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ROM Polymerization in Facilitated Synthesis

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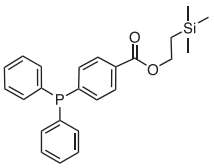
## 4-Diphenylphosphanylbenzoic acid, 2-(trimethylsilyl)ethyl ester, 0.5 M in THF

**63,801-3** — 5 mL, 25 mL

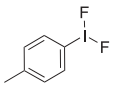


This reagent was developed to replace triphenylphosphine in the Mitsunobu reaction. The resulting phosphine oxide is easily removed from the reaction during workup.

Yoakim, C. et al. *Synlett* **2003**, 473.

## 4-Iodotoluene difluoride

**65,111-7** — 1 g, 5 g

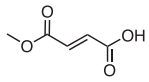


A new and efficient fluorinating reagent that is recommended for the fluorination of the α carbon of sulfanyl amides under mild conditions.

Motherwell, W. B. et al. *J. Chem. Soc., Perkin Trans. 1* **2002,** 2816.

## mono-Methyl fumarate, 97%

**65,141-9** — 1 g, 10 g

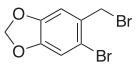


Employed in the design of affinity labels for opioid receptors[1] and in a highly stereoselective synthesis of optically active furfuryl fumarates.[2]

(1) Chang, A.-C. et al. *J. Med. Chem.* **1994**, *37,* 4490. (2) Butz, T.; Sauer, J. *Tetrahedron: Asymmetry* **1997**, *8,* 703.

## 5-Bromo-6-bromomethylbenzo[1,3]dioxole

**65,374-8** — 5 g, 25 g

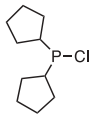


Has been utilized in the preparation of toddaquinoline, an unusual medicinal alkaloid,[1] and lignans, which are known for their biological activity and effectiveness as antineoplastic agents.[2]

(1) Harrowven, D. C. et al. *Tetrahedron* **2001**, *57,* 4447. (2) Cochran, J. E.; Padwa, A. *J. Org. Chem.* **1995**, *60,* 3938.

## Chlorodicyclopentylphosphine

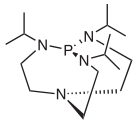
**64,906-6** — 1 g, 5 g, 25 g



A phosphine precursor for ligand preparation in Negishi and Suzuki coupling reactions.

## 2,8,9-Triisopropyl-2,5,8,9-tetraaza-1-phosphabicyclo[3,3,3]undecane, 1 M in toluene

**65,435-3** — 10 mL

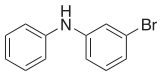


This highly useful and air-senstive reagent is now available in an easier-to-handle toluene solution in Sure/Seal™ bottles.

Verkade, J. G.; Kisanga, P. B. *Aldrichimica Acta* **2004**, *37,* 3.

## *N*-(3-Bromophenyl)aniline, 97%

**65,424-8** — 1 g, 10 g

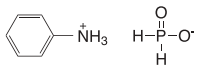


A useful building block in the preparation of triarylamines, which have been extensively employed in electroluminescent materials as hole-transport materials and hole-transport emitters,[1] and in the development of organic-based magnets.[2,3]

(1) Mitschke, U.; Bäuerle, P. *J. Mater. Chem.* **2000**, *10,* 1471. (2) Miller, J. S.; Epstein, A. J. *MRS Bull.* **2000**, *25,* 21. (3) Veciana, J.; Iwamura, H. *MRS Bull.* **2000**, *25,* 41.

## Anilinium hypophosphite

**65,411-6** — 25 g

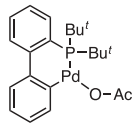


An easy-to-handle and relatively nonhygroscopic reagent that has been used in the preparation of monosubstituted phosphinic acids via Pd-catalyzed reaction with aryl halides or triflates.[1] A practical triethylborane-initiated radical addition of anilinium hypophosphite to olefins has been reported.[2]

(1) Montchamp, J.-L.; Dumond, Y. R. *J. Am. Chem. Soc.* **2001**, *123,* 510. (2) Deprele, S.; Montchamp, J.-L. *J. Org. Chem.* **2001**, *66,* 6745.

## 2-(2′-Di-*tert*-butylphosphine)biphenylpalladium(II) acetate

**65,541-4** — 250 mg, 1 g

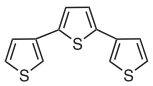


A novel, air- and moisture-stable pre-catalyst for the amination of aryl chlorides.

Zim, D.; Buchwald, S. L. *Org. Lett.* **2003**, *5,* 2413.

## 3,2′:5′,3″-Terthiophene

**65,138-9** — 1 g

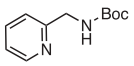


An efficient singlet-oxygen sensitizer. This compound is also associated with photoantibiotic and phototoxic properties.[1,2]

(1) Beny, J.-P. et al. *J. Org. Chem.* **1982**, *47,* 2201. (2) Moriarty, R. M. et al. *Synth. Commun.* **1985**, *15,* 789.

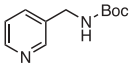
## *N*-Boc-2-aminomethylpyridine, 97%

**65,157-5** — 5 g, 25 g



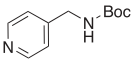
## *N*-Boc-3-aminomethylpyridine, 97%

**63,444-1** — 1 g, 5 g



## *N*-Boc-4-aminomethylpyridine, 96%

**64,976-7** — 1 g, 10 g



These Boc-protected pyridines can be used as pharmaceutical building blocks in thrombin[1] and PKC inhibitor[2] research, and can be readily hydrogenated to the protected piperidines.

(1) Hilpert, K. et al. *J. Med. Chem.* **1994**, *37,* 3889. (2) Shearer, B. G. et al. *J. Med. Chem.* **1991**, *34,* 2928.

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Joe Porwoll, President

Professor Ei-ichi Negishi of Purdue University kindly suggested that we offer *trans*-1-bromo-2-iodoethene, a useful synthon in Pd-catalyzed cross-coupling reactions. Its utility has recently been demonstrated in the synthesis of xerulin, an inhibitor of cholesterol biosynthesis,[1] *cis*- and *trans*-bupleurynol,[2] in the preparation of 1-halo-1,3-dienes,[3] and in coupling reactions with alkynylzinc reagents.[4]

(1) Negishi, E.; Alimardanov, A.; Xu, C. *Org. Lett.* **2000**, *2*, 65. (2) Ghasemi, H.; Antunes, L. M.; Organ, M. G. *Org. Lett.* **2004**, *6*, 2913. (3) Qian, M.; Huang, Z.; Negishi, E. *Org. Lett.* **2004**, *6*, 1531. (4) Negishi, E.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. *Org. Lett.* **2003**, *5*, 1597.


**57,780-4** ***trans*-1-Bromo-2-iodoethene, 97%** 5 g, 25 g

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

*The Fence* (oil on canvas, 37.8 × 45.7 cm) was signed and dated by the French painter Camille Jacob Pissarro in 1872. During the 1860s, Pissarro moved his family from Paris to various small villages in the French countryside. He was committed to the principles of socialism, and felt a strong affinity for the peasant farmers who worked the land. Like the other impressionists, Pissarro chose to represent subjects from modern life; but, while they often painted the pleasures of the urban bourgeoisie, scenes from the theatre, the opera, the ballet, or the racetrack, Pissarro was more likely to portray the rustic life of farmers working in the fields with whom he identified.

The warm colors of the trees and shrubbery in the picture show that it is the fall of the year. At the left in the foreground is a large bent and broken tree, whose almost leafless branches are silhouetted against the light sky. Near the lower right corner of the painting, a peasant couple chat together on either side of a rustic fence. In the distance, one can make out the buildings of the local village, towards which a woman moves along the path near the right edge of the picture. As in a snapshot, nothing in nature has been rearranged to create a more pleasing, harmonious, or picturesque effect. The rapidly executed brushwork is variegated to suggest the different textures of diverse objects in the painting, which was almost certainly painted in a single session on the site. One might say, in fact, that a central purpose of all the impressionist artists was not to create an invented world on canvas, but to capture the immediacy of the unique conditions of a specific moment in time in a particular place.

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

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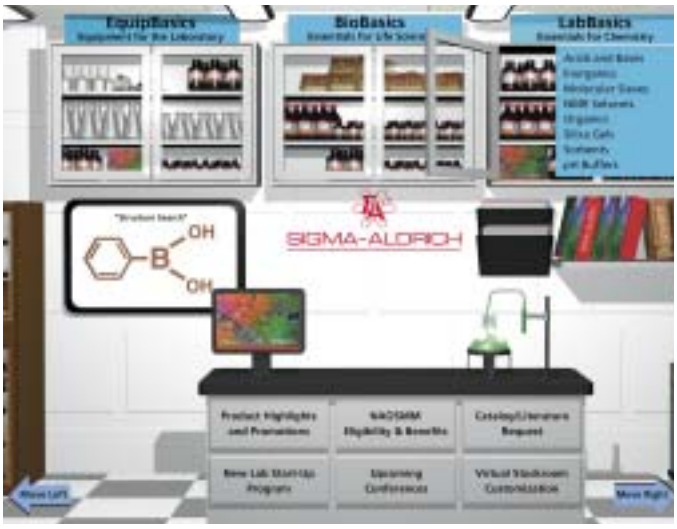


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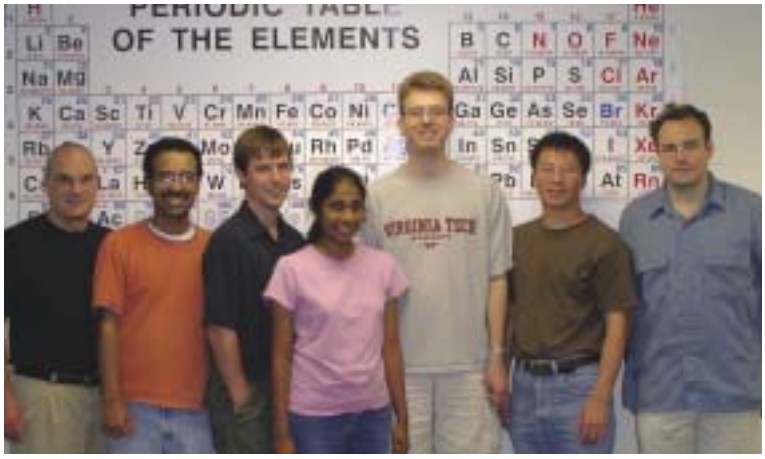
# ROM Polymerization in Facilitated Synthesis




From left to right: D. L. Flynn, S. Mukherjee, R. H. Herpel, P. Vedantham, A. M. Harned, M. Zhang, and P. R. Hanson.

*Andrew M. Harned,[§,¥] Mianji Zhang,[§,¥] Punitha Vedantham,[§,¥] Shubhasish Mukherjee,[§,¥] Russell H. Herpel,[§,¥] Daniel L. Flynn,[*,§,£] and Paul R. Hanson[*,§,¥,†]*

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## Outline



## 1. Introduction

The recent growth of high-throughput screening for biologically active agents has increased the demand for the rapid production of chemical compounds. In this context, an array of polymer-bound reagents and scavengers have been reported.[1] These effectively eliminate or circumvent the need for chromatographic purifications, which typically is a bottleneck in synthetic sequences. Recent successes in multistep total syntheses—exclusively using immobilized reagents and scavengers, whereby filtration was the sole purification protocol—are a testament to the power of this approach.[2] Despite tremendous advances in this area, *limitations in nonlinear reaction kinetics, low resin-load capacities, and the means of distributing reagents* continue to warrant the development of designer polymers.

In order to address these limitations, soluble polymers[3] and scavenger resins[1] have emerged as a means of utilizing solution-phase reaction kinetics with all the advantages of their solid-phase counterparts. Pioneering work by Barrett[4] and others[5,6] has led to the general use of ring-opening metathesis polymerization (ROMP) for the generation of high-load, immobilized reagents, while advances in ROM polymer-immobilized catalysts were simultaneously championed by Buchmeiser[7] and Bolm.[8] Overall, the ability to produce designer, ROMP-derived polymers with tunable properties has become a powerful technological advancement in the arena of facilitated synthesis. Related reviews have appeared that cover advances in this field through 2002.[4,5,6]

This review will report on more recent advances in the use of ROM polymerization for facilitated synthesis.

## 2. ROM Polymerization

Ring-opening metathesis polymerization (ROMP) has a history that harks back to the late 1950s and early 1960s.[9] Since then, it has remained in the realm of classical polymer chemistry. This, in part, can be attributed to the lack of robust, well-defined catalysts to initiate the polymerization. Some of the early initiator systems used were $MoCl_5$–$Et_3Al$, $WCl_6$–$Et_3Al$, various Ti-based systems and, later, $RuCl_3$. With the development of the highly active molybdenum imido alkylidene complexes (cat-**C**, **Figure 1**) by Schrock in the late 1980s,[10,11] the first well-defined ROM polymerizations could be accomplished in a controlled manner. Although these complexes are not water- and oxygen-tolerant, they do show a higher tolerance of Lewis basic moieties when compared to the earlier initiators. In the mid-1990s, Grubbs and co-workers introduced the highly functional group tolerant ruthenium alkylidene complexes (cat-**A** and cat-**D**, **Figure 1**).[12] This was followed by an explosion of development in ROMP and ring-closing olefin metathesis (RCM). Concurrently, a number of newer and more active Ru-based catalysts (cat-**B**, cat-**E**, and cat-**F**) have emerged that rival and, at times, surpass the activity of the Schrock systems.

## 3. Mechanism of ROMP

Grubbs and co-workers have performed a number of kinetic studies with $(PCy_3)_2(Cl)_2Ru{=}CHPh$ (cat-**A**)[13] and $(ImMesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ (cat-**B**)[14], and a detailed mechanistic picture is beginning to emerge (**Scheme 1**).[15] The first step of this process involves dissociation of a phosphine ligand from the precatalyst, **1**. The resulting 14-electron complex, **2**, undergoes a [2+2] cycloaddition with monomer **3** to give metallacyclobutane intermediate **4**, which rapidly undergoes a [2+2] cycloreversion to produce ring-opened product **5**. This sequence is highly favored due to the relief of ring strain of the initial monomer species. Intermediate **5** contains a catalytically active Ru-alkylidene, and undergoes further reactions until monomer **3** is completely consumed. The Ru center remains attached to oligomer **6** until the polymerization is quenched by the addition of ethyl vinyl ether (EVE). This quench results in polymer **8** and alkoxycarbene complex **7**. The length of oligomer **8** is conveniently controlled through the amount of catalyst employed for the polymerization; more catalyst will produce shorter oligomers, while less catalyst will produce longer oligomers. Because the initiation rate is similar to the propagation rate, 10 mol % of catalyst (10:1 monomer: catalyst) will produce mainly 10-mers, 5 mol % of catalyst (20:1 monomer:catalyst) will produce mainly 20-mers, etc.

As a polymerization technique, ROM polymerization is selective for strained, cyclic olefins. Typically, the monomers used are norbornene- or 7-oxanorbornene-based. As such, they can easily be prepared from a Diels–Alder reaction between cyclopentadiene or furan with a suitable dienophile, or from Pd-catalyzed reactions involving norbornadiene. Because of the low cost and ready availability of these starting materials, monomers can be constructed on a large scale. ROMP is also a very "organic chemist friendly" polymerization technique. The catalysts are commercially available and are no different than those used to perform the familiar RCM reaction. The only difference is that ROM polymerizations are typically performed at higher substrate concentrations (0.1 M) than RCM (0.01–0.005 M). In addition, no special equipment is required to perform ROM polymerizations. A polymerization can be carried out in flasks or screw-cap vials, inside or outside of a glove box. Reaction scale is not an issue, as polymerizations can be conducted on scales ranging from 10–20 milligrams up to kilograms.

There are a few other relevant characteristics of ROMP that should be addressed. First, the length of the ROM polymer can have a profound effect on its solubility. Typically, shorter oligomers will remain soluble in common reaction solvents ($CH_2Cl_2$, $CHCl_3$, THF, DMF), yet can often be precipitated from MeOH, $Et_2O$, EtOAc, or hexanes. It is also possible to control the solubility of the ROM polymers through the judicious use of cross-linking agents (**CL-1**, **CL-2**, and **CL-3**, **Figure 2**). ROM polymers constructed using cross-linkers typically result in insoluble gels, which retain swelling properties that are analogous to those of traditional solid-phase resins.[4]

Overall, polymers derived from ROM polymerization possess unique physical properties that depend largely upon the collective properties of the polymer backbone (*i.e., norbornene-based scaffold*), the individual functional groups (FG) that are placed on each monomer, the amount and nature of the catalyst used during the polymerization, and any cross-linker that may be added. It is these collective properties that have been the hallmark of ROM polymerization in producing designer polymers for facilitated synthesis.

## 4. ROMP-Derived Reagents and Scavengers

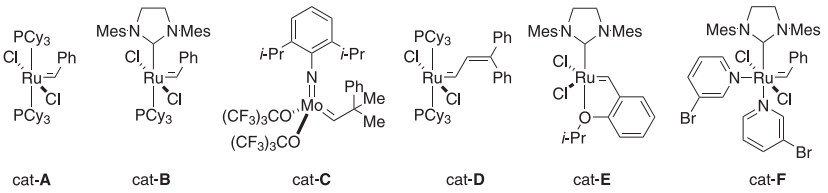
### *4.1. Barrett's ROMPgel Reagents and Scavengers*

The emergence of ROM polymerization in combinatorial chemistry was led by Barrett and co-workers, who developed a number of ROMP-derived reagents and scavengers, **9–19**, termed ROMPgels and a ROMPsphere (**Figure 3**).[4,16–23] Most of the reagents incorporated norbornenyl-derived cross-linkers to enhance swelling properties and ensure insolubility. Occasionally, the polymer backbone was hydrogenated under high pressure, as in **16** and **17**, using Wilkinson's catalyst. Barrett's seminal 2002 review[4] discusses a wide variety of ROMPgel-supported reagents (e.g., Horner–Wadsworth–Emmons reagent **9**;[16] amine- and hydrazine-scavenging agent **10**;[17] amine base **11**;[17] *N*-hydroxysuccinimide reagents **12**[18] and **13**[19], used for various acylations[18] and Mosher amide formation;[19] 4-toluenesulfonylmethyl isocyanide (Tosmic reagent) **14**;[20] allylboronate **15**;[21] biphenyl reagent **16**;[22] naphthalene reagent **17**;[22] and triphenylphosphine reagent **18**[23]) and ROMPsphere-supported peptide-coupling reagent **19**.[4]

Since 2002, additional high-load ROMP-derived reagents have been developed and are described in detail below, including: (i) ROMPgel-supported ethyl 1-diazo-2-oxopropylphosphonate for the conversion of aldehydes into terminal alkynes,[24] (ii) oligomeric benzylating agents (OBA)[25] for the benzylation of amines, and (iii) oligomeric alkyl cyclohexyl carbodiimides (OACC) for coupling reactions.[26] In addition, a number of high-load, soluble and insoluble nucleophile scavengers have been prepared, including oligomeric sulfonyl chlorides (OSC),[27] bis(acid chlorides) (OBAC),[28a] and phosphonyl chlorides (OPC).[28b]

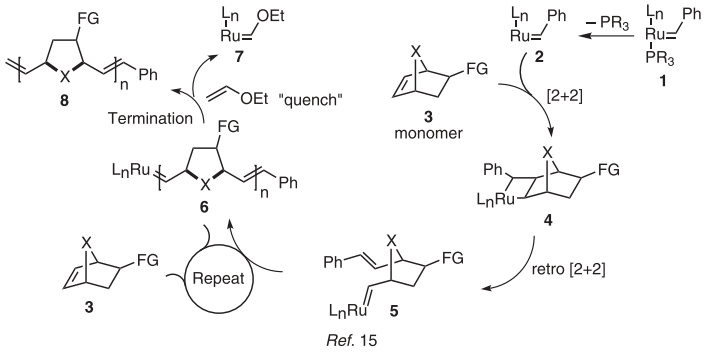
### *4.2. ROMPgel-Supported Ethyl 1-Diazo-2-oxopropylphosphonate for Seyferth–Gilbert Homologations*

The generation of alkynes using an immobilized reagent opens up new avenues for the rapid generation of chemical libraries due to the versatility of this functional group. Despite the potential utility of this chemical diversification step, only a single example existed in the literature prior to 2004,[29] when Barrett and co-workers reported the preparation of ROMPgel **25** (**Scheme 2**).[24]




Schrock's catalyst: cat-**C**; Grubbs' catalysts: cat-**A**, cat-**B**, cat-**D**, and cat-**F**; Hoveyda's catalyst: cat-**E**

