GREEN, MILD, AND VERSATILE SYNTHETIC METHODS

Aldrichimica ACTA

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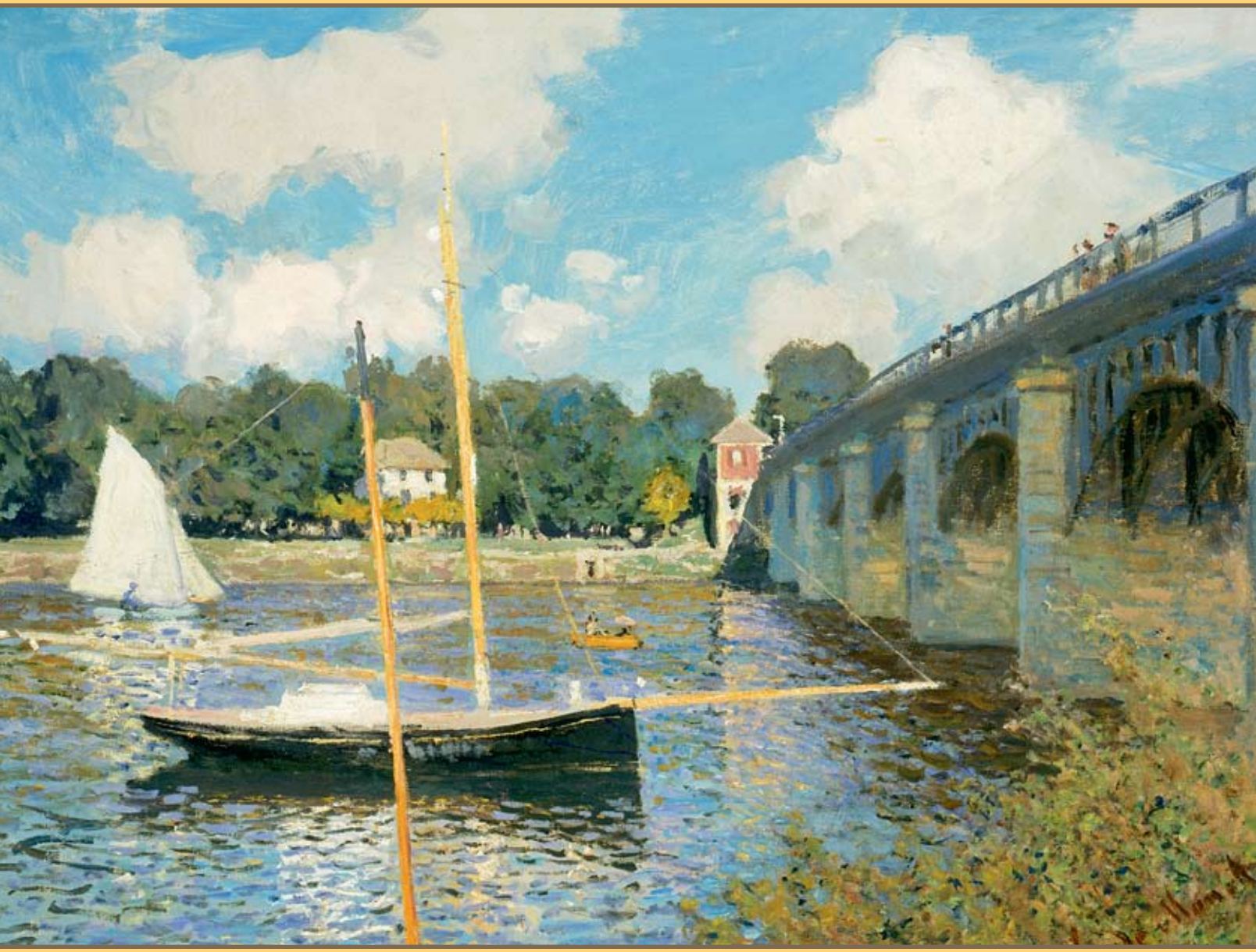
ALDRICH Chemistry



Transition-Metal-Catalyzed Cross-Couplings Going Green: in *Water* at Room Temperature

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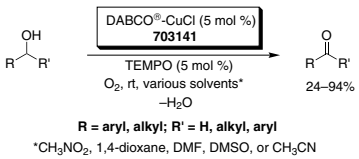
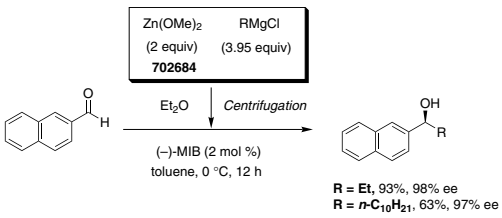


Mannam, S. et al. *Adv. Synth. Catal.* **2007**, *349*, 2253.

DABCO®-CuCl Complex	
703141	1 g
$C_6H_{12}ClCuN_2$	
FW: 211.17	

Reagent for the Preparation of Organozincs

$Zn(OMe)_2$ is an exceptional precursor for the formation of reactive and selective organozinc reagents under salt-free conditions. Historically, the difficulty in preparing organozinc reagents that has prevented their widespread use is due to their highly pyrophoric nature as well as the generation of byproducts. The use of additives, which remove these byproducts, presents other limitations. Therefore, a method to control the solubility of the byproducts so that they can be removed by simple filtration or centrifugation has been developed, and relies on the use of $Zn(OMe)_2$ as a precursor to the organozinc reagent to be formed in solution. Following formation of the active organozinc compound, filtration or centrifugation is followed by the desired organic transformation. Examples of such a transformation include the catalytic enantioselective addition of organozincs to imines, conjugate addition, addition to aldehydes (example below), and addition to β-nitrostyrene.

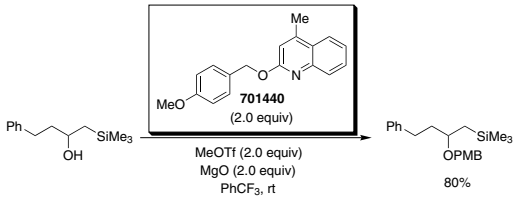


Cote, A.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 2771.

Zinc Methoxide	
702684	1 g
$C_2H_6O_2Zn$	5 g
FW: 127.46	

Reagent for the PMB-protection of Alcohols

Protection with the *para*-methoxybenzyl protecting group (PMB) has been an ongoing challenge in organic chemistry due to the limitations with regard to the reagents that can be used. Common reagents typically require acidic or basic reaction media and present problems that relate to their long-term storage. The lepidine ether below (2-(4-methoxybenzyloxy)-4-methylquinoline) was developed to address some of these limitations and, in combination with MeOTf, affords an active reagent *in situ*. A plethora of alcohols are readily protected under neutral reaction conditions. Additionally, 2-(4-methoxybenzyloxy)-4-methylquinoline is stable, and byproducts generated by its use are easily removed through aqueous workup or chromatography.

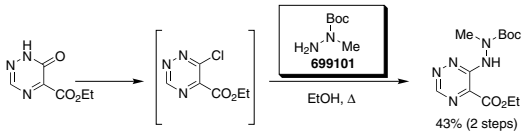


Nwoye, E. O.; Dudley, G. B. *Chem. Commun.* **2007**, 1436.

2-(4-Methoxybenzyloxy)-4-methylquinoline	
701440	1 g
[*937184-70-8*]	5 g
$C_{18}H_{17}NO_2$	
FW: 279.33	

Reagent for Selective Methylhydrazine Addition

N-Boc-*N*-methylhydrazine is a useful reagent that can be employed when reaction at the less nucleophilic nitrogen of methylhydrazine is desired. Without protection of the methylated nitrogen with a Boc group, reaction would occur also at the methylated nitrogen. As demonstrated below, reaction of the chlorotriazine provides the corresponding, properly hydrazine-functionalized arene.



Kelly, T. R. et al. *J. Am Chem. Soc.* **2006**, *128*, 5646.

1-Boc-1-methylhydrazine	
699101	5 g
[*21075-83-2*]	25 g
$C_6H_{14}N_2O_2$	
FW: 146.19	

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General Correspondence

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

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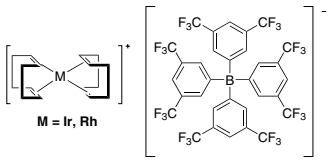
Professor Michael Krische from the University of Texas at Austin kindly suggested that we make Ir and Rh BARF (BARF = $\{3,5\text{-}(CF_3)_2C_6H_3\}_4B^-$) salts. These compounds with loosely coordinating properties catalyze various transformations, including hydrogenation and reductive coupling, that otherwise do not proceed effectively.



(1) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 280. (2) Ngai, M.-Y.; Kong, J.-R.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 1063.

693774 **Bis(cyclooctadiene)iridium(I) tetrakis(3,5-bis(trifluoromethyl)phenyl)borate**
500 mg
2 g

692573 **Bis(1,5-cyclooctadiene)rhodium(I)tetrakis[bis(3,5-trifluoromethyl)phenyl] borate**
100 mg
500 mg

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

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ABOUT OUR COVER

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

Looking at ***The Bridge at Argenteuil*** (oil on canvas, 60 × 79.7 cm) from a distance of ten feet or so, Claude Monet's brushstrokes blend to yield a convincing view of the river Seine and the pleasure boats that drew tourists to Argenteuil. Up close, however, each dab of paint is distinct, and the scene dissolves into a mosaic of paint—brilliant, unblended tones of blue, red, green, and yellow. In the water, quick, fluid skips of the brush mimic the lapping surface. In the trees, thicker paint is applied with denser, stubbier strokes. The figure in the sailboat is only a ghostly wash of dusty blue, and the women rowing nearby are indicated by mere shorthand.

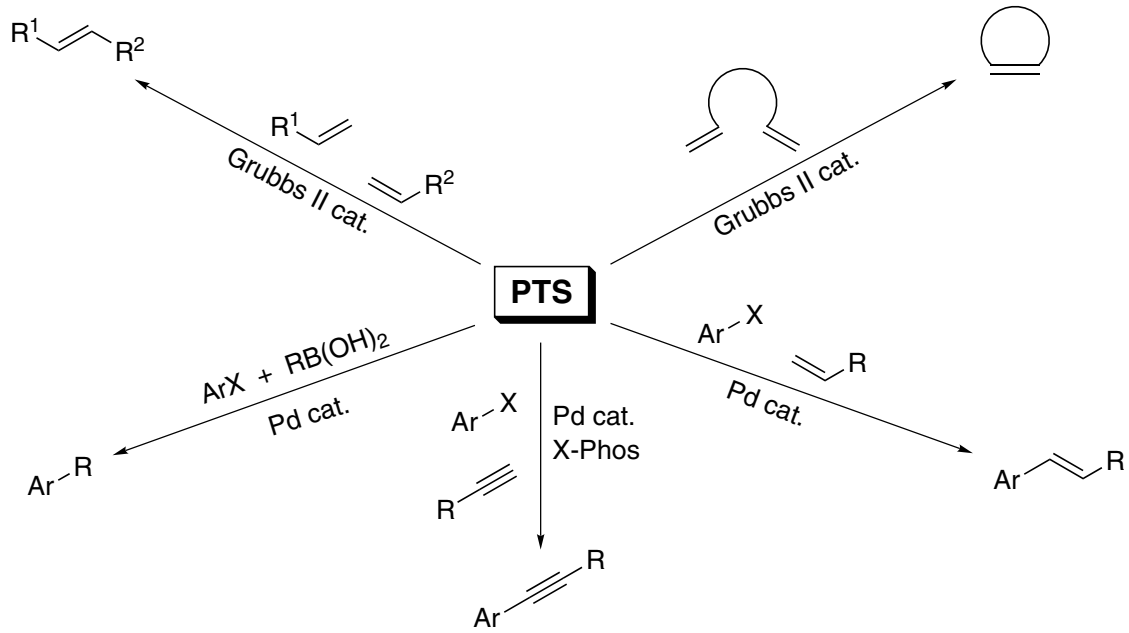
In the early years of impressionism, Monet, Renoir, and others strove to capture the fleeting effects of light and atmosphere on the landscape and to transcribe directly and quickly their sensory experience of it. Monet advised his students, "When you go out to paint, try to forget what objects you have before you, a tree, a house, a field or whatever. Merely think here is a little square of blue, here an oblong of pink, here a streak of yellow, and paint it just as it looks to you, the exact color and shape, until it gives your own naive impression of the scene before you."

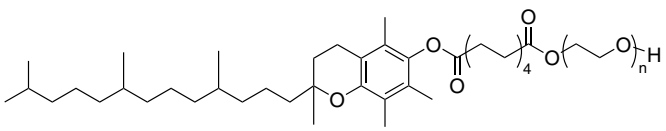
In this early work (1874), Monet (1840–1926) captures a warm, sunny, idyllic day—a motif he used often and for which he became famous. Today, Monet's characteristic style and distinctive brushstroke are still fresh, recognizable, and most popular.

This painting is part of the Collection of Mr. and Mrs. Paul Mellon at the National Gallery of Art, Washington, DC.

PTS—New Amphiphile for Metathesis and Cross-Coupling in Water

Recently introduced by Professor Bruce Lipshutz of UC, Santa Barbara, polyoxyethanyl α-tocopheryl sebacate (PTS) is a nonionic amphiphile that is proving to be a versatile "solubilizer" for organic molecules in water.[1] Lipophilic substrates and catalysts can efficiently enter micelles formed by PTS in water, leading to cross-coupling reactions at room temperature without the need for a co-solvent.[2]





PTS (n = ca. 13)

Polyoxyethanyl α-tocopheryl sebacate, 15 wt. % in H_2O	
698717	10 mL

(1) Sold under license from Zymes, LLC. (2) (a) Lipshutz, B. H. et al. *Org. Lett.* **2008**, *10*, 1325. (b) Lipshutz, B. H. et al. *Adv. Synth. Catal.* **2008**, *350*, 953. (c) Lipshutz, B. H. et al. *Org. Lett.* **2008**, *10*, 1333. (d) Lipshutz, B. H.; Taft, B. R. *Org. Lett.* **2008**, *10*, 1329. (e) Lipshutz, B. H.; Ghorai, S. *Aldrichimica Acta* **2008**, *41*, in press. (f) Lipshutz, B. H. et al. *Org. Lett.* **2008**, *10*, ASAP.

Transition-Metal-Catalyzed Cross-Couplings Going Green: in *Water* at Room Temperature

Prof. Bruce H. Lipshutz

Dr. Subir Ghorai

Bruce H. Lipshutz and Subir Ghorai*
Department of Chemistry & Biochemistry
University of California
Santa Barbara, CA 93106 USA
Email: lipshutz@chem.ucsb.edu

Outline

1. Introduction

It has now been 15 years since Sheldon introduced the environmental factor, or "E Factor", as a numerical measure of the amount of waste produced in manufacturing processes of oil, bulk or fine chemicals, and pharmaceuticals (expressed in kg waste/kg product).[1] This focus on "atom utilization" takes into account not only Trost's "atom economy",[2] but also the associated environmental impact of salt formation and organic byproducts. Today, the E Factor is "a way of life" for the industrial chemical enterprise. Academic labs are also faced with increasing external scrutiny of solvent usage and waste disposal practices, and expanding environmental safeguard requirements. Efforts to influence the extent of chemical insults to the environment at large are manifested throughout the field: journals devoted solely to this cause (e.g., *Green Chemistry*); books in their entirety on, or related to, the subject;[3a–c] and conferences dedicated solely to green chemistry.[3d] New technologies are being engineered to mitigate waste production, with advances in organometallic, organic, and bioorganic catalysis. Alternative reaction media such as fluorous, aqueous, as well as those involving supercritical CO_2 and ionic liquids, are thriving.[4] Regardless of whether these advances are driven by truly environmental issues focused on "sustainability", improved economics, public relations, and/or other factors, the trend going forward is clear.

Interestingly, the E Factor does not take water into account. The reason given is that its inclusion skews the numbers significantly upward and reduces differences between processes, rendering them more difficult to interpret and, hence, less meaningful.[1] The unstated implication is that the quantities of water involved in workups and the resulting waste streams are huge, and that accurate data are tough to get. Water as a reaction solvent, however, is an important alternative medium. Nonetheless, today's enthusiasm for the inclusion of water in one's choice of conditions has been criticized,[5] in part due to the confusion in the literature regarding terminologies, such as "in water", "with water", and "on water".[3c,6] While the use of this solvent alone has fundamental merit in that water is inexpensive, nontoxic, and safe with respect to handling, the counterargument usually focuses on downstream items: the amounts of organic solvent(s) still needed for workup, issues of product isolation, and losses of catalysts involved. Indeed, while homogeneous catalysis in organic media already plays a prominent role in green chemistry, Sheldon further notes, "Preferably, the catalyst solution remains in the reactor and is re-used".[1] Thus, the concept of catalyst recycle and, hence, minimization of organic solvent(s) invested, are also worthy practical goals.

One approach towards increasing the potential for water to compete with organic solvents highlights a reaction variable relatively underdeveloped in the synthetic community, in particular in transition-metal-based cross-couplings: micellar catalysis.[7] Micelles, in general, are formed at low concentrations (CMCs, or critical micelle concentrations, are typically 10^{-3}–10^{-4} M) in pure water.[8] They are characterized as amphiphilic aggregates that combine lipophilic interiors with hydrophilic exteriors, and come in three "flavors": cationic, anionic, and nonionic. A wealth of information (mostly physical chemistry) on micelles is available,[9] but a surprising dearth of applications to organometallic cross-couplings currently exists. Why? Could it be that to many synthetic organic chemists, all surfactants (a contraction of "surface active agents") are more or less the same, that "soap is soap"? This may seem like an oversimplification, but there is extensive evidence to document this state of affairs. For example, consider some of the most common name reactions in transition-metal-mediated organic synthesis, the Heck and Suzuki couplings, and Nobel Prize winning olefin cross-metathesis chemistry. Are there examples of such reactions run in pure water, at room temperature, and involving water-insoluble substrates? In some cases there are, but these are few in number (vide infra). In the recent monograph *Organic Reactions in Water*,[3c] there are several outstanding chapters on all

aspects of chemistry in water, including reviews by those who have contributed to organometallic chemistry in this medium.[10a] The most relevant review to transition-metal-based cross-couplings is by Chao-Jun Li on "Metal-Mediated C–C Bond Formations in Aqueous Media".[10b] From this extensive summary, and earlier work and reviews by Li's group,[10b,c] it appears that micellar catalysis has not been *commonly* applied to key cross-coupling reactions, including those catalyzed by Pd. And for reactions that do include surfactants, the choices are usually limited to those introduced decades ago when the impetus was to provide an inexpensive approach to enhancing the water solubility of compounds associated with, e.g., the petroleum, food, textile, and cosmetics industries prior to the arrival of modern organometallic cross-coupling chemistry. This is not to say that surfactant technology today is a dormant area of research; in fact, entire books are available on this field alone.[9b] But just as ligands in organometallic chemistry have evolved exponentially to meet the increasing demands of evermore-complex synthetic problems, so is there room for amphiphiles to be tailored to enhance opportunities not only in synthesis, but in green chemistry. Few uses of micelles appear in popular monographs or reference works dedicated to organometallics, such as Schlosser's *Organometallics in Synthesis: A Manual*,[11a] or Beletskaya's chapter in Negishi's *Handbook of Organopalladium Chemistry for Organic Synthesis*.[11b] Where is palladium, copper, or ruthenium in the cover artwork of the issue of *Angewandte Chemie* featuring the Oehme review on micellar catalysis in 2005?[7a] Shaughnessy's paper on Pd-catalyzed couplings in aqueous media includes a discussion, in part, on the uses of ionic surfactants (phase-transfer reagents), although product isolation is noted as potentially problematic. Nonetheless, the "trick" of solubilizing organic substrates by employing micelle-forming amphiphiles derives from the exclusive presence of water as solvent. In fact, an organic co-solvent would likely reduce the prospects for catalysis by competing with the substrate(s) for occupancy within the lipophilic core of the micelle. This may seem counterintuitive; i.e., that more "greasy" materials should, in principle, make for better substrates in water, and that any "assistance" by organic co-solvents might actually decrease reaction rates. Perhaps these observations explain, in part, the paucity of attention paid to nonionic surfactants in transition-metal-catalyzed organic synthesis. The question, however, remains as to whether all such amphiphiles are "created equal"; that is, are there significant benefits when a particular surfactant is "matched" to a particular metal-catalyzed cross-coupling? An analogous query years ago might have been: are all ligands in metal-catalyzed cross-couplings the same? Intuitively, the answer may already be obvious; in fact, there are already hints to such distinctions between amphiphiles.[12]

The benefits that "tailor-made" amphiphiles might offer catalysis: e.g., chemistry in water, rate accelerations, etc., could be substantial. However, in order for these to be realized, well-defined structure–function relationships associated with surfactants in *organic synthesis* are needed. In brief, what are the rules for micellar catalysis here? The short answer is: no one knows. But there are analytical tools—e.g., Dynamic Light Scattering (DLS) to study average particle size,[13] and Transmission Electron Microscopy (TEM)[14] to view the size, shapes, and distribution of micelles in water—that can aid greatly in our understanding; techniques that are otherwise infrequently employed by synthetic organic chemists. Thus, in this review, an early spotlight is placed on a few very common name reactions,[15] carried out at ambient temperatures and in water alone, both insofar as prior art is concerned, as well as with a focus on very recent advances with the aid of the amphiphile PTS (polyoxyethanyl α-tocopheryl sebacate) (**1**; **Figure 1**).[16] Perhaps as a library of information is accumulated as to which amphiphile(s) work best in various situations, an understanding of the structure–*re*activity relationships between amphiphile, substrates, and catalysts will emerge.

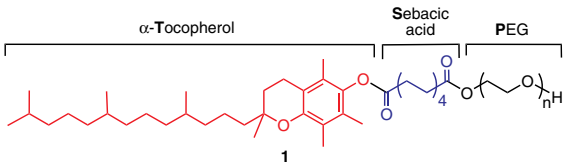


Figure 1. Structure of the Nonionic Amphiphile PTS (**1**, n = ca. 13).

