IMPROVED CATALYSTS AND LIGANDS FOR ASYMMETRIC SYNTHESIS

# Aldrichimica ACTA

VOL. 41, NO. 1 • 2008

ALDRICH Chemistry

**Practical Organocatalysis with (*S*)- and (*R*)-5-Pyrrolidin-2-yl-1*H*-tetrazoles**

**Aminophosphine Catalysts in Modern Asymmetric Synthesis**

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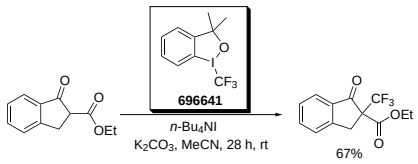


Eisenberger, P. et al. *Chem.—Eur. J.* **2006**, *12*, 2579.

**3,3-Dimethyl-1-(trifluoromethyl)-1,2-benziodoxole, 97%**

**696641** 250 mg, 1 g
[*887144-97-0*]
$C_{10}H_{10}F_3IO$
FW: 330.09

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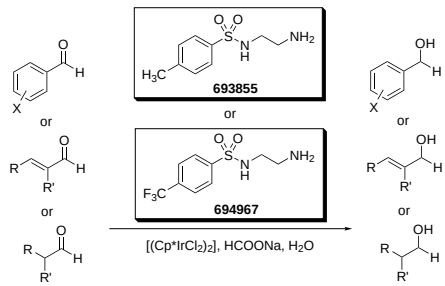
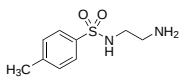
When used in conjunction with $[(Cp^*IrCl_2)_2]$, the ligands *N*-tosylethylenediamine (Ts(en)) and *N*-(2-aminoethyl)-4-(trifluoromethyl)-benzenesulfonamide ($CF_3$-Ts(en)) enable the facile and selective transfer hydrogenation of aldehydes with TOFs as high as $1.3 \times 10^5$ $h^{-1}$. Furthermore, the reactions are carried out in aqueous media and exhibit very good chemoselectivity and functional-group tolerance. In cases where α,β-unsaturated aldehydes are employed, reduction occurs selectively on the formyl group. Aliphatic aldehydes are also readily converted when the substrate is added portionwise over the course of the reaction.




Wu, X. et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 6718.

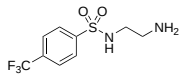
***N*-Tosylethylenediamine, 97%**

**693855** 5 g
[*14316-16-6*]
$C_9H_{14}N_2O_2S$
FW: 214.28



***N*-(2-Aminoethyl)-4-(trifluoromethyl)benzenesulfonamide, 97%**

**694967** 500 mg
$C_9H_{11}F_3N_2O_2S$
FW: 268.26



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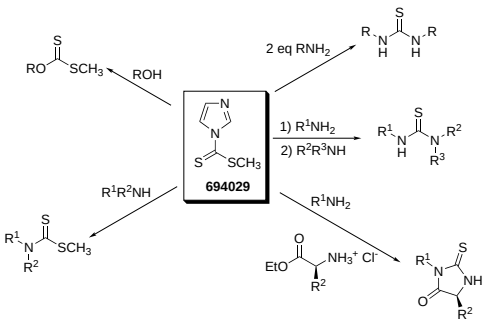
1-(Methyldithiocarbonyl)imidazole is a stable, non-hazardous reagent that can replace thiophosgene, isothiocyanates, chlorothioformates, and other high-hazard reagents as a thiocarbonyl-transfer agent for the synthesis of dithiocarbonates,[1] dithiocarbamates, symmetrical and unsymmetrical thioureas,[2] and 2-thiohydantoins.[3]




(1) Sun, W. Y. et al. *Synlett* **1997**, 1279. (2) Mohanta, P. K. et al. *Tetrahedron* **2000**, *56*, 629. (3) Sundaram, G. S. M. et al. *Synlett* **2007**, 251.

**1-(Methyldithiocarbonyl)imidazole, 97%**

**694029** 5 g
[*74734-11-5*]
$C_5H_6N_2S_2$
FW: 158.24

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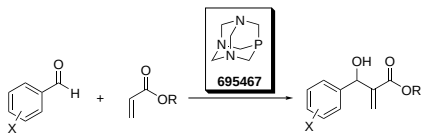


He, Z. et al. *Adv. Synth. Catal.* **2006**, *348*, 413.

**1,3,5-Triaza-7-phosphaadamantane**

**695467** 500 mg, 2 g
[*53597-69-6*]
$C_6H_{12}N_3P$
FW: 157.15

# Aldrichimica Acta

VOL. 41, NO. 1 • 2008



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## "PLEASE BOTHER US."

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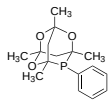
Professor Matthew Clarke of the University of St. Andrews (U.K.) kindly suggested that we make 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane. This phosphine is very stable to air and moisture and has the stereoelectronic properties of bulky phosphonites. When employed with rhodium complexes, this ligand shows high catalytic activity in the hydroformylation of various alkenes. High selectivities and conversions as high as 99% have been reported.

Clarke, M. L.; Roff, G. J. *Chem.—Eur. J.* **2006**, *12*, 7978.




| | | |
|---|---|---|
| **695459** | **1,3,5,7-Tetramethyl-6-phenyl-2,4,8-trioxa-6-phospha-adamantane, 97%** | 500 mg<br>2 g |

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

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*Dino Amoroso,* Todd W. Graham, Rongwei Guo, Chi-Wing Tsang, and Kamaluddin Abdur-Rashid,** Kanata Chemical Technologies, Inc.


## ABOUT OUR COVER

Photograph © Alfred Bader.

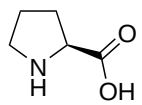
*Landscape with Tobias and the Angel, with a View of Antwerp in the Background* (oil on copper, 20.5 × 26.0 cm) was painted possibly around 1665 by Gillis Neyts, an enigmatic Flemish painter and engraver. Neyts (1623–1687) was born in Ghent, and spent a good part of his life in the city of Antwerp. He specialized in small, imaginary landscape scenes, which sometimes incorporated historical material or views of Flemish towns. His style approaches that of Lucas van Uden (1595–1672; Antwerp), who may have been his teacher.

This small painting, with its soft and delicate handling, which was typical for Neyts, shows on the left just below the horizon a part of the skyline of the city of Antwerp. The spectacular form of the arching tree in the center frames the figures of two travelers (with walking sticks) in the foreground on the right. One of them appears to waive at the viewer, while the other—dressed in red and white and with wings rising from his shoulders—is identified as the Archangel Raphael accompanying young Tobias on his journey.

Neyts has painted here a fantasy landscape in which he transposes the ancient story of Tobias and the angel onto a contemporary setting, the outskirts of the 17th-century city of Antwerp. It would appear that Neyts's purpose is to help the viewer of that period identify more closely with the story.

**This painting is in the private collection of Isabel and Alfred Bader.**

# Explore Organocatalysis



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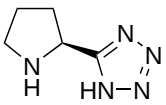

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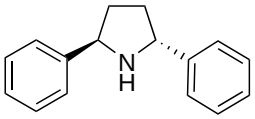

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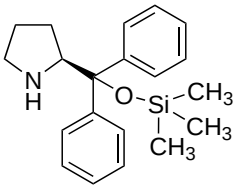

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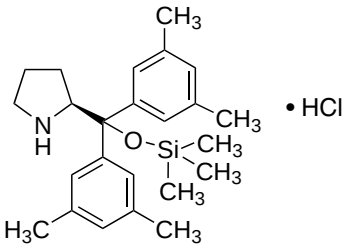

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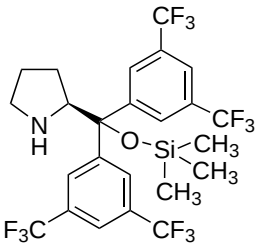

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# Practical Organocatalysis with (*S*)- and (*R*)-5-Pyrrolidin-2-yl-1*H*-tetrazoles

From left to right: Dr. Deborah A. Longbottom, Dr. Veit Wascholowski, Mr. Vilius Franckevičius, Prof. Steven V. Ley, Mr. Alexander J. Oelke, and Ms. Sirirat Kumarn.

*Deborah A. Longbottom, Vilius Franckevičius, Sirirat Kumarn, Alexander J. Oelke, Veit Wascholowski, and Steven V. Ley**
*Department of Chemistry*
*University of Cambridge*
*Lensfield Road*
*Cambridge CB2 1EW, U.K.*
*Email: svl1000@cam.ac.uk*

Professor Ley (center) receiving the Sigma-Aldrich sponsored *2007 ACS Award for Creative Work in Synthetic Organic Chemistry*. Pictured with Professor Ley are Dr. John Chan (left), Sigma-Aldrich Market Segment Manager, and Dr. Catherine T. Hunt (right), 2007 ACS President. Photo © Peter Cutts Photography, LLC.

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2. The Aldol Reaction
3. The Mannich Reaction
4. Conjugate Additions
5. α-Aminoxylation, α-Hydroxyamination, and α-Amination
6. One-Pot Reaction Processes
7. Conclusions
8. References and Notes

## 1. Introduction

The phenomenal renaissance of interest in organocatalysis has been fuelled by the ever-increasing repertoire of organocatalytic reactions of utility to the synthetic organic chemist. Innovative reactions appear weekly in research publications throughout the world, and these developments have spawned a search for newer and more effective catalysts to bring about a myriad of important chemical transformations.[1,2]

As with any evolving scientific (sub)discipline, there exists a need to provide a range of tools to solve particular problems and stimulate the creation of new concepts. The properties, function, and mechanisms of action of the individual organocatalysts are of prime importance for they must tolerate a wide range of chemistries, functional groups, and reaction conditions and, ideally, be of broad synthetic utility.

The simple amino acids L- and D-proline (**1** and **2**, **Figure 1**) have been widely utilized in many organocatalytic reactions and are often considered the benchmark with respect to which other catalysts are evaluated. Nevertheless, their lack of solubility in certain solvents and sometimes slow turnover rates have caused concern and, therefore, led to the discovery of other related catalytic systems that overcome some of these drawbacks.

For example, (*S*)- and (*R*)-5-pyrrolidin-2-yl-1*H*-tetrazole (**3** and **4**) are isosteres of proline with similar p$K_a$'s but anticipated greater solubility and, hence, reactivity in more lipophilic organic solvents. They were originally synthesized for organocatalytic applications almost simultaneously by three groups, Yamamoto's,[3] Arvidsson's,[4] and ours,[5] and have since proven very useful in a wide range of reactions.

Herein, we discuss the practical synthetic opportunities that have arisen through the development of these new catalytic species, which are shelf- and thermally stable, crystalline, and readily prepared on scale.[6–8] Emphasis is given to reaction type, rather than to detailed mechanistic discussion, as this is still the subject of much study and debate. In each reaction table, several examples have been selected from the original publication(s) to represent the breadth in substrate substitution, electronic character, and general compatibility of functional groups.

## 2. The Aldol Reaction

The aldol reaction is one of the most important carbon–carbon-bond-forming reactions and, therefore, the widespread interest in developing asymmetric variants of this transformation is not surprising. The direct asymmetric addition of unmodified ketones to aldehydes has been developed by Shibasaki's and Trost's groups by using heterobimetallic catalysts,[9] whereas others have used more nature-inspired catalytic systems

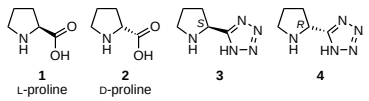
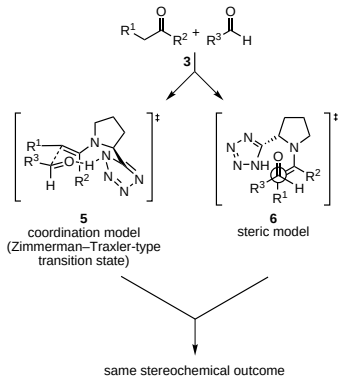
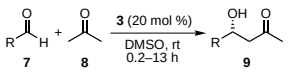



**Figure 1.** L- and D-Proline and (*S*)- and (*R*)-5-Pyrrolidin-2-yl-1*H*-tetrazole.




*Ref. 7*

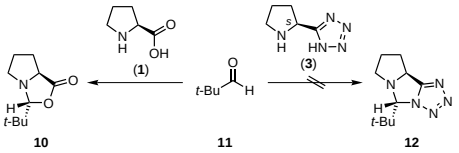
**Scheme 1.** Transition States in the Pyrrolidinyltetrazole **3** Mediated Aldol Reaction.




| 9 | R | Yield | ee |
|---|---|---|---|
| **a** | Ph | 69% | 65% |
| **b** | 4-MeOC$_6$H$_4$ | 65% | 62% |
| **c** | 4-BrC$_6$H$_4$ | 67% | 66% |
| **d** | 4-O$_2$NC$_6$H$_4$ | 82% | 79% |
| **e** | *i*-Pr | 79% | 99% |

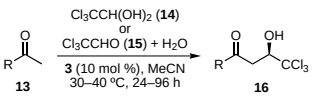
*Ref. 7*

**eq 1**




*Ref. 7*

**Scheme 2.** Parasitic Consumption of the Catalyst in the Case of L-Proline (**1**), but not in the Case of Pyrrolidinyltetrazole **3**.




| 16 | R | Yield | ee |
|---|---|---|---|
| **a** | *i*-Pr | 79% | 97% |
| **b** | EtO$_2$C | 55% | 86% |
| **c** | Me$_2$C=CH(CH$_2$)$_2$ | 93% | 82% |
| **d** | Ph | 75% | 92% |
| **e** | 2-Np | 83% | 91% |

*Ref. 3*

**eq 2**

consisting of aldolase enzymes and catalytic antibodies.[10] An organocatalytic approach that uses L-proline (**1**) as catalyst for an intramolecular aldol cyclization, known as the Hajos–Parrish–Eder–Sauer–Wiechert reaction, was reported around 35 years ago.[11] More recently, following List's important work,[2] a number of groups have confirmed that L-proline (**1**) can also mediate the analogous intermolecular aldol reaction of unmodified ketones and aldehydes.[12]

To date, there have been three publications that focus fully on the ability of pyrrolidinyltetrazole **3** to facilitate the intermolecular aldol reaction,[3,4,7] and its usefulness has now been further demonstrated in an aldol reaction applied to natural product synthesis.[13]

As alluded to previously, the details of the mechanism of these reactions are generally the subject of much debate and discussion. However, two widely accepted transition state models for the aldol reaction catalyzed by **3** produce the same stereochemical outcome and involve an enamine intermediate reacting either via a coordinated Zimmerman–Traxler-type transition state, **5**, or via transition state **6** (**Scheme 1**).[7]

Hartikka and Arvidsson have shown that aliphatic aldehydes are generally less reactive than aromatic ones in the direct asymmetric aldol reaction between acetone (**8**) and a variety of aldehydes leading to β-hydroxy ketones **9** (**eq 1**).[4,7] Nevertheless, the high catalytic activity of pyrrolidinyltetrazole **3** allowed even aliphatic aldehydes to be transformed into the corresponding chiral β-hydroxy ketones **9** with high enantioselectivities and fair yields in thirteen hours or less. The authors additionally proved that even a catalyst loading of 5% was still effective, though a longer reaction time was required.

It is interesting to note at this point that parasitic catalyst consumption[14] is observed with L-proline (**1**) but not with **3**. Arvidsson carried out NMR studies using a mixture of **1** or **3** and 2,2-dimethylpropionaldehyde (**11**) and proved that, while L-proline (**1**) easily engages in parasitic formation of bicyclic oxazolidinone **10**, pyrrolidinyltetrazole **3** does not (**Scheme 2**).[7] Consequently, in theory, this results in more of **3** being available to form the postulated enamine intermediate in the aldol reaction. The authors suggested that this could be the main reason for the increased reactivity of **3** compared to that of L-proline (**1**) in DMSO.[15] However, this does not rule out the possibility that factors relating either to the increased solubility of **3** in DMSO or to alternative mechanistic pathways operating in other solvent systems may also be contributing to the observed enhancement in reactivity of **3**.

Yamamoto's work has focused on the formation of optically active 1,1,1-trichloro-2-alkanols (**eq 2**),[3] previously demonstrated as being versatile tools for the preparation of variously functionalized compounds such as α-hydroxy and α-amino acids.[16] The formation of 1,1,1-trichloro-2-alkanols by the asymmetric aldol reaction is challenging due to the propensity of the starting aldehydes to form hydrates. However, in Yamamoto's report, **3** displayed excellent catalytic efficiency and activity in the reaction of either chloral monohydrate (**14**) or chloral (**15**) and water with a variety of aliphatic and aromatic ketones.

Ward then proved that pyrrolidinyltetrazole **3** was also useful in a total synthesis program:[13] serricornin (**21**), a sex pheromone produced by the female cigarette beetle *Lasioderma serricorne F.*, was elegantly prepared in just seven steps and overall 31% yield from the readily available *racemic* aldehyde **18** (**Scheme 3**).[13] The enantioselective direct aldol reaction of **17** with **18**, catalyzed by **3**, was the key step in the synthesis

and occurred with dynamic kinetic resolution to give adduct **19** with >98% ee. Aldol product **19** was then smoothly converted into diol **20** with excellent yield and diastereoselectivity. Because diastereomeric diols **22**, **23**, and **24** (**Figure 2**) are also readily prepared from **19**,[17] it was proposed that this powerful strategy could be extended to afford stereoisomers of **21**, which could then be tested for biological activity.

## 3. The Mannich Reaction

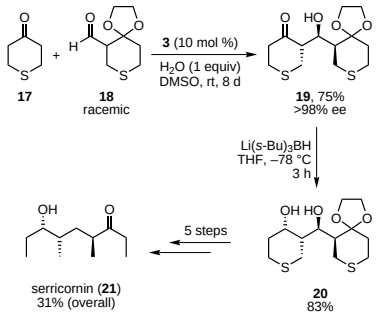
The development of syntheses that provide enantiomerically pure α-amino acids has been the subject of generations of research by organic chemists. This has engendered an array of methodologies,[18] which, not only allow for the stereoselective construction of naturally occurring amino acids, but also permit the rational design of optically active nonproteinogenic ones. These unnatural amino acids in particular have enjoyed increased popularity, mainly due to their incorporation into nonscissile peptide mimetics and peptide isosteres, known to exhibit reduced susceptibility to catabolism and thus increased bioavailability.[19]

In a similar way, chiral diamines are important building blocks for pharmaceuticals and are features that are frequently found in natural products.[20,21] As synthetic tools, chiral diamines are also used extensively as chiral auxiliaries and catalysts.[22] However, despite their significance, their asymmetric synthesis is not straightforward: they are most frequently synthesized from diols or aziridines[21] or by addition of glycine ester enolates to imines.[23] The direct reductive coupling of imines has also been reported, but this approach is limited to the preparation of symmetrical vicinal diamines and results in relatively low stereoselectivity.[24]

Thus, the organocatalytic synthesis of enantiomerically pure α-amino acids and diamines had so far represented a worthwhile challenge to organic chemists. Gratifyingly, pyrrolidinyltetrazole **3** has now been used to great effect in the synthesis of both classes of compound by employing the Mannich reaction as the key carbon–carbon-bond-forming step. In the synthesis of α-amino acid derivatives—which serves as an excellent comparison with previous work by Barbas (where L-proline (**1**) is the catalytic species)[25]—our group has showed that **3** also effectively catalyzes this reaction (**eq 3**).[5,26] Indeed, our method represents a very attractive alternative to Barbas's as the yields and stereoselectivities are comparable to those obtained with L-proline (**1**),[25] yet the reaction is carried out in solvents such as dichloromethane (avoiding dimethyl sulfoxide) and with catalyst loadings as low as 1%.[27]

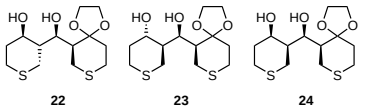
Following this report, Barbas showed that the organocatalytic asymmetric Mannich reaction of protected amino ketones with imines in the presence of **3** affords diamines with excellent yields and enantioselectivities of up to 99%.[28] The amino ketone protecting group controlled the regioselectivity of the reaction, providing access to chiral 1,2- and 1,4-diamines from azido and phthalimido ketones, respectively. Under optimized conditions, the three-component Mannich reaction of various combinations of azido ketones and aldehydes was investigated (**eq 4**).[28] All products were obtained regioselectively and with good diastereo- (syn:anti = 70:30 to 91:9) and enantioselectivities (82–99% ee, syn). A one-pot reduction–Boc-protection of Mannich product **31b** provided differentially protected 1,2-diamine **32** (**eq 5**), illustrating the potential utility of these compounds in further synthetic steps. The scope of this reaction seems very broad, and the azido ketones products, **31**, are in themselves interesting substrates for potential "click chemistry" based diversification.[29]

The Mannich reaction of phthalimidoacetone (**33**), a phthaloyl-protected amino ketone, in *N*-methyl-2-pyrrolidone (NMP) as



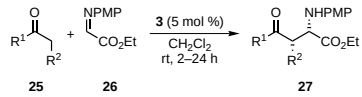

*Ref. 13*

**Scheme 3.** Enantioselective Total Synthesis of Serricornin (**21**) from Racemic Aldehyde **18**.




*Ref. 17*

**Figure 2.** **19**-Derived Diastereomeric Diols for the Synthesis of Serricornin Analogues.



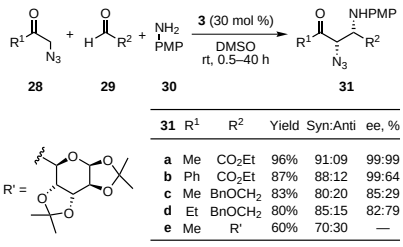

PMP = *p*-methoxyphenyl

| 27 | $R^1$,$R^2$ | Yield | Syn:Anti | ee |
|---|---|---|---|---|
| **a** | $-(CH_2)_4-$ | 65% | >19:1 | >99% |
| **b** | $-(CH_2)_5-$ | 59% | >19:1 | >99% |
| **c** | $-(CH_2)_2-$ | 74% | >19:1 | 94% |
| **d** | Me,H | 99% | —[a] | >99% |
| **e** | Me,Et | 72% | >19:1 | >99% |

[a] Reaction carried out in acetone.

*Ref. 5,26*

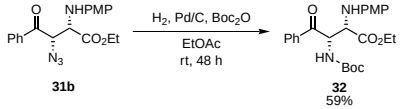
**eq 3**




| 31 | $R^1$ | $R^2$ | Yield | Syn:Anti | ee, % |
|---|---|---|---|---|---|
| **a** | Me | $CO_2Et$ | 96% | 91:09 | 99:99 |
| **b** | Ph | $CO_2Et$ | 87% | 88:12 | 99:64 |
| **c** | Me | $BnOCH_2$ | 83% | 80:20 | 85:29 |
| **d** | Et | $BnOCH_2$ | 80% | 85:15 | 82:79 |
| **e** | Me | R' | 60% | 70:30 | — |

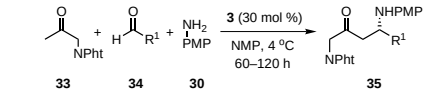
*Ref. 28*

**eq 4**




*Ref. 28*

**eq 5**



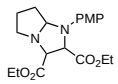

33 34 30 35

NMP = *N*-methyl-2-pyrrolidone
Pht = phthalimido

| 35 | $R^1$ | Yield | ee |
|---|---|---|---|
| **a** | $CO_2Et$ | 88% | 91% |
| **b** | 4-$O_2NC_6H_4$ | 68% | 97% |
| **c** | 4-$NCC_6H_4$ | 56% | 95% |
| **d** | Ph | 71% | 77% |

*Ref. 28*

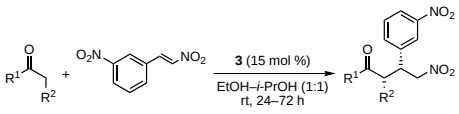
**eq 6**




**36**

*Ref. 28*

**Figure 3.** Major Product of the Mannich Reaction of Phthalimidoacetone in the Presence of L-Proline (**1**).

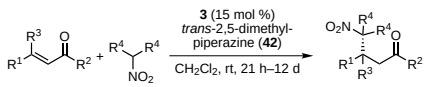



37 38 39

| 39 | $R^1$,$R^2$ | Yield | Syn:Anti | ee |
|---|---|---|---|---|
| **a** | $-(CH_2)_2SCH_2-$ | 62% | 10:1 | 70% |
| **b** | $-(CH_2)_2OCH_2-$ | 94% | 6:1 | 54% |
| **c** | Me,Me | 71% | 10:1 | 32% |
| **d** | Me,H | 72% | — | 33% |
| **e** | Et,Me | 68% | >19:1 | 65% |

*Ref. 26,30*

**eq 7**

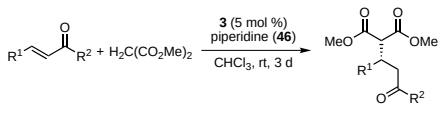



40 41 43

| 43 | $R^1$,$R^2$ | $R^3$ | $R^4$ | Yield | ee |
|---|---|---|---|---|---|
| **a** | $-(CH_2)_3-$ | Me | H | 64% | 91% |
| **b** | $-(CH_2)_2-$ | H | Me | 62% | 80% |
| **c** | Ph,Et | H | Me | 78% | 78% |
| **d** | thien-2-yl,Me | H | Me | 61% | 72% |
| **e** | $CO_2$Me,Me | H | Me | 96% | 82% |
| **f** | *n*-Pent,Me | H | Me | 44% | 58% |

*Ref. 32*

**eq 8**




44 45 47

| 47 | $R^1$,$R^2$ | Yield | ee |
|---|---|---|---|
| **a** | $-(CH_2)_3-$ | 87% | 83% |
| **b** | Ph,Me | 89% | 84% |
| **c** | 4-$F_3CC_6H_4$,Me | 84% | 78% |
| **d** | 4-$HOC_6H_4$,Me | 70% | 64% |
| **e** | furan-2-yl,Me | 69% | 81% |
| **f** | thien-2-yl,Me | 82% | 84% |

*Ref. 33*

**eq 9**

solvent exhibited excellent regioselectivity: Enamine formation was favored at the less hindered side of the carbonyl group and generated protected 1,4-diamines **35** in good yields and enantioselectivities (**eq 6**).[28] Interestingly, when the formation of **35a** was attempted using L-proline (**1**) as catalyst in NMP at room temperature, phthalimidoacetone (**33**) provided Mannich product **35a** only in trace amounts accompanying the formation of cycloadduct **36** (**Figure 3**) as the major product in 59% yield. It would thus appear that L-proline (**1**) is not a useful catalyst in this reaction.

To summarize, the pyrrolidinyltetrazole **3** mediated Mannich reaction provides efficient access to several highly important product types, namely chiral α-amino acids and diamines. It can be performed under environmentally favorable conditions without the requirement for inert atmosphere or dry solvents, and provides good-to-excellent yields and regio- and stereoselectivities.

## 4. Conjugate Additions

The organocatalytic conjugate addition of nucleophiles to nitroolefins[26,30] and enones[31–33] can also be mediated by **3** and leads to useful adducts such as γ-nitro ketones and 1,5-dicarbonyl compounds (**eq 7–9**).

In the former case (see eq 7),[26,30] ketone-derived enamines add to electrophilic nitroalkenes to form Michael adducts **39**, which are useful synthetic precursors to other functionalities that are derived from the nitro group.[34] Interestingly, when compared to the results obtained with L-proline (**1**),[35] pyrrolidinyltetrazole **3** far outperformed it in terms of yield, enantioselectivity, reaction times, and stoichiometry. However, despite the fact that the results published were the best in the literature at that time, they still left some room for improvement, and it was only when the homoproline tetrazole derivative **50** (**eq 10**) was used that the yields and enantioselectivities moved to practically useful levels.[36,37]

In the addition of nitroalkanes to enones, the same type of γ-nitro ketone adduct is formed but, due to the nature of the reaction, products with alternative structural features are obtained (see eq 8).[31,32] In this case, pyrrolidinyltetrazole **3** proved to be a versatile catalyst for the asymmetric 1,4 addition of a variety of nitroalkanes to cyclic and acyclic enones, using *trans*-2,5-dimethylpiperazine (**42**) as a stoichiometric base additive. Using **3**, the reaction was also scalable, providing enantiomeric excesses of up to 98% in relatively short reaction times (1–3 days) and employing just two equivalents of the coupling nitroalkane.[38] Kinetic investigations, combined with the observed sensitivity of certain substrates to water, support the iminium catalysis mechanism.[32]

The addition of malonates to enones (see eq 9)[33] leads to a variety of useful 1,5-dicarbonyl compounds. In the case of **3**,[39] only 1.5 equivalents of malonate is needed, and the reaction is readily scaled and practical to operate,[33] rendering the process potentially useful in a synthesis program. The utility of such addition products in synthesis has now been further proved by carrying out the decarboxylation of **47a** to the corresponding monomethyl ester (**53**, **eq 11**). While a loss in enantiomeric excess had been observed under various Krapcho conditions,[40,41] it has now been shown that sodium hydroxide or porcine liver esterase (PLE) smoothly mediates the monohydrolysis of **47a**; subsequent decarboxylation provides the corresponding methyl ester, **53**, in excellent yield, with neither step resulting in any reduction in enantiomeric purity.[41]

Finally, it was thought that an extension of these conjugate addition methods might be useful in a new organocatalytic

asymmetric nitrocyclopropanation reaction. Cyclopropane-containing structures are compounds of interest within organic chemistry as they display a relatively large amount of stereochemical information over a small, rigid framework of just three carbon atoms. They serve as versatile synthetic intermediates in a variety of reactions[42] and are widely distributed in a range of naturally occurring compounds[43] and peptidomimetics.[44] Consequently, their stereoselective preparation is a valuable goal and, to date, several methods have been developed towards this aim.[45]

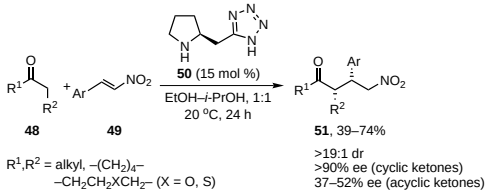
In particular, nitrocyclopropanes may be converted into a wide range of functional groups[34,46] and can be prepared by a variety of methods.[47] Therefore, it was surprising that there were only two synthetic approaches,[48] prior to the one described below,[49] that detailed their enantioselective formation. Indeed, the novel organocatalytic method developed by our group provides a higher yield and enantioselection than is found in either: following optimization studies, 7-nitrobicyclo[4.1.0]-heptanone **56** (**eq 12**) was provided in 80% yield and 77% ee, which was then easily improved to >98% ee upon a single recrystallization.[49] More recent experiments have indicated that, under further optimized reaction conditions, not only can this result be improved (87% yield, 90% ee),[50] but that the reaction is now generally applicable to a wider range of substrates such as aliphatic and aromatic enones, providing useful products in good yields and enantiomeric excesses.[50]

Thus, these conjugate addition procedures can be extremely powerful, providing, not only the products of conjugate addition, but also of tandem reactions such as the nitrocyclopropane example given above. Many further applications of this concept can be envisaged and are currently being investigated in our laboratory.