**Figure 1.** Examples of the Most Widely Used Olefin-Metathesis Catalysts.




**Scheme 1.** Mechanism of ROMP.

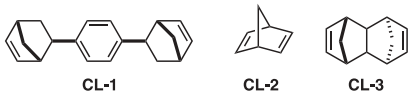



**Figure 2.** Typical Cross-Linking Agents Used in ROM Polymerization.

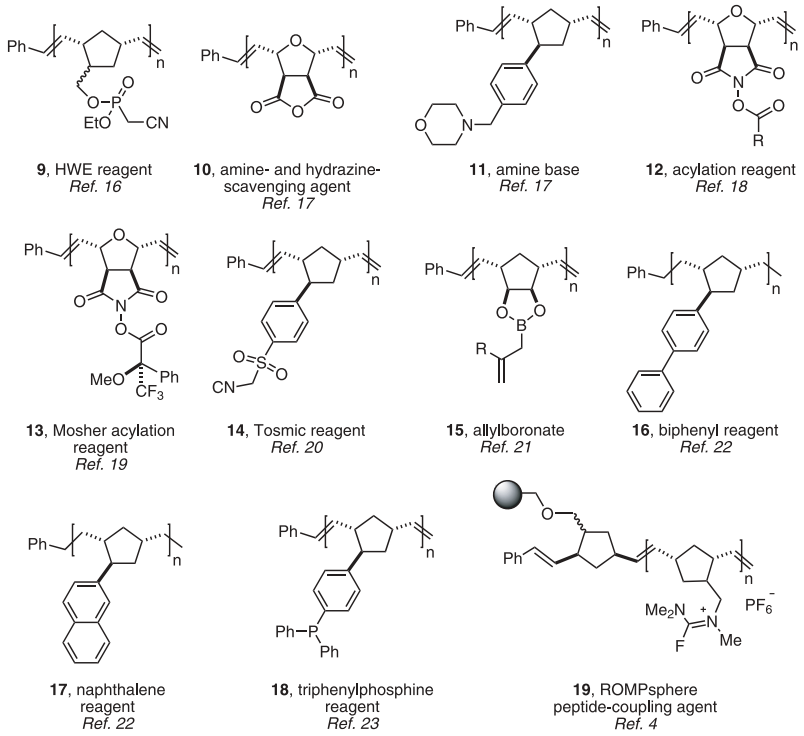
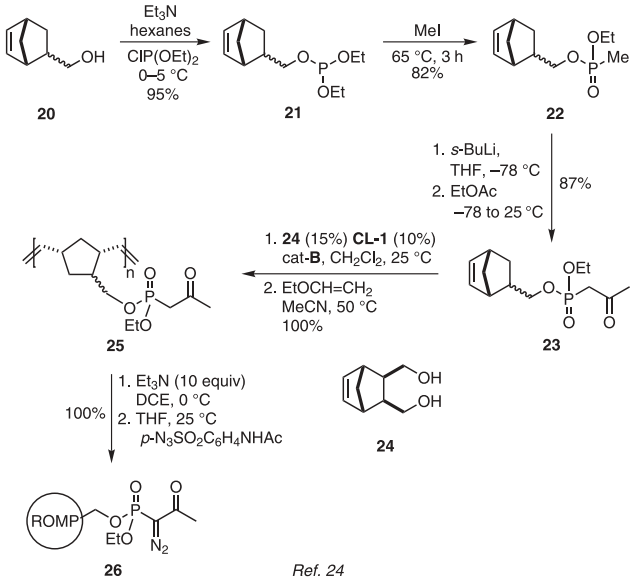
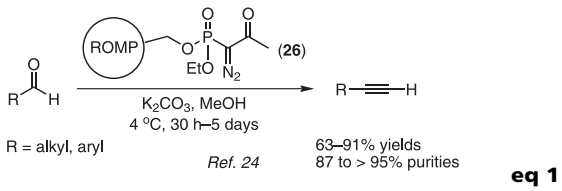



**Figure 3.** Barrett's ROMPgel (**9–18**) and ROMPsphere (**19**) Supported Reagents and Scavengers through 2002.

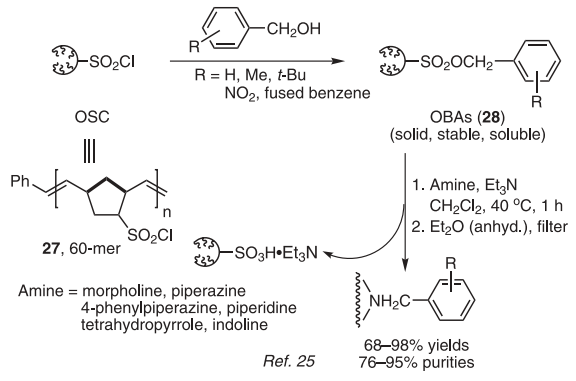
Bicyclo[2.2.1]hept-5-en-2-ylmethyl diethyl phosphite (**21**) was prepared by treating commercially available alcohol **20** with $ClP(OEt)_2$.[16] Reaction of phosphite **21** with $MeCOCH_2I$ gave the desired Michaelis–Arbuzov product **23** in variable yields (23–46%). Alternatively, phosphonate **23** was obtained in a higher overall yield by first reacting phosphite **21** with MeI to furnish phosphonate **22** (82%), followed by deprotonation of **22** with *sec*-butyllithium, and subsequent treatment with EtOAc (87%). After optimization, it was found that monomer **23** was readily polymerized in the presence of cross-linker **CL-1** (10 mol %) and co-monomer **24** (15 mol %), using cat-**B** to afford ROMPgel **25** in quantitative yield. This ROMPgel was found to have optimal swelling properties. The diazo functional group was quantitatively transferred to ROMPgel **25** under mild reaction conditions to produce ROMPgel **26** with a loading of 2.70 mmol/g. This route was found to be readily amenable to multigram-scale synthesis. Supported reagent **26** is stable at 0 °C, and retains its activity over a three-week storage period. Reaction of ROMPgel **26** with a variety of aldehydes generated the corresponding terminal alkynes in good yields and high purities (**eq 1**).[24]




**Scheme 2.** Synthesis of ROMPgel-Supported Ethyl 1-Diazo-2-oxopropylphosphonate (**26**).




**eq 1**




**Scheme 3.** Synthesis and Reactions of Oligomeric Benzylating Agents (OBA).

### 4.3. Oligomeric Benzylating Agents (OBA)

In 1996, Hunt and Roush developed immobilized alkylating agents.[30] Reitz and co-workers subsequently reported the use of a polystyrene resin bound sulfonyl chloride, which was "activated" with a variety of alcohols and further reacted in situ with a panel of amines to achieve the desired alkylation in a process termed "catch and release".[31] ROMP-derived oligomeric benzylating agents (OBA, **28**) were first reported in 2004 (**Scheme 3**).[25] These reagents were prepared from oligomeric sulfonyl chloride (OSC)[27] reagent **27** and various benzyl alcohols. They exist as free-flowing powders that dissolve readily in $CH_2Cl_2$ and are stable at refrigerated temperatures. Purification of the benzylation reaction products is accomplished by simple filtration, followed by solvent removal to deliver the desired benzylated products in good-to-excellent yields and high purities. These OBA entities have proven extremely efficient in the benzylation of cyclic, secondary amines and, with limited success, of acyclic amines. Furthermore, the solubility of OBAs enables convenient dispensing, which ultimately will provide an advantage in parallel-array synthetic protocols.

### 4.4. Oligomeric Alkyl Cyclohexyl Carbodiimides (OACC)

Carbodiimides rank as one of the most important classes of reagents in organic synthesis due to their accessibility and versatile chemical properties.[32] Complete removal of the dicyclohexyl urea (DCU) byproduct, when DCC is employed, usually necessitates additional purifications. This limitation has prompted the development of a class of soluble oligomeric reagents ($^{2G}OACC_n$),[26,33] which serve as viable alternatives to DCC.

The requisite monomer **32** was produced in three steps from commercially available *cis*-5-norbornene-*endo*-2,3-dicarboxylic anhydride (**29**) (**Scheme 4**).[26] Heating **29** at reflux with 1,2-diaminoethane (4 equiv) in toluene overnight gave mono-*endo*-amine **30**.[34] Treatment of **30** with cyclohexyl isocyanate produced the norbornenyl-tagged urea, **31**, in high yield. Dehydration of **31** with phenylsulfonyl chloride (2 equiv) in triethylamine (5 equiv) at 70 °C afforded the required monomer **32** in 73% yield. Subsequent ROM polymerization with $(H_2ImMes)(PCy_3)(Cl)_2Ru$=CHPh (cat-**B**) yielded oligomers **33** (n = 50, 100, 150) of the OACC reagent depending on the amount of cat-**B** used. Quenching of the ROM polymerization with EVE produced a free-flowing solid with a theoretical load of 3.2 mmol/g[35] and possessing a wide solubility profile: soluble in $CH_2Cl_2$, THF, DMF, and DMSO; and insoluble in $Et_2O$, EtOAc, and MeOH.

The oligomeric reagent $^{2G}OACC_{50}$ (**33**, Scheme 4) was initially developed as a coupling reagent for esterification, amidation, and dehydration of carboxylic acids (aliphatic and aromatic) with an assortment of alcohols (aliphatic 1°, 2°, and benzylic), thiols, phenols, and amines (aliphatic 1°, 2°, benzylic, and anilines). Following the coupling event, precipitation with an appropriate solvent ($Et_2O$, MeOH, or EtOAc), followed by filtration via solid-phase extraction (SPE) on silica gel provided the products in good-to-excellent yields and purities (**Scheme 5**).[26] Further studies determined that the longer oligomeric reagent $^{2G}OACC_{100}$

(**33**, Scheme 4), possesses the optimal length that provides facile precipitation during workup, while preserving the homogeneity of the reaction mixture.

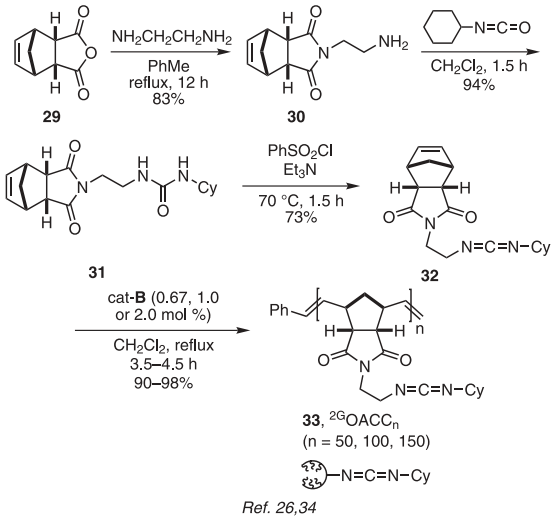
### 4.5. High-Load, Soluble Oligomeric Sulfonyl Chlorides (OSC)

The emergence of molecular scavenging[2] as a powerful purification technique has led to the development of a number of designer polymers, that are capable of discrete binding of excess reagent, in order to address limits in load and heterogeneity. In this regard, the aforementioned OSC reagent **27** was investigated as a high-load, soluble nucleophile scavenger (**Scheme 6**).[27] Simple preparation of **27** was achieved by the Diels–Alder reaction of vinylsulfonyl chloride (**34**) and cyclopentadiene to generate monomer **35** in 90% yield. ROM polymerization of **35** with cat-**B** produced **27** as a free-flowing solid. Arrays of polymers with different lengths (e.g., 10-mer, 30-mer, 60-mer, and 100-mer) were produced; the 60-mer ($^{2G}OSC_{60}$) proved to be the scavenging reagent of choice by virtue of its precipitation characteristics and differential solubility. $^{2G}OSC_{60}$ is soluble in $CH_2Cl_2$, THF, and DMF, but is insoluble in $Et_2O$, EtOAc, and MeOH.[36] The scavenging ability of $^{2G}OSC_{60}$ was investigated in the benzoylation and sulfonation of a variety of amines. Following the benzoylation or sulfonation reaction, $^{2G}OSC_{60}$ was added as a dichloromethane solution to remove the excess amine (1°, 2°, or benzylic), followed by precipitation of the scavenger to furnish the benzamides and sulfonamides in excellent yields and purities.[27]

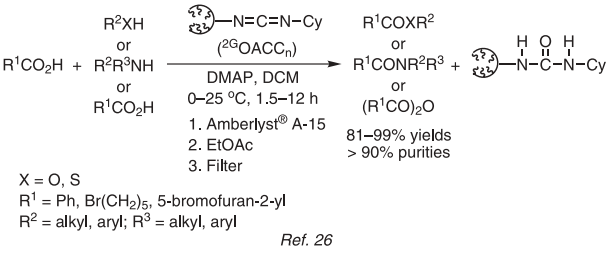
### 4.6. High-Load, Oligomeric Bis(acid chlorides) (OBAC)

In 2003, a high-load, oligomeric bis(acid chloride) (OBAC) was reported as a general nucleophile scavenger that was capable of removing alcohols and thiols in addition to amines.[28a] Like the aforementioned OSC scavenger, this system also offered flexible oligomer design and differential solubility for facile purification via simple precipitation–filtering protocols. The requisite monomer, *trans*-bicyclo[2.2.1]hept-5-ene-2,3-dicarbonyl dichloride (**37**), was conveniently prepared in two steps: a Diels–Alder reaction between fumaric acid and cyclopentadiene, followed by chlorination using oxalyl chloride and a catalytic amount of DMF (**Scheme 7**).[28a] Subsequent ROM polymerization with either 1 mol % cat-**B** or 2.5 mol % cat-**A** yielded the 100-mer (**38a**) or 40-mer (**38b**) OBAC reagents, respectively.[36] It is interesting to note that polymerization with 1 mol % of cat-**B** provided a heterogeneous, solid nucleophile scavenger ($^{2G}OBAC_{100}$), while polymerization with 2.5 mol % of catalyst cat-**A** yielded a homogeneous, soluble 40-mer ($^{1G}OBAC_{40}$).

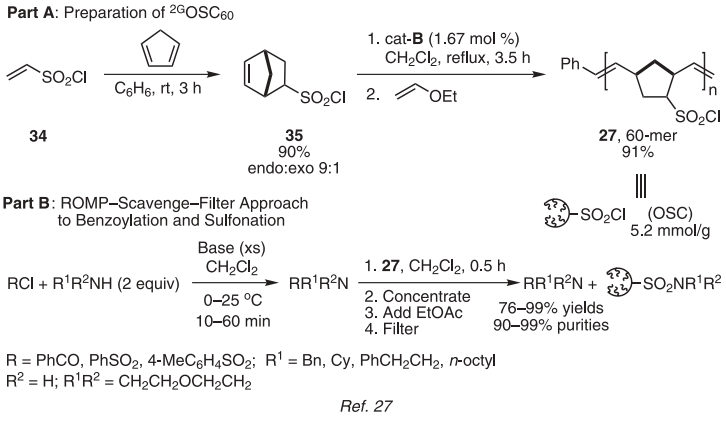
The scavenging ability of OBAC was tested with a variety of amines, alcohols, and thiols. OBAC was found to efficiently remove excess amines (1° and 2°), alcohols (1°, 2°, allylic, propargylic, and benzylic), and thiols after a common benzoylation event.[28a] While the amines were scavenged in 15–30 minutes at




**Scheme 4.** Synthesis of Oligomeric Alkyl Cyclohexyl Carbodiimides (OACC).

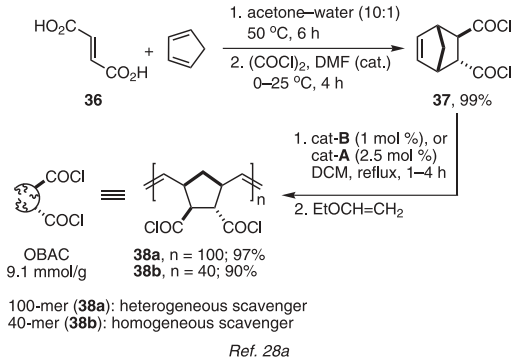



**Scheme 5.** Application of OACC Coupling Reagents.

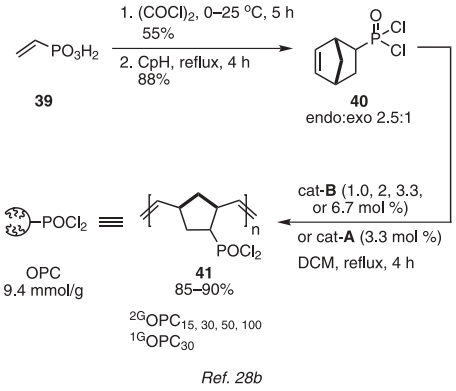



**Scheme 6.** High-Load $^{2G}OSC_{60}$ as a Nucleophile Scavenger.

room temperature, higher temperatures (refluxing DCM, 1–2 hours) were required for efficient scavenging of alcohols and thiols. The synthetic utility of OBAC scavengers was evaluated by comparing their efficiency against a commercially available nucleophile scavenger, polystyrene-based isocyanate (PS-NCO) resin.[1e,37,38] One clear advantage pertains to the loadings of OBAC scavengers, which are higher than the corresponding ones for the polystyrene isocyanate resin (theoretical load of 9.1 mmol/g vs ~1.3 mmol/g). Thus, the weight of OBAC reagent required for each scavenging reaction is seven times lower than the amount of isocyanate resin for a given experimental procedure. In a typical comparison experiment, 35 mg of OBAC versus 250 mg of the polystyrene-based isocyanate was found to be optimal for scavenging.[28a] While both OBAC and PS-NCO performed similarly for amines and thiols, OBAC was more efficient in scavenging alcohols.




**Scheme 7.** Preparation of High-Load, Oligomeric Bis(acid chlorides) (OBAC).




**Scheme 8.** Synthesis of Oligomeric Phosphonyl Chlorides (OPC).

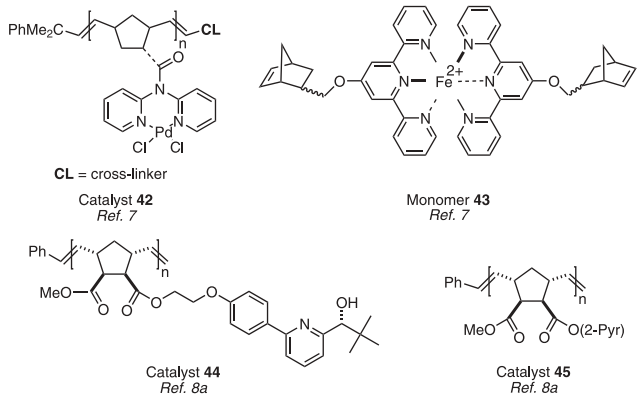



**Figure 4.** ROM Polymer-Supported Catalysts through 2002.

## 4.7. High-Load, Oligomeric Phosphonyl Chlorides (OPC)

A high-load, ROMP-derived phosphonyl chloride scavenging agent has also recently been realized. Chlorination of vinyl phosphonic acid (**39**), followed by [4+2] cycloaddition onto cyclopentadiene, furnished monomer **40** as a ~2.5:1 endo:exo mixture (**Scheme 8**).[28b] Subsequent ROM polymerization with cat-**A** or cat-**B** provided $^{1G}OPC_{30}$, $^{2G}OPC_{30}$, and $^{2G}OPC_{100}$, respectively (**41**). All OPCs efficiently removed both primary and secondary amines from reaction mixtures after benzoylation.

Overall, OSC, OBAC, and OPC scavengers have been conveniently prepared on a large scale from inexpensive and readily available starting materials. Furthermore, these scavenging reagents offer high-load benefits, exhibit wide solubility profiles, and have tunable properties that allow them to be isolated as either homogeneous or heterogeneous oligomers depending on the amount and nature of the catalyst used.

## 5. ROM Polymer-Supported Catalysts and Ligands

### 5.1. Buchmeiser's and Bolm's ROM Polymer-Immobilized Catalysts and Ligands

The use of ROM polymeric supports for immobilizing catalysts was pioneered by Buchmeiser[7] and Bolm[8] in the late 1990s, and much of this work has been reviewed.[4,6] Buchmeiser utilized ROM polymerization to generate an array of dipyridyl-based Pd(II) catalysts similar to catalyst **42** (**Figure 4**).[7] Dimeric iron complex **43** was also polymerized and used in heterogeneous atom-transfer radical polymerizations of styrene.[7] More recently, a grafted monolithic metathesis catalyst has been developed.[39] Concurrently, Bolm and co-workers developed the first soluble oligomeric chiral catalysts, **44** and **45**, for use in asymmetric diethylzinc addition reactions.[8a]

Since Barrett's review,[4] three additional ROM polymer-supported catalytic systems have been developed, including (i) a ROMPgel-supported tris(triphenylphosphine)rhodium(I) chloride for the hydrogenation of alkenes and terminal alkynes,[40] (ii) a bisphosphine oligomeric ligand used in supported, palladium-containing catalysts for the Heck, Sonogashira, and Negishi reactions,[41] and (iii) a ROMPgel-supported thiazolium iodide for use in Stetter reactions.[42a] Additionally, Tanyeli and Gümüş[42b] have developed ROMP-supported TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) catalysts for the oxidation of various primary alcohols to the corresponding aldehydes in 70–87% yields.