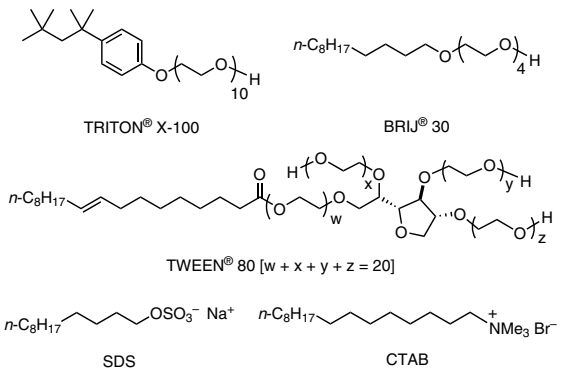


Figure 2. Commonly Used Nonionic and Ionic Surfactants. *(Ref. 17–20)*

2. Amphiphiles, Surfactants, Emulsifiers, Soaps, …

For all intents and purposes in the discussion below relating to organometallics in organic synthesis, these terms will be used interchangeably regardless of the technical definition of each. Virtually all that appear in journals that cater to organic chemistry are composed of two components: a nonpolar, usually hydrocarbon tail, and a polar, either charged or neutral head group that represents the hydrophilic (or "water-loving") segment (**Figure 2**). Examples of nonionic surfactants include TRITON® X-100,[17] BRIJ® 30,[18] and polysorbates[19] (e.g., TWEEN® 80). Perhaps the most commonly used anionic surfactant is sodium dodecyl sulfate (SDS; technically a detergent),[20] while cationic surfactant cetyltrimethylammonium bromide (CTAB) is also a frequently employed, off-the-shelf reagent. Unlike these combinations of a lipophile attached to a water-solubilizing moiety such as polyethylene glycol (PEG), PTS (**1**) is an unsymmetrical diester and, therefore, contains *three* components: a dicarboxylic acid (**S**ebacic acid in this case), a lipophilic portion in vitamin E (or α-**T**ocopherol), and a hydrophilic subsection based on **P**EG-600 (which consists of a distribution of oxyethanyl units centered at 13 in number). Very closely related to PTS is P**S**S (**Figure 3**).[16] In this amphiphile (PSS), the hydrocarbon portion of PTS containing a *linear* side chain 13 carbons in length as part of vitamin E is replaced by a *polycyclic* hydrocarbon characteristic of the cholesterol mimic, β-**S**itosterol. Note that while PSS is otherwise identical to PTS insofar as the 10-carbon spacer acid and the length of PEG are concerned, the well-known emulsifier TPGS[21] varies in the nature of the dicarboxylic acid between the lipophilic vitamin E and hydrophilic PEG moieties. That is, in TPGS, the parent chain is the 4-carbon-containing succinic

acid. Moreover, the PEG portion in TPGS is PEG-1000, which substantially shifts the ratio of water-soluble (hydrophilic PEG) to water-insoluble (lipophilic vitamin E + sebacic acid) components, usually referred to as the Hydrophilic–Lipophilic Balance (HLB).[22] At first glance, these might seem like very subtle distinctions between "soaps." However, these three molecules are quite distinct from each other: neither TPGS nor PSS functions as well as PTS as a reaction medium in C–C-bond-forming reactions in water that have been studied to date (vide infra). Perhaps even more crucial here for developing a fuller appreciation of the micellar array is recognition that the hydrocarbon interior (vitamin E in the case of PTS) *functions as the reaction solvent*. Hence, just as solvent effects can play a defining role in many organic reactions, so might the makeup of an amphiphile that is providing, in a "like-dissolves-like" way, the organic environment…albeit in water.

3. PTS: Brief History and Background

At the National Research Council (NRC) in Ottawa, scientists led by Dr. Henryk Borowy-Borowski first prepared PTS as described in U.S. Patent 6,045,826.[16] Starting with sebacoyl chloride, initial esterification with α-tocopherol led to a monoester (**Scheme 1**). Second-stage introduction of PEG-600 gave PTS (**1**) as the major product, albeit in modest yield (ca. 55%). Purification involving a variety of non-chromatographic manipulations improves the quality of the material, but given the variation in the number of oxyethanyl units [i.e., $(-OCH_2CH_2-)_n$] in most of the commonly used PEGs (in this case, n = ca.13), along with small amounts of various diesters formed as side-products, it is technically inaccurate, as well as economically unrealistic, to claim that PTS is a "pure" compound. Identical phenomena can be found for other commonly PEGylated materials, not only among surfactants but also in the pharmaceutical arena (e.g., PEGylated peptides,[23] etc.).

The NRC's goal was to leverage PTS as a carrier for the expressed purpose of solubilizing a yellow-orange and highly lipophilic solid, the dietary supplement coenzyme Q_{10} (CoQ_{10}, MW 863; **Figure 4A**), in water. Dr. Marianna Sikorska and co-workers conducted extensive biochemical studies at this national lab, relying on PTS-derived aqueous solutions of CoQ_{10}. Her team examined CoQ_{10}–PTS in both cells and animals (in vitro and in vivo) with regard to safety and efficacy in specific disease models.[24] They were particularly interested in neurodegenerative disorders and ischemic brain damage, and demonstrated the neuroprotective effect of water-soluble CoQ_{10}. The properties of PTS (vide infra) allow for the generation of translucent solutions of CoQ_{10} in pure water even at concentrations of >50 mg/mL (**Figure 4B**)!

PTS itself is a viscous, pale-yellow, honey-like substance (**Figure 4C**). In water above its critical micelle concentration (0.28 mg/mL, or 2.31×10^{-4} M), it forms essentially colorless solutions—with micelles *averaging* 22–25 nm in diameter as indicated by light-scattering data.[25] On the other hand, cryo-TEM measurements[26] show a mixture of smaller spherical (ca. 8 nm) and worm-like (ca. 50 nm) particles (**Figure 5**).[25,26] Interestingly, dissolution of CoQ_{10} within these nanometer-size micelles does not alter, on average, their size. This "trend" is corroborated by similar observations involving other "actives" such as ω-3 fatty acids (i.e., fish oil containing DHA and EPA can be solubilized in water at a remarkable 100 mg/mL),[27] as well as the practically water-insoluble antitumor agent paclitaxel which forms a clear, water-white solution even at 10 mg/mL (**Figure 4D**).[28a] Thus, as a solubilizing agent, where ratios of PTS to active will vary (e.g., PTS:CoQ_{10} = 3:1 by weight;[16] PTS:paclitaxel = 10–20:1 by weight),[28a] PTS in micelle form is capable of accommodating compounds that are essentially insoluble in water. It was the recognition of these properties of

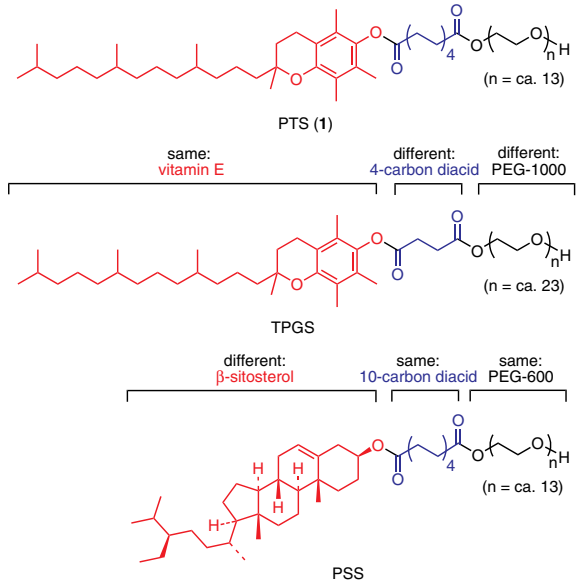
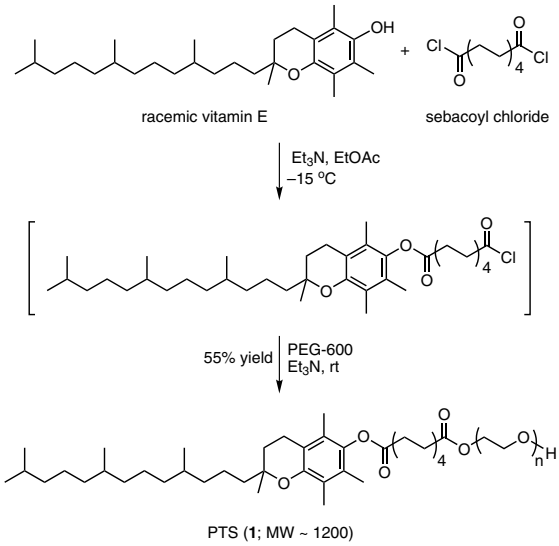


Figure 3. Structural Comparisons between PTS, TPGS, and PSS.
(Ref. 16,21)



Scheme 1. Preparation of the Unsymmetrical Diester PTS.
(Ref. 16)

PTS that triggered the question: Why not apply the benefits of water-solubilization with PTS to lipophilic substrates, additives, catalysts, etc. by putting these species into micelles? Surely, such occupants would react … and they do.

4. Synthetic Chemistry in PTS–H_2O

4.1. Heck Coupling

With so much fundamental literature on the Heck reaction dating back to the early 1970s,[11,29] how could we make a contribution of consequence today in this area? Although recent and highly effective methodologies exist for Pd-catalyzed Heck olefinations at room temperature in organic solvents,[30] and in water with heating,[31] to the best of our knowledge the overlap of these two

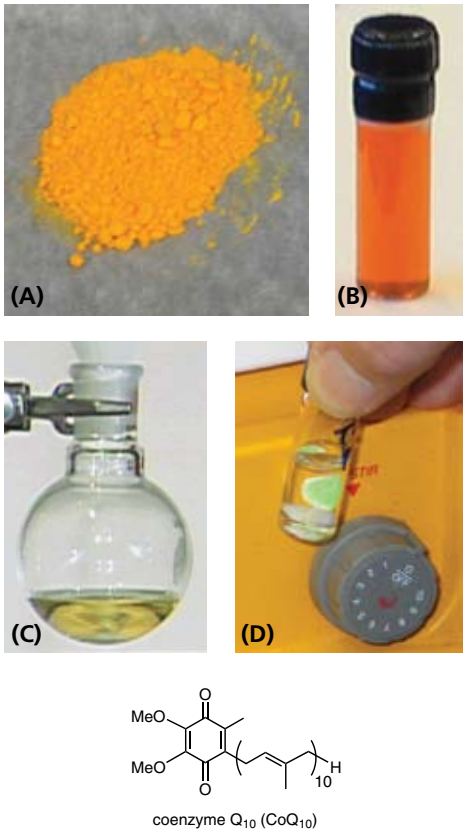


Figure 4. (A) Pure, Water-Insoluble Coenzyme Q_{10}. **(B)** Solution of 50 mg/mL CoQ_{10} in PTS–H_2O. **(C)** Neat PTS. **(D)** Solution of TAXOL® in PTS–H_2O (10 mg/mL). (Photos © B. H. Lipshutz.)

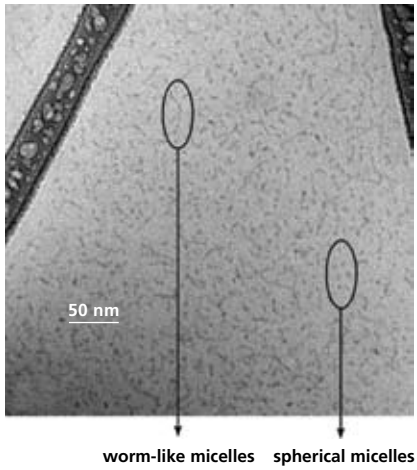
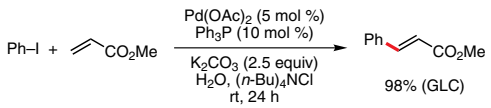


Figure 5. Cryo-TEM Image of PTS–H_2O. (Photo © B. H. Lipshutz.) *(Ref. 25,26)*



eq 1 *(Ref. 32)*

highly desirable features had not been accomplished in any general way; that is, Heck couplings with especially lipophilic aryl halides in water as the only solvent at ambient temperatures. Independent of halide (or pseudohalide), the problem of substrate and ligand solubility, in addition to substrate reactivity as well as catalyst stability, weigh heavily on the prognosis for success given these stringent requirements. As early as 1994, Jeffery's paper entitled "Heck-type Reactions in Water" suggested that the combination of an alkali metal carbonate as base and a tetraalkylammonium salt as phase-transfer agent (PTA), along with catalytic $Pd(OAc)_2$–Ph_3P, could be used in neat water to couple iodobenzene and methyl acrylate (**eq 1**).[32] The PTA is presumably providing the organic phase in which the coupling takes place. In the absence of a PTA, very low conversion was observed (5%) even at 50 °C. The following year, Bumagin et al. reported[33] the first Heck coupling of water-insoluble substrates with either styrene or acrylic acid in pure water without recourse to a PTA (such as *n*-Bu_4NBr, which is also effective as an additive in heated water [34]). Both aryl iodides and bromides gave cross-coupled products in the presence of Na_2CO_3 as base at 100 °C; most reaction times were on the order of 2–7 hours. Notably, simple palladium salts ($PdCl_2$, $Pd(OAc)_2$) served as catalyst precursors, and Ph_3P was only required in reactions of bromides (**eq 2**). A decade later, a ligand-free, nanometric form of colloidal palladium was described by Bhattacharya, Srivastava, and Sengupta that mediates Heck (and Suzuki) couplings in water at 80–100 °C (**eq 3**).[35] The key to their success was inclusion of one half to one full equivalent of the cationic surfactant CTAB (see Figure 2), which was needed to stabilize the newly formed palladium nanoclusters. Particles of these nanoclusters on average were shown by TEM to have a diameter of 5 nm. Such reactions in water are considered "non-conventional methodologies", a topic covered in detail by Alonso, Beletskaya, and Yus in their review on Heck reactions in *Tetrahedron* in 2005.[36]

Might nanoparticles of PTS in water supply the "solution" by simultaneously emulsifying the aryl iodide, olefin, and ligated palladium catalyst such that coupling would occur *without* heating above room temperature? Considering that vitamin E represents only ca. one-third the weight of PTS (MW ~1200), the effective concentration inside the micelle could be quite high, thus potentially dropping the reaction temperature due to this well-known effect in micellar catalysis.[37] Also, advantage would certainly be taken of the latest developments in ligand design, although the behavior of ligated Pd complexes in nonionic micelles of PTS had yet to be established. There were four key questions that had to be addressed for PTS to succeed: (1) Can the optimum amount of PTS in water be easily determined, and is it general? (2) Are there significant differences between metal catalysts under micellar conditions? (3) Does PTS compare favorably with other surfactants, or none at all? (4) Is product isolation from PTS *easily* achieved? Fortunately, the answer to all four turned out to be yes.

Insofar as these crucial points are concerned, 15% PTS (by weight) in water appeared to be more effective than were lower concentrations. Admittedly, this level of amphiphile seemed high (although it corresponds to only 0.124 M), but it *was* the experimentally determined amount that led to the fastest Heck reactions and highest conversions. That is, under a given set of conditions, in particular using catalyst **2a** (**Figure 6**), 2, 5, and 10 wt % levels of PTS were not nearly as effective. Only in hindsight is it now clear that this determination was due to issues specific to these conditions; i.e., precipitation of in situ generated PdI_2 and the resulting net instability of this catalyst system, both translating into a need for more PTS to maintain the catalyst in solution. Very recently, in fact, it has been found that far less PTS can be used

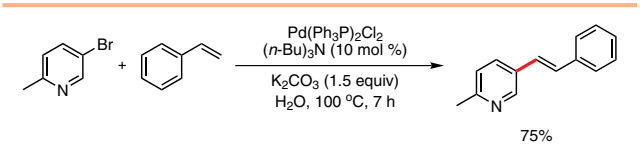
with a change in ligand on Pd (vide infra). Hence, again with the benefit of hindsight, it is not surprising that 15% is *not* the ideal amount of PTS for any of the other name reactions discussed herein; indeed, no more than 5 wt %, and more often 2.5 wt %, in water is recommended. As originally reported, using 2 mol % of palladium catalyst **2a**[38a] and Et_3N as base led to Heck couplings between aryl iodides and either acrylates or styrenes at room temperature at an arbitrarily chosen 0.5 M substrate concentration in pure water (**eq 4**, **5**).[25] Of the three common commercially available acrylate esters tested, the *least* effective was the more water soluble: methyl acrylate. The more lipophilic *t*-butyl and 2-ethylhexyl acrylates performed better in micelle-forming PTS–water. Ratios of olefin to iodide are in the 1.5–2:1 range. Depending on substrate, the ratios of *E* and *Z* products can vary, although the expected *E* isomer is strongly favored in all cases. Each of the coupling partners involved is water-insoluble. Other surfactants were also screened in a model system, including TRITON® X-100, BRIJ® 30, TPGS, PEG-400, and SDS (see Figure 2). Differences between these and PTS were substantial, with the exception of TRITON® X-100, which occasionally afforded similar results.

Dynamic Light Scattering (DLS) data on TPGS in water reveal a very narrow range of particles (12.5–12.8 nm), or about half the average size of PTS (**Table 1**).[38b] Switching from PEG-600 to PEG-1000 in the synthesis of PTS (see Scheme 1) results in TPGS and PTS now differing only in the diacid (4 vs 10 carbons) that links α-tocopherol to PEG-1000. DLS on the more hydrophilic PTS-1000 shows an average micelle diameter of only 7 nm! Remarkably, the BRIJ® 30 micelle diameter is, on average, ten times that of a TRITON® X-100 micelle. Such changes in size potentially translate into *significant* variations in lipophilic core (i.e., "solvent") volume (V), since V is proportional to r^3 (r = radius of micelle particle).

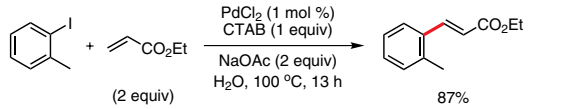
A few other sources of palladium were examined (e.g., $Pd(OAc)_2$, $PdCl_2$, and $Pd(dba)_2$), but none led to any identifiable benefit (in rate, yield, etc.). Importantly, ***product isolation*** is facile (at least on a research scale), using either a rough filtration of the reaction mixture through silica to remove both PTS and water, or by standard extractive workup. With solvents such as petroleum ether, diethyl ether, dichloromethane, and ethyl acetate, PTS is fully retained atop the silica adsorbent. The formation of *tert*-butyl (*E*)-5-(3-*tert*-butoxy-3-oxopropen-1-yl)-1*H*-indole-1-carboxylate is a representative reaction (**eq 6**).[25] Well worth noting in the conditions associated with such reactions are the items *missing*: there is no need for solvent degassing, no weighing of substrates or catalyst in a glove box or other inert atmosphere conditions (although this is catalyst-dependent), and obviously no concern about drying any materials involved (including glassware). Given the phosphine ligand present in the catalyst, however, and the time for reactions (hours), a blanket of argon is routinely maintained. Good stirring is also important, although here again, standard laboratory equipment suffices. PTS–H_2O is stable in a (preferably brown) bottle on the shelf for years.

In an effort to significantly reduce the originally prescribed 15 wt % PTS, a search for another ligand system was undertaken. The key observation focused on providing a catalyst already in the active Pd(0) state, thereby avoiding reduction of a Pd(II) precursor salt, as is required with **2a**. Thus, switching to preformed catalyst [(t-$Bu_3P)_2$Pd] (**2b**), the Heck coupling of 4-iodoanisole with *t*-butyl acrylate, now using only 5 wt % PTS under otherwise identical conditions, gave the anticipated cinnamate in very high isolated yield (**eq 7**).[28a]

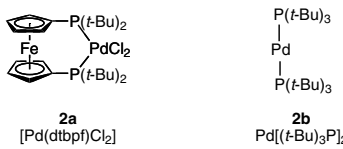
While these intermolecular Heck reactions appear well suited to the aqueous conditions developed, they involve iodides as coupling partners. Recent preliminary efforts have identified a protocol



eq 2 *(Ref. 33)*

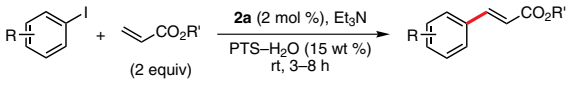


eq 3 *(Ref. 35)*

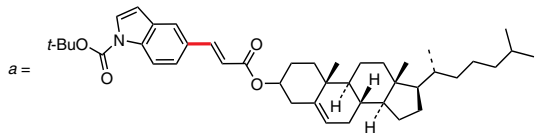


2a [Pd(dtbpf)Cl_2] **2b** Pd[(t-$Bu)_3P]_2$

Figure 6. Catalysts for Heck Coupling in PTS–H_2O. *(Ref. 38a)*

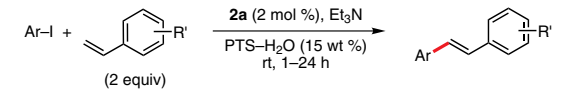


R	R'	Yield
4-MeO	*t*-Bu	92%
4-MeO	2-ethylhexyl	84%
4-(*n*-Bu)	*t*-Bu	77%
H	2-ethylhexyl	95%
a	*a*	90%

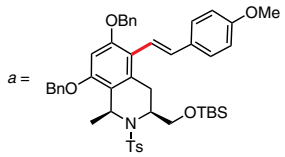


E:*Z* = 93:7

eq 4 *(Ref. 25)*



Ar	R'	Yield
4-MeOC_6H_4	4-F	94%
4-(*n*-Bu)C_6H_4	4-MeO	96%
4-Et$O_2CC_6H_4$	4-MeO	97%
4-(pyrrol-1-yl)C_6H_4	2-Cl	95%
2-MeO-1-naphthyl	2,4-Me_2	94%
a	*a*	90%



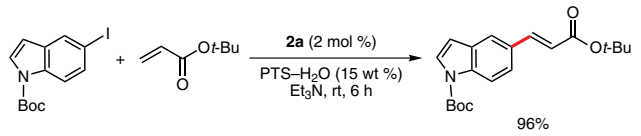
eq 5 *(Ref. 25)*

Table 1. Average Diameter of Selected Surfactants in Water (by Dynamic Light Scattering; DLS) *(Ref. 38b)*