## 5. α-Aminoxylation, α-Hydroxyamination, and α-Amination

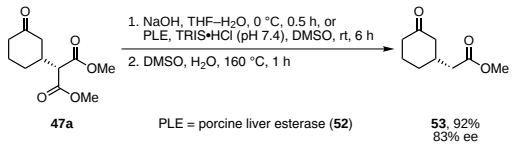
The regio- and stereoselective replacement of hydrogen by oxygen or nitrogen results in a rapid increase in molecular complexity,[51] and one can see that, with a nitrosobenzene electrophile[52] under enamine catalysis, either the oxygen- (α-aminoxylation) or nitrogen-substituted (α-hydroxyamination) product might be observed. This can give rise to optically active α,α'-disubstituted oxy- or amino aldehydes.[53]

The two major independent studies that have been carried out by Yamamoto and Kim, respectively, have shown that a reactivity pattern exists.[6,54] When ketones and aldehydes with no branching at the α position are employed (**eq 13**),[6] generally the preference is for α-aminoxylation; whereas if the substrate is α-branched, α-hydroxyamination is also observed, at least in the case of aldehydes (**eq 14**).[54] A plausible explanation for this inherent difference in reactivity is found when the reaction transition state is examined (**Figure 4**): if α branching is present, the clash between the α substituent and the phenyl group of nitrosobenzene in the usual transition state, **63**, will push the phenyl group into the pseudoequatorial position, **64**. This results in hydrogen bonding of the oxygen rather than the nitrogen atom with the tetrazole portion, thus changing the regiochemical outcome of the reaction. However, although the contrasting regioselectivity of this reaction is usually predictable, the selective formation of α-hydroxyamination products is not yet general: in order to introduce an α-nitrogen substituent, α-branched aldehydes must be utilized, and mixtures of O- and N-substituted products are usually observed.



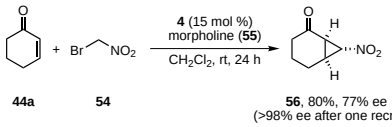

*Ref. 36*

**eq 10**



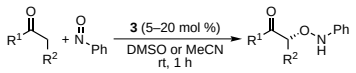

*Ref. 41*

**eq 11**




*Ref. 49*

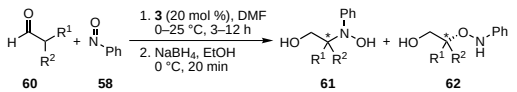
**eq 12**




| 59 | $R^1,R^2$ | Yield | ee |
|---|---|---|---|
| a | $-(CH_2)_4-$ | 94% | >99% |
| b | $-CH_2O(CH_2)_2-$ | 87% | >99% |
| c | $-CH_2C(OCH_2)_2(CH_2)_2-$ | 97% | 99% |
| d | $-CH_2N(BnCO)(CH_2)_2-$ | 95% | >99% |
| e | H,Bn | 67% | 98% |
| f | H,*i*-Pr | 65% | 98% |
| g | H,*n*-Bu | 69% | 98% |

*Ref. 6*

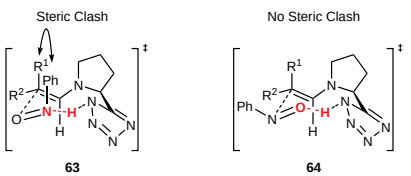
**eq 13**




| No. | $R^1$ | $R^2$ | Yield | 61:62 | ee, 61 | ee, 62 |
|---|---|---|---|---|---|---|
| a | Bn | Me | 96% | 1.0:1 | 81% | 37% |
| b | 4-MeO$C_6H_4CH_2$ | Me | 75% | 1.7:1 | 90% | 35% |
| c | 4-Br$C_6H_4CH_2$ | Me | 98% | 1.4:1 | 86% | 45% |
| d | $BnOCH_2$ | Me | 89% | 0.8:1 | 79% | 5% |
| e | allyl | Me | 91% | 0.7:1 | 62% | 27% |
| f | *n*-Bu | Et | 55% | 0.6:1 | 5% | 2% |

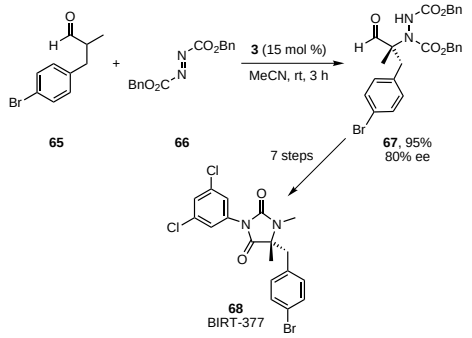
*Ref. 54*

**eq 14**



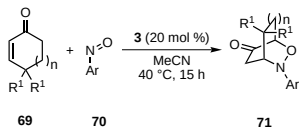

*Ref. 6*

**Figure 4.** Postulated Transition States Leading to α-Aminoxylation or α-Hydroxyamination.




*Ref. 55*

**Scheme 4.** α-Amination of Aldehydes as a Step in the Total Synthesis of BIRT-377 (**68**).

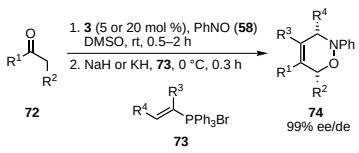



**69** **70** **71**

| 71 | n | $R^1$ | Ar | Yield | ee |
|---|---|---|---|---|---|
| **a** | 1 | Me | Ph | 64% | 99% |
| **b** | 1 | Ph | Ph | 56% | 99% |
| **c** | 1 | Me | *p*-Tol | 47% | 98% |
| **d** | 1 | Me | *m*-Xyl | 52% | 98% |
| **e** | 1 | Me | *p*-Br | 50% | 99% |
| **f** | 2 | H | H | 14% | 99% |

*Ref. 58a*

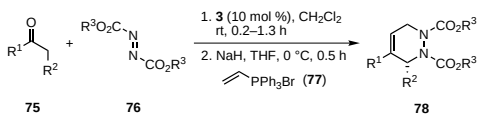
**eq 15**




| 74 | $R^1$,$R^2$ | $R^3$ | $R^4$ | Yield |
|---|---|---|---|---|
| **a** | $-(CH_2)_4-$ | H | H | 60% |
| **b** | $-(CH_2)_4-$ | Me | H | 39% |
| **c** | $-(CH_2)_4-$ | H | Me | 65% |
| **d** | $-(CH_2)_2SCH_2-$ | H | H | 51% |
| **e** | $-(CH_2)_2C(OCH_2CH_2O)CH_2-$ | H | H | 50% |
| **f** | H,*i*-Pr | H | H | 71% |
| **g** | H,*t*-Bu | H | H | 82% |
| **h** | H,$(CH_2)_3CO_2Me$ | H | H | 50% |

*Ref. 59a,b*

**eq 16**




| 78 | $R^1$,$R^2$ | $R^3$ | Yield | ee |
|---|---|---|---|---|
| **a** | H,*i*-Pr | Et | 89% | 94% |
| **b** | H,*i*-Pr | *t*-Bu | 81% | 99% |
| **c** | H,*i*-Pr | Bn | 63% | 89% |
| **d** | H,*t*-Bu | Et | 84% | 99% |
| **e** | H,allyl | Et | 69% | 90% |
| **f** | H,$(CH_2)_3CO_2Me$ | Et | 67% | 69% |
| **g** | $-(CH_2)_4-$ | Et | 52% | 76% |
| **h** | $-(CH_2)_2SCH_2-$ | Et | 40% | 83% |
| **i** | $-(CH_2)_2C(OCH_2CH_2O)CH_2-$ | Et | 50% | 76% |

*Ref. 59c,60*

**eq 17**

In their total synthesis of BIRT-377 (**68**),[55] Chowdari and Barbas have shown that, as a related reaction, pyrrolidinyltetrazole **3** mediated α-amination is possible with dibenzyl azodicarboxylate (**66**) as the nitrogen source, and that even a quaternary stereocenter can be formed (**Scheme 4**). The synthesis of quaternary amino acids through organocatalytic amination reactions is challenging, since the cis and trans enamines derived from α-branched aldehydes are energetically less distinct, as compared with their linear counterparts, and this can lead to low enantioselectivities.[55] The higher reactivity and enantioselectivity obtained with **3** relative to L-proline (**1**), in the reaction leading to **67**, was ascribed to the lower p$K_a$ and increased steric bulk of the tetrazole relative to proline's carboxylic acid moiety. Indeed, the desired key intermediate **67** was formed in an excellent 95% yield and 80% ee (compared with those observed with L-proline (**1**): 5-day reaction time, 90% yield, and 44% ee). It was suggested that analogues of **67** could be accessed by simply changing the α,α'-disubstituted aldehyde and catalyst stereochemistry. This means much scope remains for investigations into this unexploited area of research.

## 6. One-Pot Reaction Processes[56]

Presently, organic synthesis can be hampered by time-consuming and costly protecting-group strategies and (lengthy) purification procedures after each synthetic step. In order to circumvent these difficulties, the synthetic potential of multicomponent domino reactions has now been exploited in the efficient and stereoselective construction of complex molecules from simple precursors in a single process. These domino reactions often proceed with excellent stereoselectivities and are generally environmentally more appropriate. The efficiency of asymmetric domino reactions can easily be seen in the number of newly formed bonds, the number of new stereocenters, and the concomitant rapid increase in molecular complexity. In particular, domino reactions mediated by organocatalysts are of great utility as they are characterized by high efficiencies and are in a way biomimetic in origin: the same governing principles are often found in the biosynthesis of natural products.[57]

This field has grown over the last few years and, often, the advantage of employing organocatalysts is their ability to promote several types of reactions through different activation modes. Pyrrolidinyltetrazole **3** has so far been useful in two major tandem reaction types, namely the enantioselective α-aminoxylation–Michael reaction (**eq 15**),[58] and the formation of chiral 1,2-oxazines (**eq 16**)[59] and their 3,6-dihydropyridazine congeners (**eq 17**).[59c,60] In the former example (see eq 15), pyrrolidinyltetrazole **3** mediated a highly enantioselective synthesis of Diels–Alder nitroso adducts **71**,[58] and the results disclosed revealed opposite regioselectivities and increased stereochemical control over the more common and complementary Diels–Alder procedures used to make the same structural motif. In the latter tandem reaction type (see eq 16), a new method was developed for the synthesis of enantiomerically pure 1,2-oxazines **74** from achiral starting materials.[59] This procedure relies on initial α-aminoxylation of an enamine intermediate with nitrosobenzene (**58**), followed by nucleophilic attack on vinylphosphonium salt **73**, and subsequent intramolecular Wittig reaction. This tandem process is a useful addition to the toolbox of the organic chemist: it is quite general and reliable, and methods for preparing this unit in an optically pure fashion are scarce.

In addition, an analogous method was published for the synthesis of a related heterocycle, the 3,6-dihydropyridazine unit

(**78**), from aldehydes and ketones.[59c,60] In the case of aldehydes,[60] products were formed in generally good-to-excellent yields and enantioselectivities with a variety of nitrogen protecting groups. This method has now been extended to ketones,[59c] greatly increasing its scope. Furthermore, the selective α amination of aldehydes with differentially protected azodicarboxylates (e.g., BocN=NTroc) has also been developed recently, serving as a useful platform for further selective derivatization of these products.[61]

Thus, it can be seen that early results on these one-pot reaction processes show that they can be very powerful, generating molecular complexity extremely quickly. We look forward with great excitement to further publications in this area.

## 7. Conclusions

In this short review, the variety of practical synthetic opportunities offered by the (*S*)- and (*R*)-pyrrolidinyltetrazole catalysts **3** and **4** has been illustrated. Their utility has been demonstrated beyond doubt: they are indeed worthy catalysts of a number of asymmetric organocatalytic processes and are undeniably useful additions to the rapidly developing armory of shelf-stable catalysts available to the synthetic organic chemist.

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## About the Authors

**Deborah A. Longbottom** received her undergraduate degree from the University of Durham in 1997 and, following a year working in the pharmaceutical industry, came to Cambridge to carry out her Ph.D. work under the guidance of Professor Steven Ley. In 2002, she joined Professor K. C. Nicolaou's research group at The Scripps Research Institute, San Diego, California, as a postdoctoral associate and returned to Professor Ley's Group early in 2004. Her research interests have encompassed both natural product synthesis (e.g., polyenoyltetramic acids and depsipeptides) and method development (e.g., novel uses of the Burgess reagent and organocatalytic methodologies). Currently, she is a senior research associate in Professor Ley's group, and concurrently holds teaching fellowships in both the Department of Chemistry and Trinity College, Cambridge.

**Vilius Franckevičius** was born in 1983 in Kaunas, Lithuania. He studied Natural Sciences at the University of Cambridge, where he undertook his final-year project on the development of new organocatalysts under the supervision of Professor Steven Ley, and subsequently obtained his M.Sci. degree in Natural Sciences (chemistry) in 2005 (Fitzwilliam College). He is currently a Ph.D. student in Ley's research group, where he is involved in the application of organocatalytic methodology in natural product synthesis.

**Sirirat Kumarn** was born in Sukhothai, Thailand. She received her undergraduate degrees in Natural Sciences (chemistry) in 2004 from St. Catharine's College, University of Cambridge. She is currently a Ph.D. student in Professor Ley's research group, where she is working on the development of an organocatalytic route to enantiopure 1,2-oxazines and its applications to natural product synthesis.

**Alexander J. Oelke** was born in 1980 in Reinbek, Germany. He studied chemistry at the University of Hamburg, where he obtained his Diploma in 2006 under the supervision of Professor Chris Meier, and in collaboration with Professor Steven Ley, for the development of an organocatalytic tandem procedure for the synthesis of chiral pyridazine derivatives. He is currently a Ph.D. student in Ley's group at the University of Cambridge, where he is involved in the application of organocatalytic methodology in natural product synthesis.

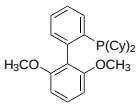
**Veit Wascholowski** was born in 1975 in Braunschweig, Germany. He studied chemistry at the University of Karlsruhe, Germany, and completed his Diploma in 2000. He received his Ph.D. degree in 2006 from the University of Leipzig, Germany, where he worked under the guidance of Professor Athanassios Giannis in the field of chemical biology, which involved the synthesis and biological evaluation of natural products and their analogues. In 2006, he joined Professor Ley's research group at the University of Cambridge as a postdoctoral research associate, where he is currently working on the development of new organocatalytic reactions and their application in the total synthesis of natural products.

**Steven V. Ley** received his Ph.D. degree from Loughborough University in 1972, after which he carried out postdoctoral research with Professor Leo Paquette at Ohio State University, and then with Professor Derek Barton at Imperial College, London. In 1975, he joined that Department as a lecturer and became Head of Department in 1989. In 1992, he moved to take up the 1702 BP Chair of Organic Chemistry at the University of Cambridge, and became a Fellow of Trinity College. He was elected to the Royal Society in 1990 and, between 2000 and 2002, was President of the Royal Society of Chemistry (RSC). In addition, Steve was made a Commander of the British Empire (CBE) early in 2002, and has been the recipient of many prizes and awards for his creative work and innovative solutions in the art of organic synthesis. Among the most recent of these are the Yamada–Koga Prize (2005), the Nagoya Gold Medal (2006), the ACS Award for Creative Work in Synthetic Organic Chemistry (2007), and the Paul Karrer Medal (2007).

# Accelerate Catalysis

## Buchwald Ligands

The Pd-catalyzed C–N-bond formation has become an important synthetic reaction in the past 20 years. Buchwald and co-workers have been very active in synthesizing and developing a portfolio of phosphine ligands for this transformation and other cross-coupling reactions. The ligands chosen are based on a biaryl skeleton with a phosphorus moiety at the 2 position of one aromatic ring and another moiety on the other aromatic ring. These ligands are very stable and active in a variety of cross-coupling reactions such as carbon–carbon, carbon–nitrogen, and carbon–oxygen coupling. Sigma-Aldrich is pleased to offer the following portfolio of Buchwald ligands.

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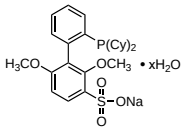


**(SPhos, water soluble)**
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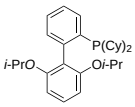


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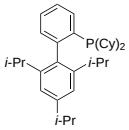


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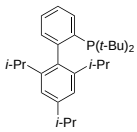


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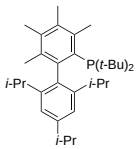


**(Tetramethyl di-tBuXPhos)**
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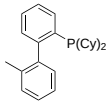


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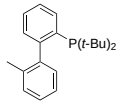


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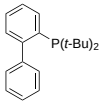


**(JohnPhos)**
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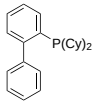


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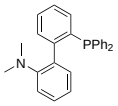


**(PhDavePhos)**
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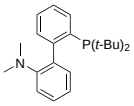


**(tBuDavePhos)**
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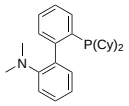



**(DavePhos)**
**638021**

**Buchwald Ligands Kit I 659932**
The kit contains:

| | | |
|---|---|---|
| **638021** | **638072** | **638099** |
| **638064** | **638080** | **638439** |

**Buchwald Ligands Kit II 687243**
The kit contains:

| | | |
|---|---|---|
| **638439** | **638080** | **638021** |
| **638099** | **663131** | **638064** |
| **675938** | **638072** | **677280** |

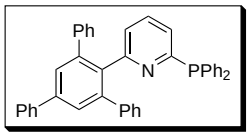
**Buchwald Ligands Kit III 698903**
The kit contains:

| | | |
|---|---|---|
| **638072** | **675938** | **695882** |
| **677280** | **695262** | **695874** |
| **663131** | **695211** | **638021** |
| **638064** | **638439** | |
| **638080** | **638099** | |

## HydraPhos Ligands

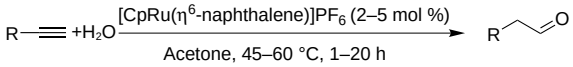
Hintermann and coworkers introduced a new set of ligands based on a pyridylphosphane backbone for the anti-Markovnikov hydration of terminal alkynes. When used with a ruthenium complex, high yields were reported for a variety of terminal alkynes.

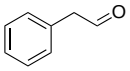
Labonne, A. et al. *Org. Lett.* **2006**, *8*, 5853.



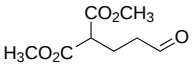
**669776**

(4 - 10 mol %)

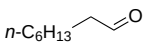


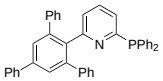
94%



99%



95%



**(ARPYPhos)**
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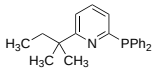

**(ALPYPhos)**
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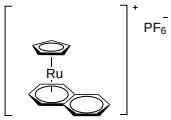
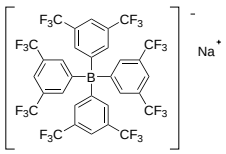


**685054**

## New Metal Precursors for Asymmetric Catalysis

Sigma-Aldrich is pleased to offer a comprehensive portfolio of rhodium and iridium BARF complexes for asymmetric transformations.



**(NaBARF)**
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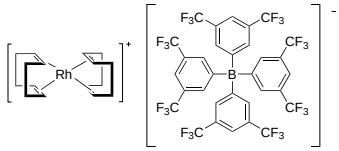

**(Rh(cod)$_2$BARF)**
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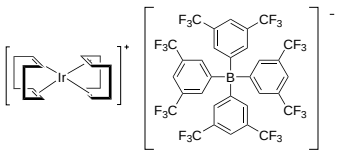
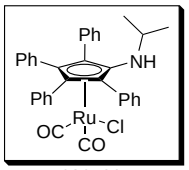


**(Ir(cod)$_2$BARF)**
**693774**

## Dynamic Kinetic Resolution Catalysts

Dynamic Kinetic Resolution (DKR) catalysis is an essential methodology for the conversion of racemic substrates into single enantiomers. Kim et al. reported the (*S*)-selective DKR of a variety of alcohols by utilizing a combination of substilisin and an aminocyclopentadienylruthenium complex. High yields and selectivities were observed for a variety of secondary alcohols.

Kim, M.-J. et al. *J. Am. Chem. Soc.* **2003**, *125*, 11494.



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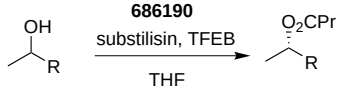
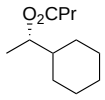
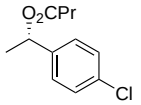
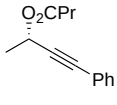


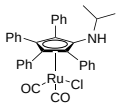
92%, 98% ee



92%, 99% ee



90%, 95% ee



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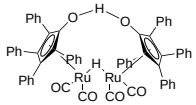

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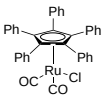
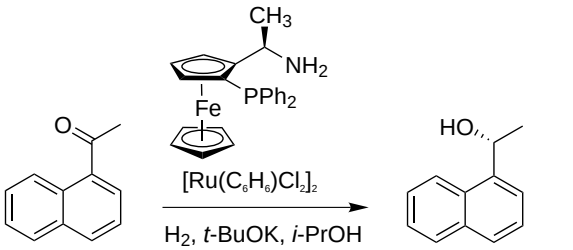


**686441**

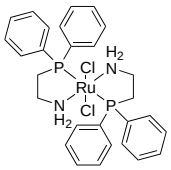
# Aminophosphine Ligands

Recently, there has been a growing interest in aminophosphine ligands for asymmetric synthesis. Researchers at Kanata Chemical Technologies, Inc., have synthesized several sets of aminophosphine ligands that show high reactivity and selectivity in a wide array of enantioselective reactions.




A growing area of application for aminophosphine ligands in asymmetric synthesis is in ruthenium-catalyzed hydrogenations. Chen et al. have described the use of ferrocenylaminophosphines in the ruthenium-catalyzed asymmetric hydrogenation of acetonaphthone. Using the precatalyst $[Ru(C_6H_6)Cl_2]_2$ and the ferrocenyl-based aminophosphine ligand, these researchers found that the hydrogenation proceeded efficiently with reasonable enantioselectivity. Aldrich is pleased to offer a portfolio of aminophosphine ligands and complexes.

Chen, W.; Mbafor, W.; Roberts, S. M.; Whittall, J. *Tetrahedron: Asymmetry* **2006**, *17*,1161.



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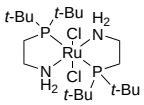

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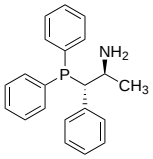

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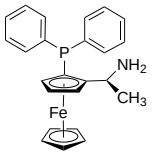

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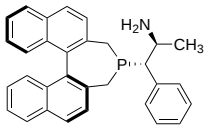

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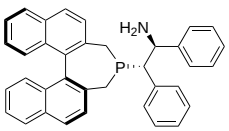

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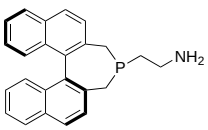

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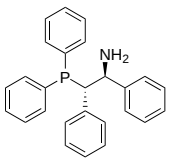

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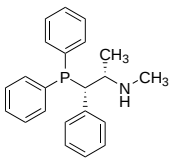

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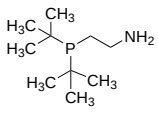

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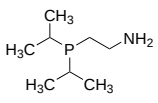

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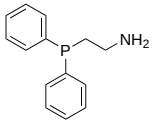
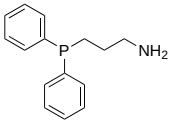


**43162**



**43163**

# Aminophosphine Catalysts in Modern Asymmetric Synthesis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## 1. Introduction

The importance of ligand composition and structure in transition-metal-catalyzed asymmetric synthesis cannot be overstated. From the simplest lock-and-key model to the most complex transition state, the interaction between catalyst and substrate can be completely dictated by the chemical composition and spatial orientation of the supporting ligands. An excellent example of this is in the direct hydrogenation of ketones, aldehydes, and imines catalyzed by ruthenium complexes supported by phosphine or amine ligands.[1] In this process, the unsaturated substrate does not bind directly to the metal center, but rather interacts simultaneously with the Ru–H and N–H bonds of an amine-containing ligand (**Figure 1, Part A**). Often generically described as metal–ligand bifunctional catalysis, the importance of the ligand composition (e.g., incorporation of an N–H bond) and structure (e.g., the spatial orientation of the N–H bond and the other spectator ligands that direct the approach of substrate and often govern stereochemistry) in this reaction manifold is clear.

A particular class of ligand, which is often involved in such ligand-dependent interactions, is chelating aminophosphines (**Figure 1, Part B**). The nature of the substituents at nitrogen, and the stereochemistry at phosphorus and in the ligand backbone, render this motif particularly versatile in catalysis. Because of the highly modular nature of this ligand type, it has found application in a broad range of asymmetric transformations and has become an invaluable tool for the preparation of chiral molecules. In this review, a subset of this ligand class, defined by restricting at least $R^1$ or $R^2$ to H, is considered. This class is of particular interest owing to the potential involvement of this functionality in catalysis. A further restriction that excludes ligands incorporating a direct P–N bond has also been imposed. However, in select instances—such as in the Rh-catalyzed hydrogenation where the direct P–N bond motif is almost exclusively employed, or in cases where ligands are readily derived from those which *are* included in the preceding subset—both restrictions have been overlooked. The synthesis of the group of chelating aminophosphine ligands that results from imposing these two restrictions, and their application in asymmetric synthesis over the last 10 years, are reviewed.

## 2. Ligand Synthesis

The growth in popularity of aminophosphine ligands in asymmetric synthesis is due in part to the increasing number of convenient synthetic pathways leading to useful ligand sets. In recent years, several general routes have been described, which allow access to a broad range of versatile aminophosphines.

Amino acids constitute a convenient class of precursors to chiral aminophosphine ligands.[2,3] Morimoto and Achiwa have described the use of L-valine (**1a**, **Scheme 1**) and other amino acids in the preparation of aminophosphine ligands of type **2**. These ligands have widespread applications in catalysis, particularly in hydrogenation, while other derivatives of L-valine have been exploited in palladium-catalyzed allylic transformations (vide infra).

Another common route to chiral aminophosphine ligands is through commercially available chiral amino alcohols such as ephedrine, norephedrine, and pseudoephedrine. Dahlenburg and Götz have reported the synthesis of chiral aminophosphines by the aziridination of amino alcohols.[4] Ring-opening of the aziridines by nucleophilic attack with diphenylphosphine affords chiral ligands **3**–**5** (**Figure 2**). The appeal of this route is in its ability to dictate the stereochemistry of the ring-opened aminophosphine by controlling that of the aziridine (via a judicious choice of the aziridination protocol). Indeed the ring opening of aziridines is a convenient route to a range of chiral aminophosphines (**eq 1**).[5] Yudin and co-workers employed secondary phosphines as nucleophiles to ring-open cyclohexene aziridines to cyclohexylaminophosphines,

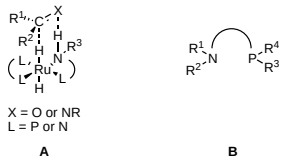
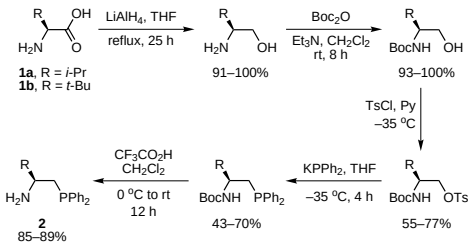
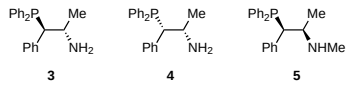



**Figure 1.** (A) Interaction Between Ligands and Substrate in the Ruthenium-Catalyzed Hydrogenation of Ketones, Aldehydes, and Imines. (B) General Structure of a Chelating Aminophosphine Ligand.



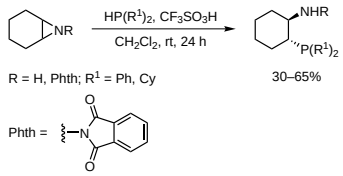

*Ref. 2a,d*

**Scheme 1.** The Synthesis of Aminophosphines from Amino Acids.




*Ref. 4*

**Figure 2.** Aminophosphines Derived from Commercially Available Amino Alcohols.




*Ref. 5*

**eq 1**

which were optically resolved with D-tartaric acid. It is worth noting that pyrazole derivatives were also prepared from the cyclohexylaminophosphines.

An alternate route employing amino alcohols has been disclosed by our group (**Scheme 2**)[6] and others.[7] The route involves the formation of cyclic sulfamidates from the corresponding N-protected sulfamidites. Treatment of the sulfamidate with a metal phosphide, followed by removal of sulfate with dilute acid and N-deprotection, yield the chiral or achiral aminophosphine. The route described by Hilmersson and co-workers differs in that they include an N-alkylation step prior to sulfamidite formation. This allows them to proceed without protecting the amine. Some representative examples of the ligands prepared by our method are shown in **Figure 3**.

We have also described a simple route to aminophosphines via haloalkylammonium salts (**Scheme 3**).[6] Many haloalkylammonium salts are commercially available, although they can also be readily prepared from amino alcohols. The procedure involves neutralization of the salt and protection of the amine, followed by halide substitution with a metal phosphide. Hydrolysis then leads to the desired aminophosphine ligand. Representative examples are depicted in **Figure 4**.