### 5.2. ROMPgel-Supported Tris(triphenylphosphine)rhodium(I)

Wilkinson's catalyst, $(Ph_3P)_3RhCl$, is widely used for the selective hydrogenation of sterically unhindered, nonconjugated alkenes.[43,44] Despite its advantages, Wilkinson's catalyst suffers from the need to separate the catalyst from the product. In 2003, Barrett's group prepared a novel ROM polymer-supported Wilkinson's catalyst. The monomeric ligands **48** and **52** were

synthesized in two or three steps from commercially available starting materials (**Scheme 9**).[40]

4-Bromoiodobenzene (**46**) was coupled to norbornadiene via a reductive Heck reaction to furnish aryl bromide **47**, which was allowed to react with BuLi and $Ph_2PCl$ to produce phosphine ligand **48**.[23] *N*-Alkylimidazole **50**[45] reacted with BnCl in toluene to give imidazolium chloride **51**, which underwent ion exchange with $KPF_6$ in $CH_2Cl_2$ to yield ligand **52**. ROM polymerization of **48**, **52**, and a 2:3 mixture of **48:52**, with cross-linker **CL-1** (10 mol %) and cat-**B**, generated oligomeric ligands **49**, **53**, and **54**, respectively.[40] Wilkinson's catalyst (**56**) was anchored to ROMPgels **49**, **53**, and **54** by heating a suspension of the polymer and the rhodium complex **55** or **56** in $CH_2Cl_2$ to give the ligand-displaced catalysts **57** and **58**, and the noncovalently bonded ionic catalyst **59** (**eq 2** and **3**).[40] ROMPgels **57** and **58** have been effectively utilized in the selective hydrogenation of a variety of alkenes and terminal alkynes. ROMPgel **57** turned out to be significantly more active than **58**, whereas ROMPgel **59** showed no activity in the hydrogenation reaction.[40]

### 5.3. Oligomeric Bisphosphine Ligand for Pd-Catalyzed C–C-Bond Formation

In 2003, Yang and Luh reported the preparation of bisphosphine polymer **64** (**Scheme 10**) by ROM polymerization of the corresponding monomer, **63**, and the use of **64** as a polymer-supported ligand in palladium-catalyzed, C–C-bond-forming reactions.[41] Treatment of **61** with $K_2CO_3$ and 4-bromobenzyl bromide in refluxing $CH_3CN$ afforded dibromide **62** in 78% yield. Reaction of **62** with *n*-BuLi at –78 °C, followed by displacement with $ClPPh_2$, gave monomer **63** in 60% yield. Polymerization of **63** using cat-**B** in THF (rt for 24 h) generated polymer **64** in powder form and 90% yield. Phosphine polymer **64** has a theoretical load of 2.8 mmol/g and, at room temperature, is soluble in moderately polar organic solvents such as THF, toluene, or dichloromethane; but is insoluble in alkanes, ether, and DMF. However, a homogeneous solution of **64** in DMF was obtained at an elevated temperature (80 °C).

A series of coupling reactions were examined to test the efficiency of polymeric ligand **64**. All Heck, Sonogashira, and Negishi reactions (**eq 4**, **5**, and **6**) proceeded smoothly to give high yields of the coupled products.[41] Furthermore, the catalysts retained most of their activities in subsequent cycles (4–5 cycles). When the small-molecule counterpart, 4-(methoxymethylphenyl) diphenylphosphine [$(4\text{-}MeOCH_2C_6H_4)Ph_2P$], was used as the ligand under identical conditions, no reactions were observed in the third cycle of the Heck and Sonogashira reactions and the second cycle of the Negishi reaction. This is presumably owing to the difficulty of recovering enough of the Pd catalyst from cycle to cycle because of its solubility in the solvent.

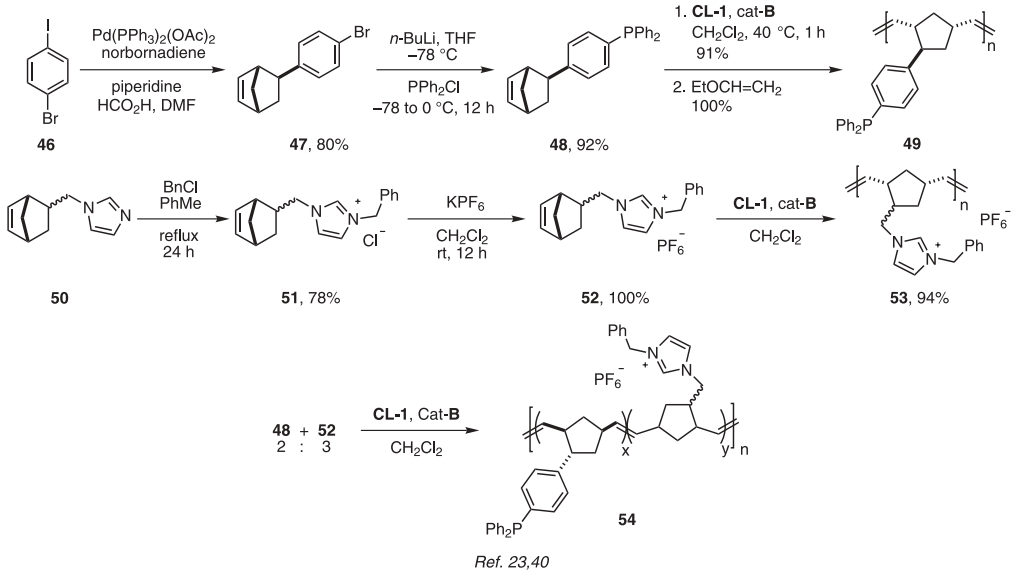
### 5.4. ROMPgel-Supported Thiazolium Iodide in Stetter Reactions

In 2004, Barrett and co-workers reported a high-load, ROMPgel-supported thiazolium iodide, that was prepared in three steps overall via ROM polymerization of the corresponding norbornene-derived monomer (**Scheme 11**).[42a] The Diels–Alder reaction between commercially available 4-methyl-5-vinyl-1,3-thiazole (**65**) and cyclopentadiene gave a 53% yield of a 1:9.5 mixture of exo and endo cycloadducts, **66**. Methylation of **66** with MeI gave the thiazolium salt monomer, **67**, which was polymerized with cat-**B** in the presence of cross-linker **CL-1** (11 mol %) to afford ROMPgel **68** possessing a theoretical load of 2.52 mmol/g.

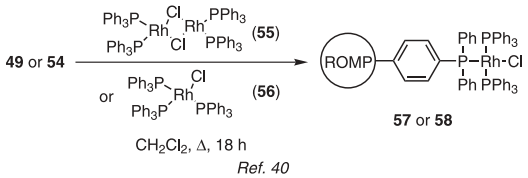
Ionic ROMPgel **68** proved to be an efficient organic catalyst for Stetter reactions, especially for the reaction of aliphatic aldehydes with a range of enones (**eq 7**).[42a] The resulting 1,4-dicarbonyl products, which are important intermediates in the synthesis of cyclopentenones and heterocycles, were obtained in high yields and excellent purities after minimal purification. ROMPgel **68** maintained its catalytic activity, when used in up to four consecutive reaction cycles.

## 6. Purification by in Situ Polymerization

One purification strategy that has gained popularity in recent years is the use of chemically tagged reagents.[46] A chemical tag allows for the selective removal of reaction components (reagents, products, byproducts) through specific chemical interactions. Examples of chemical tagging strategies include: the fluorous-phase chemistry developed by Curran;[47] metal chelation as

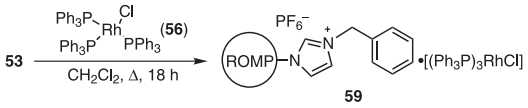



**Scheme 9.** ROM Polymer-Supported Wilkinson's Catalyst.



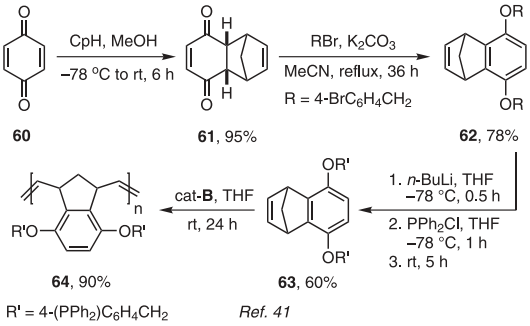

*Ref. 40*

**eq 2**



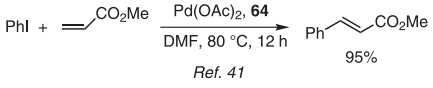

*Ref. 40*

**eq 3**



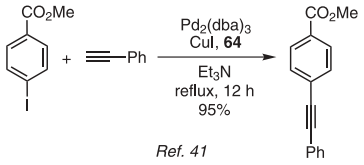

*Ref. 41*

**Scheme 10.** Preparation of Polymer-Supported Bisphosphine Ligand.



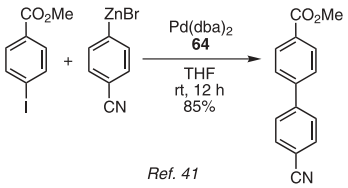

*Ref. 41*

**eq 4**



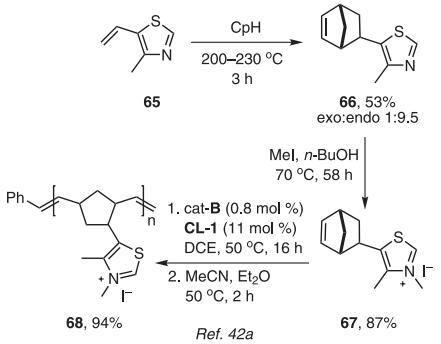

*Ref. 41*

**eq 5**



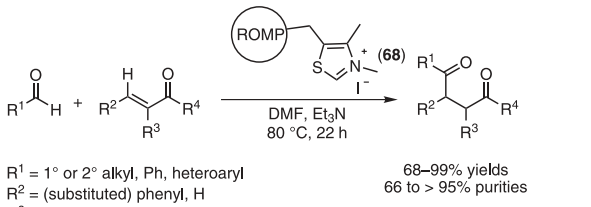

*Ref. 41*

**eq 6**



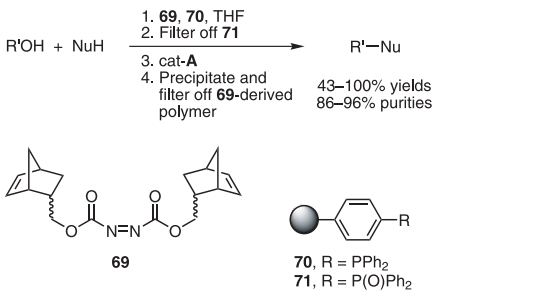

*Ref. 42a*

**Scheme 11.** Preparation of a High-Load, ROMPgel-Supported Thiazolium Iodide.



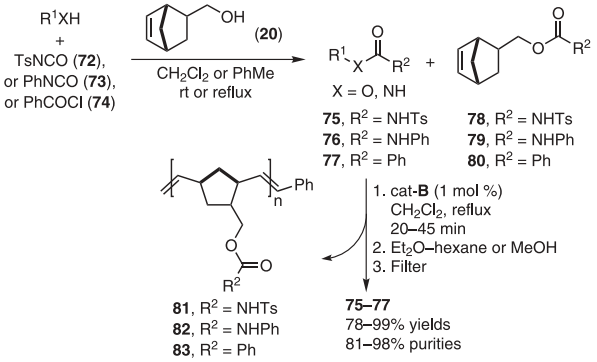

*Ref. 42a*

**eq 7**



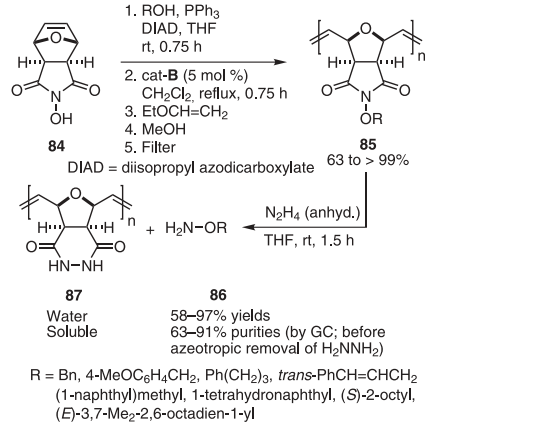

*Ref. 51*

**Scheme 12.** Illustration of the Scavenge–ROMP–Filter Approach to Product Purification.




*Ref. 52*

**Scheme 13.** Scavenge–ROMP–Filter Approach to Purification of Reaction Mixtures.




*Ref. 53*

**Scheme 14.** Illustration of the Capture–ROMP–Release Approach to Product Purification.

reported by Ley;[48] and the precipiton tag developed by Wilcox's group,[49] which takes advantage of the light-induced isomerization and differential solubility of *cis*- and *trans*-stilbenes. When utilized in conjunction with the highly functional group tolerant olefin metathesis catalysts, the norbornene ring system offers attractive possibilities for use as a chemical tag. First, the ring system can be obtained on a large scale and in high yield through the use of Diels–Alder or reductive Heck reactions.[50] Secondly, the ring system is stable to many reaction conditions; and lastly, this strained olefin ring system can be selectively polymerized in the presence of other functional groups, and in some cases other olefins. For these reasons, in situ ROM polymerization is an appealing purification method that is not possible with other polymerization methods.

### 6.1. Reagent Annihilation: Norbornenyl-Tagged DEAD

Barrett was the first to report the use of in situ ROM polymerization of the norbornenyl-tagged azodicarboxylate **69** and polymer-bound triphenylphosphine (**70**) to purify Mitsunobu reactions (**Scheme 12**).[51] Upon completion of the reaction, **71** needed to be filtered away due to the incompatibility of the phosphine oxide polymer **71** with the soon-to-be-added cat-**A**. The hydrazine dicarboxylate byproduct was then polymerized by addition of cat-**A**. Subsequent filtration of the resulting diazodicarboxylate polymer afforded the Mitsunobu products in high yields and purities.

### 6.2. Scavenge–ROMP–Filter

Emergence of the more versatile cat-**B**[14] presented new opportunities for in situ scavenging, whereby norbornenyl-tagging was used to chemically tag electrophiles. Addition of cat-**B** initiated ROM polymerization, which ultimately phase-trafficked the resulting undesired polymeric species out of solution, leaving the reaction products in solution (**Scheme 13**).[52] To this end, an alcohol or an amine was reacted with an excess of an electrophilic reagent. Once the starting nucleophile was consumed, commercially available alcohol **20** was added as a scavenger to sequester excess electrophile. Upon completion of the scavenging event, cat-**B** was added in order to polymerize the scavenged electrophile, **78**–**80**, and excess alcohol **20**. The resulting polymer, **81**–**83**, was filtered away from the reaction products, **75**–**77**, which were subsequently isolated in excellent yields and purities.

### 6.3. Capture–ROMP–Release

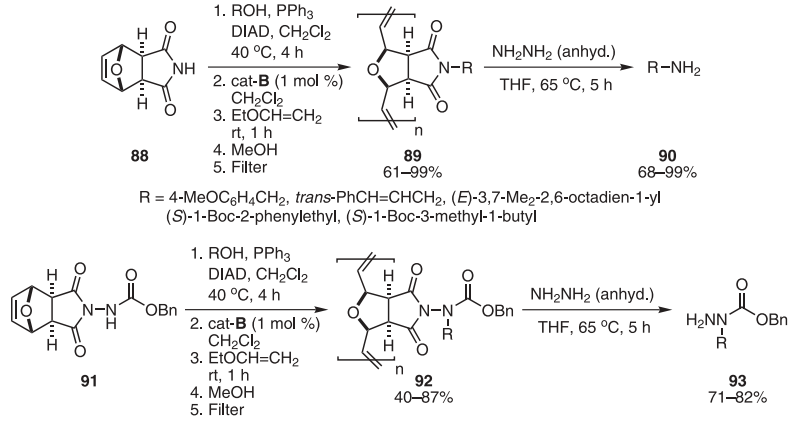
We have applied the in situ polymerization concept to the Mitsunobu reaction by targeting the acidic component/product (**Scheme 14**).[53] Commercially available oxanorbornenyl-tagged *N*-hydroxysuccinimide **84** was reacted with a variety of alcohols under traditional Mitsunobu conditions (DIAD and $PPh_3$). The resulting alkoxysuccinimides were then polymerized with cat-**B** in the presence of DIAD and $Ph_3PO$. The resulting polymers, **85**, were precipitated with MeOH, collected by filtration, and treated with hydrazine to release the desired alkoxyamines, **86**. Surprisingly, cleaved polymer **87** was water-soluble and was thus eliminated through a simple water–ether extraction.

We have also reported a similar strategy for the chromatography-free purification of amines and hydrazine derivatives (**Scheme 15**).[54] Various substituted alcohols were captured onto oxanorbornenyl derivatives **88** and **91** via the Mitsunobu reaction followed by in situ polymerization. Polymers **89** and **92** displayed differential solubility: soluble in organic solvents such as THF, $CH_2Cl_2$, and $CHCl_3$; but insoluble in MeOH. Excess Mitsunobu reagents and byproducts, which were soluble in MeOH, were phase-separated from the insoluble polymers via precipitation of the latter from MeOH, followed by simple filtration. The amines and hydrazine derivatives were cleaved from the polymers by heating at reflux in THF in the presence of hydrazine. Finally, the polymeric byproducts were removed by biphasic extraction ($Et_2O$–$H_2O$) to produce amines **90** and hydrazine derivatives **93** in good yields and purities.

## 7. ROM Polymerization in Supported Synthesis

### 7.1. Vanishing Supports, ROMPspheres, and Soluble Supports

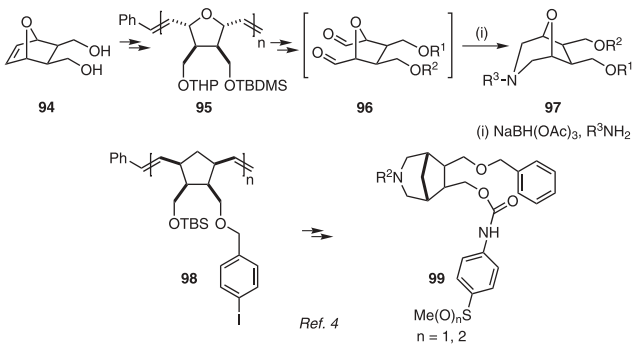
In 1998, Barrett and co-workers devised the concept of polymerizable templates and vanishing supports,[55] as outlined in **Schemes 16** and **17** and in their 2002 review.[4] This work addressed the classical problem of low loading of substrates on a polymer support. In addition, it offered the advantage of allowing chemical modifications to be conducted in a homogeneous environment, thus avoiding the poor solvation typically experienced with solid supports. In this approach, they produced diverse cyclic amines, **97** and **99**, in a strategy that employed late-stage ozonolysis as a means of disassembling the ROM polymer support. Subsequently, Barrett's group utilized two strategies in developing ROMPspheres. In the first, cross-metathesis between vinyl polystyrene and norbornene



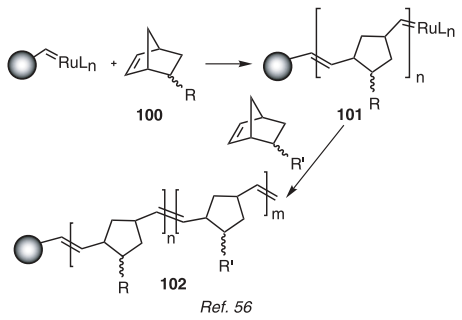

**Scheme 15.** Chromatography-Free Purification Employing the Capture–ROMP–Release Approach.

derivatives afforded high-load ROM polymer supports.[56] In the second approach, shown in Scheme 17, they incubated **100** with cat-**A** to obtain polystyrene-bound ruthenium complex **101**. ROMPsphere **102** was produced via subsequent treatment with norbornenyl monomer, followed by termination with EVE. The ROMPspheres were larger than the original resin, yet still retained their solvent-dependent swelling properties.[4]

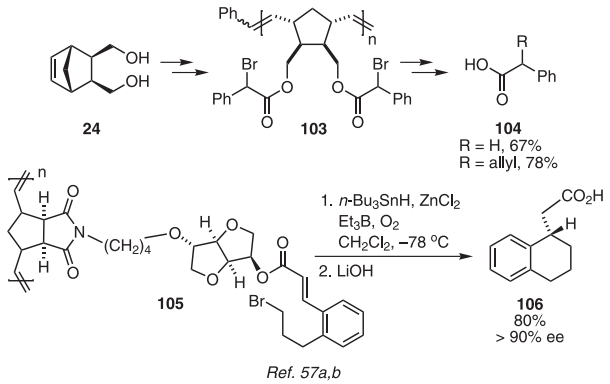
Enholm and co-workers reported the first examples of stereoselective radical reactions on a ROMP-derived, soluble support using norbornenediol **24** to assemble support **103** for subsequent radical allylation en route to **104** (**Scheme 18**).[57]




**Scheme 16.** Barrett's Vanishing Supports.




**Scheme 17.** Barrett's ROMPspheres.




**Scheme 18.** Enholm's High-load, Soluble Supports for Radical Transformations.

Another radical reaction was used in the $Bu_3SnH$-mediated cyclization of **105** which, upon saponification with LiOH, gave the carboxylic acid **106** in good yield. Each soluble support consisted of a radical precursor embedded in each monomer subunit, thus providing a maximum 100% loading capacity.