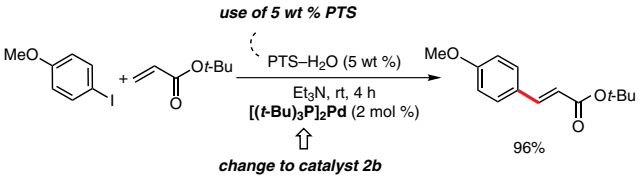
Amphiphile	Diameter	Comparisons
PTS with PEG-600 (**1**)	24 nm	*increased length of PEG: smaller particles*
PTS with PEG-1000	7 nm	*only difference: 4- vs 10-carbon acid linker*
TPGS	13 nm	
PSS	20 nm	
TRITON® X-100	10 nm	*more hydrophilic PEG, much smaller particles*
BRIJ® 30	110 nm	

linear vs cyclic grease: give different results

involving aryl bromides, but not quite yet at room temperature; very gentle heating to 38–50 °C is still necessary (**Scheme 2**).[39] As alluded to earlier, the change from iodide to bromide avoids potential precipitation of palladium halide salts; hence, 5 wt % PTS along with the Pd(0) catalyst **2b** also work well together here. These conditions approach the mildest of those known to date… even in organic solvents.[30] Given the usual dramatic influence of the environment surrounding the metal, prospects for finding a ligand that further lowers the reaction temperature also seem reasonable.



eq 6 *(Ref. 25)*



Heck coupling using 5 wt % PTS–H_2O.[28a] The catalyst {Pd[P(*t*-Bu)$_3$]$_2$, 5.1 mg, 0.01 mmol} and 4-iodoanisole (117 mg, 0.50 mmol) were introduced under argon into a 5.0-mL microwave vial equipped with a stir bar and a TEFLON®-lined septum. The PTS–H_2O solution (1.0 mL, 5 wt % PTS), triethylamine (208 µL, 1.50 mmol), and *tert*-butyl acrylate (145 µL, 1.0 mmol) were then added by syringe. The heterogeneous mixture was stirred vigorously at room temperature, becoming almost homogeneous after 10–30 min, and its progress was monitored by TLC (10 vol % EtOAc–hexane). Upon consumption of 4-iodoanisole (4 h), the dark-purple mixture was diluted with EtOAc (~1.5 mL), filtered through a pad of silica gel to remove PTS–H_2O, and the pad was rinsed with additional EtOAc (2 × 5 mL). The ethyl acetate filtrates were combined and the volatiles were removed in vacuo. The resulting crude product was purified by silica gel chromatography (5 vol % EtOAc–hexane) to yield 112 mg (96%) of *tert*-butyl (*E*)-3-(4-methoxyphenyl)propenoate as a colorless liquid. The ^{1}H NMR data of this product matched those previously reported.[28b]

eq 7 *(Ref. 28a)*

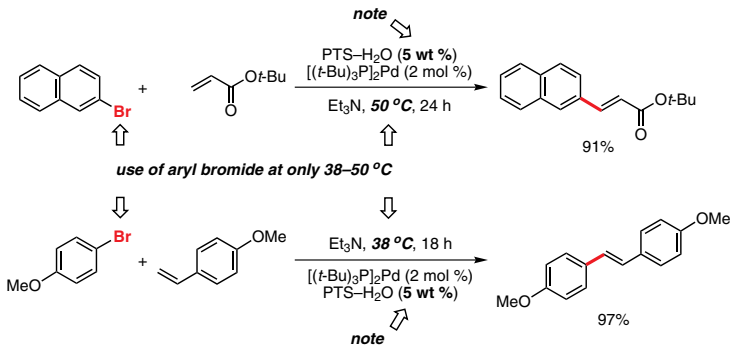
4.2. Suzuki–Miyaura Coupling

With the groundwork laid for the use of PTS–water in Heck reactions, the only potential major difference between the Heck and Suzuki–Miyaura couplings was the partner: a boronic acid rather than an acrylate or styrene. Of course, details had to be addressed such as (a) the amount of PTS, (b) which aryl halide(s) react(s) at room temperature, and (c) the "scope and limitations" with substitution patterns associated with each educt. However, catalyst **2a** (see Figure 6) and base (Et_3N) were both carried forward from our experience with Heck reactions.

That only 1–2 wt % PTS in water is needed was established early on, using an aryl iodide and arylboronic acid.[40] Lesser amounts of PTS gave higher levels of conversion more rapidly than did solutions containing 5, 10, or 15 wt % in H_2O. Relatively little effort was directed towards couplings with (water-insoluble) iodides, as they reacted quickly as expected. Bromides were also excellent partners, both of the electron-rich and electron-poor varieties (**eq 8**). Products were easily isolated from PTS upon workup; there are no issues of frothing or stickiness. Other surfactants (e.g., TRITON® X-100, TPGS, and BRIJ® 30) served in a similar capacity to varying extents, as was observed with Heck couplings.[25] In general, however, PTS was the carrier of choice for a wide range of aryl bromides and boronic acids. Nonetheless, there are several alternatives for effecting Suzuki–Miyaura couplings of aryl bromides in water at room temperature. Again, a 2008 critical overview of "non-conventional methodologies" is available from the team composed of Alonso, Beletskaya, and Yus.[41] A number of advances of late are noteworthy, including Shaughnessy's development of trialkylphosphino ligands, in particular *t*-Bu-Amphos (**3**), which is best used with unhindered systems (**eq 9**).[42] In the presence of palladacycle **4** or **5** (**Figure 7**), more sterically demanding cases couple at 80 °C. Recycling the catalyst system based on **5** is also possible.[43] Related complex **6** and palladacycle **7**, described by Sudalai and co-workers,[44] likewise, effect couplings in water at 25 °C in the presence of KOH (2 equiv).

Lee and co-workers generated spherical micellar aggregates of ca. 10–15 nm in diameter associated with amphiphilic rod–coil molecules (**eq 10**).[45] In this system, hydrophobic disk-like rod bundles function as a reaction medium, surrounded by hydrophilic PEG chains. Interactions between aromatic moieties within the host micelle and the substrates (aryl halides and boronic acids) account for the enhanced rates of C–C-bond formation in water at room temperature.

The lingering question regarding participation by aryl *chlorides* has also been asked and answered insofar as PTS is concerned, but not to the same level of satisfaction as with bromides—at least initially. That is, some aryl chlorides did, in fact, react at room temperature, while others that would be expected to form biaryls



Scheme 2. The Heck Reaction with Aryl *Bromides* in 5 wt % PTS–H_2O. *(Ref. 39)*

reacted sluggishly. The problem in these cases could be oftentimes "fixed" by applying mild heat: no more than 50 °C was usually enough to drive the reactions essentially to completion. However, how does one achieve a more general room-temperature Suzuki–Miyaura coupling with aryl chlorides in PTS–water? The answer: change the ligand.

Although the Pd-dppf complex **2a**, and more recently catalyst **2b** (see Figure 6), function extremely well in most Heck[25] and Suzuki–Miyaura couplings[40] in water, the N-heterocyclic carbene containing complex **8** (**Figure 8**) leads best to biaryl couplings with aryl chlorides (**eq 11**).[40] Thus, under otherwise identical conditions (1–2 wt % PTS–water, room temperature, Et_3N) catalyst **8** gave cross-coupled products in high isolated yields. Worthy of mention is the case of tri-ortho-substituted biaryls (e.g., **10d**), which appear to represent the steric limit of this technology to date. A more extensive study of catalysts, however, has not been made as yet. Lowering the amount of PTS 10-fold (i.e., to 0.1% by weight; **eq 12**) may provide enough surfactant given the appropriate catalyst. By way of comparison with the "on water" experiment, coupling to make terphenyl **11** in the complete absence of PTS, under otherwise identical conditions, gave significantly lower results: 99% vs 73% conversion; 93% vs 57% isolated yield (**eq 13**).

Other technologies that result in biaryl couplings using aryl chlorides in water also exist, although reaction temperatures tend to be in excess of 80 °C. There is a hint that room-temperature couplings may be possible, using capillary microreactors.[46] Otherwise, known processes rely on ligands carefully crafted for such Pd-catalyzed purposes, such as sulfonated biarylmonophosphine **12**[47] and *t*-Bu-Amphos (**3**),[42] usually aided by heat and/or some degree of substrate water solubility (**eq 14**).

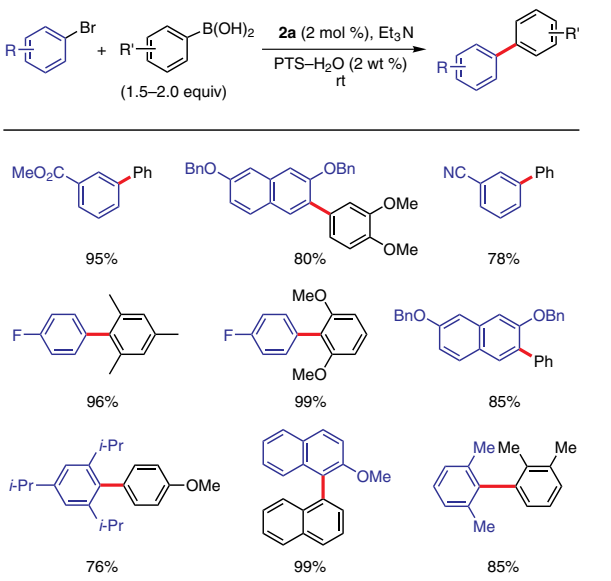
Phase-transfer agents, including Bu_4NBr[48] and, more recently, CTAB as part of the unusual combination with heterogeneous Pd/C in water, provide access to unsymmetrical biaryls from activated chloroarenes (**eq 15**).[49]

Phenol-based leaving groups represent another opportunity in PTS-assisted Suzuki–Miyaura couplings. While triflate ($CF_3SO_2^-$) and nonaflate ($C_4F_9SO_2^-$) derivatives smoothly react, less common by far is the use of the perfluorooctanesulfonate moiety, $C_8F_{17}SO_2^-$, as a leaving group (**eq 16**).[50] The additional fluorinated carbon *increases* lipophilicity and, hence, the presumed solubility in the vitamin E core of PTS micelles.[40] In terms of cost, it is the least expensive of these three leaving groups.

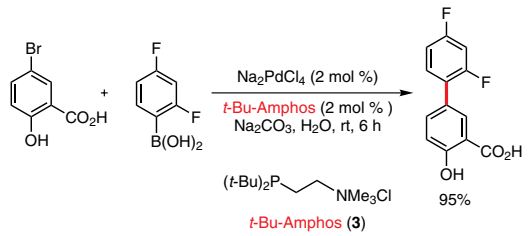
Currently under study are Suzuki–Miyaura couplings involving heteroaromatic halides, heteroaromatic boronic acids, or combinations of both. Judging from the early returns (e.g., **eq 17**),[51] the breadth of potential applications looks encouraging, although it is unrealistic to attempt to examine all the combinations from just commercially available partners.

4.3. Olefin Metathesis

Included within the broad area of olefin metathesis are subcategories such as cross-metathesis (CM) and ring-closing metathesis (RCM). Both have been warmly embraced by the synthetic community,[52] as they offer astounding functional group tolerance, efficiency, and potential for fine-tuning via ligand modification on a ruthenium-based catalyst (**Figure 9**).[53–59] Distinctly missing in the arsenal of metathesis weapons is a process for conducting CM in water at room temperature. Up until very recently, such olefin exchanges were performed exclusively in organic media, typically in (refluxing) CH_2Cl_2. Advances in ligand design have altered not only the reactivity profile of Grubbs and Grubbs–Hoveyda catalysts, but also produced water-soluble variants (**Figure 10**).[60–64] Nonetheless, accommodation of water-insoluble *substrates* has



eq 8 *(Ref. 40)*



eq 9 *(Ref. 42)*

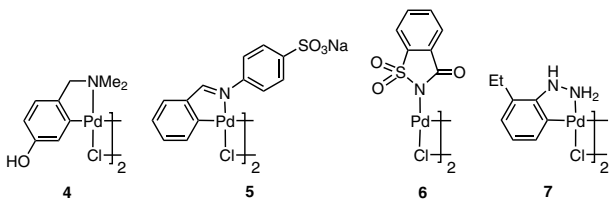
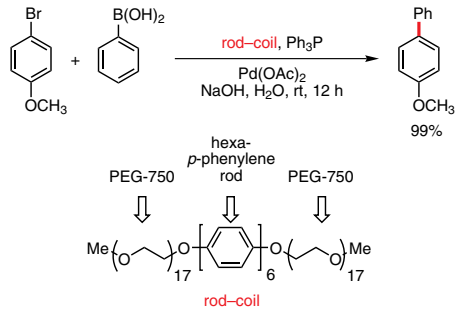
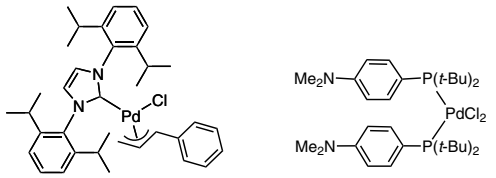


Figure 7. Palladacycle and Related Catalysts for the Suzuki–Miyaura Coupling. *(Ref. 42,44)*

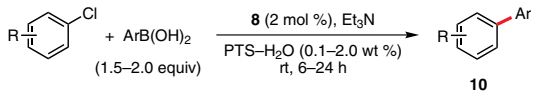


eq 10 *(Ref. 45)*



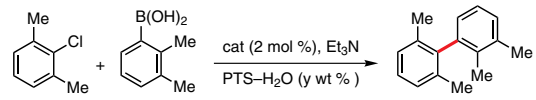
8, NEOLYST® CX31 **9**, Pd(A-^{ta}Phos)$_2$Cl$_2$

Figure 8. Catalysts Used in Suzuki–Miyaura Cross-Couplings of Aryl Chlorides in PTS–H_2O. *(Ref. 40)*



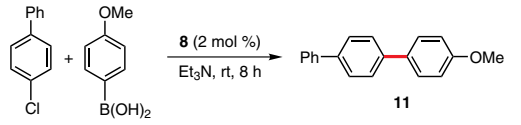
10	R	Ar	Yield
a	2-MeO	Ph	100%
b	2,6-Me_2	4-$MeOC_6H_4$	99%
c	4-NC	2,4-$F_2C_6H_3$	96%
d	2,6-Me_2	1-Np	100%

eq 11 *(Ref. 40)*



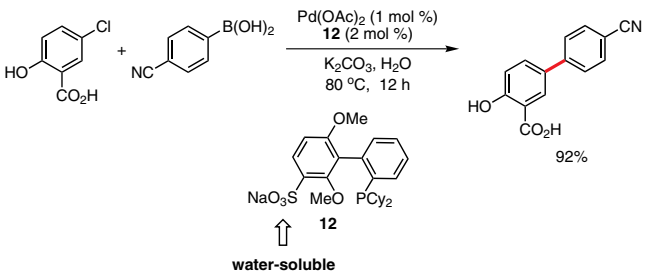
Cat.	y	T, °C	t, h	Yield
2a	1	50	24	28%
8	1	23	4	98%
only 0.1 wt % PTS–H_2O used ⇨ **8**	0.1	23	24	97%

eq 12 *(Ref. 40)*

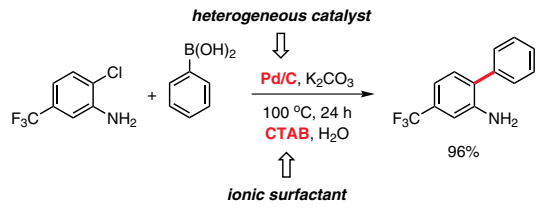


Medium	Conv.	Yield
PTS–H_2O (1 wt %)	99%	93%
No PTS ("on water")	73%	57%

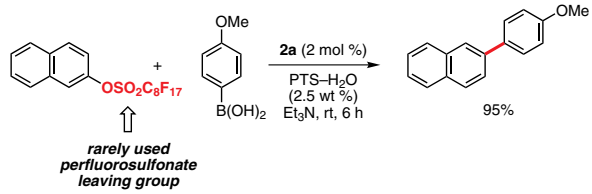
eq 13 *(Ref. 40)*



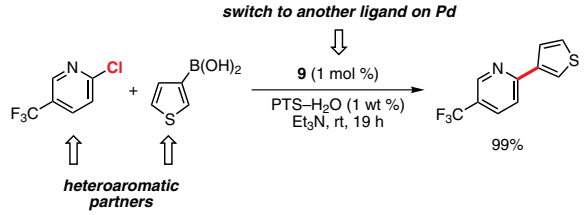
eq 14 *(Ref. 47)*



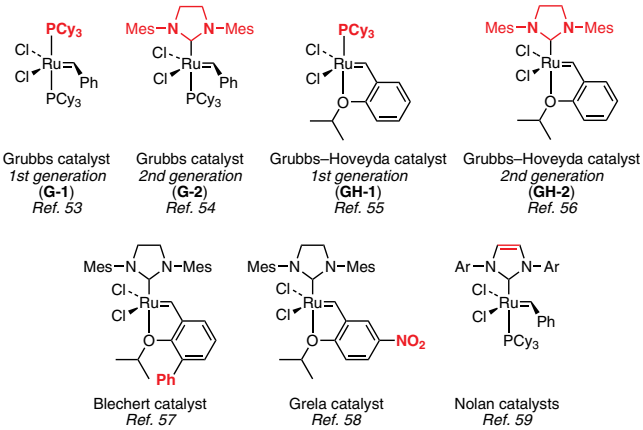
eq 15 *(Ref. 49)*



eq 16 *(Ref. 50)*



eq 17 *(Ref. 51)*



Grubbs catalyst *1st generation* (**G-1**) *Ref. 53*

Grubbs catalyst *2nd generation* (**G-2**) *Ref. 54*

Grubbs–Hoveyda catalyst *1st generation* (**GH-1**) *Ref. 55*

Grubbs–Hoveyda catalyst *2nd generation* (**GH-2**) *Ref. 56*

Blechert catalyst *Ref. 57*

Grela catalyst *Ref. 58*

Nolan catalysts *Ref. 59*

Figure 9. Representative, Water-Insoluble Metathesis Catalysts.

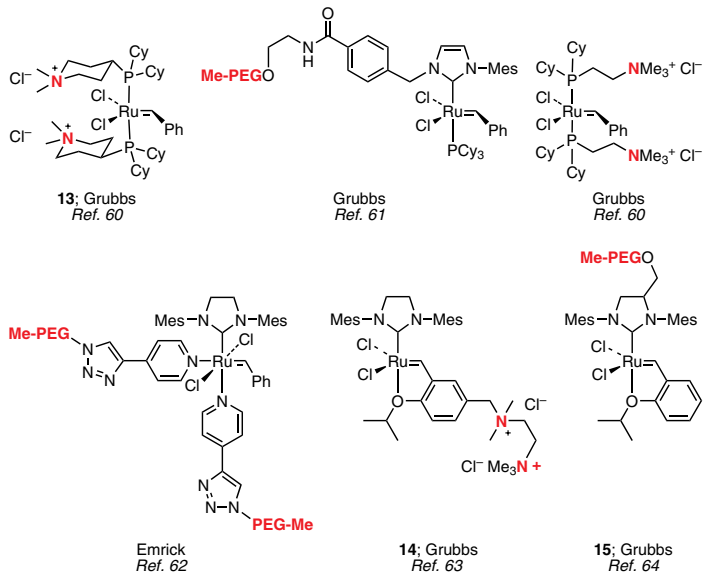
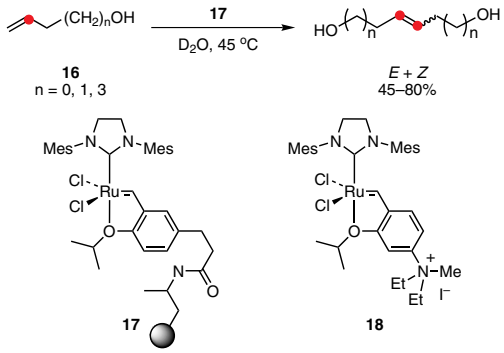


Figure 10. Representative Water-Soluble Catalysts for Metathesis.

remained of paramount concern, oftentimes forcing employment of low-molecular-weight (and hence, somewhat water-soluble) educts (e.g., **16**), or charged species that have innate solubility in aqueous media. For example, Blechert, Connon, and co-workers prepared a PEGA-NH_2-derived catalyst, **17** (**eq 18**),[65,66] which was used in homocouplings of hydroxyl-functionalized olefins, **16**, in heavy water at 45 °C. Levels of conversion, however, were variable. Related cross-metatheses, specifically on allyl alcohol (**16**, n = 0), were achieved in high yields (99%) by Grela and Mauduit employing catalyst **18**, although the best results with species **18** were obtained for the related analogous RCM reactions in CH_2Cl_2.[67,68] PTS represents one remarkably enabling technology that goes a long way towards eliminating concerns regarding the solubility characteristics of both catalysts and substrates. What organic chemists oftentimes refer to as "dump and stir" procedures are now in hand for both olefin CM and RCM, conducted at ambient temperatures; just add water.

For cross-metathesis, introduction of a Type I and Type II olefin[69] combination to a mixture of 2.5 wt % PTS–water containing the Grubbs 2nd-generation[54] catalyst leads to product olefins **19** in good isolated yields (**eq 19**).[70] The reagents (simple acrylates and enones, and Ru catalysts) and the reaction medium (PTS–H_2O) are readily available items of commerce. No special precautions are needed with respect to either solvent degassing or protection of reactions from air. Purification follows from established protocols (vide supra) usually involving simple filtration of reaction mixtures through a silica gel plug, followed by a standard extractive workup. Other functional groups that withstand these mild aqueous metathesis conditions include epoxides, allylic silanes, and nonracemic N-protected amino acid derivatives. Most reactions, run at overall concentrations of 0.5 M in PTS–water, usually take ≤12 hours to reach completion, and afford mainly, if not exclusively, *E* enones or enoates.

