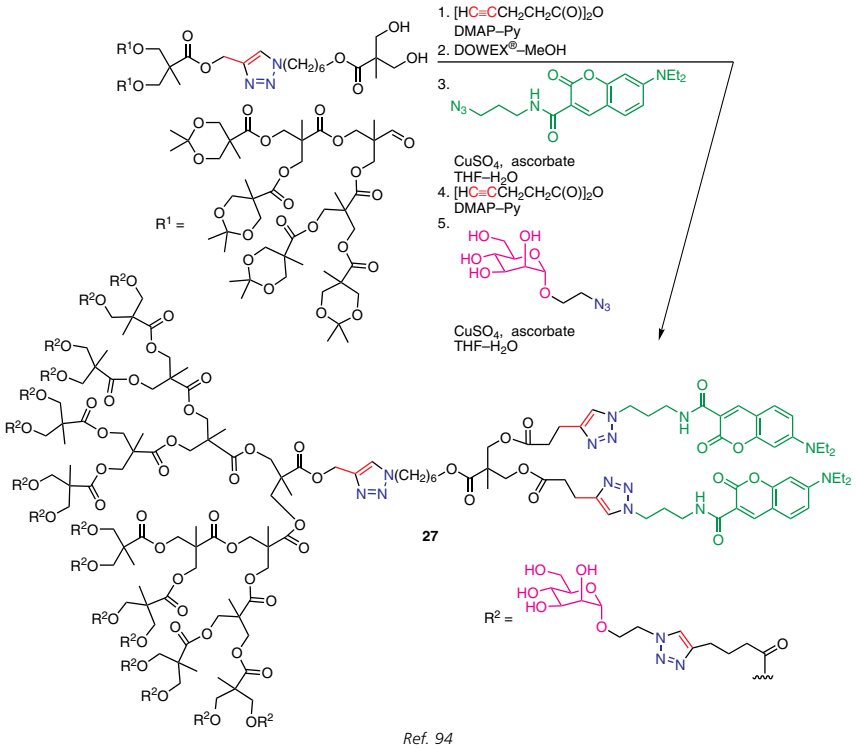
Ref. 68

Scheme 9. Chemoenzymatic Functionalization of the Antibiotic Tyrocidine.



Ref. 69–71

eq 7



Scheme 10. CuAAC-Enabled Synthesis of a Bifunctional Dendrimer.

3.4. Bioconjugation: Following the Dynamics of Proteomes

Incorporation of amino acids containing small bioorthogonal groups into the proteome of an organism, either metabolically (i.e., by "tricking" the organism's own biosynthetic machinery to co-translationally introduce unnatural amino acids into its proteins) or through site-directed mutagenesis,[72,73] allows the tracking of proteome dynamics in response to external stimuli. The advantages of the azide functionality for selective chemical ligation have been demonstrated in many studies involving the modified Staudinger ligation.[74–76] CuAAC has thus emerged as a complementary strategy, boasting high reaction rates and exquisite selectivity.[40,77,78] This methodology was used by Tirrell and co-workers to selectively label azide- or alkyne-containing amino acids, such as azidohomoalanine, homopropargylglycine, or ethynylphenylalanine, which were co-translationally incorporated into the newly synthesized proteins of *E. coli*.[78,79] In the last step, the exposed azide or alkyne residues were conjugated with either a biotin label or a "pro-fluorescent" coumarin derivative, which is activated once the azide is converted to the 1,2,3-triazole heterocycle.[80] The ligand TBTA was essential for the functionalization step. Since the pro-fluorescent coumarin labeling reagent contributes only weakly to background signals, the labeled protein could be directly observed without the need for washing, Western blotting, or secondary labeling steps. The approach has been recently extended to the study of proteomes in mammalian cells.[81] This method complements the gene-encoded labeling approaches[77,82,83] for investigating protein structures and functions in vivo.

3.5. Synthesis of Functional Dendrimers

As highly ordered, regularly branched, globular macromolecules of defined structure, dendrimers are ideal scaffolds for creating bioactive nanomaterials. The high fidelity of CuAAC, its tolerance of most functional groups, and simple product isolation have enabled the efficient construction of dendrimers utilizing procedures that involved little more than mixing stoichiometric quantities of reactants, stirring, and isolating the dendrimeric products.[34,84–87] Purification was not required up to the third generation.[88] The same features of CuAAC that allowed the synthesis of novel dendrimers have also been exploited for chain-end functionalization of dendrimers and hyperbranched polymers.[89–93] An example is the covalent attachment of 3'-azido-3'-deoxythymidine to the dodeca-alkyne dendritic core, providing the nucleoside-terminated dendrimer in 94% isolated yield at room temperature in aqueous solution.[33] The ability to covalently label dendritic scaffolds with nearly any functional group allows the preparation of complex dendritic libraries in multigram quantities under very mild conditions. For example, CuAAC enabled a high-yield synthesis of a chemically heterogeneous dendrimer **27** containing 16 α-D-mannose units and two coumarin-derived fluorescent chromophores (**Scheme 10**).[94] The performance of this bifunctional dendrimer was evaluated in a standard hemagglutination assay using the mannose-binding protein concanvalin A and rabbit red blood cells. Dendrimer **27** exhibited a 240-fold greater potency than monomeric mannose, which translates into a 15-fold increase in activity per unit. Syntheses of peptidodendrimers,[95] unprotected glycodendrimers,[93,96] and redox-active dendrimers for sensor applications[97] have also been described.

3.6. Polyvalent Display with Viruses

Viruses present another opportunity for the polyvalent presentation of functional molecules.[98–100] A number of plant viruses of different sizes have been structurally characterized, and many of these are available in large quantities. They are

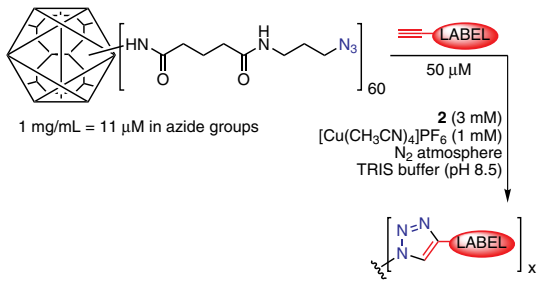
stable to a variety of chemical agents, and their capsid proteins can be selectively modified using site-directed mutagenesis, allowing facile introduction of azide or alkyne handles. For example, the cow pea mosaic virus (CPMV) has been derivatized with single carbohydrate compounds producing a dendrimer-like display with polyvalent lectin-binding properties (**eq 8**);[101] with PEG to give well-controlled loadings of polymer on the outer surface of the coat protein assembly;[102] and, more recently, with glycopolymers.[67]

3.7. Functionalization of Self-Assembled Monolayers

The chemical modification of surfaces precoated with self-assembled monolayers (SAMs) of alkanethiols facilitates studies aimed at the fundamental understanding and rational control of electron-transfer events at the electrochemical interface.[103] As reported by Collman et al. and others, cycloaddition chemistry allows the facile introduction of redox-active ferrocene derivatives onto SAM-coated electrode surfaces.[104,105] In one example, monolayers containing azide terminal groups were formed by coadsorption of azidoundecanethiols with decanethiols to gold-coated silicon wafers. Ethynylferrocene was coupled to the monolayers using 1 mol % of copper(II) sulfate and 15 mol % of sodium ascorbate, and the progress of the reaction was followed by the disappearance of azide absorption in infrared spectra. The density of coverage was quantified using cyclic voltammetry. In another report, the copper(I) catalyst was electrochemically formed on the surface of independently addressed microelectrodes (separated by 10 μm). Application of a –300-mV potential to the targeted electrodes resulted in the instantaneous formation of Cu(I) from the Cu(II) salt, thereby providing a catalytically active species that effected cycloaddition of ethynylferrocene to the azide-containing SAM.[106]

4. Summary and Outlook

The rapid emergence of wide-ranging applications of the copper-catalyzed azide–alkyne cycloaddition (CuAAC) in a few short years since its discovery underscores the immense need for other reliable, chemically orthogonal transformations for establishing covalent connections between diverse building blocks. Equally important, the revived interest in the well-known, yet notably underutilized, class of heterocycles, 1,2,3-triazoles, has served as an impetus for the development of other selective methods leading to this functionality. Thus, ruthenium(II) complexes were recently reported to catalyze the cycloaddition of both terminal and internal alkynes, resulting in the formation of 1,5-disubstituted- and 1,4,5-trisubstituted-1,2,3-triazoles, isomers that are not obtained via CuAAC.[107] Noncatalytic variants of the cycloaddition, which rely on the activation of the alkyne component by means of electron-withdrawing substituents or strain have also been revisited. For example, a strain-promoted cycloaddition, which takes advantage of the reactive nature of cyclooctyne and, therefore, does not require a catalyst, was used to label *N*-azidoacetyl neuramic acid residues on cell surfaces.[108,109] This application also highlights a current limitation of CuAAC: free copper ions are cytotoxic and may cause degradation of proteins and nucleic acids in vitro. Although Cu(I)-stabilizing ligands provide an acceptable solution in many cases, the development of new catalysts and ligands that prevent the leaching of copper ions into the reaction medium, yet do not impair the catalytic activity of copper, will significantly expand the reach of this already widely utilized transformation, and might enable the selective manipulation of living systems at the molecular level—a powerful, yet challenging strategy.[76]



Ref. 42,98–102

eq 8

5. Acknowledgment

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About the Authors

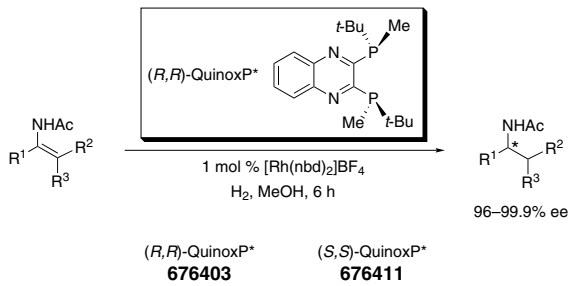
Peng Wu was born in Yaan, China. After receiving his B.S. degree in chemistry from Peking University in 1999, he joined Professor Kenneth G. Caulton's research group at Indiana University, Bloomington, where he studied ruthenium and copper pincer complexes. In 2001, he entered the graduate program at The Scripps Research Institute and, in 2005, received the Ph.D. degree under the guidance of Professors K. Barry Sharpless and Valery V. Fokin. While at Scripps, he developed a general method for the synthesis and functionalization of dendrimers using the newly discovered copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction. From September 2004 to early 2005, he was a visiting student in the laboratory of Professor Craig J. Hawker at IBM Almaden Research Center and at the University of California, Santa Barbara. Currently, Dr. Wu is an HHMI postdoctoral fellow in the group of Professor Carolyn R. Bertozzi at the University of California, Berkeley.

Valery V. Fokin was born in 1971 in Nizhny Novgorod, Russia. He received his *Diploma* in chemistry in 1993 from the University of Nizhny Novgorod, and his Ph.D. degree in 1998 from the University of Southern California, Los Angeles, where he worked under the direction of Professor Nicos A. Petasis. He then joined the group of Professor K. Barry Sharpless at The Scripps Research Institute in La Jolla, California, as a postdoctoral fellow, where he studied catalytic oxidations of olefins. In 2000, he was appointed Assistant and, in 2006, Associate Professor in the Chemistry Department at Scripps. His research is centered on understanding chemical reactivity and its applications in chemistry, biology, and materials science.

New Products for Asymmetric Synthesis

QuinoxP*: Air-Stable and Highly Efficient Chiral Ligands

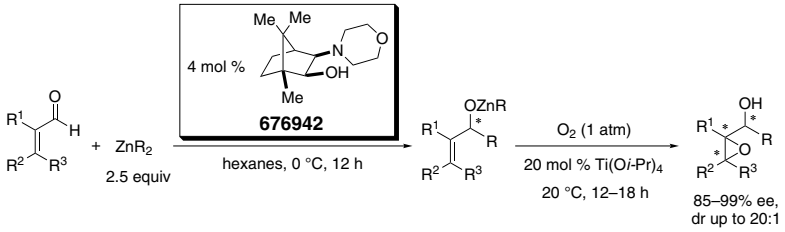
Professor Imamoto and co-workers have designed innovative chiral ligands, QuinoxP*, that mediate an impressive breadth of valuable transformations.[1] These powerful, efficient ligands exhibit high levels of enantiocontrol in synthetic processes ranging from metal-catalyzed asymmetric 1,4-additions of arylboronic acids, to enantioselective alkylative ring opening, to asymmetric hydrogenations. It is worth noting that QuinoxP* is not oxidized at the stereogenic phosphorus center on standing at ambient temperature in air for more than 9 months. Sigma-Aldrich, in collaboration with Nippon Chemical, is pleased to offer both enantiomers of QuinoxP* for the research market.



(1) Imamoto, T. et al. *J. Am. Chem. Soc.* **2005**, *127*, 11934.

Highly Selective One-Pot Synthesis of Epoxy Alcohols

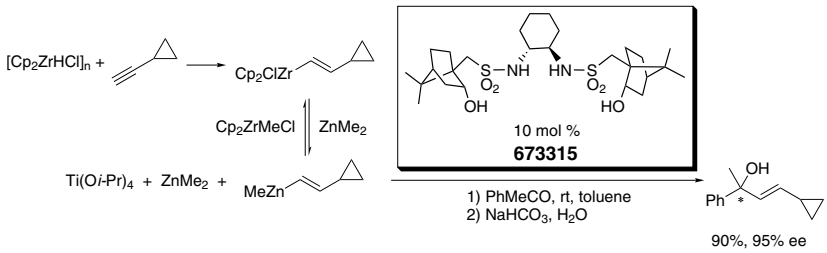
Professor Walsh and co-workers have invented a novel methodology for the production of chiral epoxy alcohols that contain three contiguous stereocenters.[2] This process, which complements the Sharpless asymmetric epoxidation,[3] is effectively mediated by a zinc catalyst built around Nugent's (–)-MIB ligand.[4] This asymmetric chemistry is highlighted by excellent levels of enantiocontrol, as well as yielding moderate to exceptional diastereomeric ratios for a diverse array of substrates.



(2) (a) Jeon, S.-J. et al. *Org. Lett.* **2005**, *7*, 1729. (b) Lurain, A. E. et al. *J. Org. Chem.* **2005**, *70*, 1262. (3) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Gao, Y. et al. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (4) Nugent, W. A. *J. Chem. Soc., Chem. Commun.* **1999**, 1369.

Enantioselective Addition of Organozinc Reagents to Ketones

Walsh and co-workers have invented a chiral diamine ligand that has been used by Walsh and others for the efficient, catalytic alkylation, arylation, and vinylation of ketones under high enantiocontrol.[5] The bis-sulfonamide ligand illustrated here represents an impressive evolution, wherein the second generation "constrained-geometry" ligand is less bulky than previous versions and thus greatly enhances overall catalyst activity. This ligand affords several distinct advantages over the prior art in the field including: (i) catalyst loadings are typically ≤1 mol %, (ii) room temperature reactions are complete in 24–36 h, (iii) high ee's are generated in gram-scale reactions, and (iv) asymmetric alkylations have been applied in conjunction with successive epoxidations.

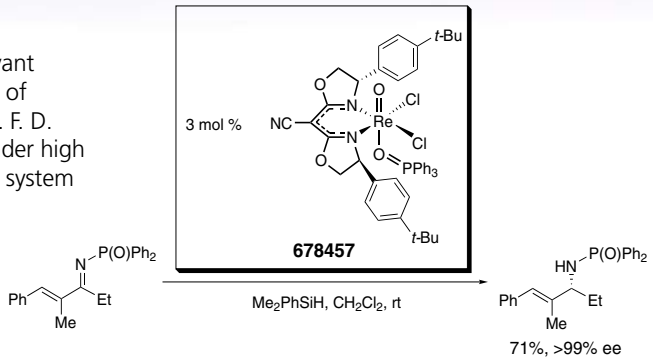


(5) (a) Garcia, C. et al. *J. Am. Chem. Soc.* **2002**, *124*, 10970. (b) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284. (c) Jeon, S.-J. et al. *J. Org. Chem.* **2005**, *70*, 448. (d) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 8355.

Re(V)-Oxo-Catalyzed Asymmetric Reduction of Imines

Chiral amines are ubiquitous in natural products and pharmaceutically relevant molecules. Thus, extensive research has been undertaken in the production of novel catalysts that mediate asymmetric C–N bond-forming processes. Prof. F. D. Toste and co-workers have successfully achieved the reduction of imines under high enantiocontrol by utilizing a rhenium(V) terminal oxo complex. This catalyst system offers several advantages including: "open-flask" reactivity, broad functional group tolerance, and excellent chemoselectivity.[6]

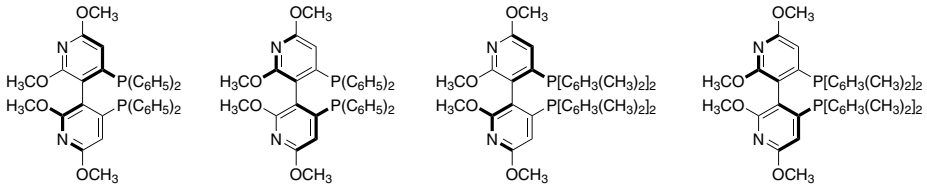
(6) Nolin, K. A. et al. *J. Am. Chem. Soc.* **2005**, *127*, 12462.



Chiral P-Phos Ligands

Developed by Professor Albert S. C. Chan, these chiral dipyridylphosphine ligands have shown impressive results in asymmetric hydrogenation reactions of β-keto esters, 2-arylacrylates, aryl ketones, and other substrates.[7]

(7) Wu, J.; Chan, A. S. C. *Acc. Chem. Res.* **2006**, *39*, 711.

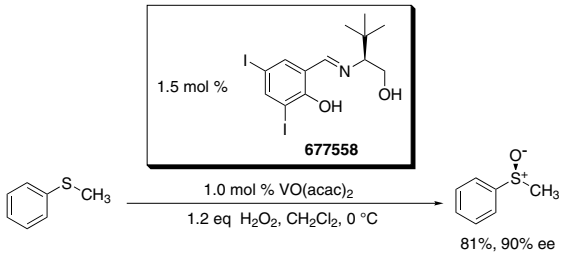


(*R*)-P-Phos **675806** | (*S*)-P-Phos **675792** | (*R*)-Xylyl-P-Phos **676004** | (*S*)-Xylyl-P-Phos **675946**

Vanadium-Catalyzed Asymmetric Oxidation

Anson and co-workers have reported that the 3,5-diiodo Schiff base shown here, in combination with $VO(acac)_2$, gives excellent results in the catalytic asymmetric sulfoxidation of alkyl aryl sulfides.[8] Recently, Jackson and co-workers have demonstrated its use in the kinetic resolution of alkyl aryl sulfoxides with high enantioselectivities.[9]

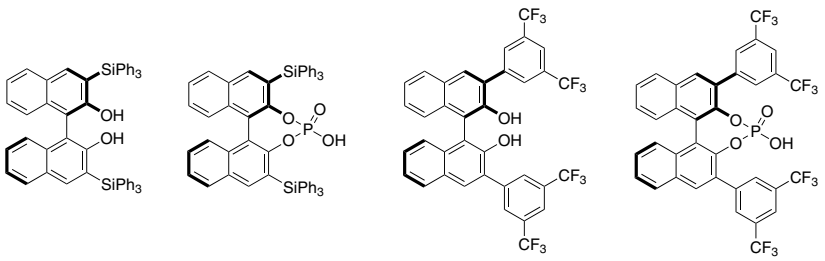
(8) Pelotier, B. et al. *Synlett* **2002**, 1055.
(9) (*R*)-isomer used. Drago, C. et al. *Angew. Chem., Int. Ed.* **2005**, *44*, 7221.



Chiral BINOLs

MacMillan and co-workers recently reported the first direct enantioselective organocatalytic reductive amination reaction, relying on the silylated BINOL phosphoric acid derivative **674745**.[10] Similarly, Rueping and co-workers have utilized **674605** in the organocatalytic transfer hydrogenation of imines using Hantzsch dihydropyridine as a hydrogen source.[11]

(10) Storer, R. I. et al. *J. Am. Chem. Soc.* **2006**, *128*, 84.
(11) Rueping, M. et al. *Org. Lett.* **2005**, *7*, 3781.



674737 | **674745** | **674591** | **674605**

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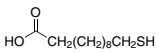
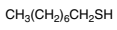
NanoThinks™ ACID11 NEW
11-Mercaptoundecanoic acid solution, 5 mM in ethanol
[*71310-21-9*]
$C_{11}H_{22}O_2S$
FW: 218.36



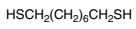
662925-100ML	100 mL

NanoThinks™ 8 NEW
1-Octanethiol solution, 5 mM in ethanol
[*111-88-6*]
$C_8H_{18}S$
FW: 146.29



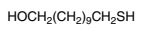
662208-100ML	100 mL

NanoThinks™ THIO8 NEW
1,8-Octanedithiol solution, 5 mM in ethanol
[*1191-62-4*]
$C_8H_{18}S_2$
FW: 178.36



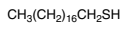
662615-100ML	100 mL

NanoThinks™ ALCO11 NEW
11-Mercapto-1-undecanol solution, 5 mM in ethanol
[*73768-94-2*]
$C_{11}H_{24}OS$
FW: 204.37



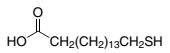
662224-100ML	100 mL

NanoThinks™ 18 NEW
1-Octadecanethiol solution, 5 mM in ethanol
[*2885-00-9*]
$C_{18}H_{38}S$
FW: 286.56



662194-100ML	100 mL

NanoThinks™ ACID16 NEW
16-Mercaptohexadecanoic acid solution, 5 mM in ethanol
[*69839-68-5*]
$C_{16}H_{32}O_2S$
FW: 288.49



662216-100ML	100 mL

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Selecting and Driving Monolayer Structures through Tailored Intermolecular Interactions

Mr. T. J. Mullen

Dr. A. A. Dameron

Professor A. M. Andrews

Professor P. S. Weiss

*Thomas J. Mullen, Arrelaine A. Dameron, Anne M. Andrews, and Paul S. Weiss**
104 Davey Laboratory
Departments of Chemistry, Physics, and Veterinary and Biomedical Sciences
The Pennsylvania State University
University Park, PA 16802-6300, USA
Email: stm@psu.edu

Outline

1. Introduction

The development of self- and directed-assembly techniques is key for the fabrication of molecularly precise structures for applications ranging from biocompatible and/or bioactive systems to microelectronics.[1–3] These applications now demand patterned surface structures with ever smaller features down to the sub-100 nm scale; however, traditional lithographic techniques such as photolithography cannot reproducibly fabricate such structures with molecular-scale organization.[4] By employing a library of molecules with a spectrum of intermolecular-interaction strengths in conjunction with a variety of thin-film-processing techniques, it is becoming possible to fabricate nanometer-sized surface features with molecular precision.

To characterize chemically patterned surface structures, it is necessary to employ techniques that can distinguish features at the molecular scale. Ensemble-averaging techniques, such as Fourier transform infrared spectroscopy (FTIR) and X-ray photoelectron spectroscopy (XPS), determine the macroscopic properties and can give chemically specific information about thin films.[5] However, these techniques lack the ability to characterize molecular-scale surface structures.[6–9] In contrast, scanning probe techniques, such as scanning tunneling microscopy (STM) and lateral force microscopy (LFM), are localized techniques that can visualize the surfaces of chemically patterned thin films with ultrahigh resolution and are thus employed extensively in the area of molecular imaging.[10–12]

Over the last 10 years, we have discovered how to fabricate mixed-component self-assembled monolayers (SAMs) in order to create patterned film structures. This review outlines our efforts to develop and to apply molecules—with distinctive chemical and physical properties and with varying intermolecular-interaction strengths and surface stabilities—in patterning monolayer-film structures. In addition to employing molecules with tailored interactions, SAM coadsorption, postadsorption, and displacement processing techniques are used to create a variety of patterned films. We will highlight three applications where specifically tuned molecules and customized SAM

processing techniques are utilized: molecular electronics, chemical patterning, and biomolecular tethering. More comprehensive reviews on patterning self-assembled monolayers and methodologies to fabricate phase-separated SAMs have been published.[13–16]

2. Varying the Intermolecular-Interaction Strengths within Monolayers

2.1. n-Alkanethiolate Self-Assembled Monolayers

The adsorption of *n*-alkanethiol molecules onto noble metal substrates has been studied extensively, and, therefore, the intermolecular-interaction strength of *n*-alkanethiolate SAMs will be used as a benchmark for comparing the intermolecular strengths of other monomolecular films.[11,14,17] *n*-Alkanethiol molecules consist of a thiol head group with a hydrocarbon tail that can be tuned to have from 2 to over 20 methylene units. In general, longer-chain molecules have larger intermolecular interactions when compared to those of shorter-chain molecules due to increased van der Waals forces.[18,19] The formation of *n*-alkanethiolate SAMs on Au{111} occurs in two steps. Initially, the thiol head groups of the *n*-alkanethiol molecules spontaneously adsorb onto the gold surface. Then, an ordering process occurs where the hydrocarbon tails interact, forming a crystalline structure with a nominally all-trans configuration.[20,21] If the SAM is formed in solution, an additional adsorption–desorption exchange process occurs during the ordering step.[22] **Figure 1A** is a molecularly resolved STM image of a 1-dodecanethiolate (C12) SAM deposited on a Au{111} substrate via exposure to ethanolic solution for 24 h. The C12 molecules formed a hexagonally close-packed lattice (with nearest-neighbor spacings of 5.0 Å) in a $(\sqrt{3} \times \sqrt{3})R30°$ unit cell conformation with respect to the underlying gold lattice. In addition to the $(\sqrt{3} \times \sqrt{3})R30°$ unit cell, a primitive c(4 × 2) superlattice was observed and was due to an alternating azimuthal orientation of one molecule with respect to its neighbor. The C12 molecules tilt 30° with respect to the surface normal to maximize their interactions with neighboring molecules. This molecular tilt resulted in different domains of C12 molecules that were defined by substrate vacancy islands, substrate step edges, and domain boundaries.[23]

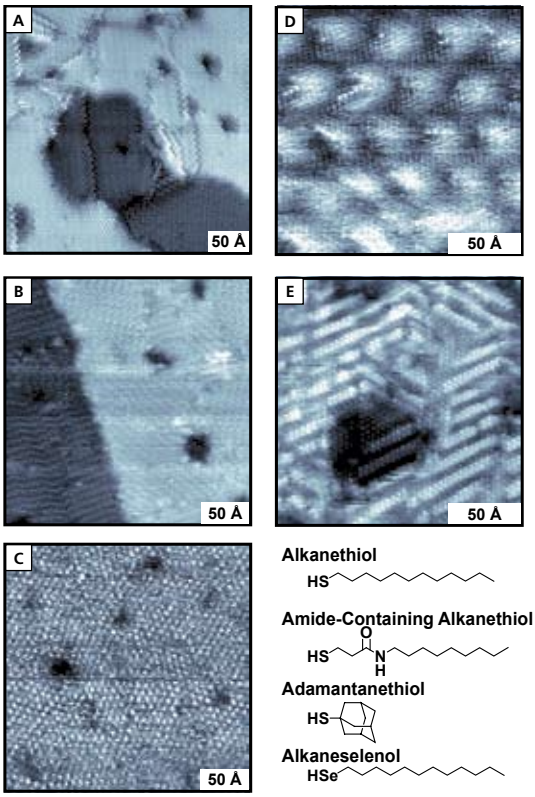

Figure 1. STM Images of Single-Component (**A**) 1-Dodecanethiolate (V_{sample} = –0.75 V, I_{tunnel} = 3 pA, 250 Å × 250 Å), (**B**) *N*-Nonyl-3-mercaptopropionamide (V_{sample} = –1.0 V, I_{tunnel} = 3 pA, 250 Å × 250 Å), (**C**) 1-Adamantanethiolate (V_{sample} = –0.75 V, I_{tunnel} = 3 pA, 250 Å × 250 Å), (**D**) Densely Packed Structure of 1-Dodecaneselenolate (V_{sample} = +1.0 V, I_{tunnel} = 3 pA, 165 Å × 165 Å), and (**E**) Missing-Row Structure of 1-Dodecaneselenolate (V_{sample} = –1.0 V, I_{tunnel} = 3 pA, 165 Å × 165 Å) SAMs Formed on Au{111} Substrates by Exposure to Ethanolic Solution for 24 h.

2.2. Amide-Containing Alkanethiolate Self-Assembled Monolayers

Amide-containing alkanethiols, such as *N*-nonyl-3-mercaptopropionamide (1ATC9), have a hydrocarbon backbone with internal amide functionality. The amide functionality allows adjacent molecules to form hydrogen bonds between the carbonyl and amino moieties. As a result, the interaction strengths of amide-containing alkanethiolate SAMs are significantly larger than those of *n*-alkanethiolate SAMs.[24–26] **Figure 2** shows a family of amide-containing alkanethiol molecules, including *N*-(*N'*-*n*-hexylacetamido)-3-mercaptopropionamide (2ATC6) and *N*-(*N'*-(*N''*-*n*-propylacetamido)acetamido)-3-mercaptopropionamide (3ATC3), where the intermolecular-interaction strength is increased by the number of amide functional groups that are buried within the monolayer.[27]

The amide-containing alkanethiolate SAM formation process is analogous to those of *n*-alkanethiolate SAMs. Initially, the thiol head group of an amide-containing alkanethiol adsorbs onto the gold surface, followed by an ordering process dictated by the hydrocarbon tail interactions. In addition to the hydrocarbon tail interactions, the buried amide functionality imparts directionality in the molecular lattice with a strong tendency to form linear networks.[28] **Figure 1B** shows a molecularly resolved STM image of a 1ATC9 SAM adsorbed onto a Au{111} substrate by exposure to ethanolic solution for 24 h. The 1ATC9 molecules formed hexagonally close-packed lattices (with nearest-neighbor spacings of 5.0 Å) with features—such as unit cell conformation, substrate vacancy islands, step edges, and protruding domain boundaries—that are comparable to those of *n*-alkanethiolate SAMs. However, rather than the c(4 × 2) and related superlattice structures observed for *n*-alkanethiolate SAMs, there was a p(3 × 3√3) superlattice due to lines of molecules that were formed via hydrogen bonding.

2.3. Adamantanethiolate Self-Assembled Monolayers

1-Adamantanethiol (AD) is based on adamantane, the smallest member of the diamondoid family, which consists of a ten-carbon cage that can be described as four fused cyclohexane rings in their chair conformations.[29] The intermolecular-interaction strengths of AD SAMs are considerably weaker than those of *n*-alkanethiolate SAMs due to the lattice spacings and the round topology of the molecule. As a result, AD SAMs are labile when exposed to other thiol molecules by contact, in solution, or in the vapor phase.[30,31] **Figure 1C** shows a molecularly resolved STM image of an AD SAM deposited on a Au{111} substrate by exposure to ethanolic solution for 24 h. The AD molecules formed a hexagonally close-packed lattice (with a nearest-neighbor spacing of 6.9 Å) in a (7 × 7) unit cell with respect to the underlying gold lattice. These

nearest-neighbor spacings for AD SAMs are considerably larger than those of *n*-alkanethiolate SAMs. Substrate vacancy islands and step edges observed in AD SAMs have similar structures to those of *n*-alkanethiolate SAMs; however, AD SAMs lack the large variety of domain boundaries associated with the tilt of *n*-alkanethiolate SAMs. Instead, AD SAMs have "depressed" domain boundaries (as observed in STM images) resulting from mismatched rotational domains of the AD molecules.

2.4. n-Alkaneselenolate Self-Assembled Monolayers

n-Alkaneselenol molecules consist of a hydrocarbon backbone with a selenol (SeH) head group. Similar to *n*-alkanethiol molecules, the length of the hydrocarbon tail, which can range from 2 to over 20 methylene units, affects the strengths of the resulting intermolecular interactions. However, *n*-alkaneselenolate SAMs have larger head group–head group interactions than those of *n*-alkanethiolate SAMs, which affects their monolayer structures. 1-Dodecaneselenolate (C12Se) SAMs form two coexisting phases, a densely packed distorted hexagonal lattice and a missing-row lattice, after exposure to a tetrahydrofuran solution for 24 h.[32] **Figure 1D** shows a molecularly resolved STM image of the densely packed structure of a C12Se SAM deposited on a Au{111} substrate. The C12Se molecules in this phase formed a distorted hexagonal lattice with nearest-neighbor spacings of 4.9 Å and 5.2 Å. A moiré pattern was observed indicating that the distorted densely packed lattice was incommensurate to the underlying gold substrate (i.e., the selenolate molecules were not located on sites in registry with the Au lattice). **Figure 1E** shows a molecularly resolved STM image of the missing-row structure of a C12Se SAM deposited on a Au{111} substrate. The molecules in this phase formed a commensurate but incomplete lattice with variants of the $(\sqrt{3} \times \sqrt{3})R30°$ unit cell with respect to the underlying gold lattice. The unit cell variants arise from selenolate head groups shifting between adjacent Au adsorption sites (bridge and 3-fold lattice sites). The proposed formation process of *n*-alkaneselenolate SAMs consists of two steps. Initially, *n*-alkaneselenolate molecules adsorb rapidly onto the gold surface, forming the missing-row lattice. This rapid adsorption is followed by a slow rearrangement of the selenolate head groups through adsorption of additional *n*-alkaneselenolate molecules. This rearrangement leads to the formation of the distorted hexagonal lattice. Similarly to what occurs during *n*-alkanethiolate SAM formation, the hydrocarbon tails of *n*-alkaneselenolates interact and develop into a crystalline lattice.[32]

3. Monolayer-Film Processing Techniques

3.1. Coadsorption Preparations

Coadsorption combines two different adsorbate molecules in a single deposition (solution or vapor).[33,34] If there is a sufficient difference in the intermolecular-interaction strengths between the two adsorbate molecules, then the molecules will aggregate into separated domains in order to maximize their respective intermolecular interactions. However, if there is insufficient difference in the intermolecular interactions between the two adsorbate molecules, then a mixed monolayer forms, where the two molecules are dispersed throughout the SAM.[35] The intermolecular interactions can be tuned by modifying the structure of the adsorbing molecule. Additionally, the interaction strengths of the coadsorbing molecules influence the adsorption affinities of the molecules. This is reflected by the surface concentrations of the two adsorbates not directly mirroring the solution concentrations of the two species. We have demonstrated the ability to fabricate phase-separated SAMs by tailoring the terminal functional group, the hydrocarbon backbone, and the head group of the adsorbing molecule.[28,36,37] In all cases, equilibrium structures are not reached, due to the restricted mobility of the molecules and their limited ability to exchange between the surface and the deposition medium.

Phase-separated SAMs with domains of molecules with different reactivities can be dictated by the *terminal functionality* of the two molecules that are coadsorbed. Stranick et al. demonstrated this method by fabricating phase-separated SAMs of coadsorbed 1-hexadecanethiol (C16) molecules and methyl 15-mercapto-1-pentadecanoate (C15ME) molecules.[38] Both of these molecules have similar hydrocarbon-chain lengths and differ only in the terminal functional groups. **Figure 3A** displays an STM image of the phase-separated SAM consisting of methyl-terminated molecules (less protruding domains) and methyl-ester-terminated molecules (more protruding domains). This and related STM images show that there are phase-separated, nanometer-scale domains of the two molecules on the surface; the domains were identified (C15ME appears more protruding) by varying the surface coverage ratios.[39,40]

Another method of fabricating phase-separated SAMs is to coadsorb molecules that drive the formation of separated SAMs as a result of their *internal* functionalization. Smith et al. demonstrated phase-separated SAMs obtained by the internal functionalization method by the coadsorption of 1ATC9 and 1-decanethiol (C10).[28] **Figure 3B** shows an STM image of a phase-separated 1ATC9 (appears as a more protruding lattice) and C10 (appears as a less protruding lattice) SAM.[41] Although the phase-separated SAMs had the same terminal functionality in both domains, they were separated due to different intermolecular-interaction strengths and domain stabilities. For example, the C10 domains adsorb onto the surface less strongly and desorb more readily than 1ATC9 domains.[27] Note that the advantage of having buried hydrogen bonds can only be exploited when the amide functionality is present in adjacent properly oriented molecules. This leads to linear hydrogen-bonding networks that result in significant effects in the monolayer structure.[13,27,28]

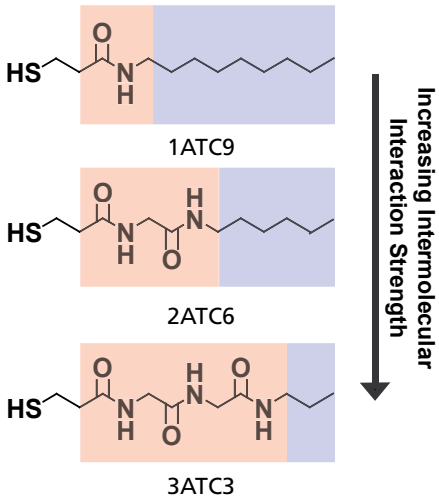

Figure 2. Amide-Containing Alkanethiol Molecules Exhibiting Increased Intermolecular-Interaction Strength as the Number of Amide Functional Groups Increases.

Head-group functionality also directs phase separation in coadsorbed SAMs.[37] **Figure 3C** displays an STM image of a phase-separated C12Se (more protruding regions) and C10 (less protruding regions) SAM.[41] These molecules have identical terminal groups and similar hydrocarbon chain lengths, but differ in their head-group functionalities. However, unlike phase separation that is driven by terminal or internal functionality, the two lattice types of the separated SAM in Figure 3C have vastly different structures. The different head groups offer a method to create molecular films with separated domains that have distinct conductance differences. This quality may be useful in the design of molecular electronic devices.[42]

Generally, the solution composition (i.e., solution mole fraction) before coadsorption dictates the surface composition (i.e., fractional surface coverage). However, the solution mole fraction is not necessarily directly reflected in the fractional surface coverage. For example, Lewis et al. varied the molar ratios of 1ATC9 and C10 in deposition solutions.[27] It was observed that at high concentrations of 1ATC9 the solution mole fraction and the fractional surface coverage were correlated. As the 1ATC9 concentration decreased, a dramatic and nonlinear decrease in the ratio of the fractional surface coverage to solution mole fraction was observed. This effect was attributed to the 1ATC9 molecules having larger intermolecular-interaction strengths than C10 molecules and, therefore, being stabilized on the surface by adjacent 1ATC9 molecules. Additionally, the solvation of the 1ATC9 molecules and the C10 molecules also influences the adsorption process. Molecules that are preferentially solvated or aggregated, such as 1ATC9, may not adsorb as quickly onto the surface. Moreover, as the 1ATC9 solution mole fraction decreases, the large number of solvated C10 molecules, in combination with fewer 1ATC9 molecules on the surface, stabilizes the SAM. Thus, the exchange process favors desorption of 1ATC9 and adsorption of C10 molecules.

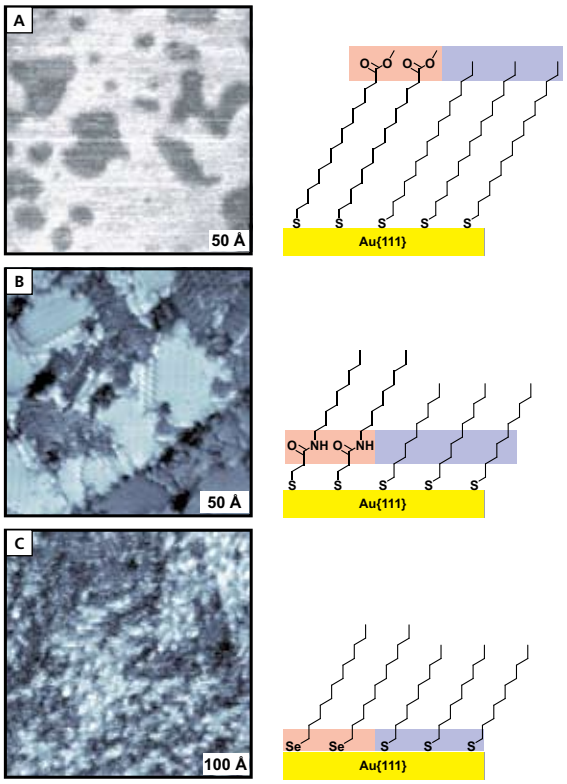

Figure 3. (**A**) STM Image (V_{sample} = –1.0 V, I_{tunnel} = 1 nA, 310 Å × 310 Å) of a Separated Methyl Ester ω-Functionalized 1-Pentadecanethiolate (More Protruding Lattice) and 1-Hexadecanthiolate (Less Protruding Lattice) SAM Formed on a Au{111} Substrate from a 75% Methyl Ester ω-Functionalized 1-Pentadecanethiol and 25% 1-Hexadecanethiol Solution (1 mM in Total Thiol). (**B**) STM Image (V_{sample} = –1.0 V, I_{tunnel} = 1 pA, 250 Å × 250 Å) of a Separated *N*-Nonyl-3-mercaptopropionamide (More Protruding Lattice) and 1-Dodecanethiolate (Less Protruding Lattice) SAM Formed on a Au{111} Substrate from an Equimolar Solution of *N*-Nonyl-3-mercaptopropionamide and 1-Decanethiol (1 mM in Total Thiol). (**C**) STM Image (V_{sample} = –1.0 V, I_{tunnel} = 1 pA, 500 Å × 500 Å) of a Separated SAM of 1-Dodecaneselenolate (More Protruding Lattice) and 1-Decanethiolate (Less Protruding Lattice) Formed on a Au{111} Substrate from a 90% 1-Dodecaneselenol and 10% 1-Dodecanethiol Solution (1 mM Total).

3.2. Postadsorption Processing

One form of postadsorption processing modifies a pre-existing SAM with heat, the presence of extra thiol molecules in the vapor phase, or thiol molecules in solution.[43–45] These modifications enable the fabrication of separated SAMs with adsorbate molecules that form mixed monolayers when coadsorbed.

Thermal annealing creates multicomponent SAMs by heating a preformed single-component SAM and subsequently exposing that SAM to another thiol. Bumm et al. employed thermal annealing to fabricate separated C12 and C10 SAMs.[45] Initially, a single-component C12 SAM was fabricated via solution deposition in ethanol for 1 h at 78 °C. The partially desorbed SAM was then immersed into an ethanolic solution of C10 for 6 h at room temperature. **Figure 4A** shows an STM image of the separated C12 and C10 SAM produced via thermal annealing. This SAM was composed of virtually defect-free islands of C12 molecules (more protruding lattice) surrounded by domains of C10 molecules (less protruding lattice), where the defect density and domain boundaries were consistent with the SAMs adsorbed at room temperature. The C10 molecules adopted the same orientation and packing as the C12 molecules in order to maximize their intermolecular interactions. Additionally, molecularly sharp domain boundaries free of physical defects were observed throughout the SAM.

Vapor-phase annealing modifies a pre-existing SAM with thiol molecules from the vapor phase. These molecules insert into defect sites—such as vacancy islands, step edges, and domain boundaries—of the preformed SAM, creating a patterned multicomponent SAM.[43] **Figure 4B** shows a molecularly resolved STM image of a single-component 1-octanethiolate (C8) SAM vapor-annealed with C10 for 1 h at room temperature. The more protruding lattice is attributed to C10 and the less protruding one to C8.[41] From the STM image, one finds that the C10 molecules insert around the vacancy islands and domain boundaries present in the SAM. As in the case of thermal annealing, the C10 molecules adopt the same packing and orientation as the C8 molecules.

Solution-phase insertion exposes a preformed single-component SAM to thiols in solution.[44,46,47] However, rather than a large number of molecules inserting in connected bundles at defect sites as with vapor-phase annealing, the solvated molecules tend to insert individually at defect sites of the single-component SAM. This technique can be used to isolate single molecules in order to probe their respective chemical and physical properties. For example, **Figure 4C** is an STM image of oligo(phenylene ethynylene) (OPE) molecules inserted into a C8 host SAM.[41] The STM images showed that the OPE molecules (most protruding features) inserted at defect sites, such as substrate vacancy islands

and domain boundaries, and that the crystalline order of the host C8 SAM was preserved after insertion.

The relative sizes of the domains of the two lattice types of the separated SAM were determined by the postadsorption processing time and from the solution concentration of the second molecule. For example, by tailoring the OPE solution concentration and the insertion time, the number of molecules that were inserted from the solution phase into the preformed C8 SAM was controlled, allowing for single-molecule measurements to be acquired for a large number of molecules in a single STM image.[46] Additionally, solution-phase insertion techniques have been employed to isolate, to dilute optimally, and to anchor single-molecule polymer precursors to surfaces, where ring-opening polymerization can proceed to grow single polymer chains.[48] Likewise, insertion of larger bundles of tethers can be used to grow anchored polymer brushes.

3.3. Displacement Methods

Displacement employs a single-component SAM composed of molecules that are labile when exposed to other thiol molecules by contact, in solution, or in the vapor phase.[30,31,49] As displacement occurs, ordered separated domains of both molecules can be observed until the SAM is composed entirely of the second thiolated molecule. Single-component AD SAMs are ideal for this process due to their lower density of molecule–surface bonds and low intermolecular-interaction strengths as compared to those of *n*-alkanethiolate SAMs.

Solution displacement exposes a single-component SAM to a solvated thiol molecule. The solvated molecules insert at defect sites of the pre-existing SAM and grow into domains until the preformed SAM is displaced completely.[31] **Figure 5A** is an STM image of a separated C12-and-AD SAM created via solution displacement for 1 h. The most protruding lattice that originates at the substrate defects is attributed to C12, while the less protruding lattice is attributed to AD.[41] As discussed above, the lattice spacings of the AD molecules are significantly different from those of the C12 lattice. This difference, together with the differences in the apparent heights of the two lattices, simplifies identification of the different regions in the separated C12-and-AD SAM. At long displacement times, the separated SAM becomes composed entirely of C12 molecules.

Vapor displacement exposes a single-component SAM to thiol molecules in the vapor phase. The molecules in the vapor phase insert at defect sites and grow into domains until completely displacing the preformed AD SAM.[30] This is in contrast to what occurs during vapor-phase annealing, where the inserted molecules do not replace the existing preformed SAM completely. **Figure 5B** is an STM image of a separated C10-and-AD SAM created by vapor displacement of AD with C10 for 15 min. The more protruding lattice is attributed to C10 domains and the less protruding one to AD domains.[41] Substrate defects, such as vacancy islands and substrate step edges are also present. Higher surface coverages by C10 have been observed for vapor displacement than for solution displacement when using similar displacement times and concentrations.

Contact displacement places an existing SAM into contact with an elastomeric stamp that is coated with molecules to be patterned; the molecules on the stamp displace the existing SAM only in places where the stamp and substrate are in contact.[49,50] **Figure 5C** is an STM image of a separated C10-and-AD SAM fabricated by contact displacement. The more protruding regions are attributed to C10 molecules and the less protruding ones to AD molecules.[41] The entire substrate was contacted with an

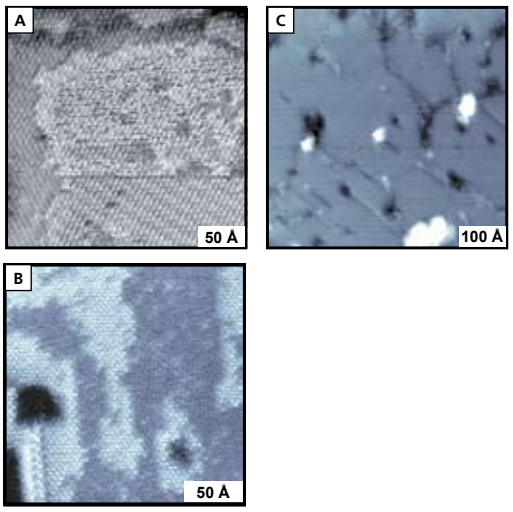

Figure 4. (**A**) STM Image (V_{sample} = –1.0 V, I_{tunnel} = 10 pA, 250 Å × 250 Å) of a Separated 1-Decanethiolate (Less Protruding Lattice) and 1-Dodecanethiolate (More Protruding Lattice) SAM Fabricated on a Au{111} Substrate by *Thermal Annealing* of a 1-Decanethiolate SAM and Subsequent Exposure to an Ethanolic Solution of 1-Dodecanethiol for 5 min. (**B**) STM Image (V_{sample} = –1.0 V, I_{tunnel} = 2 pA, 200 Å × 200 Å) of a Separated 1-Octanethiolate (Less Protruding Lattice) and 1-Decanethiolate (More Protruding Lattice) SAM Fabricated on a Au{111} Substrate by *Vapor Annealing* of a Single-Component 1-Octanethiolate SAM with 1-Dodecanethiol. (**C**) STM Image (V_{sample} = –1.0 V, I_{tunnel} = 2 pA, 500 Å × 500 Å) of a 1-Octanethiolate SAM *Solution-Inserted* with Oligo(Phenylene Ethynylene) Molecules (Protrusions) for 5 min on a Au{111} Substrate.

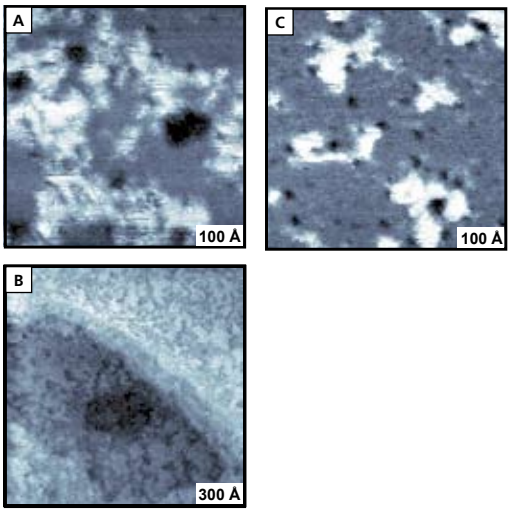

Figure 5. (**A**) STM Image (V_{sample} = –1.2 V, I_{tunnel} = 5 pA, 500 Å × 500 Å) of a Preformed 1-Adamantanethiolate SAM on a Au{111} Substrate That Was *Solution-Displaced* by 1 mM 1-Dodecanethiol for 1 h. The More Protruding Lattice Is Attributed to 1-Dodecanethiolate and the Less Protruding One to 1-Adamantanethiolate. (**B**) STM Image (V_{sample} = –1.0 V, I_{tunnel} = 2 pA, 1500 Å × 1500 Å) of a Preformed 1-Adamantanethiolate SAM on a Au{111} Substrate That Was *Vapor-Displaced* by Neat 1-Decanethiol for 15 min. The More Protruding Lattice Is Attributed to 1-Decanethiolate and the Less Protruding One to 1-Adamantanethiolate. (**C**) STM Image (V_{sample} = –1.0 V, I_{tunnel} = 1 pA, 500 Å × 500 Å) of a Preformed 1-Adamantanethiolate SAM That Was *Contact-Displaced* with 75 mM Ethanolic 1-Decanethiol for 2 min. The More Protruding Lattice Is Attributed to 1-Dodecanethiolate, and the Less Protruding One to 1-Adamantanethiolate.

unpatterned stamp inked with C10 molecules. Displacement was observed initially at defects within the SAM and, as the contact time was increased, the size of the C10 domains increased until the SAM was completely composed of C10 molecules.

Similar to postadsorption methods, there is a large array of molecules that can be employed for displacement. The molecule that makes up the sacrificial SAM is not limited to AD, but it must be sufficiently labile that it can be displaced when exposed to another thiol molecule. Additionally, the molecules that displace the existing SAM must have sufficient intermolecular-interaction strengths to form domains. Weiss's group observed striped regions rather than patches of molecules when hexanethiol (C6) was used as the displacing molecule.[31] These striped regions were attributed to the lower intermolecular-interaction strength associated with the shorter-chain C6 molecules. Additionally, vapor- and contact-displacement processing produced separated SAMs without solution, allowing for the use of molecules that could not be patterned before due to solubility problems.[30]

4. Applications

4.1. Molecular Electronics

Semiconductor microelectronic devices have physical-size limitations; therefore, new approaches are needed to fabricate smaller and faster devices. Electron transport through a single molecule is the ultimate limitation, but little is understood at a fundamental level of the behavior, operation, and optimization of the functional molecules in molecular electronics. By modifying the interaction strength of both individual molecules and the surrounding matrix, and tailoring the local environment through SAM processing techniques, the behavior of molecular devices has been modified in order to test and elucidate their respective mechanisms. Solution insertion techniques have been developed specifically to isolate single molecules within a host matrix and to characterize their electronic and structural properties with STM.[44,46,51]

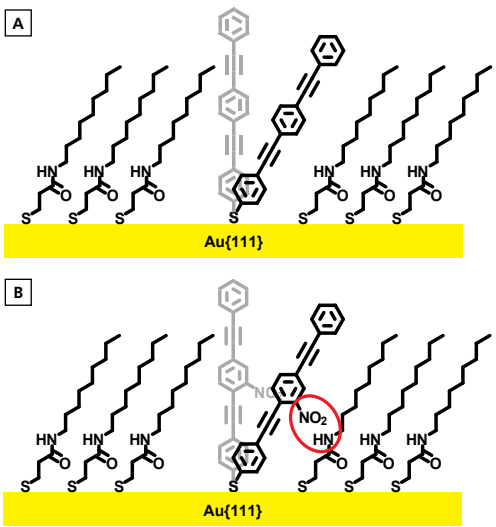

Figure 6. (**A**) Schematic of an Unfunctionalized Oligo(Phenylene Ethynylene) Molecule Inserted into a Preformed *N*-Nonyl-3-mercaptopropionamide SAM Showing How the Inserted Molecule Switches Stochastically but Does Not Form Hydrogen bonds with the Amide Functional Group of the *N*-Nonyl-3-mercaptopropionamide SAM. (**B**) Schematic of an Oligo(Phenylene Ethynylene) Molecule Functionalized with a Nitro Group (NO_2) Inserted into a Preformed *N*-Nonyl-3-mercaptopropionamide SAM Showing the Hydrogen Bonding (Red Oval) between the Nitro and the Amido Functional Groups.

The stochastic switching in single OPE molecules was mediated by tuning the intermolecular-interaction strength between the molecules and the host matrix. Lewis et al. tailored the host matrix by employing an amide-containing alkanethiolate SAM rather than an *n*-alkanethiolate SAM.[52,53] For an unfunctionalized OPE molecule, stochastic switching of the OPE molecule was observed; no hydrogen bonding between the OPE and the matrix was possible, but the tightness of the matrix affected the switching rate (**Figure 6A**).[53] However, when a nitro group (NO_2) was included as part of the OPE molecule and the proper matrix was selected, bias-dependent switching was observed and attributed to the nitro group of the functionalized OPE molecule interacting with the applied electric field and stabilized by hydrogen bonding with the amide-containing host matrix (**Figure 6B**).[52,53] This strategy of modifying the chemical functionality of both the molecular device and the host matrix demonstrated the ability to modulate the switching behavior of molecular devices.

In addition to tailoring the intermolecular interactions of the SAM, the stochastic switching activity of single-molecule devices was controlled by modifying the local environment via molecular processing techniques.[47] The order and density of the host matrix film played a crucial role in mediating the stochastic switching activity of OPE molecules.[46] Donhauser et al. employed vapor-phase annealing of C12 molecules to increase the density of the host matrix around single OPE molecules that had been solution-inserted into preformed C10 SAMs.[43] **Figure 7A** shows a diagram of the vapor-phase annealing of C12 into a preformed C10 SAM that had previously had OPE molecules inserted in it from solution. The C12 molecules in the vapor phase inserted around the defect sites where the OPE molecules were already adsorbed. **Figure 7B** shows a representative STM image of this type of SAM. The red arrow indicates where the OPE molecule inserted into the host matrix; the most protruding domains surrounding the defects were attributed to C12 molecules and the less protruding domains on the terraces were attributed to C10 molecules.[41] The switching rate of the OPE molecules and the number of OPE molecules that switched were observed to be significantly lower than the switching rate of OPE molecules that were solution-inserted into a C10 SAM without vapor-phase annealing. This chemical processing of the C10 SAM allowed the switching activity of the OPE molecules to be controlled.

From experiments that tuned the intermolecular interactions of the OPE molecules and the host matrix SAM, and those that modified the local environment of the host SAM via molecular processing techniques, the conductance switching mechanism was determined to be caused by a change in the hybridization of the OPE molecules that occurs with a change in the molecule–substrate contact. Moore et al. engineered OPE molecules with varying structures designed to test several proposed switching mechanisms.[54] Although this work supports the proposed mechanism that switching is due to a change in the hybridization of the OPE molecule–substrate bond, a more detailed discussion of it is beyond the scope of this review.