### 7.2. Ring-Opening-Metathesis–Phase-Trafficking (ROMpt) Synthesis

The aforementioned capture–ROMP–release approach has also been utilized as a means of generating ROM oligomers for subsequent use as soluble supports in multistep reaction sequences (**Scheme 19**).[58] In this strategy, norbornene sulfonamide **107** was subjected to a three-component coupling protocol with chlorosulfonyl isocyanate and an amino acid ester to yield **108**. The tagged norbornenyl monomer was next reacted with cinnamyl alcohol under Mitsunobu conditions. The norbornenyl tagged products were then induced to undergo phase-trafficking purification by in situ polymerization mediated by cat-**B**. Quenching of the polymerization with ethyl vinyl ether, followed by precipitation of the oligomers with methanol, provided oligomers **109**, free of Mitsunobu byproducts. The terminal phenyl group was utilized as a protecting group of the double bond during the ROM polymerization event. Allylation of the soluble oligomer yielded **110**, which was subjected to RCM conditions to generate **111**. Purification was achieved by differential precipitation of the oligomer. Finally, oligomer **111** was treated with 1:1 TFA–$CH_2Cl_2$ to effect the release of cyclic sulfamide **112** from the soluble support, whereby the crude products were passed through a small SPE ($SiO_2$) and eluted with 1:1 hexane–ethyl acetate (49–53% over four steps).

### 7.3. Oxidative Cyclorelease Strategy Using Soluble ROM Polymer Supports

Floreancig and co-workers have also utilized soluble oligonorbornene polymers as supports in an oxidative cyclorelease strategy, where the soluble supports were found to be stable toward redox chemistry (**Scheme 20**).[59] Monomer **113** was polymerized utilizing 5 mol % cat-**A** to provide oligomer **114** in 95% yield. Oligomer **114** was subjected to a three-step sequence of $TiCl_4$–$Ti(O\textit{i}\text{-}Pr)_4$-mediated acetal opening, ruthenium-catalyzed acetic acid addition, and TBS protection to yield enol acetate polymer **115** in high yield. Cyclorelease of **115** with CAN provided **116** as a single stereoisomer in 41% yield and good purity.[59]

### 7.4. Unsaturated ROMP (U-ROMP) Resins

Janda and co-workers have employed a technique termed suspension-ROMP to construct insoluble, spherical resins with good swelling properties for use in solid-phase organic synthesis (**Scheme 21**).[60] It was found that 1 mol % of cross-linker **117** gave optimal results in terms of swelling properties, with alcohol **20** being present in 1 mmol/g theoretical loading. The swelling properties of unsaturated ROMP resin (U-ROMP) **118** were intermediate between those of the Merrifield and *J*anda*J*el™ resins.

U-ROMP resin **118** was subjected to hydrogenation, bromination, chlorination, and hydrofluorination conditions to remove the olefinic backbone. The authors were then able to use these new norbornene-based resins for reactions that are incompatible with traditional cross-linked polystyrene resins (i.e., Friedel–Crafts acylations and aromatic nitration). They also reported utilizing these resins for two multistep SPS reaction sequences: the synthesis of benzimidazole and hydantoin derivatives.[60]

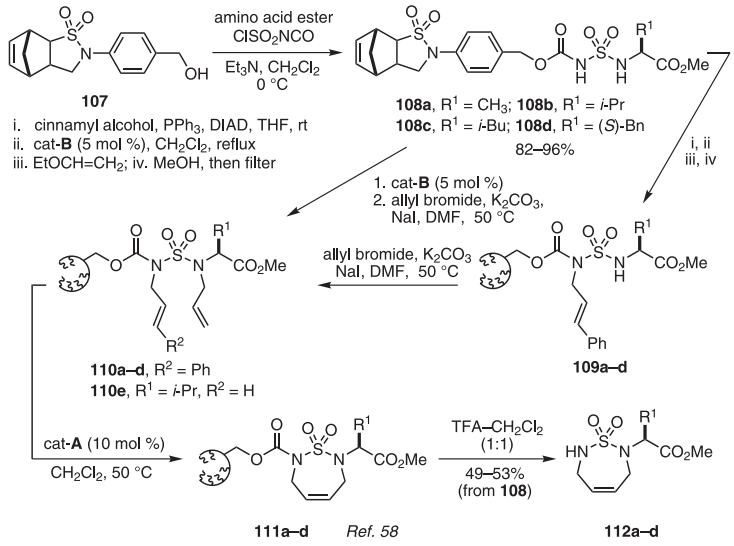
## 8. New Strategies Employing ROM Polymerization

### 8.1. Polymer-on-Polymer Approach

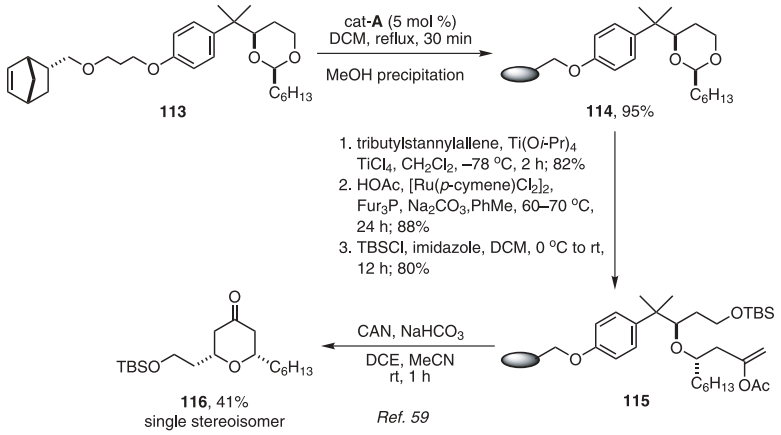
Recently, we have dramatically demonstrated the power of soluble ROM polymers with the realization of the first polymer-on-polymer Mitsunobu reaction, in which a polymeric phosphine is used *simultaneously* with a polymeric azodicarboxylate (**Scheme 22**).[61] Historically, the Mitsunobu reaction has faced a number of purification challenges,[62] and popular opinion has asserted that a multipolymer, solid-on-solid approach is not feasible.[62b] The use of high-load, short, and soluble oligomers, however, circumvents classical problems associated with solid-on-solid approaches. The oligomeric triphenylphosphine (OTPP, **119**) was prepared through polymerization of phosphine **48** with cat-**B** (see Scheme 22). The required hydrogenated oligomeric azodicarboxylate (HO-DEAD, **121**) was prepared from alcohol **120**. The hydrazine dicarboxylate generated from **120** was polymerized with cat-**F**, and the resulting polymer hydrogenated in the presence of cat-**A**, prior to oxidation with $Br_2$, to give **121**. Both **119** and **121** display a wide solubility profile: they are soluble in benzene, toluene, $CH_2Cl_2$, $CHCl_3$, and THF; but insoluble in MeOH, $Et_2O$, and heptane. $^{31}P$ NMR analysis revealed that the two polymers were interacting to generate the Mitsunobu products. In addition, application of this approach to several other substrates, as well as comparison experiments with other polymeric reagents, have been described.[61]

### 8.2. ROMPgel Beads in IRORI℠ Format

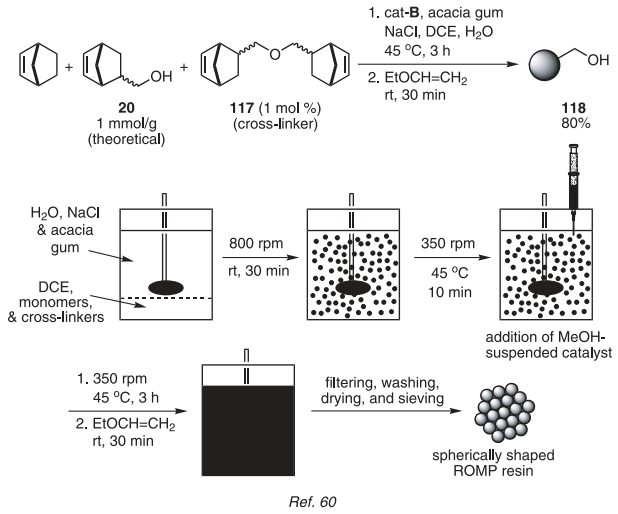
Roberts recently integrated the convenience of handling polystyrene beads in an IRORI℠ KAN™ format with high-load ROMPgels to generate a reusable acylating agent for parallel synthesis (**Scheme 23**).[63] The high load and site accessibility of the ROMPgel resin was not compromised by incorporation into a bead, while the convenience of a KAN™ format was added. Thus, linker **122** was synthesized from 4-iodophenol via hydroarylation of norbornadiene. Linker **122** was attached to Wang resin (1.1 mmol/g) utilizing Mitsunobu conditions to afford linker resin **123** in 79% yield. The norbornene moiety in the linker was subjected to ROM polymerization conditions with cat-**A**. After washing the resin to remove excess unreacted catalyst in solution, it was treated with a large excess of monomer **124** for 48 h yielding resin **125** in 94% yield with a loading of 2.92 mmol/g. Treating resin **125** with an excess of benzylamine and washing with 15%



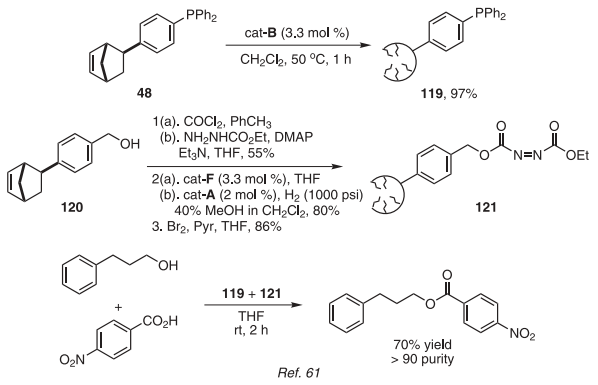

**Scheme 19.** Application of Ring-Opening-Metathesis–Phase-Trafficking (ROMpt) in Supported Synthesis.



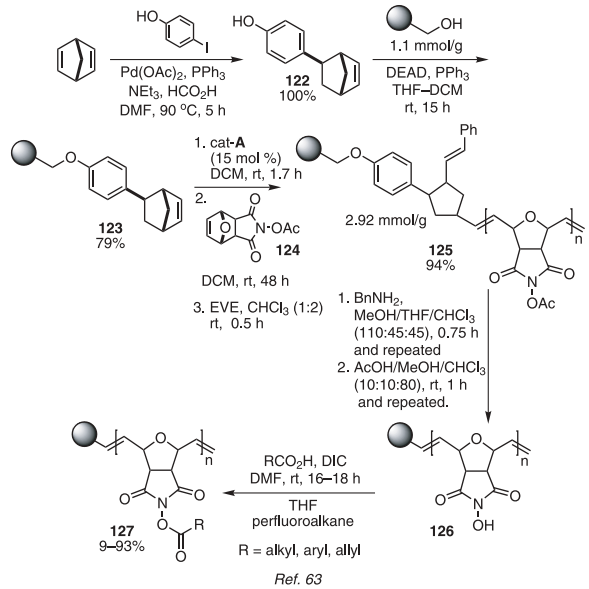

**Scheme 20.** Application of Soluble Oligonorbornene Polymers as Supports in an Oxidative Cyclorelease Strategy.




**Scheme 21.** Preparation of Spherical, Unsaturated ROMP (U-ROMP) Resins by Suspension-ROMP.




**Scheme 22.** Application of the Polymer-on-Polymer Approach in the Mitsunobu Reaction.




**Scheme 23.** ROMPgel Beads in IRORI℠ Format: High-Load and Reusable Acylating Agents.

AcOH in dichloromethane generated *N*-hydroxysuccinimide resin **126**, which was coupled with a variety of carboxylic acids to produce an array of high-load acylating agents **127**.

## 9. Conclusions

This review has outlined new developments of ROM polymerization in facilitated synthesis. From its beginning, ROM polymerization has advanced as a general and viable means of immobilizing reagents, catalysts, and supports, and will undoubtedly expand beyond these borders in the near future. The continued development of well-defined, homogeneous catalysts can only add to the growing utility of this enabling technology, and thus its potential has yet to be fully realized. In addition, automated protocols have yet to be fully adapted to this technology, which will only further strengthen its role in combinatorial chemistry.

## 10. Acknowledgements

This work was partially funded by the National Science Foundation (NSF Career 9984926), the University of Kansas Research Development Fund (KU-RDF), and the National Institutes of Health (KU Chemical Methodologies and Library Development Center of Excellence, P50 GM069663). Additional funding was provided by the State of Kansas and the National Institutes of Health Center for Cancer Experimental Therapeutics (NIH-COBRE P20 RR15563, Core-D). The authors thank Neogenesis Pharmaceuticals, Inc., for providing generous postdoctoral support (M. Z.), the ACS Division of Organic Chemistry for a Nelson J. Leonard Fellowship sponsored by Organic Syntheses, Inc. (A. M. H.), and Materia, Inc., for supplying catalysts and helpful discussions.

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## About the Authors

**Andrew M. Harned** graduated from Virginia Polytechnic Institute and State University (Virginia Tech) in 1999 with a B.S. in biochemistry. While an undergraduate, he worked in the laboratories of Professors Neal Castagnoli, Jr., and Michael Calter. As a graduate student at the University of Kansas, he studied under the guidance Professor Paul R. Hanson. While at KU, he was supported by an NIH Dynamic Aspects of Chemical Biology Training Grant and an American Chemical Society Division of Organic Chemistry Nelson J. Leonard Fellowship sponsored by Organic Syntheses, Inc. In the fall of 2004, he assumed a postdoctoral position in the research group of Professor Brian M. Stoltz at the California Institute of Technology.

**Mianji Zhang** received his M.S. degree in organic chemistry in 1992 from Nankai University (China). After working in Tianjin University in China for five years, he joined Professor Robert T. LaLonde's group at the State University of New York, College of Environmental Science & Forestry (SUNY-ESF) in 1997. He worked on the synthesis of antitumor drug candidates and completed the requirements for his Ph.D. degree in 2002. He is currently a postdoctoral research associate working on the development of ROMP-derived high-load reagents under the guidance of Professor Paul R. Hanson at the University of Kansas.

**Punitha Vedantham** obtained her master's degree in 1996 from the Indian Institute of Technology in Delhi, India. Her doctoral studies on natural product synthesis and organic photochemistry were carried out at the Indian Institute of Technology, Bombay, under the guidance of Professor Vishwakarma Singh. She is currently working with Professor Paul R. Hanson on ROM polymerization and facilitated synthetic methods for use in combinatorial chemistry.

**Shubhasish Mukherjee** graduated from the Indian Institute of Technology, Delhi, with an M.Sc. degree in chemistry. He received his Ph.D. degree in chemistry in 2000 from the University of Delhi, India, for research and studies carried out under the guidance of Professor V. S. Parmar. He worked for a year in the area of bioconjugate chemistry with Professor Kalle Levon at The Polytechnic University, New York. In 2001, he moved to the University of Kansas, where he is currently working for Professor Paul R. Hanson in the area of ROM polymerization and phosphorus chemistry.

**Russell H. Herpel** graduated from Missouri Western State College in 1997 with an ACS certified B.S. degree in chemistry. In the summer of 1996, he worked for Professor Rich Givens at the University of Kansas in the National Science Foundation Research Experience for Undergraduates (NSF-REU) Program. He then carried out graduate-level studies at the University of Kansas under the guidance of Professors Rich S. Givens (1997–2000) and Paul R. Hanson (2002–2004). In the fall of 2004, he assumed a position at Highland Community College as a chemistry instructor.

**Daniel L. Flynn** received his B.S. degree in pharmacy (1977) and his Ph.D. degree in medicinal chemistry (1981, with Professor Lester Mitscher) from the University of Kansas. After completing postdoctoral studies at Indiana University with Professor Paul Grieco, he joined Warner-Lambert/Parke-Davis Pharmaceuticals in 1983. In 1988, he moved to Searle Pharmaceuticals, where he rose to the positions of Section Head, Medicinal Chemistry, and Research Fellow over a ten-year period. Between 1998 and 2002, he was engaged in research at Amgen, Inc., and Millennium Pharmaceuticals as senior director of chemistry. In 2002, he founded Deciphera Pharmaceuticals, Inc., where he has remained as its president and CEO. His research interests include phase-trafficking approaches to organic synthesis and purification, chemical proteomics, and innovative ways to selectively control enzymatic activity by binding small molecules onto novel allosteric sites.

**Paul R. Hanson** received his B.S. degree, with a major in chemistry, in 1985 from Luther College (Decorah, IA) under the direction of the late Adrian Docken. In 1993, he obtained his Ph.D. in chemistry from the University of Minnesota under the mentorship of Thomas R. Hoye. From 1993 to 1996, he served as an NIH postdoctoral fellow at Stanford University under the guidance of Barry M. Trost. In 1996, he was hired as an assistant professor of chemistry at the University of Kansas and was promoted to associate professor in 2001. His current research interests lie in the development of new approaches to the synthesis of biologically and synthetically useful phosphorus and sulfur heterocycles, natural product synthesis, and the design of high-load oligomers with tunable properties for use in facilitated synthesis.

# Rasta Resins from Sigma-Aldrich

Solid-supported reagents have been utilized in a variety of ways to facilitate combinatorial synthesis. They are also being used in solution-phase parallel synthesis and multistep organic synthesis as scavengers to ease reaction workup and product purification.[1] One important specification for solid-supported reagents is loading. A high loading for scavenger resins allows for decreased reaction workup volume.

Sigma-Aldrich is proud to offer a line of resins called Rasta Resins. These resins have increased loading with minimal swelling. For most solid-supported reagents, the functional groups are attached to polystyrene that is cross-linked with divinylbenzene. A nonpolar solvent is normally required to swell the polystyrene beads, which allows more attachment sites to be exposed. The unique bead structure of the Rasta Resin has a long and linear polymer chain connected to a nonfunctionalized, cross-linked core that allows for increased functional-group loading, spacing, and accessibility with minimal swelling.[2]

One example of increased loading is isocyanate on Rasta Resin. The maximum loading for methyl isocyanate on polystyrene is typically 1.0–1.5 mmol/g; for isocyanate on Rasta Resin it is 2.0 mmol/g.

Sigma-Aldrich currently offers five Rasta Resins. If you would like to suggest a Rasta Resin that we do not offer, please email us at **DrugDiscovery@sial.com**.

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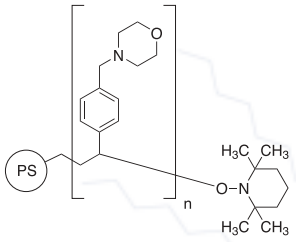
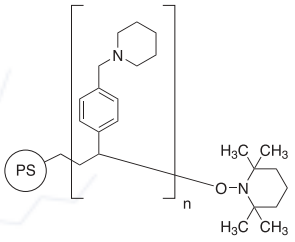
## Rasta Resin Bases

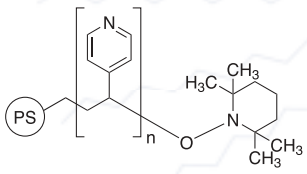
**64,359-9**
Morpholine on Rasta Resin
50–100 mesh, 5.0 mmol/g loading, 1% cross-linking
5 g
25 g




**64,360-2**
Piperidine on Rasta Resin
50–100 mesh, 5.0 mmol/g loading, 1% cross-linking
5 g
25 g

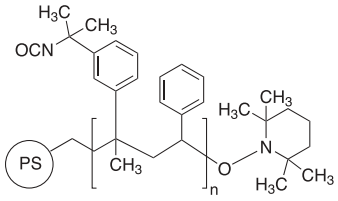



**65,545-7**
Pyridine on Rasta Resin
50–100 mesh, 6.9 mmol N/g loading, 1% cross-linking
5 g
25 g

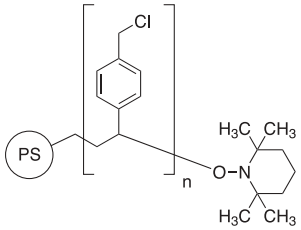



## Rasta Resin Scavengers

**56,966-6**
Isocyanate on Rasta Resin
100–200 mesh, 2.0 mmol/g loading, 1% cross-linking
5 g
25 g



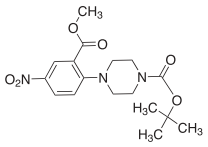

**64,366-1**
Chloromethyl on Rasta Resin
50–100 mesh, 5.0 mmol/g loading, 1% cross-linking
5 g
25 g



# New Piperazine Building Blocks from Sigma-Aldrich

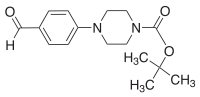
### 1-Boc-4-(2-methoxycarbonyl-4-nitrophenyl) piperazine, 97%

**65,193-1** 1 g
MW 365.38 5 g
$C_{17}H_{23}N_3O_6$



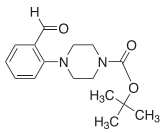
### 1-Boc-4-(4-formylphenyl)piperazine, 97%

**65,142-7** 1 g
MW 290.36 5 g
$C_{16}H_{22}N_2O_3$



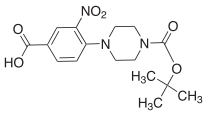
### 1-Boc-4-(2-formylphenyl)piperazine, 97%

**65,151-6** 1 g
MW 290.36 5 g
$C_{16}H_{22}N_2O_3$



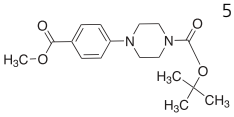
### 4-(Boc-piperazin-1-yl)-3-nitrobenzoic acid, 97%