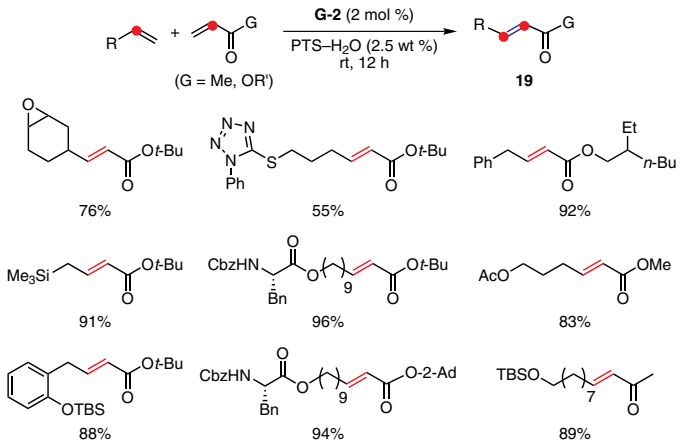
Ring-closing-metathesis (RCM) reactions in water have been of interest for over a decade.[52,71] Most approaches rely on ruthenium complexes that bear ligands modified to ensure water solubility (see Figure 10). An amphiphilic catalyst consisting of a block co-polymer based on poly(2-oxazoline) also shows promise



eq 18 *(Ref. 65,67)*

in water, with good prospects as well for ease of separation and recycling.[72] With water-soluble substrates, good conversions to cyclic products were achieved. A summary of the current state of ring-closing metathesis in water can be found in **Table 2**.[60b,63,64,72–76] Just earlier this year, ultrasonication was shown by Grela to afford carbo- and heterocyclic rings in excellent yields without recourse to surfactants.[74,75] Presumably, RCM occurs under acoustic emulsification within the droplets of each diene, which are otherwise water-insoluble. In the absence of water, oligomerization is a competing pathway (**eq 20**).[74]

The ionic surfactant SDS had been examined in 2002 by Davis and Sinou in related RCM reactions in water,[76] although in this early study use of the less reactive Grubbs 1st-generation catalyst precluded formation of tri- and tetrasubstituted olefinic products. Relatively high percentages (ca. 5 wt %) of amphiphile were also part of this recipe. The conclusion from this study was that a surfactant may not be essential for RCM reactions in water. Use of PTS in this context relies on less surfactant (1.5–2.5% by weight) than that used in CM reactions (i.e., 2.5 wt %), and

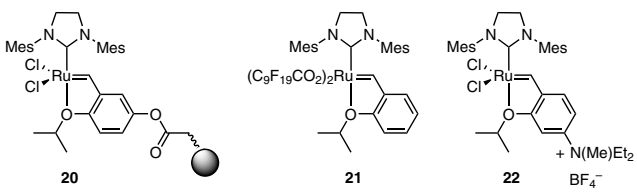


eq 19 *(Ref. 70)*

Table 2. Literature Reports on RCM Reactions in Water

Year	Catalyst	Additive	Examples	Comments	Senior Author	Ref.
1998	**13**	-	2	5–60% conversions, 5–10 mol % catalyst, degassed H_2O, 45 °C under argon, ring size: 5	Grubbs	*60b*
2002	Grubbs 1st Gen	SDS[a]	8	23–100% conversions, 5 mol % catalyst, degassed H_2O, 25 °C under N_2, 0.5 h, 0.05 M SDS, ring sizes: 5 and 6	Sinou	*76*
2004	**20**	-	1	90% conversion, 1 mol % catalyst, degassed H_2O, 25 °C under N_2, 1 h, ring size: 5	Weberskirch	*72*
2006	**15**	-	5	5–95% conversions, 5 mol % catalyst, degassed H_2O, 25 °C under argon, 12–36 h, ring sizes: 5 and 6	Grubbs	*64*
2007	**21**	DTAC[b]	1	91% conversion, 25 °C, 3.5 h, 0.048 M DTAC, ring size: 5	Mingotaud	*73*
2007	**14**	–	5	5–95% conversions, 5 mol % catalyst, degassed H_2O, 30–45 °C, under argon, 24 h, ring sizes: 5 and 6	Grubbs	*63*
2008	Grubbs 2nd Gen	–	5	65–99% yields, 5 mol % catalyst, 40 °C ultrasonication, 5 h, ring sizes: 5 and 6	Grela	*74*
2008	**22**	–	4	95–99% conversions, 5 mol % catalyst, 25 °C, 5–24 h, ring size: 5	Grela	*75*

[a] *SDS = sodium dodecyl sulfate.* [b] *DTAC = dodecyltrimethylammonium chloride.*



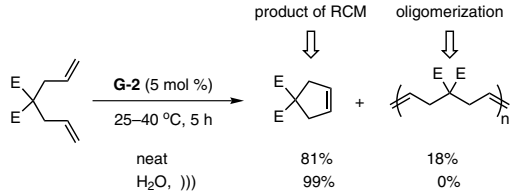
leads to *consistently* high conversions and hence, isolated yields.[77] RCM reactions in neutral PTS micelles take high place fairly quickly (1–3 hours), including the formation of seven-membered rings and trisubstituted arrays, mediated by the Grubbs 2nd-generation or Grubbs–Hoveyda 2nd-generation catalyst without high dilution (0.10 M) (**eq 21**).[77] Although most examples to date have been carried out under these conditions, increasing the total concentration of substrate to 0.30 M did not significantly alter the reaction rate, or the extent of conversion or homocoupling.

Applications of cross-metathesis to tandem processes can easily be envisioned. One recent example of dienoate formation calls for the coupling of an acrylate with a simple phenolic derivative of homoallyl alcohol (**23**; formed via *O*-alkylation of *p*-nitrophenol).[78] The resulting initial product readily undergoes elimination to generate the corresponding doubly unsaturated ester **24** (**Scheme 3**). Although most examples were studied in organic media, results in PTS–H_2O were essentially identical.

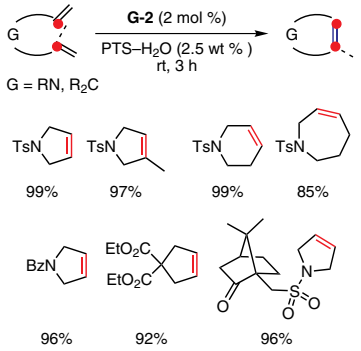
So, what about "seawater", rather than water out of the bottle, as the solvent for these cross-couplings using PTS? The answer is "yes"; at least insofar as CM and RCM reactions go, they work equally well in this medium (**Scheme 4**).[79] Of course, we can only make this claim for water taken from the shores of the Pacific Ocean in Southern California! Interestingly, DLS indicates that such PTS–seawater contains 75-nm particles; thus, the presence of Na^+ (and likely other cations as well) increases the size of these nanoreactors (from 24 nm, in sweet water), presumably due to elongation of PEG as a result of greater ionic strength of the water.

5. Summary and Outlook

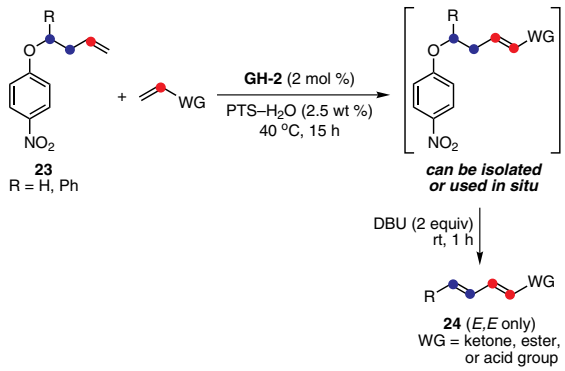
Studies to date on Heck and Suzuki–Miyaura couplings, as well as olefin metathesis reactions, in pure water at room temperature have been very encouraging. The presence of the nanometer-micelle-forming amphiphile PTS may provide the foundation for these aqueous conditions, but the catalysis is still metal-dependent, and the quality of the resulting coupling is highly ligand-driven. In other words, PTS offers an aqueous advantage, and while the metal counts, *the ligand rules*. It is also somewhat premature to assume that many of the remaining important cross-coupling reactions in transition-metal-catalyzed organic synthesis are amenable and will simply follow suit. Nonetheless, based on additional preliminary data in



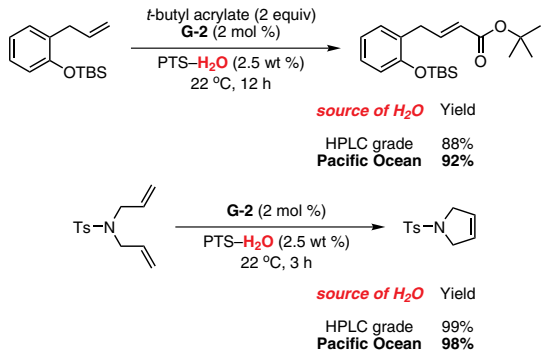
eq 20 *(Ref. 74)*



eq 21 *(Ref. 77)*



Scheme 3. Tandem Cross-Metathesis–Elimination to Form Polyenes. *(Ref. 78)*



Scheme 4. Metathesis Reactions in PTS–Seawater. *(Ref. 79)*

hand, there is good reason to suspect that related methodologies will be forthcoming. For example, Sonogashira couplings in PTS–H_2O suggest that aromatic acetylenes can be fashioned *from aryl bromides in the absence of copper at 25 °C* (**eq 22**).[80a]

Initial attempts at asymmetric hydrosilylation of a challenging case such as isophorone with catalytic CuH, ligated by Takasago's nonracemic bisphosphine DTBM-SEGPHOS® (**25**)[81] in PTS–H_2O, also look promising (**eq 23**).[82] Thus, PTS is part of the puzzle; one member of a class of "designer" surfactants. That such tailor-made materials in pure water could be viewed simply as supplying "solvents" for several fundamental processes done in pure water intuitively has appeal. Creating new enabling technologies for transition-metal-catalyzed reactions based on micellar catalysis in water may constitute only one approach among many under the umbrella of green chemistry, but it has the potential for considerable impact; getting organic solvents out of organic reactions just makes good sense, and the numbers support this notion. Estimates suggest that, on a yearly basis, 3.2 *million* MT of solvents are used in chemical manufacturing; a shift of only 1% based on (readily hydrolyzed, safe,[83] and non-polluting) levels of PTS in water would amount to a savings of 32,000 MT of organic solvents (1 MT = 1,000 kg). Thus, it is not hard to see why along "The Road to Sustainability", as conveyed by Sheldon, Arends, and Hanefeld in their recent monograph *Green Chemistry and Catalysis*,[3b] "***The Medium is the Message***."

6. Acknowledgements

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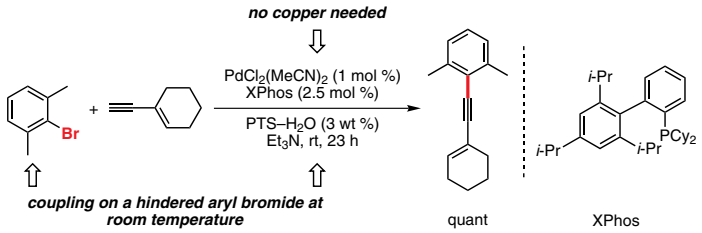
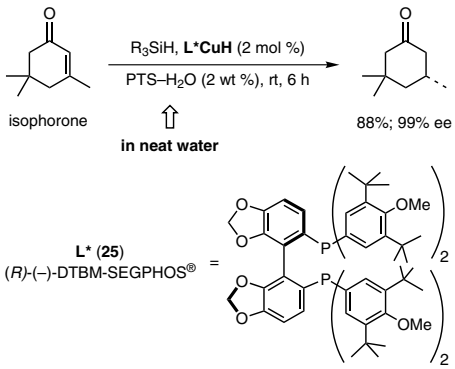
7. References and Notes

(1) Sheldon, R. A. *Green Chem.* **2007**, *9*, 1273.
(2) Trost, B. M. *Science* **1991**, *254*, 1471.
(3) (a) Li, C.-J.; Chan, T.-H. *Comprehensive Organic Reactions in Aqueous Media,* 2nd ed.; Wiley-VCH: Hoboken, NJ, 2007. (b) Sheldon, R. A.; Arends, I.; Hanefeld, U. *Green Chemistry and Catalysis*; Wiley-VCH: Weinheim, Germany, 2007. (c) *Organic Reactions in Water: Principles, Strategies, and Applications*; Lindström, U. M., Ed.; Blackwell Publishing: Oxford, U.K., 2007. (d) 12th Annual Green Chemistry and Engineering Conference; ACS Green Chemistry Institute, Washington, D.C., June 24–26, 2008 (http://www.gcande.org/; accessed July 24, 2008).
(4) (a) Sheldon, R. A. *Green Chem.* **2005**, *7*, 267. (b) *Green Chem.* **2003**, *5*, 99. (Special Issue on Green Solvents for Catalysis; Leitner, W., Seddon, K. R., Wasserscheid, P., Eds.)
(5) Blackmond, D. G.; Armstrong, A.; Coombe, V.; Wells, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3798.
(6) (a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275. (b) Hayashi,



Representative Sonogashira coupling in PTS–H_2O. Preparation of 2-(cyclohexen-1-ylethynyl)-1,3-dimethylbenzene.[80a] $Pd(CH_3CN)_2Cl_2$(1.8 mg, 0.007 mmol) and XPhos (6.9 mg, 0.014 mmol) were introduced under argon into a 5-mL, round-bottom flask equipped with a stir bar. The following were then added via syringe under a positive flow of argon in the order shown: degassed PTS solution (1.0 mL, 3 wt %), Et_3N (150 µL, 1.08 mmol), 2-bromo-*m*-xylene (70 µL, 0.52 mmol), and 1-ethynylcyclohexene (100 µL, 0.85 mmol). A milky, brown mixture developed over 20 min while stirring at rt. The reaction progress was monitored by GC. After 23 h, the mixture was diluted with brine and extracted with EtOAc. The organic extracts were combined and dried over anhydrous Na_2SO_4, filtered, and concentrated by rotary evaporation to give a crude brown oil that was purified by silica gel chromatography (eluting with hexanes) to afford the title compound (110 mg, 100%) as a colorless oil. Its ^1H NMR (400 MHz, $CDCl_3$) spectral data matched those previously reported.[80b]

eq 22 *(Ref. 80a)*



eq 23 *(Ref. 82)*

Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8103. (c) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159. (d) Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317. (e) Nyberg, A. I.; Usano, A.; Pihko, P. M. *Synlett* **2004**, 1891.

(7) (a) Dwars, T.; Paetzold, E.; Oehme, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7174. (b) Khan, M. N. *Micellar Catalysis*; CRC Press: Boca Raton, FL, 2006.

(8) Huibers, P. D. T.; Lobanov, V. S.; Katritzky, A. R.; Shah, D. O.; Karelson, M. *Langmuir* **1996**, *12*, 1462.

(9) (a) *Dynamics of Surfactant Self-Assemblies: Micelles, Microemulsions, Vesicles, and Lyotropic Phases*; Zana, R., Ed.; Surfactant Science Series 125; Taylor & Francis: Boca Raton, FL, 2005. (b) Myers, D. *Surfactant Science and Technology*, 3rd ed.; Wiley: Hoboken, NJ, 2006.

(10) (a) Ogawa, C.; Kobayashi, S. Acid Catalysis in Water. In *Organic Reactions in Water*: *Principles, Strategies, and Applications*; Lindström, U. M., Ed.; Blackwell Publishing: Oxford, U.K., 2007; Chapter 3, pp 60–91. (b) Li, C.-J. Metal-Mediated C–C Bond Formations in Aqueous Media. In *Organic Reactions in Water*: *Principles, Strategies, and Applications*; Lindström, U. M., Ed.; Blackwell Publishing: Oxford, U.K., 2007; Chapter 4. (c) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68.

(11) (a) *Organometallics in Synthesis: A Manual*, 2nd ed.; Schlosser, M., Ed.; Wiley: Chichester, U.K., 2002. (b) Beletskaya, I. P.; Cheprakov, A. V. Aqueous Palladium Catalysis. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Eds.; Wiley-Interscience: New York, NY, 2002; Vol. 2, Part X.1, pp 2957–3006.

(12) (a) Kobayashi, S.; Wakabayashi, T.; Nagayama, S.; Oyamada, H. *Tetrahedron Lett.* **1997**, *38*, 4559. (b) Kobayashi, S.; Wakabayashi, T.; Oyamada, H. *Chem. Lett.* **1997**, 831. (c) Kobayashi, S.; Busujima, T.; Nagayama, S. *Synlett* **1999**, 545. (d) Kobayashi, S.; Busujima, T.; Nagayama, S. *J. Chem. Soc., Chem. Commun.* **1998**, 19.

(13) Borkovec, M. Measuring Particle Size by Light Scattering. In *Handbook of Applied Surface and Colloid Chemistry*; Holmberg, K., Ed.; Wiley: Chichester, U.K., 2002; Vol. 2, pp 357–370.

(14) Wei, H.; Cheng, C.; Chang, C.; Chen, W.-Q.; Cheng, S.-X.; Zhang, X.-Z.; Zhuo, R.-X. *Langmuir* **2008**, *24*, 4564.

(15) (a) Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis: Background and Detailed Mechanisms*; Elsevier Academic Press: Burlington, MA, 2005. (b) Li, J. J. *Name Reactions*, 2nd ed.; Springer-Verlag: New Delhi, India, 2003.

(16) (a) Borowy-Borowski, H.; Sikorska-Walker, M.; Walker, P. R. Water-Soluble Compositions of Bioactive Lipophilic Compounds. U.S. Patent 6,045,826, Apr 4, 2000. (b) Borowy-Borowski, H.; Sikorska-Walker, M.; Walker, P. R. Water-Soluble Compositions of Bioactive Lipophilic Compounds. U.S. Patent 6,191,172, Feb 20, 2001. (c) Borowy-Borowski, H.; Sikorska-Walker, M.; Walker, P. R. Water-Soluble Compositions of Bioactive Lipophilic Compounds. U.S. Patent 6,632,443, Oct 14, 2003.

(17) For a summary of the properties of TRITON® X-100 (CAS Registry No. 9002-93-1), see http://www.sigmaaldrich.com/sigma/product%20information%20sheet/t8532pis.pdf (accessed Jul 2008).

(18) For more information on BRIJ® 30 (CAS Registry No. 9002-92-0), see Satkowski, W. B.; Huang, S. K.; Liss, R. L. Polyoxyethylene Alcohols. In *Nonionic Surfactants*; Schick, M. J., Ed.; Dekker: New York, 1967; pp 86–141.

(19) For more information on TWEEN® 80 (CAS Registry No. 9005-65-6), see http://en.wikipedia.org/wiki/Polysorbate_80#cite_note-DannyK-3 (accessed Jul 2008).

(20) For a discussion of the properties of sodium dodecyl sulfate (CAS Registry No. 151-21-3), see Powney, J.; Addison, C. C. The Properties of Detergent Solutions. *Trans. Faraday Soc.* **1937**, *33*, 1243.

(21) For applications and properties of Eastman Vitamin E TPGS NF, see http://www.eastman.com/NR/rdonlyres/A2FE037B-0778-4A90-A0FC-5D07BE51064A/0/PCI102.pdf (accessed Jul 2008).

(22) (a) Griffin, W. C. *J. Soc. Sosmet. Chem.* **1949**, *1*, 311. (b) Niraula, B. B.; Chun, T. K.; Othman, H.; Misran, M. *Colloids Surf., A: Physicochem. Eng. Aspects* **2004**, *248*, 157.

(23) (a) Lumb, K. J.; DeCarr, L. B.; Milardo, L. F.; Mays, M. R.; Buckholz, T. M.; Fisk, S. E.; Pellegrino, C. M.; Ortiz, A. A.; Mahle, C. D. *J. Med. Chem.* **2007**, *50*, 2264. (b) Gatouillat, G.; Odot, J.; Balasse, E.; Nicolau, C.; Tosi, P.-F.; Hickman, D. T.; López-Deber, M. P.; Madoulet, C. *Cancer Lett.* **2007**, *257*, 165. (c) Li, J.; Kao, W. J. *Biomacromolecules* **2003**, *4,* 1055.

(24) Naderi, J.; Somayajulu-Nitu, M.; Mukerji, A.; Sharda, P.; Sikorska, M.; Borowy-Borowski, H.; Antonsson, B.; Pandey, S. *Apoptosis* **2006**, *11*, 1359.

(25) Lipshutz, B. H.; Taft, B. R. *Org. Lett.* **2008**, *10*, 1329.

(26) (a) González, Y. I.; Kaler, E. W. *Curr. Opin. Colloid Interf. Sci.* **2005**, *10*, 256. (b) Cryo-TEM data was provided by Dr. Jingshan Dong at the NSF Regional Center, University of Minnesota.

(27) Borowy-Borowski, H.; Berl, V.; Lipshutz, B. H. University of California, Santa Barbara, CA. Unpublished work.

(28) (a) Lipshutz, B. H.; Taft, B. R. University of California, Santa Barbara, CA. Unpublished work. (b) Huang, Z.-Z.; Ye, S.; Xia, W.; Yu, Y.-H.; Tang, Y. *J. Org. Chem.* **2002**, *67*, 3096.

(29) (a) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320. See also: (b) Tsuji, J. *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: Chichester, U.K., 2000. (c) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; Wiley: Chichester, U.K., 2004.

(30) (a) Knowles, J. P.; Whiting, A. *Org. Biomol. Chem.* **2007**, *5,* 31. (b) Phan, N. T. S.; van der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609. (c) See reference 11b. (d) Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 2677. (e) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

(31) (a) Alacid, E.; Najera, C. *Synlett* **2006**, 2959. (b) Schönfelder, D.; Nuyken, O.; Weberskirch, R. *J. Organomet. Chem.* **2005**, *690*, 4648. (c) Schönfelder, D.; Fischer, K.; Schmidt, M.; Nuyken, O.; Weberskirch, R. *Macromolecules* **2005***, 38*, 254.

(32) Jeffery, T. *Tetrahedron Lett.* **1994**, *35*, 3051.

(33) Bumagin, N. A.; Bykov, V. V.; Sukhomlinova, L. I.; Tolstaya, T. P.; Beletskaya, I. P. *J. Organomet. Chem.* **1995**, *486*, 259.

(34) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170.

(35) Bhattacharya, S.; Srivastava, A.; Sengupta, S. *Tetrahedron Lett.* **2005**, *46*, 3557.

(36) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771.

(37) (a) Menger, F. M.; Portnoy, C. E. *J. Am. Chem. Soc.* **1967**, *89*, 4698. (b) Fuji, K.; Morimoto, T.; Tsutsumi, K.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2409.

(38) (a) [Pd(dtbpf)Cl_2] (CAS Registry No. 95408-45-0) was kindly supplied to us by Dr. Thomas J. Colacot, Johnson Matthey (email: colactj@jmusa.com). (b) Lipshutz, B. H.; Taft, B. R.; Ghorai, S. University of California, Santa Barbara, CA. Unpublished work.

(39) Lipshutz, B. H.; Monzon, G. A.; Abela, A. R.; Taft, B. R. University of California, Santa Barbara, CA. Unpublished work.

(40) Lipshutz, B. H.; Petersen, T. B.; Abela, A. R. *Org. Lett.* **2008**, *10*, 1333.

(41) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64*, 3047.