4.2. Chemical Patterning

Chemical patterning techniques are straightforward and versatile methods to direct the location of molecules on the micro- to nanometer scale.[15] Several approaches that will be discussed below include soft lithography and artificial separation methodologies. Soft-lithography techniques, such as microcontact printing and

dip-pen nanolithography, fabricate chemical features on a substrate without the direct assistance of traditional lithographic techniques.[55] Artificially separated SAMs allow for the creation of chemically patterned films not possible with other processing methods.[56]

Microcontact printing, a common soft-lithography technique, applies onto a substrate an elastomeric stamp that is coated with the molecules to be patterned. The molecules transfer from the stamp to the substrate only where the stamp and the substrate come in contact.[7,57–59] This patterning technique is limited to molecules that have sufficiently strong intermolecular interactions and are not susceptible to lateral diffusion across the surface. Employing AD SAMs in conjunction with contact displacement, it is possible to pattern molecules with weak intermolecular interactions by employing *microdisplacement printing*.[49,50] **Figure 8A** shows a schematic diagram of the microdisplacement printing process. Initially, a single-component AD SAM was formed on a gold substrate. Subsequently, an elastomeric stamp coated with the molecules to be patterned was brought in contact with the substrate possessing the AD SAM; the molecules on the stamp transferred to the substrate in places where the stamp and substrate came in contact. The AD SAM was labile enough to be displaced by the molecules to be patterned through competitive adsorption, which resulted in patterned regions of both AD and the subsequently patterned molecules. **Figure 8B** is an LFM image of a patterned Au{111} substrate fabricated by microdisplacement printing. The low-friction squares (shown as dark) were attributed to the stamped C8 molecules, and the high-friction background (shown as light) to the preformed AD SAM. This molecular pattern combination was not possible with microcontact printing because of the high mobility of C8.[59,60]

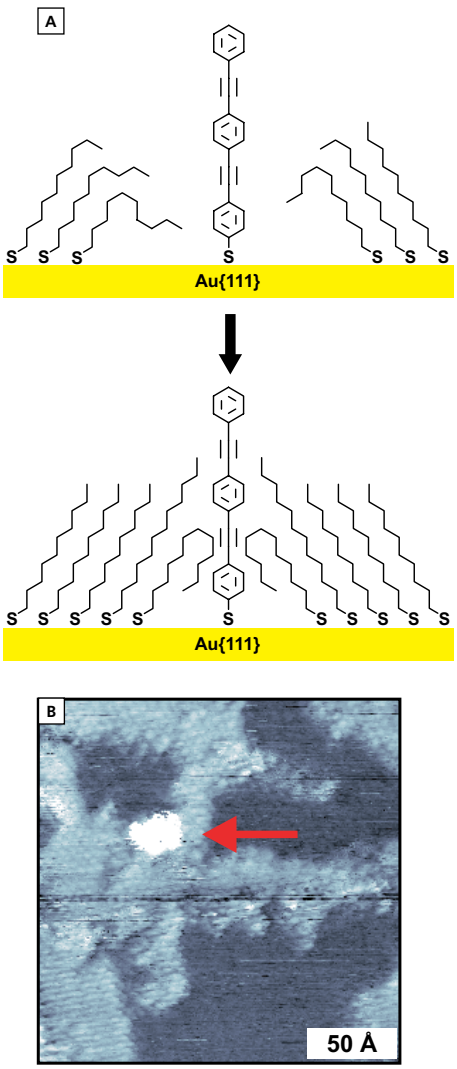

Figure 7. (**A**) 1-Dodecanethiol Vapor-Phase Annealing of an Oligo(Phenylene Ethynylene) Molecule Inserted into a Preformed 1-Decanethiolate SAM on a Au{111} Substrate. (**B**) STM Image (V_{sample} = –1.0 V, I_{tunnel} = 5 pA, 200 Å × 200 Å) of 1-Dodecanethiol Vapor-Phase Annealed into a 1-Decanethiolate SAM on a Au{111} Substrate That Was Inserted with Oligo(Phenylene Ethynylene) Molecules. The More Protruding Lattice Is Attributed to 1-Dodecanethiolate and the Less Protruding One to 1-Decanethiolate. The Red Arrow Indicates the Single Oligo(Phenylene Ethynylene) Molecule.

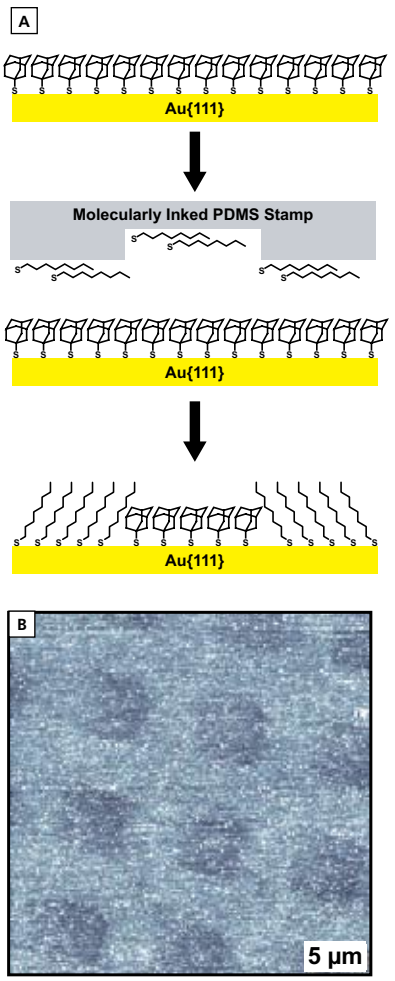

Figure 8. (**A**) Microdisplacement Printing Where a Preformed 1-Adamantanethiolate SAM Was Contacted with a Molecularly Coated Elastomeric Stamp. The Molecules to Be Patterned (1-Octanethiol) Displaced the 1-Adamantanethiol Molecules in Places Where the Stamp and Substrate Were in Contact. (**B**) Lateral Force Microscopy Image (30 µm × 30 µm, Scan Rate = 1.0 Hz, Force Setpoint = 1.0 nN) of a Patterned Au{111} Substrate Fabricated by Microdisplacement Printing, Showing the Presence of Two Molecules on the Surface. The Low-Friction Squares (Shown as Dark) are the Stamped 1-Octanethiol Molecules, and the High-Friction Background (Shown as Light) is the Preformed 1-Adamantanethiolate SAM.

Microdisplacement printing increased the library of patternable molecules and the precision of soft-lithography techniques as compared to microcontact printing by hindering the diffusion of the stamped molecules across the substrate both during and following the stamping process. By hindering the diffusion of the stamped molecules during the stamping process, it was possible to pattern molecules with low intermolecular interactions by blocking the lateral motion of the molecules. Microcontact printing often requires solvent exposure to prevent the degradation of the patterned film over time due to diffusion across the surface. Solvent exposure also reduces the precision of the patterned structures due to molecular exchange. With microdisplacement printing, solvent exposure is not required because AD molecules are still present in places where the stamp did not contact the surface. Additionally, multiple stamping steps can be used to produce proximate structures, circumventing the difficulty of precise registration of neighboring patterns in conventional soft-lithography techniques.[50]

Coadsorption techniques and *n*-alkanethiols of varied intermolecular-interaction strengths have been utilized to understand and control the thiol-transport mechanism in dip-pen nanolithography. *Dip-pen nanolithography* directly writes molecular inks from an atomic-force-microscope tip onto a surface.[61,62] Salaita et al. fabricated microscopically phase-separated monolayers employing cantilever tips that were inked with two molecules.[63] When the chemical structures were patterned, the more hydrophilic *n*-alkanethiol formed the interior phase, and the more hydrophobic *n*-alkanethiols formed the outer phase. To understand the ink transport mechanism, Hampton et al. fabricated surface structures by patterning 1-octadecanethiol (C18, hydrophobic) and 16-mercaptohexadecanoic acid (MHDA, hydrophilic) sequentially.[64] **Figure 9** depicts the proposed mechanism of the sequential double-ink experiments. When MHDA was patterned atop a C18 SAM, the water meniscus was compact, resulting in a lower transport rate of the MHDA molecules. In contrast, when C18 was patterned atop an MHDA SAM, the water meniscus was spread out, resulting in a higher transport rate of the C18 molecules. This double-ink study demonstrated that the rate and direction of transport, as well as the ability of the molecular ink to pattern, are affected by the chemical functionality of the surface.[64]

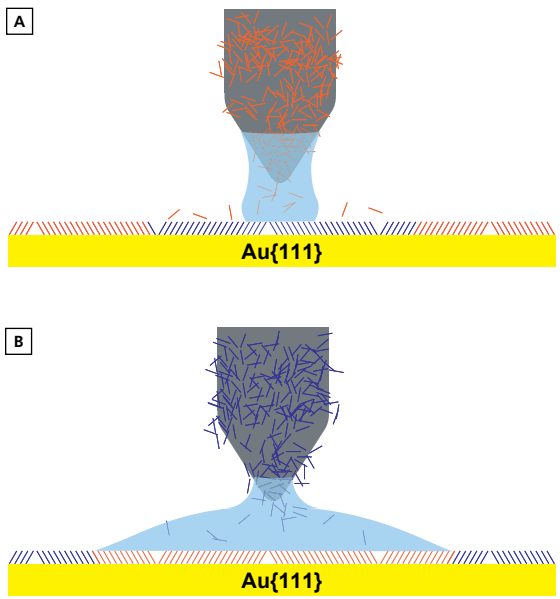

Figure 9. Schematic of the Double-Ink, Dip-Pen Nanolithography Experiments. (**A**) The Water Meniscus Was Compact When 16-Mercaptohexadecanoic Acid (MHDA) Molecules (Red) Were Patterned atop a 1-Octadecanethiolate SAM (Blue), Which Resulted in a Lower Transport Rate of the MHDA Molecules. (**B**) The Water Meniscus Was Spread Out When 1-Octadecanethiol Molecules (Blue) Were Patterned atop an MHDA SAM (Red), Which Resulted in a Higher Transport Rate of the 1-Octadecanethiol Molecules.

Chemically patterned structures can be further manipulated by employing *electrochemical desorption*.[65–70] We employed electrochemical desorption in conjunction with coadsorption, postadsorption, and displacement processing techniques to fabricate separated SAMs of molecules that cannot endure other chemical processing techniques. This is especially useful for biomolecules, where the bioactivity of the molecule needs to be preserved after patterning. Separated SAMs of C8 and C12 were fabricated to demonstrate this technique.[56] **Figure 10A** outlines the fabrication of artificially separated C12-and-C8 SAMs. Initially, a separated C12-and-AD SAM was fabricated by solution displacement of a preformed AD SAM on a Au{111} substrate. Subsequently, the sample was immersed in a solution of C8, thereby producing self-assembled monolayers with separated domains of C12 and C8. **Figure 10B** is an STM image of an artificially separated C12 (more protruding lattice) and C8 (less protruding lattice) SAM fabricated by electrochemical desorption and replacement.[41] The C12 domains remained intact, although smaller, throughout the electrochemical processing, and the C8 molecules adsorbed in regions where the gold surface was exposed.

4.3. Tether and Capture of Biomolecules

By employing chemical processing techniques, it is possible to construct monolayer films that selectively capture large biomolecules, such as receptor proteins and antibodies, that specifically recognize small-molecule binding partners. This type of film can be used to elucidate molecular interactions between known proteins and their small-molecule targets, as well as to identify unknown proteins that bind to specific small molecules.[71]

Figure 11A shows a schematic of the solution insertion of the precursor tether molecule 23-(9-mercaptononyl)-3,6,9,12,15,18,21-heptaoxatricosanoic acid [a carboxylic acid terminated oligo(ethylene glycol) *n*-alkanethiol] into a preformed 11-(9-mercaptononyl)-3,6,9-trioxaundecanol [a hydroxyl-terminated oligo(ethylene glycol) *n*-alkanethiolate] SAM. The solution insertion time was tailored to ensure optimal dilution of the tether molecules into the existing SAM. If tether molecules that are later functionalized with small-molecule probes are spaced too closely, nonspecific binding increases; if these derivatized tethers are spaced too far apart, then the efficiency of capturing large biomolecules is diminished. In the specific example shown in Figure 11A, the isolated precursor tether molecules were then functionalized with the small-molecule neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) via EDC/NHS coupling chemistry.[72] **Figure 11B** shows a schematic of how serotonin antibodies specifically recognize and bind to the 5-HT-functionalized tether molecules. In additional experiments, we have shown that antibodies selective for other closely related small molecules are not captured by serotonin-functionalized surfaces. Thus, this system demonstrates that small-molecule-derivatized surfaces can be fabricated and patterned at the molecular level to

optimize biospecific recognition. Furthermore, this approach is being adapted and applied to other important neurotransmitters and additional small molecules of analytical and medical importance.[73]

5. Conclusions

In summary, we have fabricated chemically patterned structures with high precision and functionality by exploiting molecules with a range of intermolecular forces and employing an array of chemical patterning techniques. We designed specific postadsorption techniques to isolate, to manipulate, and to characterize single-molecule switches and other functional molecules. The stochastic switching activity of OPE molecules was controlled by manipulating their intermolecular interactions, as well as those of the surrounding matrix. The selective and optimized capture of biomolecules has also been demonstrated by appropriately functionalized and tailored surfaces.

Exploiting the labile nature of AD SAMs, chemical patterning techniques were enhanced by hindering the lateral movement of molecules across a patterned surface, and the difficulty in the precise registration of adsorbates was avoided. By tuning the intermolecular-interaction strengths of molecular inks, we elucidated the transport mechanism of *n*-alkanethiolate molecules on a functionalized surface in dip-pen nanolithography.

We also fabricated artificially separated SAMs employing electrochemical processing techniques, otherwise not possible by coadsorption methods. This approach can be used to isolate molecules that cannot withstand chemical processing techniques.

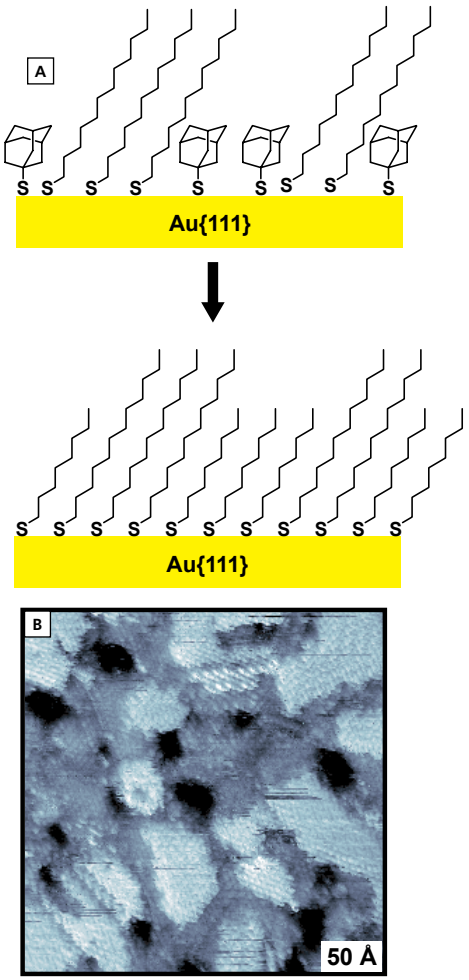

Figure 10. (**A**) The Fabrication of an Artificially Separated SAM. Initially, the 1-Adamantanethiolate Lattice of a Separated 1-Dodecanethiolate and 1-Adamantanethiolate SAM Was Desorbed Selectively from the Surface. Subsequently, 1-Octanethiol Molecules Were Adsorbed onto the Exposed Surface, Forming the Artificially Separated 1-Dodecanethiolate and 1-Octanethiolate SAM. (**B**) STM Image (V_{sample} = –1.0 V, I_{tunnel} = 1 pA, 300 Å × 300 Å) of an Artificially Separated 1-Dodecanethiolate and 1-Octanethiolate SAM on a Au{111} Substrate Showing the Two Distinct Domains of Molecules. The More Protruding Domains Are Attributed to 1-Dodecanethiolate and the Less Protruding Ones to 1-Octanethiolate.

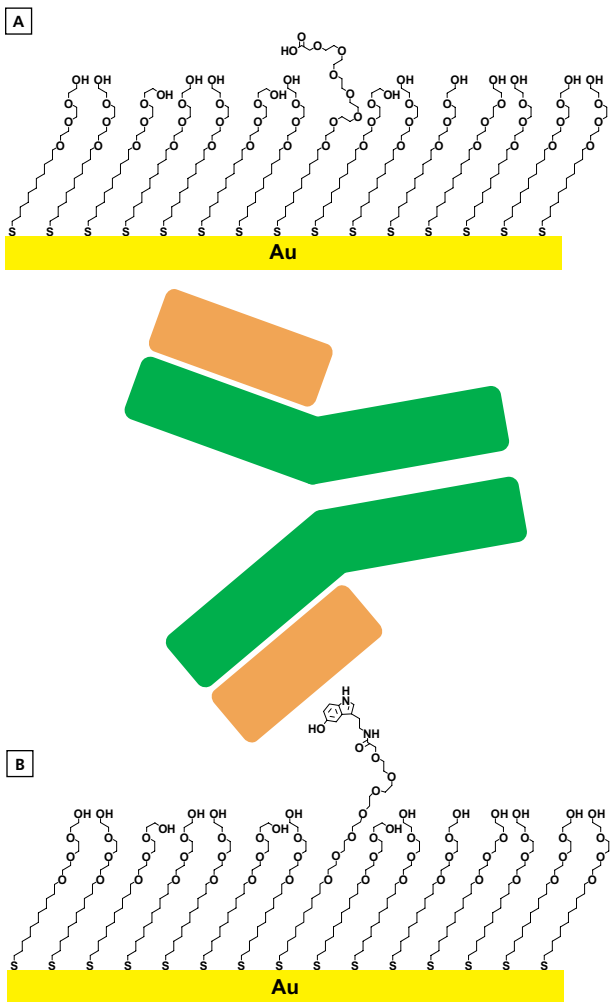

Figure 11. (**A**) The Solution Insertion of Precursor Tether Molecules [Carboxylic Acid Terminated, Oligo(Ethylene Glycol) Functionalized *n*-Alkanethiols] into a Preformed Oligo(Ethylene Glycol) Functionalized *n*-Alkanethiolate SAM. (**B**) The Capture of a Serotonin Antibody by the 5-HTP Functionalized Tether Molecule.

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About the Authors

Thomas J. Mullen is a Ph.D. candidate in chemistry under the direction of Professor Paul S. Weiss at The Pennsylvania State University. He received his B.S. degree in chemistry in 2003 from the University of Florida. In the summers of 2002 and 2003, he was an Office of Navy Research intern studying the dynamics of thin-film polymers with Dr. Kathy J. Wahl at the Naval Research Laboratory. Currently, Thomas is investigating self- and directed-assembly techniques of self-assembled monolayers in order to understand and to exploit their underlying processes and mechanisms with the aim of enhancing chemical patterning capabilities.

Arrelaine A. Dameron received her B.S. degree in creative studies in 2001 from the University of California at Santa Barbara. During her graduate research on molecular assemblies under the direction of Professor Paul S. Weiss at the Pennsylvania State University, she extensively investigated the self-assembly and directed patterning of 1-adamantanethiol before receiving her Ph.D. in January of 2006. Currently, Dr. Dameron is studying atomic layer deposition as a postdoctoral researcher with Professor Steven George at the University of Colorado in Boulder, Colorado.

Anne M. Andrews is an assistant professor of veterinary and biomedical sciences at The Pennsylvania State University (Penn State) and a member of Penn State's Neuroscience Institute and Molecular Toxicology Program. She received her B.S. degree in 1985 from Penn State and her Ph.D. in chemistry in 1993 from American University. Her thesis work on selective neurotoxicity was conducted at the National Institute of Mental Health with Dr. Dennis L. Murphy, where she was an NIH predoctoral fellow, an NIH postdoctoral fellow, and ultimately a senior staff fellow.

Research in Professor Andrews's group is centered on the chemistry of the serotonin neurotransmitter system. The primary goal is to understand more fully the role of serotonin in complex behavior, and the etiology and treatment of psychiatric disorders (depression and anxiety) and neurodegenerative diseases (Alzheimer's and Parkinson's). Genetically engineered mice, as well as selective drugs and neurotoxins are used as tools to investigate normative behavior and disease processes. Neurochemistry in these model systems is studied using both in vivo and ex vivo bioanalytical techniques, which are also developed in her laboratories. Neurotransmitter-derivatized self-assembled monolayer "neurochips" recently have been designed to facilitate the development of novel biosensors and functionally directed proteomics.

Professor Andrews has been awarded an NIH Fellows Award for Research Excellence (1997), the American Parkinson's Disease Association Award (2001), and the Eli Lilly Outstanding Analytical Chemist Award (2001, 2002).

Paul S. Weiss is Distinguished Professor of Chemistry and Physics at The Pennsylvania State University, where he began his academic career as an assistant professor in 1989. He received his S.B. and S.M. degrees in chemistry from MIT in 1980 and his Ph.D. degree in chemistry from the University of California at Berkeley in 1986, having worked with Professor Yuan T. Lee on crossed-molecular-beam reactions of excited atoms. He was a postdoctoral member of the technical staff at Bell Laboratories (1986–1988) and a visiting scientist at IBM's Almaden Research Center (1988–1989). He was also a visiting professor at the University of Washington Department of Molecular Biotechnology (1996–1997), and at the Kyoto University Electronic Science and Engineering Department and Venture Business Laboratory (1998 and 2000).

Professor Weiss investigates the chemical, physical, optical, mechanical, and electronic properties of surfaces at the atomic scale. He and his students have developed new techniques to expand the applicability and chemical specificity of scanning probe microscopies and spectroscopies. They have applied these to the study of catalysis, self- and directed assembly, molecular- and nanoscale electronics, and single-molecule motors. They work to advance nanofabrication down to ever-smaller scales and greater chemical specificity in order to create test beds for molecular devices and platforms for sensors.

Since joining Penn State, Dr. Weiss has been awarded a National Science Foundation Presidential Young Investigator Award (1991–1996), the Scanning Microscopy International Presidential Scholarship (1994), the B. F. Goodrich Collegiate Inventors Award (1994), an Alfred P. Sloan Foundation Fellowship (1995–1997), the American Chemical Society Nobel Laureate Signature Award for Graduate Education in Chemistry (1996), a John Simon Guggenheim Memorial Foundation Fellowship (1997), and a National Science Foundation Creativity Award (1997–1999). He was elected a Fellow of the American Association for the Advancement of Science (2000) and of the American Physical Society (2002).

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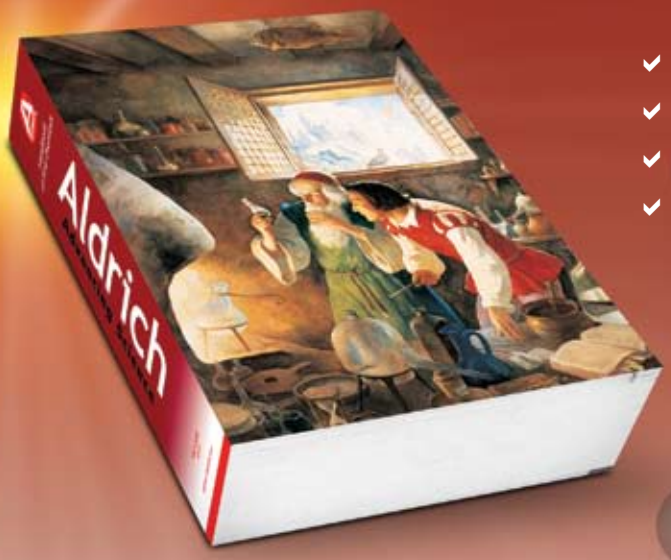

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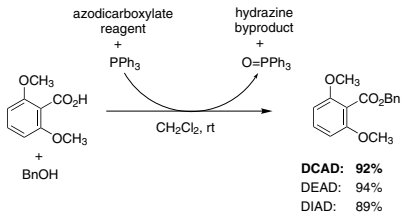
Lipshutz DCAD Coupling Reagent

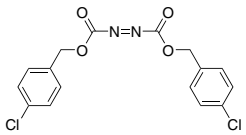
The Mitsunobu reaction is one of the most extensively used coupling reactions in organic synthesis and typically employs azodicarboxylate reagents such as DEAD or DIAD. However, these reagents have drawbacks such as low room-temperature stability and difficulty in removing the hydrazine byproducts. Professor Bruce Lipshutz and co-workers have developed an attractive alternative to the existing reagents: di(4-chlorobenzyl) azodicarboxylate (DCAD). DCAD is a stable solid that has an activity comparable to those of DEAD and DIAD in typical Mitsunobu reactions such as substitutions, esterifications, and etherifications. However, unlike the standard reagents, the hydrazine byproduct can be removed by simple precipitation directly from the reaction mixture, and is easily recycled in high yield to regenerate DCAD.



Lipshutz, B. H. et al. *Org. Lett.* **2006**, *8*, 5069.

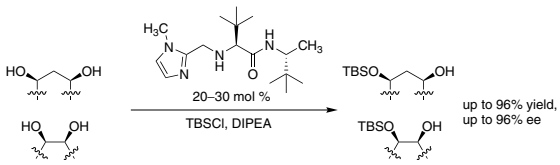
Di(4-chlorobenzyl) azodicarboxylate
DCAD

680850 1 g, 10 g
$C_{16}H_{12}Cl_2N_2O_4$
FW: 367.18



Hoveyda–Snapper Silylation Catalyst

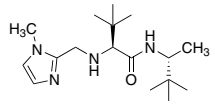
Because of the ease of preparation of *meso*-diols, synthetic methods that can desymmetrize these substrates are critically important. Professors Marc Snapper and Amir Hoveyda at Boston College have reported the first practical enantioselective silylation of *meso*-1,2- and 1,3-diols relying on an amino acid derived organocatalyst. The reactions do not require the rigorous exclusion of air or moisture, and the catalyst can be nearly quantitatively recovered by an aqueous wash. This catalyst greatly increases the efficiency with which optically enriched molecules can be prepared.



Zhao, Y. et al. *Nature* **2006**, *443*, 67.

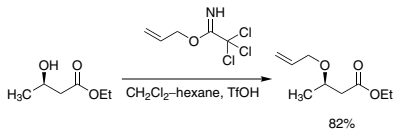
(*S*)-*N*-((*R*)-3,3-Dimethylbutan-2-yl)-3,3-dimethyl-2-((1-methyl-1*H*-imidazol-2-yl)methylamino)butanamide, 97%

680826 1 g
$C_{17}H_{32}N_4O$
FW: 308.46



Trichloroacetimidate Reagents

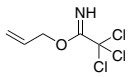
Trichloroacetimidates are useful reagents for protection of alcohols as their allyl and benzyl ethers. We are delighted to offer two new reagents, allyl 2,2,2-trichloroacetimidate and 4-methoxybenzyl 2,2,2-trichloroacetimidate, that have been extensively employed in organic synthesis. These reagents are particularly attractive in applications where base-sensitive functional groups are present that would not tolerate the standard alkoxide alkylation method of alcohol protection.



Clark, J. S. et al. *Tetrahedron* **2006**, *62*, 73.

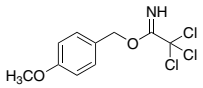
O-Allyl 2,2,2-trichloroacetimidate, 96%

678414 5 g
$C_5H_6Cl_3NO$
FW: 202.47



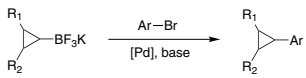
4-Methoxybenzyl 2,2,2-trichloroacetimidate

679585 5 g, 25 g
$C_{10}H_{10}Cl_3NO_2$
FW: 282.55



Potassium Cyclopropyltrifluoroborate

Cyclopropyl groups are found in a variety of natural products and are increasingly incorporated into pharmaceuticals such as the broad-spectrum antibiotic ciprofloxacin. Both the Charette[1] and Deng[2] groups have reported success in the cross-coupling of potassium cyclopropyltrifluoroborates with aryl bromides in the presence of common palladium catalysts. The trifluoroborate salts exhibit enhanced stability and more certain stoichiometry relative to their boronic acid counterparts. However, like boronic acids, post-reaction byproducts are easily removed. We are pleased to add this useful reagent to our ever-growing arsenal of organoboron compounds.



(1) Charette, A. B. et al. *Synlett* **2005**, *11*, 1779. (2) Fang, G.-H. et al. *Org. Lett.* **2004**, *6*, 357.

Potassium cyclopropyltrifluoroborate

662984 1 g, 5 g
$C_3H_5BF_3K$
FW: 147.98

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"PLEASE BOTHER US."

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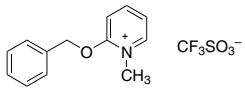
Professor Gregory B. Dudley of Florida State University kindly suggested that we make 2-benzyloxy-1-methylpyridinium triflate. This crystalline, neutral, and stable organic salt is an excellent reagent for the protection of an alcohol as a benzyl ether under mild conditions. Reaction with this reagent can be performed under near-neutral pH, unlike other benzylation protocols, which require strongly acidic or basic reaction media (e.g., the use of benzyl trichloroacetimidate or benzyl halides).[1,2]

(1) Poon, K. W. C.; Dudley, G. B. *J. Org. Chem.* **2006**, *71*, 3923. (2) Poon, K. W. C.; House, S. E.; Dudley, G. B. *Synlett* **2005**, 3142.



679674 2-Benzyloxy-1-methylpyridinium triflate 1 g
5 g

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the inside back cover.

TABLE OF CONTENTS

ABOUT OUR COVER

Photograph © Alfred Bader.

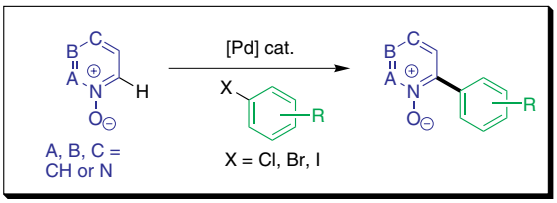
Panoramic Landscape with Hunters (oil on canvas, 105 × 135 cm) was painted in the mid-1660s by Philips Koninck (1619–1688), one of the great Baroque landscape artists of the Golden Age of Dutch Art (ca. 1600–1680). Although a contemporary of Rembrandt, Koninck is not believed to have studied with him. However, Koninck knew the master and some of his pupils and was certainly familiar with Rembrandt's paintings, which had some influence on him.

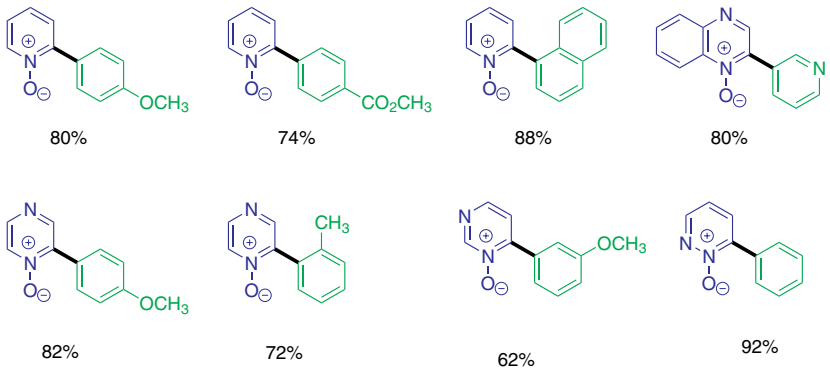
This painting illustrates Koninck's method of bringing together details of real-life scenes to create fictional but convincing sweeping landscapes featuring streams, fields, abundant flora, and rural dwellings. The translucent colors of the sky, the receding diagonal lines, and the horizontal striations denoting successive planes that recede into the distance add to the great allure of this landscape.

This painting is in the private collection of Isabel and Alfred Bader. Dr. Bader is a perennial "chemist collector" and a former Aldrich and Sigma-Aldrich president.

Reagents for Direct Arylation

Pd-catalyzed cross-coupling of organometallic nucleophiles with aryl halides has become the most commonly used method for biaryl synthesis. However, the range of biaryls that can be prepared is limited to those organometallic reagents that are commercially available or easily made. Nitrogen-containing heterocyclic organometallic reagents are often difficult to prepare and success of their coupling reactions can be sporadic. Professor Keith Fagnou and co-workers at the University of Ottawa have developed a novel method for biaryl synthesis by the direct arylation of heterocyclic *N*-oxides.[1–3] Yields are typically very good, and the oxide residue is easily reduced to give the free azine or diazine.





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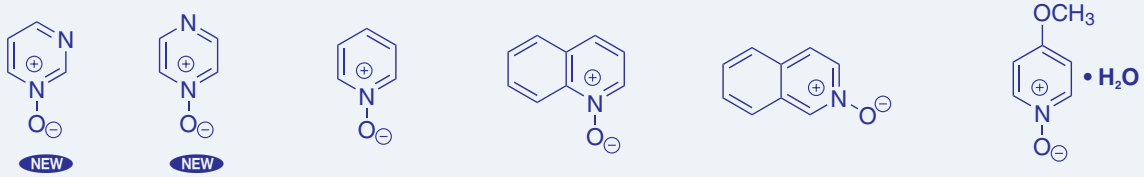
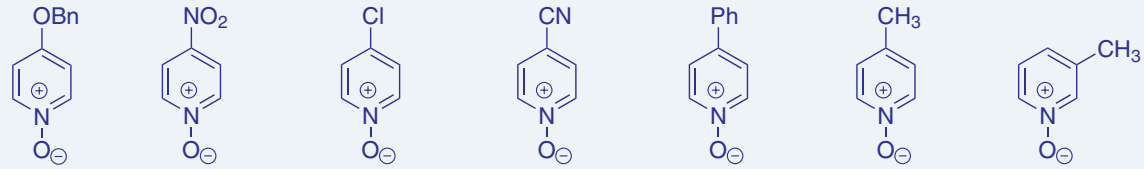
(1) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781. (2) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (3) Campeau, L.-C.; Stuart, D.R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35.





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Recent Advances in Intermolecular Direct Arylation Reactions


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Mr. David R. Stuart


Professor Keith Fagnou

*Louis-Charles Campeau, David R. Stuart, and Keith Fagnou**
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University of Ottawa
10 Marie Curie
Ottawa, ON K1N 6N5, Canada
Email: kfagnou@uottawa.ca

Outline

1. Introduction

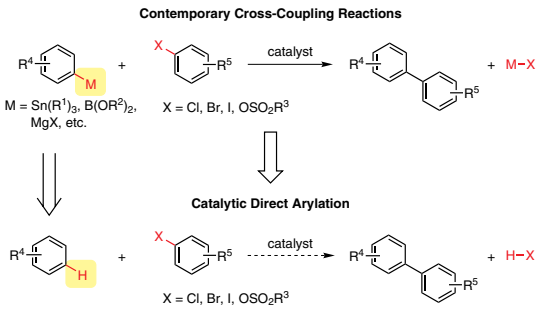
Biaryl molecules are important building blocks in both materials and medicinal chemistry, and have attracted the attention of the synthetic organic chemistry community for over 100 years.[1] The past quarter century has witnessed the development of transition-metal-catalyzed biaryl cross-coupling reactions that can be performed with a number of organometallics (boron, tin, silicon, magnesium) and a wide range of aryl halides.[2] While high yields and selectivities can be obtained, the requisite arene preactivation involves several manipulations prior to the cross-coupling, generating waste from reagents, solvents, and purifications. Furthermore, a stoichiometric amount of metal waste is produced from the arene-activating groups upon completion of the cross-coupling. In some cases, not all regioisomers of the organometallic reagents are readily available and, in the worst cases, they may be insufficiently stable to participate in the coupling reaction. For these reasons, there is a compelling need to continue the search for more efficient methods for the preparation of unsymmetrical biaryl molecules.

In recent years, direct arylation reactions have emerged as attractive alternatives to traditional cross-coupling methods.[3] These reactions substitute one of the preactivated coupling partners with a simple arene. In most cases, the more-difficult-to-prepare organometallic component is replaced, which also reduces the metal waste generated in the overall process (**Scheme 1**). In the past few years, the field of direct arylation has undergone rapid growth and continues to garner worldwide attention. This review will discuss only the most recent advances in the field, with an emphasis on reports from 2005–2006. Furthermore, only reactions leading to the formation of biaryl compounds will be addressed. For reports prior to these dates, and for catalytic arylation reactions leading to the formation of other product classes, the reader is directed to other excellent reviews of the field.[3] Examples have been chosen for their synthetic value and their conceptual advances. The first section outlines recent advances in the direct arylation of heterocyclic substrates. Subsequent sections present advances in reactions with simple arenes, including directed and nondirected reactions.

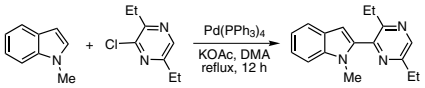
2. Arylations of Heterocycles

One of the first examples of heterocycles used in the direct arylation was reported by Ohta and co-workers in 1989.[4] *N*-Alkylindoles were arylated at the 2 or 3 position, depending on the nature of the N-substituent (**eq 1**). It was subsequently demonstrated that these reactions could be extended to a number of π-rich heterocycles using similar reaction conditions.[3d,5] It is commonly accepted that, in direct arylation reactions, π-electron-rich substrates can react via an electrophilic palladation step and that the arylations are facilitated by the highly nucleophilic nature of these arenes.[6] In recent years, researchers have sought to develop novel strategies that might allow for milder reaction conditions as well as broaden the substrate scope.

In 2005, Sames and co-workers reported the development of C-2 selective indole arylation reactions with palladium and rhodium catalysts. Of note, the rhodium-catalyzed reactions are compatible with unprotected indoles and aryl iodides and afford moderate-to-good yields of 2-arylindoles (**eq 2**).[7] The proposed catalytic cycle is outlined in **Scheme 2**. The rhodium catalyst first inserts into the aryl iodide to afford a rhodium(III) intermediate. This species was isolated and found to be a competent catalyst for the reactions, further validating this as the first step in the catalytic cycle. This arylrhodium(III) intermediate can then bind and metallate the indole to afford the diarylrhodium(III) species, which can reductively eliminate the product and regenerate the rhodium(I) catalyst. The use of cesium pivalate as the base is key to obtaining high yields. While no insight into the intimate details of the indole

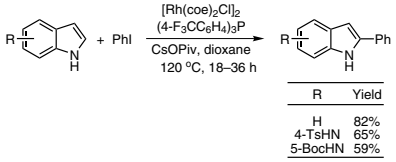


Scheme 1. Direct Arylation vs Cross-Coupling Reactions.



Ref. 4

eq 1



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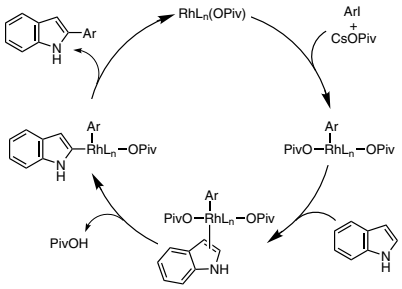
eq 2



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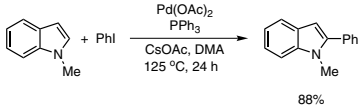
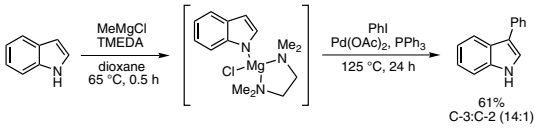
Scheme 2. C-2 Selective Rhodium-Catalyzed Arylation of Indoles.



Ref. 6,8

eq 3



Ref. 6

eq 4

metallation step could be provided, the authors postulated that the pivalate may be serving as an intramolecular base.

Sames also reported further studies dealing with palladium-catalyzed indole arylation reactions that enable a wide range of N-substituted indole substrates to be employed.[6,8] Most of these reactions are selective typically for C-2 of the indole, but a remarkable base effect has been observed with N–H indoles where the proper selection of the base counterion allows for the selective formation of either the C-2 (**eq 3**) or the C-3 arylation isomer (**eq 4**).

The authors have postulated that the observed selectivity arises from a migration of palladium during the metallation event (**Scheme 3**).[6] Kinetic data and isotope effects support an initial electrophilic palladation at C-3 followed by deprotonation to give the C-3 isomer. If migration of the arylpalladium moiety to C-2 takes place prior to deprotonation, the C-2 regioisomer is obtained instead.

Sanford and co-workers have established an alternative strategy to the site-selective arylation of indoles at the C-2 position.[9] Instead of exploiting the Pd(0)/Pd(II) catalytic manifold, they developed reactions functioning under a Pd(II)/Pd(IV) redox couple. In these reactions, an initial metallation of indole by a palladium(II) salt is followed by oxidation with a diaryliodonium salt to generate a diarylpalladium(IV) intermediate, which can reductively eliminate the biaryl product and regenerate the catalytically active palladium(II) species (see the related catalytic cycle in Scheme 5 of Section 3.1). Unlike prior studies, which commonly reported heating the reactants to very elevated temperatures, Sanford's arylations can be carried out under remarkably mild conditions in acetic acid at 25 ºC (**eq 5**).[9] A number of substituted indoles participate in the reaction and, if the C-2 position is blocked, reaction at the indole C-3 position occurs in lower yields. It is also possible to perform the reaction with a number of functionalized diaryliodonium salts.

Azoles are another class of heterocycles that have been studied as substrates for the direct arylation reaction. Bergman, Ellman, and co-workers found that rhodium compounds can form carbene complexes with azoles,[10] which has provided a valuable mechanistic entry point for the further development of rhodium-catalyzed direct arylation reactions. The rhodium–carbene intermediates, **1**, have been isolated and are postulated to be crucial to the reactivity (**Scheme 4**).[10] Following the formation of the rhodium–carbene complex, oxidative addition of the aryl iodide leads to the formation of a diarylrhodium(III) species, which can undergo reductive elimination to give the corresponding arylazole. In 2006, Bergman and Ellman also described studies leading to the development of a new catalytic system for the arylation of azoles.[11] The new reaction conditions employ aryl bromides, which had been until then rarely utilized in the direct arylation of azoles. Under microwave heating at 250 °C, a number of different azole substrates were used with various aryl bromides to give the arylazoles in moderate-to-high yields (**eq 6**).[11]

Another rhodium-catalyzed transformation of π-rich heterocycles was reported by Itami and co-workers.[12] The reaction employed an electron-deficient rhodium complex bearing strong π-accepting perfluoroalkylphosphite ligands, which were postulated to favor the electrophilic rhodation of the electron-rich heterocycle. Aryl iodides participated in the reaction with various heterocycles such as thiophenes, furans, pyrroles, and indoles (**eq 7**).[12] Simple arenes were also successfully employed (see Section 3.2).

In contrast to the number of reports of the utilization of π-rich heterocycles in the direct arylation reaction, the use π-deficient heterocycles, such as azines and diazines, is rare. In 2005, Campeau, Rousseaux, and Fagnou reported a high-yielding and site-selective method for the arylation of pyridine *N*-oxides.[13] The reaction is broadly applicable to a number of aryl bromides and pyridine substrates, and deoxygenation of the 2-arylpyridine *N*-oxide products gives rapid access to 2-arylpyridines. The methodology was also extended to other azine *N*-oxides including quinolines and isoquinolines, as well as to diazine *N*-oxides including the *N*-oxides of pyrazines, pyridazines, and pyrimidines (**eq 8**).[14] Competition experiments as well as DFT calculations were consistent with a concerted palladation–deprotonation pathway, which is described in detail in Section 3.2.[15]

Recently, Zhuravlev reported a very mild direct arylation reaction between aryl halides and oxazolo[4,5-*b*]pyridines.[16] The arylations were carried out with $Pd(OAc)_2/PPh_3$ in acetone at 30 ºC, and led to the corresponding C-2 products in moderate-to-good yields (**eq 9**). The superior reactivity of these substrates is attributed to the high acidity of the hydrogen that is replaced by the aryl group.

A clear indication of the growing acceptance of the direct arylation methodology by the synthetic community is its use in industry. For example, researchers at Merck & Co. reported in 2005 that the direct arylation of imidazo[1,2-*b*][1,2,4]triazine can be successfully employed as an alternative to the Suzuki cross-coupling reaction in a key fragment coupling reaction for the preparation of a selective GABA agonist (**eq 10**).[17]

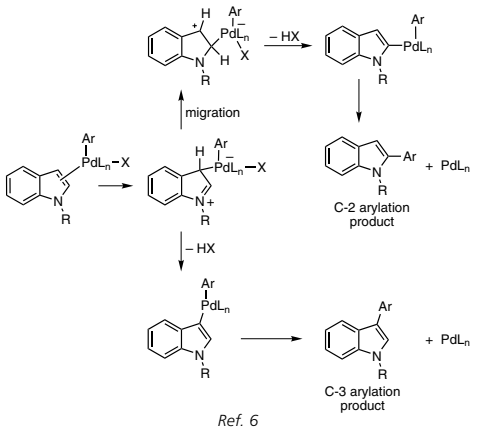
3. Arylations of Simple Arenes

3.1. Directed Reactions

The catalytic direct arylation of simple arenes is challenging due to the attenuated nucleophilicity of the aromatic rings. To promote the necessary substrate–catalyst interactions, Lewis basic directing groups have been used; these groups enable the metallation by bringing the metal into close proximity to the reactive center.

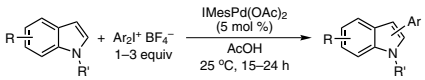
Sanford and co-workers have reported the use of pyridine moieties as efficient directing groups in the Pd-catalyzed direct arylation of 2-arylpyridines with aryliodonium salts (**eq 11**).[18] They have also demonstrated that a wide variety of other directing groups, including quinolines, pyrrolidinones, oxazolidinones, and acetanilides are compatible. A diverse functionality on the pyridine or the aryl moiety is also tolerated, and the reactions can be carried out in ambient air and moisture and do not require expensive ligands or strong bases. Mechanistic investigations suggest that the arylation proceeds via a cyclopalladated 2-arylpyridine that is oxidized by the aryliodonium salt to generate a very reactive Pd(IV) intermediate. Reductive elimination of the arylated product regenerates the catalytically active Pd(II) species (**Scheme 5**).[18]

Aryl iodides have also been utilized in direct arylation reactions of simple arenes by Daugulis and Zaitsev, who reported the successful Pd(II)-catalyzed diarylation of acylanilides with aryl iodides.[19] Stoichiometric amounts of AgOAc were required for each equivalent of aryl iodide consumed. It was observed that the reaction is faster for electron-rich aryl iodides, contrasting the typical trend observed in Pd(0)/Pd(II) catalytic cycles. Acylanilides with electron-donating substituents react faster than their electron-neutral or electron-poor counterparts, which is consistent with an electrophilic aromatic metallation pathway. A mechanistic proposal has been advanced involving



Ref. 6

Scheme 3. Mechanistic Rationale for the Observed Regioselectivity in the Arylation of Indoles.

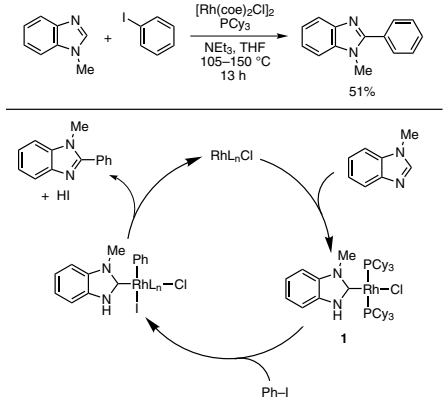


R	R'	Ar	Yield
H	H	2-Ph	81%
5-NO_2	Me	2-Ph[a]	70%
5-MeO	H	2-Ph	58%
3-Me	Me	2-Ph	89%
5-Br	H	2-Ph[a]	74%
2-Me	Me	3-Ph	29%
H	Me	2-(3-$F_3CC_6H_4$)	64%
H	Me	2-(4-MeC_6H_4)	70%
H	Me	2-(4-FC_6H_4)	80%
H	Me	2-(4-ClC_6H_4)	90%
H	Me	2-(4-$MeOC_6H_4$)[a]	80%
H	Me	2-(2-MeC_6H_4)	62%

[a] The reaction was carried out at 60 ºC.

Ref. 9

eq 5



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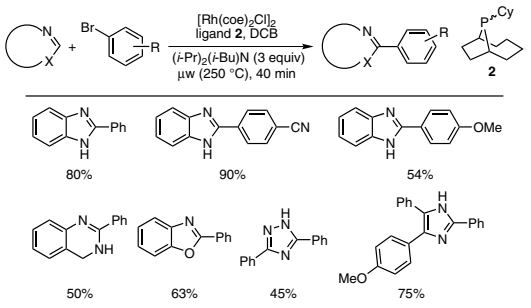
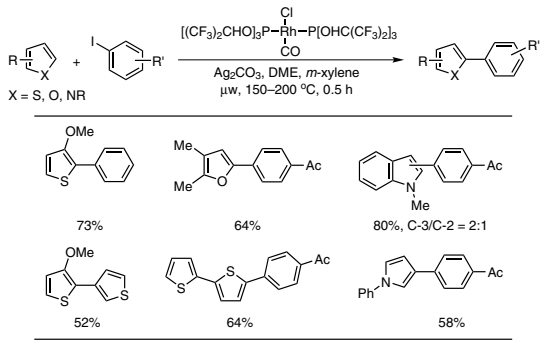
Scheme 4. Proposed Catalytic Cycle for the Rhodium-Catalyzed Arylation of Azoles.



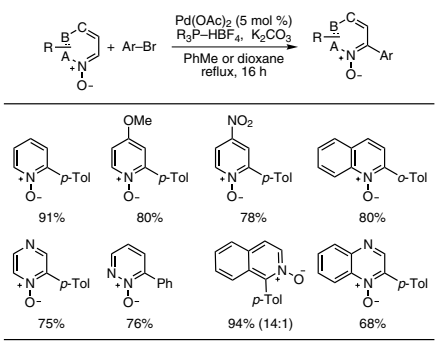
Ref. 11

eq 6



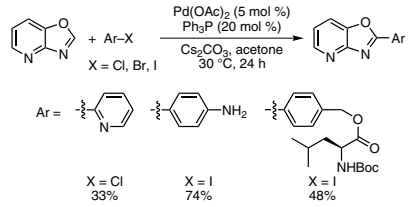
Ref. 12

eq 7



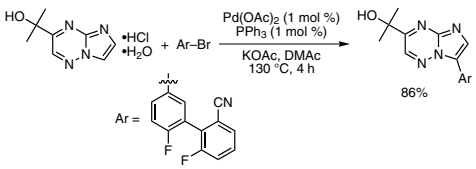
Ref. 14

eq 8



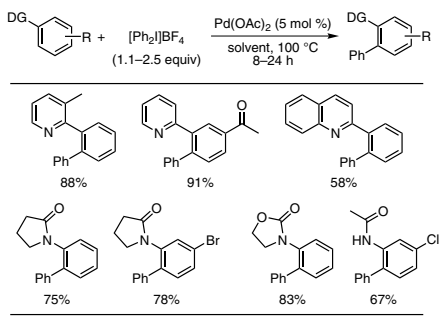
Ref. 16

eq 9



Ref. 17b

eq 10



Ref. 18

eq 11

a cyclopalladated complex that undergoes oxidative addition of the aryl iodide to produce a Pd(IV) intermediate. Pyridines,[20] benzamides,[21] and benzylamines[22] have all been successfully used as directing groups (**eq 12**).[19–22]

Ackermann has also reported the use of pyridines and other Lewis basic groups as directing groups in direct arylation reactions. Importantly, these reactions were carried out successfully with aryl chlorides and tosylates by using the appropriate ruthenium catalyst.[23] While such reactivity is now common with other traditional cross-coupling reactions, achieving direct arylation with aryl chlorides and tosylates is exceedingly rare. Both electron-rich and electron-poor aryl chlorides are compatible and afford diarylated products of 2-arylpyridines in good yields (**eq 13**).[23a] It is also possible to achieve monoarylation with the ruthenium catalyst if imines derived from acetophenones are utilized as substrates. Conveniently, the products are then isolated as the ketones after hydrolysis of the imines (**eq 14**).[23]

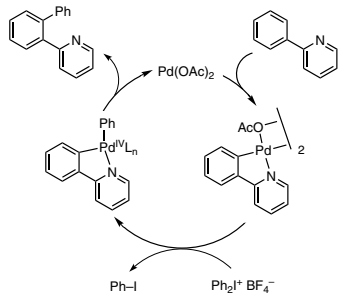
Imines have also been utilized in rhodium-catalyzed direct arylation reactions. In a 2005 report on the development of a rhodium-catalyzed Suzuki-type coupling, Ueura et al. observed that, with arenonitriles, benzophenone imines were formed that were subsequently arylated ortho to the imine (**eq 15**).[24] When similar reaction conditions were applied directly to the imine, it was possible to isolate a mixture of the mono- and diarylated products (**eq 16**).[24]

Çetinkaya and co-workers reported the direct ortho arylation of benzaldehyde derivatives with aryl chlorides and bromides (**eq 17**).[25] Good yields were obtained through the use of $Pd(OAc)_2$, an imidazolium salt as a carbene ligand precursor, and Cs_2CO_3 in dioxane at 80 ºC. The authors postulated that the aldehyde oxygen was acting as an ortho-directing group. When aryl bromides were employed, diarylation took place and led to 2,6-diarylbenzaldehyde derivatives.

3.2. Nondirected Reactions

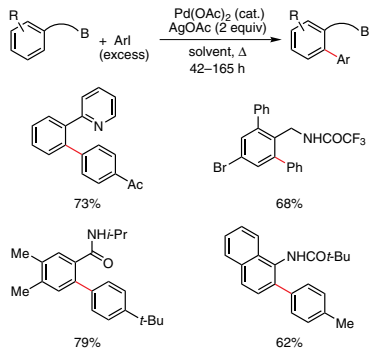
In a 2006 article focusing predominantly on the arylation of heterocycles, Itami and co-workers described direct arylation reactions with anisole and 1,3-dimethoxybenzene.[12] In both cases, the observed regioselectivity was consistent with an electrophilic metallation mechanism occurring preferentially at the para and ortho positions relative to the electron-donating methoxy groups (**Scheme 6**). Given the small number of nondirected reactions of simple arenes in direct arylation, this result shows significant promise for the development of other rhodium-catalyzed direct arylations with simple arenes.

The same year, Fagnou and co-workers explored the direct arylation of perfluorinated arenes. While the π deficiency of these arenes prohibited their use in an electrophilic metallation process, their direct arylation occurred in high yield with 1–5 mol % palladium catalyst in the presence of $P(t\text{-}Bu)_2Me{\bullet}HBF_4$ (**eq 18**).[26] It was even possible to achieve reaction with fluorobenzene, albeit in 8% yield. Based on mechanistic studies by Maseras, Echavarren, and co-workers, who described a concerted palladation–deprotonation pathway in intramolecular direct arylation reactions,[27] experimental and computational mechanistic studies were performed, which led to the formulation of two possible pathways (**Scheme 7**).[26] Pathway A involves a concerted palladation and loss of HBr to afford the diarylpalladium(II) intermediate. Alternatively, an exchange of the bromide ligand with a carbonate anion allows for a related palladation–deprotonation process through transition state **4** (pathway B). Although pathway B was



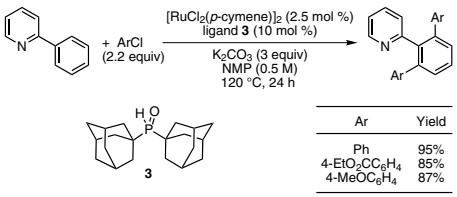
Ref. 18

Scheme 5. Catalytic Cycle of Oxidative Direct Arylation with Diaryliodonium Salts.



Ref. 19–22

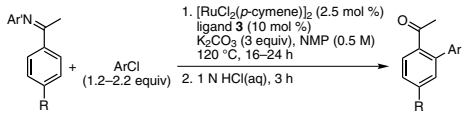
eq 12



Ar	Yield
Ph	95%
4-$EtO_2CC_6H_4$	85%
4-$MeOC_6H_4$	87%

Ref. 23a

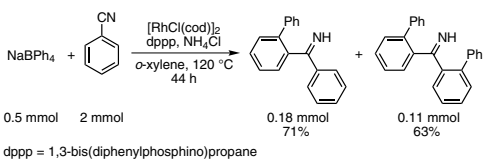
eq 13



R	Ar	Yield
Me	4-AcC_6H_4	77%
H	4-$MeOC_6H_4$	74%
H	4-$EtO_2CC_6H_4$	72%

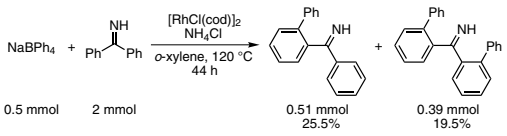
Ref. 23a

eq 14



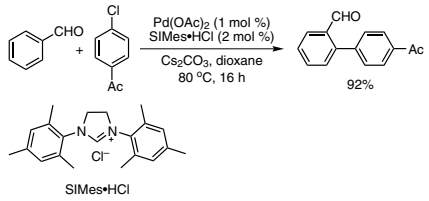
Ref. 24

eq 15



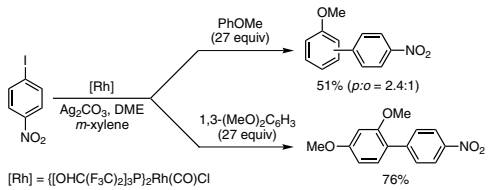
Ref. 24

eq 16



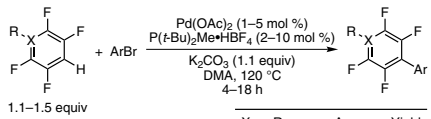
Ref. 25

eq 17



Ref. 12

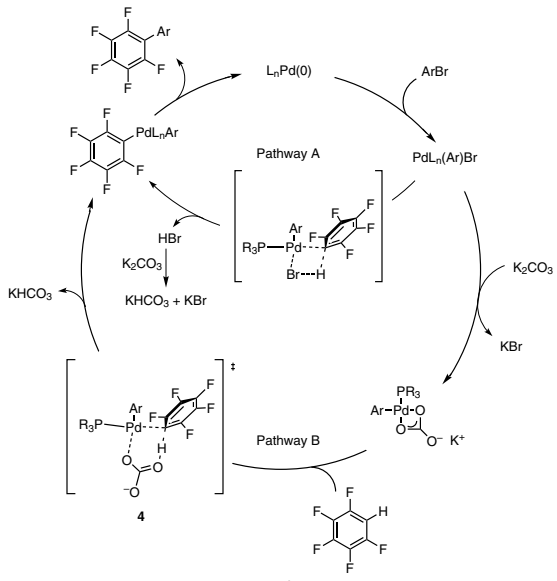
Scheme 6. Nondirected Reactions of Simple Arenes in the Direct Arylation Reaction.



X	R	Ar	Yield
C	F	4-MeC_6H_4	98%
C	F	4-$MeOC_6H_4$	76%
C	F	3-Py	78%
C	Me	4-MeC_6H_4	86%
C	MeO	4-MeC_6H_4	92%
N	---	4-MeC_6H_4	86%

Ref. 26

eq 18



Ref. 26

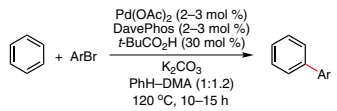
Scheme 7. Proposed Catalytic Cycle for the Direct Arylation of Pentafluorobenzene.

deemed lower in energy by DFT calculations (9.9 kcal/mol vs 23.7 kcal/mol), the near-complete insolubility of K_2CO_3 under the reaction conditions prevented pathway A from being ruled out and provided an enticing clue into how the reaction might be improved.