**65,192-3** 1 g
MW 351.35 5 g
$C_{16}H_{21}N_3O_6$



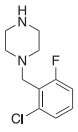
### 1-Boc-4-(4-methoxycarbonylphenyl)piperazine, 97%

**65,238-5** 1 g
MW 320.19 5 g
$C_{17}H_{24}N_2O_4$



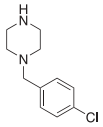
### 1-(2-Chloro-6-fluorobenzyl)piperazine, 98%

**65,015-6** 1 g
MW 228.69 10 g
$C_{11}H_{14}ClFN_2$



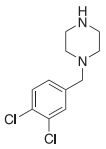
### 1-(4-Chlorobenzyl)piperazine, 98%

**65,021-8** 1 g
MW 210.70 5 g
$C_{11}H_{15}ClN_2$



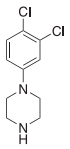
### 1-(3,4-Dichlorobenzyl)piperazine, 97%

**64,426-9** 1 g
MW 245.15 5 g
$C_{11}H_{14}Cl_2N_2$



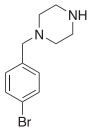
### 1-(3,4-Dichlorophenyl)piperazine, 99%

**55927** 5 g
MW 231.12 25 g
$C_{10}H_{11}Cl_2N_2$



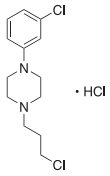
### 1-(4-Bromobenzyl)piperazine, 97%

**04695** 1 g
MW 255.15 5 g
$C_{11}H_{15}BrN_2$



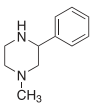
### 1-(3-Chlorophenyl)-4-(3-chloropropyl)piperazine monohydrochloride, 97%

**16843** 5 g
MW 309.66 25 g
$C_{13}H_{19}Cl_3N_2$



### 1-Methyl-3-phenylpiperazine, 97%

**64,843-4** 1 g
MW 176.26 5 g
$C_{11}H_{16}N_2$

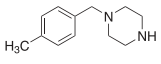


### 2-Phenylpiperazine, 96%

**63,864-1** 5 g
MW 162.23 25 g
$C_{10}H_{14}N_2$

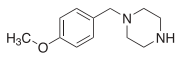
### 1-(4-Methylbenzyl)piperazine, 97%

**64,617-2** 1 g
MW 190.28 5 g
$C_{12}H_{18}N_2$



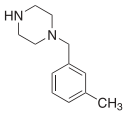
### 1-(4-Methoxybenzyl)piperazine, 97%

**64,615-6** 1 g
MW 206.28 5 g
$C_{12}H_{18}N_2O$



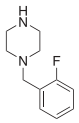
### 1-(3-Methylbenzyl)piperazine, 97%

**64,852-3** 1 g
MW 190.28 5 g
$C_{12}H_{18}N_2$



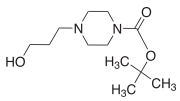
### 1-(2-Fluorobenzyl)piperazine, 96%

**65,024-2** 1 g
MW 194.25 5 g
$C_{11}H_{15}FN_2$



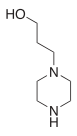
### 1-Boc-4-(3-hydroxypropyl)piperazine, 97%

**64,346-7** 5 g
MW 244.33 25 g
$C_{12}H_{24}N_2O_3$



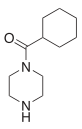
### 1-(3-Hydroxypropyl)piperazine, 97%

**64,164-2** 1 g
MW 144.21 5 g
$C_7H_{16}N_2O$



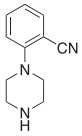
### 1-(Cyclohexylcarbonyl)piperazine, 97%

**64,712-8** 1 g
MW 196.29 5 g
$C_{11}H_{20}N_2O$



### 1-(2-Cyanophenyl)piperazine, 99%

**56,718-3** 1 g
MW 187.24 5 g
$C_{11}H_{13}N_3$



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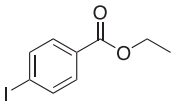
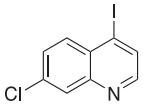
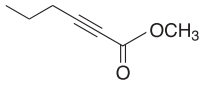
**Ethyl 4-iodobenzoate, purum, 98%**
**75022** 10 g



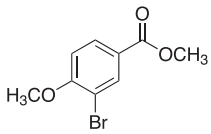
**7-Chloro-4-iodoquinoline, 97%**
**64,738-1** 1 g, 10 g



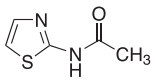
**Methyl 2-hexynoate, 98%**
**64,909-0** 5 g, 25 g



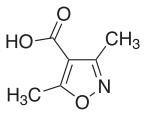
**Methyl 3-bromo-4-methoxybenzoate, 98%**
**64,757-8** 1 g, 10 g



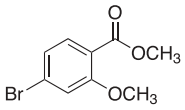
**2-Acetamidothiazole, purum, 98%**
**65,295-4** 5 g



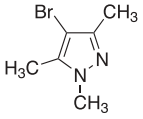
**3,5-Dimethylisoxazole-4-carboxylic acid, puriss., 98%**
**65,287-3** 1 g, 5 g



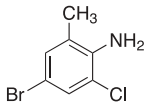
**Methyl 4-bromo-2-methoxybenzoate, puriss., 98%**
**65,309-8** 1 g, 10 g



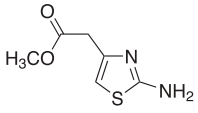
**4-Bromo-1,3,5-trimethylpyrazole, 98%**
**64,766-7** 1 g, 5 g



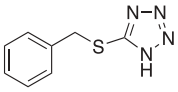
**4-Bromo-2-chloro-6-methylaniline, puriss., 98%**
**65,293-8** 5 g, 25 g



**Methyl (2-amino-4-thiazolyl)acetate, 98%**
**64,972-4** 1 g, 5 g



**5-(Benzylthio)-1*H*-tetrazole solution, ~0.25 M in acetonitrile**
**16998** 100 mL, 500 mL



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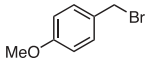
# More New Products from Aldrich R&D

## Organic Reagents and Building Blocks

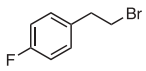
### 4-Methoxybenzyl bromide

**56,128-2** 5 g
$C_8H_9BrO$



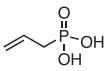

### 4-Fluorophenethyl bromide

**65,200-8** 5 g
$C_8H_8BrF$



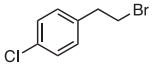

### Allylphosphonic acid

**65,398-5** 250 mg, 1 g
$C_3H_7O_3P$



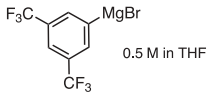

### 4-Chlorophenethyl bromide

**65,199-0** 5 g
$C_8H_8BrCl$



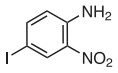

### 3,5-Bis(trifluoromethyl)phenylmagnesium bromide solution, 0.5 M in THF

**63,905-2** 50 mL
$C_7H_4BrF_6Mg$




### 4-Iodo-2-nitroaniline

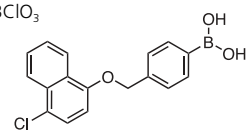
**65,410-8** 1 g, 10 g
$C_6H_5IN_2O_2$




## Boronic Acids and Esters

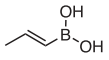
### 4-[(4′-Chloro-1-naphthyloxy)methyl]phenylboronic acid

**64,565-6** 1 g, 5 g
$C_{17}H_{14}BClO_3$



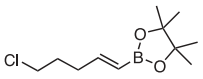

### *trans*-Propenylboronic acid

**57,663-8** 1 g, 5 g
$C_3H_7BO_2$



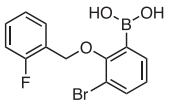

### (*E*)-5-Chloro-1-pentenylboronic acid, pinacol ester

**65,206-7** 5 g, 25 g
$C_{11}H_{20}BClO_2$



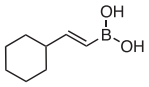

### 3-Bromo-2-(2′-fluorobenzyloxy)phenylboronic acid

**64,583-4** 1 g, 5 g
$C_{13}H_{11}BBrFO_3$



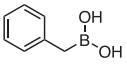

### 2-Cyclohexylvinylboronic acid

**59,625-6** 1 g, 10 g
$C_8H_{15}BO_2$



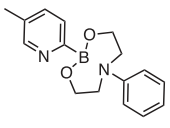

### Benzylboronic acid

**65,235-0** 1 g, 5 g
$C_7H_9BO_2$



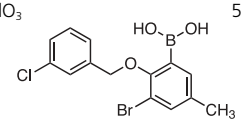

### 5-Methyl-2-pyridineboronic acid, *N*-phenyldiethanolamine ester

**64,882-5** 500 mg, 1 g, 5 g
$C_{16}H_{19}BN_2O_2$



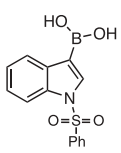

### 3-Bromo-2-(3′-chlorobenzyloxy)-5-methylphenylboronic acid

**64,549-4** 1 g, 5 g
$C_{14}H_{13}BBrClO_3$



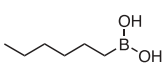

### 1-(Phenylsulfonyl)-3-indoleboronic acid

**56,387-0** 1 g
$C_{14}H_{12}BNO_4S$




### Hexylboronic acid

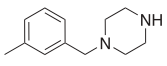
**65,159-1** 1 g, 5 g
$C_6H_{15}BO_2$



## Heterocyclic Building Blocks

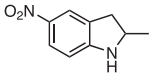
### 1-(3-Methylbenzyl)piperazine, 97%

**64,852-3** 1 g
$C_{12}H_{18}N_2$ 5 g



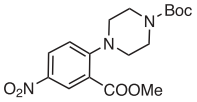
### 2-Methyl-5-nitroindoline

**64,984-8** 1 g
$C_9H_{10}N_2O_2$ 5 g



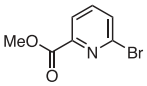
### Methyl 2-(4-Boc-piperazin-1-yl)-5-nitrobenzoate

**65,193-1** 1 g
$C_{17}H_{23}N_3O_6$ 5 g



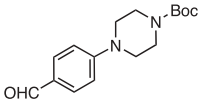
### Methyl 6-bromo-2-pyridinecarboxylate, 97%

**65,011-0** 1 g
$C_7H_6BrNO_2$ 5 g



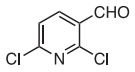
### 1-Boc-4-(4-formylphenyl)piperazine

**65,142-7** 1 g
$C_{16}H_{22}N_2O_3$ 5 g



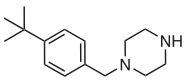
### 2,6-Dichloropyridine-3-carboxaldehyde

**65,195-8** 1 g
$C_6H_3Cl_2NO$ 5 g



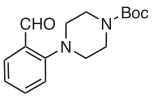
### 1-(4-*tert*-Butylbenzyl)piperazine

**65,012-9** 1 g
$C_{15}H_{24}N_2$ 5 g



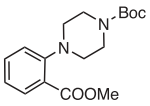
### 1-Boc-4-(2-formylphenyl)piperazine

**65,151-6** 1 g
$C_{16}H_{22}N_2O_3$ 5 g



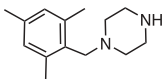
### 1-Boc-4-(2-methoxycarbonylphenyl)piperazine

**65,237-7** 1 g
$C_{17}H_{24}N_2O_4$ 5 g



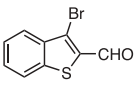
### 1-(2,4,6-Trimethylbenzyl)piperazine

**65,168-0** 1 g
$C_{14}H_{22}N_2$ 5 g



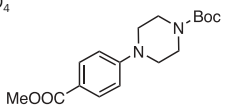
### 3-Bromobenzothiophene-2-carboxaldehyde

**65,153-2** 1 g
$C_9H_5BrOS$ 5 g



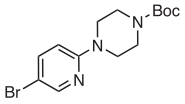
### 1-Boc-4-(4-methoxycarbonylphenyl)piperazine

**65,238-5** 1 g
$C_{17}H_{24}N_2O_4$ 5 g



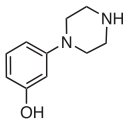
### 4-Boc-1-(5-bromo-2-pyridyl)piperazine

**65,376-4** 1 g
$C_{14}H_{20}BrN_3O_2$ 5 g



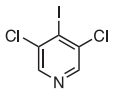
### 1-(3-Hydroxyphenyl)piperazine

**65,167-2** 1 g
$C_{10}H_{14}N_2O$ 5 g



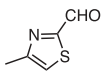
### 3,5-Dichloro-4-iodopyridine, 97%

**65,313-6** 1 g
$C_5H_2Cl_2IN$ 10 g



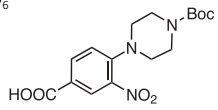
### 4-Methyl-2-thiazolecarboxaldehyde

**64,974-0** 1 g
$C_5H_5NOS$ 5 g



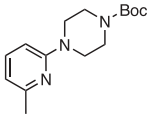
### 4-(4-Boc-piperazin-1-yl)-3-nitrobenzoic acid

**65,192-3** 1 g
$C_{16}H_{21}N_3O_6$ 5 g



### 4-Boc-1-(6-methyl-2-pyridyl)piperazine

**65,375-6** 1 g
$C_{15}H_{23}N_3O_2$ 5 g



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# Sigma-Aldrich Hot Plate Stirrer

## and Automatic Temperature Controller

This new, low-profile, ceramic-top hot plate stirrer offers optimal temperature control when used with the temperature controller listed below. The 230 V unit includes both European- and U.K.-style plugs. 3-year warranty.

- Stirring capacity: 13 L
- Speed range: 150 to 1,200 rpm
- Temp. range: ambient to 450 °C
- Ceramic top plate: 30 $in.^2$ (5.5 × 5.5 inches)
- CE compliant

### Sigma-Aldrich hot plate stirrer

| | |
|---|---|
| 115 Volts | **Z55,784-6** |
| 230 Volts | **Z55,818-4** |

### Digital temperature controller

Fuzzy logic control provides constant feedback to hot plate to ensure perfect temperature control of the medium without overshooting the set temperature. Connects to above stirring hot plates with a DIN 12878 socket. Includes a 250-mm (l) × 3-mm (o.d.) stainless steel temperature probe.

**Z55,785-4**

### Mounting hardware

Order one of each item to mount temperature controller onto hot plate stirrer.

| | |
|---|---|
| *Vertical support rod*<br>stainless steel rod threads into top of stirrer base | **Z40,356-3** |
| *Boss head clamp* | **Z40,357-1** |
| *Holding rod for controller* | **Z40,359-8** |

### Sigma-Aldrich hot plate stirrer sets

Sets contain one each of the following items: hot plate stirrer, digital temperature controller, vertical support rod, boss head clamp, and holding rod for controller.

| | |
|---|---|
| Hot plate stirrer set, 115 V | **Z55,854-0** |
| Hot plate stirrer set, 230 V | **Z55,855-9** |

***Save 20% when purchasing a hot plate stirrer set***

Mention promo code 993 when placing order before June 30, 2005.

# Polyurea-Encapsulated Palladium Catalysts: The Development and Application of a New and Versatile Immobilized-Homogeneous-Catalyst Technology§

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## Outline



## 1. Introduction

The cross-coupling of organic halides with organometallic reagents mediated by transition-metal catalysts has become a pivotal approach for carbon–carbon-bond formation. Organotin,[1] organoboron,[2] organozinc,[3] and organosilicon[4] are all useful precursors that are commonly employed in palladium-catalyzed cross-couplings.

The need for a practical and economic translation of these laboratory methods into large-scale manufacturing operations, coupled with the drive for clean manufacturing processes, have led to the development of new techniques for reagent and catalyst immobilization. These new techniques allow for the efficient recovery and reuse of the catalyst.[5] For example, the pharmaceutical industry anticipates ever more demanding API targets that require ever lower levels of metal residues from reaction catalysts.

The traditional heterogeneous transition-metal catalyst consists of a metal adsorbed on a variety of high-surface-area support materials such as silica, alumina, calcium carbonate, barium sulfate, powdered KF with $Al_2O_3$,[6a] poly(ethyleneimine) on alumina[6b] or silica,[6c] and so on. For these traditional adsorbed-

metal supports, the usual role of the support is to extend the surface area of the metal, although the nature of the support can significantly alter the rate and course of a chemical reaction.

In recent years, there has been significant development work reported on the synthesis and use of supported transition-metal catalysts[7a] produced by coordination of the metal to an immobilized ligand.[7b] These catalyst systems are often referred to as "supported" or "polymer-anchored" homogeneous catalysts. For example, Fenger and Le Drian introduced a polystyrene-supported palladium catalyst for use in the Suzuki cross-coupling reaction.[8] More recently, Ikegami and co-workers have reported a supported palladium catalyst for the Suzuki–Miyaura reaction, which is based on the non-cross-linked amphiphilic copolymer poly(*N*-isopropylacrylamide-*co*-4-(diphenylphosphino)styrene).[9,10] Industrial activity in this area has been led by workers at Johnson Matthey, who, in collaboration with Oy Smoptech, have developed immobilized, homogeneous palladium catalysts through the use of polyethylene fibers with grafted phosphine ligands.[11]

In general, these approaches require the synthesis of polymer-bound ligands either through copolymerization of a ligand monomer or postgrafting of a ligand onto a preformed polymer matrix. Such methodologies tend to be lengthy and expensive, and there can be problems associated with leaching and reactivity of the resulting catalyst.

An alternative approach for entrapping homogeneous catalysts within a polymeric coating has been developed by Kobayashi and co-workers.[12–14] Microcapsules of polymer-coated catalyst are formed upon cooling a homogeneous solution of the catalyst and a polymer or copolymer. This technique was exploited in the preparation of polystyrene-coacervated $OsO_4$,[12] $Pd(Ph_3)_4$,[13] and $Sc(OTf)_3$.[14] However, Schager and Bonrath reported that the coacervated $Sc(OTf)_3$ catalyst could not be recovered following use, and that there was evidence for leaching of the catalyst. The authors concluded that the catalytically active compound works as a homogeneous species.[15] More recently, Kobayashi and co-workers have further developed this technique by building a reactive oxirane functionality into the copolymer.[16] In this case, following coacervation of the homogeneous catalyst, the copolymer can be cross-linked thermally to form more chemically resistant cross-linked microcapsules. This technique has been exploited to form so-called "polymer-incarcerated" homogeneous $Pd(Ph_3)_4$ catalysts.[16]

Various other methods and materials have been described in the literature for entrapping homogeneous metal complexes and metal nanoclusters including sol-gel materials,[17] dendrimers,[18] and polyoxyalkylene resins.[19]

The purpose of this article is to review the area of microencapsulated palladium catalysts prepared by interfacial polymerization, which promises to be one of the most useful developments for immobilizing homogeneous catalysts to have originated over the past few years. We have, in collaboration with Professor Steven Ley, pioneered the technique based on interfacial microencapsulation to immobilize homogeneous transition-metal salts, and have demonstrated the application of these as versatile catalysts. This review will cover all aspects of catalyst preparation, physical properties, and applications.

## 2. Microencapsulation

In 2002, Ley and co-workers first reported the use of interfacial microencapsulation to immobilize homogeneous catalysts, suggesting that it might solve problematic limitations of previous approaches.[20] Microencapsulation is a process for entrapping materials within a shell or coating, which is typically polymeric in nature. Microencapsulation is widely practiced industrially and has found use in such diverse applications as drug delivery systems,[21] radiation therapies,[22] cell entrapment,[23] and the controlled release of pesticides.[24,25]

Ley utilized the interfacial microencapsulation method, which involves dispersing an organic phase (consisting of the material(s) being encapsulated and reactive multifunctional monomers or oligomers, and typically containing a solvent) into an aqueous phase containing colloid stabilizers, dispersants and, optionally, salts and chain extenders. Upon dispersion, the reactive groups at the oil–water interface undergo spontaneous in situ polymerization to form the microcapsule walls. The walls consist of a highly cross-linked polymer network, which entraps the material within. The permeability and size of the microcapsules, and the coordinating properties of the matrix can be tuned by selecting the type of wall-forming oligomer or monomer, type and quantity of porogenic (i.e., organic) solvent, agitation conditions, chain extenders, and other additives. The polyurea matrix was selected, because of its ability to ligate transition-metal salts, which was considered important for both efficient microencapsulation and subsequent retainment of the metal within the matrix when used as a catalyst.[20] It was also considered that the polyurea matrix would be relatively inert to chemical modification and give a physically robust material. In addition, the process facilitates a cost-effective method of production, which is an important consideration if the catalysts are to be utilized for industrial-scale manufacturing.

## 3. Catalyst Preparation

The method described by Ley to form the microcapsules involves the dispersion of a solution of an aromatic polyfunctional isocyanate and palladium acetate in dichloroethane into water containing a combination of industrial colloid stabilizers and surfactants.[20] The oil-in-water dispersion is obtained under medium shear stirring to give oil droplets in the 20–250-μm size range. Once the correct oil droplet size distribution is obtained, the polymerization is initiated by heating (**Figure 1**).[20] This causes some isocyanate groups at the oil–water interface to hydrolyze to the amine (via the unstable carbamic acid), which immediately reacts further intermolecularly with nonhydrolyzed isocyanate to form the urea-linked polymeric matrix (**Scheme 1**).[20] The resulting polyurea microcapsules are typically hard, porous, highly cross-linked spheres with a particle size average around 150 μm (**Figure 2a**). The beads are washed with water and organic solvents to remove stabilizers, loosely coordinated palladium, and any low-molecular-weight matrix material.