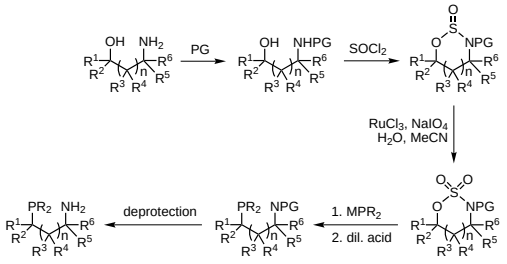
While chiral amino alcohols and acids represent a convenient source of chirality for ligand construction, so too does the 1-ferrocenylalkyl fragment that has been exploited for the development of chiral ferrocenylaminophosphines by Boaz[8] and Chen.[9] Boaz prepared chiral ferrocenylaminophosphines of type **6**, which were subsequently derivatized into phosphinoferrocenyl-aminophosphines and extensively studied in asymmetric synthesis (**Scheme 4**).[8] Chen synthesized similar compounds by a modified procedure, which provides entry into a range of P-chiral ligands with nonidentical substituents on phosphorus. An attractive feature of all such ferrocenylaminophosphines is their remarkable stability toward air oxidation, as samples of material exposed to air for up to 3 years showed no loss in enantioselectivity or activity in Rh-catalyzed hydrogenations.[8d]

A library of compounds aimed at elucidating ligand structural effects in the asymmetric transfer hydrogenation of prochiral ketones was described by Jubault and co-workers.[10] This group employed two different routes to arrive at intermediate amides that were subsequently reduced and deprotected (**Scheme 5**). Both the coupling and reduction of the amides proceeded in moderate-to-high yields, while the removal of borane took place quantitatively.

A simple route to enantiopure β-aminophosphines through vinylphosphine oxides (**Scheme 6**) was employed by Maj et al.[11] While these workers described several variants of aminophosphine oxides and their use as ligands in transfer hydrogenation,[11a] aminophosphines **7b** and **8b** were also prepared and tested vis-à-vis their oxidized precursors.[11b]

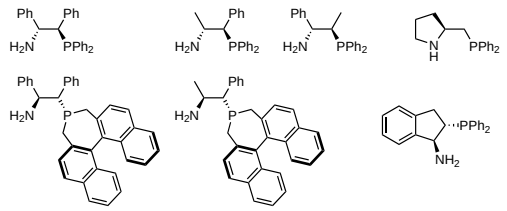
Hii and co-workers have employed a similar methodology to prepare other *N*-alkylaminophosphine (and aminodiphosphine) ligands from vinylphosphine oxides, and reported on their use in ruthenium-catalyzed transfer hydrogenation.[12] These workers also described the development of a range of chiral aminophosphine ligands (**Figure 5**)[12c,d] subsequent to their initial disclosure of several achiral variants.[12a,b]

A strong base containing a guanidine functional group was utilized by Fu et al. to catalyze the phospha-Michael reaction between a number of diarylphosphine oxides and various aryl-substituted nitroalkenes. Subsequent reduction of the nitro and phosphine oxide groups led to the corresponding aminophosphines in good yields and >99% ee's (**Scheme 7**).[13]



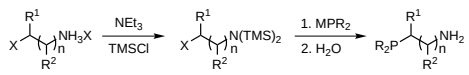
*Ref. 6*

**Scheme 2.** The Sulfamidate Route to Aminophosphines.



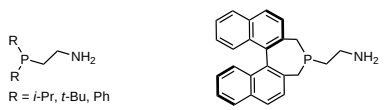
*Ref. 6*

**Figure 3.** Representative Chiral Aminophosphines Prepared by the Sulfamidate Route.



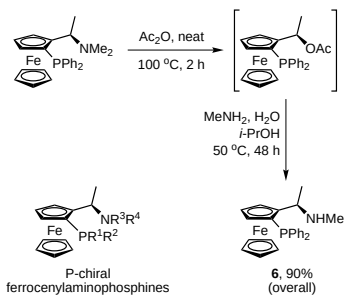
*Ref. 6*

**Scheme 3.** The Haloalkylammonium Route to Aminophosphines.



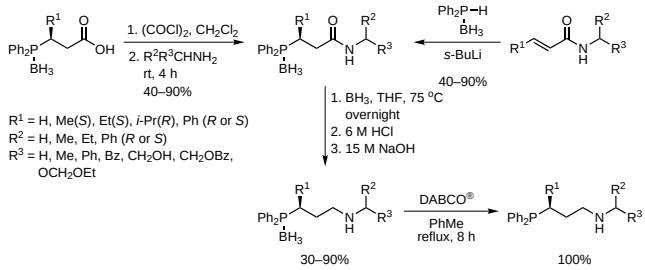
*Ref. 6*

**Figure 4.** Representative Aminophosphines Prepared from Haloalkylammonium Salts.



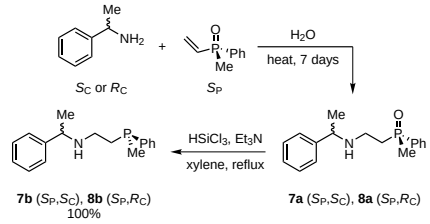
*Ref. 8c*

**Scheme 4.** Aminophosphines Prepared from Ferrocene Derivatives.



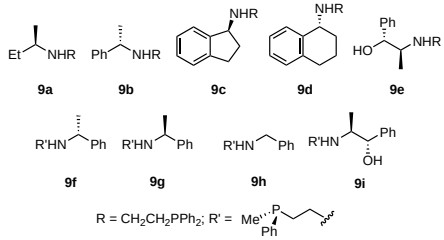
*Ref. 10*

**Scheme 5.** Aminophosphines Derived from Amides.



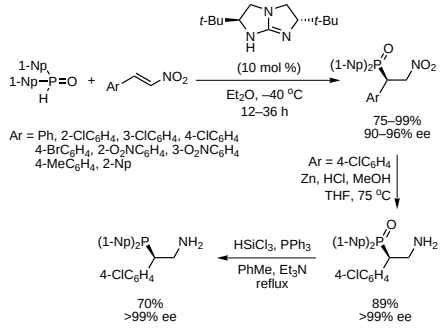
*Ref. 11b*

**Scheme 6.** β-Aminophosphines Derived from Vinylphosphine Oxides.



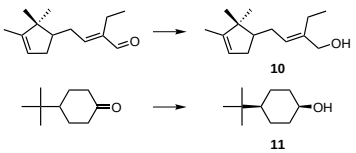
*Ref. 12d*

**Figure 5.** Chiral Aminophosphines Derived from Vinylphosphine Oxides.



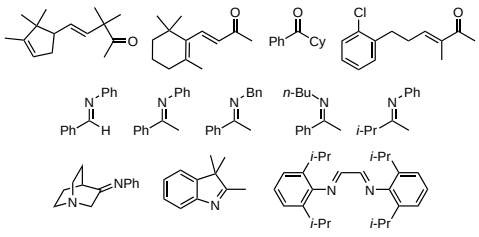
*Ref. 13*

**Scheme 7.** Synthesis of Aminophosphines Catalyzed by the Guanidine Functional Group.



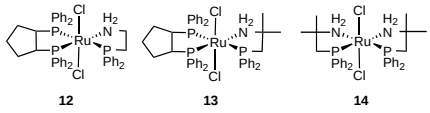

Ref. 17

**Scheme 8.** Industrially Significant Alcohols Prepared by the Ruthenium–Aminophosphine-Catalyzed Hydrogenation.



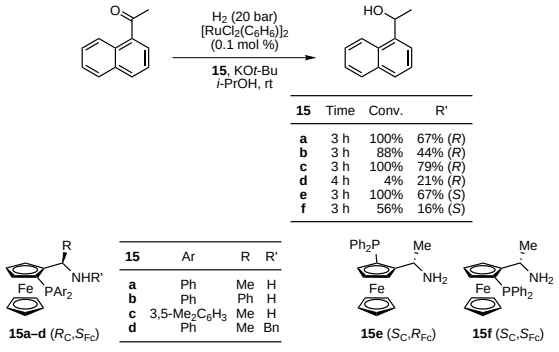

Ref. 17

**Figure 6.** Representative Ketones and Imines that Have Been Reduced to the Corresponding Alcohols and Amines by the Ruthenium–Aminophosphine-Catalyzed Hydrogenation.




Ref. 18

**Figure 7.** Ruthenium–Aminophosphine Complexes Employed in the Hydrogenation and Transfer Hydrogenation of Ketones.




Ref. 9b

**eq 2**

## 3. Hydrogenation

### *3.1. Ruthenium Catalysts*

A heavily exploited application area for aminophosphine ligands in asymmetric synthesis is the ruthenium-catalyzed hydrogenation. This process is integral to the preparation of alcohols and amines that are useful in the flavor and fragrance, pharmaceutical, agrochemical, materials, and fine chemicals industries.[14] Our group and others have reported extensively on the use of ruthenium aminophosphine complexes, and has studied the relationship between catalyst structure and enantioselectivity.[3,15,16,17] The industrially relevant compounds (*E*)-2-ethyl-4-(2,2,3-trimethylcyclopent-3-en-1-yl) but-2-en-1-ol (**10**) and *cis*-4-*tert*-butylcyclohexanol (**11**) are two examples of the type of product that can be very efficiently produced from the corresponding aldehyde or ketone by using ruthenium aminophosphine catalysts (**Scheme 8**).[17] With precatalysts of the type $RuCl_2$(aminophosphine)$_2$ or $RuCl_2$(diphosphine)(aminophosphine), substrate:catalyst ratios of 100,000:1 or greater are typical in the direct hydrogenation. This approach was applied to a broad range of ketones, aldehydes, and imines (**Figure 6**).[17] The advantage of a ruthenium-catalyzed hydrogenation over a conventional stoichiometric reduction with a hydride-transfer reagent (e.g., alkali metal borohydrides or aluminum hydrides) is quite apparent: avoid the use of large quantities of expensive and difficult-to-handle materials that produce inorganic hydroxides in favor of utilizing catalytic amounts of robust materials. It should also be pointed out that these ruthenium catalysts selectively reduce only the ketone, aldehyde, or imine while leaving carbon–carbon double bonds intact.

Dahlenburg and Kühnlein have described the use of ruthenium–aminophosphine complexes **12–14** (**Figure 7**) in the transfer hydrogenation and, in the case of **14**, the direct hydrogenation of acetophenone.[18] They observed an induction period in the transfer-hydrogenation experiments corresponding to the time needed for the active catalyst to arise from the precatalyst complexes. Variations in induction times were observed and found to correlate directly to the extent of steric shielding of the amino group. Catalyst **14** was effective in the direct hydrogenation of acetophenone to 1-phenylethanol as well. It was shown, through the use of isotopically labeled solvent, that, under the direct hydrogenation conditions, the source of hydrogen atoms in the alcohol product was indeed hydrogen gas.

Chen and co-workers have described the use of ferrocenylaminophosphines in the ruthenium-catalyzed asymmetric (direct) hydrogenation of 1-acetonaphthone (**eq 2**).[9b] In the presence of precatalysts of type $RuCl_2$(**15**)$_2$, derived from the reaction of $[RuCl_2(C_6H_6)]_2$ and **15**, the hydrogenation proceeded rapidly and with reasonable enantioselectivity when ligands **15a**, **15c**, and **15e** were used. When the steric bulk of the phosphine aryl substituent was largest (**15c**), enantioselectivity was highest. In contrast, increasing the steric bulk at or near nitrogen resulted in significantly diminished activity and selectivity (e.g., **15d** and **15f**). This was anticipated as increased steric bulk at nitrogen should limit the ability of the substrate to interact with the N–H bond. The carbon-centered chirality was found to dictate the sense of induction in the product.

Using aminophosphines derived from vinylphosphine oxides (see Scheme 6), a comparison of the catalytic activities between reduced and oxidized β-aminophosphines has been reported.[11] In the transfer hydrogenation of various aromatic ketones, the reduced aminophosphine ligands had activities comparable to those of the corresponding aminophosphine oxide ligands, but gave rise to consistently higher ee's. Hii and co-workers have also used similarly derived β-aminophosphines (and their oxides) in the

transfer hydrogenation of ketones (**eq 3**).[12] They initially described the use of achiral ligands (**17a–d**) and reported that increasing the steric bulk of the N-substituent led to diminished activity. Upon examination of chiral ligands **9a–e** (see Figure 5), they found that incorporation of the alcohol functionality in the ligand resulted in dramatically improved enantioselectivity. They obtained a 79% ee (*R* form) in the hydrogenation of acetophenone using ligand **9e,** compared to 39% ee (*R* form) with **9b** as the next best of the five chiral ligands tested in this transformation. It is worth noting that Hii's group also discovered that the optimal metal-to-ligand ratio (when $[RuCl_2(p\text{-cymene})]_2$ was used as the Ru source) was 1:1, in contrast to the 2:1 ratio traditionally employed in Ru-catalyzed transfer hydrogenations.

The library of aminophosphines developed by Jubault and co-workers (see Scheme 5) was tested in the transfer hydrogenation of acetophenone, propiophenone, and isobutyrophenone.[10] These researchers found that acetophenone and propiophenone were most effectively reduced when $R^1$ = Et (*S*), $R^2$ = Ph (*S*), and $R^3$ = Me. For isobutyrophenone, the best results were obtained when $R^1$ = H, $R^2$ = Ph, and $R^3$ = $CH_2OBz$. Jubault's group was also able to glean the impact of the nature and position of the substituents on this particular class of ligands. For instance, the introduction of a chiral center adjacent to phosphorus has a dramatic effect on enantioselectivity, while the sense of induction is most strongly governed by the chiral center adjacent to the amine.

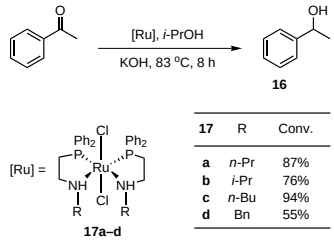
### 3.2. Rhodium Catalysts

When combined with rhodium, the versatile chiral phosphine–aminophosphine and phosphine–phosphoramidite ligands, derived by combining phosphorus and nitrogen functional groups in one molecular structure, represent a particularly important class of catalyst.

In 2002, Boaz first introduced the hybrid phosphine–aminophosphine ligands **18**–**22** (**Figure 8**), based on a chiral ferrocenylethylamine backbone, for the rhodium-catalyzed asymmetric hydrogenation of olefins.[8] Ligands **18** and **19** showed excellent enantioselectivities in the hydrogenation of dehydro-α-amino acid and itaconic acid derivatives, while **22** showed very good enantioselectivity in the hydrogenation of α-keto esters (**Scheme 9**).[8c] Ligand ($S_C$,$R_{Fc}$)-**19** was successfully utilized for the preparation of single-enantiomer 2-naphthylalanine derivatives on multikilogram scale by Eastman Chemical Company (**Scheme 10**).[19] The catalyst system Rh–($S_C$,$R_{Fc}$)-**19** showed high activity and enantioselectivity, as the hydrogenation product **23** was obtained in 96% isolated yield and >99% ee after one crystallization from toluene–heptane. Further elaboration of **23** led to the final product in high yield and >99.5% ee.[19]

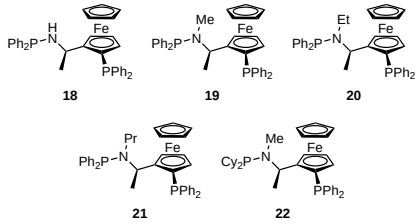
While Rh–BoPhoz catalysts show high activity and enantioselectivity in the hydrogenation of dehydro-α-amino acid derivatives, they result in only moderate enantioselectivity in the hydrogenation of α-aryl enamides (~80% ee). Chan introduced fluorinated phosphinoferrocenylaminophosphine ligands **24** and **25**, which showed excellent enantioselectivities in the hydrogenation of dehydro-α-amino acid derivatives (≤99.7% ee) and α-aryl enamide substrates (≤99.7% ee) (**eq 4**).[20] A significant feature of this catalyst system is that the rhodium complexes are exceptionally air- and moisture-stable, even when dissolved in an organic solvent.[20]

Hu, Zheng, and co-workers recently introduced a modified BoPhoz ligand with three chiral centers, **26**, for the highly enantioselective (≤97% ee) rhodium-catalyzed hydrogenation of γ-phthalimido-substituted α,β-unsaturated carboxylic acid esters (**Scheme 11**).[21] The catalyst system Rh–**26** was successfully applied to the synthesis of the optically active pharmaceuticals (*R*)-baclofen,



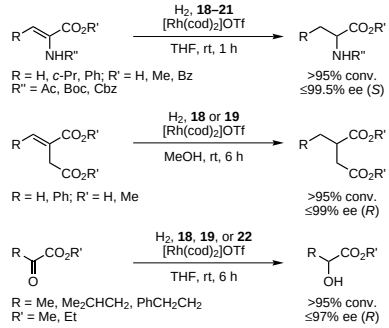

*Ref. 12b*

**eq 3**



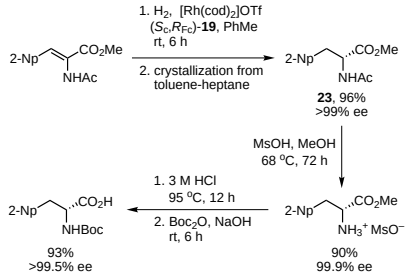

*Ref. 8c*

**Figure 8.** BoPhoz Ligands Derived from Phosphinoferrocenylethylamine.



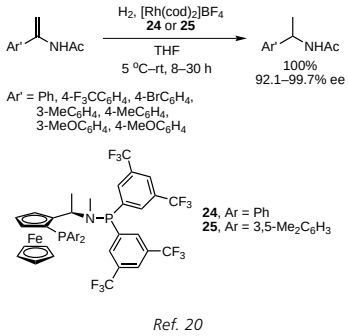

*Ref. 8c*

**Scheme 9.** Hydrogenations with Rh–BoPhoz Ligands.



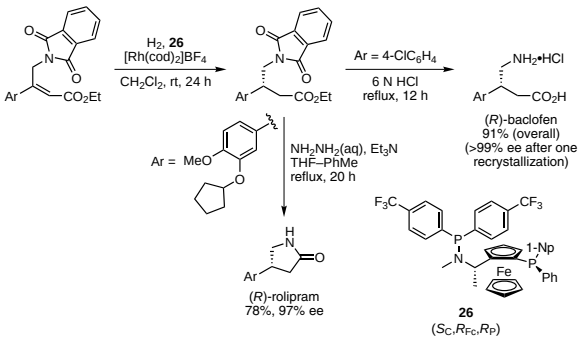

*Ref. 19*

**Scheme 10.** Multikilogram Hydrogenation Process with the Rh–($S_C$,$R_{Fc}$)-**19** Catalyst System.



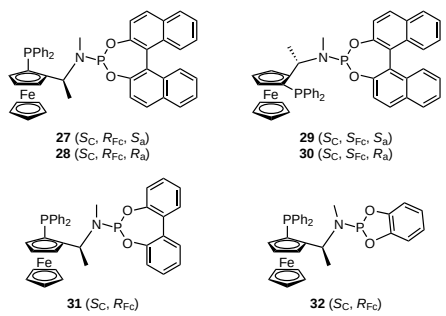

*Ref. 20*

**eq 4**



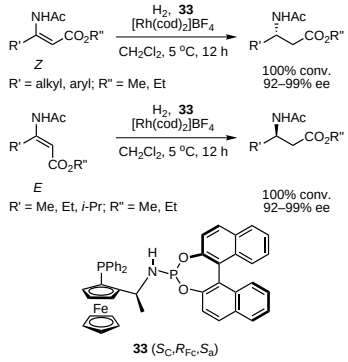

*Ref. 21*

**Scheme 11.** Application of Rh–**26** Catalyst System to the Preparation of (*R*)-Baclofen and (*R*)-Rolipram.




*Ref. 22*

**Figure 9.** Phosphine–Phosphoramidite Ligands.




*Ref. 23*

**Scheme 12.** Rhodium–**33** Hydrogenation of Dehydro-β-amino Acid Derivatives.

which is widely used as an antispasmodic agent, and (*R*)-rolipram, which is employed as an antidepressant and anti-inflammatory agent.

In 2004, Hu and Zheng employed a new set of phosphine–phosphoramidite ligands, **27–32** (**Figure 9**), as alternatives to BoPhoz ligands for the Rh-catalyzed hydrogenation of olefins.[22] The enantioselectivity with the Rh–**27** catalyst system in the hydrogenation of *N*-(1-phenylethenyl)acetamide was greater than 99% ee (S/C = 5,000/1). Rh–**27** also led to >99% ee for the hydrogenation of dimethyl itaconate and (*Z*)-acetamidocinnamate at low catalyst loadings (S/C = 10,000). The rhodium-catalyzed hydrogenation reactions employing these ligands were carried out under ambient conditions, taking no precautions to exclude air or moisture, with no loss in activity or enantioselectivity.[22]

While **27** showed high enantioselectivities in the rhodium-catalyzed hydrogenation of enamides, itaconates, and dehydro-α-amino acid derivatives, very low enantioselectivities were observed for the rhodium-catalyzed hydrogenation of the *Z* and *E* isomers of dehydro-β-amino acid derivatives (20–60% ee's). After expanding the ligand scope, Zheng's group found that **33**, bearing a proton instead of a methyl group on nitrogen, showed excellent enantioselectivity in the rhodium-catalyzed hydrogenation of *Z* and *E* β-aryl- or β-alkyl-β-(acylamino)acrylates, leading to the two products with opposite configurations (**Scheme 12**).[23]

Leitner, Faraone, and co-workers introduced chiral phosphine–phosphoramidite ligands **34** and **35** (*n*-Bu-QuinaPhos) for the rhodium-catalyzed hydrogenation of dimethyl itaconate and methyl 2-acetamidoacrylate (**eq 5**).[24] Excellent activity and enantioselectivity were observed for the reaction. Moreover, the rhodium-catalyzed hydroformylation of styrene with *n*-Bu-QuinaPhos gave rise to high regioselectivity and moderate enantioselectivity.[24]

Me-AnilaPhos (**36**) and IndolPhos ligands **37** and **38** were recently reported by the groups of Kostas and Reek (**Figure 10**).[25,26] These chiral phosphine–phosphoramidite ligands, derived from achiral aminophosphine ligands, also show high enantioselectivity in the rhodium-catalyzed hydrogenation of enamides and itaconate derivatives (≤97% ee for enamides and 98% ee for itaconates). Owing to the simple structure and the wide range of available aminophosphine precursors, **36**–**38** represent a highly versatile ligand class.

The novel phosphine–phosphoramidite ligands **39**–**42** (PEAPhos), derived from chiral α-phenylethylamine, and **43**, derived from 1,2,3,4-tetrahydro-1-naphthylamine, were disclosed by Zheng and co-workers.[27] The Rh–**39** catalyst system showed excellent enantioselectivity (>99% ee) in the hydrogenation of olefins (**Scheme 13**).[27] Ligand **43** was also successfully applied to the synthesis of α-hydroxyphosphoric acid derivatives by the rhodium-catalyzed hydrogenation (a significant achievement) of β-substituted α-acyloxyphosphonates. A greater than 99% ee was achieved for a range of substrates bearing β-aryl, β-alkoxy, and β-alkyl substitutents (**eq 6**).[27]

### 3.3. Iridium Catalysts

The class of aminophosphine ligands discussed so far has found only limited application in iridium-catalyzed hydrogenations. Dahlenburg and collaborators have employed aminophosphine ligands in the iridium-catalyzed hydrogenation of unsaturated substrates.[4,28] They described a series of chiral and achiral aminophosphine-chelated iridium(I) complexes prepared by treating $[Ir(cod)_2]BF_4$ with the β-aminophosphine or by treating $Ph_2PCH_2CMe_2N(Li)H$ and 2-$(Ph_2P)C_6H_4N(Li)Me$ with $[Ir(cod)(\mu\text{-}Cl)]_2$ to give the neutral alkyl and aryl amido compounds. When

combined with an alkali or amine base in methanol, all of the iridium complexes acted as catalysts for the direct hydrogenation of alkyl aryl ketones to the corresponding 1-phenylalkanols. The reactions, carried out at 25–50 °C and 10–50 bar of hydrogen, occurred with modest-to-good enantioselectivities (20–75% ee).

## 4. Allylic Alkylation

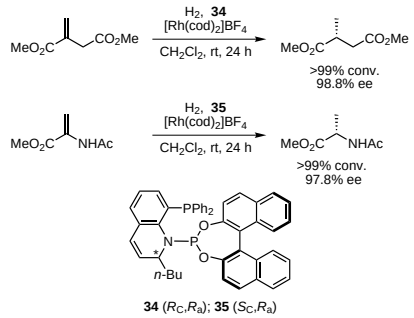
The palladium-catalyzed allylic alkylation has emerged as a powerful carbon–carbon-bond-forming reaction, and is now widely used in organic synthesis. The reaction is believed to proceed by nucleophilic addition to either C-1 or C-3 of a coordinated $\eta^3$-allyl ligand (**Scheme 14**).[2,29] The asymmetric version of this reaction has become quite popular, and aminophosphine ligands may provide a distinct advantage over symmetrical analogues as alkylation tends to occur at the position that is trans to the more strongly π-acidic $PR_2$ group.[2,29] The enantioselective C–C-bond-formation step occurs via the major diastereomer of the equilibrating diastereomeric π-allyl intermediates.

Achiwa and co-workers have reported the synthesis of the chiral amidine ligand VALAP (**44**) from L-valine by condensation of aminophosphine **2a** with $Me_2NCH(OMe)_2$ (**eq 7**).[2a] VALAP has been utilized in the Pd-catalyzed asymmetric allylation of 1,3-diphenyl-2-propenyl acetate and pivalate (**eq 8**) with dimethyl malonate in the presence of BSA and LiOAc, affording excellent yields and up to 95% ee's. Loadings of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as low as 0.01 mol % still allowed for reasonable reaction times.

Morimoto modified the VALAP ligand (and the *tert*-butyl leucine analogue) via reaction of **44** with pyrrolidine and piperidine, or reaction of **2a** with para-substituted aromatic aldehydes (**Scheme 15**).[2d] An examination of the effect of ligands **45c–h** on the allylic alkylation reaction showed a clear electronic effect wherein electron-donating substituents in the para position resulted in higher yields and ee's (**eq 9**).[2d,30] This effect is most dramatic when comparing R = $CF_3$ (entry 3) and $CH_3$ (entry 4) which have a similar steric profile, yet the presence of the $CH_3$ group resulted in a marked improvement in both yield and ee. With the strongly electron-donating substituent, $NMe_2$, both the catalytic activity and enantioselectivity are higher still than those obtained with the less electron-donating substituents. Indeed, use of this substituent allowed the $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ loading to be reduced to 0.005 mol % while still retaining excellent reactivity and leading to only a slight decrease in selectivity.

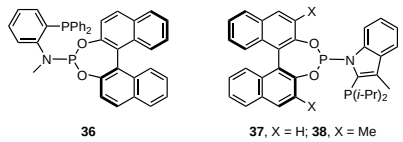
Saitoh et al. have also investigated the allylation reaction with silyl acetals and ketals **46a–d** and found that $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$–VALAP and related systems exhibit low-to-moderate activities with moderate-to-high enantioselectivities: ≤93% ee using ligand **44** with acetal **46d** (**eq 10**).[2d] When the analogous reaction with RR′C=C(OMe)(OM) (M = Li, $NR_4$) as the nucleophile was examined, a low enantioselective induction was observed.

Yudin's group has employed iminophosphine ligands of type **47** (**eq 11**) in the palladium-catalyzed allylation.[31] The $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$–**47** catalyzed allylation of 1,3-diphenyl-2-propenyl acetate in the presence of BSA and diethyl malonate was explored in order to determine the efficiency of the new chiral ligands for asymmetric induction. In the presence of aminocyclohexylphosphines, the precursors to ligands **47**, the reaction resulted in low yields and low enantioselectivities. When the catalytic reaction was carried out in the presence of the iminophosphine ligands, more favorable results were obtained. The yield and asymmetric induction for **47a** and **47b** were similar (≤89% yield and 87% ee), indicating that the ortho-methoxy fragment had little effect, whereas an electron-withdrawing



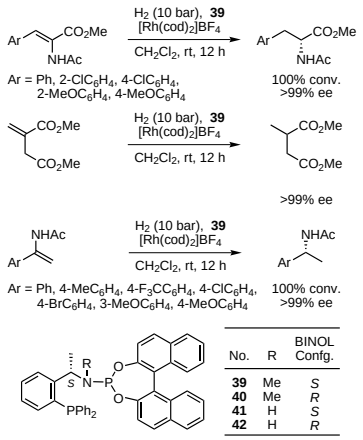

*Ref. 24a*

**eq 5**



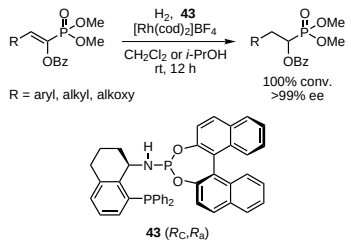

*Ref. 25,26*

**Figure 10.** Me-AnilaPhos and IndolPhos.



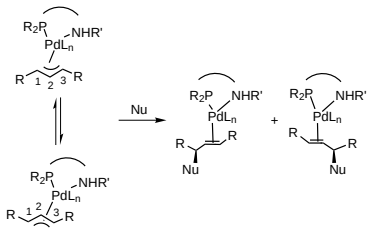

*Ref. 27a*

**Scheme 13.** Hydrogenation of Olefins with Rh–PEAPhos.



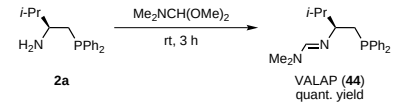

*Ref. 27b*

**eq 6**



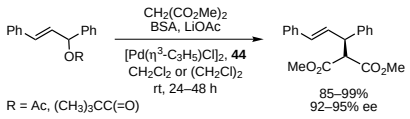
Ref. 2a,29

**Scheme 14.** Palladium-Catalyzed Allylic Alkylation.



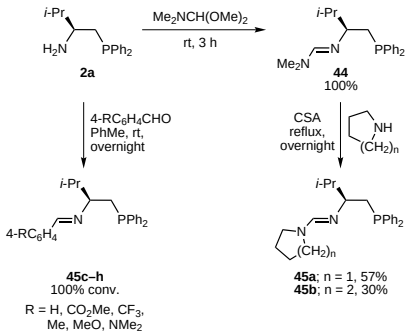
Ref. 2a

**eq 7**



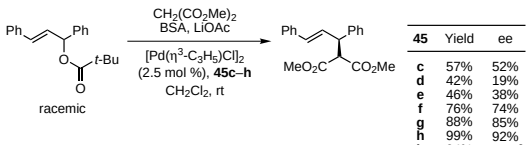
Ref. 2a

**eq 8**



Ref. 2d

**Scheme 15.** Modified VALAP and Leucine Ligands.



| 45 | Yield | ee |
|---|---|---|
| **c** | 57% | 52% |
| **d** | 42% | 19% |
| **e** | 46% | 38% |
| **f** | 76% | 74% |
| **g** | 88% | 85% |
| **h** | 99% | 92% |
| **h** | 94% | 89%[a] |

[a] 0.5 mol % of the Pd catalyst was used.