With the goal of favoring pathway B in more challenging arylations of benzenes, the use of soluble acid co-catalysts was investigated in conjunction with a stoichiometric and insoluble potassium carbonate base. The proper choice of the carboxylic acid was crucial, and the use of 30 mol % PivOH proved to be optimal.[28] Using this protocol, a number of aryl bromides were reacted with benzene to afford the biaryl products in high yields (**eq 19**). The carboxylic acid additive is believed to facilitate the exchange of the bromide ion on the metal for a carboxylate ligand that can undergo a similar concerted palladation–deprotonation (**Scheme 8**).[28]

4. Conclusions

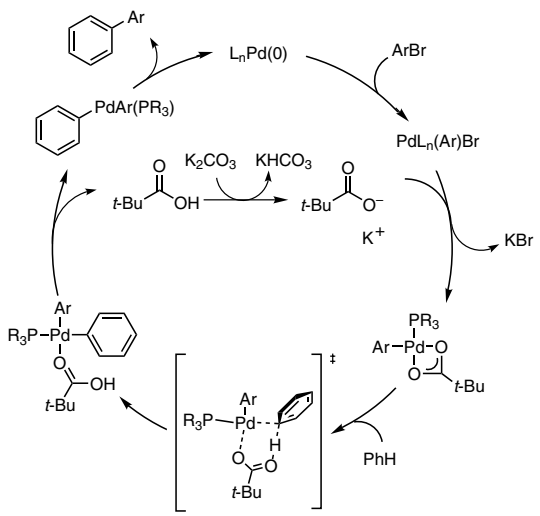
Direct arylation reactions are gaining an increasingly convincing track record in the construction of biaryl compounds. The many recent reports have allowed for the use of milder reaction conditions and equimolar amounts of coupling partners. The number of diverse catalysts and mechanisms by which direct arylation reactions can be performed show promise for a more frequent use in everyday organic synthesis and should stimulate the development of novel processes with expanded scope and efficacy. This should make these methods increasingly attractive for the preparation of biaryl molecules in an industrial setting.



Ar	Yield
o-Tol	85%
m-Tol	84%
p-Tol	81%
1-Np	80%
2-Np	55%
m-An	69%
3-ClC_6H_4	63%
2-Me-4-$NO_2C_6H_3$	81%

Ref. 28

eq 19



Ref. 28

Scheme 8. Role of Pivalic Acid Co-Catalyst in the Direct Arylation of Benzene.

5. Acknowledgements

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About the Authors

Louis-Charles Campeau was born in 1980 in Cornwall, Ontario, Canada. In 2003, he received his bachelor's degree with distinction in biopharmaceutical sciences (medicinal chemistry option) from the University of Ottawa. He then joined the research group of Professor Keith Fagnou, where he is currently working towards his Ph.D. degree by conducting studies on the development of new transition-metal-catalyzed processes. He has been a recipient of an Ontario Graduate Scholarship in Science and Technology (M.Sc.), and is currently holding an NSERC PGS-D doctoral scholarship. This summer, he will be joining the process research group at Merck Frosst.

David R. Stuart was born in 1981 in Victoria, British Columbia, Canada. In 2005, he received his B.Sc. degree in chemistry, with distinction, from the University of Victoria. He then joined the research group of Professor Keith Fagnou at the University of Ottawa, where he is currently conducting Ph.D. level studies on the development of new transition-metal-catalyzed processes. He has been a recipient of an NSERC CGS-M (M.Sc. level scholarship), and is currently holding an NSERC PGS-D doctoral scholarship.

Keith Fagnou was born in 1971 in Saskatoon, Saskatchewan, Canada. He received a Bachelor of Education (B.Ed.) degree with distinction from the University of Saskatchewan in 1995 and, after teaching at the high school level for a short period of time, he continued his studies in chemistry at the University of Toronto. In 2000, he received an M.Sc. degree and, in 2002, completed his Ph.D. requirements under the supervision of Mark Lautens. He has since been on the chemistry faculty at the University of Ottawa, and has initiated research programs focusing on the development of new catalytic reactions for use in organic synthesis.

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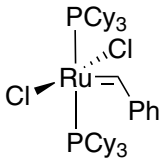
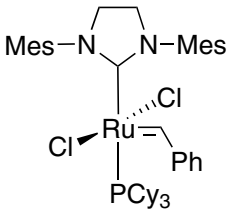


Grubbs 1st generation catalyst

579726

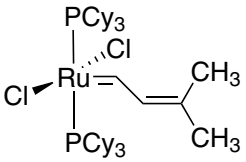
Useful in ROMP of strained cyclic olefins, ethenolysis of internal olefins, and in ADMET, CM, and RCM of terminal olefins.



Grubbs 2nd generation catalyst

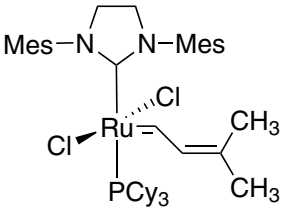
569747

More active than 1st generation catalysts. Increased activity in RCM and has been employed in challenging CM of sterically demanding or deactivated olefins.



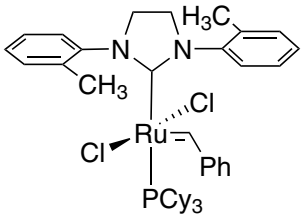
578681

Kinetic and application profile similar to that of Grubbs 1st generation catalyst.



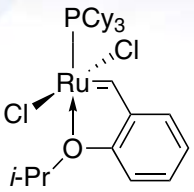
682365 NEW

Slower to initiate than Grubbs 2nd generation catalyst, thus potentially useful in exothermic ROMP applications. Typically, reaction temperatures of 50 to 60 °C are employed.



682284 NEW

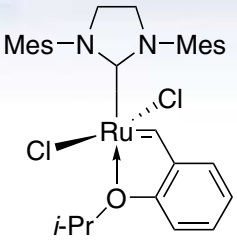
Highly efficient catalyst for the preparation of tetrasubstituted olefins by RCM or CM of sterically hindered olefins.



Hoveyda–Grubbs 1st generation catalyst

577944

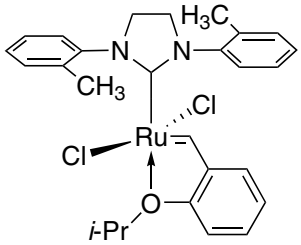
Similar reactivity as Grubbs 1st generation catalyst. Proved to be particularly useful in the industrial production of macrocycles via RCM.



Hoveyda–Grubbs 2nd generation catalyst

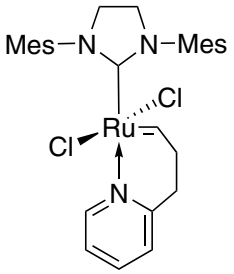
569755

Comparable reactivity to Grubbs 2nd generation catalyst, but initiates more readily at lower temperatures. Efficient for the metathesis of electron-deficient substrates.



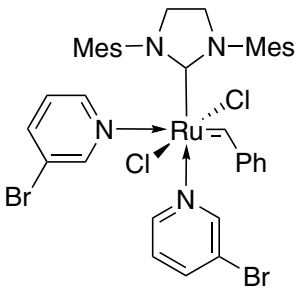
682373 NEW

Hoveyda–Grubbs analog of 682284 with similar reactivity profile. Depending on substrate and reaction conditions, may prove more efficient than 682284.



682381 NEW

Latent initiator that possesses the high activity of 2nd generation catalysts once initiated. Useful in ROMP applications where longer monomer/catalyst resin handling times are desired.



682330 NEW

Faster initiator than Grubbs 2nd generation catalyst; can be used at low temperatures (~0 °C, depending on reaction conditions). Less soluble than Grubbs 2nd generation catalyst in nonpolar solvents. Has been employed in polymer synthesis.

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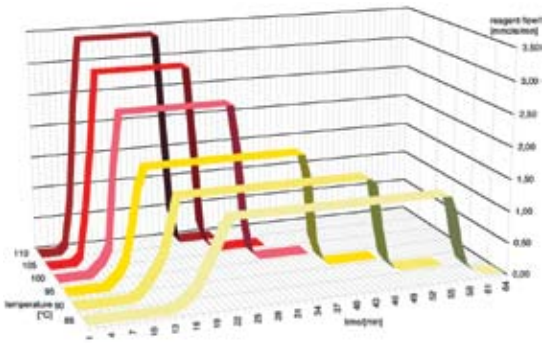
Cartridge for Phosgene Generation, 0.05 mol	$COCl_2$	98.92	75-44-5	519766-1PAK 519766-5PAK



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Evolution and Applications of Second-Generation Ruthenium Olefin Metathesis Catalysts


Dr. Yann Schrodi


Dr. Richard L. Pederson

Yann Schrodi[*,†] *and Richard L. Pederson*[‡]
Materia, Inc.
12 N. Altadena Drive
Pasadena, CA 91107, USA
Email: yschrodi@materia-inc.com

[†] *Catalyst R&D Department*
[‡] *Fine Chemicals R&D Department*

Outline

1. Introduction

Olefin metathesis is a fundamental chemical reaction involving the rearrangement of carbon–carbon double bonds, and can be used to couple, cleave, ring-close, ring-open, or polymerize olefinic molecules. The widely accepted view that olefin metathesis revolutionized the different fields of synthetic chemistry led to the awarding of the 2005 Nobel Prize in Chemistry to Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock "for the development of the metathesis method in organic synthesis".[1] While Chauvin had proposed the "carbene" mechanism to explain how the metathesis process functions[1a,2] and Schrock had prepared the first well-defined highly active metathesis catalysts,[1b,3] Grubbs provided synthetic chemists with active catalysts that could be handled in air and were tolerant of various functional groups, such as esters, amides, ketones, aldehydes, and even protic functionalities like alcohols, water, and acids.[1c,4]

The Grubbs catalysts are based on a ruthenium atom surrounded by five ligands: two neutral electron-donating entities (e.g., trialkylphosphines, N-heterocyclic carbenes), two monoanionic groups (e.g., halides), and one alkylidene moiety (e.g., unsubstituted and substituted methylidenes). These catalysts are divided into two categories based on the nature of the neutral ligands: $L_2X_2Ru{=}CHR$ complexes (where L is a phosphine ligand) were discovered first and are referred to as the first-generation Grubbs catalysts, and $(L)(L')X_2Ru{=}CHR$ complexes (where L is a phosphine ligand and L' a saturated N-heterocyclic carbene or NHC ligand) were subsequently developed and are referred to as the second-generation Grubbs catalysts (**Figure 1**).

The first-generation Grubbs catalysts have demonstrated attractive functional-group tolerance and handling properties, and have been widely used as highly efficient promoters for ring-opening metathesis polymerizations,[5] ring-closing metathesis reactions to make disubstituted olefins,[6] ethenolysis (i.e., cleavage of the carbon–carbon double bond),[7] cross-metathesis of terminal olefins,[8] and the preparation of 1,3-dienes via enyne metathesis.[9] As such, these catalysts and analogues[10] remain very useful and are still employed in important processes, including the ethenolysis of feedstocks derived from bio-renewable seed oils[7b,c] and the manufacture of macrocyclic hepatitis C therapeutics.[11] Nonetheless, the utility of first-generation catalysts is somewhat limited, because they suffer from reduced activity as compared to the more sensitive but highly active Schrock catalysts. Examples of transformations that are poorly or simply not enabled by first-generation Grubbs catalysts include the ring-closing metathesis to form tri- and tetrasubstituted cycloalkenes and the cross-metathesis of sterically hindered or electronically deactivated olefins. Many of these limitations have been addressed through the development of the second-generation Grubbs catalysts, which possess excellent metathesis activity while retaining the

handling characteristics and broad functional-group tolerance of the earlier Grubbs catalysts.

Since their discovery in 1999, second-generation Grubbs systems have rapidly evolved into a large family of catalysts with varying properties. These catalysts have been widely utilized to facilitate new transformations and to allow important applications that extend to a broad range of areas including fine chemicals, pharmaceuticals, and materials. As it is often the case in homogeneous catalysis, there does not exist a single second-generation catalyst that is best for all transformations and applications. In fact, many of the second-generation catalysts have been developed to provide systems with optimal characteristics for specific purposes. Therefore, the aim of this article is to review the evolution of this group of catalysts, point out the properties and specificity of its members, and present some of the very interesting applications enabled by them.

2. Second-Generation Grubbs and Other Early NHC-Based Catalysts

2.1. Discovery of NHC-Based Olefin Metathesis Catalysts

The first examples of NHC-containing, olefin metathesis catalysts were disclosed by Herrmann and co-workers in 1998.[12] These complexes were bis-NHC ruthenium benzylidene species, **1**, where the NHC ligands were unsaturated and contained identical or different, chiral or achiral alkyl substituents on the nitrogen atoms (**Figure 2**). These systems were originally aimed at tuning the properties of the catalysts by changing the nature of the alkyl substituents on the nitrogen atoms and at producing chiral complexes.[13] Although they were first thought to be more active than the first-generation catalysts,[12] this notion turned out not to be generally true.[14] A year later, mixed NHC–phosphine ruthenium metathesis catalysts were reported: Herrmann and co-workers had focused on species containing alkyl-substituted unsaturated NHCs, **2**,[15] while the Grubbs[16] and Nolan[17] groups independently developed catalysts derived from aryl-substituted unsaturated NHCs, in particular 1,3-dimesitylimidazolin-2-ylidene or IMes, **3**. The mixed NHC–phosphine complexes **2** and **3** were found to possess greater metathesis activity and enhanced thermal stability than the first-generation Grubbs catalysts.[15a,c,16,17] In particular, compound **3**, developed by Grubbs and Nolan, proved to be an especially efficient catalyst.[18] Other IMes-based systems containing moieties such as vinylidene,[19] allenylidene,[20] or indenylidene[21] were prepared by the Grubbs, Fürstner, and Nolan groups. The allenylidene systems turned out to be inactive in metathesis, while the vinylidene complexes were active but slower than their ruthenium benzylidene analogues, and the indenylidene complexes proved to be "equipotent" to the benzylidene derivatives. Soon after developing the IMes catalyst, the Grubbs group discovered that replacing one phosphine of the first-generation systems with a *saturated* mesityl-substituted NHC (or SIMes) ligand afforded a catalyst with even greater activity than the IMes-based compounds.[22] The SIMes catalyst, **4**, commonly referred to as the second-generation Grubbs catalyst, quickly superseded the IMes species because it demonstrated superior efficiency in practically all metathesis reactions.[23,24]

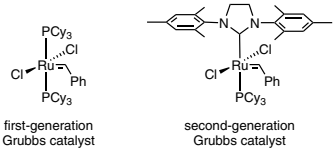


Figure 1. Most Commonly Used First- and Second-Generation Grubbs Catalysts.

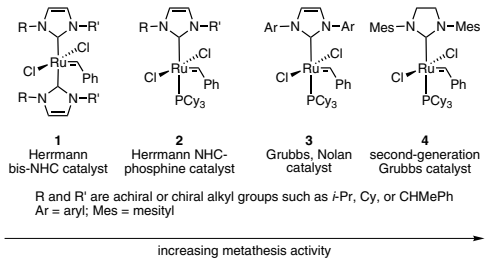
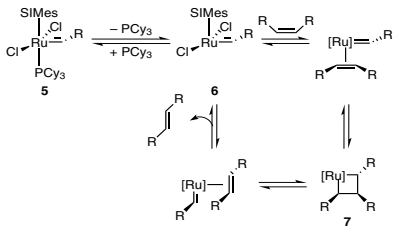


Figure 2. Evolution and Relative Activity of Early NHC-Based Metathesis Catalysts.



Ref. 25

Scheme 1. Mechanism of the Metathesis of a Symmetrical Cis Olefin to Its Trans Isomer.

2.2. Mechanistic Considerations and Development of Second-Generation Derivatives

Mechanistic studies of **4** indicated that the catalytic steps involve an initiation event where a 16-electron species, **5**, undergoes reversible phosphine dissociation to furnish a 14-electron, active catalytic complex, **6**. Complex **6** can either rebind a dissociated phosphine or proceed to reversibly coordinate an olefinic substrate to form a ruthenacyclobutane, **7**. The breaking apart of the ruthenacyclobutane follows to expel the new olefinic products (**Scheme 1**).[25] In addition, these studies showed that the second-generation catalysts initiate much more slowly than the first-generation ones, and that their enhanced activity is due to the fact that their affinity to coordinate an olefinic substrate in the presence of free phosphine is much greater than that of the first-generation systems.

These mechanistic insights guided Grubbs and co-workers to prepare a family of second-generation catalysts with different initiation rates by varying the detachable phosphine ligands. Depending on the application, it is advantageous to employ catalysts that initiate more or less rapidly. For example, when performing ring-opening olefin metathesis polymerizations (ROMP) of strained cyclic olefinic monomers, slower-initiating catalysts are often desirable because they allow for longer handling of the monomer/catalyst resin before the polymerization starts.[26] Conversely, fast-initiating catalysts, able to promote metathesis at reduced temperatures, are useful in applications where low reaction temperatures are required to prevent catalyst decomposition and formation of undesired byproducts.[27]

Thus, analogues of **4**, such as complexes **8**–**10** containing tri(*n*-butyl)phosphine, tri(*p*-tolyl)phosphine, and triphenylphosphine, have been synthesized and their phosphine dissociation rates found to vary dramatically with the nature of the phosphine

ligand (**Figure 3**).[28,29] Indeed, the phosphine dissociation rate of **10** was about *60 times greater,* and that of **8** about *170 times smaller*, than that of **4** (measured at 80 °C in toluene).[29,30]

The nature of the halide and alkylidene ligands also has an impact on the catalyst initiation rate. In particular, catalysts containing larger halide ligands initiate more rapidly, while systems with smaller alkylidene moieties (e.g., methylidene) initiate more slowly.[25b] Similarly, complex **13**, containing a large NHC ligand (i.e., 1,3-bis(2,6-diisopropylphenyl)imidazo lidin-2-yl or SIDIPP) and first synthesized by Fürstner and co-workers,[31] has proved to be a fast initiator and a highly active catalyst (**Figure 4**).[23,25b,32]

2.3. Applications of Second-Generation Grubbs Catalysts

By virtue of their greatly enhanced activity vis-à-vis their first-generation counterparts, the second-generation catalysts promote the metathesis of sterically demanding or deactivated olefins. In particular, second-generation Grubbs complexes have shown increased activity in ring-closing metatheses (**eq 1–3**),[22,33,34] and in macrocyclizations.[35] They also catalyze challenging cross-metatheses[1h,36] including the coupling of olefins with α,β-unsaturated carbonyls,[37] vinylphosphonates,[38] and 1,1-disubstituted alkenes (**Scheme 2**).[39]

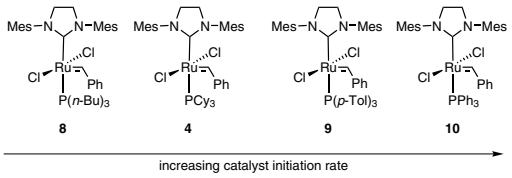
A model for the prediction of the outcome of cross-metathesis reactions has been developed based on the categorization of olefins according to their relative propensity to homodimerize via cross-metathesis and the ability of their homodimers to undergo secondary metathesis.[40] Based on this model, olefinic substrates are divided into four different types. Whether a certain olefin belongs to one type or another depends on the nature of the metathesis catalyst used (**Table 1**). Cross-metatheses between two olefins of Type I yield product mixtures that correspond to statistical distributions. Additionally, reactions between two olefins of the same type (but not of Type I) give nonselective product mixtures, while reactions between olefins of two different types are selective processes.

The ability of the second-generation catalysts to couple olefins with α,β-unsaturated carbonyls has been utilized to prepare A,B-alternating copolymers by ring-opening insertion metathesis polymerization (ROIMP).[41] Additionally, these catalysts promote the enyne metathesis of alkynes to make interesting 1,3-dienes (**eq 4,5**).[9,34,42,43] Finally, second-generation systems are often the catalysts of choice for the preparation of novel ROMP polymers, including ROMP-based immobilized reagents and scavengers.[44]

3. Phosphine-Free, SIMes-Based Second-Generation Catalysts

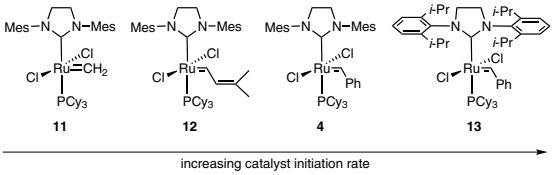
A phosphine-free catalyst, **14**, containing an SIMes and a chelating benzylidene ether ligand has been introduced by Hoveyda and co-workers (**Figure 5**).[45,46] This complex shows efficiencies similar to the Grubbs systems, but has slightly different substrate specificities. It is a particularly efficient catalyst for metatheses involving highly electron-deficient substrates such as acrylonitrile and fluorinated alkenes.[47]

Other phosphine-free catalysts of the Hoveyda type have been prepared by introducing different substitution patterns on the chelating benzylidene ether ligand. Thus, Blechert and co-workers have reported complexes bearing more sterically hindered chelating ligands (**15** and **16**),[48] while Grela and co-workers have disclosed benzylidene ether moieties with



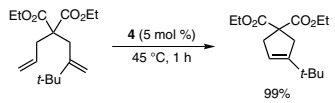
Ref. 28,29

Figure 3. Effect of the Nature of the Phosphine Ligand on the Initiation Rate of the Second-Generation Catalyst.



Ref. 23,25b,32

Figure 4. Influence of the Nature of the Alkylidene and NHC Ligands on the Initiation Rate of the Second-Generation Catalyst.

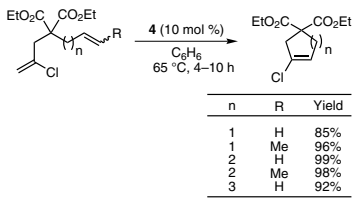


Ref. 22

eq 1

Ref. 34b

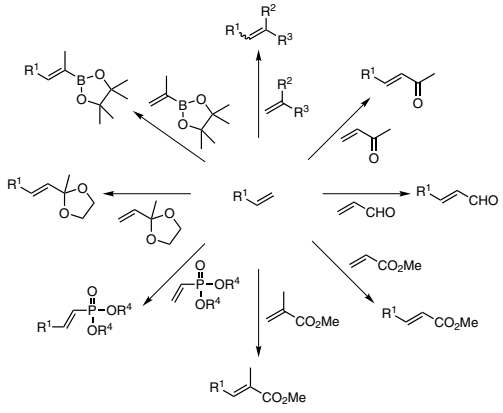
eq 2



n	R	Yield
1	H	85%
1	Me	96%
2	H	99%
2	Me	98%
3	H	92%

Ref. 34c

eq 3

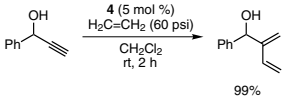


Ref. 37–39

Scheme 2. Cross-Metatheses Catalyzed by Second-Generation Grubbs Catalysts.

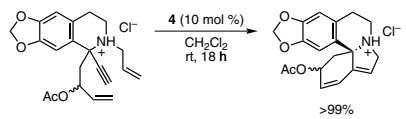
Table 1. Olefin Categories Based on Their Metathesis Reactivity

Olefin Type	First-Generation Grubbs Catalysts	Second-Generation Grubbs Catalysts
Type I (facile homodimerization; homodimers are readily consumable)	terminal olefins; allyl silanes; 1° allylic alcohols, ethers, and esters; allyl boronate esters; allyl halides	terminal olefins, 1° allylic alcohols and esters; allyl boronate esters; allyl halides; styrenes (without large ortho substituents); allyl phosphonates; allyl silanes; allyl phosphine oxides; allyl sulfides; protected allylic amines
Type II (more difficult homodimerization; homodimers sparingly consumable)	styrenes; 2° allylic alcohols; vinyl dioxolanes; vinyl boronates	styrenes (with large ortho substituents); acrylates; acrylamides; acrylic acid; acrolein; vinyl ketones; unprotected 3° allylic alcohols; vinyl epoxides; 2° allylic alcohols; perfluorinated alkane olefins
Type III (no homodimerization)	vinyl siloxanes	1,1-disubstituted olefins; nonbulky trisubstituted olefins; vinyl phosphonates; phenyl vinyl sulfone; 4° allylic hydrocarbons; protected 3° allylic alcohols
Type IV (spectator substrates: do not undergo cross-metathesis)	1,1-disubstituted olefins; disubstituted α,β-unsaturated carbonyls; 4° allylic carbon-containing olefins; perfluorinated alkane olefins; protected 3° allylic amines	olefins with vinylic nitro group; protected trisubstituted allylic alcohols



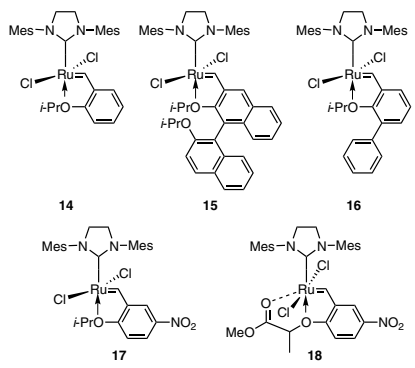
Ref. 42

eq 4



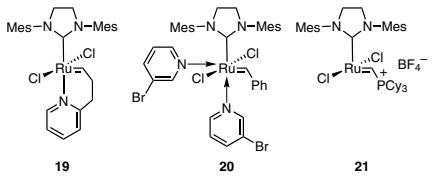
Ref. 43

eq 5



Ref. 45,48,49

Figure 5. Phosphine-Free, SIMes-Based Second-Generation Catalysts.



Ref. 50,52,55

Figure 6. Very Slow and Very Fast Initiating, Second-Generation Catalysts.

electron-withdrawing substituents in the position para to the alkoxy group to make catalysts such as compounds **17** and **18**.[49] Both of these steric and electronic alterations of the original ligand have resulted in faster-initiating catalysts than the parent Hoveyda complex **14**, presumably because the ether ligands in species **15–18** dissociate faster from the ruthenium than the ether ligand in catalyst **14**.

4. Slow- and Fast-Initiating NHC-Based Catalysts

Additional tuning of the initiation rates led to the development of exceptionally slow- and exceptionally fast-initiating metathesis catalysts. Thus, complex **19** (**Figure 6**) is a latent phosphine-free initiator, but a highly active catalyst once it has initiated.[50,51] As such, complex **19** is a useful promoter for the ROMP of strained cyclic olefinic monomers such as dicyclopentadiene.[26] On the other hand, catalyst **20** is a very fast phosphine-free initiator,[52] which has proved useful for the production of polymers with narrow polydispersities and for the synthesis of block copolymers.[53,54]

Catalysts such as compound **21**, developed by Piers and co-workers, are extremely fast initiators and are capable of catalyzing the ring-closing metathesis of terminal dienes at 0 °C.[55] The ability of Piers's systems to turn over at very low temperatures has proved useful in very elegant mechanistic studies resulting in the direct observation of olefin metathesis metallacyclobutane intermediates,[56] and has made them ideal candidates for low-temperature applications.

5. Other Recent Developments in the Design of Second-Generation Catalysts

5.1. Second-Generation Catalysts Based on Unsymmetrical Alkyl,Aryl-NHC Ligands

Second-Generation-type systems bearing unsymmetrical saturated NHC ligands, substituted with an alkyl group on one nitrogen atom and an aryl group on the other, were initially investigated by Mol and co-workers, who prepared the mixed 1-adamantyl,mesityl complex **22** (**Figure 7**).[57] This compound turned out to be an extremely poor metathesis catalyst, presumably because of the large steric hindrance resulting from the adamantyl substituent.[57]

More recently, Blechert's research group reported the preparation of mixed methyl,mesityl and ethyl,mesityl systems of the Grubbs and Hoveyda–Grubbs types (**23** and **24**).[58] These complexes demonstrated activities comparable to the Grubbs and Hoveyda–Grubbs analogues **4** and **14** in the metathesis of several common substrates. However, catalyst **24** performed much more poorly than **14** in a challenging cross-metathesis with acrylonitrile.[58] Additionally, complex **23** gave lower *E/Z* ratios than **4** and **14** in various cross-metatheses. While this specificity may prove useful in certain applications, it is also an additional hint that mixed alkyl,aryl systems tend to be less active than bisaryl ones.[59]

5.2. Chiral, Second-Generation Ruthenium Metathesis Catalysts[60]

Although the syntheses of the first ruthenium metathesis catalysts with chiral, saturated NHC ligands (e.g., complex **25**) go back to the time of the discovery of the second-generation catalysts,[22] asymmetric metatheses affording appreciable enantiomeric excesses were not achieved until chiral complexes such as **26** and **27** were developed by the Grubbs and Hoveyda groups, respectively (**Figure 8**).[61,62] Complex **26** effectively catalyzed the desymmetrizing RCM of prochiral trienes to

afford enantiomeric excesses ranging from 13% to 90%.[61] Catalyst **27** led to high enantioselectivities in the asymmetric, tandem, ring-opening metatheses–cross-metatheses of tricyclic norbornene derivatives.[62] However, complex **27** is altogether a less active catalyst and requires elevated reaction temperatures and prolonged reaction times. Hoveyda and co-workers have subsequently reported analogs of **27** with enhanced catalytic activity using lower catalyst loadings.[63] More recently, Grubbs and collaborators developed highly active analogues of catalyst **25** (e.g., **28**) that can induce chirality with greater efficiency than **25**.[64]

5.3. Immobilized, Second-Generation Catalysts and Related Developments

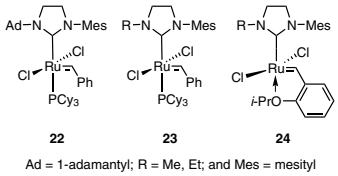
Considerable research efforts have been applied to immobilizing second-generation catalysts on various supports.[65] Many of the systems prepared involve the attachment of the ruthenium complex via its alkylidene moiety.[45,66] This approach, by its nature, does not lead to a permanent anchoring of the system on the support, but rather to a controlled release of the catalytic species into the reaction solution. Depending on the specific systems employed, the released metal species have been observed to partially return and reattach themselves to the support.[45] Other approaches consist of attaching the ruthenium catalysts via the NHC or the anionic ligands.[66c,67] The most noteworthy examples of this approach are the catalysts immobilized on silica, polymers, or monolithic supports developed by Buchmeiser and co-workers.[68] Using similar strategies, Grubbs and co-workers have prepared an active, water-soluble catalyst by connecting the NHC ligand to a poly(ethylene glycol) chain.[69] A related development was recently reported by the Gladysz group, who prepared a second-generation Grubbs catalyst bearing a fluorinated phosphine ligand and used it in biphasic reactions.[70]

5.4. Second-Generation Catalysts for the Metathesis of Hindered Olefins

The most exciting recent additions to the family of second-generation catalysts concern the metathesis of hindered olefins and, in particular, RCM to form tetrasubstituted cycloalkenes. While catalysts **2**, **3**, **4,** and **14** have enabled several such transformations,[15c,16,23,24] RCM to make tetrasubstituted, five-membered-ring olefins (e.g., RCM of dimethallylmalonates) had remained especially challenging until very recently. Indeed, catalysts **4** and **14** gave a 6% and a 17% conversion, respectively, in the RCM of diethyl dimethallylmalonate *after 4 days* at 30 °C.[23] The best catalyst systems for making tetrasubstituted, five-membered cycloalkenes, the unsaturated NHC-based catalysts (e.g., complexes **2** and **3**), gave *a modest 31% conversion after 4 days* at 30 °C.[23] As a result, an extensive search for improved catalysts for the metathesis of hindered olefins was undertaken. Complexes **29**–**31**, prepared by Grubbs and co-workers (**Figure 9**),[71–73] are more efficient catalysts for such transformations than **2**–**4** and **14**. For example, **29**–**31** all afford high conversions (~ 90%) in the RCM of diethyl dimethallylmalonate after 24 hours at 60 °C.[72,73] However, attempts to optimize and scale up the preparation of these catalysts revealed that they would be relatively difficult and expensive to produce at scale.[74] Most recently, catalysts **32** and **33** were developed and the scope of their utility investigated. These complexes proved to be the most efficient catalysts in the benchmark RCM of dimethallylmalonates, affording *greater than 95% conversion in less than 1 hour* (**eq 6**).[75]

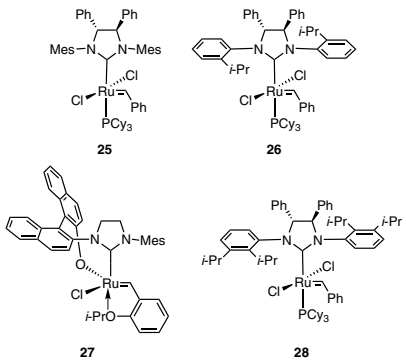
6. Practical Considerations for Using Olefin Metathesis Catalysts

Many of the first- and second-generation Grubbs and Hoveyda–Grubbs catalysts discussed so far are commercially available. Olefin metathesis reactions catalyzed by these ruthenium-based catalysts can be conducted in neat olefinic substrates or in solvents of varied polarities. Toluene and dichloromethane are most commonly used, but 1,2-dichloroethane, chlorinated benzenes, diethyl ether, tetrahydrofuran, ethyl acetate, acetone, and methanol may also be employed. Of further utility,



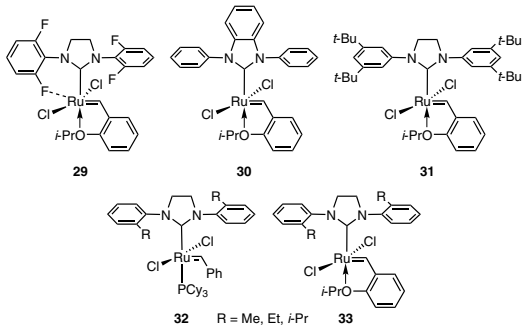
Ref. 57,58

Figure 7. Second-Generation Catalysts Based on Unsymmetrical Alkyl,Aryl-Substituted NHCs.



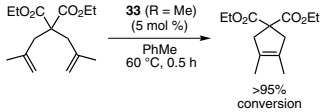
Ref. 22,61,62,64

Figure 8. Examples of Chiral Ruthenium Olefin Metathesis Catalysts.



Ref. 71,72,73,75

Figure 9. Highly Efficient Catalysts for the Metathesis of Hindered Olefins.



Ref. 75

eq 6

solvents and substrates do not need to be anhydrous. Although ruthenium-based catalysts are relatively robust to oxygen, degassing the reaction solvents and olefinic substrates before adding the catalysts is recommended. Additionally, improved efficiencies may be obtained upon further purification of the olefinic substrates by filtration through silica gel or activated alumina.

Reaction temperatures of about 30 to 50 °C are typical for second-generation Grubbs and Hoveyda–Grubbs catalysts (i.e., complexes **4** and **14**, respectively). Catalysts **8**, **12**, and **19** will usually require higher temperatures (e.g., about 50 to 60 °C for **12**, and about 60 to 80 °C for **8** and **19**) to perform adequately, while catalysts **10** and **20** may be used at lower temperatures (e.g., about 10 °C for **10**, and about 0 °C for **20**). **Table 2** summarizes the specificities of different catalysts. Optimal catalyst and substrate loadings may vary depending on the metathesis reaction, the catalyst, and the reaction conditions, but typical loadings are in the range of 0.1–5 mol %. Finally, upon completion of the metathesis reaction, the catalyst can be removed from the products or from the organic phase by employing published methods.[76]

7. Conclusions

Although first-generation olefin metathesis catalysts such as the first-generation Grubbs and Hoveyda–Grubbs systems remain extremely useful tools in synthetic chemistry, the introduction and evolution of the second-generation catalysts have greatly widened the scope of chemical transformations enabled by metathesis reactions. The second-generation Grubbs (e.g., **4** and **12**) and Hoveyda–Grubbs (e.g., **14**) catalysts have opened the way to new metathesis applications including the formation of trisubstituted cycloalkenes via RCM and the polymerization and cross-metathesis of sterically hindered or electronically deactivated olefins. Moreover, many second-generation catalysts have been developed to address additional needs of synthetic chemists. Slow-initiating, phosphine-containing (e.g., **8**) and phosphine-free (e.g., **19**) catalysts were designed for the controlled ROMP of strained cyclic olefins, while fast-initiating phosphine-containing (e.g., **10**) and extremely fast-initiating phosphine-free (e.g., **20**) systems may be used in low-temperature metathesis processes or in the production of polymers with narrow polydispersities. Additionally, recently developed systems that contain small, saturated NHC ligands (e.g., **32** and **33**) are very efficient at promoting the metathesis of hindered alkenes, even RCM to form tetrasubstituted, five-membered-ring cyclic olefins. By opening these new avenues, catalysts **32** and **33** promise to lead to new exciting applications.

Together, compounds **4**, **8**, **10**, **12**, **14**, **19**, **20**, **32,** and **33**, along with the first-generation Grubbs and Hoveyda–Grubbs complexes, constitute a powerful tool kit that allows synthetic chemists to perform most metathesis transformations currently facilitated by the class of ruthenium-based olefin metathesis catalysts. These catalysts have enabled and will continue to enable the preparation of previously unattainable molecules and materials in all fields of chemistry and materials science.

Table 2. Specificities of Olefin Metathesis Catalysts

Catalyst	Comments
First-generation Grubbs	Useful in the ROMP of strained cyclic olefins, in the ethenolysis of internal olefins, as well as in the ADMET, CM, and RCM of terminal olefins.
First-generation Hoveyda–Grubbs	Possesses reactivity similar to that of first-generation Grubbs. Especially useful in the industrial production of macrocycles via RCM.
4	Known as the second-generation Grubbs catalyst and is considerably more active than the first-generation catalysts. Has shown increased activity in RCM and has been employed in challenging CMs of sterically demanding or deactivated olefins, including 1,1-disubstituted olefins and α,β-unsaturated carbonyls. Typically used at 30–50 °C.
8	A much slower initiator than **4** and requires higher reaction temperatures (e.g., 60–80 °C).
10	A faster initiator than **4** and can therefore be used at lower temperatures than **4** (e.g., 10–30 °C).
12	Slower to initiate than **4**, but faster than **8**. Requires reaction temperatures of typically 50 to 60 °C.
14	Known as the second-generation Hoveyda–Grubbs catalyst and possesses reactivity comparable to that of **4**. However, it initiates more readily at lower temperatures (e.g., 5–30 °C), depending on the other reaction conditions such as catalyst loading and substrate concentration. Is also an efficient catalyst for the metathesis of highly electron-deficient substrates such as acrylonitrile.
19	A latent initiator that possesses the high activity of second-generation catalysts once it has initiated. Was developed mainly for industrial ROMP applications, in which longer monomer or catalyst resin handling times are desired. Its latency could also prove useful in other applications.
20	A much faster initiator than **4** and can therefore be used at lower temperatures (e.g., ~0 °C), depending on the other reaction conditions. It tends to be less soluble than **4** in nonpolar solvents, and is generally less stable than **4** in solution. Has been employed in the production of block copolymers and polymers with narrow polydispersities.
32 (R = Me)	A highly efficient catalyst for the metathesis of hindered olefins. Is particularly useful in the preparation of tetrasubstituted olefins via RCM and in CM involving sterically highly demanding olefins.
33 (R = Me)	This is the Hoveyda–Grubbs analogue of **32** (R = Me). Is also useful in the synthesis of tetrasubstituted olefins via RCM and in CM involving sterically highly demanding olefins. Depending on the substrate and reaction conditions, it may prove more efficient than **32** (R = Me).

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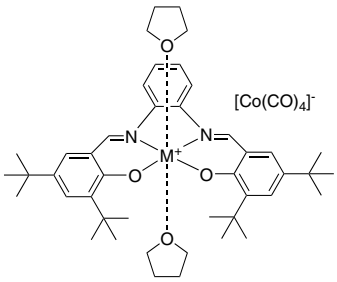
About the Authors

Yann Schrodi was born in 1972 in Strasbourg, Alsace, France. He obtained a B.S. degree in chemistry in 1994 and an M.S. degree in transition-metal chemistry in 1995 from L'Université Louis Pasteur Strasbourg, where he worked under the supervision of Professor John A. Osborn. After serving in the French military for ten months, he spent five years in the laboratory of Professor Richard R. Schrock at MIT, where he earned his Ph.D. degree in inorganic chemistry in 2001. Dr. Schrodi joined Materia, Inc., in 2001, where he is currently leading the Catalyst Research and Development Group. Notable achievements of this group under his leadership and in collaboration with Professor Robert H. Grubbs include the development of several new olefin metathesis catalysts, such as highly active but latent catalysts for ring-opening metathesis polymerizations, highly efficient and selective ethenolysis catalysts, and highly efficient catalysts for the production of tetrasubstituted olefins. Dr. Schrodi is a coauthor on several publications and patents in the area of homogeneous catalyst development and catalytic process development.

Richard L. Pederson was born in 1962 in Albert Lea, Minnesota. He earned his B.S. degree in chemistry in 1985 from the University of Wisconsin-River Falls, where he did research under Professor John Hill. He worked under the supervision of Professor Chi-Huey Wong at Texas A&M University, earning his Ph.D. degree in organic chemistry in 1990. He joined Bend Research, Inc. in Bend, Oregon, where, in 1997, he and Professor Robert H. Grubbs patented the production of insect pheromones using ruthenium metathesis catalysts. Dr. Pederson has spent the last twelve years in entrepreneurial start-ups using olefin metathesis to develop new routes to insect pheromones and pharmaceutical intermediates, while also managing numerous projects and technical personnel. In 2000, he joined Materia, Inc., to start up the Fine Chemicals Group, where he is the Director of Fine Chemicals R&D. Dr. Pederson is the author of numerous patents and publications, including key patents related to the production of chelating metathesis ligands and the use of metathesis in the production of insect pheromones.

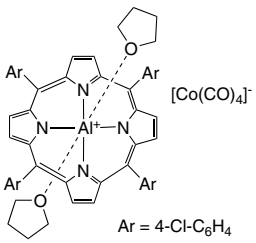
Coates Carbonylation Catalysts

These complexes are efficient and versatile carbonylative ring-expansion catalysts that have been applied in the synthesis of various lactones and cyclic anhydrides.[1–3]



674699 M = Al

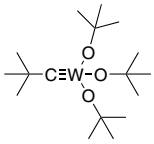
674680 M = Cr



681474

New Schrock Alkyne Metathesis Catalyst

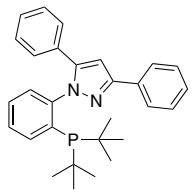
Tris(*tert*-butoxy)(2,2-dimethylpropylidyne)tungsten(VI) has emerged as an effective alkyne metathesis catalyst under fairly mild conditions. The usefulness of this catalyst is illustrated by the concise and stereoselective synthesis of *cis*-civetone—a valuable, macrocyclic, olfactory compound.[4]



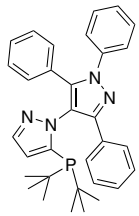
666440

New Efficient Systems for Cross-Coupling

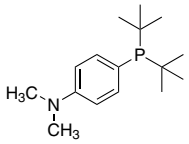
Developed at pharmaceutical companies, these non-proprietary ligands and catalyst are efficient in mediating Pd-catalyzed aminations[5] or Suzuki–Miyaura cross-coupling reactions.[6]



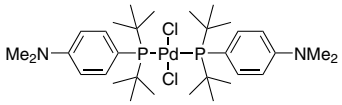
BippyPhos
681555



TrippyPhos
676632



A-$^{t\text{a}}$Phos
677264



(A-$^{t\text{a}}$Phos)$_2$PdCl$_2$
678740

Nanoparticulate Pd and Rh

Nanoparticulate palladium in an aluminum hydroxide matrix **(674133)** is a versatile, recyclable, and amphiphilic heterogeneous catalyst that can be applied to a variety of reactions with low catalyst loadings.[7] Nanoparticulate rhodium entrapped in a highly porous and fibrous boehmite matrix **(679488)** has been used in the facile and mild hydrogenation of a variety of arenes, can be recovered effortlessly by simple filtration, and reused several times without a noticeable loss of activity.[8–9]

Other Metal Catalysts

679771 (2-Biphenyl)di-*tert*-butylphosphinegold(I) chloride, 98%

677876 Trichloro(pyridine)gold(III), 97%

677892 Tetrakis(acetonitrile)copper(I) tetrafluoroborate, 97%

679763 Bis(dibenzylideneacetone)platinum(0)

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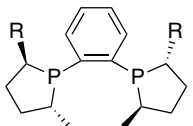
ChiroSolv™ kits are 96-well format kits that enable rapid screening of resolving agents and solvents for chiral separation. Each of these ready-to-use disposable kits contains a combination of eight resolving agents and twelve solvents. Racemates that can be separated include: acids, bases, alcohols, amino acids, aldehydes, and ketones. Optimum resolution that typically requires over two months can be achieved within one day.

Available in three Acid Series kits (**681431, 681423, 681415**) and three Base Series kits (**681407, 681393, 681377**). For more information visit sigma-aldrich.com/chirosolv.

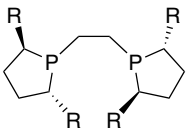
Chiral Phospholane Ligands

Chiral phospholane ligands have been used extensively in transition metal catalyzed asymmetric hydrogenations and other novel asymmetric reactions including [4+1] cycloadditions, imine alkylations, and allylborations.

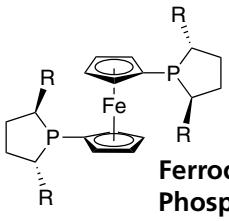
Available in either enantiomeric form with Me, Et, and *i*-Pr substituents. For a detailed product listing, visit sigma-aldrich.com/phospholane.



DuPhos



BPE



Ferrocenyl Phospholanes

Chiral phospholane ligands are sold in collaboration with Kanata Chemical Technologies Inc. for research purposes only. These compounds were made and sold under license from E. I. du Pont de Nemours and Company; license does not include the right to use the compounds in producing products for sale in the pharmaceutical field.

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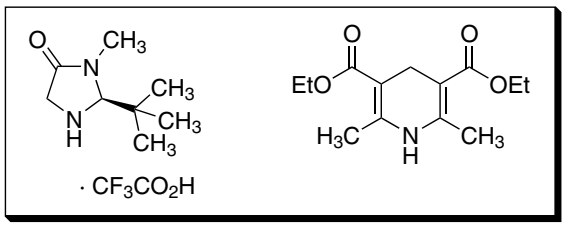
Mac-H is a convenient formulation of the MacMillan Imidazolidinone OrganoCatalyst™ and Hantzsch ester for asymmetric reductions, effectively serving as "asymmetric hydrogenation in a bottle."

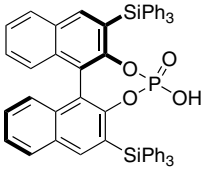
Mac-H



683558

MacMillan TiPSY Catalysts have been used in the first direct enantioselective organocatalytic reductive amination reaction.

MacMillan TiPSY Catalysts



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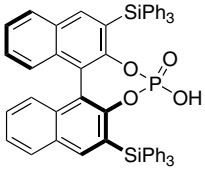

680184

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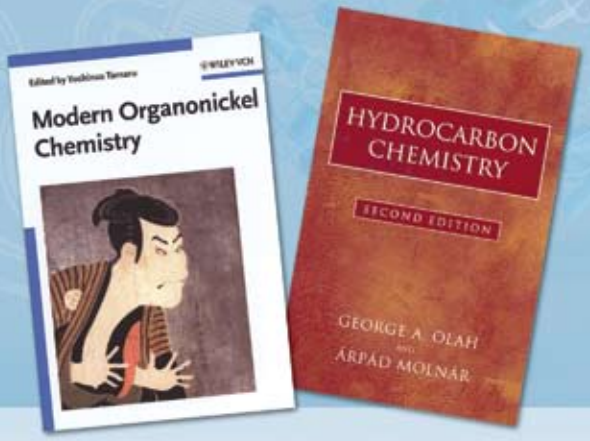
Z564397	Micro	11½	17 x 17	2
Z564400	Mini	22	27 x 17	2
Z564419	Small	22½	27 x 27	2
Side Entry				
Z564427	Mini	12	20 x 20	4
Z564435	Small	12	30 x 20	2
Dual-Side Entry				
Z564443	Mini	12	20 x 20	2
Z564451	Small	12	30 x 20	2

Visit sigma-aldrich.com for full details.



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CHEMICAL SYNTHESIS

Handbook of Metathesis, 3-Volume Set

R. H. Grubbs, Ed., Wiley-VCH, 2003, 1234 pp. Hardcover. There is probably no name more closely linked to metathesis than that of Robert H. Grubbs of the California Institute of Technology. His pioneering work has led to the success of this important and fascinating reaction, and, in this comprehensive three-volume set, he presents all of its important aspects. The team of contributing authors reads like a "Who's Who" of metathesis. The handbook is clearly divided into three major topics: catalyst developments, organic synthesis applications, and polymer synthesis.

Z551570-1EA

Modern Organonickel Chemistry

Y. Tamaru, Ed., Wiley-VCH, 2005, 346 pp. Hardcover. Nickel catalyzes many unique reactions and thus enormously widens the scope of feasible transformations in organic chemistry. Over the past few years, interest in organonickel chemistry has grown such that it is now just as keen as that in organopalladium chemistry. Yet, while there are numerous books on the latter topic, a book specializing in organonickel chemistry is long overdue. This volume covers the many discoveries made over the past 30 years. Active researchers working at the forefront of organonickel chemistry provide a comprehensive review of the topic, including Nickel-Catalyzed Cross-Coupling Reactions, Reactions of Alkenes Including Allylnickel Complexes, Reactions of Alkynes, Reactions of Dienes and Allenes, Cycloisomerization; Carbonylation and Carboxylation, Asymmetric Synthesis, and Heterogeneous Catalysis.

Z705802-1EA

Handbook of Heterocyclic Chemistry, 2nd Edition

A. R. Katritzky and A. F. Pozharskii, Pergamon Press, 2000, 758 pp. Hardcover. Heterocyclic chemistry is the largest of the classical divisions of organic chemistry. Heterocyclic compounds are widely distributed in nature, playing a vital role in the metabolism of living cells. Their practical applications range from extensive clinical use to fields as diverse as agriculture, photography, biocide formulation, and polymer science. The range of known heterocyclic compounds is enormous, encompassing the whole spectrum of physical, chemical, and biological properties. This handbook is illustrated throughout with thousands of clearly drawn chemical structures and contains over 1500 chemical figures and reactions. The highly systematic coverage given to the subject makes this handbook one of the most authoritative single-volume accounts of modern heterocyclic chemistry available.

Z515213-1EA

Hydrocarbon Chemistry, 2nd Edition

G. A. Olah and Á. Molnár, Wiley, 2003, 871 pp. Hardcover. *Hydrocarbon Chemistry* begins by discussing the general aspects of hydrocarbons, the separation of hydrocarbons from natural sources, and the synthesis from C1 precursors with recent developments for possible future applications. Each successive chapter deals with a specific type of hydrocarbon transformation. The second edition includes a new section on the chemical reduction of carbon dioxide—focusing on catalytic, ionic, electrocatalytic, photocatalytic, and enzymatic reductions—as well as a new chapter on new catalysts and activation methods, combinatorial chemistry, and environmental chemistry.

Z550949-1EA

Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals, 2nd Revised and Enlarged Edition, 2-Volume Set

M. Beller and C. Bolm, Eds., Wiley-VCH, 2004, 1344 pp. Hardcover. Already in its second edition, over 70 internationally renowned authors cover the vast range of possible applications for transition metals in industry as well as academia. This two-volume work presents the current state of research and applications in this economically and scientifically important area of organic synthesis. Over 1,000 illustrations and a balanced presentation allow readers fast access to a thorough compilation of applications, making this an indispensable reference for everyone working with such metals.

Z703451-1EA

Supported Catalysts and Their Applications

D. C. Sherrington and A. P. Kybett, Eds., Royal Society of Chemistry, 2001, 278 pp. Hardcover. The need to improve both the efficiency and environmental acceptability of industrial processes is driving the development of heterogeneous catalysts in commodity, specialty and fine chemicals, as well as in pharmaceuticals and agrochemicals. This book discusses aspects of the design, synthesis, and application of solid-supported reagents and catalysts, including supported reagents for multistep organic synthesis, selectivity in oxidation catalysis, mesoporous molecular sieve catalysts, and the use of Zeolite Beta in organic reactions. In addition, the two discrete areas of heterogeneous catalysis (inorganic oxide materials and polymer-based catalysts) that were developing in parallel are now shown to be converging.

Z555517-1EA

Handbook of Organopalladium Chemistry for Organic Synthesis, 2-Volume Set

E. Negishi, Ed., Wiley, 2002, 3424 pp. Hardcover. This is the authoritative reference on organopalladium compounds, designed for synthetic chemists. Transition metals and their complexes represent one of the most important groups of catalysts for organic reactions. Among these, palladium has emerged as one of the most versatile catalysts in modern organic synthesis. Negishi assembles contributions from several dozen international authorities on the use of palladium reagents and catalysts. The handbook's contents are organized by reaction type, which provides maximum utility to the synthetic chemist.

Z513865-1EA

Microwaves in Organic and Medicinal Chemistry (Methods and Principles in Medicinal Chemistry Series, Volume 25)

C. O. Kappe and A. Stadler, Eds., Wiley-VCH, 2005, 422 pp. Hardcover. The authors of this guide are experts on the use of microwaves for drug synthesis, as well as having extensive experience in teaching courses held under the auspices of ACS and IUPAC. In this handy source of information for any practicing synthetic chemist, they focus on common reaction types in medicinal chemistry, including solid-phase and combinatorial methods. They consider the underlying theory and the latest developments in microwave applications, and include a variety of examples from the recent literature, as well as less common applications that are equally relevant for organic and medicinal chemists.

Z704679-1EA

Modern Rhodium-Catalyzed Organic Reactions

P.A. Evans, Ed., Wiley-VCH, 2005, 496 pp. Hardcover. Rhodium is an extremely useful metal due to its ability to catalyze an array of synthetic transformations. Hydrogenation, C–H activation, allylic substitution, and numerous other reactions are catalyzed by this metal, which presumably accounts for the dramatic increase in the number of articles that have recently emerged on the topic. P. Andrew Evans has assembled an internationally renowned team to present the first comprehensive coverage of this important area. The book features contributions from leaders in the field of rhodium-catalyzed reactions, and thereby provides a detailed account of the most current developments.

Z705810-1EA

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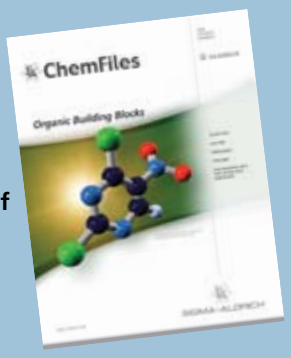

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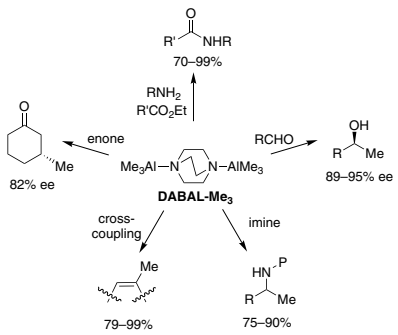
DABAL-Me$_3$

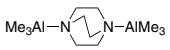
Trimethylaluminum is a versatile methylation reagent in organic synthesis. However, because of its pyrophoric nature, it cannot be handled in open air. Developed by the Woodward group (University of Nottingham, U.K.), DABAL-Me$_3$ is a free-flowing solid adduct of trimethylaluminum and DABCO® that can be manipulated without the need for an inert atmosphere.[1] This bench-stable reagent has been employed in numerous reactions including methylations of aldehydes and imines,[1,2] methylation of aryl and vinyl halides,[3] conjugate additions to enones,[4] and amide-bond formation.[5] In the presence of the appropriate chiral ligand and catalyst, many of these reactions can be performed asymmetrically.



(1) Woodward, S. *Synlett* **2007**, 1490. (2) Mata, Y. et al. *J. Org. Chem.* **2006**, *71*, 8159. (3) Cooper, T. et al. *Adv. Synth. Catal.* **2006**, *348*, 686. (4) Alexakis, A. et al. *Chem. Commun.* **2005**, 2843. (5) Novak, A. et al. *Tetrahedron Lett.* **2006**, *47*, 5767.

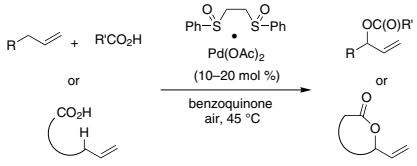
Bis(trimethylaluminum)–1,4-diazabicyclo[2.2.2]octane adduct (DABAL-Me$_3$)

682101 1 g, 5 g
[*137203-34-0*]
$C_{12}H_{30}Al_2N_2$
FW: 256.34



White Catalyst for Allylic C–H Oxidation

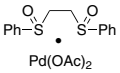
Professor Christina White's group (University of Illinois) recently reported selective allylic C–H oxidation reactions catalyzed by a Pd(II)–bis-sulfoxide system that furnishes branched allylic esters from α-olefins and carboxylic acids.[1] These reactions can be performed in an inter- or intramolecular fashion, the latter being capable of yielding highly functionalized, large-ring macrolactone products.[2] Finally, the catalyst system allows for a one-pot sequential allylic oxidation–C–H arylation to afford the *E* arylated allylic ester from the corresponding olefin, carboxylic acid, and arylboronic acid.[3]



(1) Chen, M. S. et al. *J. Am. Chem. Soc.* **2005**, *127*, 6970. (2) Fraunhoffer, K. J. et al. *J. Am. Chem. Soc.* **2006**, *128*, 9032. (3) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076.