In addition to microencapsulation of Pd(II) salts, typically $Pd(OAc)_2$, Ley also reported the successful encapsulation of Pd(0) nanoparticles stabilized by tetraoctylammonium bromide.[20] Following solvent washing to remove the stabilizers, transmission-electron-microscopic (TEM) analysis of the microcapsules revealed the presence of palladium nanoparticles of 5 nm average diameter, suggesting that the nanoparticles were being stabilized by the polyurea matrix.

### 3.1. Microcapsule Morphology

Scanning- and transmission-electron-microscopic studies showed the interior of the spherical microcapsules to be made up of a uniform porous microstructure with no evidence for the core–shell morphology (**Figures 2b** and **2c**). The energy dispersive X-ray (EDX) pattern from SEM analysis of ultramicrotone cross sections of the microcapsules showed a homogeneous distribution of Pd throughout the cross-sectional area (**Figure 2d**). Analysis of

all X-rays coming off the microcapsule section showed evidence for Pd, Cl, N, O, and C, where Cl is derived from the solvent used in the preparation process and, as expected, shows a higher concentration in the center of the microcapsule.

### 3.2. Microcapsule Porosity

The porosity of the microcapsule is controlled—as in the case of other macro- and mesoporous organic polymers—by the composition of the organic phase (functionality of the isocyanate in this case) and, in particular, the ratio of porogenic solvent to aromatic isocyanate. Ley reported that the ratio of isocyanate to solvent was normally 40:60 (w/w), and the quantity of palladium acetate microencapsulated in dry microcapsules was 0.4 mmol/g as determined by inductively coupled plasma (ICP) analysis.[20] In the rest of this review, the microcapsule products will be described by the following shorthand: **metal loading** (mmol/g), **metal type**, **EnCat™**, **isocyanate in organic phase** (%). Thus, 0.4 Pd(II) EnCat™ 40 defines a polyurea-microencapsulated palladium(II) catalyst with an oxidation state of +2, where the organic phase had contained 40% isocyanate monomer.

The porosity of the 0.4 Pd(II) EnCat™ 40 microcapsules was determined in both the dry and solvent-wet states. In the dry state, the Brunauer–Emmett–Teller (BET) $N_2$ adsorption method gave a surface area of only 0.07 $m^2/g$ and an isotherm shape characteristic of a nonporous or macroporous material. Mercury intrusion porosimetry showed no evidence for accessible macropores in the dry resin.[26] Similar results were obtained for analogous microcapsules prepared with 30% polyfunctional isocyanate in the organic phase (0.4 Pd(II) EnCat™ 30).[26a] However, for a catalyst designed to work in solvents, the porosity of the solvent-swollen matrix is of more interest. An indication of how this porosity might change with solvent was obtained by measuring the percent gain in weight of a range of microencapsulated catalysts, including 0.4 Pd(II) EnCat™ 40, following immersion in various solvents at room temperature for over two hours (**Table 1**).[26a] As expected, polar aprotic solvents (e.g., DMA and DMF) and those able to disrupt intermolecular hydrogen-bonding interactions between polymer chains are the most efficient at swelling the polyurea matrix. It was also noted that reducing the isocyanate functionality of the matrix-forming oligomer produced an intrinsically more swellable matrix (Table 1, column 4). The reason for this is that the ability of a cross-linked polymer to swell in a solvent is inversely proportional to the length of polymer chain between cross-linked sites, which will therefore decrease as the monomer functionality increases.

The porosity of the polyurea matrix in the solvent-swollen state was investigated for Pd(II) EnCat™ 30 and Pd(II) EnCat™ 40 using chromatographic porosimetry.[27] This investigation was performed by passing standard solutions of polystyrene and alkylbenzenes through an HPLC column packed with a known mass of Pd(II) EnCat™, pre-swollen in THF, and recording the retention times. Averaged, normalized retention volumes per gram of Pd(II) EnCat™ for each analyte were used by PSS's POROCheck software program[28] to calculate the average pore volumes, surface areas, and pore diameters. The data in **Table 2**[26a] and **Figure 3**[26a] show that Pd(II) EnCat™ 40 has a significantly lower pore volume and diameter than Pd(II) EnCat™ 30. A consequence of this is that relatively low-molecular-weight molecules (>400 polystyrene equivalents) could be excluded from the pores in the Pd(II) EnCat™ 40 matrix, whereas molecules of molecular weight up to 1,000 polystyrene equivalents can gain access to the pores within the Pd EnCat™

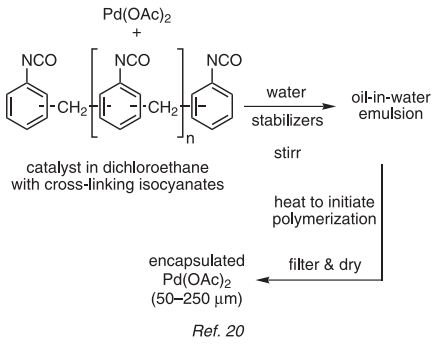
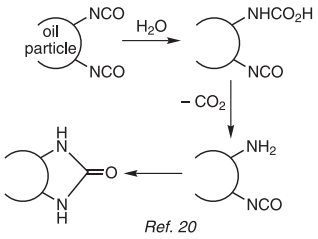



**Figure 1**. Interfacial Microencapsulation of Palladium in a Polymer Matrix.




**Scheme 1**. The Polyurea-Matrix-Forming Reaction That Occurs at the Oil–Water Interface.


**Figure 2a**. Scanning Electron Microscope (SEM) Image of Microcapsules Containing $Pd(OAc)_2$.
(Photo courtesy of Avecia Ltd, and is reproduced with permission.)

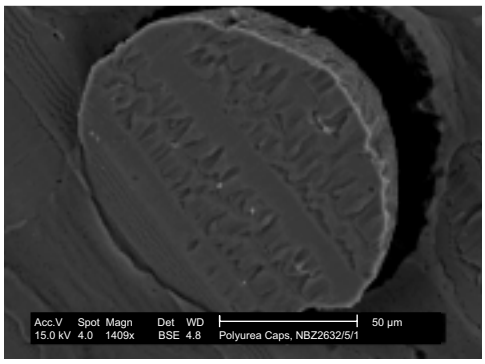



**Figure 2b**. SEM Image of the Interior of a $Pd(OAc)_2$-Containing Microcapsule.
(Photo courtesy of Avecia Ltd, and is reproduced with permission.)

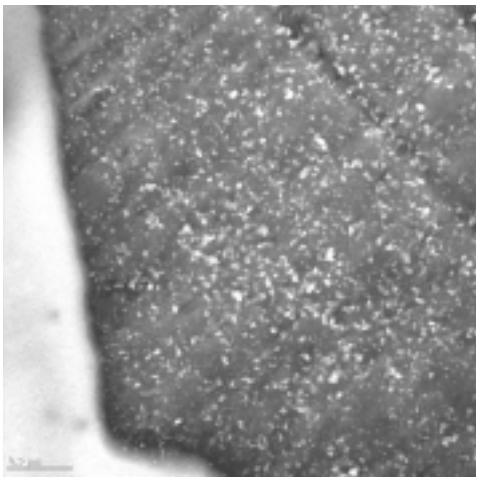


**Figure 2c**. Transmission Electron Microscope (TEM) Image of Ultramicrotone Cross Sections of $Pd(OAc)_2$-Containing Microcapsules. (Photo courtesy of Avecia Ltd, and is reproduced with permission.)

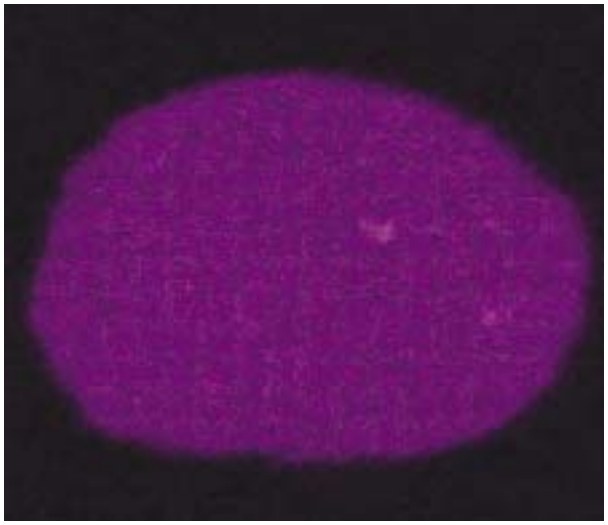


**Figure 2d**. Energy Dispersive X-ray (EDX) Pattern from SEM Analysis of Ultramicrotone Cross Sections of $Pd(OAc)_2$-Containing Microcapsules. (Photo courtesy of Avecia Ltd, and is reproduced with permission.)

**Table 1. Microcapsule Swelling Behavior as a Function of Solvent[a] and Matrix**

| | % Weight Gain | | | |
|---|---|---|---|---|
| Solvent | Pd(II) EnCat™ 40 | Pd(II) EnCat™ 30 | Pd(II) EnCat™ 20 | Reduced Cross-Linked Pd(II) EnCat™ 40[b] |
| PhMe | 0 | 30 | 30 | 0 |
| *i*-PrOH | 5 | 30 | 30 | 10 |
| EtOH | 10 | 30 | 30 | 20 |
| MeC(O)Me | 20 | 20 | 40 | 20 |
| THF | 10 | 60 | 40 | 10 |
| $MeC(O)NMe_2$ | 100 | 140 | 140 | 200 |
| $HC(O)NMe_2$ | 100 | 120 | 120 | 260 |

[a] The listed solvents are arranged in order of increasing polarity from top to bottom of column. [b] Half of the 2.7-functional isocyanate oligomer was replaced with a 2.0-functional isocyanate (2,4-toluene diisocyanate).

*Ref. 26a*

30 matrix. The higher porosity of the Pd(II) EnCat™ 30 matrix leads to improved access of reagents to the active metal centers, which results in higher yields and faster conversions.

### 3.3. Metal Leaching

A key feature of the polyurea encapsulation approach is the ability of the microcapsules to retain the palladium by virtue of the ligating functionality of the polymer. This was elegantly demonstrated by carrying out palladium leaching experiments in a range of solvents (**Table 3**).[26b] The results indicate that only in solvents capable of strongly swelling the matrix (Table 3, entries 1, 9, and 10) is there any significant metal leaching, while >99.8% of the metal remains within the microcapsule in all other solvents.

## 4. Catalytic Applications of Encapsulated Pd(II)

### 4.1. The Suzuki Reaction

Initial screening of the catalytic activity of 0.4 Pd(II) EnCat™ 40 was reported by Ley in the Suzuki-type cross-coupling of arylboronic acids with aryl bromides (**eq 1**).[20] ICP analysis of the crude products, following facile removal of the catalyst by filtration and evaporation of the solvent, detected palladium levels of about 13 ppm, which correspond to just 0.2% of the palladium originally in the microcapsules. Typically, for a homogeneous catalyst used at a similar equivalence, there would be several thousand ppm of palladium in the crude product. It was also reported that the catalyst was reused at least four times without significant loss of reactivity. A further benefit noted was that these reactions proceeded without the addition of phosphine ligands, which are both expensive and difficult to remove from the product.

Holmes, Ley, and co-workers recently evaluated a range of homogeneous tetrabutylammonium salts in order to develop protocols for carrying out Suzuki reactions using Pd(II) EnCat™ 40 under mild conditions with just stoichiometric quantities of base.[29] Typically, such reactions entail elevated temperatures (>90 °C) and the use of 2 to 4 equivalents of base. Initial investigations centered upon batch-type Suzuki reactions in toluene–methanol (9:1, v/v) in the presence of stoichiometric quantities of $(n\text{-Bu})_4NOAc$ or $(n\text{-Bu})_4NOH$ (1 M in MeOH), $(n\text{-Bu})_4NOMe$ (20% w/v in MeOH), or $(n\text{-Bu})_4F$ (1 M in THF). At 110 °C, and in the presence of Pd(II) EnCat™ 40, all four $(n\text{-Bu})_4NX$ salts were extremely effective at facilitating the cross-coupling of bromobenzene and *p*-tolylboronic acid, thereby giving rise to 4-methylbiphenyl in near-quantitative yields (**eq 2**).[29] At 40 °C, high coupling yields were obtained with $(n\text{-Bu})_4NOH$ and good yields with $(n\text{-Bu})_4NOMe$ and $(n\text{-Bu})_4F$. It was suggested that the higher coupling yields observed at 40 °C for $(n\text{-Bu})_4NX$ (X = OH, OMe, and F) relative to that seen with $(n\text{-Bu})_4NOAc$ may be attributed to the strongly nucleophilic nature of the hydroxide, methoxide, and fluoride anions, which facilitates the transmetalation process. These results demonstrate that the Suzuki cross-coupling reaction can be effected in organic solvents at low temperatures without the need for excess base.

A similar study was carried out with the more porous Pd(II) EnCat™ 30, 4-bromofluorobenzene and phenylboronic acid in isopropyl alcohol at 70 °C (**eq 3**).[26b] The results demonstrated that these batch reactions proceeded in high yields in less than 30 minutes in all cases except with $(n\text{-Bu})_4F$. Following removal of the catalyst by simple filtration and evaporation of the solvent, the crude products were found to contain just 20–50 ppm of palladium by ICP analysis. The high speed of these reactions and the low extent of catalyst leaching suggest that this system could be appropriate for a continuous-flow Suzuki application.

### 4.1.1. The Suzuki Reaction in Supercritical Carbon Dioxide

Supercritical carbon dioxide has a potential as an alternative solvent for organic synthesis,[30] and there has been considerable interest in performing hydrogenations[31] and C–C-bond-forming reactions[32] in this versatile solvent. Ley, Holmes, and co-workers further demonstrated the versatility of the microencapsulated catalyst in a series of Suzuki reactions, between *p*-tolylboronic acid and aryl halides in $scCO_2$, which proceeded in yields similar to those obtained in conventional organic solvents (**eq 4**).[33] Separation of the catalyst was achieved by simple filtration of the ethyl acetate solution into which the reaction mixture had been vented.

With a view to extending this technique to continuous-flow reactions, Lee et al. screened a series of tetrabutylammonium salts at 100 °C and 40 °C in the Pd(II) EnCat™ 40 mediated Suzuki coupling between bromobenzene and *p*-tolylboronic acid (**eq 5**).[29] At 100 °C and 3000 psi of $CO_2$, all four $(n\text{-Bu})_4NX$ salts gave 4-methylbiphenyl in near-quantitative yields. At 40 °C and 1400 psi, a good yield was obtained only with $(n\text{-Bu})_4NOMe$.

### 4.1.2. The Suzuki Reaction Under Continuous-Flow Conditions

Ley, Holmes, and co-workers were the first to achieve a continuous-flow Suzuki coupling over a Pd(II) EnCat™ 40 stationary phase.[29] In this feasibility study, a stock solution containing iodobenzene, *p*-tolylboronic acid, and $(n\text{-Bu})_4NX$ was passed through an HPLC column packed with Pd(II) EnCat™ 40 catalyst at 55 °C. The yield per pass through the column was determined by GC (**eq 6**).[29] These preliminary results were very encouraging in the case of $(n\text{-Bu})_4NOH$ and $(n\text{-Bu})_4NOMe$, giving rise to the biphenyl product in 70% and 85% yields, respectively, after just 3 passes. Even more impressive was the performance of $(n\text{-Bu})_4NOMe$ at 70 °C (entry 5), which gave a quantitative yield after one pass through the Pd(II) EnCat™ 40 stationary phase. In the case of the reactions with $(n\text{-Bu})_4NOAc$, $(n\text{-Bu})_4NF$, and $(n\text{-Bu})_4NOH$ at 55 °C, there was some phase separation of the reaction mixture, which probably explains the lower yields. It was suggested that the methanol liberated from $(n\text{-Bu})_4NOMe$ during the reaction solubilizes the other species, thus maintaining a homogeneous solution.

## *4.2. Carbonylation*

The Cambridge researchers have also reported the formation of a range of substituted aryl esters in high yields by the Pd(II) EnCat™ 40 catalyzed addition of carbon monoxide to aryl iodides in *n*-butyl alcohol at 90 °C (**eq 7**).[33] The encapsulated catalyst was simply removed by filtration. Following solvent evaporation, the crude products contained approximately 79 ppm of Pd (w/w) corresponding to about 1% leaching of palladium from the microcapsules.

## *4.3. The Heck Coupling*

Pd(II) EnCat™ 40 has been effectively utilized in a series of Heck couplings in conventional organic solvents (**eq 8**) and in $scCO_2$ (**eq 9**).[33] With $(n\text{-Bu})_4NOAc$, a series of unsaturated esters were produced in high yields (with the exception of the reaction with 4-bromoanisole) without the addition of phosphine ligands. It was noted that the yields were generally higher in $scCO_2$ even at a lower catalyst loading. Following removal of the catalyst and evaporation of the solvent, the crude products contained 60 ppm of palladium by ICP analysis.

Vickerstaffe et al. have recently reported the use of Pd(II) EnCat™ 40 in a Heck reaction that formed a key step in the first

**Table 2. THF-Wet-State Microcapsule Pore Dimensions by Chromatographic Porosimetry[a]**

| Property | Pd(II) EnCat™ 30 | Pd(II) EnCat™ 40 |
|---|---|---|
| Swollen bulk density (g/mL) | 0.330 | 0.469 |
| Swollen pore volume (mL/g) | 1.65 | 0.73 |
| Pore surface/pore volume ($m^2/cm^3$) | 1686.5 ± 20.3 | 2875.8 ± 46.2 |
| Average pore radius (nm) | 1.19 ± 0.01 | 0.70 ± 0.01 |

[a] Calculations use molecular statistical theory, and are based on a relationship between molecular weight and radius of gyration valid for polystyrene at molecular weights > 10,000 Daltons. Extrapolations below this molecular weight lead to unreliable absolute pore dimension data, but are valid for comparisons of similar materials using similar probe molecules.

*Ref. 26a*

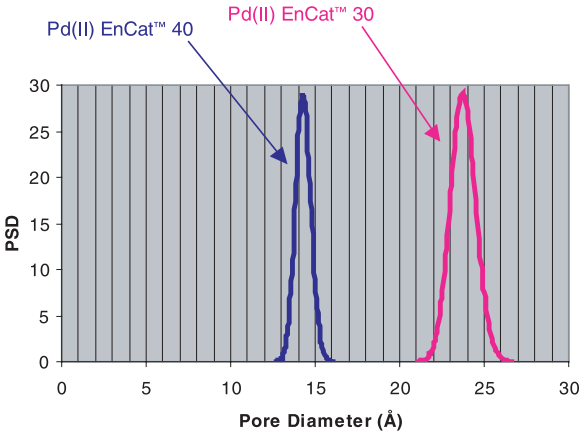


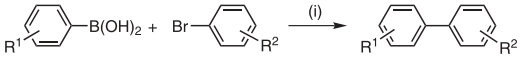

**Figure 3**. Pore Size Distribution (PSD) for Pd(II) EnCat™ 30 and Pd(II) EnCat™ 40 in the Tetrahydrofuran-Swollen State as Determined by Chromatographic Porosimetry. (Graph courtesy of Avecia Ltd, and is reproduced with permission.)

**Table 3. Palladium Leaching from Microcapsules[a]**

| | | 0.4 Pd(II) EnCat™ 40 | | 0.4 Pd(II) EnCat™ 30 | |
|---|---|---|---|---|---|
| Entry | Solvent | Pd (ppm) | % Pd Extracted[b] | Pd (ppm) | % Pd Extracted[b] |
| 1 | THF | 1 | 0.15 | 4 | 0.30 |
| 2 | Acetone | <1 | <0.15 | 1 | 0.08 |
| 3 | Ethanol | <1 | <0.15 | <1 | <0.08 |
| 4 | Acetonitrile | 1 | 0.15 | <1 | <0.08 |
| 5 | IPA | <1 | <0.15 | <1 | <0.08 |
| 6 | Toluene | <1 | <0.15 | <1 | <0.08 |
| 7 | Dioxane | 1 | 0.15 | <1 | <0.08 |
| 8 | Ethyl Acetate | <1 | <0.15 | <1 | <0.08 |
| 9 | DMF | 7 | 1.08 | 5 | 0.39 |
| 10 | DMA | 6 | 0.93 | 3 | 1.00 |

[a] The catalyst (0.3 g) was stirred and heated at 80 °C in the solvent (20 mL) for 2 days. The solid catalyst was then filtered off, and the palladium content of the filtrate determined by ICP analysis and expressed as ppm Pd in the solvent and as a percent of the total available Pd that was extracted by the solvent.
[b] Pd extracted as a percent of total palladium available.