Ref. 2d

**eq 9**

substituent in this position, as in **47d**, had a deleterious effect on the reaction (60% yield and 51% ee). The bulky anthryl group, **47e**, greatly enhanced the reaction rate (complete in ca. 5 min), but resulted in a large decrease in enantioselectivity (21% ee).

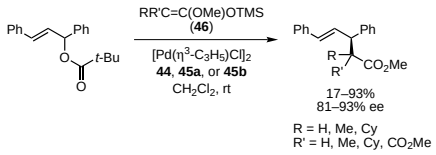
Zheng and co-workers have recently reported on ferrocenylaminophosphine ligands that are capable of producing high yields and excellent asymmetric induction in the catalytic alkylation of 1,3-diphenyl-2-propenyl pivalate with dimethyl malonate.[32] The ligands are prepared in one step from aminophosphines or phosphinoacetates and chloropyrimidines, chlorotriazines, or aminopyridines (**Scheme 16**). Their report indicates that increasing the number of nitrogen atoms in the ligand dramatically increases both the catalytic activity and enantioselectivity. For example, substituting the $NMe_2$ group with MeN(2-Py) results in an increase in enantioselectivity from 48% to 81% ee. When the pyrimidine-substituted ligand **51b** is used, an ee of 93% is obtained. The triazine-substituted ligand **50b** results in an enantioselectivity of 98% ee.

Gong, Mi, and co-workers have disclosed a series of aminophosphinite ligands, **53–54** (**Figure 11**), that give good-to-excellent asymmetric induction in the Pd-catalyzed allylation of 1,3-diphenyl-2-propenyl acetate with dimethyl acetate.[33] The chiral ligands were prepared in one step by the reaction of aminoethanols with chlorodiphenylphosphine. These workers found that ligands with an NHR fragment (**54a–c**) gave higher ee's than ligands with an NMeR group (**53a–d**). The authors indicated that the N–H group was essential for optimal catalyst activity and selectivity, and proposed that the selectivity was a result of substrate interaction with the NH group.

## 5. Hydroformylation

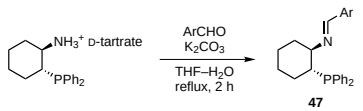
While the hydroformylation of olefins employing rhodium catalysts represents an area of significant interest,[34] few recent reports have focused on the use of aminophosphine ligands bearing an NH group. Despite the relative scarcity of information, much is understood about the role and efficacy of such ligands in this process.

In a report by Andrieu and co-workers, diastereomeric trifunctional diaminophosphine ligands were derived from bidentate aminophosphine ligands by nucleophilic addition of a phosphinoalkyl carbanion (generated by lithiation) onto an imine (**Scheme 17**).[35] Both the bifunctional precursors and the derived trifunctional ligands were tested in the hydroformylation of styrene. Andrieu's group found that, while there was no impact on the isomer ratio, a substantial increase in activity was observed as a result of variation in the ligand set. An approximate threefold increase in activity using **55** or **56** relative to its precursor ligand suggested a dependence on the proximity and/or basicity of the dangling amine functionality. In subsequent studies,[36] it was determined that under catalytically relevant conditions, the aminophosphine ligand binds in a monodentate fashion through phosphorus while the amine functionality remains uncoordinated. The role of Brønsted base was proposed for the uncoordinated amine, which could assist in either the heterolytic splitting of dihydrogen or in the reductive elimination of HCl. Either scenario leads to an ammonium functionality in the dangling ligand. Based on a series of experiments designed to elucidate the mechanism, the authors proposed that a key step in rhodium-catalyzed hydroformylations employing aminophosphine ligands involves Rh–acyl racemization. This occurs via interaction of the acyl intermediate with the ammonium functionality of the dangling ligand (**eq 12**).




*Ref. 2d*

**eq 10**

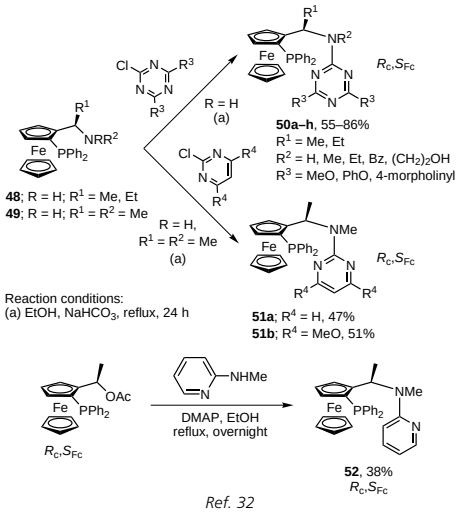



**47**

| 47 | Ar | Yield |
|---|---|---|
| **a** | Ph | 89% |
| **b** | 2-MeOC$_6$H$_4$ | 80% |
| **c** | 2-FC$_6$H$_4$ | 70% |
| **d** | 2-Py | 80% |
| **e** | 9-Anth | 89% |
| **f** | 2-HOC$_6$H$_4$ | 88% |
| **g** | 2-HO-3-MeOC$_6$H$_3$ | 89% |

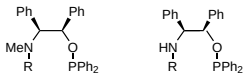
*Ref. 31*

**eq 11**




*Ref. 32*

**Scheme 16.** Ferrocenylaminophosphine Ligands for Allylation Reactions.



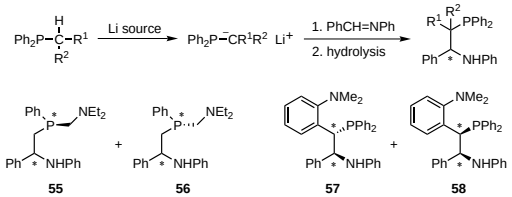
**53a**, R = Me
**53b**, R = Et
**53c**, R = *i*-Pr
**53d**, R = Bn



**54a**, R = Bn
**54b**, R = *n*-Bu
**54c**, R = *i*-Pr

*Ref. 33*

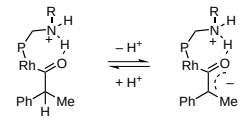
**Figure 11.** Aminophosphinite Ligands Used in Allylation Reactions.




**55** **56** **57** **58**

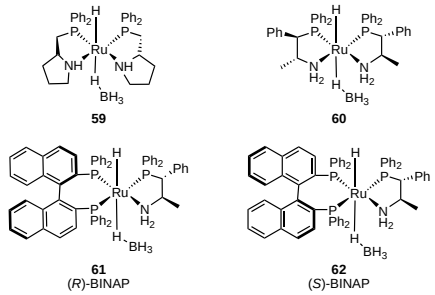
*Ref. 35*

**Scheme 17.** Preparation of Trifunctional Diaminophosphine Ligands via Nucleophilic Addition of Phosphinoalkyl Carbanions onto Imines.



*Ref. 36b*

**eq 12**

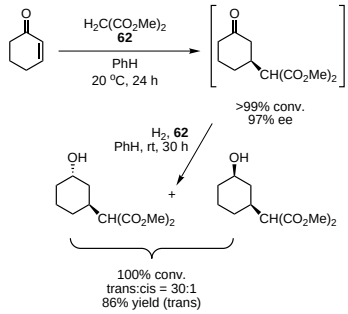


**59** **60**

**61** (*R*)-BINAP **62** (*S*)-BINAP

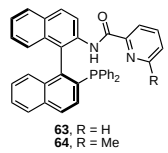
*Ref. 15b*

**Figure 12.** Ruthenium–Aminophosphine Complexes as Catalysts in the Asymmetric Michael Addition.




*Ref. 15b*

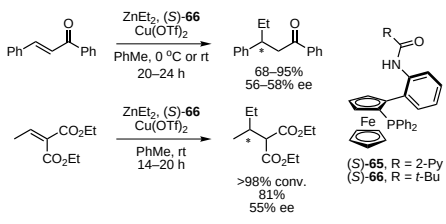
**Scheme 18.** Tandem Michael Addition–Hydrogenation Catalyzed by Ruthenium–Aminophosphine Complexes.



**63**, R = H
**64**, R = Me

*Ref. 37*

**Figure 13.** Binaphthyl Aminophosphines for the Copper-Catalyzed Conjugate Addition to Enones.




*Ref. 38*

**Scheme 19.** Amidoarylferrocenyldiphenylphosphine Ligands in the Copper-Catalyzed Addition of Diethylzinc to Enones.

## 6. Conjugate Additions

### 6.1. Asymmetric Michael Addition to Enones

Ruthenium complexes of aminophosphines catalyze the asymmetric Michael addition reaction.[15b] A range of such complexes (**Figure 12**) containing borohydride ligands were employed in the addition of dimethylmalonate to 2-cyclohexenone and, in a tandem process, were subsequently used in the asymmetric hydrogenation of the Michael adduct to the alcohol (**Scheme 18**).

The results of the Michael addition reaction clearly showed that catalyst activity and enantioselectivity were sensitive to solvent and ligand structure, respectively. While the activity of all of the catalysts employed in the Michael addition was insensitive to ligand structure, their sensitivity to solvent was pronounced. Enantioselectivity also displayed a strong dependence on solvent as a clear preference for aprotic solvents emerged (strongly coordinating acetonitrile also displayed deleterious effects on enantioselectivity). A pronounced favorable effect of ligand rigidity on enantioselectivity was observed, with the more rigid BINAP-supported catalysts (**61** and **62**) affording the highest enantiomeric excess (≤97%). Furthermore, while (*R*)-BINAP (**61**) provided the *R* product, (*S*)-BINAP (**62**) gave the *S* isomer and the highest ee. In the subsequent hydrogenation, excellent diastereoselectivity was observed as a 30:1 trans:cis ratio was achieved for the alcohol product.

Zhang and co-workers reported on the use of larger-bite-angle aminophosphines in the copper-catalyzed addition of diethylzinc to enones.[37] The performance of the chiral binaphthyl ligands **63** and **64** (**Figure 13**) was evaluated in the conjugate addition of diethylzinc to 2-cyclohexenone and several acyclic enones, including chalcone and substituted chalcones, as well as an entirely aliphatic acyclic enone. In the case of 2-cyclohexenone, Zhang's group found that nonpolar solvents favored higher conversions and enantioselectivities over coordinating solvents. Mixtures of solvents such as toluene–dichloroethane were also effective. Removal of dissociated $CH_3CN$ from the copper precursor $[Cu(CH_3CN)_4]BF_4$ was important in realizing higher conversions and ee's and improved enantioselectivity was also gained from decreasing the temperature. $[Cu(OTf)]_2 \bullet C_6H_6$ was the preferred copper precursor, as it allowed for room-temperature reactions albeit with diminished selectivity. Enantioselectivity was dependent on the ligand:metal ratio and was highest with a ligand:metal ratio of 5:1, but only slightly better than with a ratio of 2.5:1. The methyl-substituted ligand, **64**, gave modest improvements in ee over the unsubstituted analogue **63**. Ligand **64** provided much higher ee's in the alkylation of acyclic enones. The mixed solvent system toluene–dichloroethane was optimal with respect to yield and enantioselection, likely owing to the improved solubility of the substrates. This system proved to be competent in the asymmetric addition of diethylzinc to the entirely aliphatic acyclic enone as well.

A pair of amidoarylferrocenyldiphenylphosphines have also found application in the copper-catalyzed asymmetric addition of diethylzinc to enones (**Scheme 19**).[38] Johannsen and co-workers reported that the alkylated product from the addition of diethylzinc to *trans*-chalcone was obtained in reasonable yields and modest enantioselectivities. A strong dependence on solvent was observed as the highest yield (95%) and ee (58%) were realized in toluene, whereas halogenated solvents resulted in a dramatic reduction in both yield and ee. The better performance by ligand (*S*)-**66** in this alkylation prompted the authors to investigate the asymmetric addition of diethylzinc to the more challenging substrate diethyl ethylidenemalonate. In this case, a conversion of >98% was obtained with moderate enantioselectivity (55%). No dependence on the ligand–metal ratio was observed in either of the enone addition reactions.

Adding to the diversity of scaffolds of aminophosphine ligands for conjugate additions, a series of carbohydrate-based aminophosphines were tested by Diéguez and his team in the copper-catalyzed addition of diethylzinc to 2-cyclohexenone.[39] The furanoside-supported aminophosphines (**Figure 14**) showed good activity, with phosphoramidite **70** being best in this regard (TOF >1200). In these systems, dichloromethane was the preferred solvent giving the highest conversions and enantiomeric excesses (≤63%). The optimal temperature was 0 °C, as either increasing or decreasing the temperature resulted in diminished selectivity. Replacing the *tert*-butyl group at the para position of the biphenyl moiety with a methoxy group resulted in a decreased enantioselectivity. The aminomethyl substituent that gave both the greatest enantioselectivity and TOF was the phenylaminomethyl group. The sense of enantioselectivity was also influenced by the aminomethyl substituent. The more sterically demanding *tert*-butylamino group of ligand **67** gave preferentially the *R* product, while the less demanding isopropylamino and phenylamino substituents of **68** and **69**, respectively, provided the *S* isomer. Ligand **72**, having the opposite configuration at C-3 of the furanoside ring to that of ligand **69**, showed similar activity to **69**, however the enantioselectivity was dramatically reduced (only 8% ee). As mentioned above, phosphoramidite **70** gave the highest reaction rate, but the corresponding enantioselectivity was lower than that of **68** and **69**.

### 6.2. Asymmetric Addition of Organolithiums to Aldehydes

The asymmetric addition of organolithium reagents to aldehydes is a recent entry into the repertoire of transformations in which aminophosphine ligands play an important role.[7] A series of aminophosphine ligands have been employed in the addition of *n*-butyllithium to benzaldehyde (**eq 13**).[40] A comparison of the aminophosphines with the corresponding ether and thioether ligands showed that the aminophosphines gave comparable high yields of the alcohol in consistently (and sometimes substantially) higher enantiomeric excess (≤98% ee).

## 7. Cycloaddition Reactions

While a broad range of both metals and ligand scaffolds have been employed in selective cycloaddition reactions,[41] only recently has the potential utility of aminophosphines bearing NH groups come to light. The enantioselective addition of dimethyl maleate to iminoester **73a** is efficiently catalyzed by silver acetate in the presence of ferrocenyl-based aminophosphines (**eq 14**).[42] The significance of this account lies in the fact that incorporation of H, rather than alkyl or aryl substituents, on nitrogen leads to the opposite absolute configuration of the product pyrrolidine **74a** (compare **75a** with **75b**). The ability of the H substituent to participate in substrate–ligand hydrogen bonding is implicated in the observed results. Increasing the steric bulk at phosphorus leads to improved enantioselectivity and the same reversal of configuration (**75c** vs **75d**). The mixed, NHMe-containing ligand, **75e**, gives dramatically reduced enantioselectivity (19%). Lowering the temperature to –25 °C results in greater selectivity than when the temperature is equal to 0 °C. A broad range of iminoesters and dipolarophiles were tested, and successful reversal of absolute configuration was maintained (**eq 15**).[42]

## 8. Conclusions

Aminophosphines are a highly versatile class of ligands for asymmetric synthesis. While their applications in metal-catalyzed hydrogenations predominate, involvement of these ligands in other

asymmetric processes continues to gather interest. Simplicity and diversity in structure and preparation, coupled with a unique ability to become an integral component in chiral syntheses, guarantee continued development. With the current level of understanding of the role that these ligands assume in catalysis, researchers can apply them in catalytic transformations based on the nature of the substrate of interest. That is, in catalytic transformations where hydrogen-bonding interactions may play a role, aminophosphine ligands should be leading candidates in the ligand selection process.

## 9. Acknowledgment

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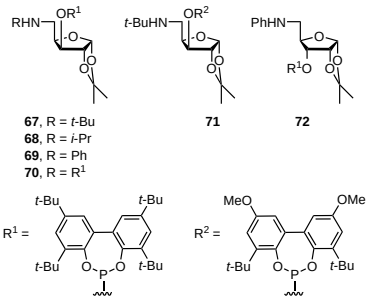
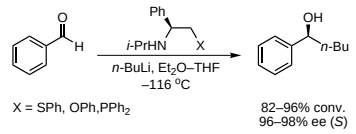


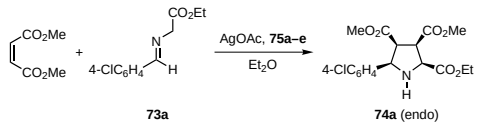

*Ref. 39*

**Figure 14.** Furanoside-Supported Aminophosphines for Conjugate Additions.




*Ref. 40*

**eq 13**

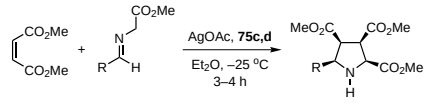



| 75 | Ar | R |
|---|---|---|
| a | Ph | $NMe_2$ |
| b | Ph | $NH_2$ |
| c | 3,5-$Me_2C_6H_3$ | $NMe_2$ |
| d | 3,5-$Me_2C_6H_3$ | $NH_2$ |
| e | Ph | NHMe |

| | | 74a | |
|---|---|---|---|
| 75 | T, °C | Yield | ee |
| a | 0 | 95% | –76% |
| b | 0 | 91% | 83% |
| c | 0 | 95% | –84% |
| d | 0 | 94% | 84% |
| e | 0 | 71% | –19% |
| c | –25 | 95% | –92% |
| d | –25 | 90% | 92% |

*Ref. 42*

**eq 14**




| | | 74 | |
|---|---|---|---|
| 75 | R | Yield | ee |
| d | Ph | 95% | 90% |
| c | Ph | 96% | –85% |
| d | 4-$MeOC_6H_4$ | 93% | 90% |
| c | 4-$MeOC_6H_4$ | 98% | –87% |
| d | 4-$ClC_6H_4$ | 96% | 88% |
| c | 4-$ClC_6H_4$ | 91% | –91% |
| d | 2-$MeC_6H_4$ | 95% | 88% |
| c | 2-$MeC_6H_4$ | 95% | –85% |
| d | 2-Np | 98% | 91% |
| c | 2-Np | 91% | –87% |
| d | Ph | 90% | 97% |
| c | Ph | 90% | –78% |
| d | 2-$MeC_6H_4$ | 96% | 94% |
| c | 2-$MeC_6H_4$ | 89% | –79% |
| d | Ph | 98% | 36% |
| c | Ph | 98% | –92% |

*Ref. 42*

**eq 15**

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ASYMMETRIC CATALYSIS WITH TRIP AND NHC–Cu(I)

# Aldrichimica ACTA

VOL. 41, NO. 2 • 2008

ALDRICH Chemistry

**TRIP—A Powerful Brønsted Acid Catalyst for Asymmetric Synthesis**

**N-Heterocyclic Carbene–Copper Complexes: Synthesis and Applications in Catalysis**

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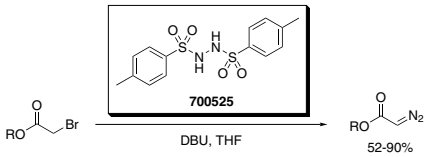
## *Aldrich Is Pleased to Offer Cutting-Edge Tools for Organic Synthesis*

### *Reagent for the Synthesis of Diazoacetates*

Diazoacetates are extremely useful reagents for a variety of reactions, such as cyclopropanations and C–H insertions. *N,N′*-Bis-(*p*-toluenesulfonyl)hydrazine is a stable, crystalline reagent that offers a useful alternative to tosyl azide for the production of diazoacetates. A variety of diazoacetates can be synthesized from the corresponding bromoacetates by treatment with *N,N′*-bis(*p*-toluenesulfonyl)-hydrazine in moderate-to-high yields in relatively short reaction times.




Toma, T. et al. *Org. Lett.* **2007**, *9*, 3195.

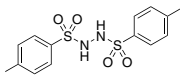
**N,N′-Bis(*p*-toluenesulfonyl)hydrazine**

**700525** 1 g

[*14062-05-6*]

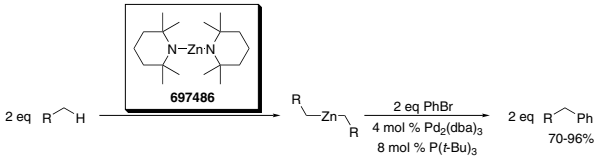
$C_{14}H_{16}N_2O_4S_2$

FW: 340.42



### *Zn(tmp)$_2$ for the Selective Functionalization of C–H bonds*

The selective functionalization of C–H bonds by neutral organozincs has typically been limited to fairly acidic carbon acids due to the slow kinetics of most dialkyl- and diarylzinc reagents. Bis(2,2,6,6-tetramethylpiperidinyl)zinc, Zn(tmp)$_2$, is an effective and versatile base for the mild, selective deprotonation of a broad range of substrates. The resultant organozincs can be conveniently coupled with aryl bromides using typical Pd-catalyzed cross-coupling methods.



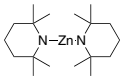

Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2007**, *26*, 4105.

**Bis(2,2,6,6-tetramethylpiperidinyl)zinc, 0.5 M in toluene**

**697486** 50 mL

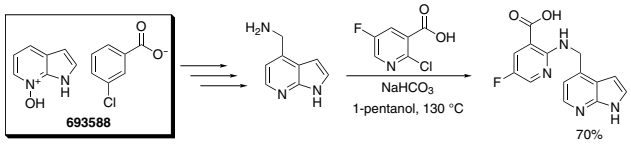
$C_{18}H_{36}N_2Zn$

FW: 345.88



### *7-Azaindoles*

The derivatives of 7-azaindole (1*H*-pyrrolo[2,3-*b*]pyridine) have emerged as an important and promising class of compounds in agrochemistry and medicinal chemistry. Recent years have seen an exponential increase in reports about pharmaceutically active 7-azaindole derivatives in the medicinal chemistry literature. One recent report details the practical synthesis of the key pharmaceutical intermediate 2-[(7-azaindol-4-yl)methylamino]-5-fluoronicotinic acid from the 7-azaindole *N*-oxide MCBA salt, **693588**.




Wang, X. et al. *J. Org. Chem.* **2006**, *71*, 4021.

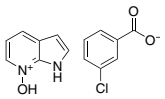
**7-Azaindole *N*-oxide 3-chlorobenzoate, 95%**

**693588** 1 g

[*611197-49-0*]

$C_{14}H_{11}ClN_2O_3$

FW: 290.71



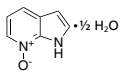
**7-Azaindole *N*-oxide hemihydrate, 97%**

**696838** 1 g

[*55052-24-9*]

$C_7H_6N_2O \cdot ½\ H_2O$

FW: 134.14



**4-Chloro-7-azaindole, 97%**

**696218** 250 mg

1 g

[*55052-28-3*]

$C_7H_5ClN_2$

FW: 152.58

**3-Nitro-7-azaindole**

**699268** 1 g

[*23709-47-9*]

$C_7H_5N_3O_2$

FW: 163.13

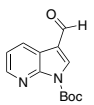
**1-Boc-7-azaindole-3-carboxaldehyde**

**696811** 1 g

[*144657-66-9*]

$C_{13}H_{14}N_2O_3$

FW: 246.26



**3-(Dimethylaminomethyl)-7-azaindole, 97%**

**696846** 1 g

5 g

[*5654-92-2*]

$C_{10}H_{13}N_3$

FW: 175.23

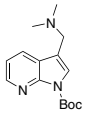
**1-Boc-3-[(dimethylamino)methyl]-7-azaindole, 97%**

**699209** 1 g

[*144657-65-8*]

$C_{15}H_{21}N_3O_2$

FW: 275.35



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VOL. 41, NO. 2 • 2008



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## "PLEASE BOTHER US."

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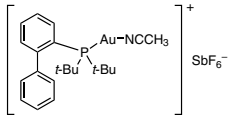
Aldrich Chemical Co., Inc.

Professor Antonio M. Echavarren from the Institute of Chemical Research of Catalonia (ICIQ) (Tarragona, Spain) kindly suggested that we make (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate. This crystalline gold complex is air-stable and can be handled under ordinary bench-top conditions. The cationic complex is capable of catalyzing various unique intramolecular cyclization reactions.[1–3]

(1) Nieto-Oberhuber, C. et al. *J. Am. Chem. Soc.* **2008**, *130*, 269. (2) Jiménez-Núñez, E. et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 5452. (3) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105.




**697575** **(Acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate** 250 mg, 1 g

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

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

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## ABOUT OUR COVER

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

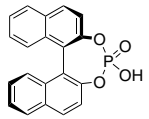
Camille Pissarro (1830–1903), one of the creators of the impressionist style, painted our cover, ***Orchard in Bloom, Louveciennes*** (oil on canvas, 45.1 × 54.9 cm) in 1872. Early in his career, Pissarro designated himself a pupil of Corot and, in this painting, Pissarro's broad method of composing and choice of a tranquil rural setting inhabited by a few small peasant figures still recall the older artist.

Pissarro completed this work shortly after he had returned to his home in Louveciennes after fleeing France during the Franco-Prussian War and Paris Commune. (Born in the Virgin Islands, then a possession of Denmark, Pissarro was a Danish citizen.) During the war, his house had been used by Prussian troops, and many of the canvases he left there were destroyed. He must have viewed the freshly plowed earth, like the spring blossoms that bring life to the dormant landscape, as a signal of renewed hope for his adopted country and for his career.

When the idea arose for a group exhibition of work by the artists who would come to be called impressionists, Pissarro was among the earliest and most enthusiastic supporters. Pissarro drafted the group's written statement of purpose and was the only artist to participate in all eight impressionist exhibitions. This painting was one of five he showed at the first exhibition in 1874.

**This painting is part of the Ailsa Mellon Bruce Collection at the National Gallery of Art, Washington, DC.**

# Chiral Phosphoric Acids



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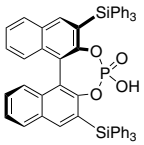

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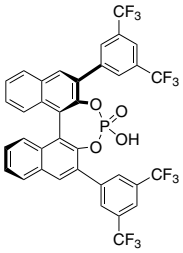

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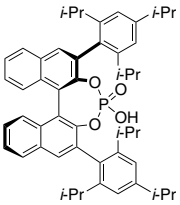

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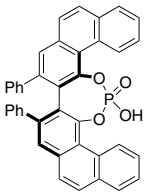
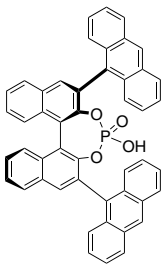


**688320**



**695718**

BINOL-derived chiral phosphoric acids are useful organocatalysts for a range of transformations: reductive aminations and Pictet–Spengler, aza-Diels–Alder, addition, and cascade reactions are all effected with excellent enantioselectivities.

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# TRIP—A Powerful Brønsted Acid Catalyst for Asymmetric Synthesis


Dr. Gareth Adair


Dr. Santanu Mukherjee


Prof. Dr. Benjamin List

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*Kaiser-Wilhelm-Platz 1*
*D-45470 Mülheim an der Ruhr, Germany*
*Email: list@mpi-muelheim.mpg.de*

## Outline

1. Introduction
2. Brønsted Acid Catalysis
   2.1. Asymmetric Transfer Hydrogenation
   2.2. Asymmetric Friedel–Crafts and Related Reactions
   2.3. Aza-Diels–Alder Reaction
3. Asymmetric Counteranion Directed Catalysis (ACDC)
   3.1. ACDC in Organocatalysis
   3.2. ACDC in Transition-Metal Catalysis
4. Conclusions
5. Acknowledgements
6. References

## 1. Introduction

Asymmetric organocatalysis has become one of the most active areas of research in chemistry since the beginning of this century.[1–5] In particular, the last five years have witnessed an enormous growth in terms of new catalyst design and reaction development and, most importantly, several new catalytic concepts have emerged. Asymmetric Brønsted acid catalysis[6–9] is one of the newly developed organocatalytic concepts that has had a substantial impact on this area. This type of catalysis can be subdivided into two classes, general acid catalysis and specific acid catalysis.[7] While general Brønsted acid catalysis implies substrate activation via hydrogen bonding in the transition state, specific Brønsted acid catalysis, or proton catalysis, indicates a more or less complete proton transfer from the catalyst to the substrate (**Figure 1**).[7] The proton can be regarded as the simplest activator for Lewis basic organic compounds. Nevertheless, the lack of a suitable chiral "ligand" for the proton has hindered the development of a chiral proton catalyst that would allow complete proton transfer to the substrate and at the same time transfer stereochemical information to the product.[10–12] In 2004, Akiyama[13] and Terada[14] introduced chiral BINOL-based phosphoric acids as efficient organocatalysts for Mannich-type transformations. Although chiral phosphoric acids had been utilized as chiral resolving agents[15] and as chiral ligands in metal-catalyzed reactions,[16,17] their application as chiral proton catalysts was unknown. Akiyama's and Terada's pioneering contributions led to the birth of the asymmetric specific Brønsted acid catalysis. Alongside new catalytic reactions, numerous structurally diverse BINOL-based chiral phosphoric acids, **1**, (**Figure 2**)[7,8] and, subsequently, a chiral *N*-triflylphosphoramide,[18] have been developed. It is particularly noteworthy that the catalytic activity and stereoselectivity imparted by these catalysts can change dramatically with the reactions and substrates, making a prediction of the catalytic behavior of chiral phosphoric acids quite difficult. Nevertheless, some of these catalysts appear to provide consistantly higher efficiencies in a number of reactions. 3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (abbreviated as **TRIP**) represents one such privileged catalyst (see Figure 2).[19] First reported by our group,[20,21] **TRIP** has emerged as one of the most active and enantioselective phosphoric acid catalysts reported to date.