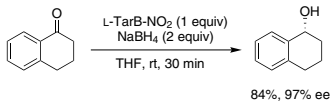
White Catalyst

684821 250 mg, 1 g
[*858971-43-4*]
$C_{18}H_{20}O_6PdS_2$
FW: 502.90



TarB-NO$_2$ Reducing Reagents

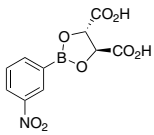
In conjunction with $NaBH_4$, Singaram's chiral TarB-NO_2 boronic esters rapidly reduce prochiral ketones to optically active secondary alcohols with enantiomeric excesses as high as 99%.[1-3] The reagents cleanly reduce aromatic ketones with high enantioselectivity and, in many cases, aliphatic ketones can be reduced with a similar degree of selectivity. Typically, TarB-NO_2 reagents perform as well as, or better than, existing hydridic asymmetric reduction methods such as those employing DIP-Chloride™ or the CBS reagents.



(1) Kim, J.; Singaram, B. *Tetrahedron Lett.* **2006**, *47*, 3901. (2) Kim, J. et al. *Org. Process Res. Dev.* **2006**, *10*, 949. (3) Cordes, D. B. et al. *Eur. J. Org. Chem.* **2005**, 5289.

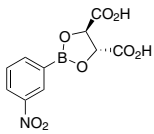
3-Nitrophenylboronic acid D-tartaric acid ester, 1 M in THF (D-TarB-NO_2)

682748 5 mL, 25 mL
$C_{10}H_8BNO_8$
FW: 280.98



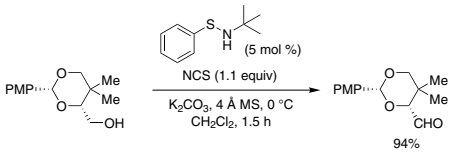
3-Nitrophenylboronic acid L-tartaric acid ester, 1 M in THF (L-TarB-NO_2)

682713 5 mL, 25 mL
[*467443-01-2*]
$C_{10}H_8BNO_8$
FW: 280.98



N-tert-Butylbenzenesulfenamide

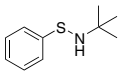
In the presence of NCS, *N-tert*-butylbenzenesulfenamide catalyzes the selective oxidation of a variety of primary and secondary alcohols to the corresponding aldehydes and ketones in high yield and under mild conditions.[1,2] The catalytic oxidation tolerates various functional groups including silyl ethers, epoxides, urethanes, esters, and olefins. The reaction is particularly useful for the preparation of labile or easily epimerized aldehydes.



(1) Mukaiyama, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 5590. (2) Matsuo, J.-i. et al. *Tetrahedron* **2003**, *59*, 6739.

***N-tert*-Butylbenzenesulfenamide, 97%**

681792 1 g, 5 g
[*19117-31-8*]
$C_{10}H_{15}NS$
FW: 181.30



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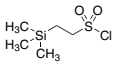
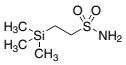
"PLEASE BOTHER US."

Joe Porwoll, President
Aldrich Chemical Co., Inc.

Professor Carsten Bolm of RWTH Aachen University, kindly suggested that we make 2-(trimethylsilyl)ethanesulfonyl chloride (SES-Cl). This reagent is employed to protect an amine in the form of its sulfonamide. In contrast to the harsh conditions sometimes needed to deprotect tosyl-protected amines, the SES group is readily cleaved under mild conditions using a fluoride ion source, regenerating the parent amine along with volatile byproducts. We have also prepared SES-NH_2, a useful reagent for the introduction of a protected nitrogen atom into a substrate.[1,2]

(1) Weinreb. S. M. et al. *Tetrahedron Lett.* **1986**, *27*, 2099. (2) Ribière, P. et al. *Chem. Rev.* **2006**, *106*, 2249.





681334	**2-(Trimethylsilyl)ethanesulfonyl chloride** (SES-Cl)	1 g 5 g
681326	**2-(Trimethylsilyl)ethanesulfonamide** (SES-NH_2)	1 g

Naturally, we made these useful reagents. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the inside back cover.

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ABOUT OUR COVER

Photograph © Board of Trustees, National Gallery of Art, Washington.

Oarsmen at Chatou (oil on canvas, 81.2 × 100.2 cm) was painted in 1879 by the French impressionist painter, Pierre Auguste Renoir (1841–1919), on the river Seine west of Paris. His use of light fresh colors in this painting and throughout his career was the result of his love of paintings from the Rococo period and of his training in a porcelain factory as a young man.

Rowing was the foremost attraction at Chatou. The man in this boat—wearing the typical costume of a short jacket and a straw hat—may be the artist's brother, Edmond. The man standing on the bank, similarly attired, is probably the painter Gustave Caillebotte, a devoted rowing enthusiast and a friend of Renoir. The woman is most likely Aline Charigot, who was his favorite model and later became his wife.

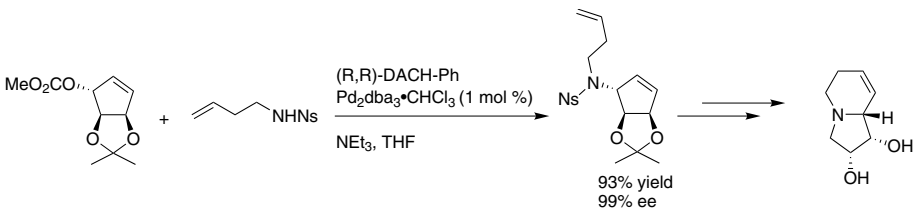
The painting captures the brilliance of sun and water, summer and youth. In the water, strong blues and white alternate. Their shimmering intensity is enhanced by the equally strong presence of orange in the boat's reflection and the scarlet accent of Aline's bow. Renoir has put into practice the principle of simultaneous contrast: colors are perceived stronger when juxtaposed with their opposites—orange with blue, for example, or green with red. The silky texture of Renoir's feathery brushstrokes mirrors the languid and leisurely scene.

This painting is a gift of Sam A. Lewisohn to the National Gallery of Art, Washington, DC.

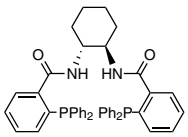
Trost Ligands for Asymmetric Allylic Alkylation

Asymmetric allylic alkylation is a versatile catalytic reaction allowing access to a diversity of chiral molecules. This transformation converts both enantiomers of the substrate into the same enantiomer of the product, allowing theoretical yields of 100% of one enantiomer. Professor Trost developed a series of ligands based on diphenylphosphinobenzoic acid (DPPBA) and used them with a variety of palladium complexes for the asymmetric allylic alkylation. These ligands perform with a high degree of enantioselectivity and high yields.

DACH-Phenyl Trost Ligands



Ovaa, H. et al. *Chem. Commun.* **2000**, 1501.

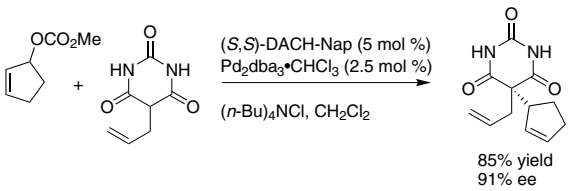


692808

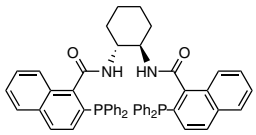
(*R,R*)-DACH-Phenyl Trost Ligand
692808

(*S,S*)-DACH-Phenyl Trost Ligand
692794

DACH-Naphthyl Trost Ligands



Trost, B. M.; Schroeder, G. M. *J. Org. Chem.* **2000**, *65*, 1569.

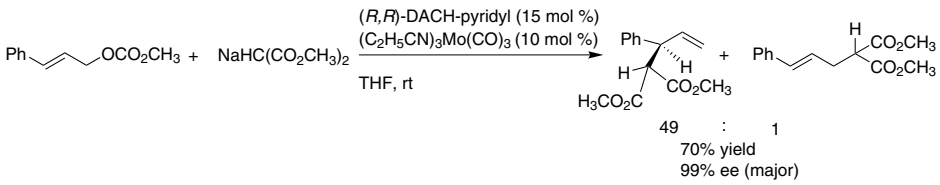


692778

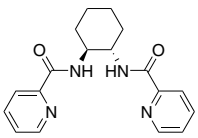
(*R,R*)-DACH-Naphthyl Trost Ligand
692778

(*S,S*)-DACH-Naphthyl Trost Ligand
692786

DACH-Pyridyl Trost Ligands



Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104.



692743

(*R,R*)-DACH-Pyridyl Trost Ligand
692751

(*S,S*)-DACH-Pyridyl Trost Ligand
692743

For more information, see Professor Trost's review in this issue.

Sold in collaboration with DowPharma℠ for research purposes only. US Patent 5739396 applies.

Palladium-Catalyzed Dynamic Kinetic Asymmetric Allylic Alkylation with the DPPBA Ligands

Professor Barry M. Trost

Dr. Daniel R. Fandrick

Barry M. Trost and Daniel R. Fandrick*
Department of Chemistry
Stanford University
Stanford, CA 94305-5080, USA
Email: bmtrost@stanford.edu

Outline

1. Introduction

The synthesis of chiral molecules is a prominent theme in organic chemistry. The synthetic community has come under increased pressure to prepare synthetic building blocks in an environmentally benign or "green" manner. To minimize waste, syntheses should be designed as catalytic transformations and should take place in an efficient and atom-economical fashion.[1] Asymmetric catalysis has enabled the cost-effective preparation of these building blocks. One such general method is the palladium-catalyzed asymmetric allylic alkylation (AAA). The methodology has demonstrated its ability to afford chirality through numerous enantiodiscriminating events.[2] Although several reviews have been published on AAA,[3,4] none has focused on the many palladium-catalyzed dynamic kinetic asymmetric transformations (DYKATs) that have been developed. To our knowledge, the only palladium-catalyzed DYKATs, wherein asymmetric induction results from the chirality of the palladium ligand, are those that take place through AAAs. This review will focus on the scope and synthetic utility of the palladium-catalyzed dynamic kinetic AAA with our diphenylphosphinobenzoic acid (DPPBA) and related family of ligands (**Figure 1**). These basic ligands are constructed with *o*-diphenylphosphinobenzoic or naphthoic acid moieties tethered by a chiral diamine backbone. The most common of these ligands are the standard ($\mathbf{L_S}$), naphthyl ($\mathbf{L_N}$), stilbene ($\mathbf{L_{ST}}$), and anthracene ($\mathbf{L_A}$) ones. The former two are commercially available.

There are several general mechanisms for asymmetric induction in catalyzed transformations. The most common one derives chirality from a prochiral substrate, typically through differentiation of the enantiotopic π faces (**Scheme 1**). Other asymmetric processes utilize a racemic substrate. In these cases, the transformation can proceed through either a kinetic resolution or DYKAT.[5] A kinetic resolution (KR) results when the enantiomers of a racemic substrate are converted to the chiral products at different rates (**Scheme 2**). Numerous catalytic and enzymatic transformations have shown high enantioselectivity for such a process. In the best-case scenario, only one substrate enantiomer reacts for a theoretical maximum yield of 50%, in addition to the 50% of recovered starting material. As such, this process is no more efficient than a physical resolution. To overcome this limitation, several processes commonly known as dynamic kinetic resolutions (DKRs) have been developed wherein both enantiomers of the substrate are converted into the same enantiomer of the product. This allows for a theoretical 100% yield. A resolution implies separation of a racemic substrate into its enantiomers. Therefore, we prefer the phrase dynamic kinetic asymmetric transformation (DYKAT)[6] rather than dynamic kinetic resolution, since these processes are not resolutions as the latter phrase implies. Currently, there are three general processes for a DYKAT. In the first one the substrate rapidly racemizes under the reaction conditions and the subsequent transformation is selective for one substrate enantiomer (**Scheme 3**). The second DYKAT converts the substrate into a meso or a prochiral intermediate, and the subsequent asymmetric induction results from differentiation of the enantiotopic termini or faces of this intermediate (**Scheme 4**). To prevent a KR, both substrate enantiomers must be completely converted into the meso intermediate. The third DYKAT is

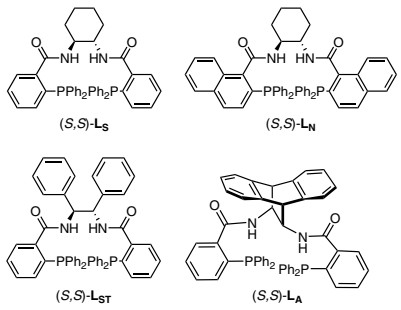
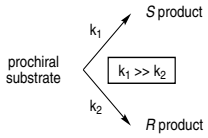
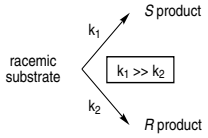


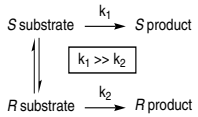
Figure 1. The Most Commonly Used DPPBA Ligands.



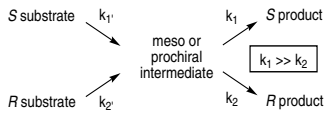
Scheme 1. Typical Asymmetric Induction.



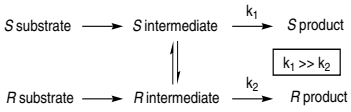
Scheme 2. Kinetic Resolution (KR).



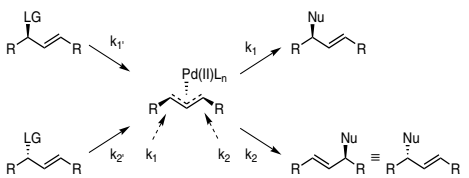
Scheme 3. DYKAT through Racemization of the Substrate.



Scheme 4. DYKAT through Conversion to a Meso or Prochiral Intermediate.



Scheme 5. DYKAT through the Rapid Interconversion of Intermediates.



Scheme 6. DYKAT of Symmetrical Allylic Substrates.

accomplished through a rapid interconversion of intermediates, and asymmetric induction results from a selective reaction with one intermediate (**Scheme 5**). Considering that enantioselectivity results from a kinetic reaction of one intermediate, the third DYKAT requires a Curtin–Hammett condition be established wherein the enantioselectivity is not dependent, in principle, upon the thermodynamic ratio of the intermediates.

Palladium-catalyzed dynamic kinetic AAAs have been accomplished primarily by using the latter two DYKAT processes. More specifically, DYKATs have been achieved through conversion of the chiral substrates into a pseudo-meso or prochiral intermediate, or through a rapid π–σ–π interconversion between the enantiotopic faces of the π-allylPd(II) intermediate.

2. DYKAT through Conversion of a Racemic Substrate into a Meso Intermediate

The most general type of palladium-catalyzed DYKAT proceeds through a pseudo-meso-π-allylPd(II) intermediate. In this process, oxidative addition of each enantiomer affords different unsymmetrical π-allylPd(II) complexes, which requires equilibration to an effectively symmetrical complex for high enantioselectivity. Asymmetric induction subsequently results from enantiodiscrimination of the termini (**Scheme 6**). Due to the chiral catalyst, the two enantiomeric substrates undergo oxidative addition with palladium at different rates. Therefore, for a successful DYKAT, complete substrate conversion into the π-allylPd complex is required. Two basic types of allylic substrates have been employed in this kind of DYKAT. The π-allylPd complexes of acyclic substrates adopt the preferred syn,syn conformation and, due to conformational restrictions, the π-allylPd complexes of cyclic substrates adopt the anti,anti conformation (**Figure 2**).[7] Although these complexes are structurally distinct, their reaction scopes and efficiencies are similar.[3,4] AAA of the acyclic systems preferentially generates the trans allylic products as a result of the formation of the favored syn,syn intermediates.

2.1. Acyclic Substrates

The most common palladium-catalyzed DYKAT involves the asymmetric allylic alkylation of 1,3-diphenyl-3-acetoxypropene (**1**) (**eq 1**).[8] Early results showed only moderate enantioselectivities with the sodium salt of the nucleophile and BINAP (R^1 = Me; 81%, 50% ee) or BINAPO (R^1 = Me; 75%, 68% ee) ligands. However, this reaction has become the standard test for new ligands.[3,4] As a result, extensive research has been focused on the development of a large number of diverse chiral ligands for this transformation.[9] High enantiomeric excesses have been obtained with many types of chiral ligands such as chiraphos (**3**) (R^1 = AcNH; 98%, 86% ee),[10] P–N ligand **4** (R^1 = H; 99%, 99% ee),[11] sparteine (**5**) (R^1 = H; 77%, 75% ee),[12] isosparteine (**6**) (R^1 = AcNH; 90%, 92% ee),[13] and Evans's P–S ligand **7** (R^1 = H; 97%, 98% ee).[14] A useful extension to the fluorous ligand **8** has enabled high selectivity (R^1 = Me; 96%, 90% ee) for an easily recyclable catalyst.[15] However, substrate **1** is the least sensitive in determining the asymmetric induction ability of the chiral catalyst.

Although the DPPBA ligands typically afford low conversions and enantioselectivities for the parent substrate, **1**, these ligands have demonstrated high levels of asymmetric induction with the more challenging carbonate, **9**. This discrepancy has been rationalized by the DPPBA ligands encountering unfavorable steric interactions with the larger substrate **1**. However, due to this sterically restrictive chiral environment, DPPBAs are some of the most general ligands for the palladium catalyzed AAA. For example, high enantioselectivity and yield for the DYKAT with carbonate **9**

have been achieved by utilizing the standard diaminocyclohexyl (DACH) ligand $\mathbf{L_S}$ (**eq 2**).[16]

These initial results revealed the need for establishing a symmetrical π-allyl intermediate for asymmetric induction or one that becomes the equivalent of a symmetrical species because of rapidly equilibrating nonsymmetrical structures. Our group also observed that the enantioselectivity of the AAA for the acyclic substrate **9** was dependent upon the size of the countercation of the nucleophile.[16] With the sodium salt of malonate, only 29% ee was obtained, but the enantioselectivity increased to 92% as the size of the cation increased with the use of the cesium salt. The π-allylPd(II) intermediate from the initial oxidative addition is proposed to be a tight ion pair, which requires relaxation to the necessary symmetrical intermediate for high asymmetric induction.[17] The exact nature of the asymmetry may derive from the conformations of the metal-bound ligand, although other explanations have also been proffered. Reactions with scalemic substrates and different enantiomers of the ligand demonstrated a moderate memory effect supporting the requirement for equilibration. The higher enantiomeric excess obtained with cesium was suggested to derive in part from a slower rate of alkylation with an effectively larger nucleophile that allowed for sufficient relaxation of the π-allylPd(II) intermediate. Additionally, the cesium nucleophile may also afford a less tight ion pair and lead to a faster equilibration. Further support for this requirement for relaxation was obtained when a derivative of the Trost ligand with dipodal arms, **13**, furnished high enantioselectivity and reactivity in the AAA with the previously sluggish sodium salt of the malonate nucleophile (**eq 3**).[18] A possible explanation relates to a faster equilibration by coordination of the cation to the polyether side chain of the ligand. A similar base and countercation effect on the enantioselectivity was observed with BINAP-based ligands.[19]

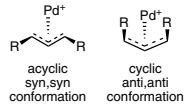
Other carbon nucleophiles, in analogy to malonate, undergo this type of DYKAT with high asymmetric induction. The standard ligand, $\mathbf{L_S}$, also affords high diastereoselectivity for the addition of nitroethane (**eq 4**).[20] This example demonstrates the ability of the catalyst to simultaneously discriminate between both the enantiotopic termini of the allyl ligand and the enantiotopic faces of the enolized nucleophile.

Barbiturates are also effective and useful soft carbon nucleophiles for DYKAT.[21] Utilization of the standard ligand, $\mathbf{L_S}$, and a fluoride additive to slightly improve the ee (vide infra), led to good enantioselectivity in the AAA (**Scheme 7**). Simple hydrogenation of the initial product completed the concise synthesis of pentobarbital, a sedative and hypnotic agent.

Similar to other AAAs, numerous soft heteroatom nucleophiles can be employed for DYKAT. In an extension of the Gabriel amine synthesis, high enantioselectivity was achieved for the asymmetric allylic alkylation with the standard ligand, $\mathbf{L_S}$, and phthalimide as the nucleophile (**Scheme 8**).[16,22] In this example, DYKAT tolerated the unprotected alcohol functionality, and the product provided a useful building block for the preparation of polyoxamic acid, the novel amino acid in several antifungal agents.[16]

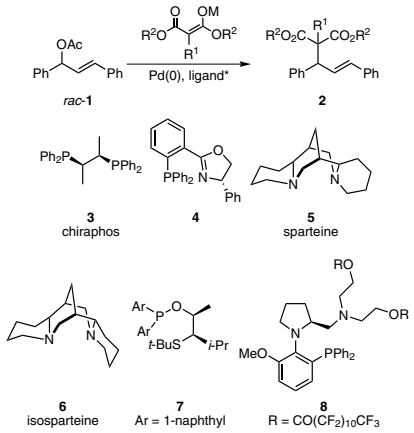
2.2. Cyclic Substrates

Similar to acyclic electrophiles, palladium-catalyzed dynamic kinetic AAAs of cyclic substrates afford excellent enantioselectivities for a broad range of soft nucleophiles. In the basic alkylation, excellent enantioselectivities were achieved with malonate and phthalimide nucleophiles for 5-, 6-, and 7-membered substrates (**Scheme 9**).[23] As in the case of the acyclic substrates, the nature of the countercation and malonate nucleophile had a dramatic effect on the enantioselectivity, which again emphasizes the importance of equilibration to the



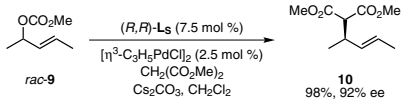
Ref. 7

Figure 2. Coordination Geometries for Acyclic and Cyclic π-AllylPd Complexes.



Ref. 8,10–15

eq 1



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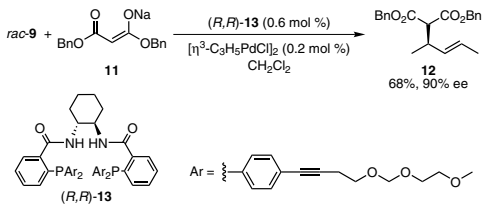
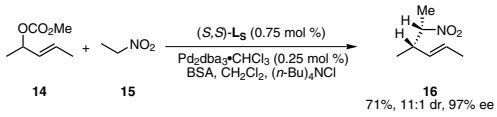
eq 2



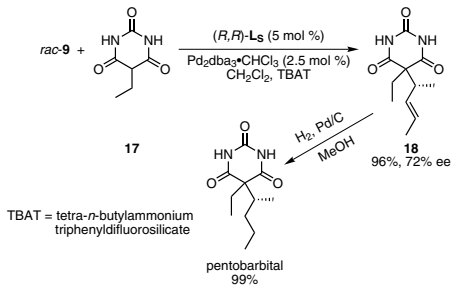
Ref. 18

eq 3



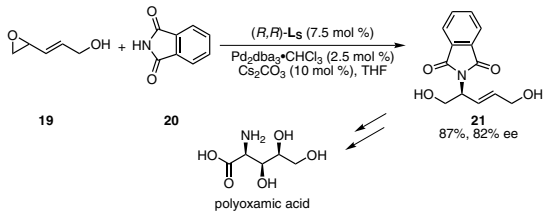
Ref. 20

eq 4



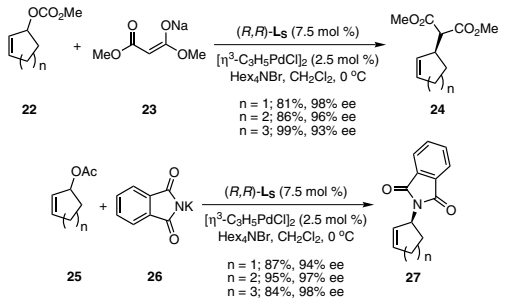
Ref. 21

Scheme 7. DYKAT with Barbiturates and Application to the Synthesis of Pentobarbital.



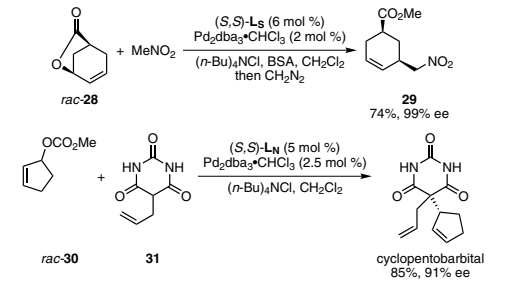
Ref. 16

Scheme 8. DYKAT with Phthalimide and Application to the Synthesis of Polyoxamic Acid.



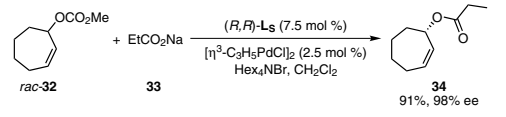
Ref. 23

Scheme 9. Dynamic Kinetic AAA of Cyclic Substrates with Malonate and Phthalimide Nucleophiles.



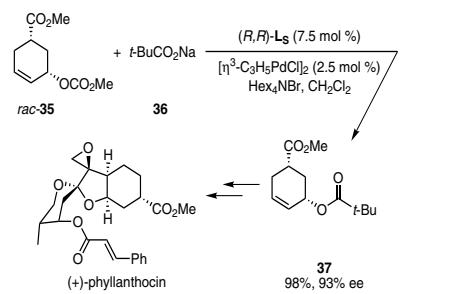
Ref. 21,25

Scheme 10. DYKAT of Cyclic Substrates with Nitromethane and Barbiturates.



Ref. 26

eq 5



Ref. 27

Scheme 11. Application of the Deracemization of Allylic Carbonates to the Formal Synthesis of Phyllanthocin.

equivalent of a symmetrical *meso*-π-allylPd(II) intermediate. The addition of tetrahexylammonium bromide (THABr) increased the ee from 38% to 82% in THF. A further increase in the enantioselectivity to 98% was obtained by utilizing methylene chloride as the solvent. Reetz et al. observed that tetra-*n*-butylammonium malonate exists as a dimer in polar solvents,[24] and attributed the effects of the additive and solvent to variations in the nature of the nucleophile and substrate ion pairs in solution. Therefore, tetraalkylammonium malonate is effectively larger than the sodium counterpart and, by analogy to the acyclic substrates, allows the equilibration of the initially formed π-allylPd(II) intermediate to the effectively symmetrical complex.[17,18]

The DYKAT of cyclic substrates with nitromethane[25] and barbiturates[21] affords excellent enantioselectivities with the standard and naphthyl ligands (**Scheme 10**). In the latter example, the AAA provided a concise and efficient synthesis of cyclopentobarbital, a sedative and hypnotic agent.

The dynamic kinetic asymmetric addition of oxygen nucleophiles to racemic substrates is one of the more synthetically useful DYKATs for the synthesis of complex natural products. The simplest reaction is the formal deracemization of allylic alcohols by the dynamic kinetic AAA with carboxylate nucleophiles.[26] In order to obtain high enantioselectivities, both the matched and mismatched oxidative addition of the substrate must effectively compete with ionization of the product, otherwise the product will equilibrate to the racemate. The utilization of the carbonate leaving group and a carboxylate nucleophile has proved effective, providing high enantioselectivities for the typical cyclic substrate **32** with a variety of carboxylic acid nucleophiles (**eq 5**). The methodology was applied successfully to the racemic allylic carbonate **35,** which furnished pivalate **37** in high yield and ee to constitute a formal synthesis of the antitumor agent phyllanthocin (**Scheme 11**).[27]

Extending our use of carbonate and bicarbonate nucleophiles,[28] Gais and co-workers developed another practical method for a similar deracemization of allylic carbonates.[29] In this procedure, the reaction proceeds in high enantioselectivity through alkylation with bicarbonate and subsequent in situ decarboxylation to the chiral allylic alcohol (**eq 6**). An attractive feature of this AAA is that hydrolysis of the ionized carbonate leaving group in situ generates the bicarbonate nucleophile. The reaction is general for both acyclic and cyclic substrates and requires the use of allylic carbonates.

One of the most synthetically useful alkylations is with 2-halophenols. After AAA with these nucleophiles, a subsequent intramolecular Heck reaction can construct the dihydrobenzofuran core of numerous biologically significant natural products. In the presence of the stilbene ligand, $\mathbf{L_{ST}}$, carbonate **40** provided efficiently and highly enantioselectively **41**, an intermediate in the total synthesis of (–)-galanthamine[30] and (–)-morphine[31] (**Scheme 12**). The DYKAT between **39** and **40** illustrates the tolerance by the catalyst of aryl bromides and functionality in the 2 position of the electrophile.

Similarly, AAA with sulfonamide nucleophiles furnished synthetically valuable protected amines.[32] An interesting example of this alkylation is the highly enantioselective reaction of cyclopentene **42** (**Scheme 13**).[33] Due to the inversion in the oxidative addition,[34] the palladium catalyst is positioned on the same face of the cyclopentene as the acetonide substituent which, by this example, did not hinder the AAA. Ring-closing–ring-opening metathesis and subsequent transformations of the DYKAT product **43** quickly furnished a useful entry into the synthesis of indolizidine alkaloids.

Additionally, modification of the standard ligand, $\mathbf{L_S}$, was required to obtain high enantioselectivity in the intramolecular

cyclization leading to the azabicyclo[4.2.1]nonene DYKAT product, **47** (**Scheme 14**).[35] Standard transformations of **47** furnished the "very fast death factor" anatoxin-a. Two explanations are possible for the different results obtained with $\mathbf{L_S}$ and **45**. As discussed previously, for high asymmetric induction to occur, the initial π-allylPd intermediate must equilibrate in order to function as a meso-like intermediate prior to alkylation. Previous examples demonstrated that the larger nucleophiles afford a slower alkylation, which allows the necessary equilibration to take place. In this example, and because the alkylation occurs intramolecularly, the cyclization is fast and competes with the equilibration. This effect is likely occurring with the standard ligand, $\mathbf{L_S}$. Due to coordination to the pyridine fragment of the modified ligand **45**, the electrophilicity of the π-allylPd(II) complex is decreased thereby slowing the alkylation and allowing the required equilibration to take place. An alternative explanation is that a background reaction may compete with the metal-catalyzed process. Using a sterically less hindered and a more electron-rich Pd(0) complex that would form with the pyridyl ligand **45**, a faster oxidative addition may then allow the metal-catalyzed process to out-compete the background reaction.

Heterocycles are also effective nucleophiles in DYKAT. Application of the typical conditions with the standard ligand, $\mathbf{L_S}$, and Cs_2CO_3 allowed the preparation of indolocarbazole proaglycons with high enantioselectivity (**eq 7**).[36] Additionally, the more acidic indole was selectively alkylated.

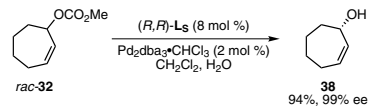
Burger and Tunge reported an interesting example, wherein the allylic alkylation was performed with a ketone enolate for a formal asymmetric Claisen reaction.[37] In this case, decarboxylation[38] of the initially formed β-keto carboxylate π-allylPd(II) complex afforded the reactive enolate nucleophile, **53** (**eq 8**). Good-to-excellent enantioselectivities were achieved for both cyclic and acyclic substrates. Interestingly, the reaction proceeded through coordination of the carboxylate to the palladium(II) intermediate or, namely, through a covalently bonded "ion pair" which has sufficient ability to equilibrate. No crossover was observed in a test reaction, suggesting a lack of significant dissociation of the ion pair prior to alkylation. However, the asymmetric induction observed is consistent with alkylation occurring on the face of the allyl ligand opposite the palladium.

In summary, the current technology has achieved high enantioselectivities in the dynamic kinetic AAA of acyclic and cyclic substrates that afford a symmetrical allylic intermediate. For asymmetric induction to occur, and in addition to using a chiral catalyst, conditions must be employed that allow relaxation of the substrates to the effective meso π-allyl intermediate.

2.3. Conduritol B Substrates

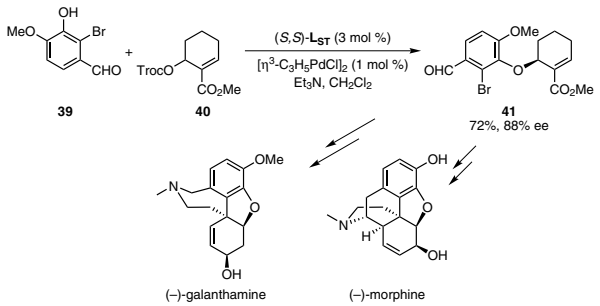
A valuable cyclic substrate for the dynamic kinetic AAA is tetra-acylated conduritol B, **55**. For this system, oxidative addition of the racemic substrate with the Pd catalyst furnishes a meso intermediate, **56**, in which asymmetric induction occurs by the selective alkylation of one terminus (**Scheme 15**).[39] For a successful DYKAT, both enantiomers of **55** must completely ionize to the symmetrical intermediate, albeit at different rates. Dialkylation of the substrate can also occur by ionization of the initial product, **57**, followed by another regio- and enantioselective alkylation. In both cases, four stereocenters are established in one asymmetric transformation through a DYKAT of racemic conduritol B.

In the AAA of tetraacetate **62** with a pivalate nucleophile, a kinetic resolution was observed with good regio- and enantioselectivity (**eq 9**).[40] This result demonstrates the different rates of the oxidative addition. Utilization of the more activated tetracarbonate substrate **66** and sodium benzoate as the nucleophile



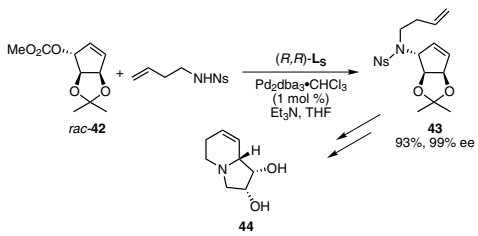
Ref. 29

eq 6



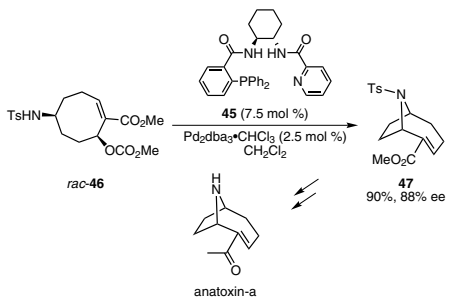
Ref. 30,31

Scheme 12. DYKAT with Phenols and Its Synthetic Applications.



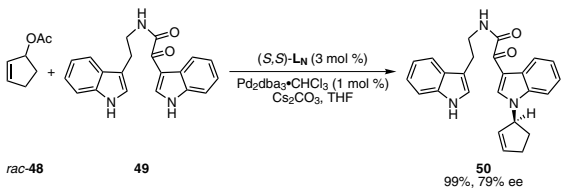
Ref. 33

Scheme 13. DYKAT with Carbonate **42**.



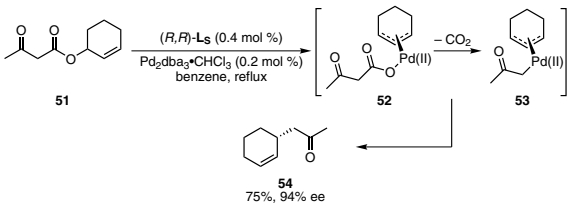
Ref. 35

Scheme 14. Intramolecular Asymmetric Cyclization of Racemic Carbonate **46**.



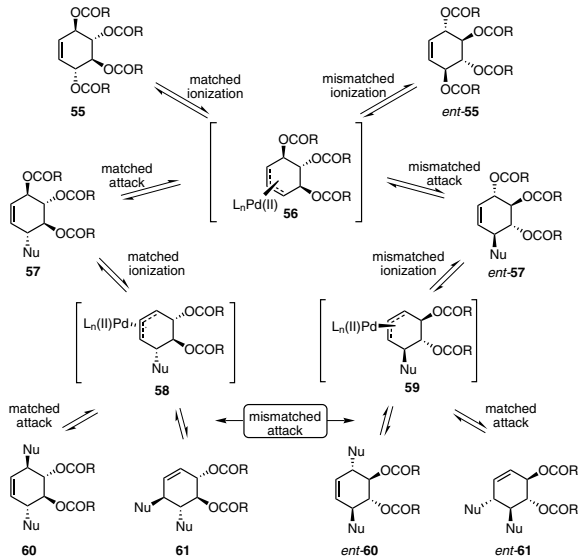
Ref. 36

eq 7



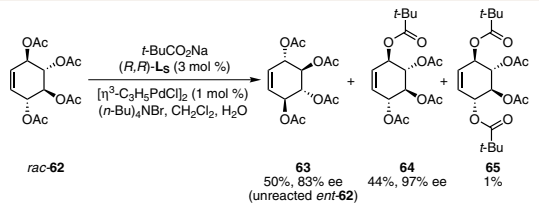
Ref. 37

eq 8



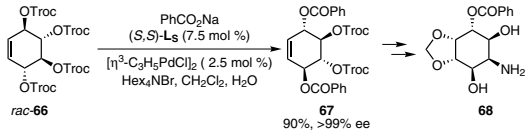
Ref. 39

Scheme 15. DYKAT Mechanism with Conduritol B Substrates.



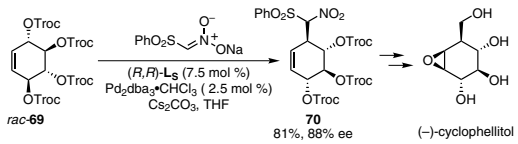
Ref. 40

eq 9



Ref. 39,41

Scheme 16. DYKAT of Conduritol B Tetracarbonate (**66**).



Ref. 42

Scheme 17. DYKAT of Conduritol B with Sulfonylnitromethane.

enabled complete consumption of the mismatched enantiomer and ultimately good enantioselectivity for the dynamic kinetic asymmetric di(allylic substitution) (**Scheme 16**).[39] The four stereocenters in aminocyclohexitol **68** of hygromycin A were efficiently established by use of this DYKAT.[41]

The choice of nucleophile offers control for either mono- or polyalkylation. Soft nucleophiles such as Meldrum's acid, (phenylsulfonyl)nitromethane, and phthalimide afford monoalkylation with good enantioselectivity. Notably, these monoalkylations demonstrate how, under the appropriate conditions, the mismatched ionization of the substrate can successfully compete with the matched ionization of the monoalkylated product. The sulfonylnitromethane DYKAT product has been applied to the efficient synthesis of the HIV inhibitor (–)-cyclophellitol (**Scheme 17**).[42]

3. DYKAT through Enolization of the Nucleophile

Palladium-catalyzed AAAs have demonstrated a unique ability to not only afford enantiodiscrimination of the π-allyl electrophile, but also to effectively differentiate the enantiotopic faces of a nucleophile. This property opened a new avenue for palladium-catalyzed DYKATs (**Scheme 18**). For this type of transformation, the racemic nucleophile is enolized into the active achiral enolate, wherein asymmetric induction results from the catalyst discriminating between the enantiotopic faces of the enolate. Due to the conversion of the racemic substrate into the prochiral nucleophile occurring without involvement of the chiral catalyst, the rate of the enolization for both enantiomers should be identical and circumvent any possible memory effect. Asymmetric alkylations of racemic enolizable nucleophiles are typically not considered DYKATs. However, a DYKAT occurs when both enantiomers of the substrate are converted into one enantiomer of the product with a theoretical yield of 100%. If one considers the overall alkylation of a racemic nucleophile, reactions wherein the nucleophile is converted into a prochiral enolate or intermediate even in a previous transformation are technically DYKATs.

3.1. Stabilized Enolates

The most common palladium-catalyzed AAA wherein chirality is established at the nucleophile is with substrates that afford a stabilized prochiral enolate. Because of this stabilization, only mild conditions are necessary to generate the active nucleophile. In the palladium-catalyzed AAA, the chiral ligand is positioned on the side of the metal opposite the allyl ligand in a square-planar geometry. The low-to-moderate enantioselectivities observed with typical chiral bidentate ligands (such as DIOP and the P–N oxazolidinone)[43] have been attributed to the distant chiral environment not effectively differentiating between the enantiotopic faces of the nucleophile. In an effort to extend the chiral environment to the nucleophile, several groups developed a series of chiral ferrocenylphosphine ligands, which incorporate a tethered functional group, to interact with the nucleophile and enhance the interaction between the nucleophile and ligand.[44] In contrast, the DPPBA ligands have shown excellent asymmetric induction for the creation of chirality at the nucleophile without the requirement of an appendant functional group. For example, the asymmetric allylation of β-keto ester **71** proceeded in high yield and enantioselectivity with use of the non-ionic base *N,N,N',N'*-tetramethylguanidine (TMG) (**Scheme 19**).[45] The utility of this alkylation was demonstrated in the synthesis of nitramine, a biologically active spiro alkaloid. With a racemic electrophile, the reaction achieved excellent diastereoselectivity, again demonstrating the catalyst's ability to simultaneously discriminate the enantiotopic faces of the nucleophile and termini of the electrophile (**eq 10**).[45]

The chiral 3-substituted indoline and *3H*-indole structural motifs are present in numerous biologically active compounds. Asymmetric allylic alkylations of racemic oxindoles provide a valuable and efficient entry into the preparation of these important heterocycles. Because of the aromatic stabilization obtained through enolization of oxindoles, only mild conditions are necessary to generate the required nucleophile in situ. The DYKAT of 3-aryloxindoles proceeded in high enantioselectivity for the preparation of a quaternary stereocenter without the addition of a base (**eq 11**).[46] Since the catalyst must discriminate between the enantiotopic faces of the nucleophile, the enantioselectivity showed a moderate dependence upon the substrate substitution. The highest enantioselectivity, 97%, was achieved with a 3-(ortho-substituted)aryl group.

3.2. Nonstabilized Enolates

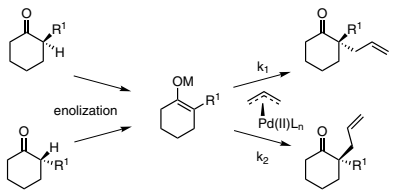
The asymmetric allylic alkylations of nonstabilized enolates have also been successful. These examples demonstrate how high asymmetric induction can also be achieved by stoichiometrically converting the ketone into the enolate or enol ether prior to alkylation. Using the standard ligand, lithium enolate, and a tin additive, the allylic alkylation of 2-methyl-1-tetralone proceeded with high enantioselectivity (**eq 12**).[47] The extent of the nucleophile aggregation showed a significant effect upon the enantioselectivity, and optimal results were obtained with two equivalents of the amide base.[48] While addition of a trialkyltin chloride gave the highest ee, only a very small loss (a few percent) in ee occurred in its absence. A related enolate-structure effect on both diastereoselectivity and enantioselectivity was observed by Braun and co-workers with BINAP ligands.[47b–d] The asymmetric induction observed with these harder nucleophiles is consistent with an intermolecular alkylation, in which alkylation occurs on the face of the allyl moiety opposite the metal, in analogy to AAA with typical soft nucleophiles. The products of this methodology have had broad synthetic applications. One particular example involves the AAA of cyclopentanone **81**, which efficiently establishes the absolute stereochemistry for the syntheses of hamigeran B[48] and allocyathin B_2 (**Scheme 20**).[49]

Modifying the arms of the standard ligand with ferrocenyl complexes has also enabled high enantioselectivity, 95% ee, in the AAA of the tetralone substrate **78** (**eq 13**).[50]

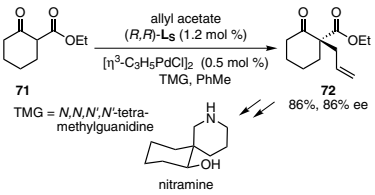
One of the main limitations of the above methodologies is enolate equilibration. Accordingly, the above examples utilize ketone substrates that afford only one possible enolate intermediate. An effective solution is the regio- and enantioselective allylic alkylation of unsymmetrically substituted ketones by use of their allyl enol carbonate derivatives. The reaction proceeds after ionization of the allylic ester through a palladium-promoted decarboxylation[38] to the enolate nucleophile. Use of the anthracene ligand, $\mathbf{L_A}$, has enabled high enantioselectivity for the formal DYKAT of racemic 2-methylcyclohexanone (**eq 14**).[51] Due to the neutral conditions employed in the reaction, the alkylation efficiently establishes tertiary stereocenters in both cyclic and acyclic substrates without racemization of the product (**Scheme 21**).[52] The synthetic utility of the process was demonstrated by application to the AAA/Stork–Danheiser addition sequence for the formation of chiral γ,γ-disubstituted cycloalkenones (**Scheme 22**).[53]

3.3. Azlactones

The asymmetric allylic alkylation of azlactones offers an efficient process for the preparation of quaternary amino acids, a structural moiety present in numerous biologically significant molecules. The azlactones provide sufficient stabilization so that enolization can be conducted in situ. Asymmetric prenylation of azlactone **94** with the standard ligand, $\mathbf{L_S}$, proceeded in moderate yield and excellent enantiomeric excess

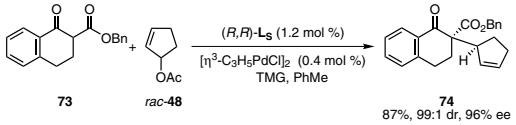


Scheme 18. DYKAT through Enolization of the Nucleophile.



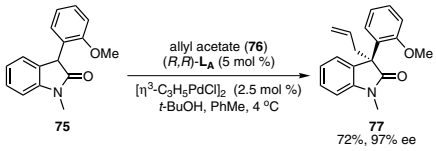
Ref. 45

Scheme 19. Asymmetric Allylic Alkylation of β-Keto Esters with the Standard Ligand.



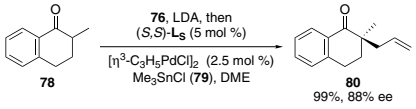
Ref. 45

eq 10



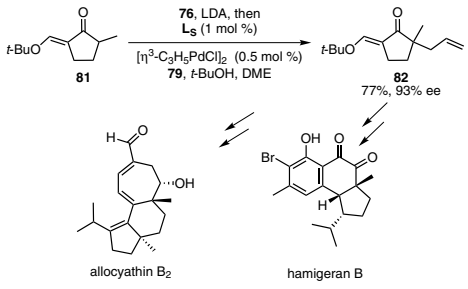
Ref. 46

eq 11



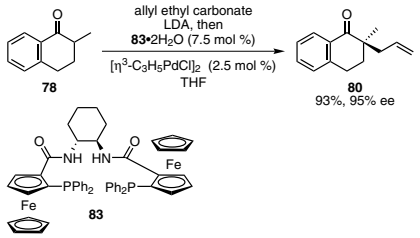
Ref. 47

eq 12



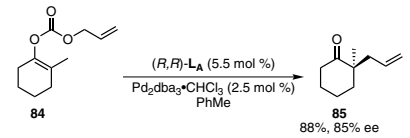
Ref. 48,49

Scheme 20. Application of the Dynamic Kinetic AAA of Nonstabilized Enolates to the Total Synthesis of Hamigeran B and Allocyathin B_2.



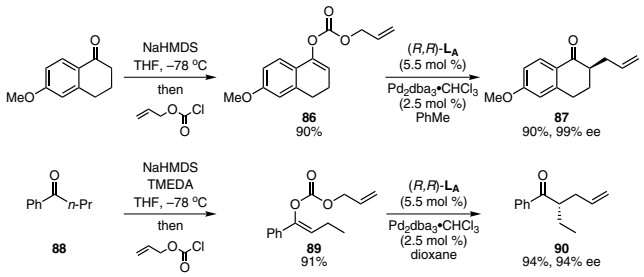
Ref. 50

eq 13



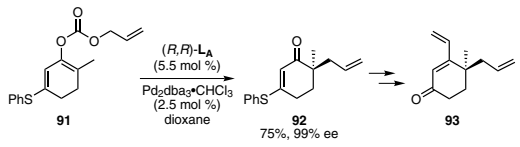
Ref. 51

eq 14



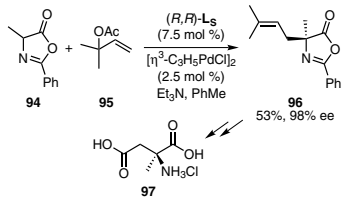
Ref. 51,52

Scheme 21. Formation of Tertiary Stereocenters by the Dynamic Kinetic AAA of Allyl Enol Carbonates.



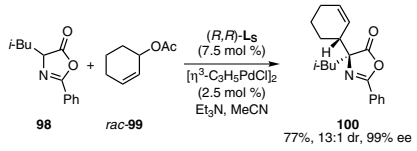
Ref. 53

Scheme 22. The Stork–Danheiser Application of DYKAT with Allyl Enol Carbonates.



Ref. 54

Scheme 23. Asymmetric Allylic Alkylation (AAA) with Azlactones.



Ref. 55

eq 15

(**Scheme 23**).[54] The chiral product, **96**, served as a useful substrate for the preparation of α-methylaspartic acid (**97**). As demonstrated in several previous examples, the chiral catalyst can simultaneously discriminate between the enantiotopic faces of the nucleophile and enantiotopic termini of the racemic electrophile. This asymmetric transformation afforded good diastereoselectivity and high ee with the racemic acetate **99** (**eq 15**).[55] The palladium-catalyzed AAA has also efficiently discriminated between enantiotopic geminal leaving groups.[56] Extension of the methodology with azlactones to geminal acetate **101** provided a useful process for the preparation of chiral vicinal amino alcohols and an efficient entry into the total synthesis of sphingofungins E and F (**Scheme 24**).[57]

4. DYKAT through Rapid π–σ–π Interconversion of Intermediates

Another effective process for a palladium-catalyzed dynamic kinetic AAA relies on the rapid interfacial exchange of the allyl ligand through a π–σ–π interconversion. Oxidative addition with inversion of each substrate enantiomer initially forms two diastereomeric π-allylPd(II) intermediates (**Scheme 25**).[2,3,4] With a chiral catalyst, a rate difference in the oxidative addition is expected, and a DYKAT occurs with complete consumption of the mismatched substrate. Asymmetric induction results from the preferential alkylation of one diastereomeric intermediate over the other. Accordingly, high enantioselectivity is achieved when, in addition to a selective alkylation ($k_1 >> k_2$), a Curtin–Hammett condition is established wherein interconversion is rapid and successfully competes with nucleophilic addition. Another requirement for this type of DYKAT is the existence of identical geminal substituents on one side of the allyl ligand. If one terminus of the allyl ligand is substituted with different geminal groups, then the π–σ–π interconversion will result in a geometrical isomerization of the allyl ligand. These π-allylPd(II) intermediates cannot "racemize" through a π–σ–π mechanism (**Scheme 26**). Further complicating the alkylation with unsymmetrical substrates is alkylation at the different termini, which leads to regioisomers (**Scheme 27**). Regioselectivity in the AAA has been achieved by both substrate and catalyst control. Although the chiral catalyst provides a significant preference for a regioselective alkylation of one diastereomeric intermediate, optimization of the reaction conditions is often necessary to establish the Curtin–Hammett situation for asymmetric induction.

4.1. Vinyl Epoxides and Aziridines as Substrates

A versatile substrate for the palladium-catalyzed dynamic kinetic AAA is vinyl epoxide, which, due to the ring strain, promotes the oxidative addition and consumption of the mismatched enantiomer required for a DYKAT. Suitable vinyl epoxides have geminal hydrogens or other identical geminal substituents on the olefin terminus, enabling a Curtin–Hammett condition to be established through a rapid π–σ–π interconversion. In the π-allylPd(II) intermediates, the alcohol or alkoxide can direct the alkylation for the branched product typically through hydrogen bonding or other covalent interaction with the incoming nucleophile (**eq 16**).

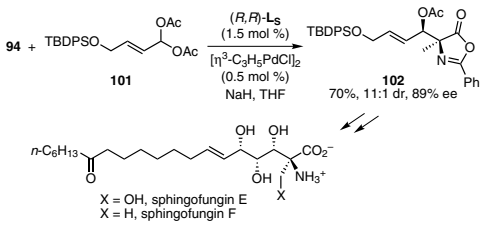
Although BINAP-based ligands have been examined for the DYKAT of vinyl epoxides,[58] high enantioselectivities for the intermolecular addition of nucleophiles to vinyl epoxides typically required the use of the DPPBA ligands. These reactions allowed the use of a broad range of nucleophiles and enabled application of this approach to numerous total syntheses. The AAA with phthalimide[59] provided the corresponding vinylglycinol derivative in high enantio- and regioselectivity (**Scheme 28**).[60] Our initial proposal was that a hydrogen-bonding interaction between the alkoxide of the π-allylPd(II) intermediate and the nucleophile would direct

the alkylation. Reactions with triphenylphosphine still favored the branched product with a slightly lower regioselectivity (4:1 B/L). Without directing effects, the linear product is favored due to alkylation at the least sterically hindered position. Therefore, both the substrate and catalyst contribute to the high regioselectivity observed in the DYKAT. The vinylglycinol derivative obtained by this methodology provided a valuable synthetic building block for the preparation of several biologically significant compounds including ethambutol, vigabatrin,[61] DMDP, bulgecinine, and broussonetine G.[62]

Alcohols are typically poor nucleophiles for the alkylation of π-allylPd(II) complexes and, accordingly, require activation for reactivity. A useful strategy to activate the alcohol nucleophile and direct the alkylation is to employ a borane co-catalyst for the dynamic kinetic asymmetric additions to vinyl epoxides.[63] In this AAA, the alkoxide of the π-allylPd(II) intermediate coordinates to the boron to form an "ate" complex, thereby activating the alcohol for an intramolecular alkylation. The process gives the glycol in high yield with excellent enantio- and regioselectivity (**eq 17**).[63] This methodology is one of the most synthetically useful of the DYKATs, and has been applied to the asymmetric synthesis of nucleosides,[64] malyngolide,[65] tipranavir,[66] and intermediate **111** in the formal synthesis of LY 333531 (**Scheme 29**).[67]

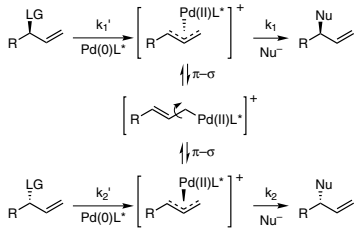
Carbonates are also effective nucleophiles with vinyl epoxides, providing an additional efficient synthesis of chiral vinylglycidols. Under biphasic conditions, the reaction of isoprene monoepoxide and bicarbonate affords the dioxolanone in 88% yield and 93% ee (**Scheme 30**).[28] The good yield and regioselectivity obtained are attributed to an intramolecular alkylation step. The alkoxide of the initial π-allylPd(II) intermediate is proposed to attack the in situ generated carbon dioxide to form **113**, which subsequently cyclizes to the dioxolanone. The high enantioselectivity results from a rapid π–σ–π equilibration occurring either prior to the addition to carbon dioxide and/or prior to the cyclization. Complementing this DYKAT, the use of a boron co-catalyst (Et_3B) and sodium carbonate as nucleophile allows for a direct alkylation with the carbonate nucleophile without cyclization to the dioxolanone. In this case, the intermediate carbonate, **115**, undergoes a facile in situ decarboxylation to vinylglycidol **116** in high yield and ee.

The asymmetric alkylation with stabilized carbon nucleophiles has shown high regio- and enantioselectivity in the DYKAT with isoprene monoepoxide. Under optimized conditions, the dynamic kinetic AAA of isoprene monoepoxide with β-keto esters affords good regioselectivity for the branched alkylation product and furnishes the corresponding tetrahydrofuran with high enantiomeric excess (**eq 18**).[68] The regioselectivity is lower in the absence of the fluoride additive, tetra-*n*-butylammonium triphenyldifluorosilicate (TBAT). This effect is attributed to an intermolecular alkylation, and formation of the linear product is due to the alkylation competing with the necessary π–σ–π interconversion. The asymmetric induction obtained in the allylic alkylations with the DPPBA ligands is rationalized by the preferential ionization and alkylation occurring under a flap in the "nun's hat" model.[69] The matched alkylation of the mismatched intermediate would favor the linear product, and the matched-intermediate matched alkylation would favor the branched product (**Scheme 31**). Halide additives increase the rate of the necessary interconversion,[70] and improve the regioselectivity by promoting the necessary Curtin–Hammett condition, thus allowing for the preferred matched alkylation of the matched intermediate. The utility of the methodology has been demonstrated by application to the synthesis of the highly substituted cyclopentyl core, **124**, of viridenomycin (**Scheme 32**).[71]



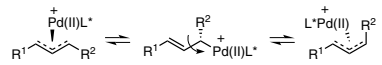
Ref. 57

Scheme 24. AAA of Allylic Geminal Acetates with Azlactones.

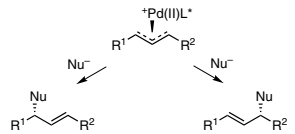


Ref. 2–4

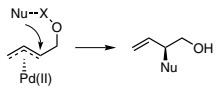
Scheme 25. DYKAT through a π–σ–π Interconversion.



Scheme 26. π–σ–π Interconversion of 1,3-Disubstituted AllylPd(II) Complexes.

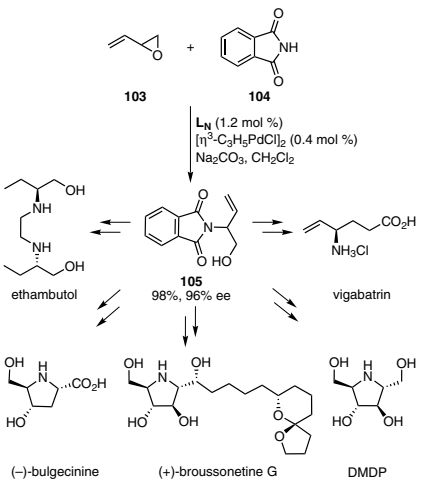


Scheme 27. Regioselective Alkylation of Unsymmetrical Allyl Complexes.



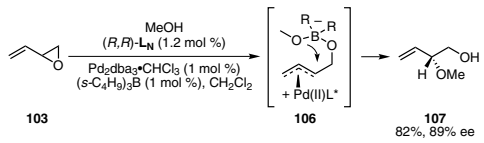
Ref. 55

eq 16



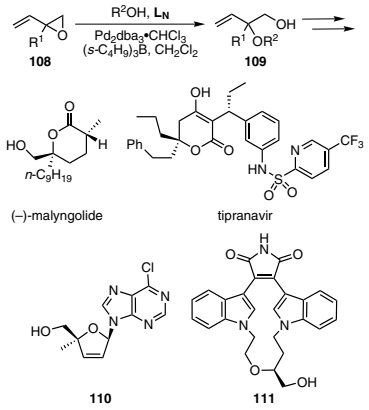
Ref. 60–62

Scheme 28. Dynamic Kinetic AAA of Vinyl Epoxide with Phthalimide.