*Ref. 26b*

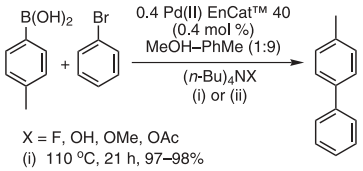



(i) 0.4 Pd(II) EnCat™ 40 (5 mol %), PhMe/$H_2O$/EtOH (4:2:1), $K_2CO_3$, 80 °C, 6–12 h
$R^1$ = H, 2-OMe, 4-OMe, 4-Ac
$R^2$ = 4-F, 2-OMe, 4-OMe, 4-$NO_2$

71–97%

*Ref. 20*

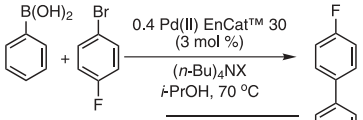
**eq 1**




X = F, OH, OMe, OAc
(i) 110 °C, 21 h, 97–98%
(ii) 40 °C, 60 h, 59–85%

*Ref. 29*

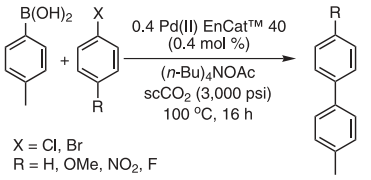
**eq 2**




| X | 0.5 h | 1.0 h |
|---|---|---|
| OAc | 84% | 84% |
| OH | 92% | 92% |
| OMe | 80% | 80% |
| F | 8% | 23% |

*Ref. 26b*

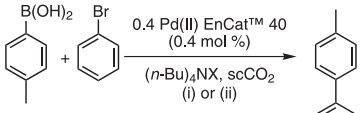
**eq 3**




X = Cl, Br
R = H, OMe, $NO_2$, F

*Ref. 33*

**eq 4**



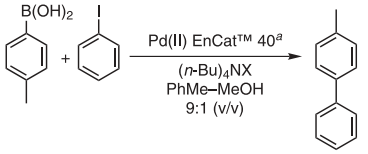

(i) 100 °C, 3,000 psi, 21 h
(ii) 40 °C, 1,400 psi, 60 h

| X | Yield (%) Method (i) | Yield (%) Method (ii) |
|---|---|---|
| OAc | 51 | — |
| OAc[a] | 96 | 38 |
| OH | 97 | 16 |
| OMe | 97 | 66 |
| F | 74 | <1 |

[a] A small amount of MeOH was used as additive.

*Ref. 29*

**eq 5**




| X | T, °C | % Yield per Pass[b] 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| OAc | 55 | 4.7 | 7.5 | 11 | 12 | 14 | 15 |
| OH | 55 | 3.1 | 13 | 70 | – | – | – |
| OMe | 55 | 12 | 48 | 85 | – | – | – |
| F | 55 | 36 | 40 | 55 | – | – | – |
| OMe | 70 | 100 | – | – | – | – | – |

[a] Used as a stationary phase in a continuous-flow Suzuki cross-coupling reaction: column 5 cm (l) × 4.5 mm (i.d.); flow rate 0.2 mL/min; residence time ca. 4 min. [b] Percent yield per pass through the HPLC column was determined by GC.

*Ref. 29*

**eq 6**

fully automated, unattended, multistep, and polymer-assisted solution-phase (PASP) synthesis of an array of histone deacetylase (HDAc) inhibitors. Despite the number of continuous steps, they were able to obtain 34 out of the 36 targeted compounds in reasonable yields and purities.[34] The Heck olefination of an iodophenyl sulfonamide with acrylic acid was investigated using the immobilized palladium catalysts Pd(II) EnCat™ 40 and Fibrecat™ 1001[35] as a way to facilitate product workup (**eq 10**).[34] Using a ReactArray SK233 automated reaction sampling system, it was demonstrated that the competing dehalogenation pathway was minimized using Pd(II) EnCat™ 40 as the source of palladium with tributylamine as base, and that the desired product was obtained in 80% yield after 13.3 h versus a 60% yield with Fibrecat™ 1001—a polyethylene-supported, phosphine-ligand-based palladium catalyst.[11]

### 4.4. The Intramolecular Heck Coupling

Smith and collaborators have reported that Pd(II) EnCat™ 40 can be effectively applied in intramolecular olefination reactions in acetonitrile or DMF (**eq 11**).[36] Unlike $Pd(PPh_3)_4$, the encapsulated catalyst does not produce triphenylphosphine oxide as a byproduct, and only a slight palladium contamination of the products is observed. Faster reactions are usually obtained with DMF, presumably because DMF allows some leaching of palladium from Pd(II) EnCat™; the encapsulated catalyst in this case probably acts as a convenient slow-release reservoir of highly active nanoparticulate Pd(0) species.

### 4.5. The Stille Coupling

The utility of Pd(II) EnCat™ 40 was further demonstrated in a series of Stille couplings in conventional organic solvents and in $scCO_2$ (**eq 12**).[33] It was noted that the yields in $scCO_2$ were lower than those in isopropyl alcohol–toluene, although less catalyst was used in $scCO_2$. The feasibility of reusing the recovered catalyst was also demonstrated by performing a series of sequential Stille reactions of phenyltrimethylstannane with 4-nitrobromobenzene. In all cases, the reactions proceeded to completion giving a near-quantitative yield (97–99%) of the coupled product. A progressive increase in reaction time in successive runs was also observed, indicating that some of the more accessible metal may have been removed in the preceding reaction or after washing with solvent following recovery of the catalyst.[33]

### 4.6. Parallel Synthesis of Chemical Libraries

The Suzuki coupling of boronic acids or boronates with aryl halides is a powerful diversity-generating reaction. Microwave heating dramatically improves reaction times and conversions and, with diverse substrates, provides an opportunity for a more general reactivity.[37]

Wang and Sauer have described the use of microwave heating in Suzuki cross-couplings that utilize FibreCat™ 1001 (**eq 13**).[38] Good yields and purities were obtained by using an excess of the boronic acid and solid-phase extraction with a silica-supported carbonate base during workup. The use of Pd(II) EnCat™ 40 in a microwave-promoted synthesis of a biaryl library from a diverse set of boronic acids and aryl halides has been reported (**eq 14**).[36,39] A Personal Chemistry Synthesizer microwave reactor was utilized together with an experimental design strategy that optimized conditions including solvent, temperature, base, stoichiometry, and time against substrate reactivity in order to generate robust general reaction conditions. The base, tetra(*n*-butyl)ammonium acetate, was dispensed in acetonitrile prior to reaction. After cooling, the microencapsulated catalyst was

filtered prior to purification. Alternatively, the reaction mixture was applied directly to disposable chromatography cartridges and purified, thus separating the catalyst at the same time. The library was constructed by reacting 19 aryl halides with 12 boronic acids to produce a set of 157 pure biaryl products (68% success rate).

## 5. Catalytic Applications of Encapsulated Palladium(0)

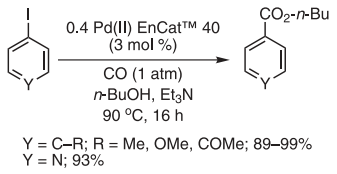
### 5.1. Hydrogenation

The reduction of Pd(II) EnCat™ 40 with hydrogen produces Pd(0) EnCat™ 40, which is an effective catalyst for the selective hydrogenation of unsaturated bonds in alkenes, alkynes, imines, and nitro groups (**eq 15**).[40] Recovery of the catalyst is simple compared to that of palladium-on-carbon, levels of metal contamination in the crude products are extremely low, and the catalyst can be readily recycled. All of the initial hydrogenations reported were carried out with Pd(0) EnCat™ 40 pre-reduced under hydrogen (50 bar) for two days. It was found that this pre-reduction of Pd(II) EnCat™ 40 was necessary for high activity and reduced reaction times. The hydrogenations were carried out under a hydrogen atmosphere either in an autoclave or maintained by a hydrogen-filled balloon.

Simple alkenes, alkynes, and aryl nitro groups were reduced at room temperature under an atmosphere of hydrogen (inflated balloon) with near-quantitative conversions as determined by GC or LCMS. Using cyclohexene as a test substrate, it was demonstrated that the catalyst could be recycled 20 times without any significant loss of activity. The reduction of electron-deficient styrenes was sluggish at room temperature and required slightly elevated temperatures (60 °C) to yield the reduced products. Reduction of *trans*-*N*-phenylbenzylidene, on the other hand, required the use of high pressure (50 bar). Interestingly, potentially labile groups such as alkyl epoxides, aryl halides, and benzyloxy groups remained unaffected even after being subjected to high pressures (up to 50 bar) and extended reaction times. However, the benzyloxycarbonyl group in *N*-Cbz-*N*-methylallylamine was cleaved under high pressure (50 bar), whereas the same group remained intact when the same reaction was performed under an atmosphere of hydrogen (maintained by a hydrogen balloon), which gave rise to the reduced product in 93% isolated yield. All of the crude products from the hydrogenations contained less than 10 ppm of palladium, as determined by ICP analysis, which corresponds to <0.025% of the original metal being lost from the encapsulated catalyst. These results demonstrate that, although less reactive than Pd/C, Pd(0) EnCat™ 40 allows the selective reduction of double bonds to be carried out in the presence of sensitive functionalities. When coupled with its ease of handling, facile removal from reaction mixtures, and apparent reduced pyrophoric tendency, this selectivity makes Pd(0) EnCat™ 40 an attractive choice for large-scale operations.

### 5.2. Transfer Hydrogenation

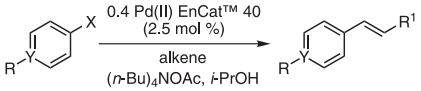
While the hydrogenation of Pd(II) EnCat™ 40 did not produce an active catalyst for transfer hydrogenation reactions,[41] the formic acid reduction of the microencapsulated Pd(II) resulted in a highly effective transfer-hydrogenation catalyst.[42] An examination of high-resolution TEM images of Pd(0) EnCat™, produced by reduction with hydrogen or with formic acid, confirmed the hypothesis that polyurea-coordinated $Pd(OAc)_2$ undergoes anionic ligand exchange with formate to form a palladium diformate complex (**Scheme 2**).[41] This complex is known to undergo decarboxylation followed by loss of molecular hydrogen to form Pd(0), which is deposited as fine nanoparticles within the




Y = C–R; R = Me, OMe, COMe; 89–99%
Y = N; 93%

*Ref. 33*

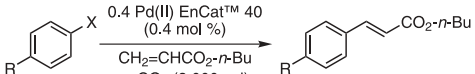
**eq 7**




| Y | R | X | $R^1$ | Yield |
|---|---|---|---|---|
| C | $NO_2$ | Br | $CO_2$(*n*-Bu) | 91% |
| C | $NO_2$ | Br | Ph | 93% |
| N | – | I | $CO_2$(*n*-Bu) | 98% |
| C | OMe | Br | $CO_2$(*n*-Bu) | 25% |

*Ref. 33*

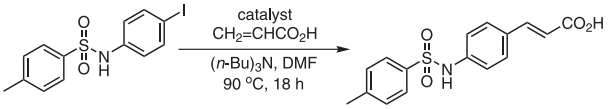
**eq 8**




| R | X | Yield |
|---|---|---|
| H | Br | 99% |
| OMe | Br | 99% |
| F | Br | 75% |
| $NO_2$ | Br | 95% |
| $NO_2$ | Cl | 58% |

*Ref. 33*

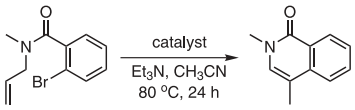
**eq 9**




0.4 Pd(II) EnCat™ 40 (0.4 mol %), 80%
Fibrecat™ 1001, 60%

*Ref. 34*

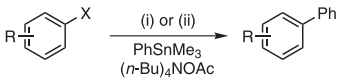
**eq 10**




0.4 Pd(II) EnCat™ 40 (5 mol %), 50%
(DMF, 120 °C, 5 h; 80%)
or
0.4 Pd(II) EnCat™ 30 (5 mol %), 50%

*Ref. 36*

**eq 11**

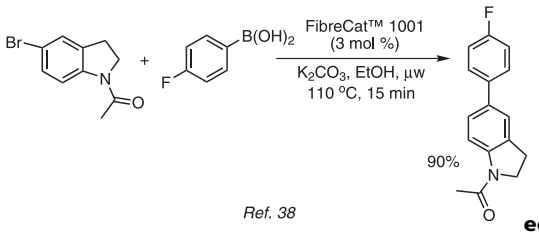



(i) 0.4 Pd(II) EnCat™ 40 (2.5 mol %),
PhMe–*i*-PrOH (1:1), 90 °C
(ii) 0.4 Pd(II) EnCat™ 40 (0.4 mol %),
$scCO_2$ (3,000 psi), 100 °C, 16 h

| R | X | Yield (i) | Yield (ii) |
|---|---|---|---|
| H | Br | – | 50% |
| 2-OMe | Br | 74% | – |
| 4-OMe | Br | 88% | 45% |
| 4-F | Br | 82% | – |
| 4-$NO_2$ | Br | 99% | >34% |
| 4-$NO_2$ | Cl | – | 50% |

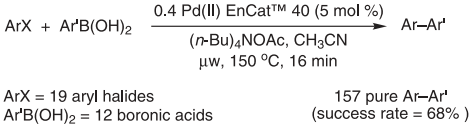
*Ref. 33*

**eq 12**



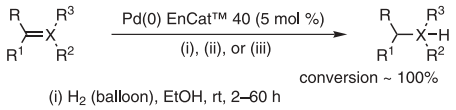

*Ref. 38*

**eq 13**



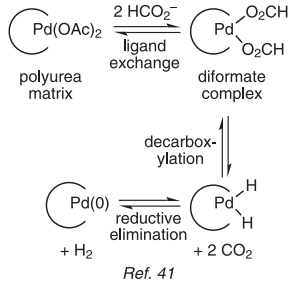

*Ref. 36,39*

**eq 14**



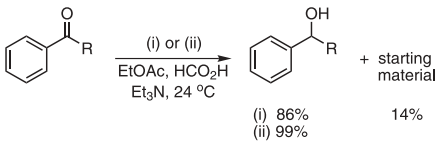

*Ref. 40*

**eq 15**



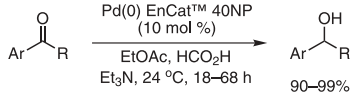

*Ref. 41*

**Scheme 2**. Formation of Nanoparticulate Pd(0) via Ligand Exchange with the Formate Anion.




*Ref. 42*

**eq 16**




*Ref. 42*

**eq 17**

polyurea matrix.[41] It was anticipated, that following reduction of the homogeneous palladium(II), the polyurea matrix would prevent agglomeration of the palladium(0) nanoparticles.

In the sample prepared by reduction of Pd(II) EnCat™ 40 with hydrogen, the majority of the Pd(0) particles were found to be larger than 5 nm in diameter. In contrast, images of Pd(0) particles produced by reduction with formic acid revealed that most of the particles have a diameter of ≤2 nm, and provided evidence for highly ordered areas corresponding to the preferred cubic, close-packed palladium cell structure.[41]

Ley and co-workers first established the efficiency and stability of this new nanoparticulate Pd(0) catalyst, Pd(0) EnCat™ 40NP, by examining the reduction of acetophenone (10 mol % Pd(0) EnCat™ 40NP, 200 μL EtOAc, 0.8 mmol $HCO_2H$, 0.8 mmol $NEt_3$, 0.016 mmol PhC(=O)Me, 24 °C).[42] The reduction proceeded to completion with excellent isolated yields (96–99%) through five successive recycle runs and, importantly, there was no evidence for compounds formed from over-reduction of the aromatic ring or cleavage of the hydroxyl group.

The superior catalytic properties of Pd(0) EnCat™ 40NP, as compared to those of 10% Pd/C, were demonstrated by carrying out the reduction of propiophenone under identical conditions: 10% Pd/C facilitated only an 86% conversion to the benzyl alcohol product (**eq 16**).[42]

It has been noted that the metal center within the Pd(0) EnCat™ 40NP catalyst is more electron-rich than Pd/C, which may account for the higher catalytic activity. It has been further suggested that the small size of the palladium nanoparticles may also have a profound effect.[41,42] The scope of this new catalyst system was established by carrying out a wide range of aryl ketone transfer reductions. In all cases, the reactions reached completion within 18 to 68 hours and led to very high yields of the secondary alcohol products (**eq 17**).[42]

### 5.3. Transfer Hydrogenation in Parallel Synthesis

More recently, nanoparticulate Pd(0) EnCat™ NP has been used as an alternative to Pd/C in automated, parallel transfer hydrogenations to prepare a library of biaryl alcohols of interest as herbicide intermediates.[36,43] This catalyst system is attractive in parallel synthesis, where chemists prefer not to use gaseous hydrogenation and potentially pyrophoric reagents. The higher activity, ease of catalyst removal by simple filtration, and the reduced risk from ignition of solvent–air mixtures should make this the catalyst system of choice in parallel transfer hydrogenations.

Pd(0) EnCat™ 40NP can be readily separated from parallel-synthesis reaction mixtures using polypropylene reaction tubes. The tubes are sintered at the bottom, allowing gravity or vacuum-assisted filtration from 48-position reactor blocks via outlet tubes with a universal locking mechanism. As part of an experiment to further explore the scope of the reduction of aryl ketones, 96 diverse ketones were reacted in parallel with Pd(0) EnCat™ 40NP under standard transfer-hydrogenation conditions [Pd(0) EnCat™ 40NP (10 mol %), EtOAc, $Et_3N$, $HCO_2H$, 24 °C, 48 h].[36,43] After filtration and evaporation, the residues in dichloromethane were treated with water and filtered through a phase-separation plate. In many cases, high conversions (79–100%) were observed, leading to pure products, the purities of which were established by GC and NMR. Very hindered or electron-rich aromatic ketones were found to be unreactive or slower to reduce. Biaryl ketones, such as benzophenone, showed significant amounts of over-reduction to the corresponding methylene compounds. Aromatic halides (except fluorine) were also rapidly reduced; for example, 1-pentoyl-2,4-dichlorobenzene gave pure α-pentyl

benzyl alcohol (100% yield). This provides a very mild method for dechlorination of aromatic substrates. 2-Acylpyridine was reduced to the corresponding alcohol (79% yield), whereas 3-acylpyridine was reduced to the corresponding tetrahydropyridine (59% yield). Reactions with electron-rich or sterically hindered ketones were much more sluggish. Optimization experiments of catalyst loading and reagent stoichiometry indicated that efficient conversions could be obtained with acetophenone down to 2 mol % Pd(0) EnCat™ 40NP and only two equivalents of formic acid and triethylamine. A comparison of Pd(0) EnCat™ 40NP with the more porous Pd(0) EnCat™ 30NP using standard conditions, showed the latter to be far more effective with the least reactive substrates (**eq 18**).[36]

### 5.4. Reduction of the Aryl Nitro Group

Pd(0) EnCat™ 40NP has been employed in the reductive cyclization of various Leimgruber–Batcho-derived enamines to form the corresponding indoles (**Scheme 3**).[44] Hydrogenation of the aryl nitro group was carried out under transfer-hydrogenation conditions to give the indole in high yield. The catalyst was recycled without noticeable loss in activity, and the reaction was accelerated by microwave irradiation at 120 °C. Thus, the combination of microwave-accelerated enamine formation and the use of a recyclable, easily removed catalyst for the reductive cyclization in the Leimgruber–Batcho reaction provides an industrially attractive route to indoles.

### 5.5. Reductive Ring Opening of Epoxides

The reductive ring opening of epoxides by hydrogenolysis in the presence of Pd(0) EnCat™ 40NP has been investigated.[41] For example, the hydrogenolysis of *trans*-stilbene oxide gave the alcohol in 99% isolated yield after 5 h. Over-reduction of the alcoholic C–O bond was not observed at a detectable level even after prolonged reaction times. This illustrates the clear advantage of Pd(0) EnCat™ 40NP over Pd/C in terms of chemoselectivity. Under identical conditions, 10% Pd/C gave the desired secondary alcohol in 80% yield from *trans*-stilbene oxide, and in only 48% yield from methylstyrene oxide.[26] In these Pd(0) EnCat™ 40NP reductions, the catalyst was recovered by simple filtration and reused without loss of activity. In the case of *trans*-stilbene oxide, the catalyst was recycled through 10 successive hydrogenolysis reactions and, in each case, gave high isolated yields (96–99%) of the corresponding benzylic alcohol. Moreover, the level of palladium in the reaction medium following filtration of the catalyst was below the detection limit (5 ppm) of ICP analysis.[41]

A range of other benzylic epoxides were also subjected to the same hydrogenolysis conditions, and good-to-excellent yields (82–99%) of the homobenzylic alcohols were consistently obtained. In each case, the epoxides were opened regioselectively at the benzylic carbon. The stereoselectivity of the ring opening was investigated by using enantiomerically pure *trans*-methylstyrene oxide, which was reduced with complete retention of configuration at the homobenzylic carbon atom (**eq 19**).[41]

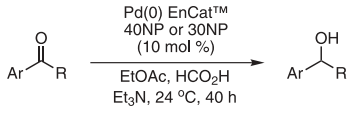
We have demonstrated that methyl styrene oxide undergoes hydrogenolysis faster with the more porous Pd(0) EnCat™ 30NP than with Pd(0) EnCat™ 40NP. A near-quantitative conversion into the anticipated product occurred in less than 30 minutes.[26b] Furthermore, the catalyst (EnCat™ 30NP or 40NP) was readily recovered and recycled and, following catalyst removal and solvent evaporation, the product contained less than 5 ppm of palladium by ICP analysis.