(42) DeVasher, R. B.; Moore, L. R.; Shaughnessy, K. H. *J. Org. Chem.* **2004**, *69*, 7919.

(43) Huang, R.; Shaughnessy, K. H. *Organometallics* **2006**, *25*, 4105.

(44) Ramesh Kumar, N. S. C.; Victor Paul Raj, I.; Sudalai, A. *J. Mol. Cat., A: Chem.* **2007**, *269*, 218.

(45) (a) Lee, M.; Jang, C.-J.; Ryu, J.-H. *J. Am. Chem. Soc.* **2004**, *126*, 8082. (b) Ryu, J.-H.; Jang, C.-J.; Yoo, Y.-S.; Lim, S.-G.; Lee, M. *J. Org. Chem.* **2005**, *70*, 8956.

(46) Basheer, C.; Hussain, F. S. J.; Lee, H. K.; Valiyaveettil, S. *Tetrahedron Lett.* **2004**, *45*, 7297.

(47) Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173.

(48) Bedford, R. B.; Blake, M. E.; Butts, C. P.; Holder, D. *Chem. Commun.* **2003**, 466.

(49) Arcadi, A.; Cerichelli, G.; Chiarini, M.; Correa, M.; Zorzan, D. *Eur. J. Org. Chem.* **2003**, 4080.

(50) Zhang, W.; Chen, C. H.-T.; Lu, Y.; Nagashima, T. *Org. Lett.* **2004**, *6*, 1473.

(51) Lipshutz, B. H.; Abela, A. R. *Org. Lett.*, submitted for publication.

(52) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (d) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (e) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (f) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003 (three-volume set). (g) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. (h) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. (i) Gradillas, A.; Pérez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086. (j) Schrodi, Y.; Pederson, R. L. *Aldrichimica Acta* **2007**, *40*, 45.

(53) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(54) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(55) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.

(56) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

(57) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2403.

(58) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4038.

(59) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674.

(60) (a) Mohr, B.; Lynn, D. M.; Grubbs, R. H. *Organometallics* **1996**, *15*, 4317. (b) Kirkland, T. A.; Lynn, D. M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 9904. (c) Lynn, D. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 3187.

(61) Gallivan, J. P.; Jordan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **2005**, *46*, 2577.

(62) Samanta, D.; Kratz, K.; Zhang, X.; Emrick, T. *Macromolecules* **2008**, *41*, 530.

(63) Jordan, J. P.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 5152.

(64) Hong, S. H.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 3508.

(65) Connon, S. J.; Blechert, S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1873.

(66) Connon, S. J.; Rivard, M.; Zaja, M.; Blechert, S. *Adv. Synth. Catal.* **2003**, *345*, 572.

(67) Rix, D.; Caïjo, F.; Laurent, I.; Gułajski, Ł.; Grela, K.; Mauduit, M. *Chem. Commun.* **2007**, 3771.

(68) For a review on aqueous olefin metathesis, see Burtscher, D.; Grela, K. *Angew. Chem., Int. Ed.* **2008**, *47*, in press.

(69) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
(70) Lipshutz, B. H.; Aguinaldo, G. T.; Ghorai, S.; Voigtritter, K. *Org. Lett.* **2008**, *10*, 1325.
(71) (a) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693.
(72) Zarka, M. T.; Nuyken, O.; Weberskirch, R. *Macromol. Rapid Commun.* **2004**, *25*, 858.
(73) Mingotaud, A.-F.; Krämer, M.; Mingotaud, C. *J. Mol. Catal., A: Chem.* **2007**, *263*, 39.
(74) Gułajski, Ł.; Śledź, P.; Lupa, A.; Grela, K. *Green Chem.* **2008**, *10*, 271.
(75) Gułajski, Ł.; Michrowska, A.; Narożnik, J.; Kaczmarska, Z.; Rupnicki, L.; Grela, K. *ChemSusChem* **2008**, *1*, 103.
(76) Davis, K. J.; Sinou, D. *J. Mol. Catal., A: Chem.* **2002**, *177*, 173.
(77) Lipshutz, B. H.; Ghorai, S.; Aguinaldo, G. T. *Adv. Synth. Catal.* **2008**, *350*, 953.
(78) Lipshutz, B. H.; Ghorai, S.; Bošković, Ž. V. *Tetrahedron* **2008**, *64*, 6949.
(79) Lipshutz, B. H.; Ghorai, S. University of California, Santa Barbara, CA. Unpublished work.
(80) (a) Lipshutz, B. H.; Chung, D. W.; Rich, B. *Org. Lett.* **2008**, *10*, 3793. (b) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993.
(81) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.
(82) Lipshutz, B. H.; Unger, J. B. University of California, Santa Barbara, CA. Unpublished work.
(83) PTS is FDA GRAS affirmed for use with CoQ_{10} in dietary supplements (Notice No. GRN 000202; http://www.cfsan.fda.gov/~rdb/opa-g202.html), and has self-affirmed GRAS status for use as a food ingredient (accessed July 2008).

Keywords: cross-couplings; green chemistry; micellar catalysis; designer surfactants; PTS.

About the Authors

Bruce Lipshutz has been at the University of California, Santa Barbara, since joining the faculty in 1979. Much of his career has been focused on developing new reagents and technologies that have broad appeal in the synthetic community, many of which are, or will soon be, commercially available (e.g., SEM-Cl, "Higher Order Cuprates", "Cuprate-in-a-Bottle", DCAD, "Copper Hydride-in-a-Bottle", Ni/C, Cu/C, PTS, etc.). The group's efforts have now turned in part to "green chemistry". Thus, an ongoing mix of methods in heterogeneous catalysis, including newly developed mixed-metal-supported cross-coupling reagents and homogeneous catalysis, are being investigated. The latter includes recent contributions in micellar catalysis, with an accent on the development of "designer" surfactants. Also being actively pursued are projects in total or partial synthesis of biaryls that possess axial chirality (e.g., the A–B biaryl section of vancomycin, and the antimalarial korupensamines), and syntheses associated with, or leading to, analogues of coenzyme Q_{10} (e.g., total synthesis of piericidin A1).

Subir Ghorai was born in 1977 in Panskura, West Bengal, India. After receiving his B.S. and M.S. degrees in chemistry from Jadavpur University, India, he joined the Indian Institute of Chemical Biology (IICB), Jadavpur, in 2000 as a CSIR research fellow. He received his Ph.D. degree in 2005 from IICB, working under the supervision of Dr. Anup Bhattacharjya on the synthesis of chiral dendrimers and heterocycles from carbohydrate precursors. From 2005 to 2006, he worked on isonitrile chemistry as a postdoctoral fellow with Professor Michael C. Pirrung at the University of California, Riverside. Since then, Subir has been a postdoctoral fellow in the research group of Professor Bruce H. Lipshutz at the University of California, Santa Barbara, where he is now working on green chemistry projects involving transition-metal-catalyzed reactions in aqueous media.

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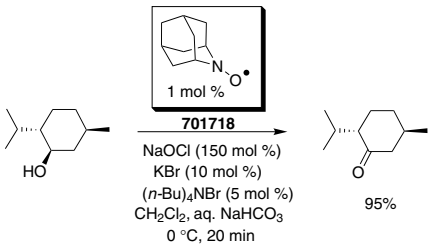
Accelerate Organic Synthesis

Organocatalyst for the Oxidation of Hindered Alcohols

The conversion of alcohols to their corresponding carbonyl compounds is a critical functional-group transformation. Green processes that can effect these transformations are of significant interest. While nitroxyl-based TEMPO has had a long-standing reputation as an environmentally friendly oxidant, the bulky nature of TEMPO's piperidine skeleton precludes its use in sterically demanding environments. Iwabuchi and coworkers have shown that the related azaadamantane organocatalyst, AZADO (2-azaadamantane *N*-oxyl) exhibits enhanced reactivity over TEMPO in mild catalytic oxidations of secondary alcohols such as menthol.

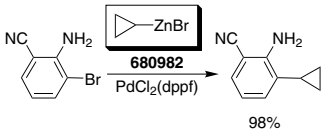


Shibuya, M. et al. *J. Am. Chem. Soc.* **2006**, *128*, 8412.

701718

Cyclopropylzinc Bromide for the Negishi Coupling

The Negishi coupling, or the palladium-catalyzed cross-coupling of organozinc reagents with aryl halides, offers a wider functional-group tolerance relative to related cross-coupling reactions. Cyclopropylzinc bromide can be used to convert aryl iodides and bromides into the corresponding cyclopropylanthranilonitriles in excellent yields, demonstrating the robust nature of these organozinc reagents in the presence of both amino and nitrile functionalities.

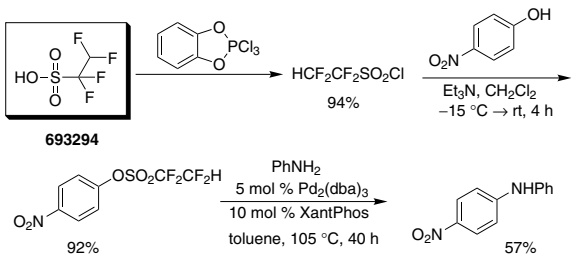


Campbell, J. B. et al. *Synth. Commun.* **1989**, *19*, 2265.

680982

TFESA as an Alternative to Triflic Acid

TFESA (1,1,2,2-tetrafluoroethanesulfonic acid) has recently been investigated as an alternative to triflic acid due to its relatively easier handling and lower volatility, yet comparable activity. Additionally, the hydrogen atom provides a ^{1}H NMR handle, allowing for ease of characterization and monitoring of experiments. TFESA can be used to prepare aryl tetraflates and has been employed in various cross-coupling reactions, including Suzuki, Heck, and Buchwald–Hartwig couplings.

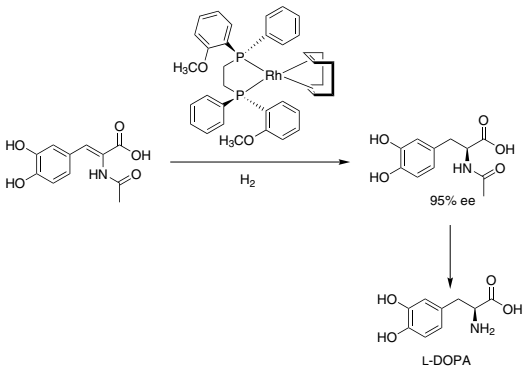


Rostovtsev, V. V. et al. *J. Org. Chem.* **2008**, *73*, 711

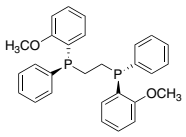
693294

New DIPAMP Ligands for Enantioselective Hydrogenation

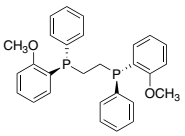
Rewarded by a Nobel Prize in 2001 for his pioneering work in asymmetric synthesis, Knowles was the first to develop a chiral transition-metal catalyst based on a chiral diphosphine ligand, DIPAMP, that could transfer chirality to a prochiral substrate with high enantiomeric excesses. He demonstrated that a chiral diphosphine chelated to rhodium could give access to catalysis that mimicks enzyme selectivity. To demonstrate the activity and selectivity of this new ligand, Knowles synthesized L-DOPA, a compound employed in the treatment of Parkinson's disease. The synthesis starts with the asymmetric hydrogenation of (*Z*)-2-acetamido-3-(3,4-dihydroxyphenyl)acrylic acid using Rh-DIPAMP, followed by deprotection of the amine. This process has been scaled up at Monsanto.



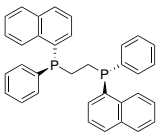
Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106.



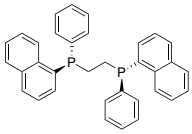
(*S,S*)-DIPAMP
697753



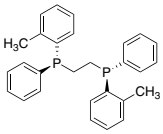
(*R,R*)-DIPAMP
697761



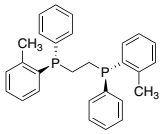
(*S,S*)-1-Naphthyl-DIPAMP
697788



(*R,R*)-1-Naphthyl-DIPAMP
697796



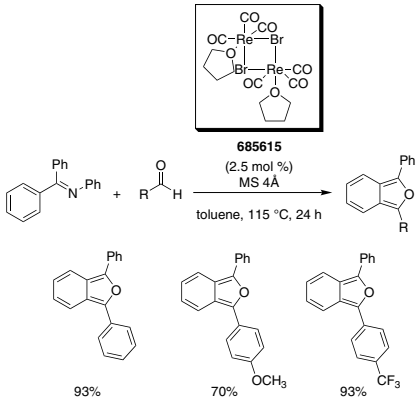
(*S,S*)-*o*-Tolyl-DIPAMP
697818



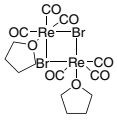
(*R,R*)-*o*-Tolyl-DIPAMP
697826

Insertion of Aldehyde into a C–H Bond

Isobenzofuran derivatives are widely used as building blocks of natural products and bioactive materials. Kuninobu et al. developed a new method to access these molecules via rhenium-catalyzed insertion of different aldehydes into a C–H bond. Using 2.5 mol % of catalyst and molecular sieves in toluene, a variety of isobenzofurans were synthesized in good yields.



Kuninobu, Y. et al. *J. Am. Chem. Soc.* **2006**, *128*, 12376.



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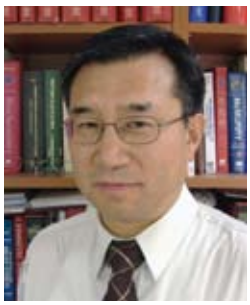
Preparation of Chiral Diamines by the Diaza-Cope Rearrangement (DCR)

Mr. Hyunwoo Kim

Dr. Soon Mog So

Prof. Jik Chin



Prof. B. Moon Kim

*Hyunwoo Kim, Soon Mog So, and Jik Chin**
Department of Chemistry
University of Toronto
80 St. George Street
Toronto, ON M5S 3H6, Canada
Email: jchin@chem.utoronto.ca

*B. Moon Kim**
Department of Chemistry
College of Natural Sciences
Seoul National University
Seoul 151-747, Korea

Outline

1. Introduction

Chiral vicinal diamines are of considerable interest as ligands for developing stereoselective catalysts and as intermediates in the synthesis of drugs (**Figure 1**). Diamine-based catalysts have been used for all types of reactions including oxidation, reduction, hydrolysis, and carbon–carbon-bond-forming reactions. Bioactive compounds that are based on vicinal diamines include anticancer, antiviral, antibacterial, antidepressant, and antihypertensive agents. In fact, the vicinal diamine structural motif could be considered "privileged"[1] when it comes to developing catalysts and drugs. Numerous publications, including several review articles,[2–4] have appeared on the synthesis and applications of chiral diamines. Although much progress has been made, it has been a challenge to develop a facile, efficient, and general route to a wide range of chiral diamines in enantiomerically pure form. Such an approach would greatly facilitate the development of new diamine-based catalysts and drugs, and would be advantageous for optimizing the performance of known diamine-based catalysts by tuning the steric and electronic properties of the attached ligands. Libraries of chiral diamines and their derivatives, such as imidazolines and piperazines, would be valuable for exploring the chiral space of selected drug receptors. The present review will start with the diaza-Cope rearrangement (DCR) as a method for preparing chiral vicinal diamines. Subsequent sections will describe some diamine-based catalysts and drugs.

2. Synthesis of Chiral, Vicinal Diamines by the Diaza-Cope Rearrangement (DCR)

The prevalence of the vicinal diamine motif in the structures of catalysts and bioactive compounds has led to the development of dozens of methods for the synthesis of vicinal diamines. Some of the more practical routes to C_2-symmetrical diaryl- and dialkyl-substituted primary diamines are shown in **Scheme 1**.

There is considerable interest in developing syntheses of vicinal diamines that are broad in scope.[2] It is often difficult or tedious to make enantiomerically pure vicinal diamines on a large scale. Moreover, the efficient production of diphenylethylenediamine (DPEN)[5] and 1,2-diaminocylcohexane (DACH)[6] (see Scheme 1) has undoubtedly contributed to the explosive growth of the field. However, a greater variation in the diamine structure is needed for discovering better catalysts and drugs. We recently developed a method for synthesizing

chiral vicinal diamines by using the diaza-Cope rearrangement (DCR).[7,8] This process provides one of the simplest and most versatile approaches to preparing a wide variety of chiral vicinal diamines, including diaryl- and dialkyl-substituted ones in C_2-symmetrical or unsymmetrical forms, from a single diamine, 1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (HPEN in Scheme 1). This rearrangement (i) generally takes place *under mild conditions without the need for any catalyst*; (ii) is highly stereospecific, thus providing an efficient and direct route to enantiopure chiral vicinal diamines; and (iii) eliminates the need for tedious and time-consuming optimizations of the chiral resolution conditions.

2.1. Diaryl Vicinal Diamines

The diaza-Cope rearrangement was first used in 1976 by Vögtle and Goldschmitt to prepare a variety of meso vicinal diamines.[9] More recently, we developed the chiral version of this rearrangement reaction.[8] DFT computation revealed that resonance-assisted hydrogen bonding is the driving force behind all of our reactions for preparing chiral vicinal diamines in high yields and enantiopurities under mild conditions. Since 1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane(HPEN, **1**) is the key starting material in the synthesis of all of our chiral vicinal diamines (see Scheme 1), we refer to it as the "mother" diamine, from which all "daughter" diamines are produced

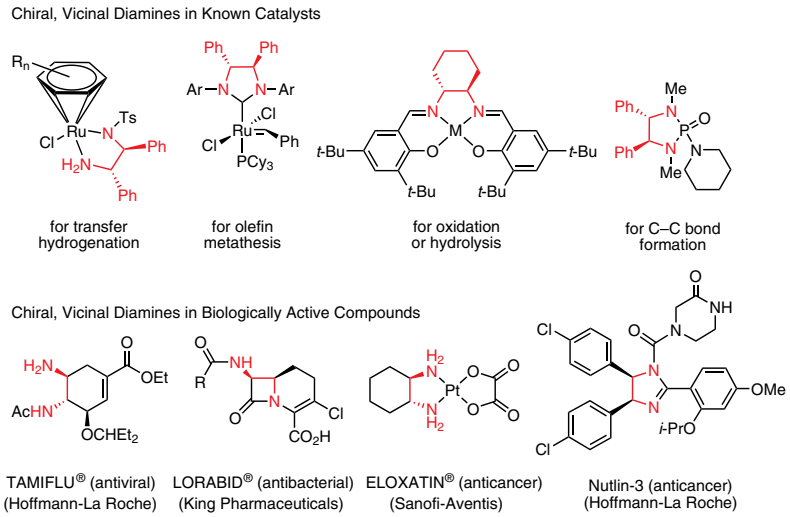
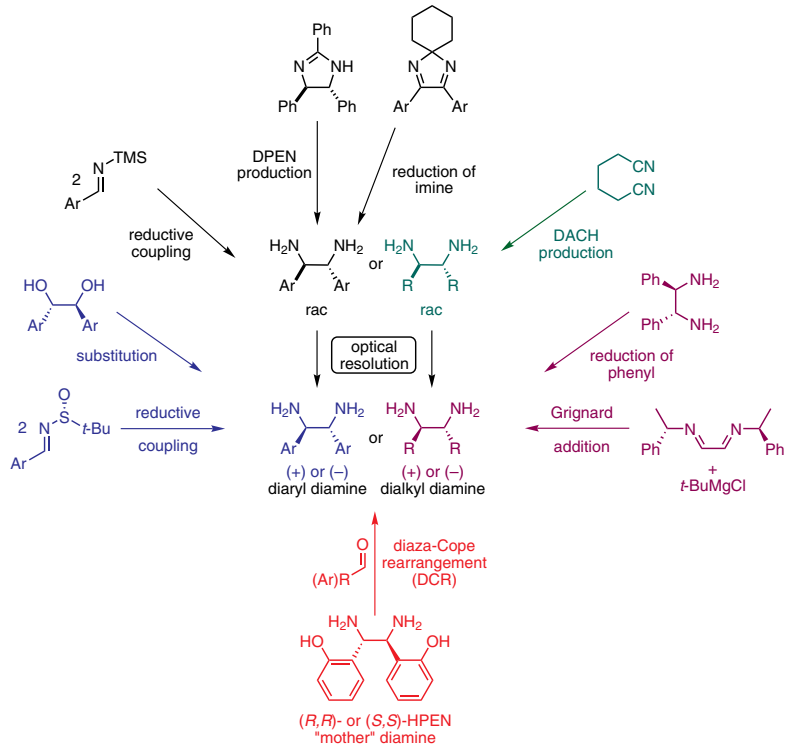
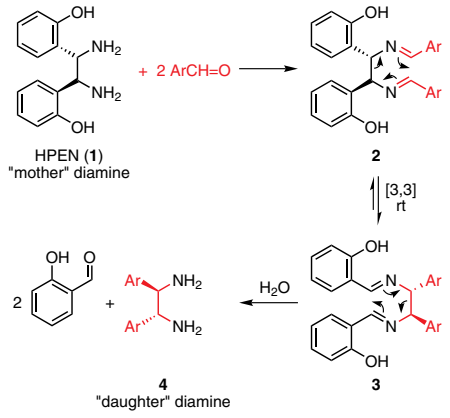


Figure 1. Vicinal-Diamine-Based Catalysts and Bioactive Compounds.



Scheme 1. Known Syntheses of C_2-Symmetrical, Primary Vicinal Diamines.



4	Ar	Yield
a	C_6F_5	77%
b	4-$O_2NC_6H_4$	73%
c	4-$MeO_2CC_6H_4$	87%
d	4-FC_6H_4	87%
e	4-ClC_6H_4	78%
f	4-$F_3CC_6H_4$	80%
g	4-NCC_6H_4	85%
h	4-$AcHNC_6H_4$	90%
i	4-$MeOC_6H_4$	78%
j	4-HOC_6H_4	74%
k	4-$Me_2NC_6H_4$	69%
l	2-$MeOC_6H_4$	79%
m	2-ClC_6H_4	81%
n	2-MeC_6H_4	75%
o	1-Np	78%
p	2,4,6-$(MeO)_3C_6H_2$	79%
q	2,4,6-$Me_3C_6H_2$	77%

ee >99% in all cases.