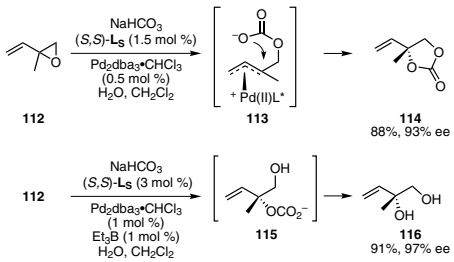
Ref. 63

eq 17



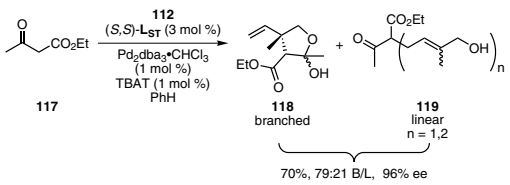
Ref. 64–67

Scheme 29. Synthetic Applications of the Asymmetric Addition of Alcohols to Vinyl Epoxides.



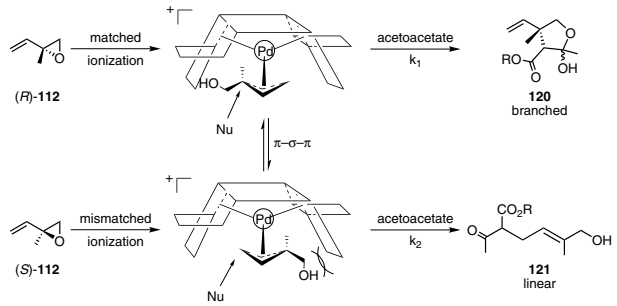
Ref. 28

Scheme 30. Dynamic Kinetic AAA of Isoprene Monoepoxide with Bicarbonate.



Ref. 68

eq 18



Ref. 68b,69

Scheme 31. Rationalization of the Regioselectivity in the Alkylation with the DPPBA Ligands.

2-Vinylaziridines are also competent substrates for the dynamic kinetic asymmetric cycloaddition with isocyanates to furnish synthetically useful chiral imidazolidinones (**Scheme 33**).[72] In this example, the use of acetic acid as a co-catalyst significantly improves the enantioselectivity. This effect is rationalized by protonation of the nitrogen tethered to the π-allylPd(II) intermediate and slowing of the acylation by the isocyanate, thereby allowing the necessary π–σ–π interconversion to effectively compete with product formation. The chiral vicinal diamine moiety is present in numerous biologically important natural products,[73] and the utility of this methodology has been demonstrated by application to the concise total synthesis of pseudodistomin D.[74]

4.2. Baylis–Hillman Adducts as Substrates

A synthetically useful substrate for the dynamic kinetic AAA is a Baylis–Hillman adduct. Similar to the DYKAT of vinyl epoxides, asymmetric induction results in this case from the kinetic alkylation of one diastereomeric π-allylPd(II) intermediate in a mixture of rapidly interconverting complexes through a π–σ–π mechanism (**Scheme 34**).[75] In a typical AAA, the syn pathway is normally strongly preferred.[7] However, in the DYKAT with Baylis–Hillman adducts, the presence of a substituent at the 2 position of the allyl ligand increases the importance of the anti pathway. For high asymmetric induction and regioselectivity, the catalyst must discriminate between the termini of the allyl ligand and afford a selective alkylation of a specific geometrical isomer of the intermediate.

The dynamic kinetic AAA of Baylis–Hillman adducts with alcohol nucleophiles provides a useful strategy for the formal deracemization of the readily available substrates. Under optimized conditions, high enantioselectivies are obtained in the DYKAT of both 2-cyano- and 2-carboethoxy-substituted adducts (**Scheme 35**).[76] An examination of the minor, linear products provides an indication of the preferred allyl geometry of the intermediates. Exclusive *Z* double-bond geometry of the minor, linear product was observed from the cyano substrate **127**, and exclusive *E* geometry was obtained for the linear product from the ester substrate **131**. This change in allyl conformation was rationalized by steric interactions within the π-allylPd(II) intermediates. For the cyano substrate, the preferred allyl complexes are syn due to minimization of the typical $A^{1,3}$ strain associated with allyl ligands. In the ester substrate, the larger ester group increases the unfavorable 1,2 repulsion and overrides the $A^{1,3}$ strain to favor the anti allyl intermediates. Additionally, similar effects have been observed with the respective linear achiral substrates to support the conclusion that the strong preference for either the syn or anti pathway is dependent on the substituent in the 2 position of the allyl intermediate. According to the above mechanism, intermediates **A** and **D** (see Scheme 34) should favor different product enantiomers, contrary to the asymmetric induction observed. However, further stereochemical analysis with other substrates has revealed that the ester and cyano substrates prefer different cants of the π-allylPd(II) intermediates. Opposite cants or allyl geometries of the π-allylPd(II) intermediate invert the sense of asymmetric induction to generate opposite enantiomers of the product. The ester substrate favors the anti allyl complex with a forward cant, and the cyano substrate furnishes the syn allyl intermediate with the typical backwards cant. Both of these intermediates, therefore, favor the same enantiomer of the product. In addition to establishing the necessary Curtin–Hammett condition, the DYKAT with Baylis–Hillman adducts affords remarkable selectivity for specific conformations of the π-allylPd(II) intermediates, and results in high enantioselectivities for the alkylation. Overall, only preliminary studies on the substrate and nucleophiles have been reported.

The synthetic utility of the DYKAT with Baylis–Hillman adducts was demonstrated by application to the total syntheses of furaquinocin E[77] and hippospongic acid A (**Scheme 36**).[76] With the long chain present in the hippospongic acid substrate, full conversion was inhibited. Thus, the observed ee evolves from a combination of a kinetic resolution and a DYKAT associated with the large chain inhibiting the ionization. Accordingly, the DYKAT with the smaller substrate **136** proceeded in high yield and enantioselectivity.

4.3. Acyloxyenoates as Substrates

For typical DYKATs with a π–σ–π mechanism, one terminus of the allyl intermediate must be substituted with identical groups. However, in acyloxyenoates that do not abide by the above requirement, high enantioselectivities have been achieved through an alternative equilibration process. In this case, asymmetric induction is due to a rapid π–σ–π interconversion, wherein equilibration between the enantiotopic faces occurs through an achiral *O*-palladium(II) enolate (**Scheme 37**).[78] High enantiomeric excess was achieved with phenol-based nucleophiles (**eq 19**), and a halide additive showed a significant effect on the asymmetric induction. During optimization studies with Cs_2CO_3, an ee of 24% was obtained without tetrabutylammonium chloride (TBACl), and increased to 75% with 30 mol % of TBACl. This effect was attributed to the halide additive increasing the rate of the π–σ–π interconversion to promote the necessary Curtin–Hammett condition.[3,4,70] Slowing the alkylation rate by removing the base further increased the ee to 84% (74% yield). The methodology efficiently provided the absolute stereochemistry for the total syntheses of (+)-aflatoxin B_1[79] and (+)-brefeldin A (**Scheme 38**).[80] As demonstrated by these examples, the ee for the DYKAT surpassed 95% by utilizing a naphthol or highly substituted phenol nucleophile.

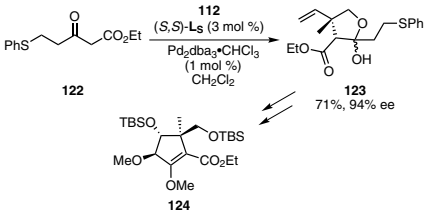
In addition to the cyclic γ-butenolide substrates, high enantioselectivities have also been achieved in an efficient AAA that results in the deracemization of acyclic acyloxyenoates and related electrophiles (**eq 20**).[29] Asymmetric induction for these acyclic substrates presumably results from an analogous π–σ–π interconversion with a prochiral Pd(II) intermediate.

4.4. Allenes as Substrates

In addition to the previous transformations wherein a stereogenic center is created, palladium-catalyzed dynamic kinetic AAAs of racemic allenes have shown high asymmetric induction for the establishment of axial chirality. In this mechanism, the Curtin–Hammett condition results from a rapid π–σ–π interconversion through a vinylPd(II) intermediate (**Scheme 39**).[81] Using the standard ligand, $\mathbf{L_S}$, high enantioselectivities and yields were obtained for the dynamic kinetic asymmetric addition of malonates and amines to racemic 2,3-alkadienyl acetates **(Scheme 40)**.[82] Similarly to the addition of malonate nucleophiles to cyclic and acyclic substrates (vida supra), the countercation of the nucleophile or base had a pronounced effect on the asymmetric induction for both types of nucleophiles. However, the observed pattern, wherein different countercations were necessary for optimal enantioselectivity, lithium with malonates and cesium with amines, is not consistent with the previously observed countercation effects (vide supra). A detailed rationalization for this discrepancy has yet to be formulated. The malonate products with a tethered diene functionality were applied to a Rh(I)-catalyzed [4 + 2] cycloaddition, in which the axial chirality was efficiently transferred to multiple stereogenic centers and exocyclic olefin geometry.

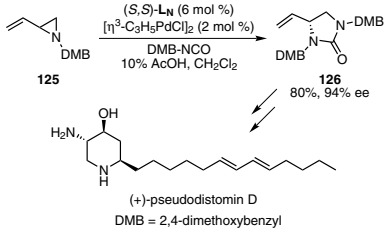
5. Other DYKAT Processes

Several DYKATs have been reported wherein the asymmetric induction cannot be rationalized by the previously described



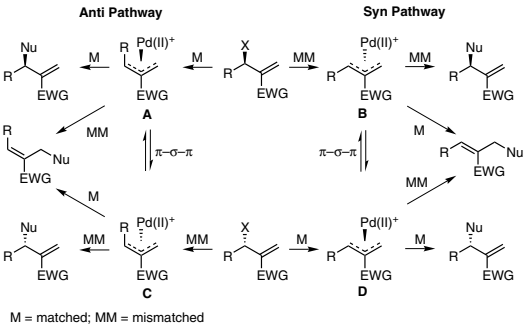
Ref. 71

Scheme 32. Application of the DYKAT of Isoprene Monoepoxide with β-Keto Esters to the Synthesis of the Cyclopentyl Core of Viridenomycin.



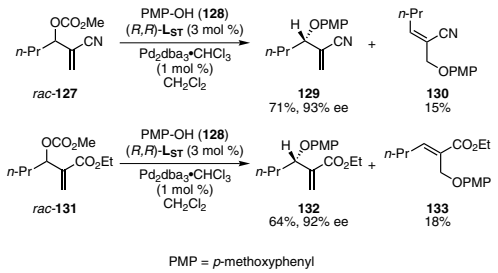
Ref. 72,74

Scheme 33. Dynamic Kinetic Asymmetric Cycloaddition of 2-Vinylaziridines with Isocyanates.



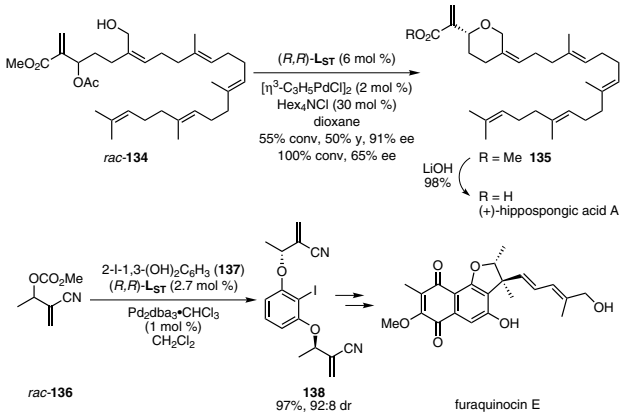
Ref. 75

Scheme 34. π–σ–π Interconversion of Baylis–Hillman Adducts.



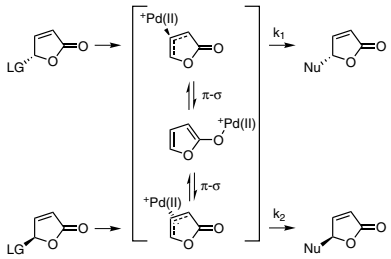
Ref. 76

Scheme 35. DYKAT of Baylis–Hillman Adducts.



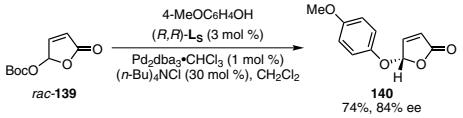
Ref. 76,77

Scheme 36. Synthetic Applications of the DYKAT of Baylis–Hillman Adducts.



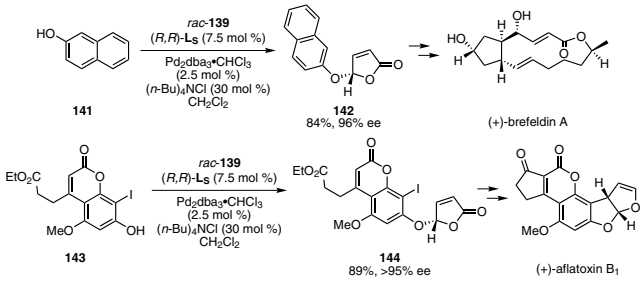
Ref. 78

Scheme 37. DYKAT Mechanism for γ-Butenolides.



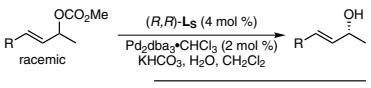
Ref. 78

eq 19



Ref. 79,80

Scheme 38. Synthetic Applications of the DYKAT with γ-Butenolides.



SM	R	Prd	Yield	ee
145	EtO_2C	**146**	87%	99%
147	PhO_2S	**148**	87%	93%
149	CN	**150**	87%	61%
151	$(MeO)_2(O)P$	**152**	83%	69%

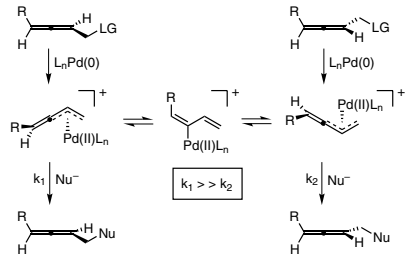
Ref. 29b

eq 20

mechanisms. Furthermore, the mechanisms that afford the observed enantioselectivities for these substrates may also be operating in the previously described reactions and contributing to the previously observed high levels of enantioselectivity in these cases too. Hoberg and co-workers[83] and Gais and co-workers[29] reported high ee's for the DYKAT of unsymmetrical acyclic substrates with the standard $\mathbf{L_S}$ and BINAP ligands (**Scheme 41**). Due to the unsymmetrical nature of the electrophile, which affords an allyl intermediate with different geminal groups on both termini of the ligand, the DYKAT cannot proceed through the previously described meso intermediate or π–σ–π mechanism. Other processes such as interfacial exchange through anti addition via a second equivalent of the Pd(0) catalyst[84] and racemization of the substrate may account for the asymmetric induction. Another possibility is that either the ionization of the carbonate or nucleophilic attack proceeds with retention in the so-called mismatched situation for an overall inversion mechanism.[85] Interestingly, only the carbonate substrates have afforded a DYKAT, while acetate substrates have furnished a selective KR.

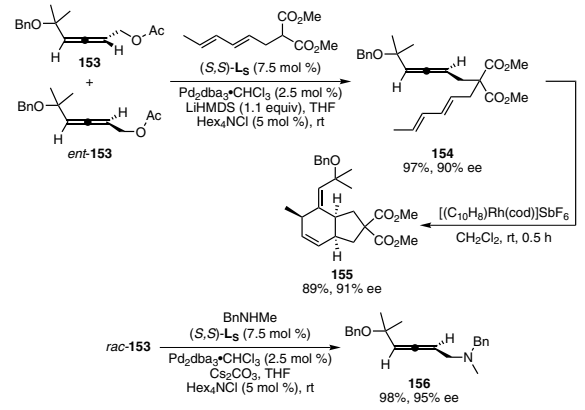
6. Conclusions and Outlook

In conclusion, the palladium-catalyzed dynamic kinetic asymmetric allylic alkylation with the DPPBA ligands is a versatile and



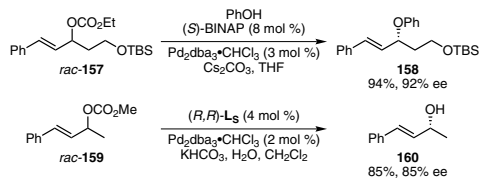
Ref. 81

Scheme 39. DYKAT Mechanism for Allenes.



Ref. 82

Scheme 40. DYKAT of Allenes.



Ref. 29b,83

Scheme 41. DYKAT of Unsymmetrical Acyclic Substrates.

synthetically useful technology. Currently, the predominant DYKAT processes for asymmetric induction are (i) discrimination of enantiotopic termini of a π-allylpalladium intermediate, (ii) discrimination of enantiotopic faces of a meso or prochiral intermediate, and (iii) kinetic alkylation of one diastereomeric intermediate of rapidly interconverting π-allylPd(II) complexes. Additionally, DYKAT has been accomplished with several substrates wherein the reaction proceeds through alternative processes. These alternative mechanisms may also be operating in the other DYKATs and contribute to the high enantioselectivities observed. As demonstrated, a wide variety of substrates and nucleophiles are tolerated in DYKAT, and have provided chiral building blocks for the synthesis of numerous complex natural compounds, validating the versatility and flexibility of the methodology. Further development is necessary to broaden the nucleophile and substrate scopes. Furthermore, mechanistic studies are required to further elucidate the sense of asymmetric induction observed in most reactions and, accordingly, unravel the full potential of this synthetically enabling methodology.

7. Acknowledgment

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About the Authors

Barry M. Trost was born in 1941 in Philadelphia, Pennsylvania, where he began his university training at the University of Pennsylvania (B.A., 1962). He obtained a Ph.D. degree in chemistry just three years later at the Massachusetts Institute of Technology (1965). He then moved to the University of Wisconsin-Madison, where he was promoted to Professor of Chemistry in 1969 and, in 1982, became the Vilas Research Professor. In 1987, he joined the faculty at Stanford University as Professor of Chemistry, and became the Tamaki Professor of Humanities and Sciences in 1990. In addition, he has been Visiting Professor of Chemistry in Germany (Universities of Marburg, Hamburg, and Munich), Denmark (University of Copenhagen), France (Universities of Paris VI and Paris-Sud), Italy (University of Pisa), and Spain (University of Barcelona). In 1994, he was presented with a *Docteur Honoris Causa* of the Université Claude-Bernard (Lyon I, France) and, in 1997, a *Doctor Scientiarum Honoris Causa* of the Technion, Haifa, Israel. In 2006, he was appointed Honorary Professor of the Shanghai Institute of Organic Chemistry.

Professor Trost's work has been characterized by a very high order of imagination, innovation, and scholarship. He has ranged over the entire field of organic synthesis, particularly emphasizing extraordinarily novel methodologies. In recognition of his many contributions, Professor Trost has received a number of awards, including the ACS Award in Pure Chemistry (1977), the ACS Award for Creative Work in Synthetic Organic Chemistry (1981), the Baekeland Award (1981), the Arthur C. Cope Scholar Award (1989), the Guenther Award in the Chemistry of Essential Oils and Related Products (1990), the Dr. Paul Janssen Prize (1990), the ASSU Graduate Teaching Award (1991), the Bing Teaching Award (1993), the ACS Roger Adams Award (1995), the Presidential Green Chemistry Challenge Award (1998), the Herbert C. Brown Award for Creative Research in Synthetic Methods (1999), the Belgian Organic Synthesis Symposium Elsevier Award (2000), the Nichols Medal (2000), the Yamada Prize (2001), the ACS Nobel Laureate Signature Award for Graduate Education in Chemistry (2002), the ACS Cope Award (2004), and the John Scott Award of the city of Philadelphia (2004). Professor Trost has been elected a fellow of the American Academy of Sciences (1992) and a member of the National Academy of Sciences (1990). He has published two books and over 790 scientific articles.

Daniel R. Fandrick received his B.S. degree with a major in chemistry in 2001 from the University of California, San Diego. During his undergraduate studies under the guidance of Professor Joseph M. O'Connor, he contributed to the synthesis of a strained cyclic ferrocenyl enediyne complex. In 2006, he received his Ph.D. degree in organic chemistry at Stanford University under the supervision of Professor Barry M. Trost. His graduate studies focused on the development of several palladium-catalyzed dynamic kinetic asymmetric allylic alkylations and their applications in total synthesis. After graduation, he joined the chemical development group at Boehringer Ingelheim in Ridgefield, Connecticut.

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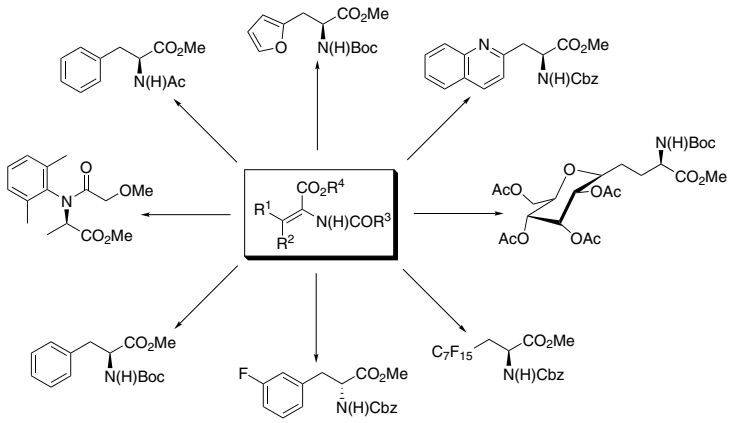

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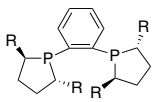
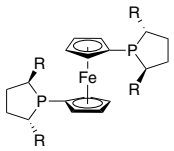


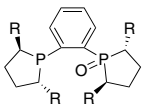
DuPhos

R	*R,R*	*S,S*
Methyl	665258	665266*
Ethyl	668494	668486*
Isopropyl	668524	668176*



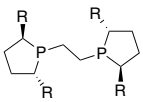
Ferrocelane™

R	*R,R*	*S,S*
Methyl	675601	675598*
Ethyl	680990	681008*
Isopropyl	684309	684406*



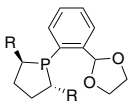
BozPhos

R	*R,R*	*S,S*
Methyl	678635	678562*



BPE

R	*R,R*	*S,S*
Methyl	665231	665207*
Ethyl	668478	668451*
Isopropyl	668443	668435*
Phenyl	667811	667854*



RajPhos™

R	*R,R*	*S,S*
Methyl	677043	677035*
Ethyl	677051	677078

DuPhos/BPE Ligands I Kit 687774

*Denotes Kit Components

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Reetz Diphosphonite Ligands

Reetz and co-workers developed a new generation of BINOL-derived diphosphonite ligands for the asymmetric hydrogenation of ketones and β-keto esters,[1,2] and the asymmetric conjugate addition of arylboronic acid derivatives to α,β-unsaturated carbonyls.[3] Used with a $RuCl_2(p\text{-cymene})_2$ complex, *(R,R)*-Reetz X-Diphosphonite converts a variety of ketones into secondary alcohols with yields and ee's up to 100% and 98% respectively.[1] Sigma-Aldrich exclusively offers this new family of ligands.

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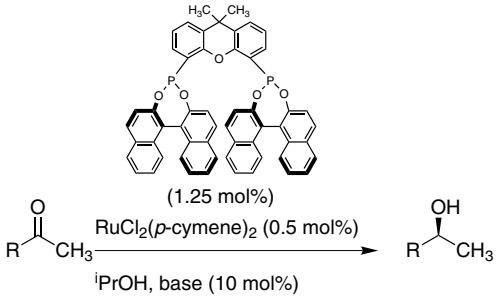
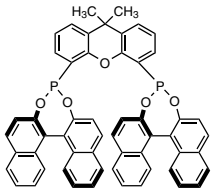
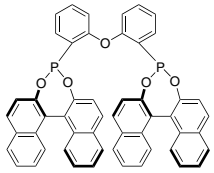


R	Yield (%)	ee (%)
Ph	93	98
m-$MeOC_6H_4$	91	93
m-BrC_6H_4	100	96
p-ClC_6H_4	96	96
p-BrC_6H_4	98	95



(R,R)-Reetz X-Diphosphonite
682977

(S,S)-Reetz X-Diphosphonite
682869



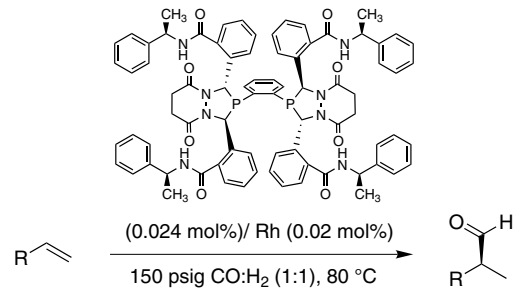
(R,R)-Reetz D-Diphosphonite
682993

(S,S)-Reetz D-Diphosphonite
682985

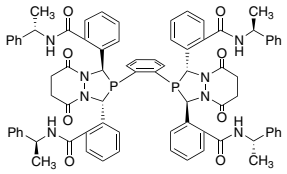
Landis Diazaphospholane Ligands

Recently, there has been an increased interest in the asymmetric hydroformylation reaction. This transformation gives access to versatile chiral building blocks that are of high interest to the pharmaceutical and fine chemicals industries. Landis and co-workers reported the synthesis of chiral diazaphospholane ligands for the asymmetric hydroformylation of a variety of terminal alkenes using a Rh catalyst. This new class of ligands has turnover frequencies of up to 9000 h^{-1} with 96% ee and 100% conversion.[1,2] Sigma-Aldrich is pleased to offer this new class of useful ligands.

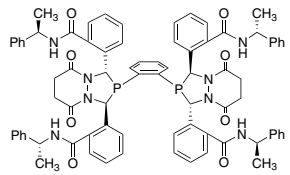
(1) Clark, T. P.; Landis, C. R. *J. Am. Chem. Soc.* **2003**, *125*, 11792. (2) Clark, T. P. et al. *J. Am. Chem. Soc.* **2005**, *127*, 5040.



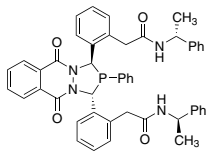
R	Yield (%)	ee (%)
Ph	100	82
CN	100	87
OAc	100	96



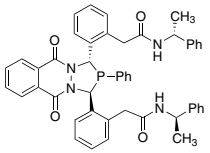
Bis[(*R,R,S*)-DiazaPhos-SPE]
685232



Bis[(*S,S,S*)-DiazaPhos-SPE]
685259



(*R,R,S*)-DiazaPhos-PPE
685089



(*S,S,S*)-DiazaPhos-PPE
685240

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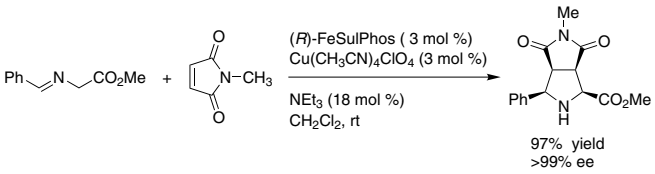
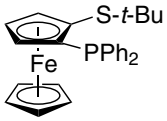
FeSulPhos Ligand for the Enantioselective 1,3-Dipolar Cycloaddition

The asymmetric 1,3-dipolar cycloaddition reaction is of the utmost importance for the enantioselective synthesis of five-membered-ring heterocycles. Cabrera et al. introduced a new family of ligands consisting of a planar-chiral P,S-ligand, named FeSulPhos, for the 1,3-dipolar cycloaddition of azomethine ylides. The catalytic reaction is carried out with the FeSulPhos ligand, a copper salt, and triethylamine in methylene chloride. This new catalytic system demonstrated complete enantiocontrol (ee >99%) with conversions up to 97%. Sigma-Aldrich is pleased to offer this new ligand for asymmetric synthesis.



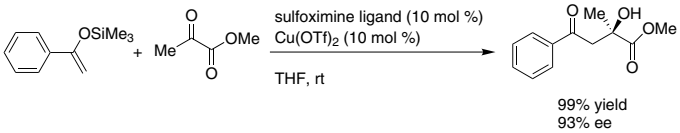
Reference: Cabrera, S. et al. *J. Am. Chem. Soc.* **2005**, *127*, 16394.



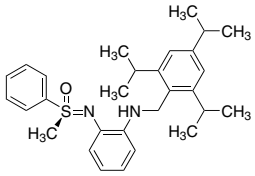
(R_p)-FeSulPhos
687561

Sulfoximine Ligands for Asymmetric Aldol Reactions

Chiral sulfoximine ligands have been studied for the past 15 years for use in catalytic asymmetric reactions. Bolm's group developed a new class of sulfoximine used with copper salts for asymmetric aldol reactions. Using these bidentate ligands, Bolm and co-workers reported up to 93% ee's and 99% yields for the Mukaiyama-type aldol reaction of 1-phenyl-1-(trimethylsilyloxy) ethane and methyl pyruvate. This new class of ligands is offered exclusively by Sigma-Aldrich.



Reference: Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482.

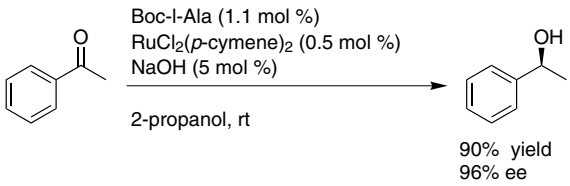


(*R*)-S-Methyl-S-phenyl-*N*-[2-(2,4,6-triisopropylbenzylamino)-phenyl]sulfoximine
669857

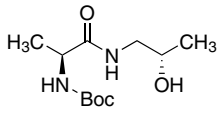
(*S*)-S-Methyl-S-phenyl-*N*-[2-(2,4,6-triisopropylbenzylamino)-phenyl]sulfoximine
669970

Boc-L-Ala Ligand for the Enantioselective Reduction of Ketones

Chemists extensively use the enantioselective reduction of ketones to secondary alcohols. This reaction gives access to important functionalities for the synthesis of natural products. Adolfsson and co-workers reported a novel class of ligands, based on pseudo-dipeptides, for the efficient reduction of ketones. The ligand is used with $RuCl_2(p\text{-cymene})_2$ in the presence of NaOH in 2-propanol. Yields of up to 90% with 96% ee have been reported. This new ligand is now part of the Sigma-Aldrich ligand library for asymmetric transformations.

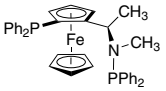


Reference: Bøgevig, A. et al. *Chem.—Eur. J.* **2004**, *10*, 294.



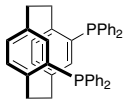
Boc-L-alanine (2*S*)-2-hydroxypropylamide
684414

BoPhoz and PhanePhos* for Asymmetric Hydrogenation



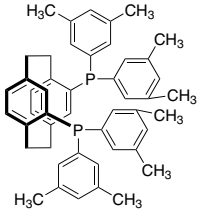
(*R*)-Methyl-BoPhoz
682322

(*S*)-Methyl-BoPhoz
682314



(*R*)-PhanePhos
682144

(*S*)-PhanePhos
682136

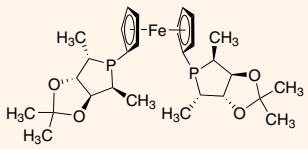


(*R*)-Xylyl-PhanePhos
682306

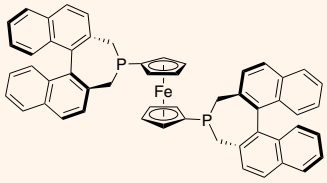
(*S*)-Xylyl-PhanePhos
682292

* Sold in collaboration with Johnson Matthey for research purposes only. US5874629 and any patents arising therefrom apply.

NEW *Chiral Quest* Ligands for Asymmetric Hydrogenation



(*S*)-Me-f-KetalPhos
685674

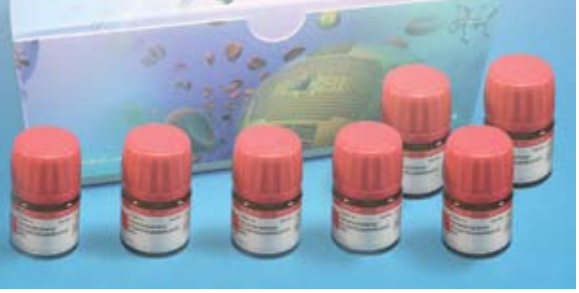


(*S,S*)-f-Binaphane
685925

Chiral Quest Ligands Kit*

Chiral Quest ligands are some of the most potent for asymmetric hydrogenation. This new kit includes 7 ligands with 100 mg of each for rapid screening of chiral catalysts. The *Chiral Quest* ligands Kit I includes (*R*)-C3-TunePhos, (*R*)-Binaphane, (*S,S′,R,R′*)-TangPhos, (*1R,1′R,2S,2′S*)-Duan-Phos, (*S*)-Binapine, (*S*)-Me-*f*-KetalPhos, and (*S,S*)-*f*-Binaphane.

* Sold in collaboration with *Chiral Quest* for research purposes only. U.S. Patent: 6,828,271; 6,525,210; and additional patents pending.



Development and Applications of C_2-Symmetric, Chiral, Phase-Transfer Catalysts

Professor Takashi Ooi

Professor Keiji Maruoka

Takashi Ooi[†] *and Keiji Maruoka**
Department of Chemistry
Graduate School of Science
Kyoto University
Sakyo, Kyoto 606-8502, Japan
Email: maruoka@kuchem.kyoto-u.ac.jp

Outline

1. Introduction

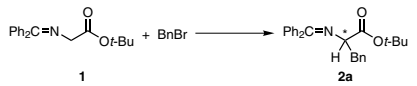
The evolution of phase-transfer catalysis (PTC) was led mainly by the demand from industry in the mid-1960s for a truly effective procedure for transferring hydrophilic anions to organic media. With its simple experimental operations, mild reaction conditions, inexpensive and environmentally benign reagents and solvents, and the possibility of conducting large-scale preparations, PTC has since been recognized as a versatile methodology for organic synthesis in both industrial and academic laboratories.[1] Asymmetric PTC, that is based on the use of structurally well-defined chiral, nonracemic catalysts, has become a topic of great scientific interest in the past two decades. Recent, enormous efforts have resulted in notable achievements, making it feasible to perform various bond-forming reactions under mild phase-transfer-catalyzed conditions.[2] This review will focus on recent advances in asymmetric reactions—which are enabled by C_2-symmetric, chiral, phase-transfer catalysts and reported between 2000 and 2006—and will showcase the variations in their designs and applications. Other asymmetric PTCs, with cinchona-alkaloid-derived, chiral quaternary ammonium salts and chiral crown ethers lacking C_2-symmetry, are not covered due to space limitation, and their relevant references are cited only in conjunction with related reactions. Other, excellent reviews on asymmetric phase-transfer catalysis have also been published.[2]

2. Alkylation

2.1. Asymmetric Synthesis of α-Amino Acids and Their Derivatives

2.1.1. Monoalkylation of Schiff Bases Derived from Glycine

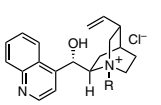
In 1989, the research group led by Martin O'Donnell successfully utilized chiral quaternary ammonium salts, prepared from naturally occurring alkaloids, for the asymmetric synthesis of α-amino acids by using glycinate Schiff base **1** as a key substrate (**eq 1**).[3] The asymmetric alkylation of **1** proceeded smoothly under mild phase-transfer conditions with *N*-(benzyl)cinchoninium chloride (**3a**) as catalyst to give the alkylation product (*R*)-**2a** in good yield and moderate enantioselectivity. This practical asymmetric alkylation procedure has been strengthened into an even more valuable protocol through the development of a new class of cinchona-alkaloid-derived catalysts bearing an *N*-anthracenylmethyl function. In 1997, Lygo's group designed *N*-anthracenylmethylammonium salts **3b** and **4a** and applied them to the asymmetric phase-transfer alkylation of **1** to synthesize α-amino acids with much higher enantioselectivities.[4] At the same time, Corey and co-workers prepared *O*-allyl-*N*-anthracenylmethyl cinchonidinium bromide (**4b**), and achieved high asymmetric induction in the enantioselective alkylation of **1** by the combined use of solid $CsOH•H_2O$ at very low temperature.[5] These reports helped generate a great deal of interest in asymmetric phase-transfer catalysis, and the enantioselective functionalization of **1**, particularly alkylation, has been extensively utilized as a benchmark reaction to evaluate the efficiencies of newly devised catalysts including C_2-symmetric ones.



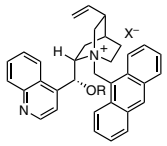
1 2a

Cat.[a]	Base	Solvent	Temp	Time	Yield	ee	Ref.
3a	50% NaOH (aq)	CH_2Cl_2	20 °C	9 h	75%	66% (*R*)	*3a*
3b	50% KOH (aq)	PhMe	20 °C	18 h	63%	89% (*R*)	*4a*
4a	50% KOH (aq)	PhMe	20 °C	18 h	68%	91% (*S*)	*4b*
4b	CsOH•H_2O	CH_2Cl_2	–78 °C	23 h	87%	94% (*S*)	*5*

[a] Catalyst loading = 10 mol %.

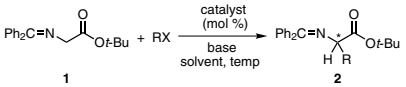


3a, R = Bn
3b, R = (9-anthracenyl)CH_2



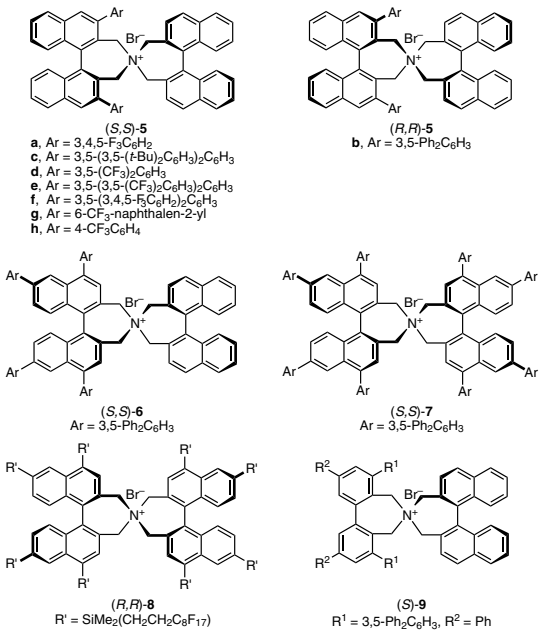
4a; X = Cl, R = H
4b; X = Br, R = allyl

eq 1



1 2

eq 2



(*S*,*S*)-**5**
a, Ar = 3,4,5-$F_3C_6H_2$
c, Ar = 3,5-(3,5-(*t*-Bu)$_2C_6H_3)_2C_6H_3$
d, Ar = 3,5-$(CF_3)_2C_6H_3$
e, Ar = 3,5-(3,5-$(CF_3)_2C_6H_3)_2C_6H_3$
f, Ar = 3,5-(3,4,5-$F_3C_6H_2)_2C_6H_3$
g, Ar = 6-CF_3-naphthalen-2-yl
h, Ar = 4-$CF_3C_6H_4$

(*R*,*F*)-**5**
b, Ar = 3,5-$Ph_2C_6H_3$

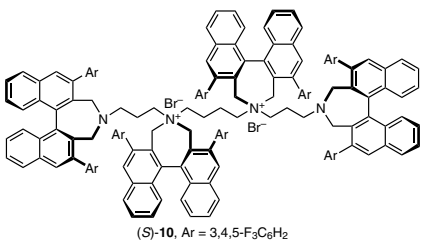
(*S*,*S*)-**6**
Ar = 3,5-$Ph_2C_6H_3$

(*S*,*S*)-**7**
Ar = 3,5-$Ph_2C_6H_3$

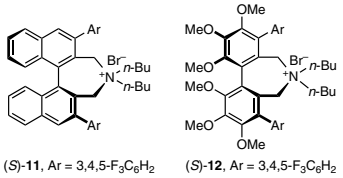
(*R*,*R*)-**8**
R' = $SiMe_2(CH_2CH_2C_8F_{17})$

(*S*)-**9**
R^1 = 3,5-$Ph_2C_6H_3$, R^2 = Ph

Figure 1. Chiral, C_2-Symmetric, Phase-Transfer Alkylation Catalysts.



(*S*)-**10**, Ar = 3,4,5-$F_3C_6H_2$



(*S*)-**11**, Ar = 3,4,5-$F_3C_6H_2$ (*S*)-**12**, Ar = 3,4,5-$F_3C_6H_2$

Figure 2. Chiral, C_2-Symmetric, Phase-Transfer Alkylation Catalysts.

In 1999, our group reported the structurally rigid, chiral quaternary ammonium salts of type **5a**—derived from commercially available (*S*)- or (*R*)-1,1'-bi-2-naphthol—as new C_2-symmetric, chiral, phase-transfer catalysts, which were successfully applied to the highly efficient, catalytic, and enantioselective alkylation of **1** under mild phase-transfer conditions (**eq 2, Figure s 1–2**, **Table 1**).[6] The aromatic substituents (Ar) at the 3 and 3' positions of one binaphthyl subunit of the catalyst had a significant effect on the enantiocontrolling ability of the catalyst, and **5a** was the catalyst of choice for the preparation of a variety of essentially enantiopure α-amino acids by this transformation.

To fully exploit the potential catalytic activity of chiral ammonium salts such as **5b**, binary phase-transfer catalysis—using an appropriate achiral co-catalyst—has been developed. For instance, the phase-transfer-catalyzed benzylation of **1** under the influence of (*R*,*R*)-**5b** (0.1 mol %) and 18-crown-6 (0.1 mol %) proceeded smoothly to furnish (*S*)-**2a** in 98% yield and 98% ee [4% yield (92% ee) without 18-crown-6 as co-catalyst].[7]

With the critical role of the 3,3'-diaryl substituents of **5** in mind, our group also examined the effect of the 4,4' and 6,6' substituents of one binaphthyl subunit on the stereoselectivity of the alkylation of **1** through the preparation of (*S*,*S*)-**6**.[8] We also assembled the symmetrical phase-transfer catalyst **7**, which exhibited high catalytic and chiral efficiencies.[9] The symmetrical structural motif in **7** led us to the development of fluorous, chiral, phase-transfer catalyst **8**. After the alkylation reaction, **8** was easily recovered by simple extraction with FC-72 (perfluorohexanes) as a fluorous solvent and was used for the next run without any loss of reactivity or selectivity.[10]

Although the conformationally rigid, N-spiro structure created by two chiral binaphthyl subunits represents a characteristic feature of **5** and related catalysts (such as **6**), it also imposes limitations on catalyst design due to the imperative use of the two different chiral binaphthyl moieties. Accordingly, our group developed the C_2-symmetric chiral quaternary ammonium bromide **9**, incorporating a conformationally flexible yet easily modifiable achiral biphenyl subunit, which exerted chiral efficiencies as high as those of a series of conformationally rigid homochiral catalysts.[11]

Our group also undertook efforts to substantially enhance the reactivity of N-spiro, chiral, quaternary ammonium salts and simplify their structures for the purpose of developing a truly practical method for the asymmetric synthesis of α-amino acids and their derivatives. Our initial attempt was to design polyamine-based chiral phase-transfer catalysts with the expectation of a multiplier effect of the attached chiral auxiliaries. Gratifyingly, catalyst (*S*)-**10**, bearing a 3,4,5-trifluorophenyl group at the 3 and 3' positions of the chiral binaphthyl moieties, gave rise to 95% ee.[12] This observation led to the discovery that chiral quaternary ammonium bromide (*S*)-**11**, possessing flexible straight-chain alkyl groups instead of rigid binaphthyl moieties, functions as an unusually active chiral phase-transfer catalyst.[13] The reaction of **1** with various alkyl halides proceeded smoothly and with excellent enantioselectivities under mild conditions in the presence of only 0.01–0.05 mol % of (*S*)-**11**. Furthermore, our group succeeded in assembling a highly reactive catalyst, (*S*)-**12**, from the readily available, gallic acid derived (*S*)-4,4',5,5',6,6'-hexamethoxybiphenyldicarboxylic acid.[14]

The usefulness of other chiral sources for the molecular design of C_2-symmetric phase-transfer catalysts has recently been demonstrated in quite an attractive manner (**Figure 3, Table 1**). In connection with the intensive investigation of the ability of chiral metal–salen complexes as chiral phase-transfer catalysts in the synthesis of α,α-dialkyl-α-amino acids from α-substituted α-amino

acids, Belokon's group reported on the effectiveness of **13** in the asymmetric monoalkylation of **1**.[15]

Nagasawa and co-workers reported a C_2-symmetric chiral cyclic guanidine of type **14** for the asymmetric alkylation of **1**.[16] The structurally related **15** was also evaluated as a chiral phase-transfer catalyst by Murphy and co-workers.[17]

Shibasaki's group designed a tartrate-derived bis(ammonium salt), **16**, based on the concept of two-center asymmetric catalysis, and systematically optimized the reaction parameters for achieving high enantioselectivity.[18] By combining a tartrate derivative and 2,5-dimethylpyrroline, MacFarland's group prepared diastereomeric bis(ammonium salts) **17**, and tested them as chiral phase-transfer catalysts.[19]

The structurally unique, spiro-type bis(ammonium salt) **18** was synthesized and successfully applied to similar asymmetric alkylations of **1** by Sasai and co-workers.[20] His group also prepared the chiral crown ether (*S*)-**19**, which gave rise to moderate enantioselectivity in the benzylation of **1** in the presence of KOH.[21]

The C_3-symmetric, amine-based, chiral phase-transfer catalyst **20** has been developed by Takabe's group.[22] The hydroxyl groups are expected to play an important role as hydrogen-bond donors in the formation of chiral ion pairs.

The development of C_2- and C_3-symmetric catalysts by using naturally occurring alkaloids as chiral units has also been pursued by several research groups (**Figure 4, Table 1**). The group of Jew and Park designed dimeric and trimeric cinchona-alkaloid-derived catalysts **21**,[23] **22**,[24] and **23**,[25] which substantially enhanced the enantioselectivity of the alkylation of **1** and expanded the scope of usable alkyl halides when compared to their monomeric counterparts. Moreover, the same workers investigated the ideal aromatic spacer for optimal dimeric catalysts and found that catalyst **24**, derived from 2,7-bis(bromomethyl)naphthalene and two cinchona alkaloid units, exhibited remarkable catalytic and chiral efficiencies.[26] Nájera's group also prepared a dimeric salt, **25**, which incorporates a dimethylanthracenyl bridge as a spacer.[27] In addition, Siva and Murugan utilized a cyclic tetraamine as a spacer for the assembly of **26**, which exhibited an extremely high performance as chiral phase-transfer catalyst.[28]

These developments, together with the emergence of other chiral phase-transfer catalysts,[29] have led to important, enantiomerically enriched α-amino acids and their derivatives being readily prepared by the asymmetric alkylation (**Figure 5**).[30–35] These α-amino acids and derivatives have been employed in the total synthesis of biologically active compounds.

2.1.2. Dialkylation of Schiff Bases Derived from α-Alkyl-α-amino Acids

Nonproteinogenic, chiral α,α-dialkyl-α-amino acids possessing stereochemically stable quaternary carbon centers have been significant synthetic targets, not only because they often are effective enzyme inhibitors, but also because they are indispensable for the elucidation of enzymatic mechanisms. Accordingly, numerous studies have been conducted to develop truly efficient methods for their preparation,[36] and phase-transfer catalysis has made unique contributions.

On the basis of O'Donnell's pioneering study of the asymmetric alkylation of the aldimine Schiff base derived from alanine under phase-transfer conditions,[37,38] Belokon et al. demonstrated that (*R,R*)-TADDOL (**28**)[39] and the copper(II)–salen complex, **13**,[15,40] were employable for the enantioselective alkylation of alanine-derived imines **27** and **29** (**Scheme 1**).

Our group developed a one-pot, highly enantioselective double alkylation of glycine-derived aldimine **30** by utilizing chiral quaternary ammonium bromide (*S,S*)-**5a** (**Scheme 2**).[41] This provides an attractive and powerful strategy for the asymmetric synthesis of structurally diverse α,α-dialkyl-α-amino acids.

Since the stereochemistry of the newly created quaternary carbon center was apparently determined in the second alkylation process, the core of this method should be applicable to the asymmetric alkylation of aldimine Schiff base **32** derived from the corresponding α-alkyl-α-amino acids. This approach was pursued by our group,[41] as well as Shibasaki's[18b] and Maeda's,[42] by using C_2-symmetric quaternary ammonium salts as catalysts (**Scheme 3**). *dl*-Alanine-, phenylalanine-, leucine-, and phenylglycine-derived imines **32a–d** were alkylated smoothly with (*S,S*)-**5a** and (*S,S*)-**16b** under similar conditions, affording the desired noncoded dialkylamino acid esters **31** with excellent asymmetric induction. This powerful quaternization method has also allowed the catalytic asymmetric synthesis of quaternary isoquinoline derivatives[30] and 4-hydroxy-2-phenylproline derivatives[42] from **32c**.

The efficient phase-transfer-catalyzed alkylation strategy that utilizes (*S,S*)-**5a** was successfully applied by Jew and Park's group to the asymmetric synthesis of α-alkylserines starting with phenyloxazoline derivative **33a**. The reaction is general and practical, and leads to a variety of optically active α-alkylserines after acidic hydrolysis (**Scheme 4**).[43]

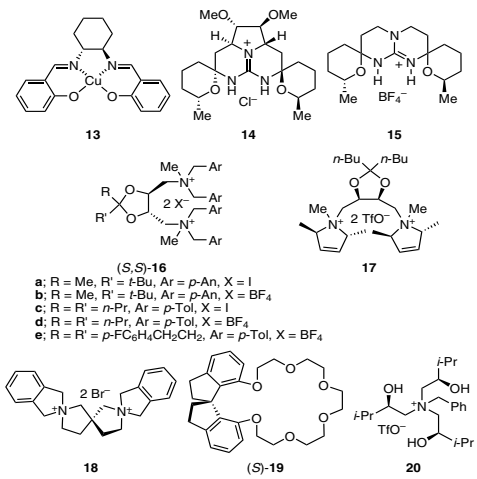


Figure 3. Chiral, C_2- and C_3-Symmetric, Phase-Transfer Alkylation Catalysts.

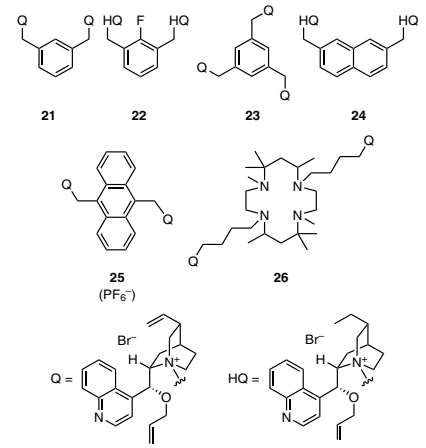


Figure 4. Chiral, C_2- and C_3-Symmetric, Phase-Transfer Alkylation Catalysts.

Table 1. Mild, Catalytic, and Enantioselective Phase-Transfer Alkylation of **1** as Depicted in Equation 2.

Catalyst	Cat. Mol %	RX	Base	Solvent	Temp	2			
						R/S	Yield	ee	*Ref.*
(S,S)-**5a**	1.0	BnBr	50% KOH(aq)	PhMe	0 °C	*R*	90%	99%	*6*
(S,S)-**5a**	1.0	C_3H_5Br	50% KOH(aq)	PhMe	0 °C	*R*	80%	99%	*6*
(S,S)-**5a**	1.0	EtI	CsOH(sat)	PhMe	–15 °C	*R*	89%	98%	*6*
(R,R)-**5b**[a]	0.1	BnBr	50% KOH(aq)	PhMe	0 °C	*S*	98%	98%	*7*
(R,R)-**5b**[a]	0.1	C_3H_5Br	50% KOH(aq)	PhMe	0 °C	*S*	87%	85%	*7*
(R,R)-**5b**[a]	0.5	EtI	50% KOH(aq)	PhMe	0 °C	*S*	63%	94%	*7*
(S,S)-**6**	1.0	BnBr	50% KOH(aq)	PhMe	0 °C	*R*	88%	96%	*8*
(S,S)-**6**	1.0	C_3H_5Br	50% KOH(aq)	PhMe	0 °C	*R*	92%	88%	*8*
(S,S)-**6**	1.0	EtI	50% KOH(aq)	PhMe	0 °C	*R*	18%	71%	*8*
(S,S)-**7**	1.0	BnBr	50% KOH(aq)	PhMe	0 °C	*R*	87%	97%	*9*
(S,S)-**7**	1.0	C_3H_5Br	50% KOH(aq)	PhMe	0 °C	*R*	76%	93%	*9*
(S,S)-**7**	1.0	EtI	50% KOH(aq)	PhMe	0 °C	*R*	12%	88%	*9*
(R,R)-**8**	3.0	BnBr	50% KOH(aq)	PhMe	0 °C	*S*	82%	90%	*10*
(R,R)-**8**	3.0	EtI	CsOH•H_2O	$PhCF_3$	–20 °C	*S*	83%	87%	*10*
(S)-**9**	1.0	BnBr	CsOH(sat)	PhMe	–15 °C	*R*	87%	94%	*11*
(S)-**9**	1.0	C_3H_5Br	CsOH(sat)	PhMe	–15 °C	*R*	85%	93%	*11*
(S)-**9**	1.0	EtI	CsOH(sat)	PhMe	–15 °C	*R*	61%	93%	*11*
(S)-**10**	3.0	BnBr	50% KOH(aq)	PhMe	0 °C	*S*	76%	63%	*12*
(S)-**11**	0.05	BnBr	50% KOH(aq)	PhMe	0 °C	*R*	98%	99%	*13*
(S)-**11**	0.05	C_3H_5Br	50% KOH(aq)	PhMe	0 °C	*R*	87%	98%	*13*
(S)-**11**	0.1	EtI	CsOH•H_2O	PhMe	–20 °C	*R*	67%	99%	*13*
(S)-**12**	0.1	BnBr	50% KOH(aq)	PhMe	25 °C	*R*	96%	97%	*14*
(S)-**12**	0.5	C_3H_5Br	50% KOH(aq)	PhMe	0 °C	*R*	99%	96%	*14*
(S)-**12**	0.1	EtI	50% KOH(aq)	PhMe	25 °C	*R*	80%	94%	*14*
13	2.0	BnBr	NaOH(s)	PhMe	25 °C	*R*	>95%	80%	*15*
13	2.0	C_3H_5Br	NaOH(s)	PhMe	25 °C	*R*	>90%	81%	*15*
14	30.0	BnBr	KOH (1 M)	CH_2Cl_2	0 °C	*R*	55%	90%	*16*
14	30.0	C_3H_5Br	KOH (1 M)	CH_2Cl_2	0 °C	*R*	61%	81%	*16*
15	10.0	BnBr	NaOH (2 M)	CH_2Cl_2	0–25 °C	*R*	>97%	86%	*17*
(S,S)-**16a**	10.0	BnBr	CsOH•H_2O	PhMe–CH_2Cl_2	–70 °C	*R*	87%	93%	*18*
(S,S)-**16a**	10.0	C_3H_5Br	CsOH•H_2O	PhMe–CH_2Cl_2	–70 °C	*R*	79%	91%	*18*
17	5.0	BnBr	CsOH	CH_2Cl_2	–45 °C	*R*	73%	30%	*19*
17	5.0	C_3H_5Br	CsOH	CH_2Cl_2	–45 °C	*R*	75%	28%	*19*
18	20.0	BnBr	50% KOH(aq)	CH_2Cl_2	0 °C	*R*	>95%	95%	*20*
(S)-**19**	5.0	BnBr	KOH(s)	PhMe	0 °C	*S*	79%	50%	*21*
20	1.0	BnBr	50% KOH(aq)	PhMe	0 °C	*S*	55%	58%	*22*
21	5.0	BnBr	50% KOH(aq)	PhMe–$CHCl_3$	–20 °C	*S*	94%	95%	*23*
21	5.0	C_3H_5Br	50% KOH(aq)	PhMe–$CHCl_3$	–20 °C	*S*	86%	94%	*23*
21	5.0	EtI	50% KOH(aq)	PhMe–$CHCl_3$	–20 °C	*S*	50%	92%	*23*
22	5.0	BnBr	50% KOH(aq)	PhMe–$CHCl_3$	–20 °C	*S*	94%	98%	*24*
22	5.0	C_3H_5Br	50% KOH(aq)	PhMe–$CHCl_3$	–20 °C	*S*	92%	97%	*24*
23	3.0	BnBr	50% KOH(aq)	PhMe–$CHCl_3$	–20 °C	*S*	94%	94%	*25*
23	3.0	C_3H_5Br	50% KOH(aq)	PhMe–$CHCl_3$	–20 °C	*S*	90%	95%	*25*
24	1.0	BnBr	50% KOH(aq)	PhMe–$CHCl_3$	0 °C	*S*	95%	97%	*26*
24	1.0	C_3H_5Br	50% KOH(aq)	PhMe–$CHCl_3$	0 °C	*S*	95%	97%	*26*
24	1.0	EtI	50% KOH(aq)	PhMe–$CHCl_3$	0 °C	*S*	83%	97%	*26*
25	5.0	BnBr	50% KOH(aq)	PhMe–$CHCl_3$	0 °C	*S*	62%	84%	*27*
25	5.0	C_3H_5Br	50% KOH(aq)	PhMe–$CHCl_3$	0 °C	*S*	70%	90%	*27*
26	1.5	BnBr	20% KOH(aq)	PhMe–CH_2Cl_2	–10 °C	*S*	98%	94%	*28*
26	1.5	C_3H_5Br	20% KOH(aq)	PhMe–CH_2Cl_2	–10 °C	*S*	98%	97%	*28*

[a] Using 18-crown-6 (0.1 mol %) as co-catalyst.