The application of BINOL-derived phosphoric acids in asymmetric catalysis has not been restricted to chiral, specific Brønsted acid catalysis, but has included their conjugate bases as efficient chiral counteranions to induce enantioselectivity in other reactions that proceed via cationic intermediates. A new term has been coined for this type of catalysis, **A**symmetric **C**ounteranion **D**irected **C**atalysis (ACDC).[22]

## 2. Brønsted Acid Catalysis

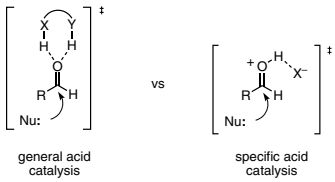
### *2.1. Asymmetric Transfer Hydrogenation*

The reduction of double bonds is one of the most fundamental transformations in organic chemistry. This area has received enormous attention, and has produced a number of elegant methods for the enantioselective reduction of alkenes,[23] ketones, and imines[24] using metal catalysts or stoichiometric amounts of metal hydrides. The recent development of organocatalysis has opened up the possibility of reducing double bonds without utilizing traditional metal catalysts, thus eliminating the need to remove heavy-metal contaminats.

In 2005, our group,[20] along with Rueping's,[25] reported the catalytic asymmetric reduction of ketimines using chiral Brønsted acid catalysts and Hantzsch esters **2** (**Figure 3**) as the stoichiometric hydrogen source.[26]

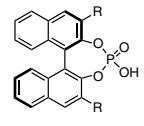
A wide variety of chiral phosphoric acid catalysts were screened for the reduction of ketimine **3a** (PMP = *para*-methoxyphenyl). Among these, **TRIP** initially gave the highest enantioselectivity but the lowest conversion (**eq 1**).[20]

Optimization of the reaction conditions, including the reduction of catalyst loading to only 1 mol % improved the enantioselectivity and yield of the **TRIP**-catalyzed reaction. Subjecting a variety of ketimines to the optimized reaction conditions revealed a fairly wide substrate scope, and allowed



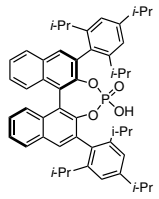

*Ref. 7*

**Figure 1.** General and Specific Acid Activation of a Carbonyl Group toward Nucleophilic Addition.



(*R*)-**1**

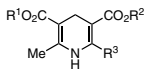
| 1 | R | 1 | R |
|---|---|---|---|
| **a** | Ph | **g** | 3,5-$(CF_3)_2C_6H_3$ |
| **b** | 4-biphenyl | **h** | 3,5-(*t*-Bu)$_2C_6H_3$ |
| **c** | 1-Np | **i** | $Ph_3Si$ |
| **d** | 2-Np | **j** | 2,4,6-$Me_3C_6H_2$ |
| **e** | 9-anthryl | **k** | 4-$O_2NC_6H_4$ |
| **f** | 9-phenanthryl | **l** | 2,6-$Me_2C_6H_3$ |



(*R*)-**TRIP**

*Ref. 7,8,20,21*

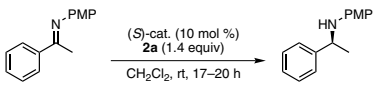
**Figure 2. TRIP** and Other Commonly Used BINOL-Derived Chiral Phosphoric Acid Organocatalysts.



| 2 | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| **a** | Et | Et | Me |
| **b** | Me | *t*-Bu | Me |
| **c** | Me | Me | *i*-Pr |

*Ref. 20,25,26*

**Figure 3.** Hantzsch Esters Commonly Used in Transfer Hydrogenations.

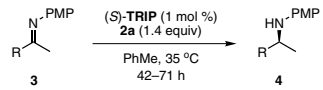



**3a** **4a**

| Cat. | Conv. | er |
|---|---|---|
| **1a** | 59% | 70:30 |
| **1d** | 34% | 72:28 |
| **1l** | 28% | 82.5:17.5 |
| **TRIP** | 10% | 90.5:9.5 |

*Ref. 20*

**eq 1**




**3** **4**

| R | Yield | er |
|---|---|---|
| 4-$O_2NC_6H_4$ | 90% | 90:10 |
| 3,4-$(MeO)_2C_6H_3$ | 84% | 94.5:5.5 |
| 2-$MeC_6H_4$ | 91% | 96.5:3.5 |
| *i*-Pr | 80% | 95:5 |

*Ref. 20*

**eq 2**

the reduction of imines **3** bearing electron-withdrawing, electron-donating, or sterically hindered aromatic substituents in high yields (80–98%) and with high enantioselectivities (up to 96.5:3.5 er). Remarkably, it was even possible to reduce an aliphatic ketimine to the corresponding amine in 80% yield and a 95:5 er (**eq 2**).[20]

This enantioselective transfer-hydrogenation methodology was subsequently applied to other imines such as α-imino esters.[27,28] Upon reduction, the optically enriched α-amino esters produced can be easily converted into the corresponding acids.

As imines are easily generated from the corresponding carbonyl compounds and amines, a one-pot enantioselective reductive amination reaction was performed. This in situ protocol gave the enantioenriched amine product **7** without any loss of enantioselectivity, even after removal of the PMP group (**eq 3**).[20] Shortly after publication of these results, MacMillan's group disclosed an enantioselective direct reductive amination of ketones using an alternative chiral phosphoric acid.[29]

The power of the reductive amination reaction to allow the high-yield synthesis of chiral amines prompted us to research this area further, which led us to disclose the first enantioselective reductive amination of α-branched aldehydes **8** (**Scheme 1**).[30] This reaction provides access to β-branched chiral amines **9** by taking advantage of a rapid imine–enamine tautomerization, which serves to racemize substrates in situ. The selective transfer hydrogenation of one of the two imine enantiomers sets the configuration of the stereocenter in the amine product.

The catalyst screening process once again identified **TRIP** as the best catalyst, which provided superior yields and enantioselectivities (**eq 4**).[30]

Reaction optimization pinpointed the efficient removal of water from the reaction mixture with the use of 5 Å molecular sieves as particularly important in achieving high enantioselectivities; the exclusion of oxygen was also necessary to prevent side reactions. Once again, the reaction was tolerant of a wide variety of functional groups, allowing the reductive amination of aldehydes bearing electron-withdrawing, electron-donating, or sterically hindered aromatic substituents in high yields (81–92%) and with high enantioselectivities (up to 99:1 er). The reaction also accomplished the reductive amination of aliphatic aldehydes, although the yields and enantioselectivities achieved were slightly lower (**eq 5**).[30]

Cascade reactions have the potential to provide efficient methods for the rapid synthesis of complex molecules from simple building blocks.[31] Very recently, our lab has demonstrated the utility of organocatalysis in this area by developing an asymmetric cascade reaction for the highly enantioselective synthesis of pharmaceutically relevant 3-substituted cyclohexylamines.[32] Starting from a 2,6-diketone, **10**, a sequential aldolization–dehydration–conjugate reduction–reductive amination cascade, catalyzed by a chiral Brønsted acid and co-catalyzed by the achiral amine substrate **11**, furnished the 3-substituted cyclohexylamine products **12**. **TRIP** was quickly identified as the Brønsted acid catalyst of choice, and was crucial for the observed cis-selectivity of the reaction; other phosphoric acids provided the trans isomer with lower enantioselectivity. When applied under optimized reaction conditions, with 2.2 equivalents of Hantzsch ester **2a** and 1.5 equivalents of amine substrate **11**, cyclohexylamines **12** were synthesized with excellent dr's (up to 24:1) and er's (up to 98:2) (**eq 6**). Heterocyclic products were also prepared with similar enantioselectivities and very high diastereoselectivities.[32]

## 2.2. Asymmetric Friedel–Crafts and Related Reactions

The Friedel–Crafts reaction is one of the most powerful carbon–carbon-bond-forming reactions in organic synthesis and is regularly used in academia and industry.[33,34] A number of metal-catalyzed[35–39] and organocatalytic enantioselective versions of this reaction have already been developed. Organocatalytic variants include those that utilize chiral imidazolidinone catalysts,[40–42] chiral thioureas[43,44] and related hydrogen-bonding catalysts,[45,46] as well as chiral phosphoric acid catalysts.[47–50]

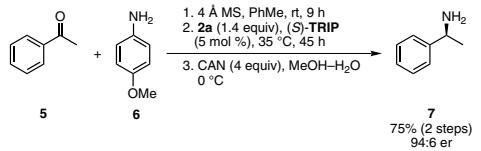
Recently, Terada and Sorimachi disclosed a **TRIP**-catalyzed enantioselective Friedel–Crafts reaction of indole and its derivatives, **13**, with enecarbamates **14** to obtain pharmaceutically and biologically important enantioenriched 1-(indol-3-yl)-1-alkylamines **15** (**eq 7**).[51] With only 5 mol % of **TRIP**, a variety of substituted indoles **13** and a broad range of enecarbamates **14** underwent facile C–C-bond formation to generate products **15** in moderate-to-excellent yields (63–98%) and high enantioselectivities (up to 99:1 er). High enantioselectivities were obtained in all cases regardless of the electronic properties of the indole moieties. An additional advantage of this method is that mixtures of geometric isomers (*E* or *Z*) of enecarbamates can be employed without affecting the enantioselectivity—an indication that the mechanism of the reaction involves an iminium ion intermediate generated by protonation of the enecarbamate (see below).

The application of this kind of Brønsted acid catalyzed Friedel–Crafts reaction to the construction of quaternary stereocenters has very recently been demonstrated by Zhou and co-workers.[52] Instead of enecarbamates **14**, α-aryl enamides **16** were employed as the electrophilic partner for the reaction with indole derivatives **13** (**eq 8**). A wide range of indole derivatives **13** and α-aryl enamides **16** were employed as substrates, affording the corresponding products **17** in excellent yields (94–99%) and enantioselectivities (up to 98.5:1.5 er). The electronic nature of the substituents on the α-aryl enamides **16** has little effect on the outcome of the reaction. Once again, among several chiral phosphoric acids tested, **TRIP** was superior both in terms of product yield and enantioselectivity (**eq 9**).[52]

As mentioned previously, these reactions proceed via *N*-acyliminium ions, which are in equilibrium with enecarbamates **14** or α-aryl enamides **16** (**eq 10**).

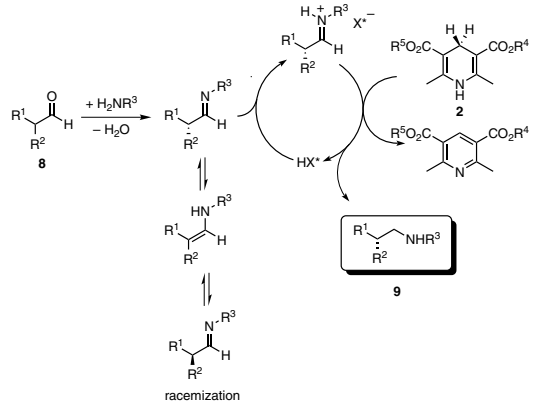
The Pictet–Spengler reaction can be formally viewed as an intramolecular Friedel–Crafts reaction. This reaction is frequently used in the laboratory and by various organisms for the synthesis of tetrahydro-β-carbolines or tetrahydroisoquinolines, which are important structural elements in many alkaloids and related biologically active compounds.[53,54] The reaction proceeds via a simple condensation of a carbonyl compound with phenylethylamines or tryptamines to form an imine, followed by a Friedel–Crafts-type carbon–carbon-bond-forming cyclization.[55,56] Although several substrate- and auxiliary-controlled diastereoselective variants of this reaction,[54] as well as one reagent-controlled enantioselective version,[57] have been described, there has been no catalytic enantioselective version until recently. Taylor and Jacobsen have developed a catalytic asymmetric acyl Pictet–Spengler reaction employing a chiral thiourea organocatalyst.[58] However, the catalytic, asymmetric "direct" Pictet–Spengler reaction of aldehydes with arylethylamines has remained an elusive target.

In 2006, our group reported the first Brønsted acid catalyzed asymmetric Pictet–Spengler reaction of substituted tryptamines to give the corresponding tetrahydro-β-carbolines.[59] The reaction



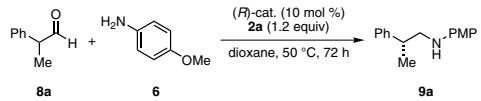

*Ref. 20*

**eq 3**




*Ref. 30*

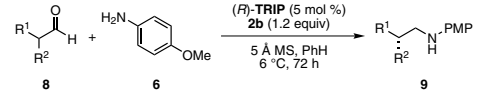
**Scheme 1.** Proposed Mechanism of the Catalytic Enantioselective Reductive Amination of α-Branched Aldehydes.




| Cat. | Yield | er |
|---|---|---|
| **1b** | 72% | 55:45 |
| **1i** | 7% | 61:39 |
| **1l** | 55% | 60:40 |
| **TRIP** | 50% | 84:16 |

*Ref. 30*

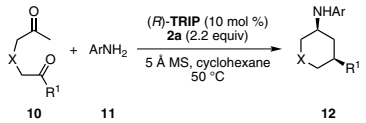
**eq 4**




| $R^1$ | $R^2$ | Yield | er |
|---|---|---|---|
| 4-$BrC_6H_4$ | Me | 92% | 97:3 |
| 4-$MeOC_6H_4$ | Me | 81% | 97:3 |
| 1-Np | Me | 85% | 99:1 |
| Ph | Et | 92% | 99:1 |
| *t*-Bu | Me | 77% | 90:10 |

*Ref. 30*

**eq 5**



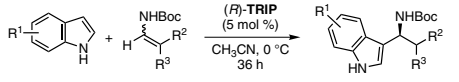

10 11 12

Ar = 4-EtOC$_6$H$_4$

| R$^1$ | X | Yield | dr | er |
|---|---|---|---|---|
| Me | O | 72% | 99:1 | 96:4 |
| 2-Np | $CH_2$ | 73% | 2:1 | 91:9 |
| $PhCH_2CH_2$ | $CH_2$ | 82% | 24:1 | 98:2 |
| *c*-$PentCH_2$ | $CH_2$ | 72% | 24:1 | 98:2 |

*Ref. 32*

**eq 6**




13 14 15

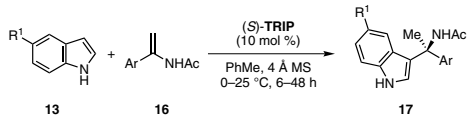
*E*, *Z*, or *E*+*Z*

| R$^1$ | R$^2$ | R$^3$ | Yield | er |
|---|---|---|---|---|
| H | *n*-Bu | H | 98% | 97:3 |
| H[a] | Me | Me | 69% | 97:3 |
| 5′-MeO | Me | H | 90% | 95:5 |
| 5′-$CO_2$Me[b] | Me | H | 86% | 96.5:3.5 |

[a] 20 h at 50 °C. [b] 6 h at rt.

*Ref. 51*

**eq 7**

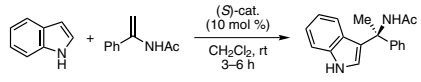



13 16 17

| R$^1$ | Ar | Yield | er |
|---|---|---|---|
| H | 3-$MeOC_6H_4$ | 99% | 98.5:1.5 |
| H | 3,4-$Me_2C_6H_3$ | 99% | 97.5:2.5 |
| Br | Ph | 98% | 95:5 |
| MeO | Ph | 99% | 96:4 |

*Ref. 52*

**eq 8**




13a 16a 17a

| Cat. | Yield | er |
|---|---|---|
| **1a** | 79% | 66:34 |
| **1d** | 87% | 55:45 |
| **1e** | 52% | 83:17 |
| **1f** | 54% | 61:39 |
| **1g** | 72% | 69:31 |
| **1i** | 58% | 62.5:37.5 |
| **TRIP**[a] | 98% | 97:3 |

[a] PhMe, 4 Å MS, 0 °C 40 h.

*Ref. 52*

**eq 9**

between tryptamine derivative **18a** and propionaldehyde **19a** served as the model reaction for catalyst screening (**eq 11**). **TRIP** was the best catalyst among various chiral phosphoric acids tested and afforded an er of 83:17. A significant improvement in enantioselectivity was achieved by conducting the reaction at a lower temperature. Under the optimum reaction conditions, a variety of different tryptamine derivatives, **18**, as well as several aliphatic and aromatic aldehydes, **19**, reacted smoothly in the presence of 20 mol % of **TRIP** to generate the cyclized products **20** in 40–98% yields and enantioselectivities of up to 98:2 er (**eq 12**).[59]

Very recently, Hiemstra and co-workers reported a chiral phosphoric acid catalyzed enantioselective Pictet–Spengler reaction of *N*-sulfenyltryptamines that proceeds via *N*-sulfenyliminium ions—an example of ACDC (see Section 3 below).[60]

### 2.3. Aza-Diels–Alder Reaction

Protonation-induced activation makes it possible for imines to be used as both dienophiles (normal) and dienes (inverse electron demand) for the Brønsted acid catalyzed enantioselective aza-Diels–Alder reaction.[61] This reaction provides an efficient route for the synthesis of functionalized piperidine derivatives, which are important building blocks of biologically active alkaloids and aza sugars. Naturally, several catalytic asymmetric variants of the aza-Diels–Alder reaction have been developed employing chiral metal complexes.[62–65] However, an organocatalytic asymmetric version of this reaction remained elusive until Akiyama and co-workers reported the first Brønsted acid catalyzed enantioselective aza-Diels–Alder reaction of Danishefsky's diene (**22**)[66] and aldimines.[67] Initial catalyst screening for the reaction between aldimine **21** and diene **22** showed **TRIP** giving rise to a higher enantiomeric ratio than other catalysts, with **1a** and **1k** affording a nearly racemic product (**eq 13**). Further improvement in enantioselectivity was achieved by changing the amine part of the aldimine from 2-aminophenol to 2-amino-4-methylphenol, as well as by adding 1.2 equivalents of an achiral Brønsted acid ($CH_3CO_2H$). Under the optimized reaction conditions, a number of aromatic aldimines, **24**, were used as dienophiles for the reaction with diene **22** (**eq 14**).[67] Cycloadducts **25** were obtained in 72–100% yields and with good enantioselectivities (up to 95.5:4.5 er).

The activation of aldimine **24** is proposed to occur through a nine-membered transition state incorporating two hydrogen bonds, one from the phosphate hydrogen and one from the hydroxyl group of the aldimine.[67] Activation through complete protonation of the aldimine nitrogen by **TRIP** cannot be ruled out (**Figure 4**).

Following Akiyama's report, a few other disclosures of chiral phosphoric acid catalyzed asymmetric normal,[68–70] as well as inverse-electron-demand,[71] aza-Diels–Alder reactions have appeared. In all cases, the products were obtained in good yields and with high stereoselectivities.

## 3. Asymmetric Counteranion Directed Catalysis (ACDC)

Most chemical reactions proceed via either charged intermediates or transition states. The introduction of a chiral anion into a reaction that proceeds via a cationic intermediate has the potential to influence the stereochemical outcome of the reaction, especially if the reaction is conducted in organic solvents in which ion pairs are ineffectively separated. While reactions proceeding via anionic intermediates have been rendered asymmetric when mediated by

a chiral cationic species,[72] the analogus transformations involving cationic intermediates and a chiral anionic species have been less successful despite several attempts.[73,74]

### 3.1. ACDC in Organocatalysis

Having previously established the metal-free transfer hydrogenation of α,β-unsaturated aldehydes with the use of salts of chiral amines,[75] we investigated the use of chiral salts formed from achiral amines and chiral phosphoric acids. Since this transfer-hydrogenation reaction proceeds through a cationic iminium ion intermediate, stereochemical information would be transferred from the chiral counteranion during the reaction, not the amine.

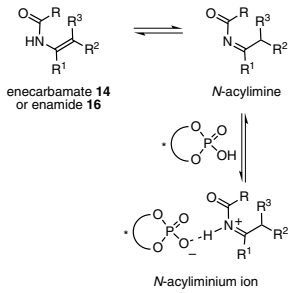
Many ammonium salts, easily prepared by simply mixing a chiral phosphoric acid with a commercially available primary or secondary amine, were screened, and the salt, **27**, formed from **TRIP** and morpholine, was identified as the optimal catalyst.[22] When used with a slight excess of Hantzsch ester **2c**, the reaction consistently provided products with high enantioselectivities (98:2 to >99:1 er) and often high yields (**eq 15**).

Interestingly, this novel asymmetric counteranion directed catalysis (ACDC) is significantly more enantioselective than those that use other chiral amine catalysts developed previously.[75,76] When applied to the transfer hydrogenation of (*E*)-citral (**29**), the **TRIP**–morpholine salt provided (*R*)-citronellal (**30**) with an enantiomeric ratio of 95:5, a significant improvement upon the reduction catalyzed by chiral amine salts **31** and **32** (**eq 16**).[22]

Further investigation of the ACDC approach to transfer hydrogenation allowed the development of a catalyst system that is capable of reducing α,β-unsaturated ketones.[77] When the transfer hydrogenation previously developed for the reduction of α,β-unsaturated aldehydes was applied to ketones, it was found that the steric bulk of secondary amines reduced the efficiency of the reaction.[78] The examination of **TRIP** salts of primary amines led to the identification of (*S*)-valine ester **34**, in combination with (*R*)-**TRIP**, as the optimal transfer hydrogenation catalyst for ketones. When applied to a variety of ketones, the yields were generally good to excellent and the enantiomer ratios up to 99:1. The reaction tolerated 5-, 6-, and 7-membered enones well, and was also used to reduce acyclic ketones, although lower enantioselectivities were observed for these substrates (**eq 17**).[77]

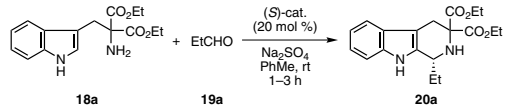
The concept of ACDC in organocatalysis is not limited to transfer hydrogenations. Catalytic enantioselective epoxidations have attracted much research over the past few decades, resulting in the disclosure of a number of elegant methods.[79] In the field of organocatalysis, iminium-catalyzed enantioselective epoxidations of α,β-unsaturated aldehydes have recently been realized.[80–83] Our group's very recent contribution to this area applies ACDC to the catalytic enantioselective epoxidation, expanding the scope of the epoxidation reaction to allow previously elusive trisubstituted, as well as disubstituted, α,β-unsaturated aldehydes to be epoxidized with excellent enantioselectivities.[84] Catalyst screening revealed that bis[(3,5-trifluoromethylphenyl)methyl]amine, when used in combination with **TRIP** and *tert*-butyl hydroperoxide, provided epoxide **38** with the highest dr and er. When applied to a wide variety of aromatic disubstituted α,β-unsaturated aldehydes, **36**, this catalyst combination showed good steric and functional-group tolerance, providing epoxides **38** in good yields and high diastereomeric (up to >99:1) and enantiomeric ratios (up to 97:3) (**eq 18**).[84]

Interestingly, when this new methodology was applied to trisubstituted α,β-unsaturated aldehydes **39**, the enantiomeric ratios of the epoxide products, **40**, were not significantly affected




*Ref. 52*

**eq 10**

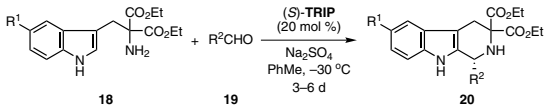



| Cat. | Yield | er |
|---|---|---|
| **1d**[a] | 75% | 65:35 |
| **1g** | 95% | 59:41 |
| **1j** | 96% | 76:24 |
| **1k** | 80% | 57:43 |
| **TRIP** | 90% | 83:17 |

[a] After 24 h.

*Ref. 59*

**eq 11**

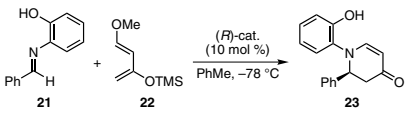



| $R^1$ | $R^2$ | Yield | er |
|---|---|---|---|
| H | Et | 76% | 94:6 |
| MeO | Et | 96% | 95:5 |
| MeO | Cy | 93% | 96.5:3.5 |
| MeO[a] | 4-$O_2NC_6H_4$ | 98% | 98:2 |

[a] At –10 °C in $CH_2Cl_2$.

*Ref. 59*

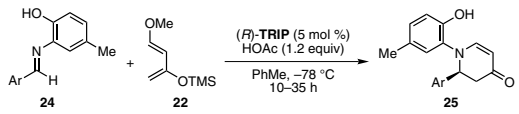
**eq 12**




| Cat. | t, h | Yield | er |
|---|---|---|---|
| **1a** | 23 | 67% | 51.5:48.5 |
| **1k** | 21 | 90% | 52.5:47.5 |
| **TRIP** | 20 | 32% | 71:29 |

*Ref. 67*

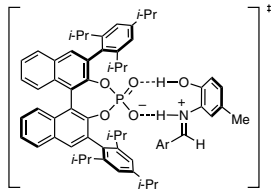
**eq 13**




| Ar | Yield | er |
|---|---|---|
| Ph | 99% | 90:10 |
| 4-$BrC_6H_4$ | 100% | 92:8 |
| 1-Np | 100% | 95.5:4.5 |

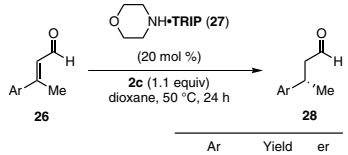
*Ref. 67*

**eq 14**



Ref. 67

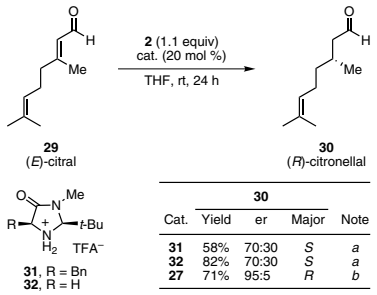
**Figure 4.** Working Hypothesis of the **TRIP**-Catalyzed Aza-Diels–Alder Reaction.



| Ar | Yield | er |
|---|---|---|
| 4-$O_2NC_6H_4$ | 90% | 99:1 |
| 4-$BrC_6H_4$ | 67% | 98:2 |
| 4-$F_3CC_6H_4$ | 63% | 99:1 |
| 2-Np | 72% | >99:1 |

Ref. 22

**eq 15**

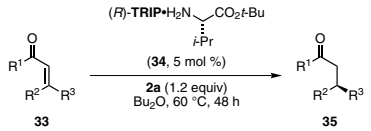


| Cat. | Yield | er | Major | Note |
|---|---|---|---|---|
| **31** | 58% | 70:30 | *S* | *a* |
| **32** | 82% | 70:30 | *S* | *a* |
| **27** | 71% | 95:5 | *R* | *b* |

[a] Hantzsch ester **2a** was used and gave higher er values than **2c**. [b] Hantzsch ester **2c** was used.

Ref. 22

**eq 16**



| $R^1,R^2$ | $R^3$ | Yield | er |
|---|---|---|---|
| $(CH_2)_3$ | Et | 98% | 98:2 |
| $(CH_2)_3$ | Ph | 99% | 92:8 |
| $(CH_2)_2$[a] | Me | 78% | 99:1 |
| $(CH_2)_4$ | Me | >99% | 98:2 |
| Me,Me | $CO_2Et$ | >99% | 92:8 |

[a] 10 mol % of **34** was used.

Ref. 77

**eq 17**

(**eq 19**).[84] No other catalytic methodology had previously been developed for the highly enantioselective epoxidation of such trisubstituted aldehydes.

The high enantioselectivities observed for this reaction imply a new enamine activation mode, whereby **TRIP** assists the formation of the three-membered epoxide ring from an achiral enamine intermediate. This new mode of activation has the potential to significantly broaden the scope of ACDC.

### 3.2. ACDC in Transition-Metal Catalysis

The potential of ACDC outside of organocatalysis has recently been demonstrated by three research groups in three different transition-metal-catalyzed asymmetric transformations. Remarkably, in all these cases the phosphate anion of **TRIP** has been used to impart enantiofacial discrimination.

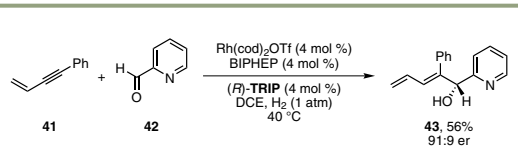
In 2006, Komanduri and Krische described a Rh-catalyzed reductive coupling of 1,3-enynes to heterocyclic aromatic carbonyl compounds using chiral bisphosphine ligands to induce high enantioselectivities.[85] Further work from Krische's group showed that Brønsted acid co-catalysts can enhance both the reaction rate and conversion of such hydrogen-mediated alkyne–carbonyl coupling reactions.[86] The authors discovered that when **TRIP** was utilized as the Brønsted acid co-catalyst in combination with an achiral bisphosphine ligand, the reductive coupling product of enyne **41** and pyridine-2-carboxaldehyde (**42**) was obtained with good enantioselectivity (91:9 er) (**eq 20**). Although the enantioselectivity obtained in this case is lower than that observed with the *chiral* bisphosphine ligands, this example clearly shows the influence of the chiral counteranion on the transition-metal-catalyzed transformation. With the support of additional experiments, the authors proposed that ion pairing with a protonated pyridine moiety (**eq 21**) was responsible for the asymmetric induction, not a cationic rhodium complex.[85] This example can therefore be viewed as a special case of ACDC in the field of transition-metal catalysis.

The first examples of the concept of combined transition-metal–ACDC catalysis were developed independently by Toste's group and ours for Au- and Pd-catalyzed transformations, respectively (vide infra). However, the application of chiral phosphates in asymmetric transition-metal catalysis was not completely unknown. In 1990, Alper and Hamel employed an unsubstituted BINOL-derived phosphoric acid for the Pd-catalyzed asymmetric hydrocarboxylation of olefins, proposing the participation of chiral phosphate as a ligand for Pd.[87]

Toste and co-workers described the first application of the metal–ACDC catalysis concept in an Au-catalyzed heteroatom cyclization reaction of allenes.[88] The hydroamination (**eq 22**) and hydroalkoxylation (**eq 23**) of allenes were chosen as model reactions. The discovery originated from these workers' previously observed dramatic counteranion influence on the stereoselectivity of the chiral bisphosphine–Au(I)-catalyzed allene hydroamination reaction.[89] The authors also described a synergistic effect between the chiral bisphosphine ligands and the chiral counteranion. This dual approach overcomes enantioselective limitations found when only a chiral ligand or a chiral counteranion were employed, either of which afforded the product with lower enantioselectivity. This dual effect was shown to be particularly pronounced in the case of hydrocarboxylation.[88] In the two model reactions utilizing **TRIP**, the silver salt of **TRIP**, not **TRIP** itself, was used together with achiral phosphine–Au(I) chloride complexes. The in situ precipitation of silver chloride allows the formation of the Au(I)–**TRIP** species. Excellent enantioselectivities were achieved in both reactions, resulting from ion pairing of the **TRIP** anion with the cationic Au–allene intermediate.