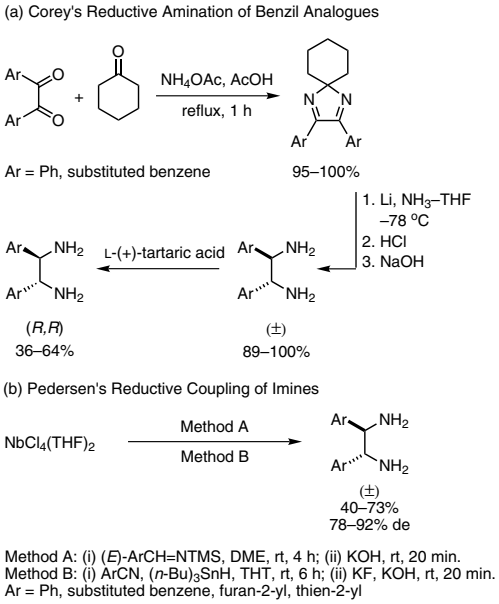
Scheme 2. "Mother-to-Daughter" Diamine by DCR. *(Ref. 7,8)*

(**Scheme 2**). In a typical reaction, addition of two equivalents of an aromatic aldehyde to **1** results in the formation of the corresponding diimine, **2**, which undergoes the DCR reaction to give the rearranged diimine, **3**. The rearranged diimine is then hydrolyzed to give the product diamine, **4**.[7,8]

In general, the rearrangement reaction goes to completion within minutes at ambient temperature without the need for any catalyst. The stability of the two resonance-assisted hydrogen bonds in the rearranged diimine, **3**, drives the rearrangement reaction to completion for the synthesis of electron-poor (**4a–4g**), electron-rich (**4h–4k**), and sterically bulky (**41–4q**) diamines.[7,8] As shown in Scheme 2, all of the diamines are produced in uniformly high enantiopurities (>99% ee's).

Some of the diamines in Scheme 2 were previously synthesized by other methods. Two of these most useful methods are (a) Corey's reductive amination of benzil analogues (**Scheme 3a**),[10] and (b) Pedersen's reductive coupling of imines (**Scheme 3b**).[11] Corey and co-workers showed that chiral vicinal diamines can be prepared as racemic mixtures in 85–100% yields from the corresponding benzil analogues. However, the yields for resolution of the diamines with tartaric acid were low (36–64% of the theoretical yield). Busacca's[12] and Denmark's[13] groups used the reductive coupling method for preparing a variety of chiral vicinal diamines as racemic mixtures. The highly bulky diamine (**4q**) was also previously synthesized by the reductive coupling method.[14] Although the reductive coupling reaction has the advantage of requiring only simple starting materials, the yield for the coupling step is 40–73% without optical resolution[11,13] and generally much lower (14–19%) after optical resolution.[12] Tartaric acid resolution gave acceptable separation of some diamine enantiomers,[10,12,13] but it failed to give satisfactory results for the separation of others such as **4a**[15] and **4n,**[16] even after several recrystallizations. In such cases, various chiral acids were screened for resolution[16] or the diamines were derivatized with a chiral reagent and separated by column chromatography.[13,15] Thus the overall yields for the synthesis of diamine enantiomers are often low (on the order of 10% of the theoretical yield).[12,13]

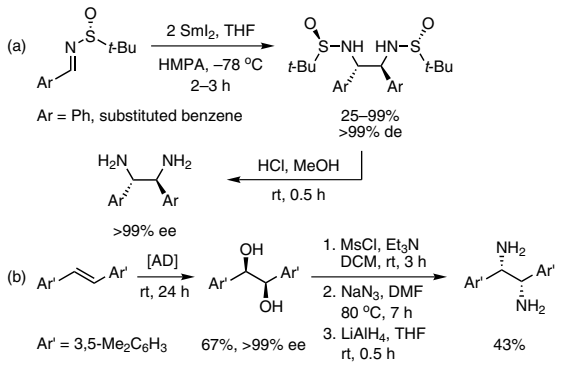
One obvious way to avoid the tedious resolution of racemic diamines is to synthesize the diamine enantiomers stereoselectively. Recently, the samarium-mediated reductive coupling of chiral sulfinyl imines has been reported by Xu and



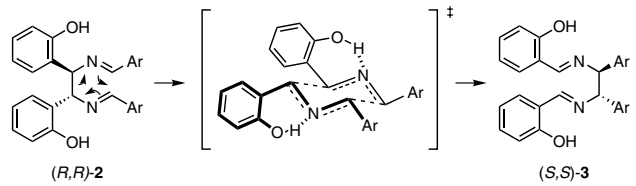
Scheme 3. Two of the Most Used Syntheses of Racemic Diaryl Vicinal Diamines. *(Ref. 10,11)*

co-workers as a direct approach to synthesize enantiomerically pure diaryl vicinal diamines (**Scheme 4a**).[17] This method gives diamine enantiomers with variable yields (25–99%). The Sharpless asymmetric dihydroxylation (AD) of alkenes can also lead to enantiopure diamines without the need for chiral resolution (**Scheme 4b**).[18,19] This method has the advantage of being catalytic, although scale-up may be difficult with a step requiring sodium azide.

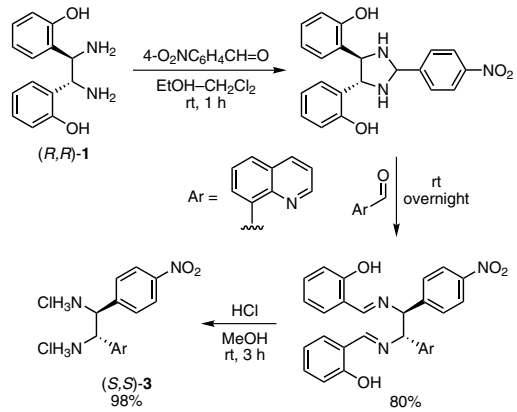
DFT computation is useful for predicting the equilibrium constant for the DCR reaction. The progress of the rearrangement reaction can be conveniently monitored by the appearance of the ^{1}H NMR signal from the resonance-assisted hydrogen bond that is highly downfield-shifted away from other signals.[8] The DCR reaction takes place by a chair-like, six-membered-ring transition state with all the substituents in pseudoequatorial positions (**eq 1**).[8a] This results in a highly stereospecific



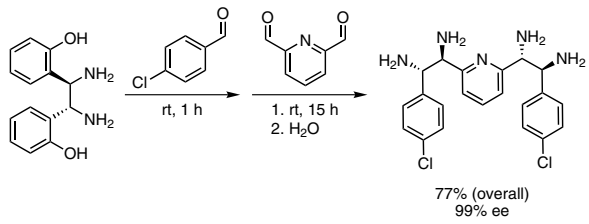
Scheme 4. Known Enantioselective Syntheses of Diaryl Vicinal Diamines. *(Ref. 17,19)*



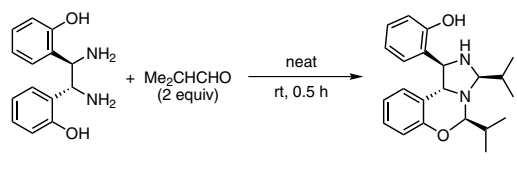
eq 1 *(Ref. 8a)*



Scheme 5. Synthesis of Mixed-Diaryl Vicinal Diamines by DCR. *(Ref. 8b)*



Scheme 6. Synthesis of a Tetraamine by DCR. *(Ref. 8c)*



eq 2 *(Ref. 8c)*

transfer of stereochemistry from the starting diimine to the rearranged diimine.[8] Indeed, chiral HPLC shows that there is no detectible loss of enantiopurity in the preparation of the daughter diamines from the mother diamine.

The rearrangement reaction takes place in various solvents including chloroform, THF, ethanol, and DMSO. The rearranged diimine (**3**) often precipitates out of solvents like ethanol and THF, simplifying the isolation of the key intermediates in pure form. Alternatively, the rearrangement in DMSO-d_6 may be monitored by ^{1}H NMR, and water may be added to precipitate out the rearranged diimine once the reaction is complete. The DCR method for the preparation of a wide range of C_2-symmetrical diamines should be useful for the steric and electronic tuning of catalysts that are based on chiral vicinal diamines (see Diamine Catalysts in Section 3).

Unsymmetrically substituted, chiral, diaryl vicinal diamines can be prepared in excellent yield and enantiopurity by a slight modification of the above method.[8b] Addition of ***one*** equivalent of an aromatic aldehyde to (*R*,*R*)-**1** or (*S*,*S*)-**1** gives the five-membered-ring aminal intermediate (**Scheme 5**).[8b] Electron-deficient aromatic aldehydes are particularly well suited for the preparation of the five-membered-ring compound, and may often be precipitated out of DMSO by addition of water. Addition of a second aldehyde to the intermediate gives the mixed diimine, which rearranges to give the product diimine. Hydrolysis of the product diimine gives the mixed diamine in excellent yield and enantiopurity.

The above process for synthesizing mixed diamines can be extended to mixed tetraamines (**Scheme 6**).[8c] Sequential addition of one equivalent of a monoaldehyde to the mother diamine, followed by addition of a half equivalent of a dialdehyde, gives the mixed tetraamine in excellent yield and enantiopurity. This reaction was utilized to make a novel pentadentate ligand with four chiral centers in enantiomerically pure form.

2.2. Dialkyl Vicinal Diamines

There has been considerable interest in developing new methods for the synthesis of aliphatic vicinal diamines, as they are found in a wide variety of bioactive compounds including antiviral, antibacterial, and anticancer drugs (e.g., TAMIFLU®, LORABID®, and ELOXATIN®).[20–22] The methods employed in the synthesis of diaryl vicinal diamines aren't always applicable to the preparation of their dialkyl counterparts. In addition, alkyl substituents are generally less effective than aryl substituents in facilitating [3,3] sigmatropic rearrangements. Initially, we encountered difficulties in synthesizing dialkyl vicinal diamines by the DCR method.

When two equivalents of an aliphatic aldehyde such as isobutyraldehyde are added to the mother diamine, the corresponding diimine, or the rearranged diimine, does not form as in the corresponding reaction with aromatic aldehydes (see Scheme 2). Instead, a compound, **5a**, containing fused imidazolidine–dihydro-1,3-oxazine rings is formed in a highly selective and stereospecific fashion (**eq 2**).[8c] In principle, one, two, or three equivalents of isobutyraldehyde could add to **1** to form one, two, or three new rings, respectively. Fourteen different products could result from the cyclization reactions including all possible stereoisomers. Interestingly, only one major product is formed when the diamine is added to two or more equivalents of the aldehyde.

Although **5a** is stable at room temperature, it cleanly gives the rearranged diimine, **7a**, with excellent stereospecificity when heated at 150 °C for 3 h (**eq 3**).[8c] We propose that **5a** is in

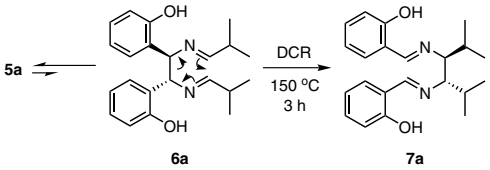
equilibrium with the initial diimine, **6a**, which rearranges to give the product diimine, **7a**. Monitoring of the reaction by ^{1}H NMR spectrometry shows that the concentration of diimine intermediate **6a** does not accumulate to any observable extent during the conversion of **5a** to **7a**. Thus, the equilibrium appears to greatly favor **5a** over **6a**. In contrast, **2** does not form the corresponding fused-ring compound to any observable extent. The dramatic difference in the tendencies of **2** and **6a** to form the fused-ring compounds is likely due to the fact that the two imine functional groups in **2** are stabilized by conjugation whereas those in **6a** are not. Acid hydrolysis of the product diimine, **7a**, gives the corresponding dialkyl diamine (*S,S*)-1,2-diamino-1,2-diisopropylethane dihydrochloride (**8a**) in high enantiopurity (>99% ee).

A variety of aliphatic aldehydes were used to make dialkyl vicinal diamines by the modified DCR method (**Scheme 7**).[8c] The enantioselectivity of the rearrangement reaction was determined by HPLC. Rearrangement of (*R,R*)-**5a** in DMSO gave (*S,S*)-**7a** in 93% yield with no observable loss in enantiopurity (>99%), while a one-pot reaction of (*R,R*)-**1** and isobutyraldehyde in toluene gave (*S,S*)-**7a** in 85% yield. The inversion of stereochemistry, confirmed by CD spectroscopy, is expected from the chair-like transition state with all substituents in equatorial positions. Although the rearrangement reaction leading to dialkyl vicinal diamines requires considerably higher temperatures than the one giving rise to diaryl vicinal diamines, the observed yield and stereoselectivity of the former remain exceptionally high.

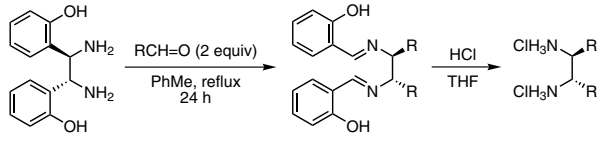
Some of the diamines in Scheme 7 were previously synthesized by other methods (**Scheme 8**).[23,24] Diamines **8a** and **8c** were synthesized by addition of Grignard reagents to chiral bisimines for the purpose of preparing NHE3 inhibitors.[25] However, the observed diastereoselectivity for this reaction was low except in the case where the bulky *tert*-butylmagnesium chloride was used.[23] 1,2-Diamino-1,2-dicyclohexylethane (**8b**) was synthesized in 85% yield by hydrogenation of DPEN at ambient temperature.[24]

2.3. Alkyl–Aryl Vicinal Diamines

The breadth in scope of the DCR method can be demonstrated in the synthesis of mixed alkyl–aryl vicinal diamines. Sequential addition of an aromatic aldehyde and an aliphatic aldehyde gives the fused imidazolidine–dihydrooxazine-ring compound in a highly regioselective and stereospecific manner. The aromatic aldehyde forms the imidazolidine ring while the aliphatic aldehyde forms the dihydrooxazine ring. When *o*-fluorobenzaldehyde and isobutyraldehyde are added in sequence to the mother diamine, compound **9** forms as the major product. Although **9** is stable at room temperature, it cleanly gives the rearranged diimine, **10**, in excellent enantiopurity when heated at 100 °C for 2 h (**Scheme 9**). Hydrolysis of the rearranged diimine gives the product diamine, **11**.



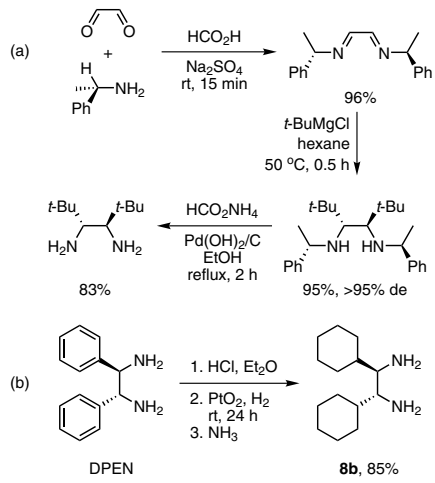
eq 3 *(Ref. 8c)*



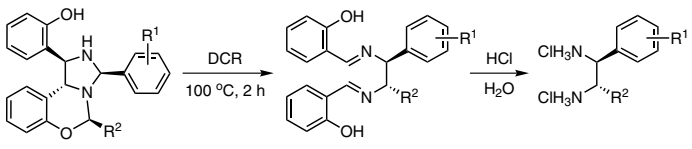
R	No.	Yield 7	Yield 8
i-Pr	**a**	85%	91%
Cy	**b**	80%	95%
c-Pr	**c**	73%	90%
Et	**d**	71%	94%

>99% ee in all cases.

Scheme 7. Dialkyl Vicinal Diamines by a Modified DCR. *(Ref. 8c)*



Scheme 8. Known Syntheses of Dialkyl Vicinal Diamines. *(Ref. 23,24)*



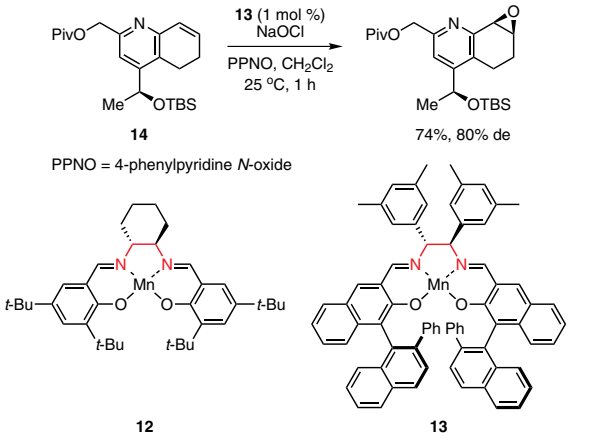
11	a	b	c	d	e
R^1	2-F	2-F	2-F	4-F	4-Cl
R^2	*i*-Pr	Cy	*n*-C_5H_{11}	Et	Et

Scheme 9. Synthesis of Mixed Alkyl–Aryl Vicinal Diamines from the Fused-Ring Compound **9**. *(Ref. 8c)*

(*S,S*)-1,2-Diamino-1-(4-fluorophenyl)butane (**11d**) had previously been synthesized by a much longer route and in a lower overall yield (~10%) for the purpose of preparing cisplatin analogues.[26]

3. Vicinal-Diamine-Based Catalysts

Chiral vicinal diamines are some of the most important ligands in the design of stereoselective catalysts.[27] They have been utilized in creative ways to develop a wide variety of innovative chiral catalysts (see Figure 1). Some of the diamine–based, stereoselective catalysts developed to date include reduction,[28] oxidation,[29] and hydrolysis catalysts.[30] Other diamine-based compounds catalyze a variety of carbon–carbon-bond-forming reactions such as allylic alkylation,[31] metathesis,[32] Michael addition,[33] Aldol,[34] Mannich,[35] cycloaddition,[36] and Strecker[37] reactions. Chiral vicinal diamines are useful not only for developing transition-metal-based catalysts but also organocatalysts.[38] Efficient methods for obtaining 1,2-diaminocyclohexane (DACH)[6] and 1,2-diphenylethylenediamine (DPEN)[5] in enantiomerically pure form have led to their widespread use over other vicinal diamines. However, a single vicinal diamine is not expected to be the best ligand for all catalysts. Even for a single catalytic system, one vicinal diamine is not expected to be the best catalyst ligand for all substrates. A greater variation in the diamine structure is desirable for developing stereoselective catalysts.[39] The DCR method for making chiral vicinal diamines may be useful for a number of applications in catalysis including (a) steric and electronic tuning of known catalysts, (b) designing new ligands, (c) developing polymer-supported catalysts, and (d) making water-soluble diamine-containing catalysts.



eq 4 *(Ref. 42)*

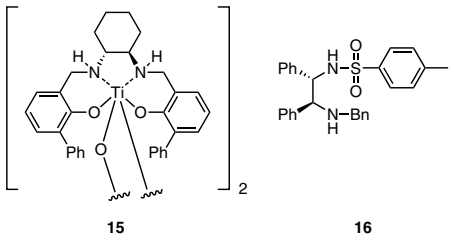


Figure 2. Oxidation Catalysts That Use Hydrogen Peroxide.
(Ref. 43,44)

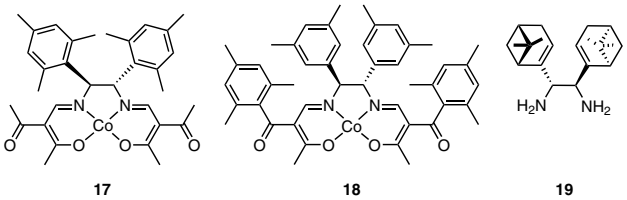


Figure 3. Catalysts Based on Sterically Bulky Vicinal Diamines.
(Ref. 45–49)

3.1. Steric and Electronic Tuning of Catalyst Structure

It is well established that steric and electronic tuning of catalysts can result in dramatic improvements in reactivity and stereoselectivity. Jacobsen and Katsuki independently developed chiral, vicinal-diamine-based Mn complexes for the catalytic epoxidation of cis alkenes. Extensive steric and electronic tuning of the salen catalysts resulted in the development of highly reactive and stereoselective epoxidation catalysts **12** and **13**.[40,41] Not surprisingly, no single catalyst is the best for all substrates. Although **12** has a broad scope in the epoxidation of alkenes, Nicolaou et al. found that **13** is much better for the epoxidation of **14** in terms of yield and stereoselectivity (**eq 4**).[42] Thus, tuning of the salen ligand, including the diamine backbone, had a profound effect on the reactivity and selectivity of the catalyst.

More recently, Katsuki and co-workers reported a titanium–salen based epoxidation catalyst that uses 30% H_2O_2 as an oxidant (**15**) (**Figure 2**).[43] Beller's group developed an iron complex of **16** for the catalytic epoxidation of trans alkenes with H_2O_2.[44] Although this catalyst is not very stereoselective, iron has the advantage of being cheap and nontoxic. While oxidation catalysts **12** and **13** have been extensively tuned, the newer ones, **15** and **16**, have yet to be tuned. Thus, it would be of considerable interest to tune the vicinal-diamine backbone of these environmentally friendly catalysts for higher reactivity and enantioselectivity.

Interestingly, the same diamine-based salen ligand that was used in the manganese complex **12** for obtaining highly stereoselective epoxidations of cis alkenes also leads to a highly stereoselective hydrolysis of epoxides when the manganese is exchanged with cobalt.[30] Thus, a properly tuned ligand for one reaction can also be highly effective for a completely different reaction.

Catalysts based on sterically bulky vicinal diamines can provide much improved stereoselectivity when compared to those based on less bulky diamines. Yamada and co-workers have shown that two such catalysts, **17** and **18** (**Figure 3**), are much more stereoselective than those based on less bulky diamines in cycloaddition[45] and cyclopropanation reactions,[46] in the borohydride reduction of ketones,[47] and in the deuteration of aldehydes and imines.[48] The DCR method provides a convenient, highly stereoselective route to the bulky diamines in **17** and **18**, as well as to novel bulky diamines such as **19**[49] in a one-pot reaction.

One of the most remarkable chiral catalysts reported to date is Noyori's catalyst, **20**,[28] which is used for the hydrogenation of prochiral ketones (**Figure 4**).[50] A turnover number of over a million has been reported for this highly stereoselective ruthenium catalyst, which consists of a chiral diphosphine ligand and a chiral vicinal diamine ligand. Ding and co-workers recently showed that the chiral diphosphine ligand could be replaced with an achiral one, leading to catalyst **21**, without sacrificing the stereoselectivity of the reaction.