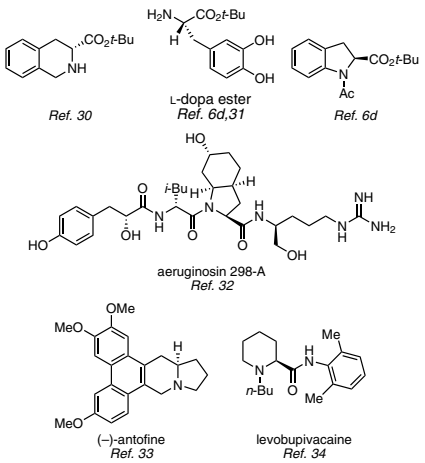
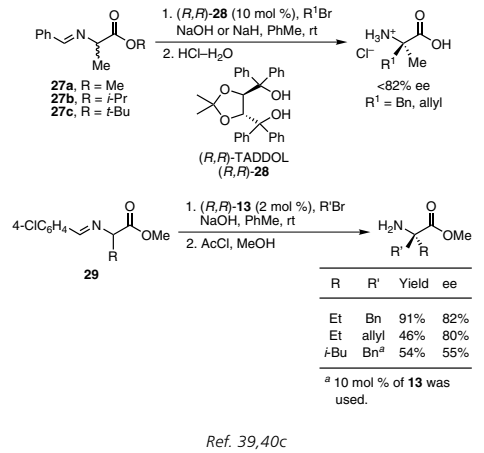


Figure 5. Important α-Amino Acids and Their Derivatives Synthesized Enantioselectively with the Assistance of Chiral, Phase-Transfer Catalysts.

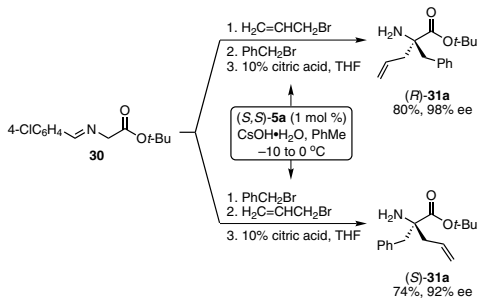


R	R'	Yield	ee
Et	Bn	91%	82%
Et	allyl	46%	80%
i-Bu	Bn[a]	54%	55%

[a] 10 mol % of **13** was used.

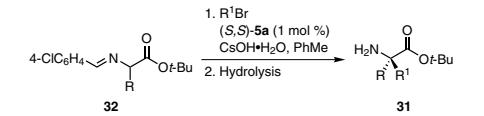
Ref. 39,40c

Scheme 1. Effectiveness of **28** and **13** as Phase-Transfer-Alkylation Catalysts.



Ref. 41

Scheme 2. Highly Enantioselective, One-Pot, Double Alkylation of **30**.

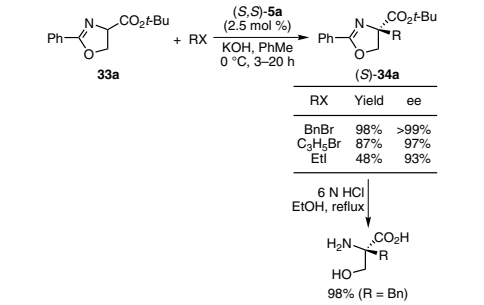


31	R	R^1	Yield	ee	Note
a	Bn	allyl	71%	97%	*a*
b	*i*-Bu	allyl	70%	93%	*a*
c	Me	allyl	73%	98%	*a*
d	Ph	allyl	77%	91%	*b*
e	Me	Bn	83%	89%	*c*

Notes: [a] At –20 °C to 0 °C. Hydrolysis with 10% citric acid in THF. [b] At –40 °C. Hydrolysis with H_2SO_4 in MeOH at 50 °C. [c] (*S,S*)-**16b** (10 mol %) and BnBr in PhMe–CH_2Cl_2 (7:3) at –70 °C under argon. Hydrolysis with 0.2 M citric acid in THF.

Ref. 18b,41,42

Scheme 3. Efficient Syntheses of Dialkylamino Acids **31** by the Asymmetric Phase-Transfer Alkylation of **32**.



RX	Yield	ee
BnBr	98%	>99%
C_3H_5Br	87%	97%
EtI	48%	93%

Ref. 43a

Scheme 4. Catalytic, Asymmetric Synthesis of α-Alkylserines.

2.1.3. Alkylation of Peptides Activated by a Schiff Base

Our group has found that PTC with C_2-symmetric chiral quaternary ammonium salts of type **5** can be successfully applied to the stereoselective N-terminal alkylation of small peptides such as Gly-L-Phe derivative **35**. For instance, the benzylation of **35** with (*S*,*S*)-**5c**—possessing sterically hindered aromatic substituents at the 3 and 3' positions of the binaphthyl moiety—under biphasic conditions proceeded with almost complete diastereocontrol (**eq 3**).[44] This method can be extended to the diastereoselective alkylation of Schiff base activated tripeptides and tetrapeptides.

2.2. Other Alkylations

Due to the relatively high acidity of the α-methine proton, α-substituted β-keto esters are considered to be suitable substrates for alkylation under phase-transfer conditions.[45] High efficiencies and enantioselectivities have been attained in the construction of quaternary stereocenters on β-keto esters by such alkylation in the presence of the suitably modified chiral quaternary ammonium bromide **5d**. This reaction system has a broad scope with respect to the β-keto esters and alkyl halides that can be used. The resulting alkylation products **37** can be readily converted into the corresponding β-hydroxy esters **38** and β-amino esters **39** (**Scheme 5**).[46,47]

3. The Michael Addition

The asymmetric Michael addition of active methylene or methine compounds to electron-deficient olefins, particularly α,β-unsaturated carbonyl compounds, represents a fundamental approach for constructing functionalized carbon frameworks. The combination of glycinate Schiff bases with α,β-unsaturated esters and ketones as electrophiles offers a practical route to various α-amino acids having an additional carbonyl functionality.[48]

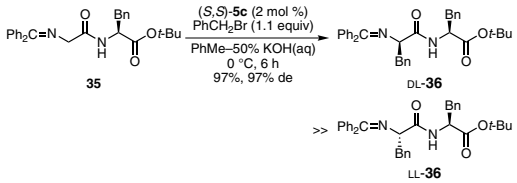
In this regard, the research groups of Shibasaki,[18] Arai and Nishida,[49,50] and Akiyama[51] have carried out the asymmetric Michael addition of glycine derivative **1** to acrylates and vinyl ketones in the presence of C_2-symmetric chiral phase-transfer catalysts such as chiral quaternary ammonium salts **16**, **40**, and **41**, and a chiral crown ether, **42** (**eq 4**).

Jew, Park, and co-workers achieved the highly enantioselective synthesis of (2*S*)-α-(hydroxymethyl)glutamic acid, a potent metabotropic receptor ligand, through the Michael addition of 2-(naphthalen-1-yl)oxazoline-4-carboxylic acid *tert*-butyl ester (**33b**) to ethyl acrylate in the presence of (*S*,*S*)-**5a** as catalyst and BEMP as base (**Scheme 6**).[52]

Nitroalkanes are valuable active methylene compounds,[53] and our group developed a diastereo- and enantioselective conjugate addition of nitroalkanes to alkylidenemalonates[54] and cyclic α,β-unsaturated ketones[55] under mild phase-transfer conditions. In this transformation, the nature of the 3 and 3' aromatic substituents of the catalyst was critical for attaining a high level of stereoselectivity with each electrophile (**Scheme 7**).

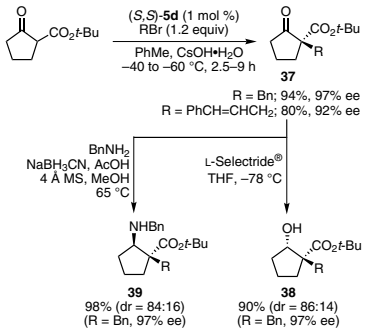
The structurally related chiral phase-transfer catalyst **5d** enables the enantioselective Michael addition of β-keto esters to α,β-unsaturated aldehydes and ketones, leading to the construction of quaternary stereocenters having three different functionalities of carbonyl origin (**Scheme 8**).[46] It is worth mentioning that the use of the fluorenyl ester greatly improved the enantioselectivity of the reaction.

In conjunction with our research effort to design effective catalysts for the asymmetric epoxidation of α,β-unsaturated ketones (see Scheme 11), our group has addressed the importance of dual-functioning chiral phase-transfer catalysts such as **46a** for



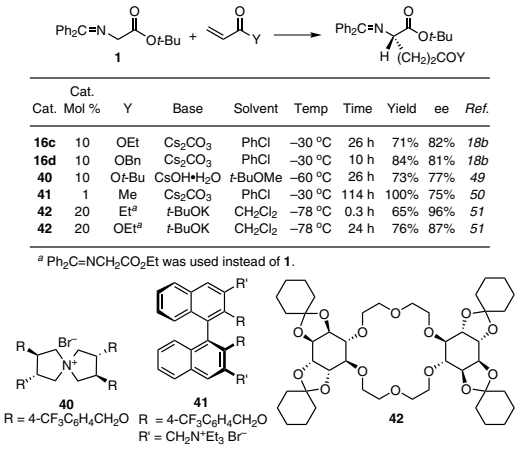
Ref. 44

eq 3



Ref. 46

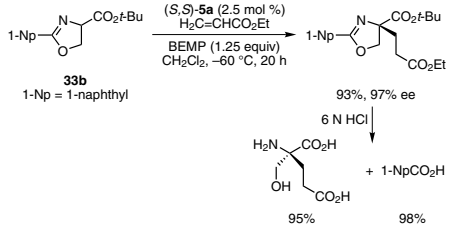
Scheme 5. Asymmetric Phase-Transfer Alkylation of β-Keto Esters for the Construction of Quaternary Stereocenters, and the Stereoselective Conversion of the Intermediates into β-Hydroxy and β-Amino Esters.



Cat.	Cat. Mol %	Y	Base	Solvent	Temp	Time	Yield	ee	Ref.
16c	10	OEt	Cs_2CO_3	PhCl	–30 °C	26 h	71%	82%	*18b*
16d	10	OBn	Cs_2CO_3	PhCl	–30 °C	10 h	84%	81%	*18b*
40	10	O*t*-Bu	CsOH•H_2O	*t*-BuOMe	–60 °C	26 h	73%	77%	*49*
41	1	Me	Cs_2CO_3	PhCl	–30 °C	114 h	100%	75%	*50*
42	20	Et[a]	*t*-BuOK	CH_2Cl_2	–78 °C	0.3 h	65%	96%	*51*
42	20	OEt[a]	*t*-BuOK	CH_2Cl_2	–78 °C	24 h	76%	87%	*51*

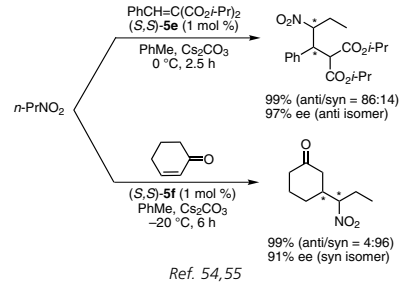
[a] $Ph_2C{=}NCH_2CO_2Et$ was used instead of **1**.

eq 4



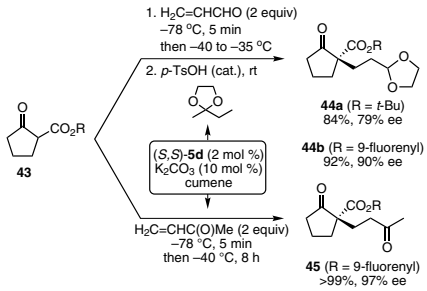
Ref. 52

Scheme 6. Asymmetric Synthesis of (2*S*)-α-(Hydroxymethyl)-glutamic Acid.



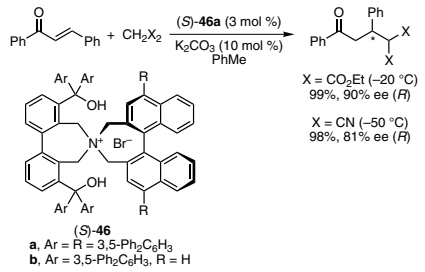
Ref. 54,55

Scheme 7. Michael Addition of Nitroalkanes to Alkylidenemalonates and α,β-Unsaturated Ketones.



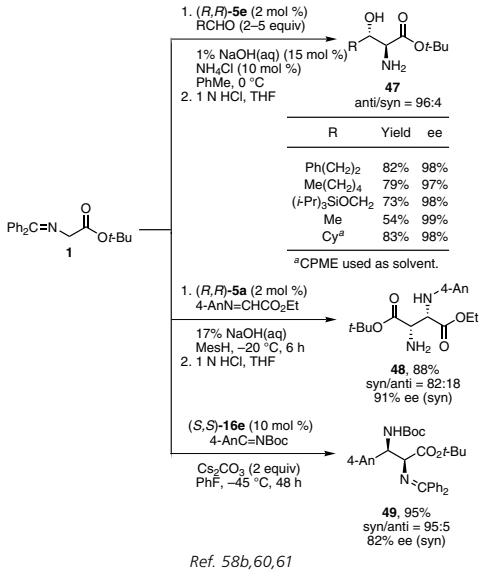
Ref. 46

Scheme 8. Asymmetric Michael Addition of β-Keto Esters to Acrolein and Methyl Vinyl Ketone.



Ref. 56

eq 5



Ref. 58b,60,61

Scheme 9. Highly Diastereo- and Enantioselective Direct Aldol and Mannich Reactions of a Glycine Derivative.

achieving a highly enantioselective Michael addition of malonates or malononitrile to chalcone derivatives (**eq 5**).[56,57]

4. The Aldol and Related Reactions

Although the phase-transfer-catalyzed, enantioselective direct aldol reaction of a glycine donor with aldehyde acceptors could provide an ideal method for the simultaneous construction of the primary structure and stereochemical integrity of β-hydroxy-α-amino acids—extremely important chiral units for pharmaceutical chemistry—the examples reported to date are very limited. Accordingly, our group recently developed an efficient and highly diastereo- and enantioselective direct aldol reaction of glycinate Schiff base **1** with a wide range of aliphatic aldehydes under mild phase-transfer conditions employing chiral quaternary ammonium salt **5e** as a key catalyst (**Scheme 9**).[58,59] The highly enantioselective phase-transfer-catalyzed, direct Mannich reaction of **1** with imines was accomplished by our group[60] and the group of Ohshima and Shibasaki[61] using the structurally related chiral ammonium bromide (*R*,*R*)-**5a** and the tartrate-derived bis(ammonium salt) (*S*,*S*)-**16e** as catalysts, respectively (**Scheme 9**).

5. The Darzens Condensation

The Darzens reaction represents one of the most powerful methods for the synthesis of α,β-epoxy carbonyl and related compounds. Arai's group synthesized a new quaternary bis(ammonium salt), **50**, from (*S*)-1,1'-bi-2-naphthol, and utilized it for the preparation of optically active α,β-epoxy amides as a mixture of cis and trans isomers, **52** and **53,** through reaction of haloamides **51** with aldehydes (**eq 6**).[62]

6. The Neber Rearrangement

The Neber rearrangement of oxime sulfonates into α-amino ketones proceeds via a nitrene or an anion pathway. If the latter mechanism is operating, the use of a chiral base could result in the discrimination of two enantiotopic α protons to furnish optically active α-amino ketones. Verification of this hypothesis was provided by the successful asymmetric Neber rearrangement of simple oxime sulfonate **55**, generated in situ from the parent oxime (*Z*)-**54**. Under phase-transfer conditions, and using C_2-symmetric chiral quaternary ammonium bromide **5g** or **5h** as catalyst, the corresponding protected α-amino ketone **56** was isolated in high yield and moderate enantiomeric excess (**Scheme 10**).[63]

7. Epoxidation

Since the first report by Wynberg's group on the asymmetric epoxidation of electron-deficient olefins under phase-transfer conditions,[64] a number of useful catalyst–oxidant combinations have been elaborated particularly for the epoxidation of chalcone derivatives.[65] Along this line, Murphy and co-workers prepared tetracyclic C_2-symmetric guanidium salts of type **15** from (*S*)-malic acid, and applied them to the enantioselective epoxidation of chalcone derivatives (**eq 7**).[17]

Our group designed a new, dual-function, and highly efficient chiral quaternary ammonium salt, **46**, for the asymmetric epoxidation of various enone substrates (**Scheme 11**).[66] In the X-ray structure of the PF_6 salt of **46a**, the exceedingly high asymmetric induction is ascribable to the molecular recognition ability of the catalyst toward enone substrates by virtue of the appropriately aligned hydroxyl functionality as well as the chiral molecular cavity. Indeed, the observed enantioselectivity highly depends on the size and the electronic properties of Ar and R in

46. The group of Jew and Park demonstrated that the combined use of a surfactant such as Span® 20 and dimeric cinchona-alkaloid-derived phase-transfer catalyst **57** enabled the highly efficient and enantioselective epoxidation of chalcone derivatives using 30% aqueous hydrogen peroxide as oxidant (**eq 8**).[67]

8. Cyanation

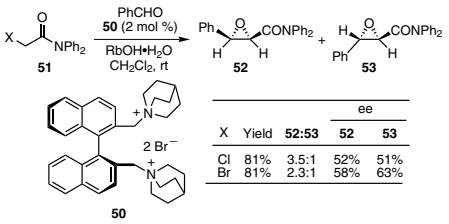
The phase-transfer-catalyzed and highly enantioselective cyanation of aldimine derivatives **58** with aqueous KCN has been realized by our group based on the chiral quaternary ammonium iodide (*R*,*R*,*R*)-**60**, which possesses a stereochemically defined tetranaphthyl backbone. A wide range of aliphatic aldimines including those having α-*tert*-alkyl substituents are tolerated by this system (**Scheme 12**).[68] The use of α-amide sulfones **59** as precursors of the reactive imines **58** was found to enhance both the chemical yields and the enantioselectivities in the presence of only a slight excess of KCN (1.05 equiv).[69,70] This study represents an essentially new approach toward the asymmetric Strecker-type reactions. It harnesses the distinct synthetic advantages of chiral phase-transfer catalysis to provide a truly practical route to various unusual, optically pure α-amino acids.

9. Conclusions

The development of C_2-symmetric, chiral, phase-transfer catalysts largely relies on the molecular design of purely synthetic chiral quaternary ammonium salts. These salts often deliver not only a higher reactivity and stereoselectivity but also create new synthetic opportunities, thus expanding the applicability of asymmetric phase-transfer catalysis in modern organic synthesis. Efforts need to continue to be made toward understanding the relationship between catalyst structure, activity, and stereocontrolling ability. The systematic accumulation of such knowledge would allow us to conduct an even more rational catalyst design for pursuing selective chemical synthesis in a reliable and practical manner.

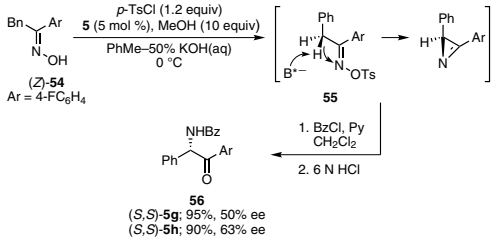
10. Acknowledgements

We thank our colleagues at Hokkaido and Kyoto Universities, whose names appear in the cited references, for their personal and scientific collaborations. Without their enthusiasm for organic chemistry, our research on the development and application of C_2-symmetric, chiral, phase-transfer catalysts would not have been achieved.



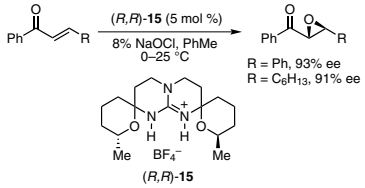
Ref. 62

eq 6



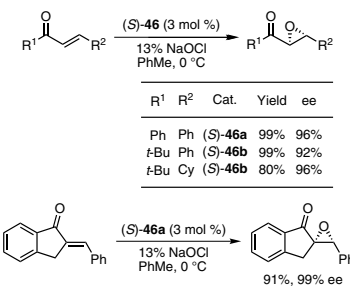
Ref. 63

Scheme 10. The Asymmetric Neber Rearrangement of Oxime Sulfonate **55**.



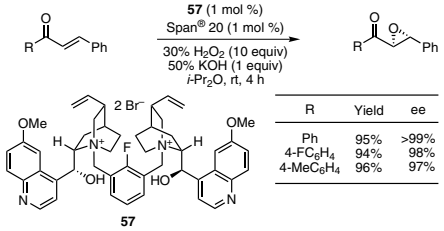
Ref. 17

eq 7



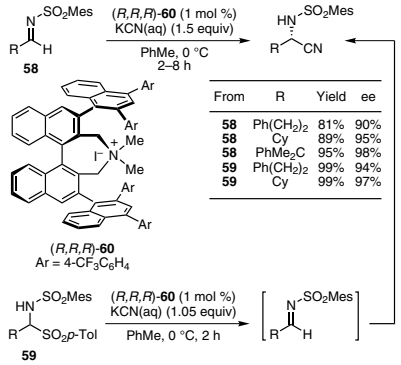
Ref. 66

Scheme 11. Dual-Functioning Catalyst, **46**, for Asymmetric Epoxidations.



Ref. 67

eq 8



Ref. 68,69

Scheme 12. The Phase-Transfer-Catalyzed Asymmetric Strecker Reaction of Aldimines and α-Amide Sulfones with (*R*,*R*,*R*)-**60**.

11. References and Notes

(†) Current address: Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Chikusa, Nagoya 464-8603, Japan.

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About the Authors

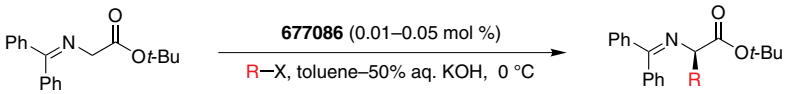
Takashi Ooi received his Ph.D. degree in 1994 from Nagoya University under the direction of Professor Hisashi Yamamoto, and then joined the group of Professor Julius Rebek, Jr., at MIT as a postdoctoral fellow (1994–1995). He was appointed assistant professor at Hokkaido University in 1995 and promoted to lecturer in 1998. In 2001, he moved to Kyoto University as an associate professor, and became a full professor at Nagoya University in 2006. He was awarded the Chugai Award in Synthetic Organic Chemistry (Japan, 1997), the Chemical Society of Japan Award for Young Chemists (1999), and the Thieme Journal Award (2006). His current research interests are focused on the development of new and useful synthetic methodologies by designing organic molecular catalysts including C_2-symmetric, chiral, quaternary ammonium salts.

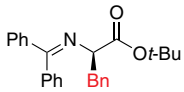
Keiji Maruoka received his Ph.D. degree in 1980 from the University of Hawaii with Prof. Hisashi Yamamoto. He was appointed assistant professor at Nagoya University in 1980, and promoted to associate professor in 1990. He moved to Hokkaido University as a full professor in 1995, and has been a professor at Kyoto University since 2000. His research interests are focused on organic synthesis with bidentate Lewis acids and designer chiral organocatalysts. His awards include the Japan Synthetic Organic Chemistry Award (2003), the Nagoya Silver Medal (2004), the GSC Award (2006), and the Chemical Society of Japan Award (2006).

Asymmetric Alkylation Phase-Transfer Catalysts

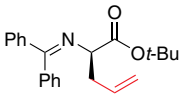
Chiral quaternary ammonium salts derived from C_2-symmetric amines or cinchona alkaloids are powerful phase-transfer catalysts for the preparation of optically active molecules. Both types of phase-transfer catalysts allow for the stereocontrolled monoalkylation of glycine-derived Schiff bases with alkyl halides to afford protected α-alkyl-α-amino acids. Catalysts developed by Maruoka effect these reactions with a high degree of enantioselectivity at exceptionally low catalyst loadings (<0.1 mol %).

C_2-Symmetric Maruoka Catalysts

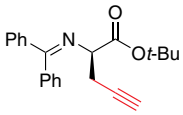




98%, 99% ee



87%, 98% ee



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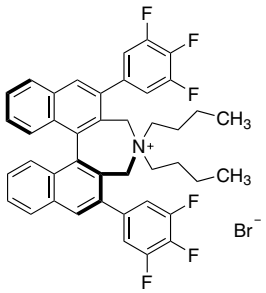

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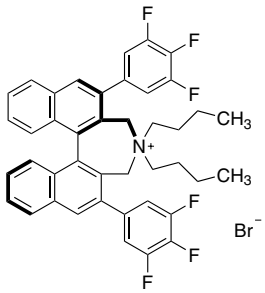

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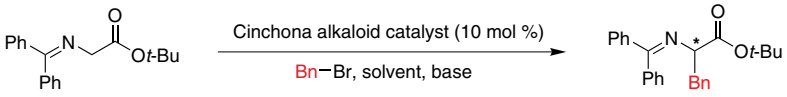
For further application information, see Professor Maruoka's review article in this issue.

Cinchona Alkaloid Catalysts



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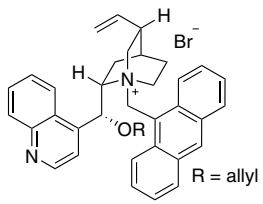

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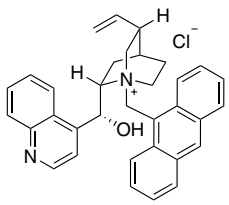

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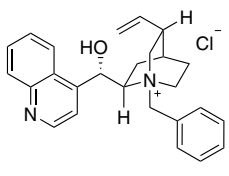

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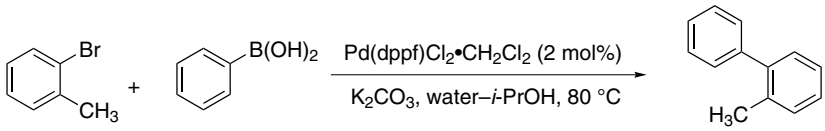

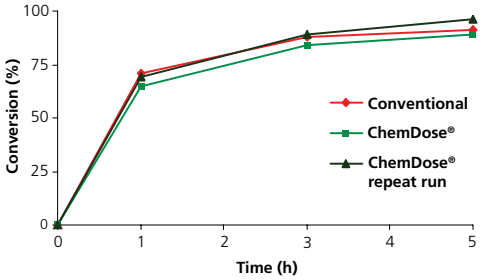

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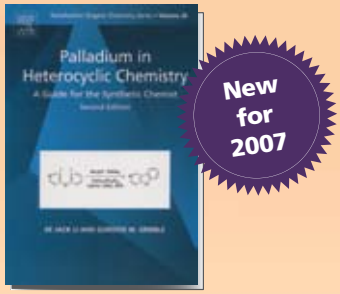

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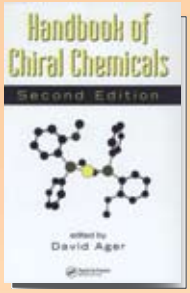

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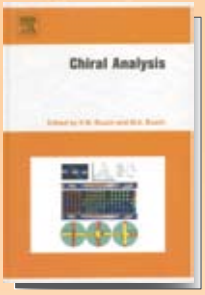

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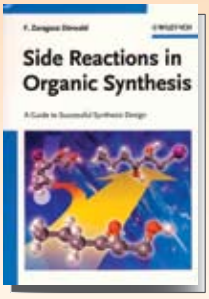

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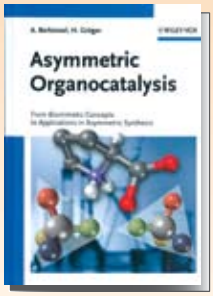

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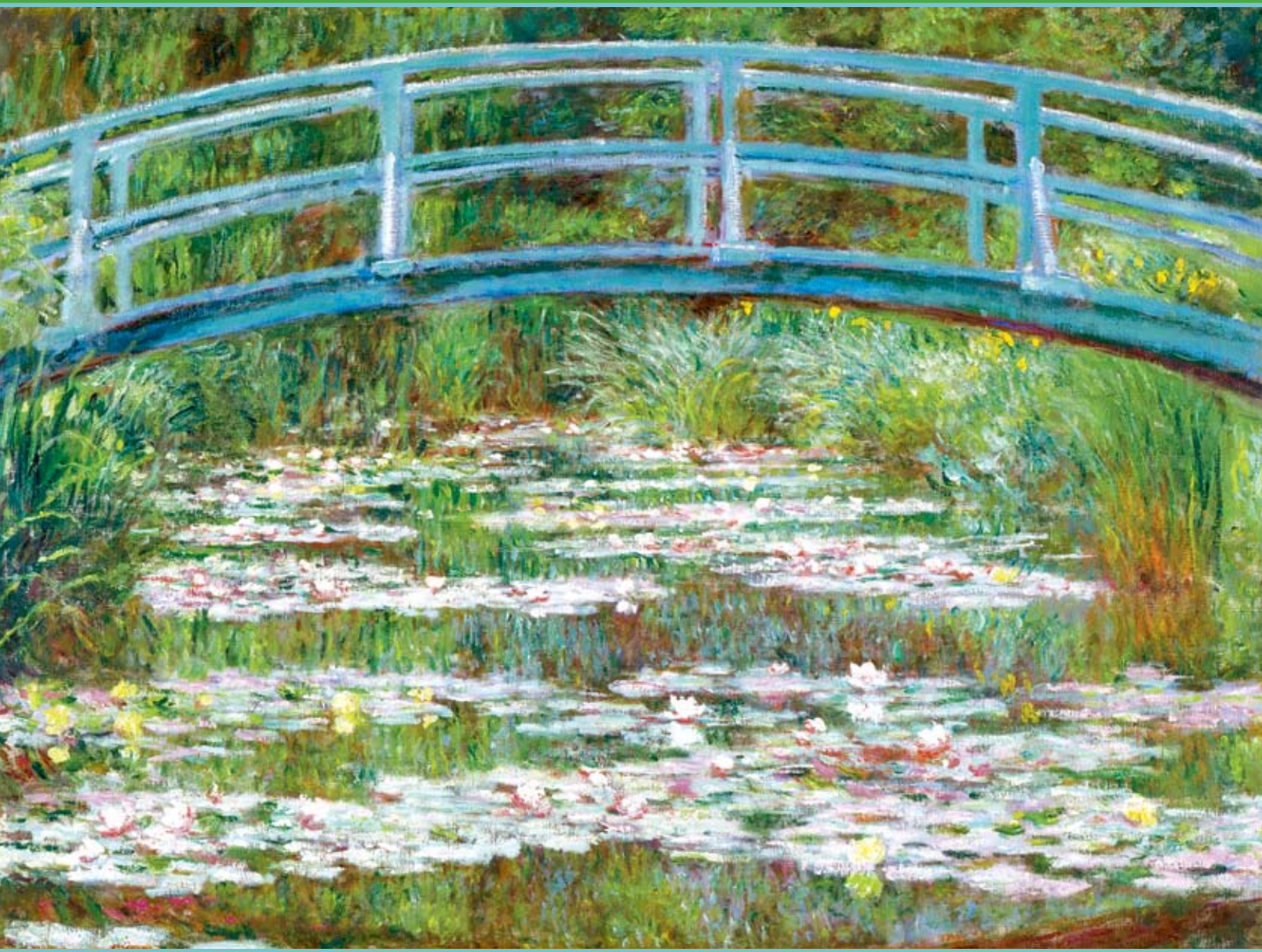

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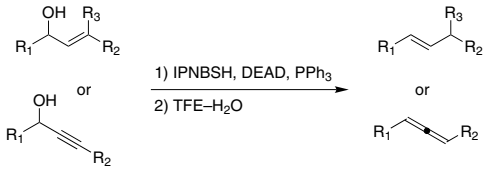

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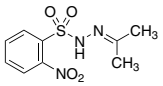
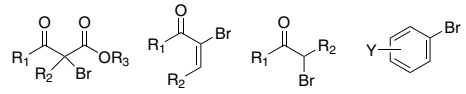
N-Isopropylidene-N′-2-nitrobenzenesulfonyl hydrazine, 97%
IPNBSH

687855 1 g
[*6655-27-2*] 5 g
$C_9H_{11}N_3O_4S$
FW: 257.27



Bromination Reagent

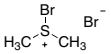
Bromodimethylsulfonium bromide (BDMS) is an easy-to-handle and highly effective bromination reagent as well as a catalyst for various organic transformations.[1] BDMS has been employed in numerous reactions including the preparation of α-bromo-β-keto esters and α-bromo enones, from their corresponding keto esters and enones, respectively;[2] the conversion of epoxides and enamines to α-bromoketones;[3] and electrophilic aromatic bromination.[4] BDMS has also been employed in the synthesis of α-aminonitriles and homoallylic amines, and in Michael additions of amines to electron-deficient olefins.[5]



(1) Choudhury, L. H. *Synlett* **2006**, 1619. (2) (a) Khan, A. T. et al. *J. Org. Chem.* **2006**, *71*, 8961. (b) Chow, Y. L.; Bakker, B. H. *Can. J. Chem.* **1982**, *60*, 2268. (3) Olah, G. A. et al. *Tetrahedron Lett.* **1979**, *20*, 3653. (4) (a) Majetich, G. et al. *J. Org. Chem.* **1997**, *62*, 4321. (b) Megyeri, G.; Keve. T. *Synth. Commun.* **1989**, *19*, 3415. (5) (a) Das, B. et al. *Synthesis* **2006**, 1419. (b) Das, B. et al. *Tetrahedron Lett.* **2006**, *47*, 5041. (c) Khan, A. T. *Tetrahedron Lett.* **2007**, *48*, 3805.

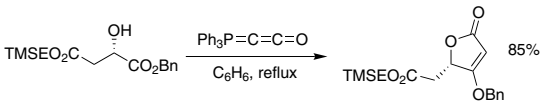
Bromodimethylsulfonium bromide, 95%
BDMS

694142 5 g
[*50450-21-0*] 25 g
$C_2H_6Br_2S$



Cumulated Ylide

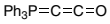
The cumulated ylide (triphenylphosphoranylidene)ketene is a versatile two-carbon building block useful in preparing numerous classes of oxygen- and nitrogen-containing heterocycles. While typically not Wittig-active itself, this reagent reacts with a host of electrophiles to yield Wittig-active products that can participate in subsequent intra- or intermolecular olefination reactions.



(1) Schobert, R.; Jagusch, C. *Synthesis* **2005**, 2421. (2) Schobert, R. et al. *Synthesis* **2006**, 3902. (3) Boeckman, R. K., Jr. et al. *J. Am. Chem. Soc.* **2006**, *128*, 11032.

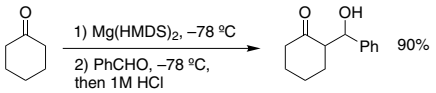
(Triphenylphosphoranylidene)ketene
Bestmann ylide

688185 1 g
[*15596-07-3*]
$C_{20}H_{15}OP$
FW: 302.31



Mg(HMDS)$_2$

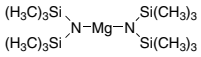
While lithium amides, such as LDA and LiHMDS, are the predominant bases of choice for the selective generation of enolates, magnesium amide bases have garnered recent attention due to their enhanced thermal stabilities and selectivity characteristics.[1] Magnesium bis(hexamethyldisilazide), $Mg(HMDS)_2$, has demonstrated efficacy in ketone–aldehyde aldol addition reactions[2] and in the regio- and stereoselective synthesis of silyl enol ethers.[3]



(1) He, X. et al. *J. Am. Chem. Soc.* **2006**, *128*, 13599. (2) Allan, J. F. et al. *Chem. Commun.* **1999**, 1325. (3) Bonafoux, D. et al. *J. Org. Chem.* **1996**, *61*, 5532.

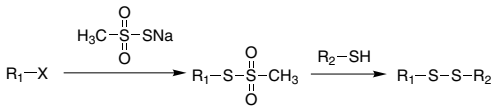
Magnesium bis(hexamethyldisilazide)
$Mg(HMDS)_2$

692352 5 g
[*857367-60-3*] 25 g
$C_{12}H_{36}MgN_2Si_4$
FW: 345.07



Reagent for Disulfide Synthesis

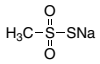
The reaction of alkyl halides or pseudohalides with the sulfur-based nucleophile sodium methanethiosulfonate (NaMTS) yields organic methanethiosulfonates, intermediates that are highly reactive towards sulfhydryl groups, yielding unsymmetrical disulfides. NaMTS has been extensively used in glycosylations, spin-labeling, and photoprobe chemistry.[1–3]



(1) Grayson, E. J. et al. *J. Org. Chem.* **2005**, *70*, 9740. (2) Kálai, T. et al. *Synthesis* **2006**, 439. (3) Guo, L.-W. et al. *Bioconjugate Chem.* **2005**, *16*, 685.

Sodium methanethiosulfonate, 95%
NaMTS

684538 1 g
[*1950-85-2*]
$CH_3O_2NaS_2$
FW: 134.15



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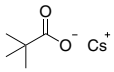
"PLEASE BOTHER US."

Joe Porwoll, President
Aldrich Chemical Co., Inc.

Professor Keith Fagnou of the University of Ottawa (Canada) kindly suggested that we make cesium pivalate. This versatile base has been used by several research groups in transition-metal-catalyzed direct arylations of indoles.[1] Cesium pivalate has also been employed as a base in the study of aryl-to-aryl palladium migration in Heck and Suzuki couplings of *o*-halobiaryls.[2]

(1) (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (b) Campeau, L.-C. et al. *Aldrichimica Acta* **2007**, *40*, 35. (c) Wang, X. et al. *J. Am. Chem. Soc.* **2005**, *127*, 4996. (2) Campo, M. A. et al. *J. Am. Chem. Soc.* **2007**, *129*, 6298.



694037 Cesium pivalate, 98% 5 g, 25 g

Naturally, we made this useful reagent. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the inside back cover.

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ABOUT OUR COVER

Photograph © Board of Trustees, National Gallery of Art, Washington.

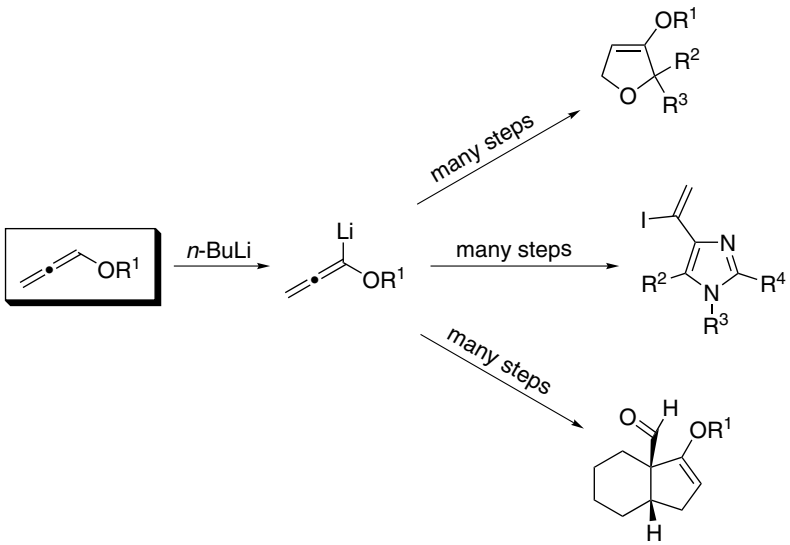
In the last decades of Monet's life, his prized water garden became his most important—and eventually his only—subject. Monet began to paint his lily pond and our cover, ***The Japanese Footbridge*** (oil on canvas, 81.3 × 101.6 cm), in his garden at Giverny in 1899. He constructed the water garden soon after he moved to Giverny with his family in 1893, petitioning local authorities to divert water from the nearby river. Monet remade the landscape with the same artifice he applied to his paintings—and then he used it, in turn, as his creative focus. When Monet exhibited his lily ponds, a number of critics mentioned his debt to Japanese art and the idea of the *hortus conclusus* (closed garden) of medieval images.

Monet painted his garden from the same vantage point as our cover twelve times, focusing on the arching blue-green bridge and a microcosm of the water. He gave equal emphasis to the physical qualities of his painting materials and to the landscape motif he depicted. In this painting, the sky has already disappeared; the lush foliage rises all the way to the horizon; and the decorative arch of the bridge flattens the space. Floating lily pads and mirrored reflections assume equal stature, blurring distinctions between solid objects and transitory effects of light. Monet had always been interested in reflections, seeing their fragmented forms as the natural equivalence for his own broken brushwork. The artist—who, as a leader of the impressionists, had espoused the spontaneity of directly observed works that capture the fleeting effects of light and color—had in these later paintings subjected a nature he re-created to sustained, meditated scrutiny.

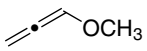
This painting is a gift to the National Gallery of Art from Victoria Nebeker Coberly, in memory of her son, John W. Mudd, and Walter H. and Leonore Annenberg.

New Reactive Allenes

Allenes are becoming highly sought building blocks for their ability to react with many different classes of substrates. In addition, the allene moiety itself is present in many bioactive natural products and pharmaceutical agents. Recent work by Reissig[1] and Zhang[2] demonstrates the utility of lithiated allenyl ethers in the synthesis of various carbocycles and heterocycles. Other work by Suginome and co-workers reports the use of cyclohexylallene in a palladium-catalyzed asymmetric silaboration.[3] Sigma-Aldrich is pleased to add these and other allenes to our expanding portfolio of reactive building blocks.



New Allenes



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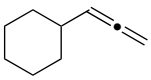

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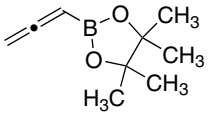

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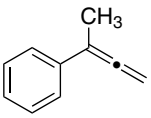

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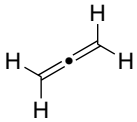
Other Allenes



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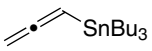

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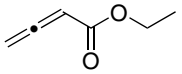

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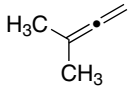

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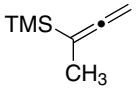

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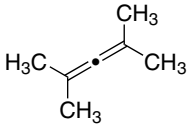

272965

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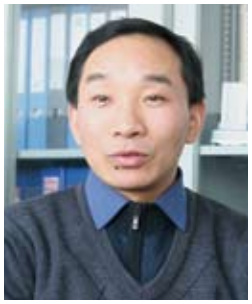
Recent Advances in the Chemistry of Allenes



Shengming Ma
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Feng Lin Lu
Shanghai 200032, P. R. of China
Email: masm@mail.sioc.ac.cn

Outline

1. Introduction

The history of allenes dates back to 1874. At that time, Jacobus H. van't Hoff, the first Nobel laureate in chemistry, predicted the correct core structure of allenes.[1] It is quite interesting to note that the first synthesis of an allene (pentadienoic acid)[2,3] was used to prove the nonexistence of this class of "highly unstable" organic compounds. During the past 10–15 years, chemists have witnessed a rapid development of the chemistry of allenes, which have proven very powerful in modern synthetic organic chemistry.[4–6] Some of these developments have been summarized in a monograph[5] and a review.[6] Following publication of these two surveys, further advances in allene chemistry have been reported in the following areas: the Myers–Saito reaction,[7] the radical chemistry of allenes,[4m,8] the reaction of allenes with metallocarbenes,[6,9] silicometallation leading to optically active allylsilanes[10] or vinylsilanes,[11] and the RCM reaction of allenes giving rise to new allene derivatives.[12] In this brief review, recent advances in the chemistry of allenes—mostly covering the period 2005 to March of 2007—specifically, ionic addition; hydro-, carbo-, or nucleometallation-initiated reactions; cycloisomerization and eliminative cyclization; cycloaddition; and cyclometallation will be described in a selective manner.

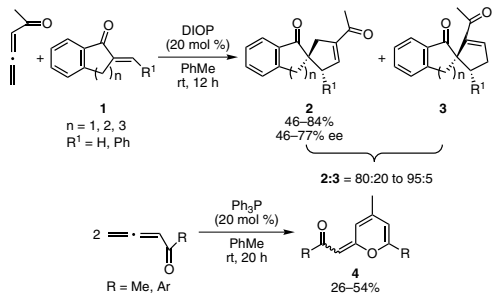
2. Ionic Addition Reactions[13]

2.1. Nucleophilic Additions

Mukai and co-workers observed that the intramolecular amination–acetate elimination reaction of 2-(2'-aminophenyl)-2,3-allenyl acetates and the subsequent Diels–Alder reaction afford tetrahydro- or dihydrocarbazole derivatives in 54–93% yields.[14] However, the yields of the corresponding reaction with alkynes are low. Alcaide et al. reported that the intramolecular nucleophilic addition of 2-phenyl-substituted buta-2,3-dienyl methyl ether with an amine, followed by elimination of the methoxy group, afford pyrroles.[15]

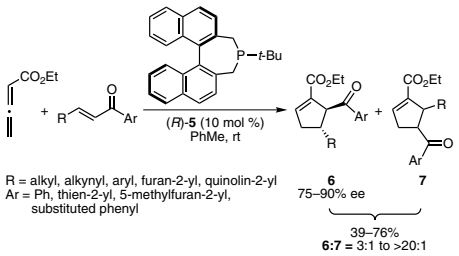
Starting in 1998, we have demonstrated that electron-deficient allenes, such as 1,2-allenylic carboxylates, carboxylic acids, ketones, sulfoxides, sulfones, nitriles, phosphine oxides, phosphonates, and others smoothly undergo conjugate addition with inorganic halides to afford β-halo-β,γ-unsaturated olefins.[16] In 2002, we also reported that stabilized carbon nucleophiles undergo tandem Michael addition and lactonization with 1,2-allenyl ketones. The reaction can be controlled to yield the conjugate addition products with an *E/Z* ratio of 96:4 to 99:1.[17] Chelated enolates of amino acid esters react similarly.[18] Huang and Shen reported in 2006 that, in addition to ketones, 2,3-allenoates react with α-cyano ketones, β-keto esters, and 1,3-diketones to afford α-pyrones.[19] Even sodium azides, thiolates, selenolates, and tellurrolates react as nucleophiles with 2,3-allenoates or 1,2-phosphine oxides to give rise to 3-alkenoates or allylphosphine oxides.[13,20] Indoles undergo $Sc(OTf)_3$-catalyzed reaction with 1,2-allenyl ketones to form *E* β-indolyl-α,β-unsaturated enones and β,β-bis(1*H*-indolyl) ketones.[21] The intramolecular conjugate addition of a carbon nucleophile or a hydroxyl group with 1,2-allenyl sulfones in the presence of *t*-BuOK generates 5–8-membered-ring products in 41–72% yields.[22]

2,3-Allenoates are known to react with electron-deficient olefins under catalysis by organophosphines to form [3 + 2] cycloaddition products.[4k,23] In 2006, Lu et al. further observed that ethyl 2,3-butadienoate underwent Ph_3P-catalyzed reaction with 2-substituted 1,1-dicyanoalkanes to form 4,4-dicyano-2-(ethoxycarbonyl)cyclopentenes as the only products.[24] The requisite 1,1-dicyanoalkanes were easily prepared in situ by condensation of aromatic aldehydes with malononitrile. Very recently, Wallace et al. reported that the Ph_3P- or DIOP-catalyzed reaction of 1,2-propadienyl methyl ketone with α,β-unsaturated enones **1** afforded cyclopentenyl diketones **2** as the major products.[25] In the absence of α,β-unsaturated enones, 1,2-allenyl methyl ketone acts as a Michael acceptor by undergoing



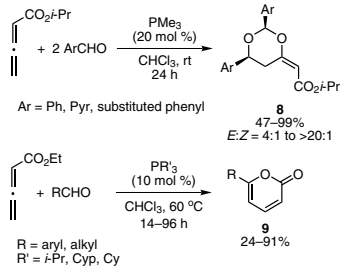
Ref. 25

Scheme 1. Reaction of Allenyl Ketones with α,β-Unsaturated Enones.



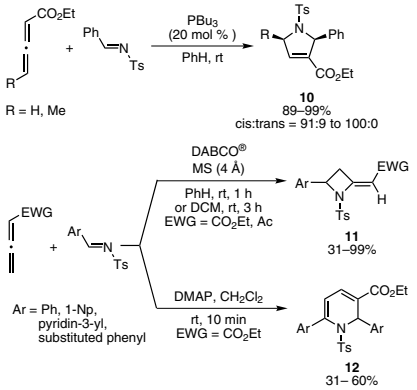
Ref. 27

eq 1



Ref. 28,29

Scheme 2. Reaction of 2,3-Butadienoate Esters with Aldehydes.



Ref. 4k,31,32

Scheme 3. The Reaction of 2,3-Allenoates with *N*-Sulfonylimines.

a [3 + 2] cyclization to form 6-acylmethylene-6*H*-pyran dimers, **4** (**Scheme 1**).[25]

The enantioselective version of this [3 + 2] cycloaddition was first investigated by Zhang and co-workers in 1997.[26] In 2006, Wilson and Fu disclosed that binaphthyl-based chiral phosphine (*R*)-**5** efficiently catalyzes the enantioselective [3 + 2] cycloaddition of ethyl 2,3-butadienoate with α,β-unsaturated aryl enones, providing 3-acyl-2-(ethoxycarbonyl)cyclopentenes, **6**, as the major products in 75–90% ee's (**eq 1**).[27]

Aldehydes can also be used instead of the electron-deficient olefins. Kwon and co-workers reported that the PMe_3-catalyzed reaction of 2,3-butadienoate with two molecules of an aromatic aldehyde afforded *cis-(E)*-2,6-diaryl-1,3-dioxan-4-ylidenecarboxylate **8** (**Scheme 2**). This overall process is believed to proceed through a sequential conjugate addition of PMe_3 to butadienoate, double 1,2 addition of the aldehyde, cyclic conjugate addition, and elimination of PMe_3.[28] However, when sterically demanding trialkylphosphines were utilized, ethyl 2,3-butadienoate reacted with just one molecule of aldehyde to form α-pyrone derivatives **9**. When aliphatic aldehydes were used in the reaction, the yields of the corresponding α-pyrones were low.[29]

Furthermore, substituted 2,3-allenoates also react with aromatic *N*-sulfonylimines under P(*n*-Bu)$_3$ catalysis to afford 2,5-disubstituted-3-pyrrolinecarboxylates **10** highly stereoselectively (**Scheme 3**).[4k] The diastereoselectivity for the cis isomer, **10**, is dependent on the steric bulk of the R group.[30] An enantioselective version of this reaction has recently been demonstrated by Marinetti's and Gladysz's groups with enantioselectivities of 37–60% being reported.[31] However, the terminal carbon–carbon double bond of 1,2-allenyl methyl ketones or of 2,3-butadienoates undergoes a DABCO®-catalyzed, highly regioselective formal [2 + 2] cycloaddition with imines to afford the unsaturated azetidines **11**. In contrast, when DMAP was employed instead of DABCO®, the same reactants afforded 1,2-dihydropyridine-3-carboxylates **12** in lower yields. The authors proposed a mechanism involving a nucleophilic addition of the amine instead of PR_3 and, for comparison, the authors reported that the $PhMe_2P$-catalyzed reaction of 2,3-pentadienoate with *N*-tosylaldimines afforded 3-pyrrolines.[32]

When the α position of 1,2-allenyl methyl ketones is blocked with an alkyl group, an aza-Baylis–Hillman-type γ-addition product, **13**, is formed in the presence of DMAP as catalyst; whereas a mixture of two tetrahydropyridines, **14** and **15**, is formed in the presence of P(*n*-Bu)$_3$.[33] The DMAP-catalyzed reaction of 1-alkyl-substituted 1,2-allenyl methyl ketones with aldehydes also provided the γ-addition products, **16**, in 45–75% yields (**Scheme 4**).

Wurz and Fu used chiral phosphine (*R*)-**5** to catalyze the reaction of *N*-tosylaldimines with 2-substituted-2,3-butadienoates or 1,2-propadienyl phenyl ketone to afford **14**-type tatrahydropyridine derivatives with high diastereo- and enantioselectivity. In most cases, the enantioselectivity reached the 96–99% level.[34] However, in the presence of quinuclidine, ethyl 2,3-butadienoate reacted with α,β-unsaturated enones to afford Baylis–Hillman-type conjugate addition products, i.e., 2-(3-oxoalkyl)-2,3-allenoates.[6,35] In the presence of 10 mol % DBU or DABCO®, salicylic aldehydes or *N*-tosylimines react with 1,2-allenyl ketones, 2,3-butadienoates, or 2-methyl-2,3-butadienoates to afford 2*H*-1-benzopyrans[36] or chromenes,[37] respectively.

Nair et al. reported that, in the reaction of 2,3-allenoates, PPh_3, and dialkyl azodicarboxylates, PPh_3 attacked the nitrogen–nitrogen double bond first to generate a new type of zwitterionic intermediate, **17**. Conjugate addition of **17** onto 2,3-allenoates, followed by intramolecular 1,2 addition and elimination of Ph_3PO

formed pyrazolines **18** or pyrazoles **19**, depending on the position of the substituent on the 2,3-allenoate starting material (**Scheme 5**).[38]

Nucleophilic attack of hydrazine on allenes initiates a cyclization reaction that leads to fused tetracyclic heterocycles or 4*H*-pyrazolo[1,2-*b*]pyrazoles, respectively.[39,40] 1,2-Allenyl bromides undergo 1,3-*anti*-substitution with (RCuBr)MgBr•LiBr to afford terminal alkynes.[41] Cu(I) catalyzes the facile coupling of 1,2-allenyl iodides with amides, carbamates, and ureas to give allenylamines.[42] 1,2-Allenyl bromides **20** and **22** undergo intramolecular substitution to form bicyclic sulfonamides **21** and **23**, respectively (**Scheme 6**).[43] Recently, an intermolecular tandem addition–cyclization of bromoallenes with malonates or 1,3-diketones led to alkylidenecyclopropanes or furans **24**, respectively.[44] In these two reactions, the nucleophile regioselectively attacks the central carbon atom of the allenyl bromide; this is followed by hydrogen transfer and intramolecular nucleophilic substitution to afford the cyclic products.

Allenyl silyl ethers, easily prepared from propargylic silyl ethers and KO*t*-Bu, reacted readily with aromatic aldehydes to afford β-branched Baylis–Hillman-type adducts.[45] In **26**, the lithium allenolate moiety reacted intramolecularly with the alkene moiety to form the 5-*tert*-butylidene-2-cyclopentenone derivative **27** in 70% yield (**eq 2**).[46]

2.2. Electrophilic Additions

On the basis of prior reports,[13] we have shown that the electrophilic cyclization of functionalized allenes affords heterocycles such as butenolides, furans, lactams, iminolactones, and others.[47] More recently, this cyclization has proven to be a very powerful tool for the synthesis of various heterocyclic products.[48] In addition, we have observed that the halohydroxylation reaction of 1,2-allenyl sulfoxides, sulfones, sulfides, or selenides results in the electrophilic halogen attacking the central carbon atom of the allene moiety.[13] The stereoselectivity is determined by the nature of the substituents: with sulfoxides and sulfones, *E* isomers are formed; while *Z* isomers are produced from sulfides and selenides.[49,50] A 5-membered-ring intermediate has recently been isolated and characterized by X-ray diffraction, which corroborates the stereochemical course of the halohydroxylation of sulfoxides and sulfones.[51]

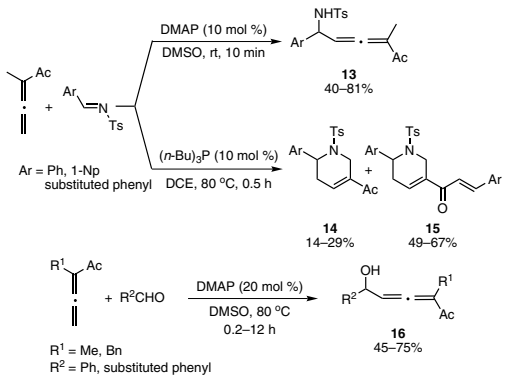
3. Reactions Initiated by Metallation

3.1. Reactions Initiated by Hydrometallation

Bäckvall and co-workers reported that 3-(2,3-alkadienyl)cyclohexenes undergo cycloisomerization in the presence of HOAc and $Pd(dba)_2$ to afford a mixture of isomeric bicyclic products. The cycloisomerization takes place through a hydropalladation, cyclic carbopalladation, and β-H elimination under microwave irradiation.[52] Hydrometallation of (1-alkoxy-propadienyl)cyclobutanols, **28**, leads to chiral 2-alkoxy-2-vinylcyclopentanones **30** in 84–95% ee's by an efficient and enantioselective ring expansion (**eq 3**).[53]

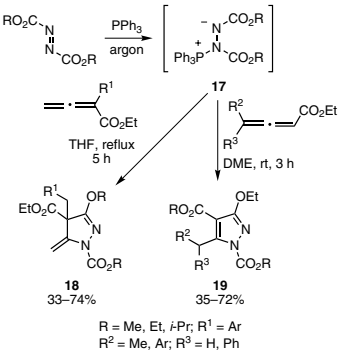
The hydrozirconation of allenes and subsequent transmetallation with dialkylzinc form allylzinc reagents, which react readily with imines to afford homoallylic amines. The regioselectivity depends on the nature of the substituents on the allenes.[54] The intermolecular hydroamination of optically active allenes with aniline efficiently forms optically active allylamines under $AuBr_3$ catalysis.[55]

Kanai, Shibasaki, and co-workers developed the enantioselective $Cu(OAc)_2$–(*R*)-DTBM–SEGPHOS®-catalyzed hydrometallation of 2,3-butadienoates and the subsequent 1,2-addition reaction with methyl ketones to afford optically active (*Z*)-5-(ethoxycarbonyl)-4-alken-2-ols, **31**, in 84–99% ee's. The corresponding CuF•3 PPh_3•2 EtOH–TANIAPHOS®-catalyzed reaction produced 3-



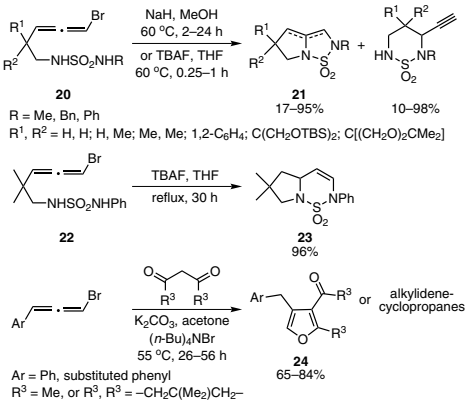
Ref. 33

Scheme 4. Reactions of 1-Alkyl-Substituted 1,2-Allenyl Methyl Ketones with *N*-Sulfonylimines and Aldehydes.