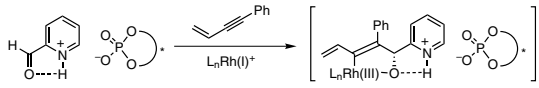
In general, stereoinduction is rather difficult in Au-catalyzed transformations. Although chiral phosphine ligands have proven successful in certain cases, they have failed in others, possibly due to the linear coordination geometry of gold, which keeps the chiral information of the ligands far from the reaction center. The current work by Toste's group has shown the applicability of ACDC in such circumstances, by providing chiral induction through a chiral counteranion which can reside close to the cationic reaction center.[88,90,91] This concept is certain to broaden the scope of asymmetric transformations, such as those catalyzed by cationic gold complexes.

Our group recently reported the first application of the chiral counteranion strategy in the Pd-catalyzed asymmetric allylic alkylation reaction.[92] Tsuji–Trost-type allylic alkylation reactions are of great importance in organic chemistry due to their general applicability and versatility in the synthesis of structurally complex building blocks.[93] This reaction is also one of the few methods that allow for the formation of all-carbon quaternary stereogenic centers.[94–96] So far, the use of chiral phosphine ligands remains the only means of achieving asymmetric induction in allylic alkylation reactions. Inspired by the report of Murahashi et al.,[97] we introduced the ACDC approach to this type of transformation. We chose as a model reaction the asymmetric α allylation of branched aldehydes **8**, which still poses a considerable challenge to the synthetic organic chemist. Although a few methods have recently been described for the direct catalytic asymmetric α allylation of aldehydes,[98,99] none of these methods allow for the formation of quaternary stereogenic centers. Using Pd(0) and **TRIP** as catalyst, a number of different α-branched aldehydes **8** underwent efficient α allylation with *N*-benzhydrylallylamines **48** as unconventional allylating reagents. The rather mild reaction conditions afforded the products **49** in good yields (up to 89%) and with high enantioselectivities (up to 98.5:1.5 er) (**eq 24**). Substitution at the 3 position of the allyl group was also explored and gave good results. The reaction most likely proceeds through a hydrogen-bonded assembly of chiral phosphate, enamine, and π-allylPd species (**Figure 5**).



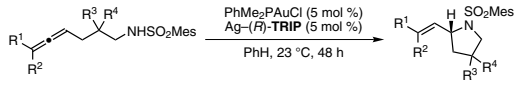

Ref. 85

**eq 20**




Ref. 85

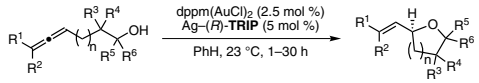
**eq 21**




| $R^1$,$R^2$ | $R^3$,$R^4$ | Yield | er |
|---|---|---|---|
| $(CH_2)_5$ | H,H | 97% | 98:2 |
| $(CH_2)_4$ | H,H | 88% | 99:1 |
| Me,Me | Me,Me | 84% | 99.5:0.5 |
| Me,Me | $(CH_2)_5$ | 73% | 99:1 |

Ref. 88

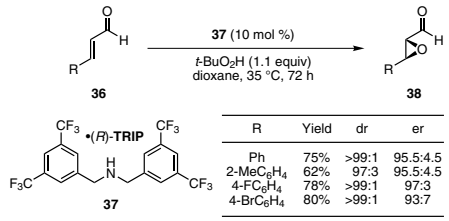
**eq 22**




| n | $R^1$,$R^2$ | $R^3$,$R^4$ | $R^5$,$R^6$ | Yield | er |
|---|---|---|---|---|---|
| 1 | Me,Me | H,H | H,H | 91% | 97.5:2.5 |
| 1 | $(CH_2)_5$ | H,H | Me,Me | 79% | 99.5:0.5 |
| 1 | $(CH_2)_5$ | Me,Me | H,H | 90% | 95:5 |
| 2 | Me,Me | H,H | H,H | 81% | 95:5 |

Ref. 88

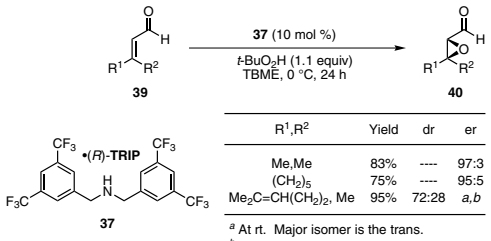
**eq 23**




| R | Yield | dr | er |
|---|---|---|---|
| Ph | 75% | >99:1 | 95.5:4.5 |
| 2-$MeC_6H_4$ | 62% | 97:3 | 95.5:4.5 |
| 4-$FC_6H_4$ | 78% | >99:1 | 97:3 |
| 4-$BrC_6H_4$ | 80% | >99:1 | 93:7 |

Ref. 84

**eq 18**

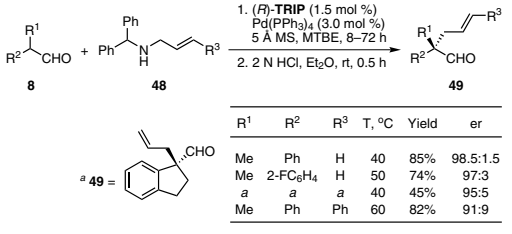



| $R^1$,$R^2$ | Yield | dr | er |
|---|---|---|---|
| Me,Me | 83% | ---- | 97:3 |
| $(CH_2)_5$ | 75% | ---- | 95:5 |
| $Me_2C{=}CH(CH_2)_2$, Me | 95% | 72:28 | *a,b* |

[a] At rt. Major isomer is the trans.
[b] er = 88:12 (trans), 96:4 (cis).

Ref. 84

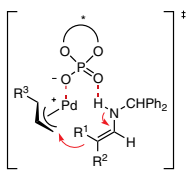
**eq 19**




| $R^1$ | $R^2$ | $R^3$ | T, °C | Yield | er |
|---|---|---|---|---|---|
| Me | Ph | H | 40 | 85% | 98.5:1.5 |
| Me | 2-$FC_6H_4$ | H | 50 | 74% | 97:3 |
| *a* | *a* | *a* | 40 | 45% | 95:5 |
| Me | Ph | Ph | 60 | 82% | 91:9 |

Ref. 92

**eq 24**




Ref. 92

**Figure 5.** Plausible Transition-State Assembly for the Asymmetric α Allylation of Branched Aldehydes.

These two examples of the application of ACDC in metal-catalyzed transformations mark just the beginning, with many more metal-catalyzed asymmetric transformations employing this concept expected in the near future.[100]

## 4. Conclusions

Over the last few years, Brønsted acid catalysis has emerged as a rich area of research in the realm of asymmetric catalysis. While initial efforts were mainly focused on the discovery of hydrogen-bonding organocatalysts such as thioureas and diols, it is chiral phosphoric acids that now dominate the field of so-called proton catalysis. The privileged structural motif of **TRIP** makes it a leading catalyst within this class. While its initial applications were limited to reactions involving imines, its activation of carbonyl compounds has also been accomplished through ACDC. The concept of ACDC has recently been extended further to transition-metal catalyzed reactions, where **TRIP** has once again been the most enantioselective of similar catalysts. The rapid and exciting evolution of this area of asymmetric catalysis will no doubt spawn many novel concepts and methodologies to add to the synthetic chemist's armory of stereoselective reactions.

## 5. Acknowledgements

We would like to thank all the current and previous members of our research group for their contributions towards the development of **TRIP** and its application in asymmetric catalysis. Generous funding has been provided by the Max-Planck Society, the Deutsche Forschungsgemeinschaft (DFG), the Fonds der Chemischen Industrie (FCI), and by Novartis.

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**Keywords:** asymmetric catalysis; organocatalysis; Brønsted acid; phosphoric acid; chiral counteranion.

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**Gareth Adair** was born in 1981 in Belfast, Northern Ireland. He studied chemistry at the University of Bath, England, where he obtained his M. Chem. (Honors) degree in 2003. Gareth returned to the University of Bath and completed his Ph.D. degree in December 2006 under the supervision of Professor Jonathan M. J. Williams, developing a metal-catalyzed deracemization of secondary alcohols. Gareth then joined the research group of Professor Benjamin List at the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr, Germany. His current research is focused on expanding the scope of asymmetric counteranion directed reactions (ACDC) in the field of organocatalysis.

**Santanu Mukherjee** was born in 1980 in Hooghly, India. After obtaining his B.Sc. degree (Chemistry Honors) in 2000 from Ramakrishna Mission Residential College, Narendrapur, he moved to the Indian Institute of Technology, Kanpur, where he finished his M.Sc. degree in 2002. He then joined the research group of Professor Albrecht Berkessel at the University of Cologne, Germany, where he worked on the enantioselective synthesis of amino acids by applying the emerging concepts of asymmetric organocatalysis. He completed his Ph.D. degree *(summa cum laude)* in February 2006, when he joined Professor List's group as a postdoctoral associate and worked on broadening the scope of ACDC in the area of transition-metal chemistry. Santanu is currently a postdoctoral fellow in Prof. E. J. Corey's research group at Harvard University.

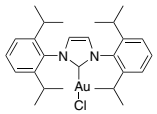
**Benjamin List** was born in 1968 in Frankfurt, Germany. He graduated in 1993 from Freie University, Berlin, and received his Ph.D. degree in 1997 from the University of Frankfurt. After postdoctoral studies (1997–1998) as a Feodor Lynen Fellow of the Alexander von Humboldt foundation at The Scripps Research Institute, he became a tenure-track assistant professor there in January 1999. Subsequently, he developed the first proline-catalyzed asymmetric intermolecular aldol-, Mannich-, Michael-, and α-amination reactions, and received a grant for research on asymmetric aminocatalysis from the National Institutes of Health. He moved to the Max-Planck-Institut für Kohlenforschung in 2003 as an associate professor (2003–2005), and is currently a director (full professor) there and an honorary professor at the University of Cologne. His research interests are new catalysis concepts, bioorganic chemistry, and natural product synthesis. He received several awards including the Carl-Duisberg-Memorial Award of the German Chemical Society (2003), the Degussa-Preis for Chiral Chemistry (2004), the Lecturer's Award of the Endowment of the Chemical Industry (2004), the Lieseberg-Preis of the University of Heidelberg (2004), The Society of Synthetic Organic Chemistry, Japan, Lectureship Award (2005), the Novartis Young Investigator Award (2005), the *Organic and Biomolecular Chemistry* (OBC) Lecture Award (2007) and, most recently, the AstraZeneca Award in Organic Chemistry. He is currently an editor of *Synfacts* and coordinates the DFG's priority program "Organocatalysis".

# Accelerate Catalysis

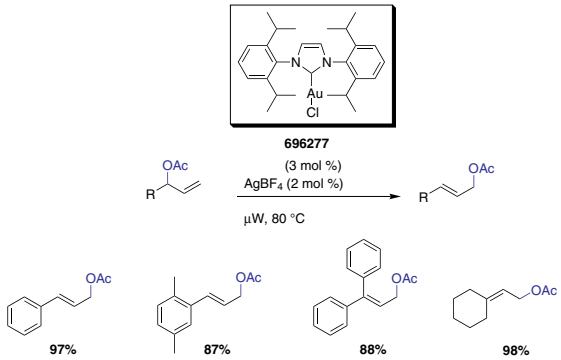
## Rearrangement of Allylic Acetates

Nolan and co-workers have recently reported the first gold-catalyzed allylic rearrangement. To illustrate the versatility of the [(NHC)AuCl] complex used, several allyl acetates were rearranged with excellent yields.

Marion, N. et al. *Org. Lett.* **2007**, *9*, 2653.



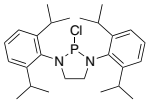
**[(NHC)AuCl]**
**696277**




## Amination of Aryl Chlorides

The amination of aryl chlorides with various amines has always been challenging, usually requiring bulky phosphines to get reasonable yields. However, the scope of the phosphine-mediated amination has been limited to a few aryl chlorides. To overcome this limitation, Ackermann et al. have synthesized a diaminophosphine ligand. When used with $Pd(dba)_2$, good yields are obtained for the catalytic amination of a wide variety of aryl halides with different primary and secondary amines.

Ackermann, L. et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 7627.



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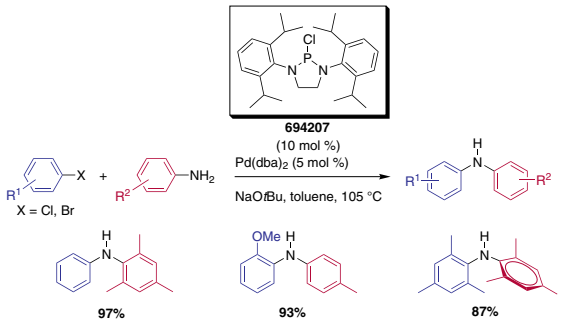
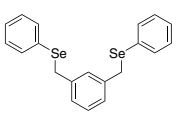



## Pincer Ligands

Functionalized allylboronates are useful building blocks in natural product synthesis. Olsson et al. have reported the use of a palladium pincer complex for the boronation of allylic alcohols. Under mild conditions, a variety of allylic alcohols were reacted with 5 mol % of catalyst to yield the corresponding boronic acids, which were reacted further to form the more stable allyltrifluoroboronate derivatives in good yields.

Olsson, V. J. et al. *J. Am. Chem. Soc.* **2006**, *128*, 4588.



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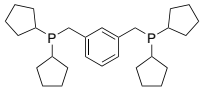

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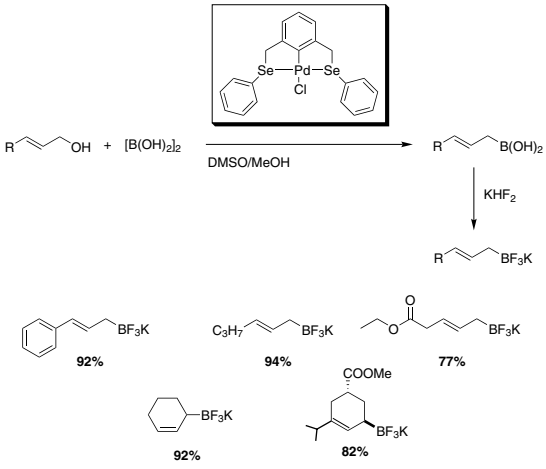
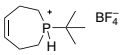


## Direct Arylation of Heterocycles

A practical, functional-group-tolerant method for the direct arylation of a range of pharmaceutically relevant heterocycles has been reported by Ellman, Bergman, and co-workers. The method relies on the use of rhodium as the transition-metal catalyst in combination with (*Z*)-1-*tert*-butyl-2,3,6,7-tetrahydro-1*H*-phosphepine (Ellman's Ligand). A variety of azoles, including unprotected NH azoles, and functionalized aryl bromides have been successfully used as coupling partners.

Lewis, J. C. et al. *J. Am. Chem. Soc.* **2008**, *130*, 2493.



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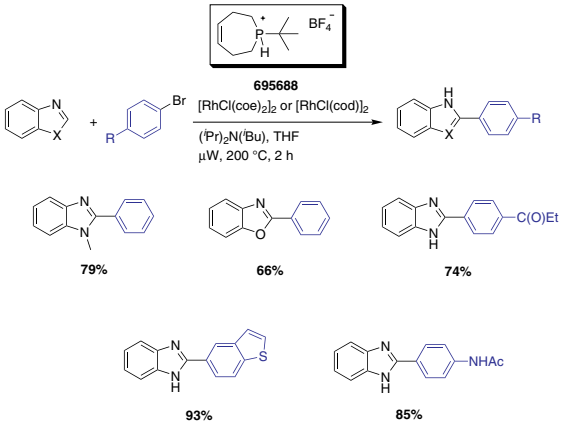
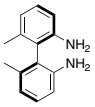



## Ligand Precursors for Enantioselective Aziridination

Aziridines are very versatile building blocks used in the synthesis of various natural products and drugs. Gillespie et al. have disclosed a new and efficient alkene aziridination that utilizes chiral biaryl diamines as ligands. Starting with 2,2'-diamino-6,6'-dimethylbiphenyl, these researchers synthesized a family of chiral biaryldiamine ligands. These new ligands led to very efficient catalysts for the aziridination of a variety of alkenes.

Gillespie, K. M. et al. *J. Org. Chem.* **2002**, *67*, 3450.



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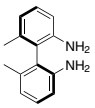

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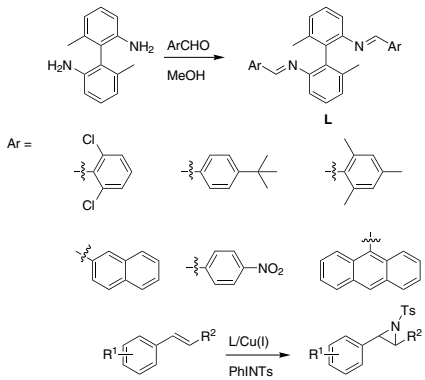
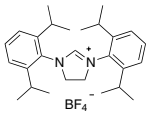



## New NHC Ligands

Sigma-Aldrich is pleased to offer an extensive portfolio of N-heterocyclic carbene ligands and precursors.



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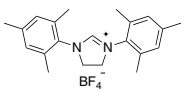

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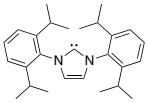

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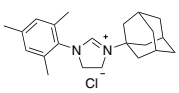

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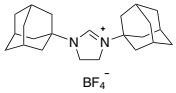

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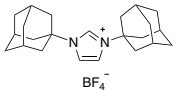

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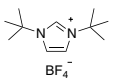

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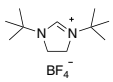

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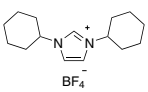
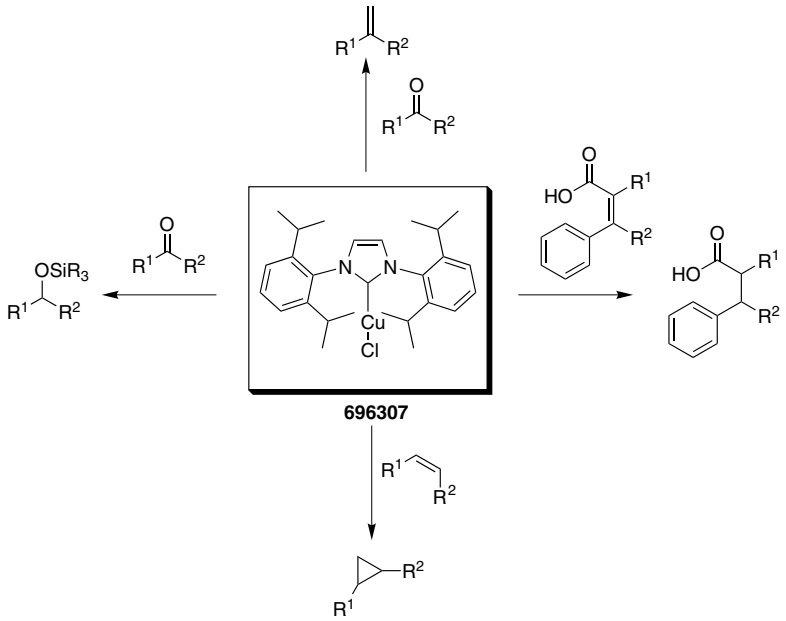


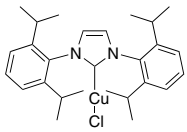
**666181**

**668400**

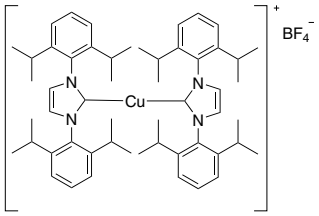
# N-Heterocyclic Carbene–Copper Complexes

N-Heterocyclic carbene (NHC) ligands have become popular in the last 20 years. Their tunable electronic and steric properties have made them candidates of choice when designing new metal complexes for catalysis. Professor Nolan, one of the pioneers of the use of NHC ligands for catalysis, has employed NHC–copper complexes in a variety of catalytic transformations such as the conjugate reduction of α,β-unsaturated ketones and esters, the hydrosilylation of ketones, the cyclopropanation of terminal alkenes, and olefination reactions. These complexes are air- and moisture-stable, and they can be used as precursors to synthesize more air-sensitive complexes. Sigma-Aldrich is pleased to offer a variety of NHC–copper complexes.

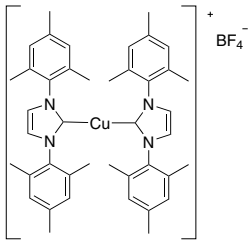


**[(IPr)CuCl]**
**696307**



**$[(IPr)_2Cu]BF_4$**
**696250**



**$[(IMes)_2Cu]BF_4$**
**696242**

For more information on the applications of NHC–copper complexes, see the review by Díez-González and Nolan in this issue.

**For product-specific information, please visit *sigma-aldrich.com***

# N-Heterocyclic Carbene–Copper Complexes: Synthesis and Applications in Catalysis

Dr. Silvia Díez-González

Prof. Steven P. Nolan

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## Outline

1. Introduction
2. Synthesis of NHC-Containing Copper Complexes
3. [(NHC)CuH]-Mediated Reactions
   3.1. Reduction of Carbonyl Compounds
      3.1.1. Activity and Scope
      3.1.2. Mechanistic Considerations
   3.2. Other Transformations
4. Conjugate Addition Reactions
   4.1. Carbon–Carbon-Bond Formation
   4.2. Carbon–Heteroatom-Bond Formation
5. Carbene-Transfer Reactions
   5.1. Cyclopropanation and Insertion Reactions
   5.2. Olefination Reactions
6. [3 + 2] Cycloaddition of Azides and Alkynes
   6.1. "Click Chemistry"
   6.2. Use of Internal Alkynes: Mechanistic Implications
7. Allylic Alkylation
8. Miscellaneous Reactions
9. Concluding Remarks
10. Acknowledgments
11. References

## 1. Introduction

N-Heterocyclic carbenes (NHCs) were first reported in the 1960s[1] However, this area of research did not flourish until free, isolable carbenes became easily accessible from imidazolium salts.[2] Originally considered as simple, two-electron-donor phosphine mimics, NHCs are now widely employed as organocatalysts.[3] Increasing experimental evidence clearly shows that NHC–metal catalysts can surpass their phosphine-based counterparts both in activity and in scope.[4] Mainly known for their impact on palladium-[5] and ruthenium-catalyzed[6] reactions, we intend here to give an overview of the contribution made by NHC ligands to the field of copper-catalyzed transformations.[7]

## 2. Synthesis of NHC-Containing Copper Complexes

The first reported NHC–copper species was a bis(NHC) cationic complex of copper(I) prepared from a triflate salt and two equivalents of an imidazol-2-ylidene.[8] Soon after, Raubenheimer and co-workers synthesized neutral monocarbene–copper(I) complexes by alkylation of thiazolyl or imidazolyl cuprates.[9] Six years later, the first monomeric imidazolylidene–copper(I) complex was obtained by deprotonation of the starting salt with copper(I) oxide.[10] This preparation avoids the use of strong bases and generates only water as byproduct. Nevertheless, this kind of complex is more generally prepared by reacting a copper(I) salt (CuCl, CuBr, CuI, or CuOAc) with a free carbene, either isolated or generated in situ (**Scheme 1**).[11]

These [(NHC)CuX] complexes are indefinitely air- and moisture-stable and have been used as convenient precursors of usually more unstable related compounds. Thus, alkoxide,[12] boryl,[13] dibenzoylmethanoate (DBM),[14] cyclopentadienyl,[15] and alkyl[16] derivatives have been prepared from the halogenated complexes. The acetate-containing complexes have been transformed into their corresponding alkyl,[11a,17] anilido, alkoxide, acetylide,[16a,18] or thiolate[19] analogues (**Scheme 2**).

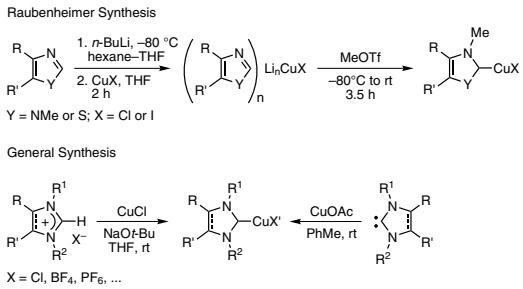
Alternatively, NHC–copper(I) complexes can be prepared by carbene transfer from the corresponding NHC–silver(I) reagents,[20] a frequent approach for the preparation of NHC complexes of late transition metals.[21] Another general method for the generation of such derivatives, namely phosphine displacement, has allowed for the preparation of ketiminate-containing complexes.[22]

Even if efforts have focused mainly on copper(I) species, some NHC–copper(II) complexes are also known in the literature. The first example, a divalent copper complex with a chelating tris(NHC) ligand, was prepared by Meyer and co-workers by oxidation of its copper(I) analogue.[23] Other copper(II) complexes have been synthesized by reactions with NHC–lithium adducts[24] or free carbenes,[23,25] and by carbene transfer from silver species.[26]

## 3. [(NHC)CuH]-Mediated Reactions

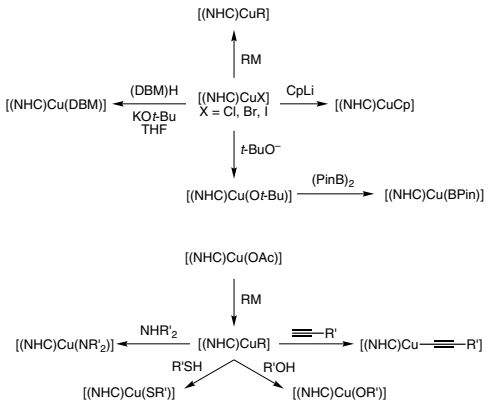
### *3.1. Reduction of Carbonyl Compounds*

The reduction of carbonyl and pseudo-carbonyl functions is a fundamental reaction in organic synthesis.[27] Transition-metal catalysis has been successfully applied to the reduction of olefins, alkynes, and many carbonyl compounds via hydrogenation or



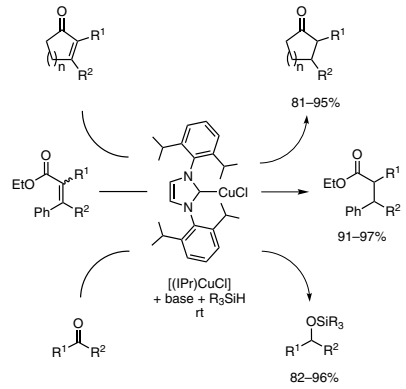

*Ref. 9,11*

**Scheme 1.** Preparation of Monomeric [(NHC)CuX] Complexes.




*Ref. 12–19*

**Scheme 2.** Derivatization of [(NHC)CuX] Complexes.




*Ref. 35,36*

**Scheme 3.** The Conjugate Reduction of α,β-Unsaturated Ketones and Esters and the Hydrosilylation of Simple Ketones Catalyzed by [(NHC)CuCl].

hydrosilylation.[28] "Cu–H" is among the earliest metal hydrides reported in the literature[29] but, for a long time, it was considered too unstable to be used in organic chemistry.[30] Pioneering work by Stryker[31] and Lipshutz[32] showed that a stabilized form of copper hydride, $[(Ph_3P)CuH]_6$,[33] is a convenient reagent for the reduction of carbonyl derivatives. Since then, copper catalysis has become a well-established method for a number of reductions.[34]

### 3.1.1. Activity and Scope

NHC–copper(I) complexes, and [(IPr)CuCl] in particular (IPr = *N,N'*-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), were first reported as catalysts in the conjugate reduction of α,β-unsaturated esters and cyclic enones (**Scheme 3**).[35] High yields were obtained in both instances at room temperature using a hydrosilane as a hydride source. Our concomitant work showed that the same complex could be used in the hydrosilylation of simple ketones to afford the corresponding silyl ethers in excellent yields.[36]

For more challenging ketones, ICy (ICy = *N,N'*-bis(cyclohexyl)imidazol-2-ylidene) is a more effective ligand. Thus, in the presence of [(ICy)CuCl], a number of ketones with varying congestion around the carbonyl function—alkyl, aromatic, aliphatic, cyclic, and bicyclic ketones—are efficiently reduced (**eq 1**).[37] Even highly congested starting materials yield the corresponding silyl ethers in high yields and acceptable reaction times. This catalytic system was also successfully applied to ketones incorporating a diversity of functional groups such as amine, ether, or halogen.

However, despite its broad scope, [(ICy)CuCl] was inefficient in the reduction of heteroaromatic ketones. In this case, the best results were obtained with SIMes (SIMes = *N,N'*-bis(2,4,6-trimethylphenyl)-2,5-imidazolin-2-ylidene) as ligand.

Interestingly, Yun et al. reported that copper(II) salts, in combination with an NHC ligand, can be employed for the hydrosilylation of ketones,[25] as they had previously shown with a chiral phosphine.[38] However, no evidence is currently available to unequivocally determine whether the active species is a copper(I) or a copper(II) hydride.

Another family of NHC-containing complexes of general formula $[(NHC)_2Cu]X$ (X = $PF_6^-$ or $BF_4^-$), has recently been the subject of a thorough study.[39] The activity of these cationic bis(NHC) complexes in the hydrosilylation of ketones was examined, and both the ligand and the counterion had a significant influence on the catalytic performance. Whereas the ligand influence could not be rationalized by using pure steric or electronic arguments,[40,41] complexes with $BF_4^-$ as counterion were consistently superior to their $PF_6^-$ analogues. For instance, under the same reaction conditions, cyclohexanone was quantitatively transformed into the corresponding silyl ether in 2 h in the presence of $[(IPr)_2Cu]PF_6$, whereas only 0.5 h was required in the presence of the $BF_4^-$ counterpart. When compared to their neutral analogues, e.g. [(NHC)CuCl], these cationic complexes offer the advantages of requiring lower reaction temperatures and smaller excesses of hydrosilane. Moreover, when submitted to comparable reaction conditions, the cationic species were generally more efficient than their neutral analogues (**eq 2**).[36a,37,39] It is worth noting that for hindered ketones, such as dicyclohexyl ketone, faster reaction is observed with [(ICy)CuCl] than with $[(ICy)_2Cu]BF_4$, but under more forcing conditions. However, when comparable reaction conditions were used (T = 55 °C, 2 equiv of hydride source), the cationic complex was the best catalyst.