Noyori's *transfer*-hydrogenation catalyst, **22**, which uses isopropanol or formic acid instead of molecular hydrogen to reduce ketones, is also based on a chiral vicinal diamine.[51] The availability of a wide range of chiral vicinal diamines should allow for tailor-fitting of the catalyst to the ketone substrate in order to achieve a high stereoselectivity. Mioskowski and co-workers showed that **23** is more reactive and stereoselective than **22** as a transfer-hydrogenation catalyst for the reduction of β-keto ester **24** under dynamic kinetic resolution conditions to give **25** (**eq 5**).[52] Electron-withdrawing sulfonyl groups increase the reactivity of the catalyst by acidifying the primary amine. While the DPEN backbone itself was not tuned in this study, electron-withdrawing substituents on the phenyl rings are expected to further modulate the activity and selectivity of the catalyst. Substituents on DPEN can significantly affect the basicity (or acidity) of the vicinal diamine. For example, the pK_a value of the protonated decafluoro-DPEN (**4a**, Scheme 2) is about three units lower than that of protonated DPEN.[15]

Busacca et al. reported on the steric and electronic tuning of the phosphinoimidazoline (BIPI) ligands that are used for the catalytic asymmetric Heck reaction (**eq 6**).[12] The reactivity and stereoselectivity of the in situ formed palladium complex was reported to be highly sensitive to the structure of the chiral vicinal diamine in the imidazoline group. The BIPI ligands have the advantage of being easier to tune than the phosphinooxazoline ligands and the BINAP ligands. The diamines in the BIPI ligands were initially synthesized by Corey's[10] or Pedersen's[11] methods. More recently, they have been prepared by the DCR method.

In addition to the metal-based catalysts described above, many organocatalysts that incorporate chiral vicinal diamines are known. Denmark et al. reported that chiral, vicinal-diamine-based phosphoramide Lewis base **26** catalyzed the aldol addition of ketone silyl enolates to aromatic aldehydes (**eq 7**).[13] Both the diastereoselectivity and enantioselectivity of the reaction were highly sensitive to the structure of the diamine portion of the organocatalyst.

We recently showed that chiral vicinal diamines themselves can be used as organocatalysts for the stereoselective synthesis of warfarin, a blood thinner for treating thrombosis (**eq 8**).[53] As was observed with **26**, the stereoselectivity of this Michael reaction is sensitive to the diamine structure. The enantioselectivity of the reaction increases from 47% ee to 92% ee on changing the diamine catalyst from DACH to the ortho-methyl-substituted DPEN, **4n**.

3.2. New Diamine Designs

The DCR method is not only useful for tuning the properties of known ligands, but is also valuable for developing novel ones. Diamines may be developed into monodentate, bidentate, tridentate, tetradentate, and penetadentate ligands with N, O, S, or P as coordinating atoms. We have reported a novel amino alcohol receptor based on a Co(III)–salen complex, **28**, possessing an axial aromatic substituent in the diamine backbone (**eq 9**).[8b] The vicinal-diamine-based, unsymmetrical, tridentate ligand, **27**, was prepared in enantiomerically pure form using the DCR method. The stereoselectivity of **28** in the coordination of amino alcohols increases from about 2.9 to 36.0 with increasing steric bulk of the amino alcohols used in the reaction.

Chiral oxazoline ligands are useful in the design of many catalysts.[54] Most of the oxazoline ligands are based on a few readily available chiral amino alcohols. Replacing chiral oxazoline ligands with a wide range of chiral diamine-based imidazoline ligands should be of considerable interest.[12]

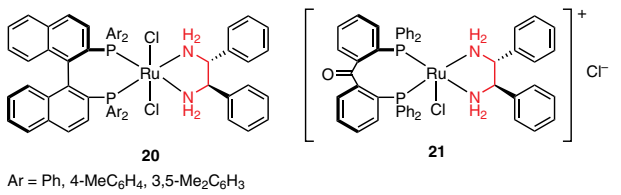
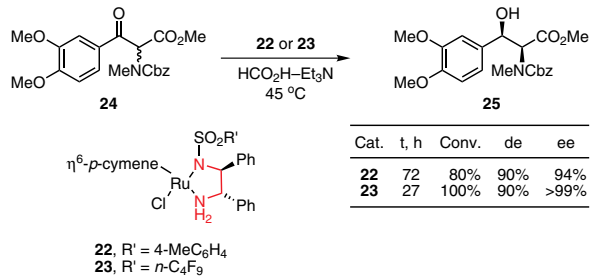
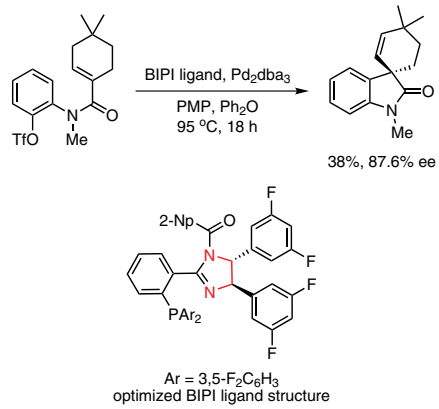


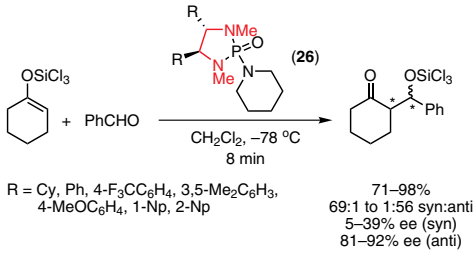
Figure 4. Vicinal-Diamine-Based Catalysts for the Hydrogenation of Prochiral Ketones. *(Ref. 50)*



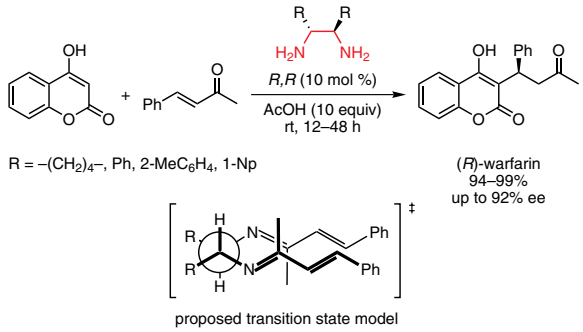
eq 5 *(Ref. 52)*



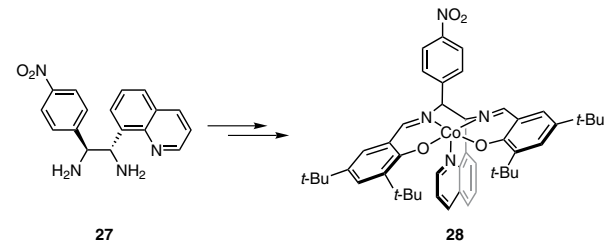
eq 6 *(Ref. 12)*



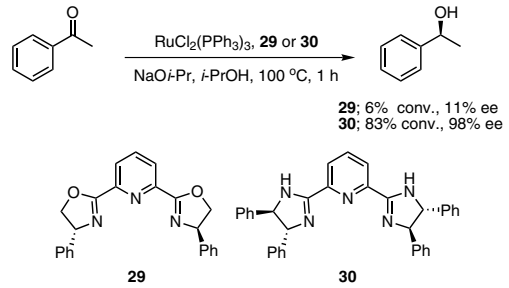
eq 7 *(Ref. 13)*



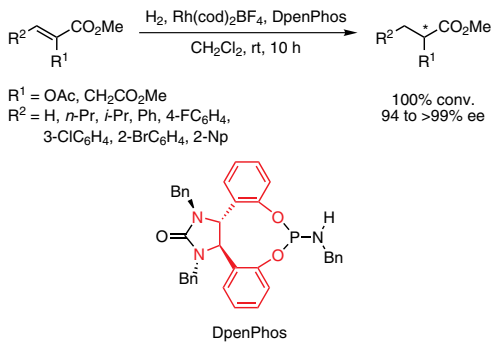
eq 8 *(Ref. 53)*



eq 9 *(Ref. 8b)*



eq 10 *(Ref. 56,57)*



eq 11 *(Ref. 61b)*

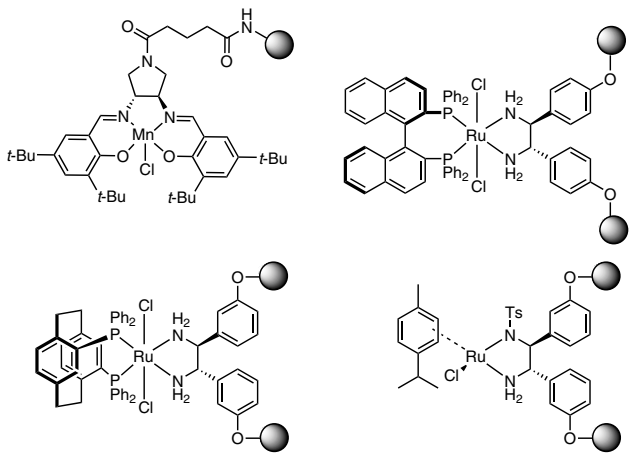


Figure 5. Chiral, Vicinal-Diamine-Based Catalysts on Solid Support. *(Ref. 63)*

Beller and co-workers have recently reported that ruthenium complexes of chiral tridentate pyridinebisimidazolines (Pybim, **30**) are effective catalysts for epoxidation[55,56] and transfer-hydrogenation reactions.[57] They found that Ru-Pybim complexes are much more reactive and stereoselective than the Ru-Pybox complex in the transfer hydrogenation of acetophenone (**eq 10**).[57]

There has been much interest in monodentate phosphorus ligands ever since the pioneering work of Feringa,[58] Reetz,[59] and Pringle.[60] The "mother" diamine (HPEN) is not only useful for making "daughter" diamines by the DCR method, but it can also be converted into an interesting monodentate phosphorus ligand (DpenPhos). Ding and co-workers showed that DpenPhos is an excellent ligand for the Rh(I)-catalyzed enantioselective hydrogenation of acrylates (**eq 11**).[61]

3.3. Diamines on Solid Support

Chiral vicinal-diamine-based catalysts are often expensive to prepare, but their polymer-supported counterparts have the advantage of being recyclable.[62] The DCR method also provides a simple route for preparing diamines that can be conveniently attached to a solid support; it also simplifies the purification of the product. Diphenylethylenediamines (DPENs) with hydroxyl groups attached at the meta or para positions of the two benzene rings (e.g., **4j**) have been used to prepare various polymer-supported catalysts (**Figure 5**).[63] Such catalysts effected the stereoselective hydrogenation of ketones and epoxidation of olefins.

3.4. Water-Soluble Diamine Catalysts

The growing interest in green chemistry and the need for environmentally friendly catalytic systems has led to the development of water-soluble, chiral, vicinal-diamine ligands.[64] Deng and co-workers[65] reported water-soluble versions of Noyori's transfer-hydrogenation catalyst (see eq 5) prepared from disulfonated *N*-tosyl-DPEN, **32** (**Figure 6**).[65] These catalysts gave excellent results in the reduction of prochiral ketones, imines, and iminium ions in aqueous solvents. The DCR method provides a convenient route to a variety of water-soluble vicinal diamines in enantiomerically pure form.[8c]

4. Diamine Drugs

A number of vicinal diamines possess a wide range of bioactivities. The amine groups are useful for modulating the solubility of the drug as well as for donating or accepting hydrogen bonds to and from a biological receptor. In addition, vicinal diamines can easily be converted into five- and six-membered rings like imidazolines and piperazines. These rigid heterocyclic compounds provide entropic advantage for binding to the biological target. Some representative diamine and diamine derivatives with interesting bioactivities are discussed below.

4.1. Acyclic Diamines

Ever since the serendipitous discovery by Rosenberg et al. of the anticancer activity of cisplatin,[66] there has been much interest in developing cisplatin analogues that are more active and less toxic (**Figure 7**). Oxaliplatin (ELOXATIN®, Sanofi-Aventis)[22] is one such analogue that is based on a chiral vicinal diamine [(*R,R*)-1,2-diaminocyclohexane (DACH)] and that is active against colorectal cancer.[67] Other studies indicate that it is also active against ovarian cancer,[68] non-small-cell lung cancer,[69] and breast cancer.[70] The wide availability of DACH undoubtedly was

an important factor in the discovery of oxaliplatin, as it was in the discovery of various stereoselective DACH-based catalysts. In a recent breast cancer and prostate cancer cell line studies, **33** showed the highest activity among a variety of platinum complexes.[26]

Interestingly, (*S,S*)-**33** gave the best result against the MDA-MB 231 breast cancer cell line and LnCaP/FGC prostate cancer cell line, while (*R,R*)-**33** gave the best result against the MCF-7 breast cancer cell line. The chiral vicinal diamine ligand in **33** (see **11d**, Scheme 9) was difficult to prepare, requiring seven steps with an overall yield of about 10%. With the DCR process, this diamine and other close analogues can be prepared in excellent yield (>90%) and stereoselectivity (99% ee) in a one-pot reaction under mild conditions.[8c]

4.2. Imidazolines

Scientists at Hoffmann–La Roche in Nutley, New Jersey, recently reported a novel strategy for cancer therapy. A cis imidazoline, that they named Nutlin-3, was shown to activate the p53 tumor suppressor pathway.[71] Initially, they screened a library of cis imidazolines that was generated from a variety of meso vicinal diamines, which were, in turn, prepared by DCR.[7,9] Another series of cis imidazolines possessing anti-inflammatory activity have been reported by Merriman et al.[72] In addition to the cis imidazolines, trans imidazolines, similarly prepared from chiral vicinal diamines, also exhibited biological activities. Clonidine, moxonidine, and ZANAFLEX® are imidazoline I1 receptor agonists that lower blood pressure. While all of these compounds are based on unsubstituted vicinal diamines, clonidine analogues made with chiral vicinal diamines were shown to be active (**Figure 8**).[25] The diamine in **34** was prepared as a racemic mixture in low yield by the Grignard method (see Scheme 8a). The DCR process is useful for making a variety of chiral dialkyl vicinal diamines in enantiomerically pure form (see Scheme 7).

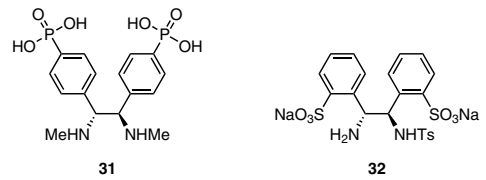
4.3. Piperazines

Simple N-substituted piperazines are found in numerous drug molecules. However, chiral piperazines are only beginning to make their mark as useful therapeutics. Chiral vicinal diamines can be readily converted into chiral piperazines and piperazinones. Tagat et al. reported piperazine-based CCR5 antagonists as potent HIV inhibitors (**Figure 9**).[73] Wurster and co-workers recently showed that a chiral, piperazine-based molecule, **35**, is a selective α_{2C}-adrenoceptor antagonist and has potential therapeutic use in several psychiatric disorders.[74]

4.4. Other Diamines

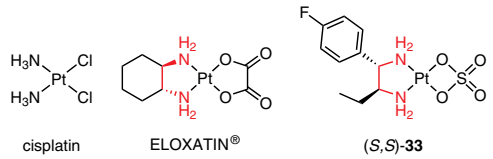
α,β-Diamino acids are a special class of chiral vicinal diamines that have potent biological activities.[75] For example, viomycin is an inhibitor of protein synthesis, and capreomycin IA, used for the treatment of tuberculosis, contain L-capreomycidine[76] as a key structural element. In addition, the appearance of penicillin- or cephalosporin-resistant pathogens has led to the development of loracarbef (LORABID®),[21] a diamino acid based antibiotic (**Figure 10**).

There has been much recent interest in oseltamivir (TAMIFLU®) and zanamivir (RELENZA®) due to the possibility of a human influenza pandemic (**Figure 11**).[77] The two inhibitors of sialidase (also known as neuraminidase) are effective therapeutics for the treatment of the avian H5N1 influenza virus. Oseltamivir is a chiral vicinal diamine monoamide that is prepared from shikimic acid.[20] The total synthesis of oseltamivir has been recently reported by several research groups.[78] While



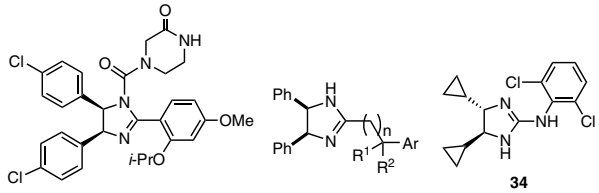
31 **32**

Figure 6. Water–Soluble, Chiral, Vicinal Diamine Ligands. *(Ref. 64,65)*



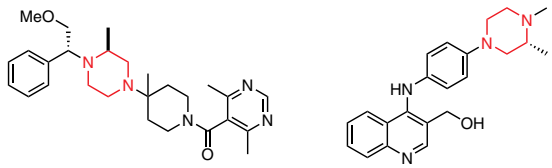
cisplatin ELOXATIN® (*S,S*)-**33**

Figure 7. Cisplatin and Other Anticancer Analogues. *(Ref. 22,26,66–70)*



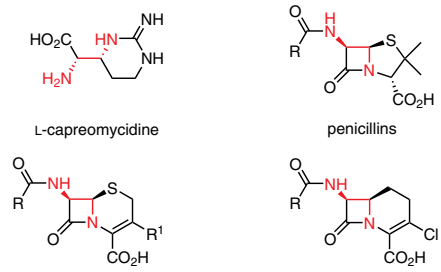
34

Figure 8. Bioactive Imidazolines. *(Ref. 25,71,72)*



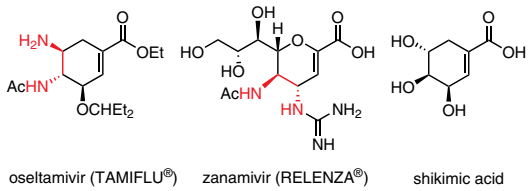
CCR5 antagonist **35** α_{2C}-adrenoceptor antagonist

Figure 9. Bioactive Piperazines. *(Ref. 73,74)*



L-capreomycidine penicillins cephalosporins LORABID®

Figure 10. Biologically Active α,β-Diamino Acids and Derivatives That Incorporate a Vicinal Diamine Motif. *(Ref. 21,75,76)*



oseltamivir (TAMIFLU®) zanamivir (RELENZA®) shikimic acid

Figure 11. Vicinal-Diamine-Based Antiviral Agents and Shikimic Acid. *(Ref. 20,77,78)*

the DCR process may not be easily applied to the synthesis of these challenging targets, it may be useful for making libraries of their analogues.

5. Conclusions

Many of the best stereoselective catalysts that we know today contain a chiral, vicinal-diamine structural element, and most of these catalysts are based on DACH or DPEN. The DCR method provides a convenient and efficient route to a wide range of "daughter" chiral, vicinal diamines in enantiomerically pure form starting from a single "mother" diamine (**1** or HPEN). This method allows not only the synthesis of C_2-symmetrical diaryl diamines but also dialkyl diamines and even mixed alkyl–aryl diamines in excellent yields and enantiopurities. Some of the advantages of the DCR method are: (a) The reaction is highly efficient and stereospecific; (b) No metals are required as catalysts or reagents; (c) The reaction generally takes place rapidly at ambient temperatures; and (d) A wide variety of diamines can be made in a one-pot process. The "daughter" diamines can be used for electronic and steric tuning of known diamine-based catalysts as well as for developing novel monodentate, bidentate, tridentate, tetradentate, and pentadentate ligands. These ligands can have N, O, S, or P as coordinating atoms. Stereoselective catalysts are becoming ever more important for the preparation of chiral drugs and materials. In addition, many bioactive compounds themselves are based on diamines or their derivatives like imidazolines and piperazines. Synthetic methods of broad scope and high efficiency for making chiral vicinal diamines in enantiomerically pure form should facilitate the discovery of new catalysts and drugs.

6. Acknowledgements

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7. References

(1) (a) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691. (b) Nieto, S.; Lynch, V. M.; Anslyn, E.; Kim, H.; Chin, J. *J. Am. Chem. Soc.* **2008**, *130*, 9232.

(2) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.

(3) Kotti, S. R. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101.

(4) *Topics in Organometallic Chemistry*; Lemaire, M., Mangeney, P., Eds.; Springer: Berlin, 2005; Vol. 15, pp 1–287.

(5) (a) Williams, O. F.; Bailar, J. C., Jr. *J. Am. Chem. Soc.* **1959**, *81*, 4464. (b) Corey, E. J.; Kühnle, F. N. M. *Tetrahedron Lett.* **1997**, *38*, 8631.

(6) (a) Andrew, I. S. U.S. Patent 3,187,045, 1965. (b) Whitney, T. A. U.S. Patent 4,085,138, 1978.

(7) Chin, J.; Mancin, F.; Thavarajah, N.; Lee, D.; Lough, A.; Chung, D. S. *J. Am. Chem. Soc.* **2003**, *125*, 15276.

(8) (a) Kim, H.-J.; Kim, H.; Alhakimi, G.; Jeong, E. J.; Thavarajah, N.; Studnicki, L.; Koprianiuk, A.; Lough, A. J.; Suh, J.; Chin, J. *J. Am. Chem. Soc.* **2005**, *127*, 16370. (b) Kim, H.-J.; Kim, W.; Lough, A. J.; Kim, B. M.; Chin, J. *J. Am. Chem. Soc.* **2005**, *127*, 16776. (c) Kim, H.; Chin, J. University of Toronto, Toronto, ON. Unpublished work, 2007. (d) Kim, H.; Nguyen, Y.; Yen, C. P.-H.; Chagal, L.; Lough, A. J.; Kim, B. M.; Chin, J. *J. Am. Chem. Soc.* **2008**, *130*, 12184. (e) Kim, H.; Yen, N.; Lough, A. J.; Chin, J. *Angew. Chem., Int. Ed.* **2008**, *47*, in press.

(9) Vögtle, F.; Goldschmitt, E. *Chem. Ber.* **1976**, *109*, 1.

(10) (a) Pikul, S.; Corey, E. J. *Org. Synth.* **1993**, *71*, 22. (b) Corey, E. J.; Lee, D.-H.; Sarshar, S. *Tetrahedron: Asymmetry* **1995**, *6*, 3.

(11) (a) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 3152.