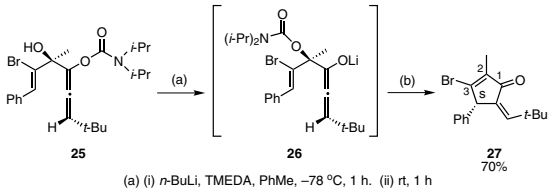
Ref. 38

Scheme 5. Reaction of 2,3-Allenoates with Azodicarboxylates.



Ref. 43,44

Scheme 6. The Reactions of 1,2-Allenyl Bromides.

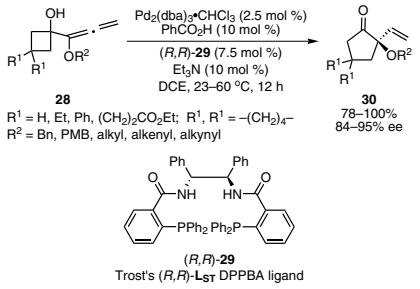


Ref. 46

eq 2

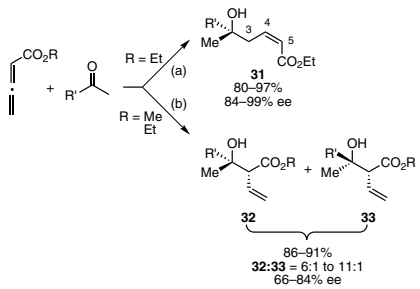
(ethoxycarbonyl)-4-alken-2-ols, **32**, in 66–84% ee's (**Scheme 7**).[56] By utilizing dialkylzinc instead of pinacolborane, the alkylative aldol reaction with methyl ketones formed α,β-unsaturated δ-lactones.[56]

The Ni(cod)$_2$-catalyzed addition of organoboronates to 1,2-allenes afforded hydroarylation or hydroalkenylation products with good *E/Z* selectivity but poor regioselectivity. However, the Pd-catalyzed reaction of allenes with organoboronic acids introduced the substituent from the organoboronic acids trans to the substituent in the starting allenes to give stereodefined functionalized alkenes as the major products.[57] A mechanism involving hydropalladation of the allenes and subsequent Suzuki coupling has been proposed based on ESI-MS studies.[58] In addition, the three-component reaction of symmetrical allenes, organoboronates, and alkynes afforded 1,3-diene derivatives stereoselectively.[59]



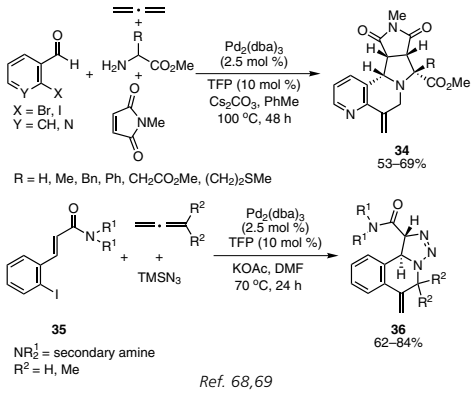
Ref. 53

eq 3



Ref. 56

Scheme 7. The Hydrometallation of 2,3-Butadienoates Followed by 1,2 Addition to Methyl Ketones.



Ref. 68,69

Scheme 8. Multicomponent Reactions Involving Carbopalladation, Intramolecular Trapping, and [3 + 2]-Dipolar Cycloaddition.

3.2. Reactions Initiated by Carbometallation

The Pd-catalyzed reaction of organic halides with allenes usually affords conjugated dienes via β-H elimination from the π-allylPd intermediate initially formed by regioselective carbopalladation.[4a,4e,6,60] Even 1,2-allenylboronates undergo the carbopalladation forming π-allylPd intermediates, which are trapped with amines or carbon nucleophiles under catalysis by $Pd_2(dba)_3$ and TFP to yield stereodefined 3-substituted 2-aryl-1-alkenylboronates highly stereoselectively.[61] However, the first Heck-type coupling of allenes with aryl halides was observed by our group in the case of 1,2-allenyl sulfones by using 5 mol % Ag_2CO_3 and 4 equivalents of K_2CO_3 as the base.[62] The following year, Chakravarty and Swamy reported a similar reaction with 3-methyl-2,3-butadienylphosphonate using Ag_2CO_3 as the base.[63] However, by switching to K_2CO_3 as the base, the reaction proceeded more readily through a π-allylPd intermediate to give 1,3-dienylphosphonates.[63] The Larock-type cyclization reaction[64] of *o*-hydroxyiodobenzene or benzoic acid with 1,2-allenylphosphonates was also reported to give benzocyclic products.[63]

Grigg's group has used amines to trap in situ formed π-allylPd intermediates to afford allylamines.[65] By utilizing allylic or homoallylic tosyl amides, bisallylic tosyl amides or mixed allylic homoallylic tosyl amides were produced, which cyclized via RCM to 3-pyrrolines or 3-piperidines.[65] Benzoxapines were also prepared by using 2-allylphenol.[66] In the presence of CO, the related four-component reaction afforded 3-acylpyrrolidines.[67] Recently, Grigg's group also developed the Pd-catalyzed four-component reaction of a 2-haloaromatic aldehyde, propadiene, amino acid ester, and *N*-methyl maleimide, providing a very powerful entry into tetracyclic products **34** via carbopalladation, intramolecular trapping, and [3 + 2]-dipolar cycloaddition (**Scheme 8**).[68] 2-Haloaryl hydrazines and oximes have also been employed.[68] The same type of π-allylPd intermediate was formed in the Pd-catalyzed reaction of 2-(2-iodophenyl)propenamides **35** with allenes and was efficiently trapped by $TMSN_3$. Subsequent intramolecular 1,3-dipolar cycloaddition produced triazolotetraisoquinolines **36** highly efficiently.[69] With 5-bromo-2-iodobenzonitrile, tetrazole derivatives were formed. In addition, these allylic palladium intermediates underwent umploung with indium to form π-allylIn intermediates, which reacted readily with *N*-sulfinyl α-imino esters to give rise to α-(2-aryl allyl) α-amino acid esters.[70]

The $Pd(PPh_3)_4$-catalyzed reaction of *N*-(*o*-bromobenzyl)-4,5-hexadienamide (**37**) with 2-thienyl iodide and $PhB(OH)_2$ forms tricyclic amide **38** via an intermolecular allene carbopalladation, amine trapping, cyclic carbopalladation, and intermolecular Suzuki coupling.[71] Cyclic carbopalladation of the aryl iodide moiety with the allene moiety in **39** has been applied to the insertion and ring opening of oxabenzonorbornadiene for the synthesis of methane derivatives **40**, possessing two benzocyclic substitutents (**Scheme 9**).[72]

Intermolecular carbopalladation of functionalized allenes has been further demonstrated to afford cyclic products via the introduction of a third component containing a C=C or N=N bond.[4g,73] The nitrogen-centered nucleophile that traps the in situ formed π-allylPd intermediate is generated by the 1,2 addition of the original carbon nucleophile in the starting allenes to the C=N or N=N bond. This type of π-allylPd intermediate also undergoes a cyclic carbopalladation with an intramolecular carbon–carbon double bond to produce a species containing an sp^3-carbon–palladium bond. Subsequent carbopalladation with the aromatic ring introduced by the first intermolecular carbopalladation efficiently affords tricyclic compound **42** with high diastereoselectivity (**eq 4**).[74]

Alkoxycarbonylnickel cyanide formed from the oxidative addition of α-cyanocarboxylate with Ni(0) undergoes sequential carbonickellation of allenes and reductive elimination to afford 2-(1-cyanoalkyl)-2-alkenoates as the major products.[75]

Transmetallation of organoboronic acids with a Pd(II) complex forms aryl-, alkenyl-, or even alkylpalladium species. These species readily undergo carbopalladation with 2,3-allenoates to form π-allylPd intermediates. Subsequent 1,2 addition with aldehydes and lactonization provide α,β-unsaturated δ-lactones.[76] Recently, our group achieved a similar reaction by employing $RhCl(PPh_3)_3$ as the catalyst.[77] Intramolecular conjugate addition of such a π-allylPd species with 2-alkynoates affords 7- or 8-membered cyclic alkenes.[78] By utilizing $[Rh(OH)((R)\text{-BINAP})]_2$ as the catalyst, Hayashi and co-workers have demonstrated that the reaction of 1-alkyl-substituted 1,2-allenylphosphine oxides with arylboronic acids leads to (*S*)-2-aryl-3-diphenylphosphinylalkenes in 96–98% ee's. In contrast, the enantioselectivity with the 1-phenyl-substituted substrate is low (69% ee).[79]

3.3. Reactions Initiated by Nucleometallation

The intramolecular oxypalladation of 2,3-allenoic acids forms differently β-substituted butenolides in the presence of ω-alkenyl bromides, 1,2-allenyl ketones, 2,3-allenoic acids, 2,3-allenols, propargylic carbonates, and propargylic propiolates.[4g,80] A similar reaction of allenylamines with organic halides affords azacyclic products.[21]

4. Cycloisomerization and Eliminative Cyclization of Functionalized Allenes

4.1. Cycloisomerization

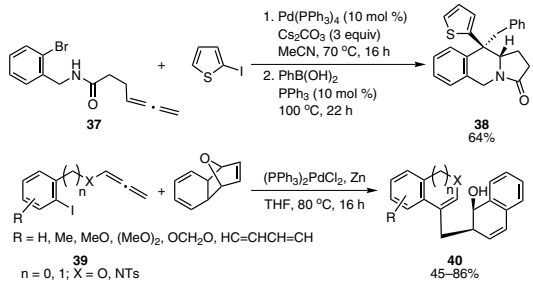
The Au(I)-catalyzed, regioselective, intramolecular hydroamination of 4,5- or 5,6-allenylamines is an efficient step in the highly regioselective synthesis of pyrrolidines, pyrrolines, and piperidines.[81,82] Toste and co-workers have reported a gold-catalyzed, enantioselective version of this reaction that efficiently forms the optically active, 5- or 6-membered-ring azacyclic compounds **44** (**eq 5**).[83] 2,3-Allenylamines undergo hydroamination to afford pyrrolines by employing inorganic Ag or Au salts or K_2CO_3.[84]

Likewise, the cycloisomerization of 2,3- or 3,4-allenols in the presence of Au(I) or Au(III) catalyst affords 2,5-dihydrofurans or dihydropyrans.[85] Morita and Krause recently reported that under AuCl catalysis, even 2,3-allenylthiols similarly cycloisomerize to yield 2,5-dihydrothiophenes.[86] An enantioselective, Au-catalyzed cyclative hydroalkoxylation of 4,5- or 5,6-allenols **45** affords 2-vinyltetrahydrofurans or tetrahydropyrans, **46**, in good-to-high yields and enantioselectivities (**eq 6**).[87]

The cycloisomerization of 1,2-allenyl ketones in the presence of a Au(III)-porphyrin complex produces 2,3,5-trisubstituted furans.[88a] Moreover, 3-halo-1,2-allenyl ketones undergo $AuCl_3$-catalyzed, 1,2-halogen migrative cyclization to generate the not-readily-available 3-halofurans.[88] The thioether group in 2-phenylthio-3,4-allenoates or ketones nucleophilically initiates a cyclization that leads to 2-phenylthiomethylfuran derivatives.[89] CuCl has been used to catalyze the cycloisomerization of 2,3-allenoic acids accompanied by a highly efficient chirality transfer.[90]

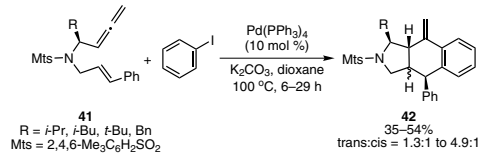
(3'-Acetoxy-1',2'-allenyl)benzenes **48** cyclize to indene derivatives **49** and **50** with the assistance of $[i\text{-PrAuCl}]–AgBF_4$ in CH_2Cl_2 (**Scheme 10**).[91] $PtCl_2$[92] or $Ph_3PAuCl–AgSbF_6$[93] catalyzes the cyclization of simple vinylic allenes **51** into cyclopentadiene derivatives **52**.

Ph_3P•AuOTf catalyzes the hydropyrrolation of allenes, leading to six-membered rings and high efficiency of chirality transfer. This reaction has been successfully applied to the total



Ref. 71,72

Scheme 9. Further Examples of Allene Carbopalladation.



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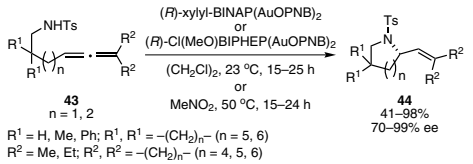
eq 4



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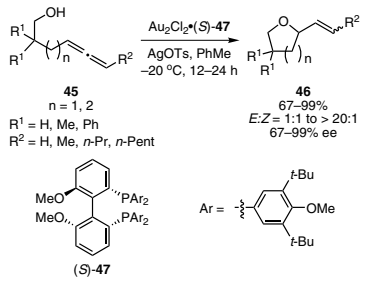
eq 5



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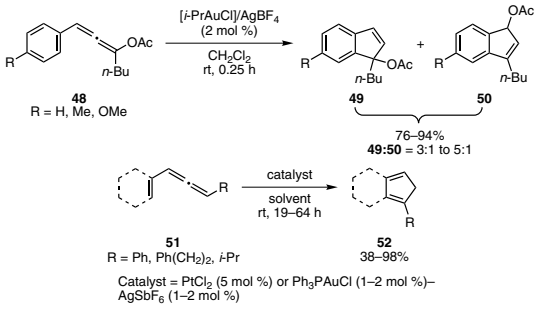
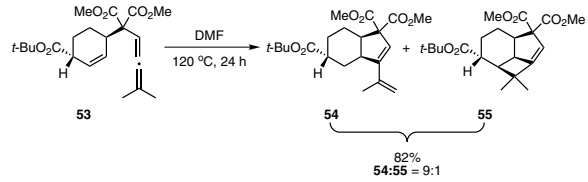
eq 6



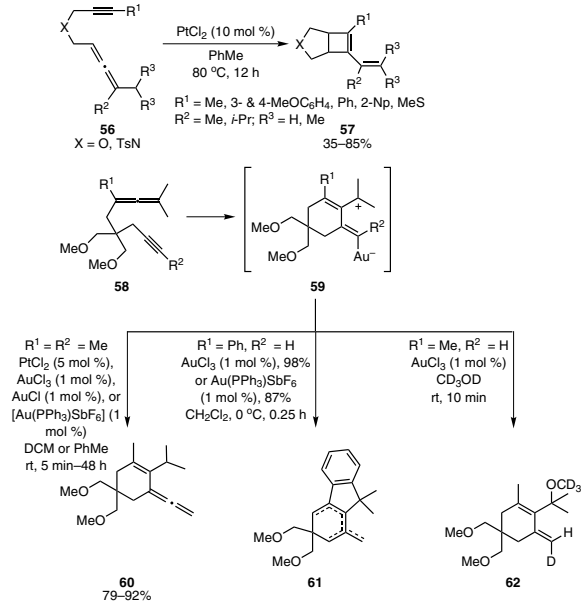
Ref. 91,92,93

Scheme 10. Cycloisomerization of Functionalized Allenes.



Ref. 95

eq 7



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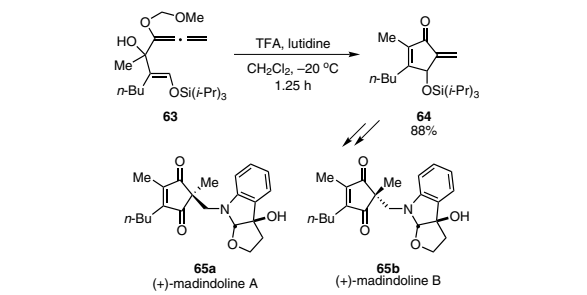
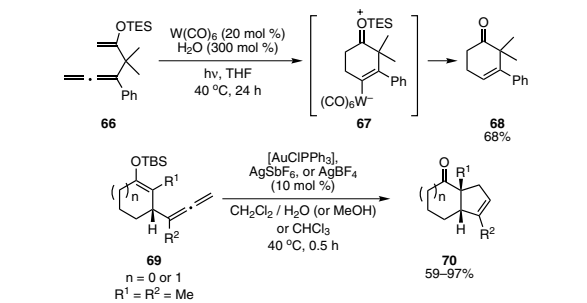
Scheme 11. Cycloisomerization of Allene–Ynes.



Ref. 100

Scheme 12. The Eliminative Cyclization of Allenyl Ethers in the Total Synthesis of (+)-Madindoline A and B.



Ref. 101,102

Scheme 13. Intramolecular Eliminative Cyclization between Allenes and Silyl Enol Ethers.

synthesis of (–)-rhazinilam,[94] and its intramolecular variant, involving indoles, has been observed by Widenhoefer and co-workers.[82] 1,4-Allene–enes **53** undergo a thermal, Alder-ene-type cycloisomerization to form the cyclopentene unit in **54** (**eq 7**).[95] The [2 + 2]-cycloaddition product, **55**, is formed as the minor product. Such a reaction also takes place with 1-(4-pentenyl)-1,2-allenyl sulfones in the presence of Grubbs second-generation catalyst.[96]

In propargyl 2,3-allenyl ethers or tosylamides, **56**, the allene functional group attacks the alkyne coordinated with Pt to form vinylcyclobutenes, **57**.[97] Similarly, the treatment of allene–ynes **58** with a catalytic amount of $AuCl_3$ or $Au(PPh_3)NTf_2$ in CH_2Cl_2 affords 6-membered-ring products **60–62** via the common intermediate **59** (**Scheme 11**).[98]

4.2. Eliminative Cyclization

$AuCl_3$ catalyzes the dealkylative cyclization of *tert*-butyl 2,3-allenoates to butenolides.[99] Wan and Tius have applied the Nazarov reaction of allenyl methoxymethyl ether **63** to the total synthesis of (+)-madindoline A (**65a**) and B (**65b**) (**Scheme 12**).[100]

The intramolecular attack of the silyl enol ether onto the tungsten-coordinated allene derived from **66** leads to the cyclic alkenyltungsten intermediate **67**, which affords 2,2-dimethyl-3-phenyl-3-cyclohexenone (**68**) upon protonolysis (**Scheme 13**).[101] Toste and co-workers observed that $Ph_3PAuCl–AgBF_4$ also catalyzes this type of transformation, converting **69** into the bicyclic product **70**.[102]

Huang and Zhang reported that, under catalysis by the gold complex **72**, vinylic 1-OMOM-1,2-propadienyl carbinol trimethylsilyl ethers, **71**, cyclize via **73**, **74**, and **75** to cyclopentene derivatives **76** in 44–99% yields (**Scheme 14**).[103]

5. Cycloaddition Reactions

1,2-Bis(1-phosphinyl-1,2-allenyl)benzenes undergo [2 + 2] cycloaddition, affording naphtha[*h*]cyclobutenes in 81–99% yields.[104] Braverman and co-workers reported that conjugated bisallenes bearing two electron-withdrawing sulfoxide or sulfone functionalities cyclize to 3,4-bis(methylene)cyclobutenes.[105] Irradiation of 3-(*N*-2,3-butadienyl)aminocyclopentenones or cyclohexenones, **77**, provides [2 + 2]-cycloaddition products **78**, which undergo an α-carbon–carbon single-bond cleavage to form pyrroles **80** via **79** (**Scheme 15**).[106]

A similar intramolecular [2 + 2] cycloaddition between an allene and a carbon–carbon double or triple bond was reported by the group of Ohno and Tanaka and that of Brummond.[107] The intermolecular [2 + 2] cycloaddition of the more electron-rich C=C bonds in 2-silyloxy-1,3-dienes with ethyl 2-methyl-2,3-butadienoate leads to vinyl 3-(ethoxycarbonylpropylidene)-cyclobutanols in 35–80% yields.[108] 1,1-Bis(ethoxy)ethene also reacts with ethyl 2-methyl-2,3-butadienoate to give 3-(ethoxy-carbonylpropylidene)cyclobutanone diethyl ketal in 28% yield.[108b] An aza-Diels–Alder reaction was observed between the 2,4-diene unit in allenyltrimethylsilylthioketenes **81** and imines, affording δ-thiolactams **82** (**Scheme 16**).[109]

The Diels–Alder reaction of 1,1,3-trioxygenated-1,3-dienes with allenes bearing two nonequivalent electron-withdrawing groups at the 1 and 3 positions gives rise to a mixture of polysubstituted aromatic products.[110] 3-(Ethoxycarbonyl)-3,4-pentadienoate isomerizes to form 3-(ethoxycarbonyl)-2,4-pentadienoate, which undergoes a $(n\text{-Bu})_3P$-catalyzed aza-[4 + 2] cycloaddition with 2-imino-*N*-methylindole. This reaction has been applied to the formal synthesis of (±)-alstonerine and

(±)-macroline.[111] The Diels–Alder reaction also occurs between the relatively electron-deficient carbon–carbon double bond of optically active allenic ketones and the 1,3-diene unit in furan.[112] Vinylallenes act as 1,3-dienes in their cycloaddition reactions with DEAD, aldehydes, or SO_2 to afford 5- or 6-membered-ring products.[113,114] (*Z*)-Bis(allenyl)ethene **84** readily undergoes a 6π electrocyclization to afford 3,4-bis(alkylidene)-1,5-cyclohexadiene, **85**. In the presence of the intramolecular C=C bond, a [4 + 2] cycloaddition follows, leading to steroid-like tetracyclic product **87** after reduction of **86** (**Scheme 17**).[115]

The diazo moiety in allenyl 1,4-dicarbonyl compounds reacts intramolecularly, under $Rh_2(OAc)_4$ catalysis, with the carbonyl group closer to the allene moiety to form a carbonyl–ylide intermediate, which undergoes intramolecular cycloaddition with the proximal C=C bond of the allene to construct tricyclic bridged products (**eq 8**).[9a,b] In addition, the intramolecular [3 + 2] cycloaddition of 3,4-allenyl azides affords pyrrolidine-containing bi- or tricyclic products in the presence of TMSCN.[116]

6. Cyclometallation Reactions

The intermolecular, three-component reaction of an aldehyde, allene, and dialkylzinc gives homoallylic alcohols.[6,117] Ng and Jamison have reported that the $Ni(cod)_2$-catalyzed intermolecular reaction of allenes and aldehydes in the presence of R_3SiH affords allyl silyl ethers in high yields and stereoselectivities. Starting with optically active allene **88** (95% ee), optically active allyl silyl ether **89** is formed in 95% ee (**eq 9**).[118]

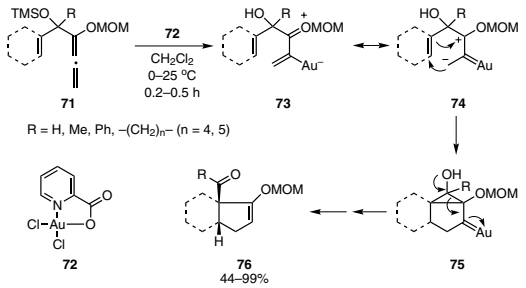
Even CO_2 undergoes $Ni(cod)_2$-catalyzed cyclometallation with 3-substituted 1,2-allenylsilanes, leading to stereodefined *syn-anti*-π-allylnickel intermediates. These intermediates react with another equivalent of CO_2 to form (*E*)-3-(methoxycarbonyl)-4-silyl-3-alkenyl carboxylates after hydrolysis with HCl and esterification with CH_2N_2.[119] $Pd(O_2CCF_3)_2$ catalyzes the efficient cyclometallation and double dehydropalladation of allene–ene **90** to produce the cis-fused bicyclic product **91** (**eq 10**).[120] In this reaction, O_2, *p*-benzoquinone (4 mol %), and iron(II) phthalocyanine (FePc) were used to complete the catalytic cycle.

Wegner et al. reported that the cyclometallation of allenes **93** with vinylcyclopropanes **92** forms intermediates **94**, which, upon β-decarbometallation to open the three-membered ring, produce intermediates **95**. Subsequent reductive elimination and hydrolysis afford 4-(1-alkynylalkylidene)cycloheptanones **96** (**Scheme 18**).[121]

Furthermore, $Pd_2(dba)_3$ catalyzes the intramolecular, overall [3 + 2] cycloaddition of the alkylidenecyclopropane and allene moieties in **97**. The overall transformation is accomplished via cyclometallation of **97**, decarbopalladation of **98**, and reductive elimination of **99**, giving rise to the fused bicyclic products **100** and **101** in 68–90% yields (**Scheme 19**).[122]

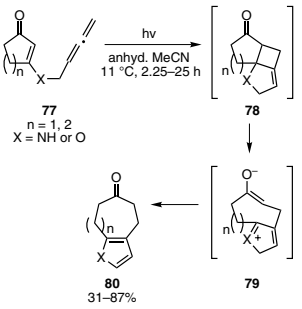
The cyclic Pauson–Khand reaction of an allene with a 1,3-diene affords bicyclic ketones.[123] Similarly, the $Mo(CO)_3(MeCN)_3$-catalyzed, intramolecular Pauson–Khand reaction of an allene and an alkyne that are tethered by a benzene ring, as in **102**, forms tricyclic ketones **103** in high yields (**eq 11**).[124]

$[RhCl(CO)(dppp)]_2$ or $[RhCl(CO)_2]_2$ catalyzes the intramolecular Pauson–Khand reaction of the 1,2-allenyl sulfone and the alkyne units in **104**, affording the expected bicyclic ketones **106** in an atmosphere of CO. However, the corresponding β-hydride and reductive elimination products, **107**, are also formed.[125] With an oxygen or nitrogen tether, the



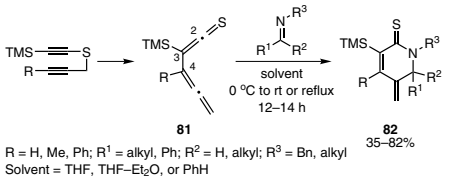
Ref. 103

Scheme 14. Gold-Catalyzed, Intramolecular, Eliminative Cyclization.



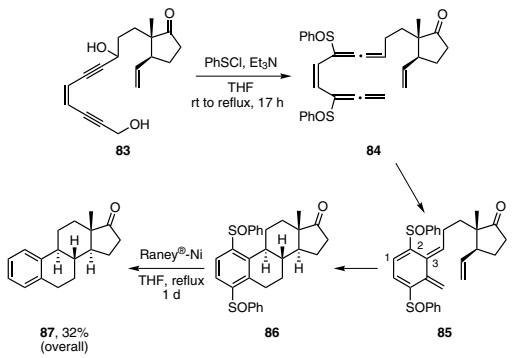
Ref. 106

Scheme 15. Intramolecular [2 + 2] Cycloaddition of Allenic Cyclic Enones.



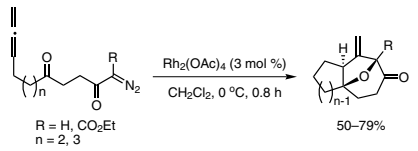
Ref. 109

Scheme 16. Aza-Diels–Alder Reaction of Imines with Allenyltrimethylsilylthioketenes.



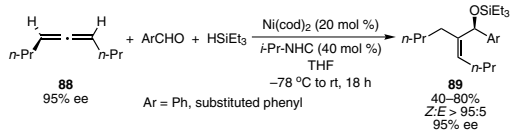
Ref. 115

Scheme 17. 6π Electrocyclization of (*Z*)-Bis(allenyl)ethene.



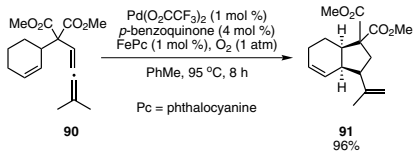
Ref. 9b

eq 8



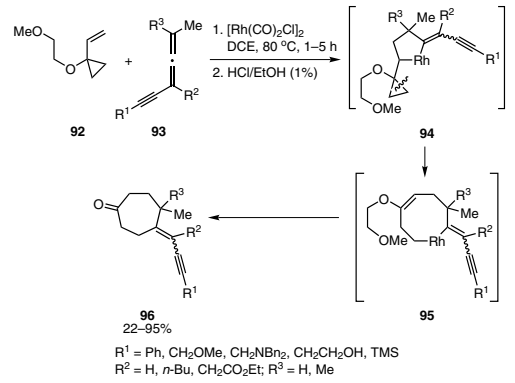
Ref. 118a

eq 9



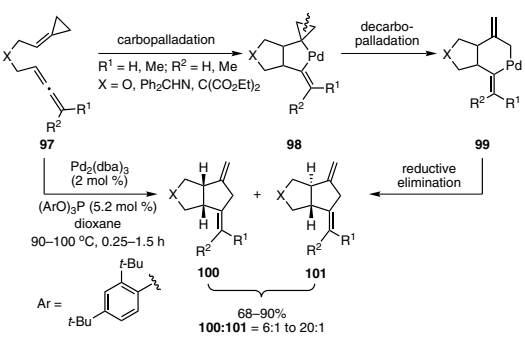
Ref. 120

eq 10



Ref. 121

Scheme 18. Cyclometallation of Allenes with Vinylcyclopropanes.



Ref. 122

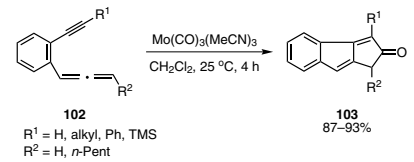
Scheme 19. The Overall, Intramolecular Allene–Alkene [3 + 2] Cycloaddition Achieved via Cyclometallation, Decarbopalladation, and Reductive Elimination.

selectivity for the formation of ketones becomes very high. Of course, under a N_2 atmosphere, the β-H elimination–reductive elimination products are the only ones formed. By employing a benzene tether to connect the alkyne and the 1,2-allenyl sulfone units, tricyclic ketones, with an eight-membered ring in the middle, are produced in high yields.[126] Similarly structured allene–ene **108** leads to bicyclic α,β-unsaturated ketones **109** efficiently (**Scheme 20**).[127]

The analogous $Mo(CO)_6$-catalyzed reaction of 2,3-allenyl 1-alkynyl carbinols or their TBS ethers, **110**, produces the bicyclic ketones **111** in good-to-high yields.[128] The metallacyclopentene intermediate formed by such a cyclometallation of allene with alkyne in **112** in the presence of $PdCl_2(PPh_3)_2$ undergoes reductive elimination to form the fused bicyclic cyclobutene **113** (**Scheme 21**).[129]

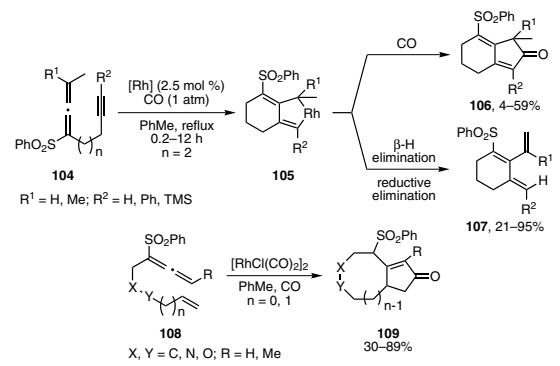
The cyclometallation, β-H elimination, and reductive elimination sequence of allenediyne **114** leads to intermediate **115** (**Scheme 22**).[6,130,131] The conjugated diene unit in **115** easily undergoes an intramolecular Diels–Alder reaction to afford tricyclic products **116** in 77% yields. This protocol has recently been applied to the synthesis of α-alkylidene-β-vinyl-β,γ-unsaturated lactams.[132] Similarly, Co(I) mediates the intramolecular [2 + 2 + 2] cyclization of allenediyne **117**, leading to the steroid-like tetracyclic ketone **118**.[133]

Dixneuf and co-workers observed a Cp*RuCl(cod)-catalyzed intermolecular [2 + 2] cycloaddition of the two terminal carbon–carbon double bonds of the two molecules of propadienylboronate. In contrast, the analogous reaction of phenylpropadienylboronate with $Cp^*Ru(MeCN)_2(PPh_3)PF_6$ afforded the [2 + 2] cycloaddition product of the internal C=C bonds.[134] We have recently demonstrated a Pd-catalyzed intramolecular



Ref. 124

eq 11



Ref. 125,127

Scheme 20. Intramolecular Pauson–Khand Reaction of an Allenyl Sulfone with an Alkene or Alkyne.

[2 + 2] cycloaddition of the two *internal* C=C bonds in 1,5-bisallenes **119**, affording bicyclic products with two exo C=C bonds. Upon heating in xylene, the two *terminal* C=C bonds in **119** undergo [2 + 2] cycloaddition.[135] We have also shown that the bimolecular cyclization of **119** forms steroid-like tetracyclic products **120** in the presence of *trans*-[RhCl(CO)(PPh_3)$_2$] as catalyst (**eq 12**).[136]

Pd(0) undergoes cyclometallation with the 1,3-diene unit in the in situ formed 2-aryl-1,3,4-pentatrienes **121** to generate α-methylenepalladacyclopentenes **122**. Palladacycles **122** react with another molecule of **121** forming palladacyclononadiene intermediates **123**. Reductive elimination affords 3,4-dimethylene-1,5-octadienes **124**, which readily undergo an intermolecular Diels–Alder reaction with a dienophile to build the fused 6-membered ring in **125** (**Scheme 23**).[137]

7. Conclusions

Through the systematic study of the chemistry of allenes, intrinsic chemical properties of allenes have been demonstrated showing their potential in modern synthetic organic chemistry. In some cases, chemists have successfully applied the developed reactions to the efficient synthesis of natural products. It is relatively safe to predict that many exciting reactions of allenes will be unveiled by chemists in the not-so-distant future. Due to their substituent-loading capability, the reactions of allenes may nicely show diversity in organic synthesis; the axial chirality in allenes may open new doors on asymmetric synthesis.

8. Acknowledgments

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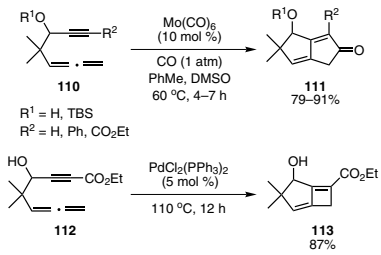
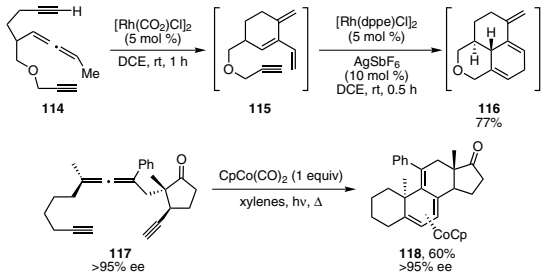


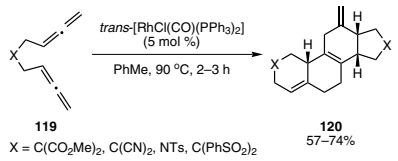
Ref. 128,129a

Scheme 21. The Intramolecular Cyclometallation of 2,3-Allenyl 1-Alkynyl Carbinols.



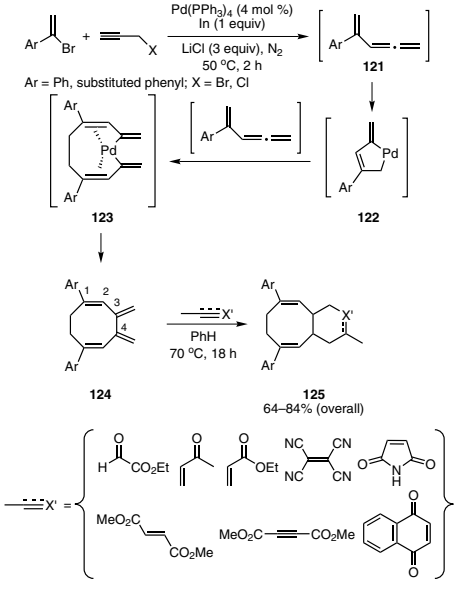
Ref. 131,133

Scheme 22. The Intramolecular Cyclometallation of Allenediynes.



Ref. 136

eq 12



Ref. 137

Scheme 23. Cyclopalladation–Reductive Elimination Sequence in 1,3,4-Pentatrienes.

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About the Author

Shengming Ma is originally from Zhejiang Province, China. He received a B.S. degree in chemistry from Hangzhou University (1986), an M.S. degree (1988) and a Ph.D. degree (1990) from the Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences. After postdoctoral research at ETH, Switzerland, and Purdue University, U.S.A., he joined, in 1997, the faculty of SIOC, where he is now the Director of the State Key Laboratory of Organometallic Chemistry. Since February 2003, he has held dual appointments: Research Professor of Chemistry at SIOC and Cheung Kong Scholars Program Professor at Zhejiang University.

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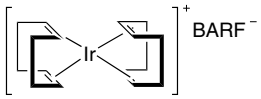

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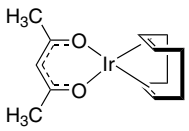

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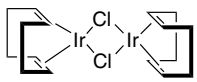

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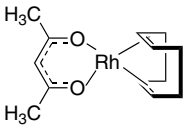

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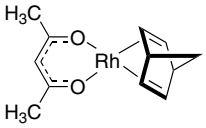

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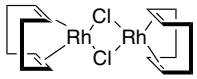

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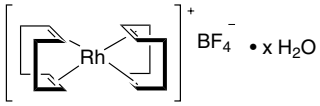

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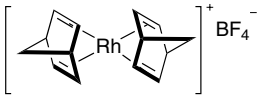

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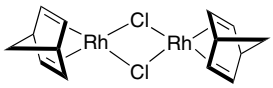

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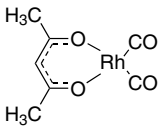

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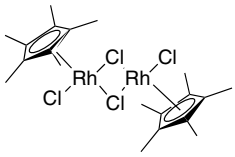

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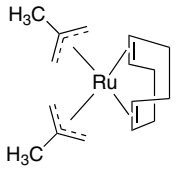

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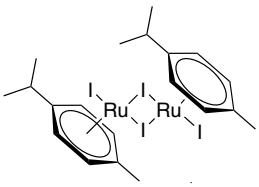

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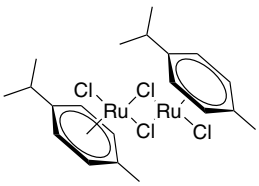

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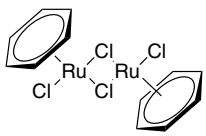

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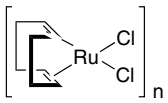

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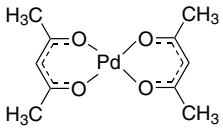

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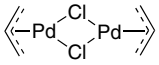

683396

$Pd(OAc)_2$

683124

Pd_2dba_3

683345

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Takasago Portfolio

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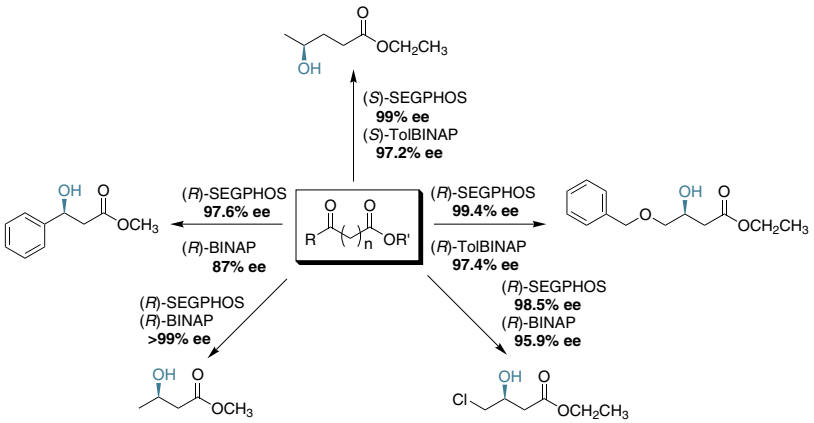
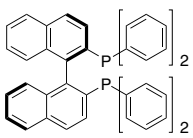


Sigma-Aldrich and Takasago International Corporation are pleased to announce their collaboration to offer a portfolio of ligands and complexes for asymmetric catalysis.

References: Saito, T. et al. *Adv. Synth. Catal.* **2001**, *343*, 264. Sumi, K.; Kumobayashi, H. *Top. Organomet. Chem.* **2004**, *6*, 63. Noyori, R. et al. *J. Am. Chem. Soc.* **1987**, *109*, 5856.



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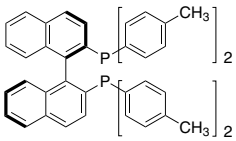
693065

(*S*)-BINAP
693057



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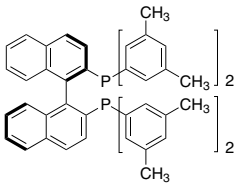
693049

(*S*)-TolBINAP
693030



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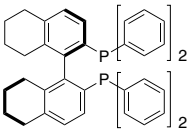
692379
U.S. Patent No. 2041996

(*S*)-XylBINAP
693022



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692387
U.S. Patent No. 2681057

(*S*)-H_8-BINAP
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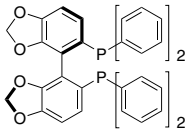

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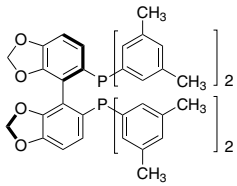
692395
U.S. Patent No. 3148136

(*S*)-SEGPHOS
693006



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692476
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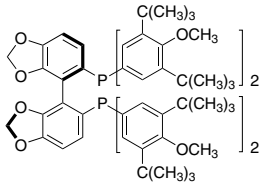

(*R*)-DTBM-SEGPHOS
692484
U.S. Patent No. 3148136

(*S*)-DTBM-SEGPHOS
692980

Takasago (*R*)-Ligand Kit I

This kit includes 50 mg of all of the Takasago (*R*)-ligands for rapid screening of chiral catalysts.

695270

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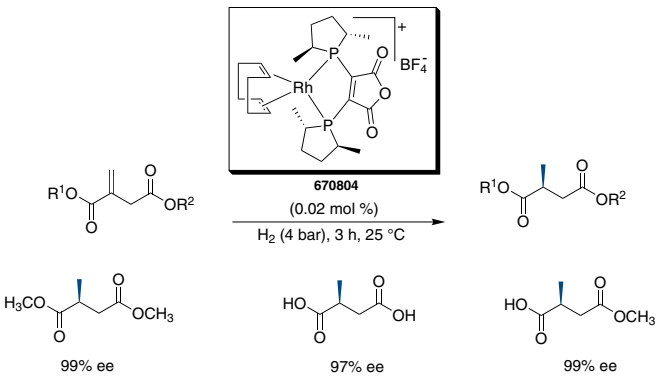
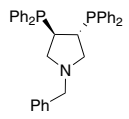
Evonik developed a new family of highly tunable chiral ligands for a variety of rhodium-catalyzed asymmetric transformations. Based on phospholane ligands, catASium® M(*R*)Rh showed high enantioselectivity for the hydrogenation of *E* or *Z* β-acylamido acrylates under mild conditions and low pressure. Several derivatives of this ligand have been synthesized with a different range of reactivities. Even with very low loadings, high enantioselectivities are obtained in the hydrogenation of terminal alkenes.

Evonik's catASium products are available as free ligands or in the form of their Rh complexes.

Reference: Holz J. et al. *J. Org. Chem.* **2003**, *68*, 1701.





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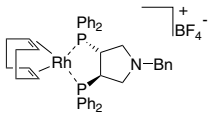

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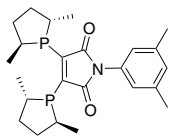

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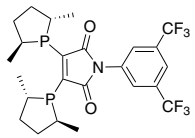

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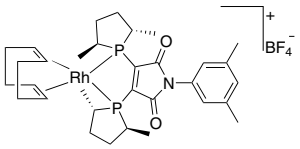

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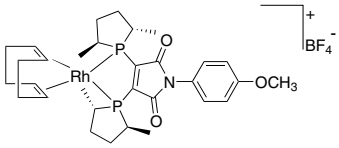

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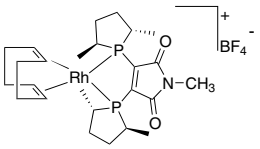

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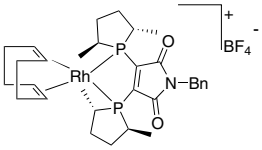

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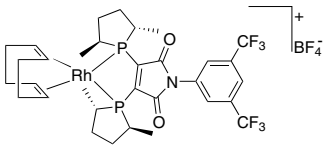

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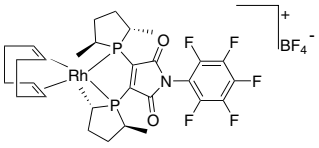

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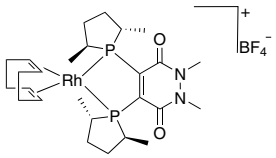

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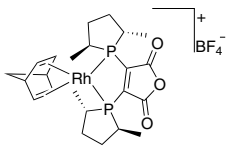

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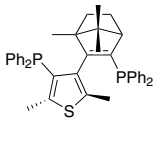

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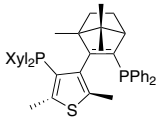

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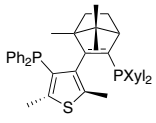

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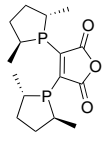

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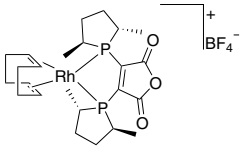

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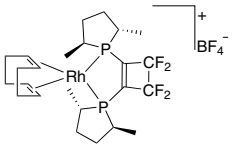

catASium MQF(*R*)Rh
670472

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ALDRICH Chemistry

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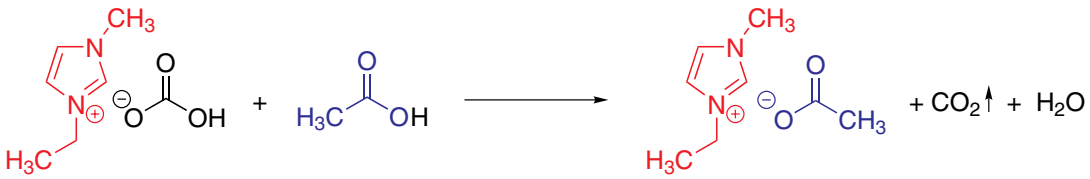


CBILS
EMIM HCO_3

Brønsted acid

Ionic liquid
EMIM acetate

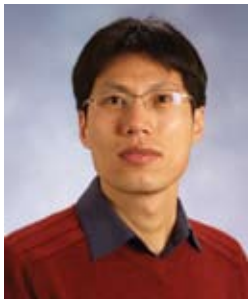
Key Features

- Choose the CBILS precursor containing the cation of interest.
- Select the anion of choice in the form of the corresponding Brønsted acid.
- Calculate the necessary stoichiometry to form the new ionic liquid.
- Mix the components and stir until CO_2 generation subsides.
- Remove the solvent and reaction byproduct (water or methanol).

For more information, please visit *sigma-aldrich.com/cbils*.

Chiral Imidazolium Ionic Liquids: Their Synthesis and Influence on the Outcome of Organic Reactions

Professor Allan D. Headley



Dr. Bukuo Ni

Allan D. Headley and Bukuo Ni*
Department of Chemistry
Texas A&M University-Commerce
Commerce, TX 75429-3011, USA
Email: allan_headley@tamu-commerce.edu

Outline

1. Introduction

Research in the field of ionic liquids (ILs) has grown exponentially in recent years. The need to have alternative solvents that are environmentally friendly, and can serve as effective substitutes for conventional organic solvents, has driven this rapid growth. The first report of a room-temperature ionic liquid appeared in 1914;[1] since then, ionic liquids have been utilized in numerous applications, including as electrolytes for batteries.[2] Ionic liquids seem to be ideal replacement solvents, since they are typically liquids below 100 °C and are thermally stable over a very wide temperature range; some maintain their liquid state at temperatures as high as 200 °C.[3] Ionic liquids consist of cations and anions and, owing to the very strong ion–ion interactions, they exhibit low vapor pressures and high boiling points. The factors that dictate their physical properties depend on the nature of both the cation and anion. Ionic liquids that contain aromatic heterocyclic cations tend to have lower melting points than those containing aliphatic ammonium ions. Ionic liquids that contain highly electronegative anions, such as organic amides, typically have lower melting points than those containing halide anions. As a result, most ionic liquids that can serve as effective organic solvents consist of imidazolium or pyridinium cations and anions such as AlX_4^-, BF_4^-, PF_6^-, $CF_3SO_3^-$, $(CF_3SO_3)_2N^-$, or halides.

The modification of the structures of the cations or anions of ionic liquids can result in unique solvent properties that dramatically influence the outcome of various reactions, including asymmetric reactions. Recently, there has been a dramatic increase in the use of room-temperature ionic liquids (RTILs) as solvents for organic synthesis.[4] RTILs have become the solvents of choice for 'green chemistry' and are employed in a wide variety of reactions.[5] One of the main advantages of ionic liquids as solvents over conventional ones is that RTILs are typically recyclable.

Ionic liquids that have gained widespread use as solvents for organic reactions can be divided into two categories: chiral and achiral RTILs. Owing to the vast number of structurally different RTILs that have been synthesized, this review focuses on imidazolium ionic liquids that possess chirality either in the imidazolium moiety or in the anion moiety. It discusses first the design and synthesis of chiral imidazolium ionic liquids, and then highlights their influence on the outcome of asymmetric reactions.

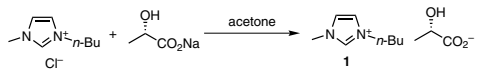
2. Design and Synthesis of Chiral Imidazolium Ionic Liquids (CIILs)

2.1. CIILs of Chiral Anions

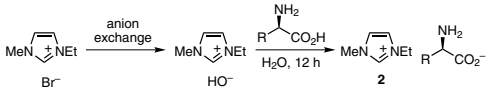
In 1999, Seddon and co-workers reported the first example of a chiral ionic liquid, 1-*n*-butyl-3-methylimidazolium L-lactate ([BMIM][lactate], **1**), prepared simply by reacting sodium (*S*)-2-hydroxypropionate and [BMIM]Cl in acetone, followed by a straightforward workup (**eq 1**).[6]

The synthesis of other ionic liquids that contain chiral anions relies on anion-exchange techniques. For example, Ohno's research group synthesized 20 room-temperature chiral ionic liquids (RTCILs) in which the chiral anions were derived from naturally occurring amino acids. The synthesis involved two steps: the conversion of 1-ethyl-3-methylimidazolium bromide ([EMIM][Br]) into 1-ethyl-3-methylimidazolium hydroxide ([EMIM][OH]) using an anion-exchange resin, followed by neutralization with a series of natural amino acids to give amino acid ionic liquids **2** (**Scheme 1**).[7]

These ionic liquids are transparent and nearly colorless liquids at room temperature; they are miscible with various organic solvents such as methanol, acetonitrile, and chloroform. However, chiral ionic liquids that are similar to **2** and contain two carboxyl groups—[EMIM][Glu] and [EMIM][Asp]—are insoluble in chloroform. Nineteen of the 20 ionic liquids are thermally stable at temperatures above 200 °C; only [EMIM][Cys] exhibits thermal stability up to 173 °C. The authors also explored the effects different side chains have on the glass transition-temperature (T_g) of ionic liquids in the temperature range –65 °C to 6 °C. It was observed that an increase in the length of the alkyl side chain results in a gradual increase in T_g, which was attributed to an increase in the van der Waals attraction between the alkyl groups.



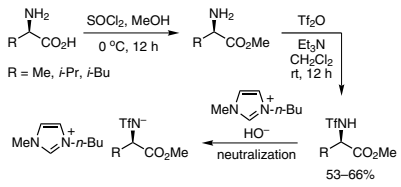
Ref. 6 **eq 1**



AA Moiety in **2**	*Tg* (°C)	Yield of **2**	AA Moiety in **2**	*Tg* (°C)	Yield of **2**
Gly	–65	82%	Phe	–36	83%
Ala	–57	86%	Trp	–31	82%
Met	–57	78%	His	–24	78%
Val	–52	79%	Tyr	–23	70%
Ile	–52	82%	Cys	–19	77%
Leu	–51	80%	Arg	–18	74%
Ser	–49	79%	Asn	–16	83%
Pro	–48	83%	Gln	–12	66%
Lys	–47	78%	Asp	5	89%
Thr	–40	84%	Glu	6	80%

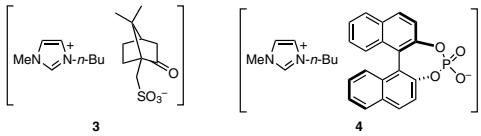
Ref. 7

Scheme 1. Synthesis of Ionic Liquids of Chiral Anions from Amino Acids.



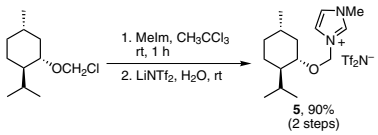
Ref. 8

Scheme 2. Preparation of CIILs from Amino Acid Derivatives.



Ref. 9

Figure 1. Chiral Imidazolium Ionic Liquids of Chiral Anions.



Ref. 10 **eq 2**

Other naturally occurring molecules have also served as starting materials for the synthesis of chiral ionic liquids that contain chirality in the anionic moiety. Machado and Dorta described the synthesis of CILs **3** and **4** on a multigram scale by a simple exchange of commercially available [BMIM]Cl with the potassium salts of (*S*)-10-camphorsulfonate and (*R*)-1,1'-binaphthyl-2,2'-diylphosphate in CH_2Cl_2–H_2O (**Figure 1**).[9] Both salts are hygroscopic; **3** is a very viscous golden oil, while **4** is a white solid with a melting point of 78–80 °C. As the preceding examples demonstrate, anion exchange using chiral anions is a proven technique for synthesizing CILs that contain the chirality in the anionic moiety.

2.2. CIILs of Chiral Cations

A greater number of known chiral ionic liquids derive their chirality from the cationic moiety. Owing to the ready availability of naturally occurring chiral amines, alcohols, and amino acids, they are typically the most prevalent in CIILs of chiral cations.

2.2.1. CIILs from Chiral Chlorides, Amines, and Alcohols

Commercially available (+)- and (–)-chloromethyl menthyl ethers have been used for the preparation of both enantiomers of CIIL **5** in two steps: alkylation followed by anion exchange (**eq 2**).[10] In 2003, Bao et al. reported the synthesis of a chiral imidazolium ionic liquid with cationic chirality obtained from the chiral amine (*R*)-(+)-α-methylbenzylamine.[11] Imidazolium salt **7** was obtained in three steps involving condensation of the chiral amine with ammonia, glyoxal, and formaldehyde; alkylation with bromoethane in CH_3CCl_3; and anion exchange with $NaBF_4$ in acetone (**Scheme 3**). Unfortunately, due to the high melting point of this ionic liquid (90 °C), it could not serve as an effective solvent for asymmetric reactions.

A similar strategy was utilized for the preparation of ionic liquid **8**, which contains two chiral centers, each bonded to a nitrogen atom of the imidazolium cation. For this synthesis, two equivalents of α-methylbenzylamine were consumed and an overall yield of 30% was obtained (**eq 3**).[10]

Recently, Génisson et al. also used (*R*)-(+)-α-methylbenzylamine as the starting material for a series of novel chiral imidazolium derivatives (**Scheme 4**).[12] Alkylation of (*R*)-(+)-α-methylbenzylamine with chloroethylamine gave chiral 1,2-diamines, which were subjected to a ring-closing reaction with an appropriate ortho ester electrophile to obtain

4,5-dihydroimidazoles. Dehydrogenation of the dihydroimidazoles with manganese-based oxidants gave various C-2 substituted and unsubstituted imidazole rings. The target CIILs, **9**, were obtained by N-alkylation with *n*-pentyl bromide and anion exchange with $NaBF_4$ or $LiNTf_2$. The resulting BF_4^- and Tf_2N^- salts are water-immiscible liquids at room temperature, and their glass-transition temperatures are as low as –39 °C and –48 °C, respectively.

The chiral alcohols (*S*)-2-hexanol and (*R*)-α-methylbenzyl alcohol were utilized for the preparation of a similar type of chiral imidazolium ionic liquid.[13] The Mitsunobu alkylation of imidazole was the key step leading to chiral *N*-alkyl-substituted imidazoles. The configuration of the stereogenic carbinol carbon was confirmed by comparison with authentic samples. The inversion of configuration was virtually complete (>99%) in the case of (*S*)-2-hexanol, but only an 86% selectivity was observed in the case of (*R*)-α-methylbenzyl alcohol. Two of the chiral *N*-alkyl-substituted imidazoles were used as precursors in the synthesis of the corresponding CIILs by N-alkylation with iodomethane (**Scheme 5**).

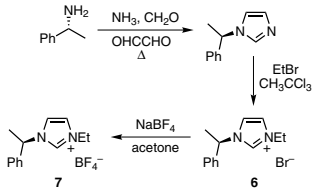
Commercially available (1*S*,2*S*,5*S*)-(–)-myrtanol has also been used as a precursor in the synthesis of another class of CIILs. Imidazolium tosylate salt **11** was formed in 63% yield from the reaction of tosylate **10** and neat methylimidazole at 100 °C for 24 h (**Scheme 6**).[9]

Novel, (3*R*)-citronellol-based CIILs have been synthesized starting with the bromination of (3*R*)-citronellol with Br_2 and PPh_3 in CH_2Cl_2 at room temperature to give the corresponding citronellyl bromide (**Scheme 7**).[14] Heating of this bromide with 1-alkyl-1*H*-imidazoles for several days provided the imidazolium bromide salts which, after anion exchange with $NaBF_4$ in acetone, led to the corresponding imidazolium tetrafluoroborates in 46–94% yields. In addition, 1,3-dicitronellyl-1*H*-imidazolium bromide was obtained by deprotonation of 1*H*-imidazole with $(n\text{-Bu})_4NOH$ and subsequent treatment with 2 equivalents of the chiral bromide. All the (3*R*)-citronellol-based CIILs thus prepared are liquids at room temperature.