### 3.1.2. Mechanistic Considerations

The first step of the proposed mechanism for the [(NHC)CuCl]-catalyzed hydrosilylation of ketones is formation of [(NHC)Cu(O*t*-Bu)] from the starting chloride complex and the base. Then, the active catalyst, an [(NHC)CuH] species, would be formed by σ-bond metathesis between the copper alkoxide and the hydrosilane. These steps are supported by the isolation and characterization of both complexes.[12] For example, [(IPr)CuH] was isolated as an unstable dimeric complex that readily reacts with a terminal alkyne to provide the corresponding hydrocupration product. Addition of the copper hydride species to the carbonyl results in a copper alkoxide that would undergo another σ-bond metathesis with the hydrosilane to form the expected silyl ether and regenerate the active catalyst (**Scheme 4**).

This mechanism is in agreement with experimental evidence for the phosphine–copper catalytic systems,[43] but it does not explain why an excess of base is generally required in order to complete the reaction with NHC-based catalytic systems. As it is well known that hydrosilanes are prone to nucleophilic attack, we proposed that the excess base that is generally required could be interacting with the hydrosilane to facilitate the second σ-bond metathesis.[37,42]

In the case of the cationic bis(NHC) complexes, the activation of $[(NHC)_2Cu]X$ towards hydrosilylation was investigated by $^1$H NMR, which showed that one of the two NHC ligands is displaced by *t*-BuO$^-$ to produce the neutral [(NHC)Cu(O*t*-Bu)], the direct precursor of the active species. The released NHC, being nucleophilic, could then facilitate the σ-bond metathesis leading to the formation of the silyl ether.[44] We postulated that the difference of activity between these two catalytic systems could arise from the more efficient activation of the hydrosilane by the NHC ligand than by *t*-BuO$^-$.[3]

## *3.2. Other Transformations*

When using a copper hydride as a reducing agent in a conjugate addition reaction, the copper enolate intermediate can be directly engaged in further reactions rather than quenched. The intramolecular conjugate reduction–aldol condensation tandem reaction was first explored with Stryker's reagent as the hydride source.[45] The use of other ligands, mainly diphosphines, has allowed for the generalization of this methodology.[46]

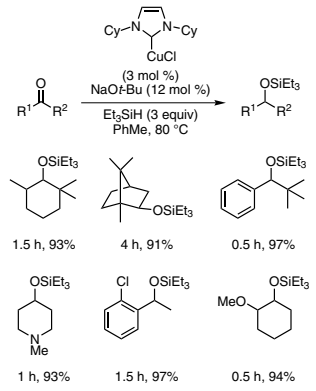
To date, there is a single example involving NHC ligands in this tandem reaction (**eq 3**).[14] With an IMes (IMes = *N,N'*-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) ligand, the direct reduction of the electrophiles (aldehydes or ketones) is minimized, and good yields are obtained from a number of electrophilic double bonds. Furthermore, moderate anti diastereoselectivities are obtained with this catalytic system.

The activity of NHC-bearing copper hydrides towards alkynes or alkenes remains greatly unexplored. Sadighi and co-workers reported the hydrocupration of 3-hexyne by an isolated, dimeric $[(NHC)CuH]_2$ complex,[12] and only the reaction of a very specific type of alkyne, propargyl oxiranes, has been thoroughly examined to date. It yielded diastereoselectively α-hydroxyallenes that were diversely functionalized.[47]

## 4. Conjugate Addition Reactions

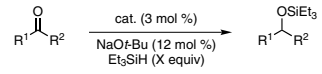
## *4.1. Carbon–Carbon-Bond Formation*

Soon after the first study of the NHC-accelerated, copper-catalyzed 1,4 addition of diethylzinc to enones by Fraser and Woodward,[48] the groups of Roland and Alexakis simultaneously reported the use of chiral ligands.[49] Since then, this has been a very active field of study[50] and, nowadays, even quaternary




*Ref. 37*

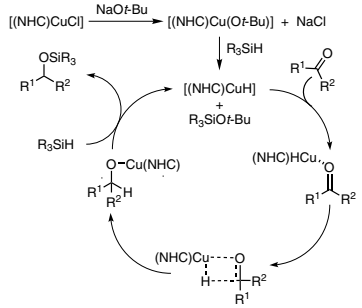
**eq 1**




| $R^1$,$R^2$ | X | Cat. | Solvent | T, °C | t, h | Yield |
|---|---|---|---|---|---|---|
| $(CH_2)_5$ | 3 | [(IPr)CuCl] | PhMe | rt | 3 | 83% |
| $(CH_2)_5$ | 2 | $[(IPr)_2Cu]BF_4$ | THF | rt | 0.5 | 98% |
| Cy,Cy | 3 | [(ICy)CuCl] | PhMe | 80 | 0.5 | 99% |
| Cy,Cy | 2 | [(ICy)CuCl] | PhMe | 55 | 1.5 | 50% |
| Cy,Cy | 3 | $[(ICy)_2Cu]BF_4$ | THF | 55 | 3 | 98% |

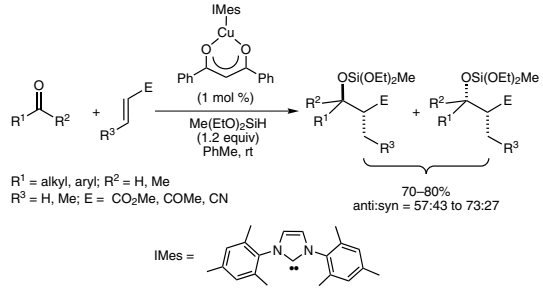
*Ref. 36a,37,39*

**eq 2**



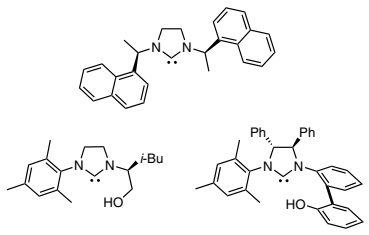

*Ref. 37*

**Scheme 4.** Proposed Mechanism for the [(NHC)CuCl]-Catalyzed Hydrosilylation of Ketones.



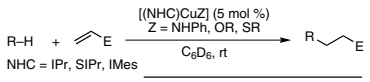

*Ref. 14*

**eq 3**




*Ref. 50a,51,52*

**Figure 1.** Chiral NHC Ligands for the Copper-Catalyzed 1,4 Addition of Diethylzinc to Enones.

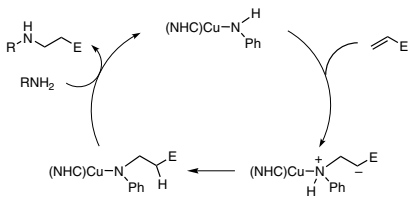



| R | E | t, h | Conv. |
|---|---|---|---|
| PhHN | Ac | 0.1 | >95% |
| EtO | Ac | 7 | >95% |
| PhS | Ac | 0.1 | >95% |
| PhHN | $(CH_2)_3C(O)$ | 3 | 85% |
| PhS | $(CH_2)_3C(O)$ | 32 | >95%[a] |
| $Et_2N$ | CN | 9 | >95% |
| EtO | CN | 20 | 93% |
| PhO | CN | 40 | 64%[b] |
| BnS | CN | 2 | >95% |

[a] At 80 °C with 0.1 mol % of catalyst.
[b] At 80 °C.

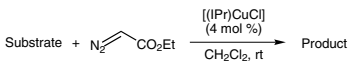
*Ref. 19,53b*

**eq 4**




*Ref. 53a*

**Scheme 5.** Proposed Mechanism for the NHC–Copper-Catalyzed Hydroamination of Alkenes.




| Substrate | Product | Yield |
|---|---|---|
| Ph | Ph, $CO_2Et$ | 93% |
| | $CO_2Et$ | 91% |
| NH | N, $CO_2Et$ | 92% |
| OH | O, $CO_2Et$ | 85% |

*Ref. 56*

**eq 5**

stereogenic centers can be formed enantioselectively through the conjugate addition of several organometallic reagents onto cyclic enones.[51] In most cases, the active species are prepared in situ from the corresponding azolium salt or NHC–silver complex. A single study screened NHC–copper complexes in this context.[52] However, it was found that well-defined complexes did not lead to improved results when compared with the analogous NHC–silver complex–copper salt catalytic system (**Figure 1**).

### 4.2. Carbon–Heteroatom-Bond Formation

NHC–copper anilide, alkoxide,[53] and thiolate[19] complexes are efficient catalysts for the addition of N–H, O–H, and S–H bonds to electron-deficient olefins to yield the corresponding anti-Markonikov products. IPr, IMes, and SIPr (SIPr = *N,N'*-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene) ligands have been studied in this context. The main advantages of these complexes are broad substrate scope and good yields under mild reaction conditions (**eq 4**). It is important to note that in the case of acrylates, transesterification and ester–amide exchange reactions can compete with the hydroalkoxylation or hydroamination, respectively.

The proposed mechanism for this hydroamination of alkenes involves, first, an intermolecular nucleophilic addition of the amido ligand to the olefin to produce a zwitterionic intermediate. Subsequent proton transfer and reaction with the nucleophile (probably via Cu coordination) would form the expected product and regenerate the catalyst (**Scheme 5**).[53] Alternatively, hydroamination with secondary amines as well as hydroalkoxylation and hydrothiolation reactions would proceed through a similar pathway in which the zwitterionic intermediate reacts with a molecule of free nucleophile.

Finally, the anti-Markonikov hydroamination and hydrothiolation reactions of related electron-deficient vinylarenes can also be conducted in the presence of the same catalysts.[54] In this case, higher reaction temperatures (60–120 °C) and strong electron-withdrawing substituents in the para position are required to achieve good yields.

## 5. Carbene-Transfer Reactions

### 5.1. Cyclopropanation and Insertion Reactions

Diazo compounds have been extensively employed as a carbene source in organic chemistry.[55] Whereas phosphorus-containing ligands are not useful in this regard due to the facile carbene transfer to phosphorus to produce ylide derivatives, NHC ligands have shown remarkable activity in the carbene transfer from ethyl diazoacetate (EDA) to an alkene or the X–H bond of amines and alcohols. Styrene and cyclooctene are converted into the corresponding cyclopropanes in nearly quantitative yields in the presence of [(IPr)CuCl]. The related insertion of the $:CHCO_2Et$ unit into the X–H bonds of amines and alcohols also leads to the desired products in high yields (**eq 5**).[56]

The most outstanding feature of this catalyst is the total suppression of the diazo coupling, which is the general drawback of this methodology. Furthermore, unlike other copper-based catalytic systems, [(IPr)CuCl] does not react with EDA even in the absence of the substrate.

The moderate diastereoselectivity obtained in these cyclopropanation reactions can be substantially increased by employing stannyldiazoacetate esters as the carbene source. Several styrenes and vinyl ethers have been successfully cyclopropanated with good-to-excellent diastereoselectivities (**eq 6**).[57] It is worth noting that, even if somewhat harsher reaction

conditions are required in these cases, the diazo coupling is still effectively suppressed.

The aziridination of olefins is often considered similar to cyclopropanation and epoxidation reactions in the sense that a nitrene group is transferred to the olefin, generating a three-membered ring. Even if the activity of NHC-based complexes in this context has not been properly examined yet, two different examples reported in the course of total syntheses, agelastatin A by Trost and Dong[58] and tamiflu by Fleming and co-workers,[59] have demonstrated the remarkable activity of [(IPr)CuCl] in the aziridination of electron-deficient alkenes (**Scheme 6**).

### 5.2. Olefination Reactions

The methylenation of carbonyl derivatives is a very important transformation among the olefination processes.[60] Despite the reliability of the Wittig reaction, hindered and base-sensitive carbonyl derivatives are usually incompatible substrates. Alternatively, phosphorus ylides can be prepared from diazo compounds in the presence of metal catalysts. The first reports dealing with the copper(I)-catalyzed olefination of carbonyl compounds with diazo carbonyl compounds revealed an inefficient formation of the carbene species.[61] However, the combined use of trimethylsilyldiazomethane as reagent and an NHC–copper complex led to the efficient methylenation of a number of carbonyl compounds.[62] Whereas [(IPr)CuCl] and [(IMes)CuCl] performed equally well for aromatic and aliphatic aldehydes, [(IPr)CuCl] was the optimal catalyst for ketone methylenation (**eq 7**).[62] Of note, even base-sensitive and electron-deficient substrates afforded the corresponding alkenes in good yields. This methodology has been successfully applied in multicatalytic one-pot processes[63] and in total synthesis.[64]

## 6. [3 + 2] Cycloaddition of Azides and Alkynes

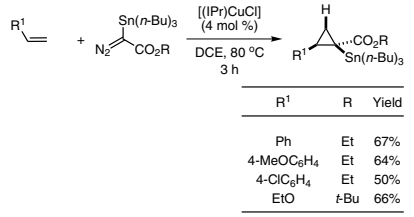
### 6.1. "Click Chemistry"

In 2001, Sharpless and co-workers introduced the concept of "click chemistry" and the criteria for a transformation to be considered as "click".[65] Inspired by nature, the objective has been to rapidly create molecular diversity through the use of reactive modular building blocks, only benign reaction conditions, and simple workup and purification procedures.

After the recent discovery of copper(I) as an efficient and regiospecific catalyst for the reaction of azides with alkynes to yield 1,2,3-triazoles[66] (1,3-dipolar Huisgen cycloaddition[67]), this transformation has become the best "click" reaction to date. Catalytic systems for this reaction most often consist of a copper(II) salt and a reducing agent due to the inherent instability of cuprous salts. A diverse family of ligands has also been shown to protect copper(I) centers during this reaction.[68]

Screening of a set of [(NHC)CuX] complexes under standard cycloaddition conditions showed that [(SIMes)CuBr] was the best catalyst for this transformation.[69] Whereas poor conversions were obtained in organic solvents, a strong acceleration was observed in water. Furthermore, neat reactions proceeded smoothly with no detectable formation of undesired byproducts and the catalyst loading could be lowered to 0.8 mol % with no loss of activity, ensuring straightforward reaction workup (**eq 8**).[69] This transformation is broad in scope, and triazoles are isolated in excellent yield and high purity after simple filtration or extraction. Pleasantly, azides generated in situ from the corresponding halides and $NaN_3$ also reacted in water at room temperature to efficiently yield triazoles.

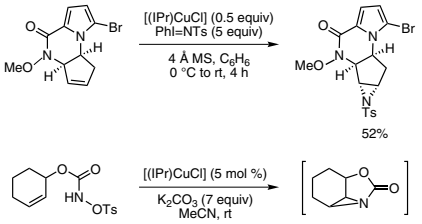
To date, [(SIMes)CuBr], or its unsaturated analogue, has been successfully employed for the preparation of triazole-containing




| $R^1$ | R | Yield |
|---|---|---|
| Ph | Et | 67% |
| 4-$MeOC_6H_4$ | Et | 64% |
| 4-$ClC_6H_4$ | Et | 50% |
| EtO | *t*-Bu | 66% |

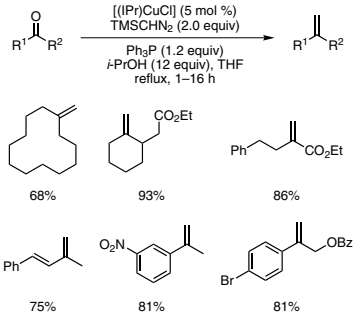
*Ref. 57*

**eq 6**



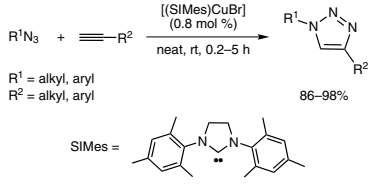

*Ref. 58,59*

**Scheme 6.** [(IPr)CuCl]-Catalyzed Aziridination Reactions in Total Synthesis.



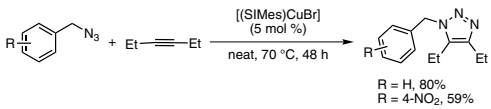

*Ref. 62*

**eq 7**



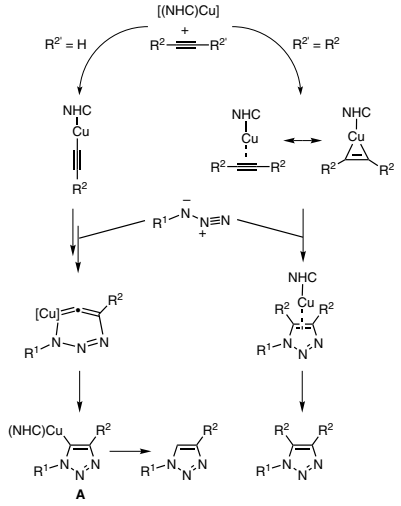

*Ref. 69*

**eq 8**



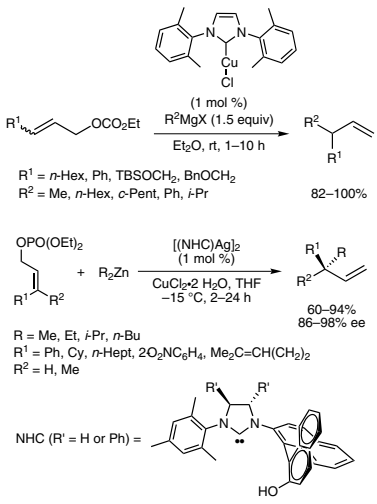

*Ref. 69*

**eq 9**




*Ref. 69*

**Scheme 7.** Proposed Mechanism of Activation of Internal Alkynes by NHC–Copper(I) Complexes.




*Ref. 77a,78*

**Scheme 8.** γ-Selective Allylic Alkylation Catalyzed by NHC–Copper(I) Complexes.

carbanucleosides,[70] porphyrins,[71] and platinum-based anticancer drugs.[72]

### 6.2. Use of Internal Alkynes: Mechanistic Implications

Traditionally, the starting point of the catalytic cycle for the copper-catalyzed Huisgen reaction is the formation of a Cu acetylide intermediate, which precludes internal alkynes as cycloaddition partners. Moreover, a hypothetical activation toward cycloaddition via π coordination of copper(I) to the alkyne (without deprotonation) has also been ruled out since the calculated activation barrier for this process exceeds that of the uncatalyzed process.[73]

However, in the presence of [(SIMes)CuBr], 4,5-disubstituted triazoles have been isolated in fair-to-good yields after heating the reactants at 70 °C for 48 h (**eq 9**).[74] Optimization studies showed that both the copper salt and the NHC ligand are essential for this transformation.

Although the copper ion is generally considered a poor π-back-donating ion, the ancillary ligands on the metal center play an essential role in its coordination to alkynes.[75] In fact, DFT calculations have indicated that π coordination of EtC≡CEt to $[(SIMes)Cu]^+$ is favored by almost 20 kcal/mol relative to π coordination to $[(MeCN)_2Cu]^+$. These results have led us to propose that the observed beneficial effect of the NHC allows for the activation of disubstituted alkynes to proceed by a π-alkyne complex (**Scheme 7**).[69] It is worth noting that the widely accepted reaction pathway for terminal alkynes would still be applicable to this system. The recent isolation of an intermediate copper(I) triazolide complex **A** bearing a SIPr ligand strongly supports this proposition.[76]

## 7. Allylic Alkylation

Highly γ-selective allylic substitution reactions can be performed with Grignard reagents using well-defined NHC–copper(I) complexes as catalysts (**Scheme 8**).[77] A control experiment showed that the ligandless reaction leads to the sole formation of the α product, which indicates that the NHC–copper bond is not cleaved during the reaction. Under these conditions, different substituents and the *E* and *Z* geometries of the allylic substrates are well tolerated. Nevertheless, the use of several optically active NHC ligands only allowed for moderate enantioselectivities (<70% ee's). Better asymmetric inductions, 86–98% ee's, were achieved with binaphtol-based NHC ligands in the alkylation of allylic phosphates with alkylzinc reagents.[26,78] In this case, a dimeric NHC–silver(I) complex, in combination with air- and moisture-stable copper(II) salts, allowed for the highly selective formation of quaternary stereogenic centers with a great diversity of zinc reagents. Of note, the derived copper(II) complexes were also synthesized and used to perform this transformation.

Overall, these NHC-oxy ligands (see Scheme 8) represent one of the most general methods for carrying out this transformation using hard metal alkyls. They have been applied further in the preparation of enantiomerically pure allylsilanes via the allylic alkylation of vinylsilanes[79] and in the addition of vinylaluminum species.[80]

## 8. Miscellaneous Reactions

Using [(IPr)CuCl] as catalyst, *N*-sulfonylimidazolines can be efficiently prepared by the reaction of methyl isocyanoacetate with aromatic *N*-sulfonylimines (**Scheme 9**).[81] The same catalyst has been reported to efficiently promote atom-transfer radical cyclization (ATRC) of allylaryl trichloroacetates under

microwave irradiation.[82] Thus, chloronaphthalenes are obtained in high yields from the corresponding allylphenyl trichloroacetates probably via an intermediate lactone.

The related [(IPr)CuI] has shown remarkable activity in the oxidative carbonylation of β-amino alcohols to produce 2-oxazolidinones in the absence of any additive.[83] Remarkably, disubstituted ureas and carbamates can also be prepared from the corresponding primary amines with this catalyst.

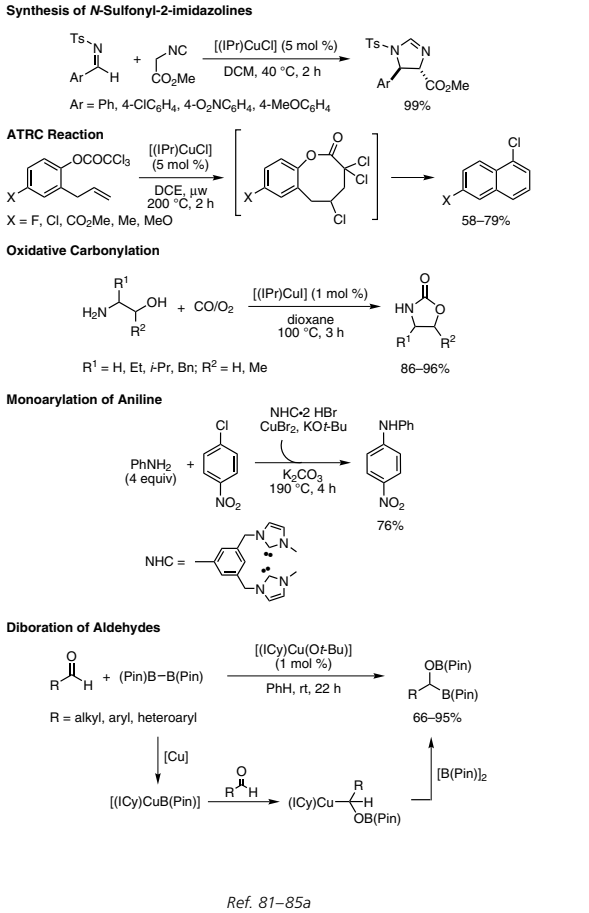
A bis(carbene) species is an active and selective ligand in the copper-catalyzed N-monoarylation of aniline.[84] However, biphenyldialkylphosphines delivered higher conversions under the same reaction conditions.

Finally, [(ICy)Cu(O*t*-Bu)] has been successfully utilized in the 1,2 diboration of aldehydes.[85] The reaction is believed to proceed through a copper boryl complex, which is easily formed under these conditions, followed by insertion of the carbonyl function into a copper–boron bond to produce a metal–carbon σ bond. Subsequent reaction with the diboron reagent and additional aldehyde would result in the formation of a carbon–boron bond.

## 9. Concluding Remarks

Since the first report on the catalytic activity of NHC–copper complexes in 2001, this family of complexes has shown a broad scope as catalysts in organic synthesis. It is important to note that the most commonly used complex, [(IPr)CuCl], is an efficient catalyst for six different reactions and the direct precursor of the active species in some others. Complementary to this great versatility, the possibility of tuning the properties of the NHCs makes these ligands interesting in virtually every copper-catalyzed transformation.

These species are also of interest in contexts other than that of catalysis. For instance, NHC–copper complexes have shown remarkable activity in important industrial processes such as the reduction of $CO_2$ to CO[13,86] and hydrogen storage applications.[87] It is also significant that studies dealing with the structure and molecular orbitals of such derivatives have revealed the existence of non-negligible π interactions between copper (and other group 11 metals) and NHC ligands,[88] which, at the time, shattered the general assumption that NHC ligands were pure σ donors. All of the above make us think that NHC–copper complexes have many more surprises in store for chemists, and we are certain that important developments in this area are forthcoming.




*Ref. 81–85a*

**Scheme 9.** Miscellaneous Reactions of NHC–Copper Complexes.

## 10. Acknowledgments

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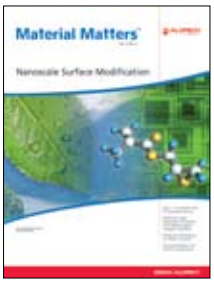


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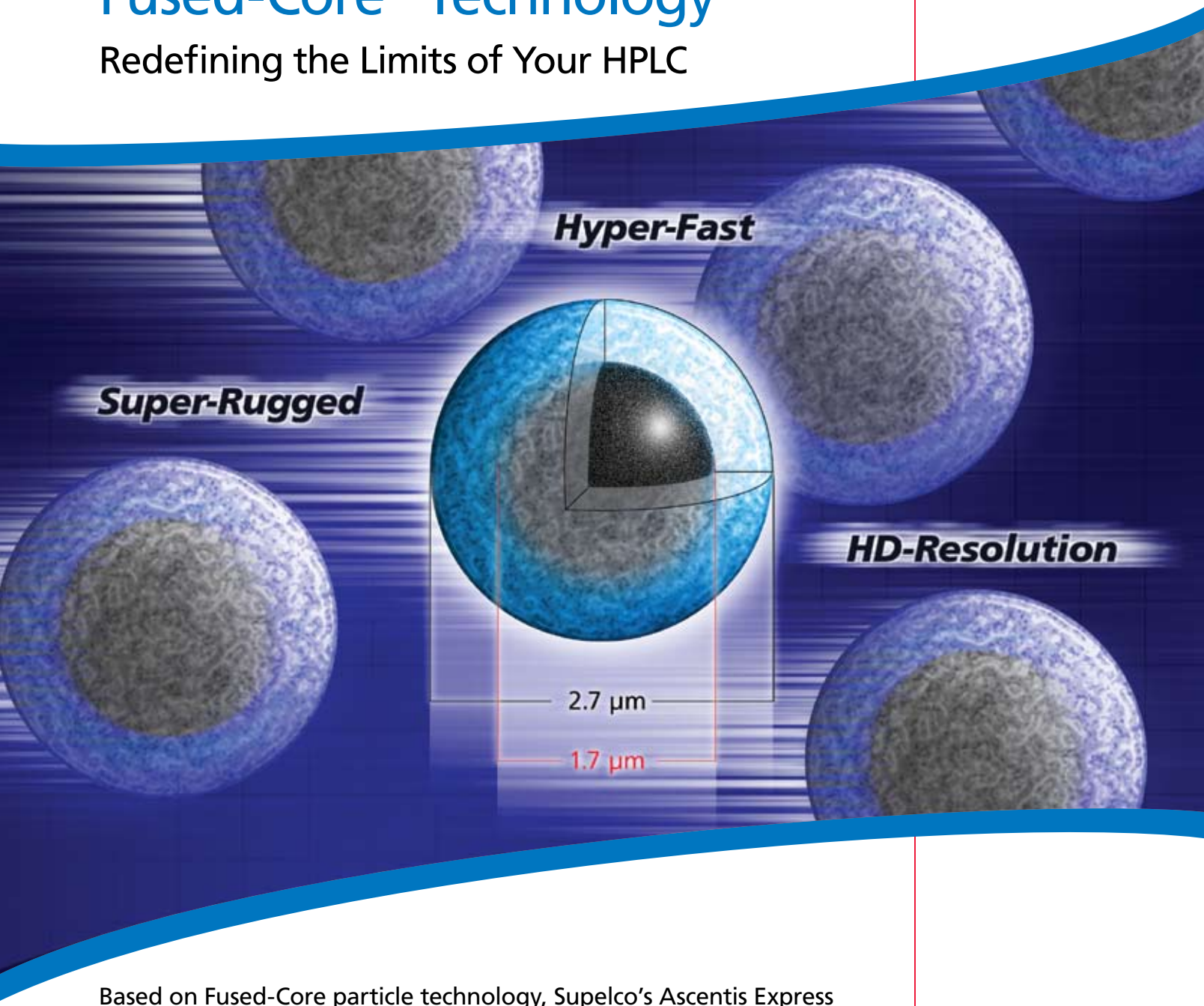


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GREEN, MILD, AND VERSATILE SYNTHETIC METHODS

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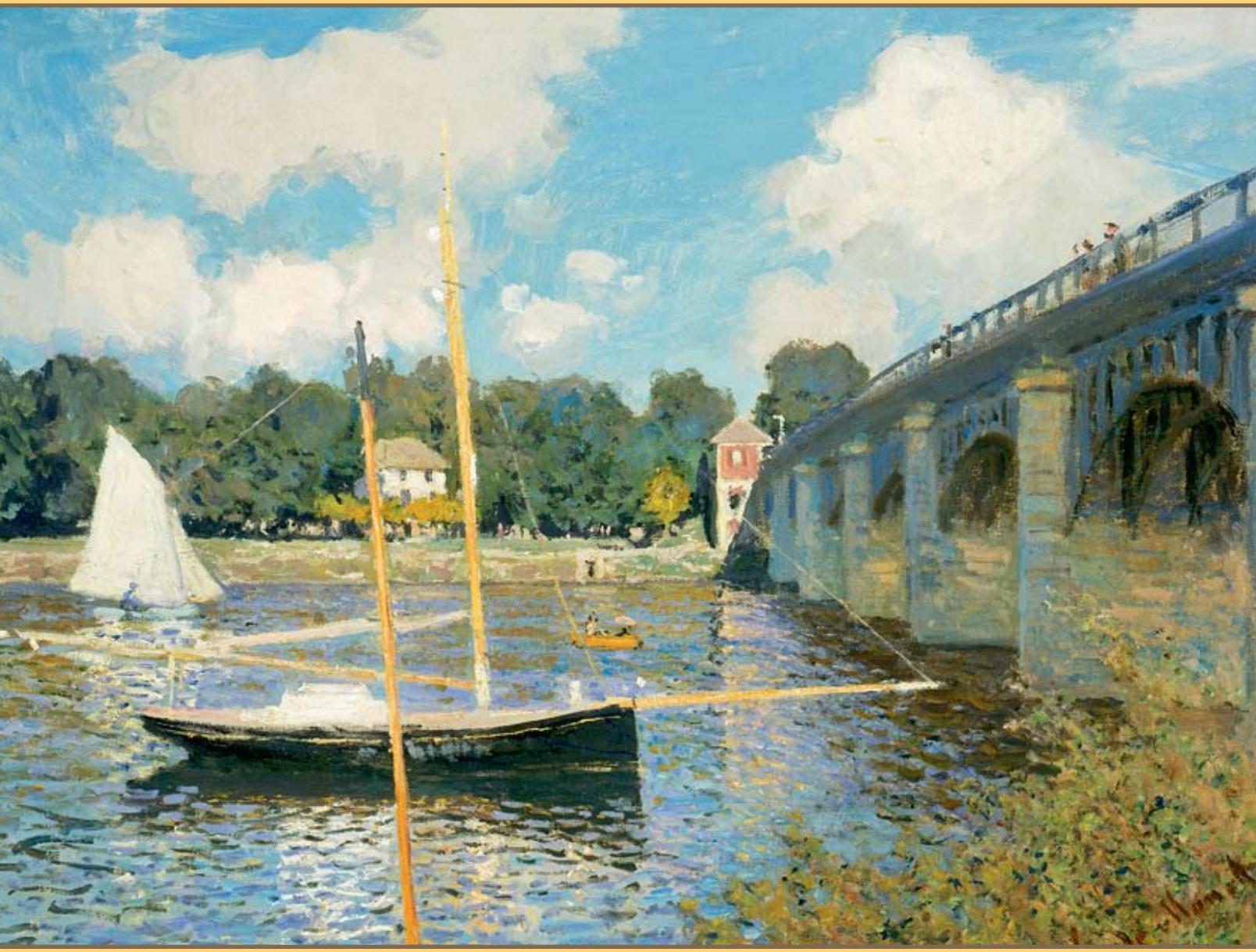
ALDRICH Chemistry



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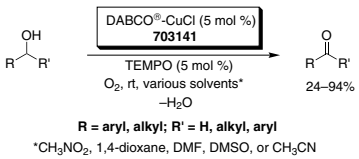
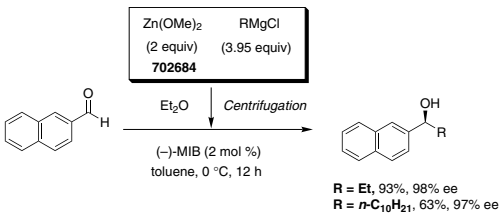



Mannam, S. et al. *Adv. Synth. Catal.* **2007**, *349*, 2253.