(12) (a) Busacca, C. A.; Grossbach, D.; So, R. C.; O'Brien, E. M.; Spinelli, E. M. *Org. Lett.* **2003**, *5*, 595. (b) Busacca, C. A.; Grossbach, D.; Campbell, S. J.; Dong, Y.; Eriksson, M. C.; Harris, R. E.; Jones, P.-J.; Kim, J.-Y.; Lorenz, J. C.; McKellop, K. B.; O'Brien, E. M.; Qiu, F.; Simpson, R. D.; Smith, L.; So, R. C.; Spinelli, E. M.; Vitous, J.; Zavattaro, C. *J. Org. Chem.* **2004**, *69*, 5817.

(13) (a) Denmark, S. E.; Pham, S. M.; Stavenger, R. A.; Su, X.; Wong, K.-T.; Nishigaichi, Y. *J. Org. Chem.* **2006**, *71*, 3904. (b) Denmark, S. E.; Su, X.; Nishigaichi, Y.; Coe, D. M.; Wong, K.-T.; Winter, S. B. D.; Choi, J. Y. *J. Org. Chem.* **1999**, *64*, 1958.

(14) Takuji, N. Jpn. Patent JP2002128745, 2002.

(15) Sakai, T.; Korenaga, T.; Washio, N.; Nishio, Y.; Minami, S.; Ema, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1001.

(16) Ryoda, A.; Yajima, N.; Haga, T.; Kumamoto, T.; Nakanishi, W.; Kawahata, M.; Yamaguchi, K.; Ishikawa, T. *J. Org. Chem.* **2008**, *73*, 133.

(17) Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 4747.

(18) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(19) (a) Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. *Tetrahedron* **1994**, *50*, 11827. (b) Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 61.

(20) (a) Kim, C. U.; Lew, W.; Williams, M. A.; Liu, H.; Zhang, L.; Swaminathan, S.; Bischofberger, N.; Chen, M. S.; Mendel, D. B.; Tai, C. Y.; Laver, G.; Stevens, R. C. *J. Am. Chem. Soc.* **1997**, *119*, 681. (b) Abrecht, S.; Harrington, P.; Iding, H.; Karpf, M.; Trussardi, R.; Wirz, B.; Zutter, U. *Chimia* **2004**, *58*, 621.

(21) (a) Palomo, C.; Aizpurua, J. M.; Legido, M.; Galarza, R.; Deya, P. M.; Dunoguès, J.; Picard, J. P.; Ricci, A.; Seconi, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1239. (b) Misner, J. W.; Fisher, J. W.; Gardner, J. P.; Pedersen, S. W.; Trinkle, K. L.; Jackson, B. G.; Zhang, T. Y. *Tetrahedron Lett.* **2003**, *44*, 5991. (c) Ciufolini, M. A.; Dong, Q. *Chem. Commun.* **1996**, 881.

(22) (a) Kidani, Y.; Inagaki, K.; Iigo, M.; Hoshi, A.; Kuretani, K. *J. Med. Chem.* **1978**, *21*, 1315. (b) Boga, C.; Fiorelli, C.; Savoia, D. *Synthesis* **2006**, 285.

(23) Roland, S.; Mangeney, P.; Alexakis, A. *Synthesis* **1999**, 228.

(24) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417.

(25) Heinelt, U.; Lang, H.-J.; Hofmeister, A.; Wirth, K. PCT Int. Appl. WO2003053434, 2003.

(26) Dullin, A.; Dufrasne, F.; Gelbcke, M.; Gust, R. *Arch. Pharm., Pharm. Med. Chem.* **2004**, *337*, 654.

(27) For recent reviews of asymmetric catalysis, see: (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, E., Eds.; Springer: New York, 1999. (b) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley-VCH: Chichester, U.K., 2000.

(28) (a) Noyori, R. *Adv. Synth. Catal.* **2003**, *345*, 15. (b) Jäkel, C.; Paciello, R. *Chem. Rev.* **2006**, *106*, 2912.

(29) (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) McGarrigle, E. M.; Gilheany, D. G. *Chem. Rev.* **2005**, *105*, 1563.

(30) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421.

(31) (a) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(32) (a) Funk. T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840. (b) Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877.

(33) (a) Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*,

11583. (b) Luo, S.; Li, J.; Zhang, L.; Xu, H.; Cheng, J.-P. *Chem.—Eur. J.* **2008**, *14*, 1273. (c) Berthiol, F.; Matsubara, R.; Kawai, N.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 7803.

(34) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432.

(35) (a) Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2507. (b) Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900.

(36) (a) Lou, Y.; Remarchuk, T. P.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 14223. (b) Trost, B. M.; Fandrick, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 11836. (c) Kim, K. H.; Lee, S.; Lee, D.-W.; Ko, D.-H.; Ha, D.-C. *Tetrahedron Lett.* **2005**, *46*, 5991.

(37) (a) Wen, Y.; Xiong, Y.; Chang, L.; Huang, J.; Liu, X.; Feng, X. *J. Org. Chem.* **2007**, *72*, 7715. (b) Su, J. T.; Vachal, P.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 197.

(38) (a) Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 3074. For recent reviews of organocatalysis, see: (b) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (d) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (e) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, Germany, 2005. (f) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (g) Wang, X.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6070. (h) Oh, S. H.; Rho, H. S.; Lee, J. W.; Lee, J. E.; Youk, S. H.; Chin, J.; Song, C. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 7872. (i) Rho, H. S.; Oh, S. H.; Lee, J. W.; Lee, J. Y.; Chin, J.; Song, C. E. *Chem. Commun.* **2008**, 1208.

(39) Taran, F.; Gauchet, C.; Mohar, B.; Meunier, S.; Valleix, A.; Renard, P. Y.; Créminon, C.; Grassi, J.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 124.

(40) Jacobsen, E. N.; Zhang, W.; Güler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703.

(41) Katsuki, T. *Curr. Org. Chem.* **2001**, *5*, 663.

(42) Nicolaou, K. C.; Safina, B. S.; Funke, C.; Zak, M.; Zécri, F. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1937.

(43) Sawada, Y.; Matsumoto, K.; Kondo, S.; Watanabe, H.; Ozawa, T.; Suzuki, K.; Saito, B.; Katsuki, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3478.

(44) Gelalcha, F. G.; Bitterlich, B.; Anilkumar, G.; Tse, M. K.; Beller, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7293.

(45) Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Org. Lett.* **2002**, *4*, 2457.

(46) Ikeno, T.; Iwakura, I.; Yamada, T. *J. Am. Chem. Soc.* **2002**, *124*, 15152.

(47) (a) Nagata, T.; Yorozu, K.; Yamada, T.; Mukaiyama, T. *Angew. Chem., Int. Ed.* **1995**, *34*, 2145. (b) Sato, H.; Watanabe, H.; Ohtsuka, Y.; Ikeno, T.; Fukuzawa, S.-i.; Yamada, T. *Org. Lett.* **2002**, *4*, 3313.

(48) (a) Miyazaki, D.; Nomura, K.; Ichihara, H.; Ohtsuka, Y.; Ikeno, T.; Yamada, T. *New J. Chem.* **2003**, *27*, 1164. (b) Miyazaki, D.; Nomura, K.; Yamashita, T.; Iwakura, I.; Ikeno, T.; Yamada, T. *Org. Lett.* **2003**, *5*, 3555.

(49) Kim, H.; Choi, D. S.; Yen, C. P.-H.; Lough, A. J.; Song, C. E.; Chin, J. *Chem. Commun.* **2008**, 1335.

(50) Jing, Q.; Sandoval, C. A.; Wang, Z.; Ding, K. *Eur. J. Org. Chem.* **2006**, 3606.

(51) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.

(52) Mohar, B.; Valleix, A.; Desmurs, J.-R.; Felemez, M.; Wagner, A.; Mioskowski, C. *Chem. Commun.* 2001, 2572.

(53) (a) Kim, H.; Yen, C.; Preston, P.; Chin, J. *Org. Lett.* **2006**, *8*, 5239. (b) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416.

(54) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561.

(55) Bhor, S.; Anilkumar, G.; Tse, M. K.; Klawonn, M.; Döbler, C.; Bitterlich, B.; Grotevendt, A.; Beller, M. *Org. Lett.* **2005**, *7*, 3393.

(56) Anilkumar, G.; Bhor, S.; Tse, M. K.; Klawonn, M.; Bitterlich, B.; Beller, M. *Tetrahedron: Asymmetry* **2005**, *16*, 3536.

(57) Enthaler, S.; Hagemann, B.; Bhor, S.; Anilkumar, G.; Tse, M. K.; Bitterlich, B.; Junge, K.; Erre, G.; Beller, M. *Adv. Synth. Catal.* **2007**, *349*, 853.

(58) Van den Berg, M.; Minnaard, A. J.; Schudde, E. P.; van Esch, J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 11539.

(59) Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889.

(60) Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun.* **2000**, 961.

(61) (a) Liu, Y.; Ding, K. *J. Am. Chem. Soc.* **2005**, *127*, 10488. (b) Liu, Y.; Sandoval, C. A.; Yamaguchi, Y.; Zhang, X.; Wang, Z.; Kato, K.; Ding, K. *J. Am. Chem. Soc.* **2006**, *128*, 14212.

(62) Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102,* 3217.

(63) (a) Song, C. E.; Roh, E. J.; Yu, B. M.; Chi, D. Y.; Kim, S. C.; Lee, K.-J. *Chem. Commun.* **2000**, 615. (b) Li, X.; Chen, W.; Hems, W.; King, F.; Xiao, J. *Org. Lett.* **2003**, *5*, 4559. (c) Li, X.; Wu, X.; Chen, W.; Hancock, F. E.; King, F.; Xiao, J. *Org. Lett.* **2004**, *6*, 3321. (d) Itsuno, S.; Tsuji, A.; Takahashi, M. *Tetrahedron Lett.* **2003**, *44*, 3825.

(64) Maillet, C.; Praveen, T.; Janvier, P.; Minguet, S.; Evain, M.; Saluzzo, C.; Tommasino, M. L.; Bujoli, B. *J. Org. Chem.* **2002**, *67*, 8191.

(65) (a) Ma, Y.; Liu, H.; Chen, L.; Cui, X.; Zhu, J.; Deng, J. *Org. Lett.* **2003**, *5*, 2103. (b) Wu, J.; Wang, F.; Ma, Y.; Cui, X.; Cun, L.; Zhu, J.; Deng, J.; Yu, B. *Chem. Commun.* **2006**, 1766.

(66) Rosenberg, B.; VanCamp, L.; Trosko, J. E.; Mansour, V. H. *Nature* **1969**, *222*, 385.

(67) Levi, F.; Perpoint, B.; Garufi, C.; Focan, C.; Chollet, P.; Depres-Brummer, P.; Zidani, R.; Brienza, S.; Itzhaki, M.; Iacobelli, S.; Kunstlinger, F.; Gastiaburu, J.; Misset, J.-L. *Eur. J. Cancer* **1993**, *29A*, 1280.

(68) Soulié, P.; Bensmaïne, A.; Garrino, C.; Chollet, P.; Brain, E.; Fereres, M.; Jasmin, C.; Musset, M.; Misset, J. L.; Cvitkovic, E. *Eur. J. Cancer* **1997**, *33*, 1400.

(69) Monnet, I.; Brienza, S.; Hugret, F.; Voisin, S.; Gastiaburu, J.; Saltiel, J. C.; Soulié, P.; Armand, J. P.; Cvitkovic, E.; de Cremoux, H. *Eur. J. Cancer* **1998**, *34*, 1124.

(70) Garufi, C.; Nisticò, C.; Vaccaro, A.; D'Ottavio, A.; Zappalà, A. R.; Aschelter, A. M.; Terzoli, E. *Ann. Oncol.* **2001**, *12*, 179.

(71) Vassilev, L. T.; Vu, B. T.; Graves, B.; Carvajal, D.; Podlaski, F.; Filipovic, Z.; Kong, N.; Kammlott, U.; Lukacs, C.; Klein, C.; Fotouhi, N.; Liu, E. A. *Science* **2004**, *303*, 844.

(72) Merriman, G. H.; Ma, L.; Shum, P.; McGarry, D.; Volz, F.; Sabol, J. S.; Gross, A.; Zhao, Z.; Rampe, D.; Wang, L.; Wirtz-Brugger, F.; Harris, B. A.; Macdonald, D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 435.

(73) Tagat, J. R.; McCombie, S. W.; Nazareno, D.; Labroli, M. A.; Xiao, Y.; Steensma, R. W.; Strizki, J. M.; Baroudy, B. M.; Cox, K.; Lachowicz, J.; Varty, G.; Watkins, R. *J. Med. Chem.* **2004**, *47,* 2405.

(74) Höglund, I. P. J.; Silver, S.; Engström, M. T.; Salo, H.; Tauber, A.; Kyyrönen, H.-K.; Saarenketo, P.; Hoffrén, A.-M.; Kokko, K.; Pohjanoksa, K.; Sallinen, J.; Savola, J.-M.; Wurster, S.; Kallatsa, O. A. *J. Med. Chem.* **2006**, *49,* 6351.

(75) Viso, A.; de la Pradilla, R. F.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167.

(76) Bycroft, B. W.; Cameron, D.; Croft, L. R.; Hassanali-Walji, A.; Johnson, A. W.; Webb, T. *Nature* **1971**, *231*, 301.

(77) Von Itzstein, M. *Nature Reviews* **2007**, *6*, 967.
(78) (a) Yeung, Y.-Y.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 6310. (b) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6312. (c) Cong, X.; Yao, Z.-J. *J. Org. Chem.* **2006**, *71*, 5365. (d) Bromfield, K. M.; Gradén, H.; Hagberg, D. P.; Olsson, T.; Kann, N. *Chem. Commun.* **2007**, 3183. (e) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5734. (f) Shie, J.-J.; Fang, J.-M.; Wang, S.-Y.; Tsai, K.-C.; Cheng, Y.-S. E.; Yang, A.-S.; Hsiao, S.-C.; Su, C.-Y.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 11892.

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Keywords: chiral diamine; organocatalyst; diamine drug; diamine catalyst; vicinal diamine.

About the Authors

Hyunwoo Kim received his B.S. degree in 2000 and M.S. degree in 2004 from Seoul National University under the guidance of Prof. B. Moon Kim. He then joined the research group of Prof. Jik Chin as a Ph.D. candidate, where he is currently working on various aspects of vicinal diamine chemistry. He is a recipient of the Government of Canada Award (2004–2006) and is the CTO of DiaminoPharm, Inc.

Soon Mog So was born in 1970 in Jeonju, Korea. After receiving his B.S. degree in chemistry (1996) from Jeonju University, he obtained his M.S. (1999) and Ph.D. (2006) degrees in chemistry from Seoul National University under the direction of Professor B. Moon Kim. He is currently a postdoctoral fellow in Professor Jik Chin's research team at the University of Toronto. His research interests focus on the synthesis of macrocycles and small-molecule-recognition studies.

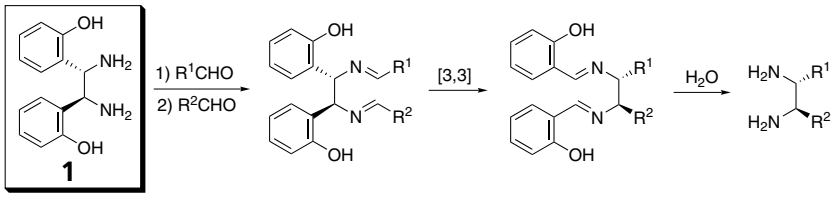
Jik Chin received his B.Sc. degree in chemistry and biochemistry (1977) from the University of Toronto. He worked on physical organic and bio-organic projects (ketophosphonate and maleamic acid hydrolysis; thiamine mechanisms) with Professor Ron Kluger for his M.Sc. (1978) and Ph.D. (1981) degrees. He then studied carbonic anhydrase mechanisms at Columbia University with Professor Ron Breslow as an NSERC postdoctoral fellow. In 1983, he joined the faculty at McGill University, where he developed mono- and dinuclear metal complexes as unified mechanistic models of esterases, proteases, nitrilases, and nucleases. He returned to the University of Toronto as a professor in 2000, working on anion and cation recognitions as well as on stereoselective recognition and catalysis. More recently, he has been investigating the preparation of chiral vicinal diamines by the DCR method for which he received the Bernard Belleau Award (2006). He is the founder and CEO of DiaminoPharm, Inc., and has been a visiting professor at the California Institute of Technology (1990), the Institute for Molecular Science in Okasaki (1997), Pohang University of Science and Technology (1998), and Seoul National University (2003, 2008).

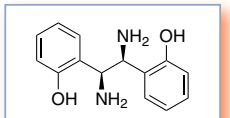
B. Moon Kim obtained his B.S. and M.S. degrees from the Department of Chemistry, Seoul National University. In 1983, he began his Ph.D. level research in the laboratory of the late Professor Satoru Masamune at M.I.T., where he studied asymmetric synthesis using organoboron compounds. Five years later, he became a postdoctoral fellow in Prof. K. B. Sharpless's laboratory at M.I.T., where he investigated the asymmetric, osmium-catalyzed dihydroxylation reaction. In 1990, he accepted a senior research chemist position at Merck Research Laboratories in West Point, Pennsylvania, where he was then promoted to research fellow. In 1995, he moved back to his alma mater in Korea as an assistant professor. In 2003, he spent a year in the laboratory of Dr. Kenner C. Rice as an adjunct investigator at the National Institute of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health, in Bethesda, Maryland. In 2003, he was a DAAD-sponsored Innovatec Guest Lecturer at Regensburg University in Germany. He is now Professor and Chairman of the Department of Chemistry, Seoul National University, and Head of the Brain Korea 21 Division of Chemistry & Molecular Engineering. His research is centered on the development of efficient synthetic methodologies based on asymmetric catalysis, and on the design and synthesis of small molecules that could be used for the treatment of various diseases such as cancer, obesity, and depression.

NEW Chiral Vicinal Diamines for Asymmetric Synthesis

Chiral vicinal diamines are of tremendous interest to the synthetic chemist as they are found in many chiral catalysts and pharmaceuticals.

Currently, there is no unified approach to making these chiral vicinal diamines, and they are often challenging to synthesize, especially if unsymmetrically substituted. Jik Chin and co-workers have recently reported some preliminary theoretical and experimental studies for converting a parent diamine (**1**) into other chiral vicinal diamines.[1–3] These diamines can be used as ligands for chiral catalysts, or they can be further elaborated to produce chiral heterocyclic rings and β-lactams via ring closure.





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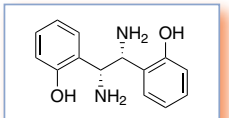

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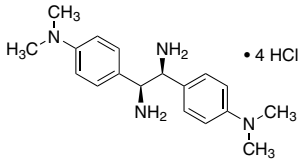
Other NEW Chiral Vicinal Diamines



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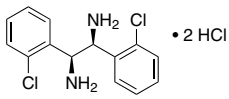

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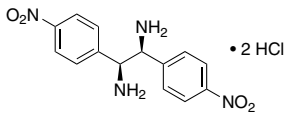

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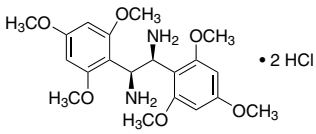

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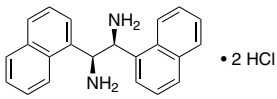

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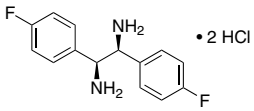

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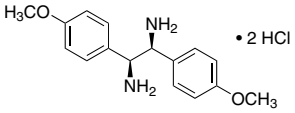

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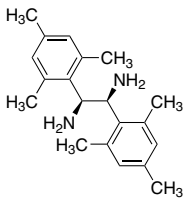

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References: (1) Chin, J. et al. *J. Am. Chem. Soc.* **2003**, *125*, 15276. (2) Kim, H.-J. et al. *J. Am. Chem. Soc.* **2005**, *127*, 16370. (3) Kim, H.-J. et al. *J. Am. Chem. Soc.* **2005**, *127*, 16776.

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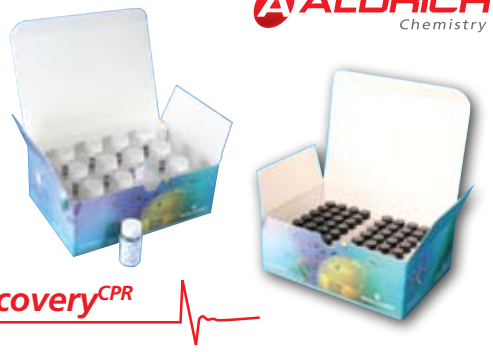

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New Delhi: (+91) 11 4165 4255
Mumbai: (+91) 22 2570 2364
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Fax
Bangalore: (+91) 80 6621 9650
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Fax: (+61) 2 9841 0500

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Fax: (+47) 23 17 60 50

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SIGMA-ALDRICH Sp. z o.o.
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Russia
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+7 (495) 621 5828
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Sweden
SIGMA-ALDRICH SWEDEN AB
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Fax: (+46) 8 742 4243

Switzerland
SIGMA-ALDRICH CHEMIE GmbH
Free Tel: 0800 80 00 80
Free Fax: 0800 80 00 81
Tel: (+41) 81 755 2828
Fax: (+41) 81 755 2815

United Kingdom
SIGMA-ALDRICH COMPANY LTD.
Free Tel: 0800 717 181
Free Fax: 0800 378 785
Tel: (+44) 1747 833 000
Fax: (+44) 1747 833 313
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United States
SIGMA-ALDRICH
P.O. Box 14508
St. Louis, Missouri 63178
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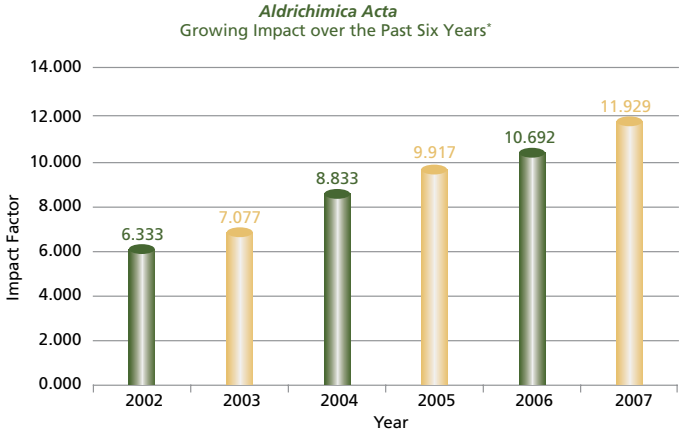

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