2.2.2. CIILs from Amino Acids and Amino Acid Derivatives

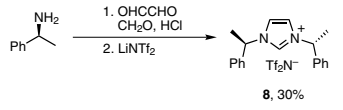
Amino acids form one of the most prominent pools of natural products that can serve as precursors for chiral ionic liquids. In 2003, Bao and co-workers reported, for the first time, the synthesis of CIILs from natural amino acids. Using L-alanine, L-leucine, or L-valine as the chiral starting material, they prepared chiral ionic liquids with one chiral carbon in four steps and in 30–33% overall yields (**Scheme 8**).[11] The imidazole ring was formed by condensation of the amino functionality of the amino acid with formaldehyde, glyoxal, and aqueous ammonia under basic conditions. The initially formed sodium salts were esterified with anhydrous ethanol saturated with dry hydrogen chloride. Reduction of the resulting ethyl esters using $LiAlH_4$ in anhydrous Et_2O led to the corresponding alcohols, which were subjected to alkylation with bromoethane to afford the desired CIILs possessing melting points in the 5–16 °C range. These CIILs are miscible with water, methanol, acetone, and other very polar organic solvents; they are immiscible with weakly polar organic solvents, such as ether and 1,1,1-trichloroethane.

More recently, Xu and co-workers described the synthesis and properties of novel chiral amine-functionalized ionic liquids, which were derived from the natural amino acids L-alanine, L-valine, L-leucine, L-isoleucine, and L-proline in four steps (**Scheme 9**).[15] The key precursors, **12**, were obtained by reduction of the amino acids with $NaBH_4/I_2$, followed by a

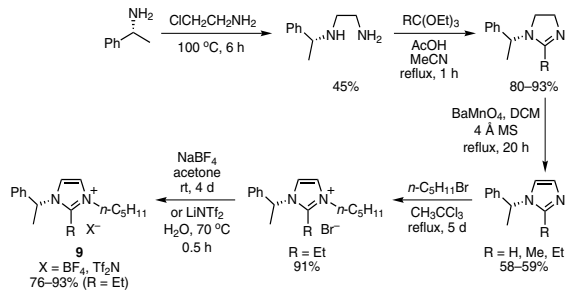


Ref. 11

Scheme 3. Bao's Synthesis of CIILs from (*R*)-(+)-α-Methylbenzylamine.

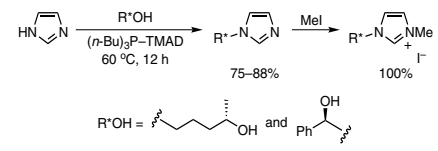


Ref. 10 **eq 3**



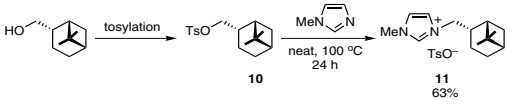
Ref. 12

Scheme 4. Génisson's Synthesis of CIILs from (*R*)-(+)-α-Methylbenzylamine.



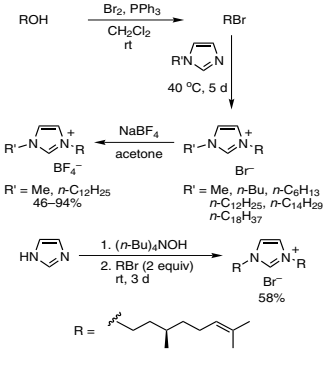
Ref. 13

Scheme 5. Synthesis of CIILs by a Mitsunobu Alkylation.



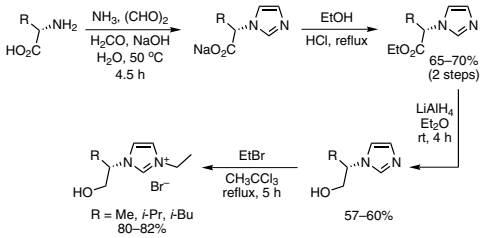
Ref. 9

Scheme 6. Synthesis of (–)-Myrtanol-Based, Chiral Imidazolium Tosylate Salt.



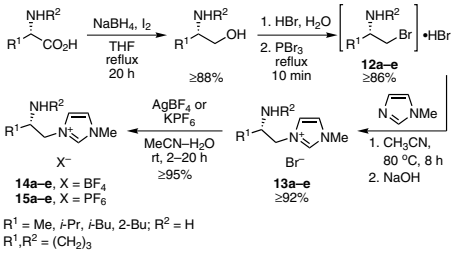
Ref. 14

Scheme 7. Synthesis of CIILs from (3*R*)-Citronellol.



Ref. 11

Scheme 8. CIILs from Naturally Occurring Amino Acids.



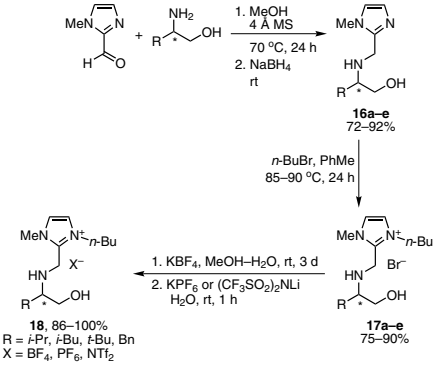
Ref. 15

Scheme 9. Chiral-Amine-Functionalized CIILs from Natural Amino Acids.

Table 1. Properties of CIILs **13a–e**, **14a–e**, and **15a–e**.

No.	R^1	R^2	X	T_m, °C	T_g, °C	T_{dec}, °C
13a	Me	H	Br	131	---	226
13b	*i*-Pr	H	Br	145	---	270
13c	*i*-Bu	H	Br	134	---	267
13d	2-Bu	H	Br	135	---	268
13e	$-(CH_2)_3-$		Br	141	---	257
14a	Me	H	BF_4	---	–46	261
14b	*i*-Pr	H	BF_4	---	–49	281
14c	*i*-Bu	H	BF_4	---	–47	291
14d	2-Bu	H	BF_4	---	–35	285
14e	$-(CH_2)_3-$		BF_4	---	–45	291
15a	Me	H	PF_6	6	---	218
15b	*i*-Pr	H	PF_6	---	38	287
15c	*i*-Bu	H	PF_6	69	---	287
15d	2-Bu	H	PF_6	73	---	281
15e	$-(CH_2)_3-$		PF_6	---	67	274

[a] The melting point (T_m) and glass-transition temperature (T_g) were determined by DSC. [b] T_{dec} was determined by TG.



Ref. 16

Scheme 10. Synthesis of CIILs Lacking an Acidic Hydrogen at C-2 of the Imidazolium Ring.

neutralization step and bromination with PBr_3. N-alkylation of **12** with methylimidazole in refluxing acetonitrile followed by neutralization with NaOH gave bromides **13a–e**. Anion exchange with $AgBF_4$ or KPF_6 in MeCN–H_2O at room temperature afforded **14a–e** or **15a–e** in 66–71% overall yields. Ionic liquid bromides **13a–e** have higher melting points (T_m's) or glass-transition temperatures (T_g's) than the corresponding tetrafluoroborates, **14a–e**. All exhibit thermal stability up to 210 °C (**Table 1**) and are more miscible in polar solvents and less miscible in nonpolar solvents than the related unfunctionalized imidazolium-type ionic liquids.

Amino acid derivatives in the form of amino alcohols are also good starting materials for the synthesis of CIILs. Recently, our group designed and synthesized a new family of CIILs from chiral amino alcohols (**Scheme 10**).[16] This was the first time that CIILs have been synthesized by introducing chiral scaffolds at the C-2 position of the imidazolium cation of ILs. Owing to the relative acidity of the hydrogen in the C-2 position,[17] the introduction of substituents at this position should result in a more inert category of chiral ionic liquids for reactions carried out under basic conditions.

The synthesis involved the condensation of 1-methyl-2-imidazolecarboxaldehyde and chiral amino alcohols [(*S*)-(+)-2-amino-3-methyl-1-butanol, (*S*)-leucinol, (*R*)-leucinol, (*S*)-*tert*-leucinol, or (*S*)-3-phenyl-2-aminopropanol] in MeOH to give the corresponding Schiff base precursors, which were reduced in situ with $NaBH_4$ to give the desired chiral imidazole derivatives **16a–e** in 72–92% yields. N-Alkylation was carried out by heating imidazoles **16a–e** with one equivalent of bromobutane in toluene at 85–90 °C for 24 h to form imidazolium bromides **17a–e**. Anion exchange of these salts with various anions [BF_4^-, PF_6^-, $(CF_3SO_2)_2N^-$] afforded a series of CIILs, **18**, in good yields as colorless oils at room temperature. These new ionic liquids avoid the shortcomings of their traditional C-2-unsubstituted counterparts, which can participate in deprotonation side reactions at their C-2 position.[18]

More recently, Ou and Huang[19] developed a practical and efficient method for synthesizing CIILs from chiral amino alcohols in two or three steps. Chiral imidazolium chlorides, **19**, were obtained in good yields by reacting 1-(2,4-dinitrophenyl)-3-methylimidazolium chloride with chiral primary amino alcohols in *n*-butanol under reflux for 18–22 h. Anion exchange of chlorides **19** with fluoroboric acid or potassium hexafluorophosphate afforded a new category of CIILs, **20** and **21**, in 67–81% overall yields **(Scheme 11)**.

2.2.3. CIILs from Proline and Histidine

The amino acid proline is a very versatile starting material for the synthesis of chiral ionic liquids; it is readily available, inexpensive, and chiral. Recently, Luo et al. designed and synthesized a series of pyrrolidine-containing CIILs from L-proline (**Scheme 12**).[20] Reduction of L-proline with $LiAlH_4$ followed by reaction with Boc_2O generated the corresponding N-Boc-protected (*S*)-prolinol. Tosylation followed by nucleophilic substitution with imidazolate anion gave the desired chiral imidazole derivative, **22**. Butylation of **22** and removal of Boc gave the pyrrolidine-based imidazolium bromide salt **24a** in 45% overall yield from L-proline. Anion exchange of **24a** with $NaBF_4$ or KPF_6 afforded CIILs **24b** and **24c**, respectively. Using a similar procedure, the authors synthesized various other CIILs, **25a–c**, that contain a methyl group at C-2 of the imidazolium moiety, and **26a,b**, that vary in the type of substitution at positions 1 and 2 of the imidazolium

fragment. CIILs **24–26** are viscous liquids at room temperature and soluble in moderately polar solvents such as chloroform, dichloromethane, and methanol; but insoluble in less polar solvents such as diethyl ether, ethyl acetate, and hexane.

Miao and Chan described the synthesis of other types of CIIL from proline (**Scheme 13**).[21] Coupling of ionic liquid **27** with commercially available Boc-Pro-OH in the presence of DCC–DMAP afforded the ionic-liquid-supported Boc-proline **28** which, upon deprotection with trifluoroacetic acid, gave TFA salt **29**. The synthesis of CIIL **32**, which retains the free carboxylic acid group, utilized a variation of this method. After coupling the ionic liquid carboxylic acid **30** with the readily available *N*-Cbz-(2*S*,4*R*)-4-hydroxyproline benzyl ester, the resulting supported proline **31** was deprotected by hydrogenation to afford the ionic-liquid-supported proline **32** in very good yield and high purity.

More recently, our group designed and synthesized a new pyrrolidine-based CIIL, **35**, from L-proline (**Scheme 14**).[22] The reaction of 3-chloropropanesulfonyl chloride with (*S*)-2-aminomethyl-1-Boc-pyrrolidine, readily obtained from L-proline, provided sulfonamide **33**. Conversion of **33** into imidazolium iodide **34** was accomplished in 86% yield (2 steps) first by iodination with NaI and then alkylation of the resulting 3-iodopropanesulfonamide with 1-methylimidazole in CH_3CN. CIIL **35** was obtained in 88% yield (2 steps) by cleavage of the Boc group, followed by anion exchange with Tf_2N^-.

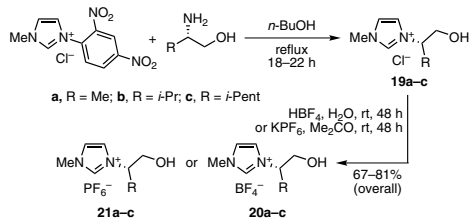
Histidine is a unique amino acid for the synthesis of imidazolium-containing ionic liquids since it is chiral and incorporates an imidazole fragment in its structure. Erker and co-workers were first to exploit histidine as a starting material for CIILs (**Scheme 15**).[23] L-Histidine was O-protected by methyl ester formation and then N-protected with benzoyl or Boc to give the CIIL precursors **36a** and **36b**. Treatment of **36a** with *n*-propyl bromide or isopropyl iodide under basic conditions in CH_3CN at reflux for several days gave CIILs **37a** and **37b**, respectively. CIILs **37c,d** were obtained similarly from histidine derivative **36b**. CIILs **37** exhibit high water solubility and have melting points in the range 39–55 °C.

A year later, Guillen et al. employed histidine as the starting material in the synthesis of a new series of imidazolium-containing chiral ionic liquids, in which the bifunctional unit of histidine remained unchanged (**Scheme 16**).[24] Protection of histidine methyl ester via a cyclic urea structure, followed by alkylation with iodomethane and opening of the cyclic urea by *t*-BuOH in the presence of $(i\text{-Pr})_2$NEt, gave histidine derivative **38**. Alkylation of **38** with bromobutane followed by anion exchange afforded CIILs **39a–c** in 65–90% yields. CIILs **39a–c**, possessing an ester and a protected amine functional groups, were conveniently transformed into various other chiral ionic liquids by known reactions (**Scheme 17**).[24]

2.2.4. CIILs from Lactate and Tartrate

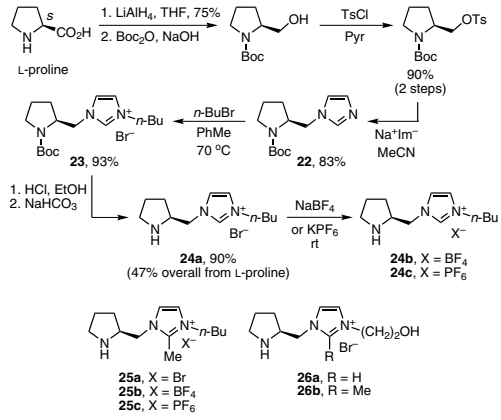
In 2004, Jodry and Mikami reported the synthesis of a new category of hydrophobic CIILs from commercially available and inexpensive (*S*)-ethyl lactate (**Scheme 18**).[25] (*S*)-Ethyl lactate was converted into the triflate derivative, which was N-alkylated to give the corresponding imidazolium triflate salt. Exchange of the triflate anion with the anions of HPF_6, $LiNTf_2$, $LiN(SO_2C_2F_5)_5$, and $LiN(SO_2C_4F_9)Tf$ provided a series of hydrophobic CIILs that are liquid at room temperature.

The research groups of Bao[26] and Kubisa[27] have also utilized lactate as a starting material for the preparation of CIILs **40a–c** in 5–6 steps and 54–60% overall yields (**Figure 2**). Ethyl tartrate



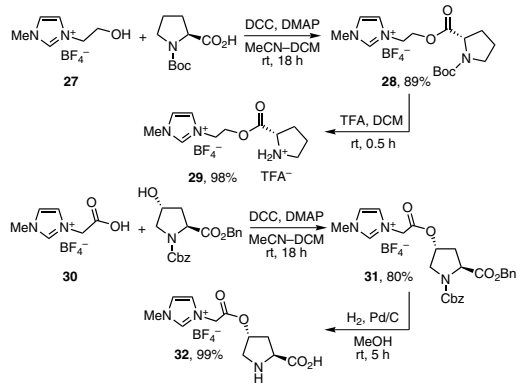
Ref. 19

Scheme 11. Synthesis of CIILs from Chiral Amino Alcohols.



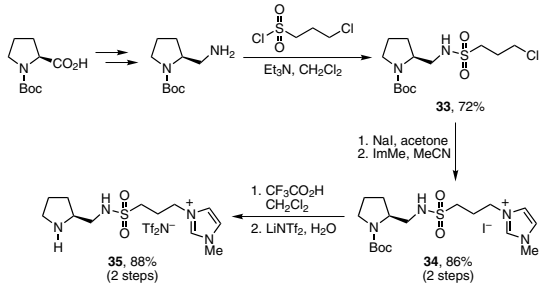
Ref. 20

Scheme 12. Synthesis of Functionalized CIILs from L-Proline.



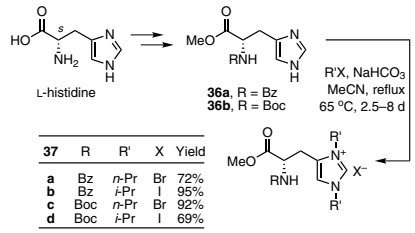
Ref. 21

Scheme 13. Preparation of Ionic-Liquid-Supported L-Proline.



Ref. 22

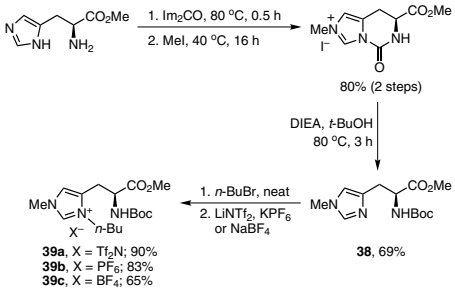
Scheme 14. Synthesis of Pyrrolidine-Based CIILs from L-Proline.



37	R	R'	X	Yield
a	Bz	*n*-Pr	Br	72%
b	Bz	*i*-Pr	I	95%
c	Boc	*n*-Pr	Br	92%
d	Boc	*i*-Pr	I	69%

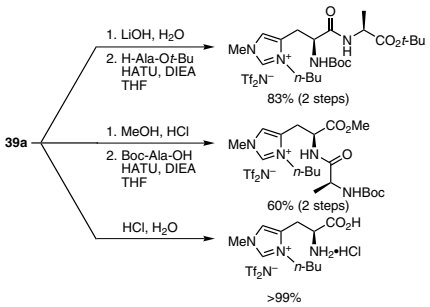
Ref. 23

Scheme 15. Erker's Synthesis of CIILs from Histidine.



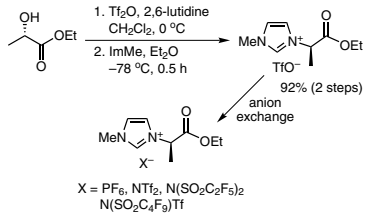
Ref. 24

Scheme 16. Synthesis of O- and N-Protected Histidinium Salts.



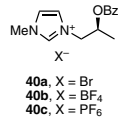
Ref. 24

Scheme 17. Transformation of O- and N-Protected Histidinium Salts into Other CHILs.



Ref. 25

Scheme 18. Preparation of Hydrophobic CIILs from (*S*)-Lactate.



Ref. 26

Figure 2. CIILs from Lactate.

has been employed as a chiral starting material for dicationic CIILs (**Scheme 19**).[25] The bis(imidazolium bromide) salt was prepared in five steps from chiral tartrate in 51% overall yield. Anion exchange with $NaBF_4$ and NH_4PF_6 gave the corresponding bis(imidazolium tetrafluoroborate) and hexafluorophosphate ionic liquids as solids at room temperature with melting points in the 41–90 °C range. Tosyl tartrate has also served as a starting material for the synthesis of a dicationic imidazolium tosylate salt (**eq 4**).[9]

2.2.5. CIILs with Fused and Spiro Rings

The introduction of a rigid skeleton into ionic liquids was envisaged as a method of creating a class of efficient, task-specific solvents capable of inducing asymmetry. Very recently, our group described the synthesis of a novel set of chiral, fused-ring RTILs, in which the chiral moiety is bonded to one of the imidazole nitrogens and, most importantly, in which the 2 position is substituted.[28] Treatment of imidazole derivatives **16**[16] with *p*-toluenesulfonyl chloride gave the corresponding double tosylates, **43**, which underwent ring closure at 90 °C in toluene to form fused-ring, chiral tosylate salts **44** (**Scheme 20**). Anion exchange of **44** led to the corresponding PF_6 and NTf_2 CIILs **45–47** in 63–68% overall yields. At room temperature, CIILs **45a**, **46a,** and **47a** (containing the PF_6 anion) are solids, whereas the NTf_2 anion-containing ones (**45b**, **46b**, and **47b**) are viscous liquids.

Sasai and co-workers synthesized another type of novel, chiral ionic liquid that contains a spiro skeleton (**Scheme 21**).[29] The alkylation of diethyl malonate with 2-(chloromethyl)-1-methyl-1*H*-imidazole hydrochloride or 2-(chloromethyl)-1-isopropyl-1*H*-imidazole hydrochloride, followed by reduction with $LiAlH_4$, produced diols **48** in high yields. Treatment of diols **48** with PBr_3 produced dibromides **49**, which underwent intramolecular N-alkylation smoothly in refluxing toluene to yield spiro imidazolium salts **50**. Anion exchange of the bromide counterions with $AgBF_4$, AgOTf, $LiNTf_2$, or bis(heptafluoropropanesulfonyl)imide gave a series of spiro CIILs, **51**. Unfortunately, the melting points of CIILs **50a,b** and **51a,b** are in the neighborhood of 166 °C, while those with the NTf_2 anion (**51c,d**) exhibit lower melting points (68–112 °C). By increasing the length of the fluoroalkyl chain of the counteranion, as in **51e**, CIILs that are liquids at room temperature (T_g = –10 °C) were obtained. To obtain CIILs with even lower melting points, Sasai's group prepared unsymmetrical spiro CIILs **52a–d** using a similar synthetic protocol (**Figure 3**). CIIL **52d**, with an *N*-propyl-*N*'-isopropyl substituent and Tf_2N^-, is a liquid at room temperature with a T_g of –20 °C.

2.2.6. CIILs with a Urea Unit

Urea derivatives serve as efficient Lewis acid catalysts in organic reactions due to the effective hydrogen bonds that are formed by their amide hydrogens. Urea compounds that contain electron-withdrawing substituents readily form stable co-crystals with a variety of proton acceptors, including carbonyl compounds.[30] Recently, our group synthesized CIILs in which the urea functional group is part of the chiral moiety that is bonded to the imidazolium ring (**Scheme 22**).[31] Reaction of 1-(3-aminopropyl)imidazole with commercially available isocyanate-substituted amino acid esters in CH_2Cl_2, followed by alkylation with one equivalent of neat iodomethane at 40 °C for 24 h, gave imidazolium iodides **53a–c** in excellent yields. Anion exchange with BF_4^-, PF_6^-, and $(CF_3SO_2)_2N^-$ produced CIILs **54–56**, all of which are viscous liquids at room temperature.

2.2.7. Other Types of CIIL

In 2002, Saigo's group described the first example of a planar-chiral ionic liquid (**Scheme 23**).[32] The cyclophane-type imidazolium salts were obtained in about 40% overall yields by monoalkylation of substituted imidazoles with 1,10-dibromodecane under basic conditions, followed by cyclization of the resulting 1-(10-bromodecyl)imidazoles in refluxing acetonitrile for 8–10 days. The introduction of a substituent at C-4 of the imidazolium ring not only induced planar chirality, but also dramatically lowered the melting point. The substituent at C-2 suppressed the racemization of these planar-chiral cyclophanes.

Using a similar synthetic methodology, planar-chiral imidazolium chlorides with a tris(oxoethylene) bridge were obtained in good yields (81–82%) without any side reactions (**Figure 4**).[33] The high selectivity for the formation of the "crowned" imidazolium salts is most likely due to the conformational preference of the tri(oxoethylene) chain. The vicinal oxygens have a strong tendency to adopt a *gauche* conformation and, as a result, the tri(oxoethylene) chain is expected to form a curved structure that is suitable for the intramolecular cyclization.

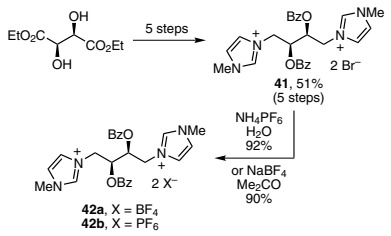
In 2004, Geldbach and Dyson introduced a class of highly active ruthenium catalysts, in which chiral 1,2-diamine or 1,2-amino alcohol ligands are coordinated to ruthenium (**Scheme 24**).[34] These new ruthenium complexes also contained η^6-arenes substituted with 2-(imidazolyl)ethyl groups. Quaternization of 1,2-dimethylimidazole with chloroethylcyclohexadiene and subsequent anion exchange with $NaBF_4$ yield the functionalized imidazolium ionic liquid **57** as a solid with a melting point of 85 °C. Reduction of $RuCl_3$ with three equivalents of **57** in methanol under reflux conditions leads to the dinuclear complex **58**, which is insoluble in most common organic solvents, but is highly soluble in water and ionic liquids. Addition of (1*R*,2*R*)-*N*-tosyl-1,2-diphenyl-1,2-ethylenediamine or (1*S*,2*R*)-2-amino-1,2-diphenylethanol to **58** in DMF affords cationic complexes **59** and **60**, respectively, in excellent yields.

3. Applications of CIILs in Asymmetric Reactions

3.1. As Solvents

Seebach and Oei first introduced the idea of using chiral solvents to influence the outcome of asymmetric reactions back in 1975.[35] Since that time, there have been many attempts to use chiral solvents to affect the outcome of asymmetric reactions, but the observed enantioselectivities have been fairly low. This has led to the conclusion that asymmetric induction effected by chiral solvents is typically low. Even though the enantioselectivity observed for the electrochemical reduction of ketones in chiral amino ethers was low, it opened up the field to develop chiral solvents to influence the outcome of asymmetric reactions. Although a large number of chiral ionic liquids have been synthesized, only a limited number have been successful in affecting the outcome of asymmetric reactions.

In 2005, Armstrong and co-workers reported the use of CIILs as chiral solvents for the photorearrangement of dibenzobicyclo[2.2.2]octatrienes.[10] This was the first report on chiral induction by CIILs for an irreversible, unimolecular photochemical isomerization, with enantioselectivities ranging from 3.3% to 6.8% ee (**eq 5**). The enantioselectivity increased to 11.6% ee when chiral *ammonium* ionic liquids were used as solvents. The authors did not observe any enantioselectivity when the corresponding methyl or isopropyl diesters were

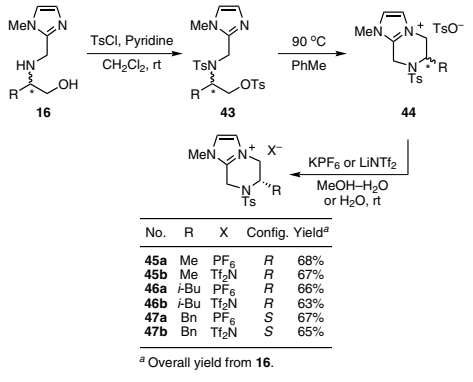


Ref. 26

Scheme 19. Synthesis of Bis(CIILs) from Tartrate.

Ref. 9

eq 4

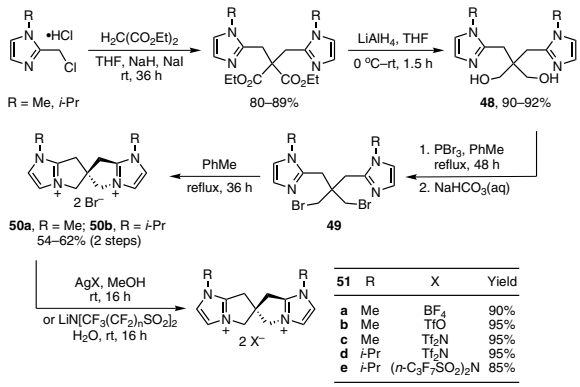


No.	R	X	Config.	Yield[a]
45a	Me	PF_6	*R*	68%
45b	Me	Tf_2N	*R*	67%
46a	*i*-Bu	PF_6	*R*	66%
46b	*i*-Bu	Tf_2N	*R*	63%
47a	Bn	PF_6	*S*	67%
47b	Bn	Tf_2N	*S*	65%

[a] Overall yield from **16**.

Ref. 28

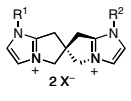
Scheme 20. Synthesis of Fused-Ring CIILs.



51	R	X	Yield
a	Me	BF_4	90%
b	Me	TfO	95%
c	Me	Tf_2N	95%
d	*i*-Pr	Tf_2N	95%
e	*i*-Pr	$(n\text{-}C_3F_7SO_2)_2N$	85%

Ref. 29

Scheme 21. Synthesis of Symmetric, Spiro Bis(imidazolium) Salts.

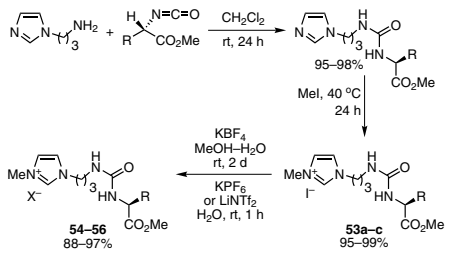


No.	R^1	R^2	X	T_m
52a	Me	Et	Br	>300 °C
52b	*n*-Pr	*i*-Pr	Br	119 °C
52c	Me	Et	Tf_2N	116 °C
52d	*n*-Pr	*i*-Pr	Tf_2N	–20 °C[a]

[a] Value for T_g.

Ref. 29

Figure 3. Physical Properties of Unsymmetrical Spiro Bis(imidazolium) Salts.

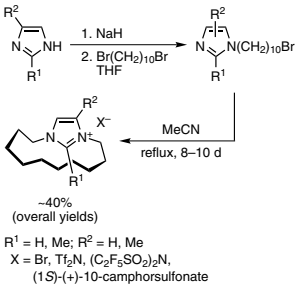


No.	54a	54b	54c	55a	55b	55c	56a	56b	56c
R	*i*-Pr	*i*-Pr	*i*-Pr	*i*-Bu	*i*-Bu	*i*-Bu	Bn	Bn	Bn
X	BF_4	PF_6	Tf_2N	BF_4	PF_6	Tf_2N	BF_4	PF_6	Tf_2N

54a–c, **55a–c**, and **56a–c** all have the *S* configuration.

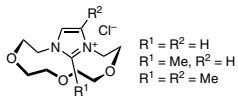
Ref. 31

Scheme 22. Chiral, Ionic Liquids Containing a Urea Functionality.



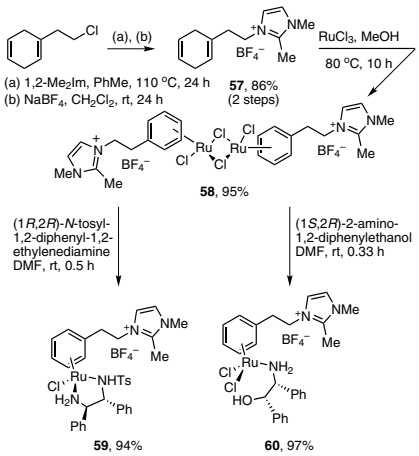
Ref. 32

Scheme 23. Cyclophane-Type Chiral Imidazolium Salts.



Ref. 33

Figure 4. Planar-Chiral Imidazolium Salts with a Tris(oxoethylene) Bridge.



Ref. 34

Scheme 24. Synthesis of Ruthenium-Based CIIL Catalysts.

employed, but noted increased enantioselectivities when the diacid was utilized in the presence of NaOH. It is believed that NaOH allows ion-pair formation by deprotonating the diacid; however, more complex interactions with the chiral discriminator may be at play.

Bao and co-workers have utilized CIILs **40a–c** and **42b** as chiral co-solvents in the asymmetric Michael addition of diethyl malonate to 1,3-diphenyl-2-propenone (**eq 6**).[26] Except in the case of **42b**, better results were obtained in toluene than in DMSO or DMF. Comparable chemical yields and enantioselectivities were obtained with **40a–c**, which differ only in their anions, with CIIL bromide **40a** giving the best yield and ee of the three.

More recently, Ou and Huang also reported on the same asymmetric Michael addition using CIILs **19–21** and acetonitrile as co-solvent (**eq 7**).[19] They found that most of these CIILs exhibited some chiral discrimination, with CIIL **20c** giving rise to the best ee (15%).

In 2003, Kiss et al. reported the palladium-catalyzed Heck oxyarylation of 7-benzyloxy-2*H*-chromene with 2-iodophenol using CIIL both as a chiral solvent and ligand (**eq 8**).[36] The transformation gave low yields (13–28%) and poor enantioselectivities (4–5%) with $Pd(OAc)_2$ and $PdCl_2$. No asymmetric induction was observed when Ph_3P was added as auxiliary ligand.

3.2. As Organocatalysts

Metal-free catalysis of asymmetric reactions by simple organocatalysts has become an important area of research in recent years.[37] Among today's organocatalysts, proline and its derivatives are particularly interesting. Pyrrolidine catalysts have been used successfully for the direct asymmetric aldol and Michael addition reactions,[37] which are regarded as two of the most powerful carbon–carbon-bond-forming reactions in organic synthesis.[37] For these reactions, the organocatalyst is usually used in substantial quantity, and the efficient recovery and reuse of the organocatalyst are a major concern. Therefore, there is a need to develop new organocatalysts, which are easily recyclable and possess enhanced catalytic abilities. In this regard, ionic liquids that contain specific functionalities and are capable of acting as organocatalysts have received much attention recently. One advantage of ionic-liquid-based chiral organocatalysts is that they can be recovered easily from the reaction mixtures simply by capitalizing on their solubility characteristics.

Recently, Miao and Chan reported proline-based chiral imidazolium ionic liquid **29** as organocatalyst for the direct asymmetric aldol reaction of 4-cyanobenzaldehyde with acetone, but obtained the aldol product, **61a**, in only 10% yield and 11% ee. CIIL **32** fared better as organocatalyst under the same conditions, leading to **61a** in 59% yield and 72% ee (**eq 9**).[21] The results indicate that the acidic proton of proline is essential for efficient catalysis to occur. Thus, the aldol reaction of a broad range of aldehyde acceptors, including aromatic and aliphatic aldehydes, and two ketone donors, acetone and 2-butanone, was carried out in good yields and enantioselectivities in the presence of organocatalyst **32** under the same conditions. Furthermore, the authors carried out the reactions of 4-nitrobenzaldehyde in deuterated acetone with CIIL **32** or proline as catalyst, respectively, and proved that CIIL **32** is a more efficient organocatalyst than proline itself. The recyclability of CIIL **32** as organocatalyst was also examined (**eq 10**). CIIL **32** was recycled and reused at least four times in the same reaction without significant loss in yield and enantioselectivity.

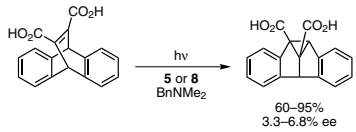
Functionalized CIILs **24a**–**26b** have been employed as highly efficient asymmetric organocatalysts for the Michael addition of cyclohexanone to nitroalkenes (**eq 11**).[20] CIILs **24a–c** and **26a,** lacking a substituent at C-2 of the imidazole ring, were superior to their 2'-methyl counterparts (**25a–c** and **26b**) in terms of yields and selectivities. Introduction of a protic group (OH) in the side chain (see **26a,b**) did not improve the catalytic activity and selectivity, and CIILs with Br^- and BF_4^- were much more active and selective than those with PF_6^-. Overall, catalysts **24a–b** performed best, leading to near-quantitative yields, excellent diastereoselectivities (syn/anti = 99:1), and enantioselectivities (97–99% ee's). These CIILs were easily recycled by precipitation with diethyl ether, and they maintained their high activity albeit with a slightly decreased selectivity, as demonstrated for **24b** over four reaction cycles.

The scope of the preceding reaction was investigated with respect to the ketone and the nitroalkene. Cyclohexanone reacted with a variety of nitroalkenes to generate Michael adducts in near-quantitative yields (94–100%), high diastereoselectivities (dr ≥ 97:3), and excellent enantioselectivities (95–99% ee). Substituting cyclopentanone or acetone for cyclohexanone showed only moderate selectivities, whereas the use of an aldehyde instead of cyclohexanone led to good selectivities (**eq 12**).

Our group also has developed a new type of pyrrolidine-based CIIL, **35**, which catalyzes the Michael addition of various aldehydes to nitrostryenes in Et_2O at 4 °C with moderate yields (≤64%), good enantioselectivities (≤82% ee), and high diastereoselectivities (syn:anti ≤ 97:3) (**eq 13**).[22] Moreover, catalyst **35** also catalyzes the Michael addition of cyclohexanone to *trans*-β-nitrostyrene in acetonitrile at room temperature to give the adduct in moderate yield and high stereoselectivities (syn:anti = 95:5, 88% ee). Our results also demonstrate that the presence of an acidic hydrogen is necessary for the selectivity; the acidic N–H adjacent to the electron-withdrawing sulfonyl group plays an important role in the selectivity of the reaction. The newly designed ionic-liquid-tethered chiral pyrrolidine catalyst, **35**, is easily recycled without loss of activity.

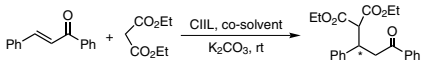
3.3. As Organometallic Catalysts

The transfer-hydrogenation reaction, in which a ruthenium complex is employed as catalyst, has attracted considerable interest.[38] Dyson's group has attached a ruthenium complex with chiral ligands onto an ionic liquid, and examined the resulting ruthenium ionic liquids, **59** and **60**, as catalysts for the asymmetric transfer hydrogenation of acetophenone (**eq 14**).[34] The reaction was carried out in 2-propanol with 2 equivalents of KOH and **60** as organometallic catalyst in 1-butyl-2,3-dimethylimidazolium hexafluorophosphate, [BDMIM][PF_6], as solvent to give the adduct with 95% conversion and 27% ee for the first run. Even under less basic conditions, catalyst **60** was deactivated quickly, and reuse of the ionic liquid phase was not viable. However, catalyst **59** was stable under the reaction conditions for at least 72 h, and recycling of the ionic-liquid phase was feasible, but conversion dropped from 80% in the first cycle to 21% in the fourth cycle. When a formic acid–triethylamine azeotrope was substituted for 2-propanol–KOH as the proton source, catalyst **59** provided essentially quantitative conversion and excellent enantioselectivity (>99%). The product was extracted from the homogeneous phase together with [BDMIM][PF_6] using hexane and Et_2O, and the remaining solution was recharged with ketone and formic acid and reused (**eq 15**). Furthermore, a range of different substrates including cyclic ketones and aldehydes have been reduced using the same **59**–[BDMIM][PF_6] combination.



Ref. 10

eq 5

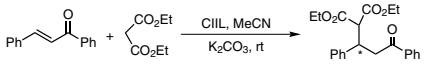


CIIL	Co-Solvent	Time	Yield	ee
40a	PhMe	10 h	96%	25%
40b	PhMe	10 h	95%	24%
40b	DMSO	6 h	90%	17%
40b	DMF	7 h	91%	16%
40c	PhMe	10 h	93%	23%
42b	PhMe	12 h	95%	10%

Enantiomeric excess was determined from the optical rotation.

Ref. 26

eq 6

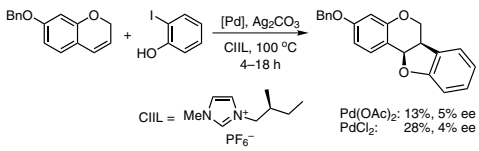


CIIL	Time	Yield	ee
19a	5 d	63%	5%
19b	5 d	76%	8%
19c	5 d	81%	11%
20a	5 d	66%	10%
20b	4 d	80%	7%
20c	4 d	86%	15%
21a	3 d	52%	3%
21b	3 d	78%	0%
21c	5 d	76%	5%

Enantiomeric excess was determined from the optical rotation.

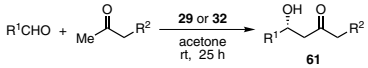
Ref. 19

eq 7



Ref. 36

eq 8

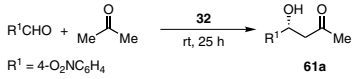


61	R^1	Yield	ee
a	4-NCC_6H_4	10%	11%
a	4-NCC_6H_4	59%	72%
b	2-Np	50%	80%
c	Ph	50%	76%
d	4-$AcNHC_6H_4$	40%	64%
e	4-BrC_6H_4	58%	73%
f	2-ClC_6H_4	92%	71%
g	Cy	43%	85%
h	4-$O_2NC_6H_4$	51%	71%
i	4-$O_2NC_6H_4$	64%	85%

[a] CIIL **32** was used in all cases, except table entry 1.
[b] In all cases, R^2 = H, except for **61h**, in which R^2 = Me.

Ref. 21

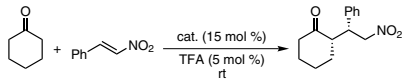
eq 9



Cycle	Yield	ee
1	68%	85%
2	68%	85%
3	66%	83%
4	64%	82%

Ref. 21

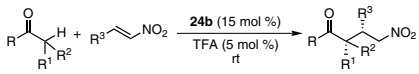
eq 10



Cycle	Cat.	Time	Yield	Syn/Anti	ee
1	**24a**	10 h	99%	99:1	98%
1	**24a**	20 h	99%	99:1	97%
1	**24b**	8 h	100%	99:1	99%
2	**24b**	8 h	97%	97:3	94%
3	**24b**	24 h	99%	96:4	91%
4	**24b**	48 h	96%	97:3	93%
1	**24c**	12 h	86%	98:2	87%
1	**25a**	20 h	97%	97:3	97%
1	**25b**	16 h	100%	96:4	94%
1	**25c**	12 h	40%	96:4	82%
1	**26a**	18 h	86%	97:3	89%
1	**26b**	18 h	25%	94:6	70%

Ref. 20

eq 11

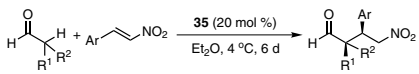


R	R^1	R^2	R^3	Time	Yield	Syn/Anti	ee
a	*a*	H	4-ClC_6H_4	10 h	100%	99:01	99%
a	*a*	H	3-$O_2NC_6H_4$	10 h	94%	98:02	96%
a	*a*	H	4-MeC_6H_4	12 h	99%	99:01	95%
a	*a*	H	4-$MeOC_6H_4$	12 h	99%	99:01	95%
a	*a*	H	2-Np	10 h	99%	99:01	97%
b	*b*	H	Ph	60 h	87%	63:37	79%[c]
Me	H	H	Ph	12 h	83%	----	43%
Me	H	H	*d*	24 h	92%	85:15	76%[e]
H	Me	Me	Ph	96 h	70%	----	86%
H	*i*-Pr	H	Ph	60 h	100%	90:10	72%

[a] R,R^1 = $(CH_2)_4$. [b] R,R^1 = $(CH_2)_3$. [c] 82% ee for the anti isomer. [d] 1-nitrocyclohexene used. [e] 80% ee for the anti isomer. [f] The yield is that of the isolated product; the syn/anti ratio was determined by ^{1}H NMR, while ee was determined by HPLC.

Ref. 20

eq 12

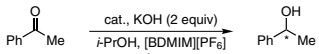


R^1	R^2	Ar	Yield	Syn/Anti	ee
Me	Me	Ph	58%	----	82%
n-Bu	H	Ph	64%	97:03	68%
n-Bu	H	*p*-Tol	60%	96:04	67%
n-Pr	H	*p*-An	29%	92:08	67%
i-Pr	H	Ph	53%	96:04	66%
i-Pr	H	*p*-Tol	64%	97:03	73%
n-Pr	H	Ph	49%	89:11	64%
n-Pr	H	*p*-Tol	38%	96:04	68%
a,b	*a,b*	Ph	38%	95:05	88%

[a] R,R^1 = $(CH_2)_4$. [b] In MeCN. The syn/anti and ee ratios are for the stereoisomer with opposite configurations at the two chiral centers.

Ref. 22

eq 13

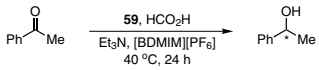


Cat.	Run	Conv.[a]	ee[b]	Leaching[c]
60	1	95%	27	5% Ru
60	2	15%		
59	1	80%	98	8% Ru
59	2	66%		
59	3	57%		
59	4	21%		

[a] Determined by GC. [b] Determined by GC using a Chromapack CP-Cyclodex B column. [c] Determined by ICP-OES.

Ref. 34

eq 14



	Recovered **59**	
Run	Meth. A[a]	Meth. B[b]
1	>99%	>99%
2	68%	>99%
3	19%	80%
4	01%	52%

[a] Product extracted with hexane, ionic liquid washed with H_2O and dried in vacuo. [b] Product extracted with hexane and ionic liquid dried in vacuo.

Ref. 34

eq 15

4. Conclusions and Outlook

The field of task-specific ionic liquids is only in its infancy, but has a very promising future. The main advantage of these types of ionic liquids is that they are easily recovered and recycled without loss of activity when used for asymmetric reactions. Owing to a readily available source of chiral compounds—such as naturally occurring amino acids and other compounds, which can serve as precursors in the synthesis of chiral ionic liquids—a new opportunity now exists for the synthesis of a very important class of organic compounds. The past few years have seen a tremendous growth in the number of chiral ionic liquids synthesized, but their effect on the outcome of asymmetric reactions has been limited, with most still giving low enantioselectivities. Therefore, a need exists for the development of additional, improved, and task-specific chiral ionic liquids that are better able to influence the outcome of asymmetric reactions.

5. Acknowledgments

We gratefully acknowledge financial support of this research by the Robert A. Welch Foundation (T-1460) and Texas A&M University-Commerce. We express our deep gratitude to our co-workers whose names appear in the cited references, and to Dr. Guigen Li for his valuable discussions.

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About the Authors

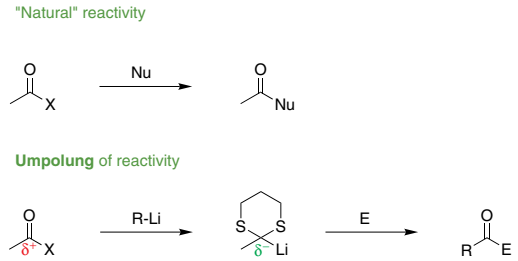
Allan D. Headley was born in Jamaica. He received his Bachelor's degree in chemistry in 1976 from Columbia Union College, Maryland, and his Ph.D. degree in chemistry in 1982 from Howard University, Washington, DC, where he worked under the supervision of Professor Martin R. Feldman. He then moved to the University of California, Irvine, where he worked with Professor Robert W. Taft as a postdoctoral associate. In 1983, he joined the faculty at the University of the West Indies, Mona, Jamaica, as a lecturer. He then worked as a lecturer in chemistry at the University of California, Irvine, before becoming assistant professor of chemistry at Texas Tech University in 1989. In 1995, he was promoted to associate professor and, in 2002, to the rank of professor. Headley's research focuses on the design and synthesis of ionic liquids and their applications to asymmetric reactions. He is presently a professor of chemistry at Texas A&M University-Commerce, where he is also the Dean of Graduate Studies and Research.

Bukuo Ni was born in Zhejiang Province, People's Republic of China. He obtained his B.S. degree in chemistry in 1999 from Zhejiang University. He received his Ph.D. degree in organic chemistry in 2004 under the direction of Professor Shengming Ma at the Shanghai Institute of Organic Chemistry of the Chinese Academy of Sciences. He developed methodologies for palladium- and ruthenium-catalyzed multicenter reactions, and applied them to the synthesis of natural products. In 2005, he joined Professor Headley's group at Texas A&M University-Commerce, where he is currently carrying out research on the design, synthesis, and application of chiral ionic liquids as solvents and catalysts for asymmetric organic reactions.

Sigma-Aldrich Congratulates Professor Dieter Seebach on His 70th Birthday

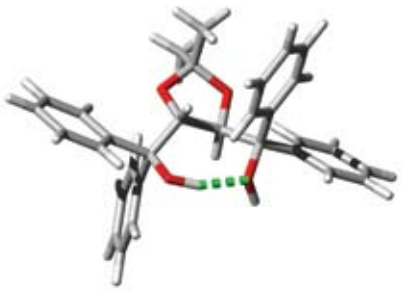
Professor Seebach

Prof. Dr. Dieter Seebach was born on October 31,1937 in Karlsruhe, Germany, and studied chemistry under Prof. Rudolf Criegee at the University of Karlsruhe, where he completed his Ph.D. thesis in 1964. He went on to Harvard University to spend two years under the supervision of Prof. E. J. Corey as a postdoctoral fellow and lecturer before returning to Karlsruhe to work on his "Habilitation" in 1969. Just two years later—and at the young age of 33—he served as Chair of Organic Chemistry at the Justus Liebig University of Giessen, Germany. In 1977, the faculty of the Swiss Federal Institute of Technology (ETH) in Zürich appointed him Professor of Chemistry to succeed the retiring Nobel laureate Vladimir Prelog as the Chair of Stereochemistry, from which he retired in 2003. Presently, Prof. Seebach is *Akademischer Gast* at ETH as well as a guest professor at Harvard University throughout the 2007 fall term.

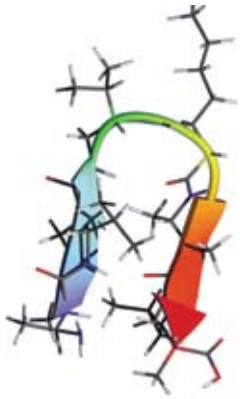


Umpolung of Reactivity

Prof. Seebach's numerous honors, awards, and prizes include the very first Fluka prize for "Reagent of the Year" (1987), the ACS Award for Creative Work in Synthetic Organic Chemistry (1995), an honorary Ph.D. degree from the University of Montpellier, France (1989), membership in the Deutsche Akademie der Naturforscher, Leopoldina (1984), FRSC fellow of the Royal Society of Chemistry (1984), corresponding member of the Akademie der Wissenschaften und Literatur in Mainz (1990), the Schweizerischen Akademie der Technischen Wissenschaften (1998), Academia Mexicana de Ciencias (2001), and Foreign Associate of the National Academy of Sciences, U.S.A. (2007).



TADDOL



β-Peptide

The extraordinarily broad scope of research activities and the exceptional creativity of Professor Seebach's work have been dedicated to the ***development of new synthetic methods*** (umpolung of reactivity; use of organometallic derivatives of aliphatic nitro-compounds, of small rings, and of tartaric acid; enantioselective synthesis and catalysis (TADDOLs); self-regeneration of stereogenic centers (SRS); use of microorganisms and enzymes; backbone modifications of peptides), ***natural product synthesis*** (macrodiolides; alkaloids, unnatural amino acids), ***mechanistic studies*** (dissociation of C–C bonds; stability of carbenoids; aggregation of Li compounds; pyramidalization of trigonal centers; TiX_4 catalysis), and ***structure determination*** (Li enolates and Li dithianes; chemical and biochemical aspects of oligo- and poly(hydroxyalkanoates); β-peptides). This last area is the focus of his present research efforts.

You can read more about Professor Seebach's life and professional career in the following accounts:

(1) Seebach, D. How We Stumbled into Peptide Chemistry. *Aldrichimica Acta* **1992**, *25*, 59–66.

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ALDRICH Chemistry

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Aldrich	157872	1,3-Dithiane
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Aldrich	220817	2-(Trimethylsilyl)-1,3-dithiane
Aldrich	282138	Bis(trimethylsilyl)methane
Aldrich	226335	Bis(methylthio)methane
Aldrich	278076	Tris(phenylthio)methane

Chiral Building Blocks

Brand	Prod. No.	Name
Fluka	20264	(*R*)-2-*tert*-Butyl-6-methyl-1,3-dioxin-4-one
Fluka	15372	(*R*)-(+)-1-Boc-2-*tert*-butyl-3-methyl-4-imidazolidinone
Fluka	96022	(*R*)-1-Z-2-*tert*-butyl-3-methyl-4-imidazolidinone
Aldrich	337579	(*S*)-1-Z-2-*tert*-butyl-3-methyl-4-imidazolidinone
Aldrich	156841	(+)-Diethyl L-tartrate
Aldrich	163457	(+)-Dimethyl L-tartrate
Aldrich	294055	(+)-2,3-*O*-Benzylidene-D-threitol
Aldrich	248223	1,4-Di-*O*-tosyl-2,3-*O*-isopropylidene-D-threitol
Aldrich	384313	(+)-Dimethyl 2,3-*O*-isopropylidene-D-tartrate

TADDOLs

Brand	Prod. No.	Name
Aldrich	265004	(4*R*,5*R*)-2,2-Dimethyl-α,α,α′,α′-tetraphenyldioxolane-4,5-dimethanol
Aldrich	264997	(4*S*,5*S*)-2,2-Dimethyl-α,α,α′,α′-tetraphenyldioxolane-4,5-dimethanol
Aldrich	395242	(4*S-trans*)-2,2-Dimethyl-α,α,α′,α′-tetra(1-naphthyl)-1,3-dioxolane-4,5-dimethanol
Aldrich	393754	(4*R*,5*R*)-2,2-Dimethyl-α,α,α′,α′-tetra-(2-naphthyl)dioxolane-4,5-dimethanol
Aldrich	393762	(4*S-trans*)-2,2-Dimethyl-α,α,α′,α′-tetra(2-naphthyl)-1,3-dioxolane-4,5-dimethanol
Fluka	40875	(–)-2,3-*O*-Benzylidene-1,1,4,4-tetraphenyl-L-threitol, polymer-bound
Fluka	40876	(+)-2,3-*O*-Benzylidene-1,1,4,4-tetraphenyl-D-threitol, polymer-bound

PHB

Brand	Prod. No.	Name
Aldrich	298360	(*R*)-(–)-3-Hydroxybutyric acid sodium salt
Aldrich	363502	Poly[(*R*)-3-hydroxybutyric acid]

Peptide Synthesis

Brand	Prod. No.	Name
Aldrich	193453	1,3-Dimethyl-2-imidazolidinone
Aldrich	251569	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
Fluka	47587	Fmoc-β-Ala-OH
Fluka	47935	Fmoc-β-Homoala-OH
Fluka	03676	Fmoc-β-Leu-OH
Fluka	47946	Fmoc-β-Homoleu-OH
Fluka	03671	Fmoc-β-Homoile-OH
Fluka	47878	Fmoc-β-Homophe-OH
Fluka	03692	Fmoc-β-Homotyr(tBu)-OH
Fluka	47901	Fmoc-β-Homotrp-OH
Fluka	03696	Fmoc-β-Homoser(tBu)-OH
Fluka	47911	Fmoc-β-Homothr(tBu)-OH
Fluka	03658	Fmoc-β-Homomet-OH
Fluka	03689	Fmoc-β-Glu(OtBu)-OH
Fluka	03652	Fmoc-β-Gln-OH
Fluka	47837	Fmoc-β-Homoglu(OtBu)-OH
Fluka	03666	Fmoc-β-Homogln-OH
Fluka	47874	Fmoc-β-Homolys(Boc)-OH
Fluka	03673	Fmoc-β-Homoarg(Pmc)-OH
Fluka	47912	Fmoc-L-β^3-Homoproline

Chiral Auxiliaries

Brand	Prod. No.	Name
Aldrich	551104	(*S*)-(–)-4-Isopropyl-5,5-diphenyl-2-oxazolidinone
Aldrich	551120	(*R*)-(+)-4-Isopropyl-5,5-diphenyl-2-oxazolidinone

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Components/Construction

- Heavy-wall borosilicate glass vessel with flanged top, internally threaded bottom with PTFE fitting and integral filter assembly
- Interchangeable glass filter frits allow for various particulate sizes
- Bottom outlet valve with tube fitting permits easy draining and piping away of filtered solvents
- Jacketed reactor body available for cooling/heating
- Removable head simplifies product loading, removal and cleaning

Reactor Assemblies Include

- Glass reactor body and head, CAPFE O-ring and stainless steel quick-release clamp
- PTFE stirrer bearing, glass shaft with PTFE agitator
- Addition funnel, West condenser, PTFE stoppers, stirrer motor chuck adapter
- Support package (holed plate, stand, chain clamp, and holder)

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600 mL	83 x 185	unjacketed	Z564079-1EA
1 L	100 x 180	unjacketed	Z564109-1EA
2 L	130 x 180	unjacketed	Z564133-1EA
600 mL	83 x 185	jacketed	Z564087-1EA
1 L	100 x 180	jacketed	Z564117-1EA
2 L	130 x 180	jacketed	Z564141-1EA

*IKA® stirrer motor (model RW 20) recommended for all reactor sizes (not included).

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India
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Fax
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Fax: (+61) 2 9841 0500

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Fax: (+47) 23 17 60 50

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Fax: (+46) 8 742 4243

Switzerland
SIGMA-ALDRICH CHEMIE GmbH
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Fax: (+41) 81 755 2815

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SIGMA-ALDRICH COMPANY LTD.
Free Tel: 0800 717 181
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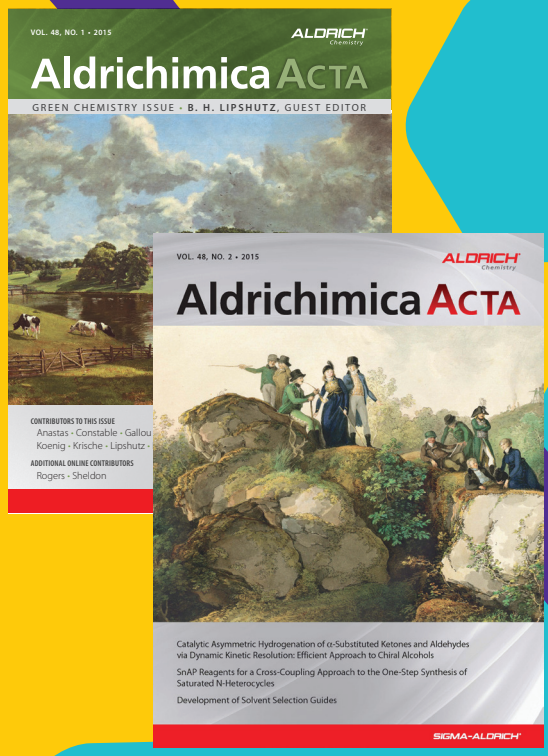

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