#### 5.5.1. Reductive Ring Opening of α,β-Epoxy Ketones

The β-hydroxy carbonyl functionality is an important structural motif, which often appears in natural products and can generally be installed by an aldol reaction. This is not always convenient, however, and reductive cleavage of α,β-epoxy ketones is an important alternative. Ley's group demonstrated that α,β-epoxy ketones undergo reductive cleavage in the presence of Pd(0) EnCat™ 40NP to give the corresponding β-hydroxy ketones in good yields (**eq 20**).[41] NMR analysis indicated that the main side product was the diketone.

#### 5.5.2. Reductive Ring Opening of Terminal Epoxides

Due to recent advances in the area of catalytic epoxidation of terminal olefins,[45] the regioselective reduction of terminal epoxides is a particularly attractive route to substituted alcohols. Unfortunately, the reduction of (2,3-epoxypropyl)benzene with Pd(0) EnCat™ 40NP under transfer-hydrogenation conditions was very slow. But, encouragingly, a good yield (85%) of the

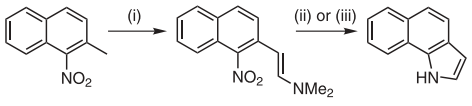



| Ar | R | Ar,R | Conversion[a] with 40NP | Conversion[a] with 30NP |
|---|---|---|---|---|
| 2-MeOC$_6$H$_4$ | Me | — | 4% | 13% |
| 3-MeOC$_6$H$_4$ | Me | — | 50% | 75% |
| 4-MeOC$_6$H$_4$ | Me | — | 28% | 54% |
| Ph | Cy | — | 55% | 93% |
| 1,3-benzodioxol-5-yl | Me | — | 10% | 29% |
| — | — | 1-indanone | 33% | 60% |
| — | — | 7-MeO-1-tetralone | <5% | 20% |
| — | — | 1-benzosuberone | 18% | 22% |

[a] Determined by GC or NMR.

*Ref. 36*

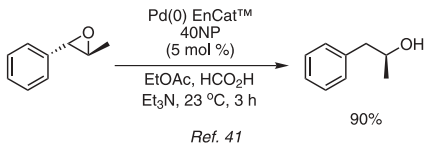
**eq 18**




(i) CuI or Yb(OTf)$_3$, DMF, μw, 180 °C, 4.5 h
(ii) Pd(0) EnCat™ 40NP (6 mol %), EtOAc, $HCO_2H$
$Et_3N$, 24 °C, 24 h
(iii) Pd(0) EnCat™ 40NP (6 mol %), EtOAc, $HCO_2H$
$Et_3N$, μw, 120 °C, 2 h

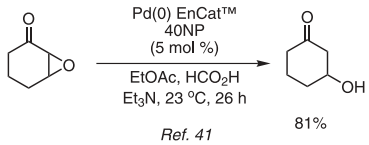
*Ref. 44*

**Scheme 3**. Leimgruber–Batcho Indole Synthesis.




*Ref. 41*

**eq 19**




*Ref. 41*

**eq 20**

secondary alcohol was obtained under conventional hydrogenation conditions [Pd(0) EnCat™ 40NP (5 mol %), MeOH, $H_2$ (40 atm), 23 °C, 19 h].[41]

## 6. Conclusions and Outlook

It is hoped that the above selected examples have demonstrated that polyurea-microencapsulated homogeneous catalysts offer advantages to the synthetic organic chemist both for laboratory-scale use and in manufacturing. The outlook for this field is exciting, with the potential to microencapsulate a range of homogeneous metal catalysts and ligands in tailored matrix materials.

## 7. Acknowledgments

This technology would not have been developed without initial funding from Syngenta for the original project at Cambridge University and the generous continuing support of the Engineering and Physical Sciences Research Council (EPSRC) and Avecia Ltd. The authors would particularly like to acknowledge the contributions of Drs. Chandra Ramarao, David Tapolczay, Ian McConvey, and Ian Shirley.

## 8. References and Notes

(§) Dedicated to Professor Steven V. Ley, CBE, FRS, on the occasion of his 60th birthday.

(†) Author to whom correspondence should be addressed. Email: david.pears@reaxa.com.

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## About the Authors

**David A. Pears** was born in St. Albans, England. He was raised in Harpenden and entered Southampton University in 1979, graduating with a B.Sc. (Honours) in 1982. He then joined Professor J. F. Stoddart's group at Sheffield University to carry out research on chiral crown ethers as enantioselective catalysts, and graduated with a Ph.D. in 1985. He joined ICI's New Science Group in the same year to work on the synthesis of novel-effect monomers for use in high-performance surface coatings. In 1990, he transferred to Holland to lead a research team within ICI's NeoResins business in developing water-based, UV rapid-cure coating systems. In 1993, he returned to the U.K. to work as Research Group Leader with Zeneca and, in 1998, was made Business Research Associate. In the same year, he joined Avecia as a group leader within its Core Polymer Group. He has published over 70 patents and scientific papers. David currently works within Avecia's Pharmaceuticals business in Manchester, England. In 2004, he was awarded the U.K.'s Chemical Industries Association "Innovation of the Year" award for the development of the Pd EnCat™ catalyst technology in collaboration with Professor Steven Ley and scientists at AstraZeneca and Syngenta.

**Stephen C. Smith** was born in Windsor, England. He studied chemistry at Imperial College, London, where he was awarded a B.Sc. degree in 1988. This was followed by a Ph.D. with Professor Steven Ley, CBE (Commander of the Order of the British Empire) at Imperial College, which was earned for work on the synthesis of the potent insect-antifeedant azadirachtin. In 1991, Steve moved to the University of California at Berkeley as a NATO fellow to conduct postdoctoral research with Professor Clayton Heathcock on the synthesis of the cytotoxic bis-steroidal cephalostatins. He returned to the U.K. to join what was then ICI Plant Protection at Jealott's Hill, Bracknell, at the end of 1992. This then became Zeneca Agrochemicals. Steve spent three years as a team leader in the Herbicide Chemistry group, working on a number of hit-to-lead and optimization projects, followed by two years on secondment in the Process Technology Department at Huddersfield in the U.K. Here, he led a team developing the first stages in a process to manufacture the active ingredient in the herbicide sulfosate. Steve returned to Jealott's Hill to work on new leads in insecticide chemistry and, in 1999, moved into his current role as Head of the Syngenta Chemical Technology Group. This encompasses combinatorial chemistry, robotic synthesis, and new synthetic technologies such as microwave chemistry, solid-phase synthesis, supported reagents, and catalysis. He is an author on over 50 scientific papers and patents. Steve led the original microencapsulated-catalyst joint collaborative project with Professor Steven Ley from 1999 to 2002. The project team (Syngenta, Avecia, AstraZeneca, and Cambridge University) received the Institute of Applied Catalysis (iAc) Innovation Award in 2004.

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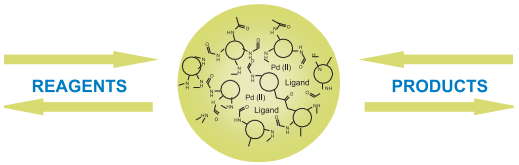
- Cost of catalyst lost during reaction workup

**Pd EnCat™** addresses these issues by using microencapsulation technology to immobilize the palladium, optionally with activating ligands, within a highly cross-linked polyurea matrix. The catalytic activity of palladium is accessed through the porous matrix, thereby leaving the palladium captured within it.

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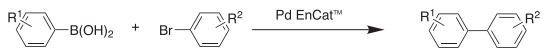
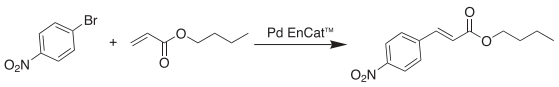
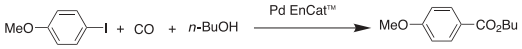
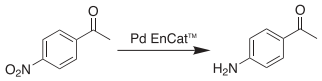
| | |
|---|---|
| Suzuki Coupling |  |
| Heck Reaction |  |
| Carbonylation |  |
| Transfer Hydrogenation |  |

**References:** (1) Yu, J.-Q. et al. *Chem Commun.* **2003**, 678. (2) Bremeyer, N. et al. *Synlett* **2002**, 1843. (3) Ley, S. V. et al. *Chem Commun.* **2002**, 1134. (4) Chandrashekar, R. et al. *Chem Commun.* **2002**, 1132. (5) Vickerstaffe, E. et al. *Org. Biomol. Chem.* **2003**, *1*, 2419. (6) Ley, S. V. et al. *Org. Lett.* **2003**, *5*, 4665.

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- Low residual metal levels in final crude product (typically <10 ppm before purification)
- Easy recovery of catalyst by filtration
- Safer and easier to handle than palladium-on-carbon
- Compatibility with a wide range of process technology options, e.g., fixed-bed, fluidized-bed, trickle-bed, and microwave reactors

| Cat No. | Name | Matrix Content (%) | %Pd (mmol/g) | P (mmol/g) | Ligand | Units | | |
|---|---|---|---|---|---|---|---|---|
| **64,472-2** | Pd EnCat™ 40 | 40 | 3.9–4.6 (0.4) | N/A | N/A | 1 g | 10 g | 100 g |
| **64,471-4** | Pd EnCat™ 30 | 30 | 3.9–4.6 (0.4) | N/A | N/A | 1 g | 10 g | 100 g |
| **64,470-6** | Pd EnCat™ TPP30 | 30 | 3.9–4.6 (0.4) | 0.26–0.35 | $Ph_3P$ | 1 g | 10 g | 100 g |
| **64,469-2** | Pd EnCat™ TOTP30 | 30 | 3.9–4.6 (0.4) | 0.15–0.20 | $(o\text{-toyl})_3P$ | 1 g | 10 g | 100 g |
| **65,366-7** | Pd EnCat™ 30NP, Wet *(45% water, unit weight excludes water)* | 30 | 3.7–4.6 (0.4) | N/A | N/A | 1 g | 10 g | 100 g |

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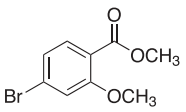


**Methyl 2-hexynoate, puriss., 98%**
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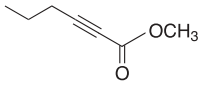
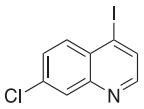
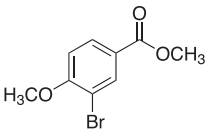


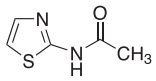

**7-Chloro-4-iodoquinoline, purum, 97%**
**65,290-3** 1 g, 10 g



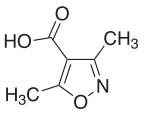

**Methyl 3-bromo-4-methoxybenzoate, puriss., 98%**
**65,283-0** 1 g, 10 g



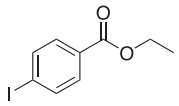

**2-Acetamidothiazole, 98%**
**64,838-8** 5 g



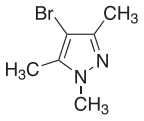

**3,5-Dimethylisoxazole-4-carboxylic acid, 98%**
**63,765-3** 1 g, 5 g



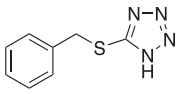

**Ethyl 4-iodobenzoate, 98%**
**66952** 10 g



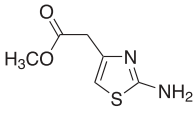

**4-Bromo-1,3,5-trimethylpyrazole, puriss., 98%**
**65,294-6** 1 g, 5 g



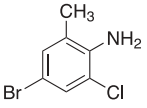

**5-(Benzylthio)-1*H*-tetrazole, ~0.25 M solution in acetonitrile**
**87757** 100 mL, 500 mL




**Methyl (2-amino-4-thiazolyl)acetate, puriss., 98%**
**65,302-0** 1 g, 5 g




**4-Bromo-2-chloro-6-methylaniline, 98%**
**64,875-2** 5 g, 25 g

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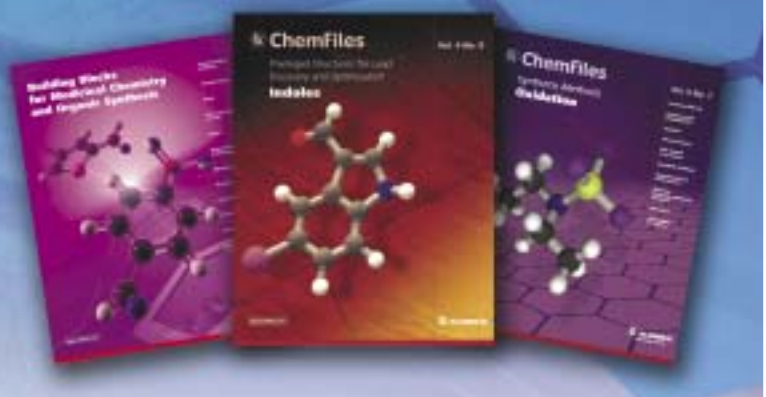


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## Dry Ice Splitter Head

For use with low-boiling solvents. Charge the 1.5-L Dewar reservoir with dry ice and solvent or liquid nitrogen for a rapid return of condensed liquid. Features ₹24/40 joints and a ₹10/30 thermometer joint, PTFE 0–3-mm metering valve, and two 4-mm glass stopcocks. Other joint sizes are also available.

| Cat. No. |
|---|
| **Z55,243-7** |

## Dean–Stark Adapter

Converts flasks, funnels, and receivers into Dean–Stark or Barrett receivers.

| ₹Joint | Cat. No. |
|---|---|
| 14/20 | **Z55,251-8** |
| 24/40 | **Z55,252-6** |
| 29/32 | **Z55,253-4** |

## Pear-Shaped Splash-Guard Adapter

Anti-climb.

| Capacity (mL) | ₹Inner Joint | ₹Outer Joint | Cat. No. |
|---|---|---|---|
| 100 | 24/40 | 14/20 | **Z55,757-9** |
| 100 | 24/40 | 24/40 | **Z55,758-7** |
| 250 | 24/40 | 14/20 | **Z55,759-5** |
| 250 | 24/40 | 24/40 | **Z55,760-9** |
| 100 | 29/32 | 14/20 | **Z55,761-7** |
| 100 | 29/32 | 24/40 | **Z55,762-5** |
| 250 | 29/32 | 14/20 | **Z55,763-3** |
| 250 | 29/32 | 24/40 | **Z55,764-1** |

## Vacuum-Filtration Adapter

Enables filtration (via Buchner funnel) directly into a single-neck, round-bottom flask. PTFE stopcock. Includes rubber sleeve.

| ₹Joint | Flange I.D. (mm) | Cat. No. |
|---|---|---|
| 14/20 | 23 | **Z55,639-4** |
| 19/22 | 23 | **Z55,640-8** |
| 24/40 | 31 | **Z55,641-6** |
| 24/40 | 38 | **Z55,642-4** |
| 29/42 | 31 | **Z55,643-2** |
| 29/42 | 38 | **Z55,644-0** |

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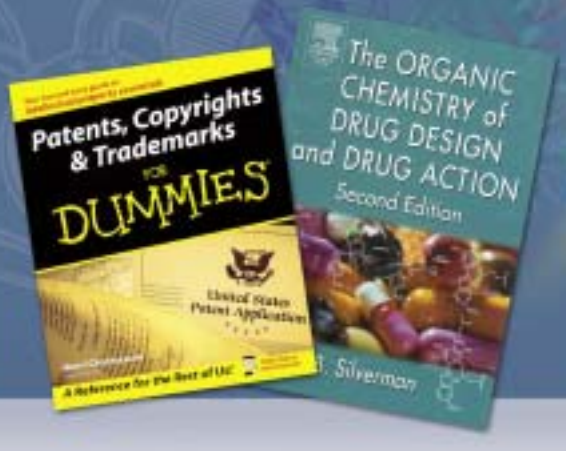


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## CHEMICAL SYNTHESIS TITLES

### Name Reactions in Heterocyclic Chemistry

*J. J. Li, Ed., Wiley, 2004, 558pp. Hardcover.* The chemistry of heterocyclic compounds and methods for their synthesis form the bedrock of modern medicinal, chemical, and pharmaceutical research. The primary topics include three- and four-membered heterocycles; five-membered heterocycles including indoles, furans, thiophenes, and oxazoles; six-membered heterocycles including quinolines, isoquinolines, and pyrimidines; and other heterocycles. Each name reaction is summarized in seven sections: description, historical perspective, mechanism, variations and improvements, synthetic utility, experimental, and references.

**Z70,312-5**

### Protecting Groups, 3rd Edition

*P. J. Kocienski, Thieme Publishers, 2004, 679pp. Softcover.* Provides a concise and understandable presentation of modern protecting group methods. The introductory chapter provides a sophisticated overview of the application of protecting groups in contemporary syntheses. At the heart of the book are seven chapters, which deal authoritatively and thoroughly with the protection of the various core functional groups, from carbonyl to amino. The final chapter presents an insight into the realities of synthetic practice and twenty-five problems for people who love to understand chemistry.

**Z55,155-4**

## DRUG DISCOVERY TITLES

### The Organic Chemistry of Drug Design and Drug Action, 2nd Edition

*R. B. Silverman, Academic Press, 2004, 617pp. Hardcover.* Standard medicinal chemistry courses and texts are organized by classes of drugs with an emphasis on descriptions of their biological and pharmacological effects. This book represents a new approach based on physical organic chemical principles and reaction mechanisms that rationalize drug action and allow the reader to extrapolate to many related classes of drug molecules. The second edition reflects the significant changes in the drug industry over the past decade, and now includes color illustrations, chapter problems, and other elements that make concepts easier to understand.

**Z70,239-0**

### Chirality in Drug Design and Development

*I. K. Reddy and R. Mehvar, Eds., Marcel Dekker, 2004, 444pp. Hardcover.* Covers every essential element in the development of chiral products, and provides a solid overview of the formulation, biopharmaceutical characteristics, and regulatory issues impacting the production of these pharmaceuticals. Supports researchers as they critically evaluate the pharmacodynamic, pharmacokinetic, and toxicological characteristics of specific enantiomers and chiral drug compounds.

**Z70,245-5**

## ANALYTICAL CHEMISTRY TITLES

### Analytical Method Validation and Instrument Performance Verification

*C. C. Chan et al., Eds., Wiley, 2004, 320pp. Hardcover.* Full of practical tips on validation techniques and detailed discussions of instrument performance verification, this guide represents a one-stop reference for today's regulatory environment. Each chapter includes general requirements, strategies and steps taken to fulfill these conditions, and a discussion of practical problems and their solutions. Coverage includes: method validation of potency, related substances, and dissolution testing; validation for pharmaceutical excipients, heavy metals, and bioanalysis; performance verification for common analytical instruments including HPLC, UV-Vis spectrophotometers, and pH meters; LCMS system calibration; proper environmental chamber qualification; and entire qualification process for computer equipment, hardware, and software.

**Z70,199-8**

### NMR Spectroscopy: Data Acquisition, 2nd Edition

*C. Schorn and B. Taylor, Wiley, 2004, 380pp. Hardcover with CD-ROM.* This key to correct structure analysis is now in its second edition. The result is a volume encouraging beginners to use high-resolution NMR, while prompting experts to evaluate new experiments using the easily manageable Bruker simulation program 1D and 2D WIN-NMR of the accompanying CD-ROM. Newcomers may come to understand basic data acquisition procedures, modular pulse sequence units, and complete sequences in NMR spectroscopy.

**Z70,309-5**

## MATERIALS SCIENCE TITLES

### Nanoparticles: From Theory to Application

*G. Schmid, Ed., Wiley, 2004, 444pp. Hardcover.* This is an introduction to the science of nanoparticles, from fundamental principles to their use in novel applications. As a basis for understanding nanoparticle behavior, the book outlines the principles of quantum-size behavior, nanoparticles architecture, formation of semiconductor and metal nanoparticles. It then goes on to describe the chemical syntheses of nanoparticles with defined characteristics, their structural, electrical, and magnetic properties, as well as current methods to monitor these properties.

**Z55,137-6**

## SPECIAL TOPICS TITLES

### High-Throughput Screening in Chemical Catalysis: Technologies, Strategies and Applications

*A. Hagemeyer et al., Eds., Wiley, 2004, 339pp. Hardcover.* This is the first book to cover all of the important aspects of this field. The editors, from Symyx Technologies Inc., have assembled a group of distinguished authors, each contributing the most up-to-date results and status in their application of high-throughput methodologies. Each chapter is devoted to a major topic including: high-throughput micro-reactor and synthesis equipment technologies, analytical approaches, experimental design and testing strategies, and fully integrated workflows for materials discovery. Examples in chemical catalysis are presented with an emphasis on heterogeneous catalysis, olefin polymerization using homogeneous catalysts, and electrocatalysis for fuel cells.

**Z70,314-1**

### Patents, Copyrights and Trademarks for Dummies

*H. Charmasson, Wiley, 2004, 380pp. Softcover.* This book explains, in layman's terms, the basic nature, function, and application of intellectual property (IP) rights, including how you can acquire those rights, wield them effectively against your competitors, or exploit them lucratively through licensing agreements and other rewarding ventures. The book covers all of these critical concepts, such as working with IP professionals, presenting a patent explanation, determining what is copyrighted and what isn't, protecting your commercial identity, inspecting the basic elements of a license, determining infringement, and avoiding the ten worst naming blunders.

**Z70,281-1**

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