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

### *Reagent for the Preparation of Organozincs*

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

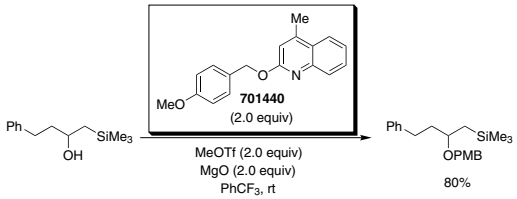



Cote, A.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 2771.

| Zinc Methoxide | |
|---|---|
| **702684** | 1 g |
| $C_2H_6O_2Zn$ | 5 g |
| FW: 127.46 | |

### *Reagent for the PMB-protection of Alcohols*

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

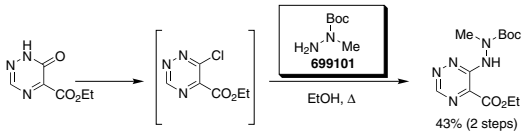



Nwoye, E. O.; Dudley, G. B. *Chem. Commun.* **2007**, 1436.

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

### *Reagent for Selective Methylhydrazine Addition*

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




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

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

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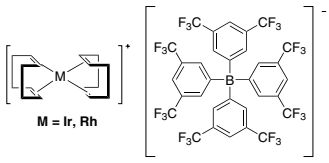


(1) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 280. (2) Ngai, M.-Y.; Kong, J.-R.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 1063.

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2 g

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

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## ABOUT OUR COVER

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

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

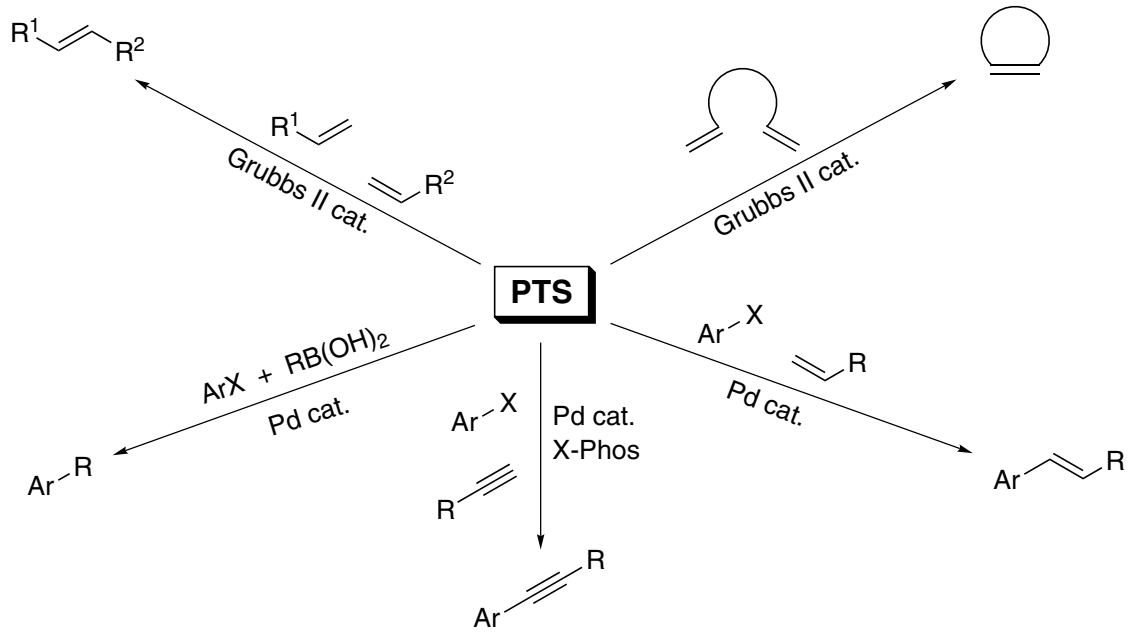
In the early years of impressionism, Monet, Renoir, and others strove to capture the fleeting effects of light and atmosphere on the landscape and to transcribe directly and quickly their sensory experience of it. Monet advised his students, "When you go out to paint, try to forget what objects you have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

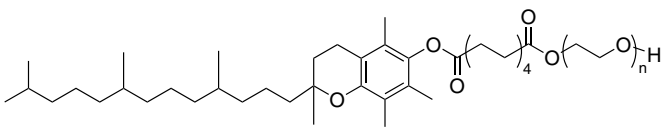
In this early work (1874), Monet (1840–1926) captures a warm, sunny, idyllic day—a motif he used often and for which he became famous. Today, Monet's characteristic style and distinctive brushstroke are still fresh, recognizable, and most popular.

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

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

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



**PTS (n = ca. 13)**

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

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

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

Prof. Bruce H. Lipshutz

Dr. Subir Ghorai

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*Department of Chemistry & Biochemistry*
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*Santa Barbara, CA 93106 USA*
*Email: lipshutz@chem.ucsb.edu*

## Outline

1. Introduction
2. Amphiphiles, Surfactants, Emulsifiers, Soaps, ...
3. PTS: Brief History and Background
4. Synthetic Chemistry in PTS–$H_2O$
   4.1. Heck Coupling
   4.2. Suzuki–Miyaura Coupling
   4.3. Olefin Metathesis
5. Summary and Outlook
6. Acknowledgements
7. References and Notes

## 1. Introduction

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

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

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

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

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

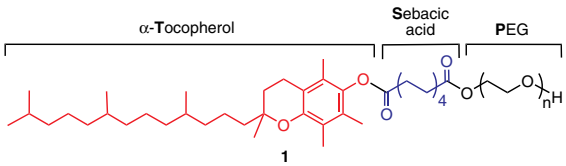



**Figure 1.** Structure of the Nonionic Amphiphile PTS (**1**, n = ca. 13).

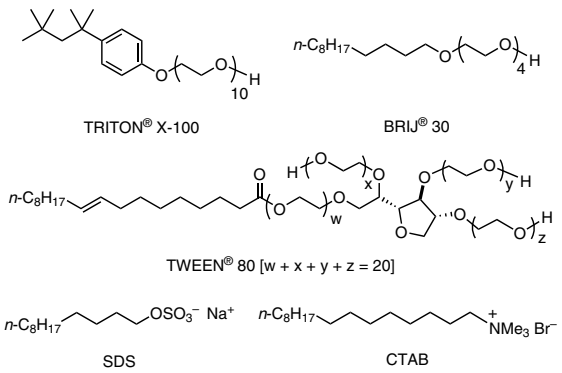



**Figure 2.** Commonly Used Nonionic and Ionic Surfactants. *(Ref. 17–20)*

## 2. Amphiphiles, Surfactants, Emulsifiers, Soaps, …

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

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

## 3. PTS: Brief History and Background

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

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

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

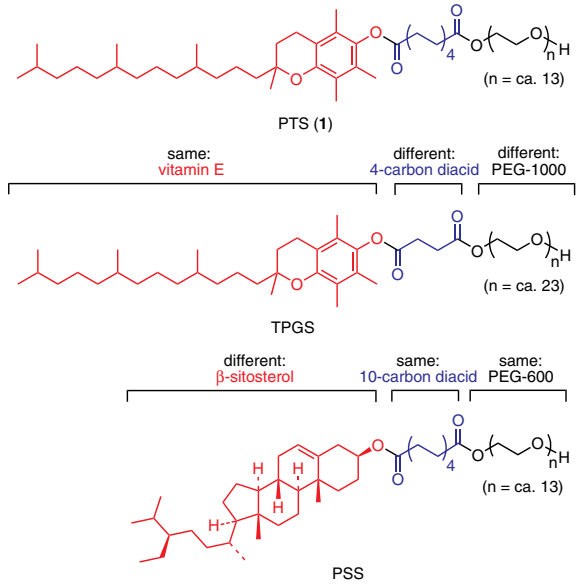
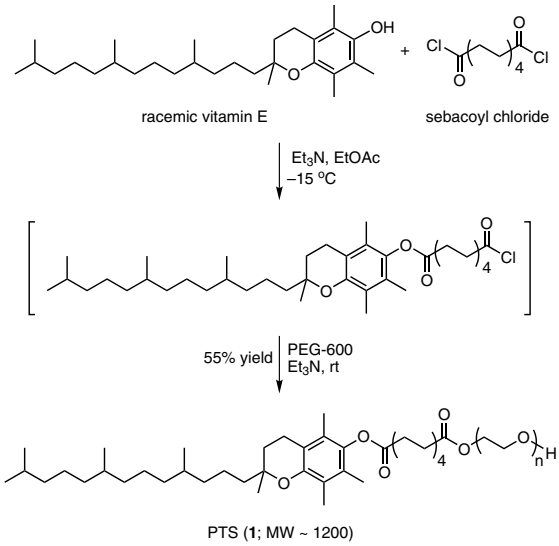



**Figure 3.** Structural Comparisons between PTS, TPGS, and PSS.
*(Ref. 16,21)*




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

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

## 4. Synthetic Chemistry in PTS–$H_2O$

### 4.1. Heck Coupling

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

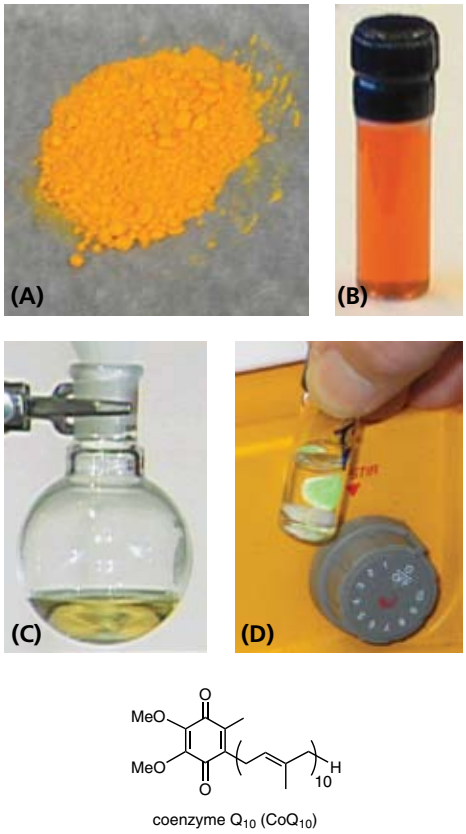



**Figure 4. (A)** Pure, Water-Insoluble Coenzyme $Q_{10}$. **(B)** Solution of 50 mg/mL $CoQ_{10}$ in PTS–$H_2O$. **(C)** Neat PTS. **(D)** Solution of TAXOL® in PTS–$H_2O$ (10 mg/mL). (Photos © B. H. Lipshutz.)

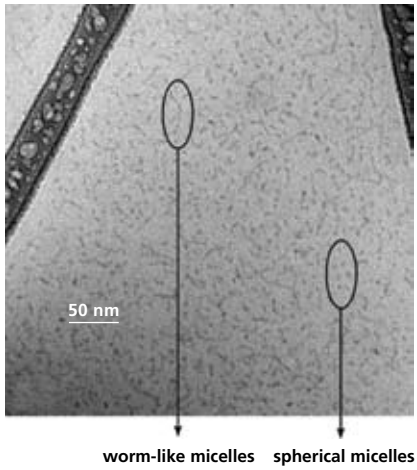
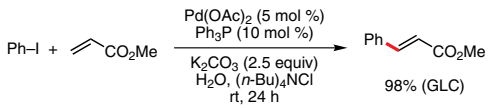



**Figure 5.** Cryo-TEM Image of PTS–$H_2O$. (Photo © B. H. Lipshutz.) *(Ref. 25,26)*




**eq 1** *(Ref. 32)*

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

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

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

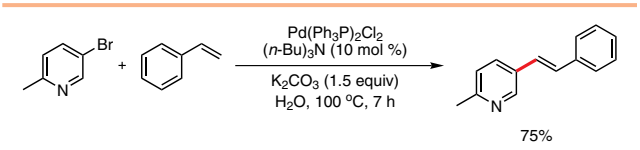
with a change in ligand on Pd (vide infra). Hence, again with the benefit of hindsight, it is not surprising that 15% is *not* the ideal amount of PTS for any of the other name reactions discussed herein; indeed, no more than 5 wt %, and more often 2.5 wt %, in water is recommended. As originally reported,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

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

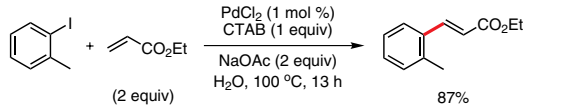
A few other sources of palladium were examined (e.g., $Pd(OAc)_2$, $PdCl_2$, and $Pd(dba)_2$), but none led to any identifiable benefit (in rate, yield, etc.). Importantly, ***product isolation*** is facile (at least on a research scale), using either a rough filtration of the reaction mixture through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

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

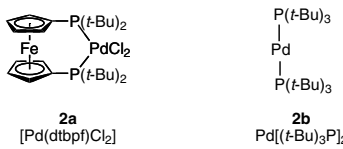
While these intermolecular Heck reactions appear well suited to the aqueous conditions developed, they involve iodides as coupling partners. Recent preliminary efforts have identified a protocol




**eq 2** *(Ref. 33)*

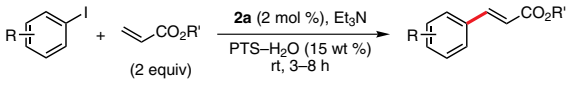



**eq 3** *(Ref. 35)*

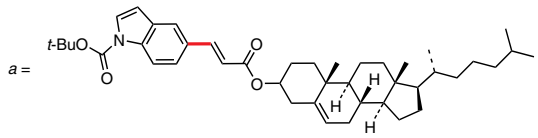



**2a** [Pd(dtbpf)$Cl_2$] **2b** Pd[($t$-$Bu)_3P]_2$

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

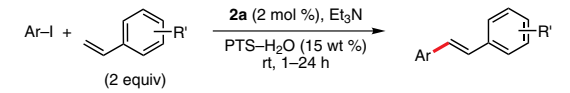



| R | R' | Yield |
|---|---|---|
| 4-MeO | *t*-Bu | 92% |
| 4-MeO | 2-ethylhexyl | 84% |
| 4-(*n*-Bu) | *t*-Bu | 77% |
| H | 2-ethylhexyl | 95% |
| *a* | *a* | 90% |

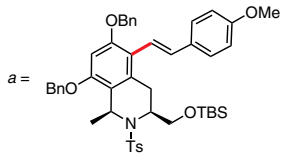



*E*:*Z* = 93:7

**eq 4** *(Ref. 25)*




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



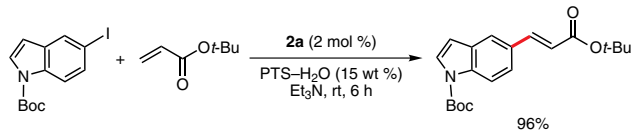

**eq 5** *(Ref. 25)*

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

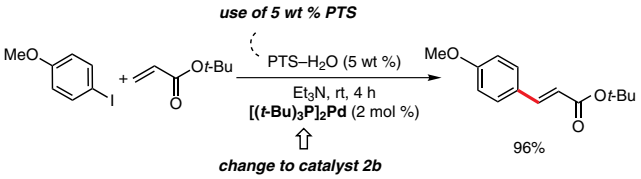
| Amphiphile | Diameter | Comparisons |
|---|---|---|
| PTS with PEG-600 (**1**) | 24 nm | *increased length of PEG: smaller particles* |
| PTS with PEG-1000 | 7 nm | *only difference: 4- vs 10-carbon acid linker* |
| TPGS | 13 nm | |
| PSS | 20 nm | |
| TRITON® X-100 | 10 nm | *more hydrophilic PEG,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

*linear vs cyclic grease: give different results*

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




**eq 6** *(Ref. 25)*




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

**eq 7** *(Ref. 28a)*

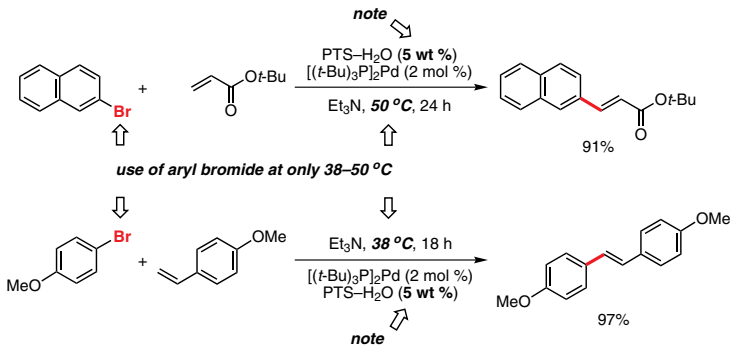
## 4.2. Suzuki–Miyaura Coupling

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

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

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

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




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

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

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

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

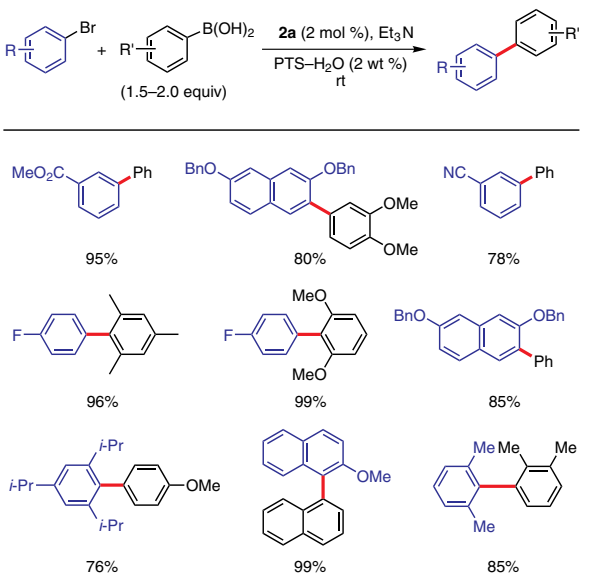
Phase-transfer agents, including $Bu_4NBr$[48] and, more recently, CTAB as part of the unusual combination with heterogeneous Pd/C in water, provide access to unsymmetrical biaryls from activated chloroarenes (**eq 15**).[49]

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

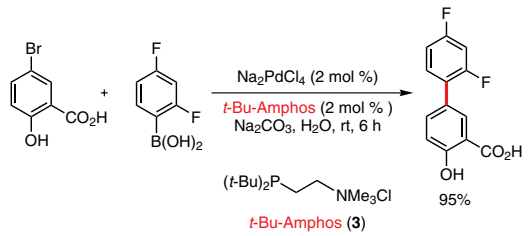
Currently under study are Suzuki–Miyaura couplings involving heteroaromatic halides, heteroaromatic boronic acids, or combinations of both. Judging from the early returns (e.g., **eq 17**),[51] the breadth of potential applications looks encouraging, although it is unrealistic to attempt to examine all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

## 4.3. Olefin Metathesis

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




**eq 8** *(Ref. 40)*




**eq 9** *(Ref. 42)*

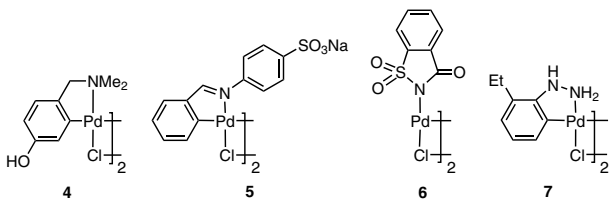
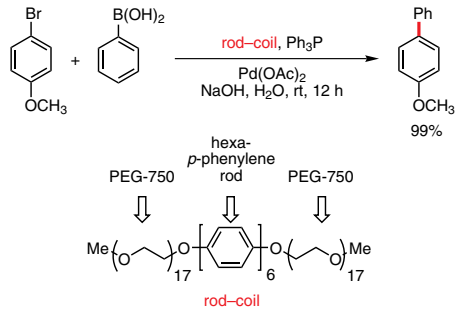
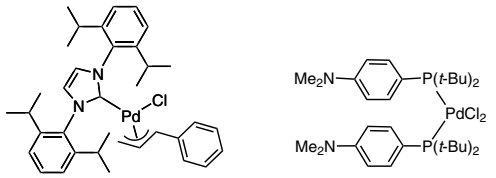



**Figure 7.** Palladacycle and Related Catalysts for the Suzuki–Miyaura Coupling. *(Ref. 42,44)*

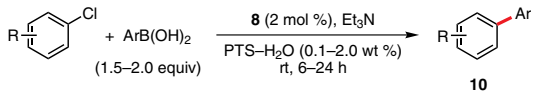



**eq 10** *(Ref. 45)*



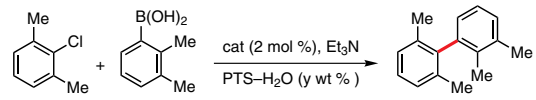

**8**, NEOLYST® CX31 **9**, Pd(A-$^{ta}$Phos)$_2$Cl$_2$

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



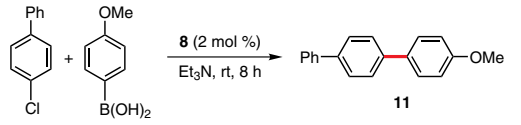

| 10 | R | Ar | Yield |
|---|---|---|---|
| **a** | 2-MeO | Ph | 100% |
| **b** | 2,6-$Me_2$ | 4-$MeOC_6H_4$ | 99% |
| **c** | 4-NC | 2,4-$F_2C_6H_3$ | 96% |
| **d** | 2,6-$Me_2$ | 1-Np | 100% |

**eq 11** *(Ref. 40)*



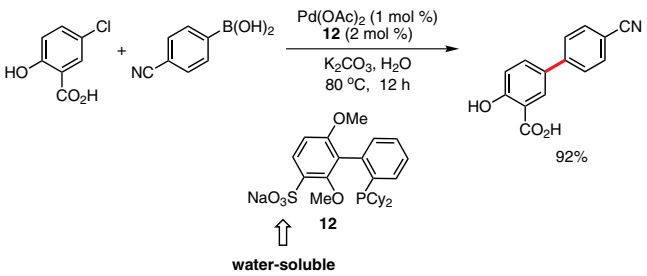

| Cat. | y | T, °C | t, h | Yield |
|---|---|---|---|---|
| **2a** | 1 | 50 | 24 | 28% |
| **8** | 1 | 23 | 4 | 98% |
| ***only 0.1 wt % PTS–$H_2O$ used*** ⇨ **8** | 0.1 | 23 | 24 | 97% |

**eq 12** *(Ref. 40)*

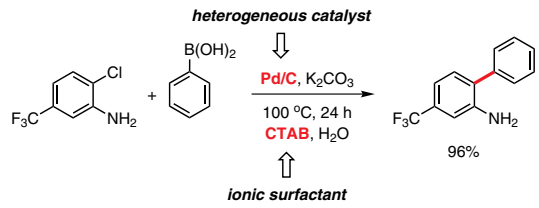



| Medium | Conv. | Yield |
|---|---|---|
| PTS–$H_2O$ (1 wt %) | 99% | 93% |
| No PTS ("on water") | 73% | 57% |

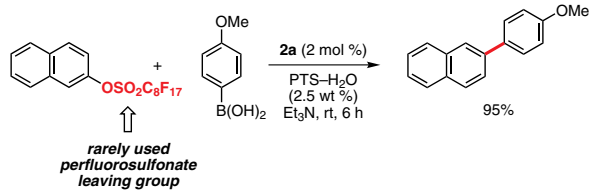
**eq 13** *(Ref. 40)*



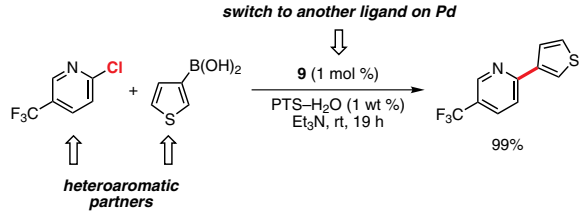

**eq 14** *(Ref. 47)*



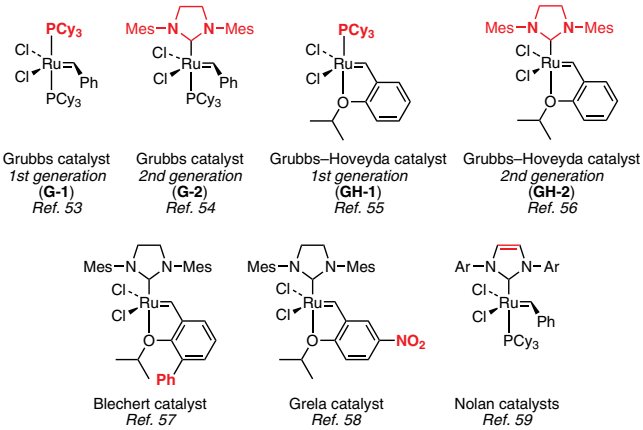

**eq 15** *(Ref. 49)*




**eq 16** *(Ref. 50)*




**eq 17** *(Ref. 51)*




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

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

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

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

Blechert catalyst *Ref. 57*

Grela catalyst *Ref. 58*

Nolan catalysts *Ref. 59*

**Figure 9.** Representative, Water-Insoluble Metathesis Catalysts.

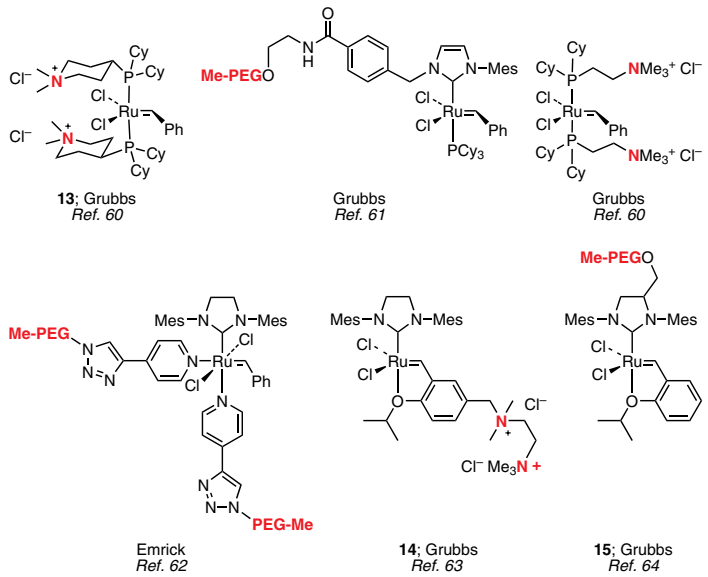
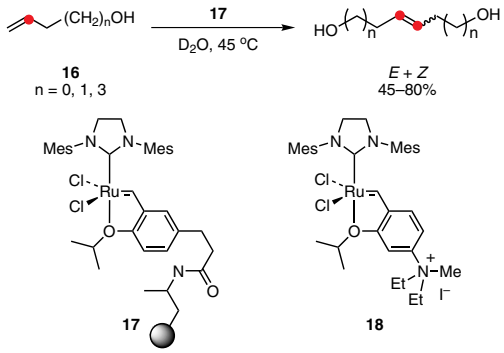



**Figure 10.** Representative Water-Soluble Catalysts for Metathesis.

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

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

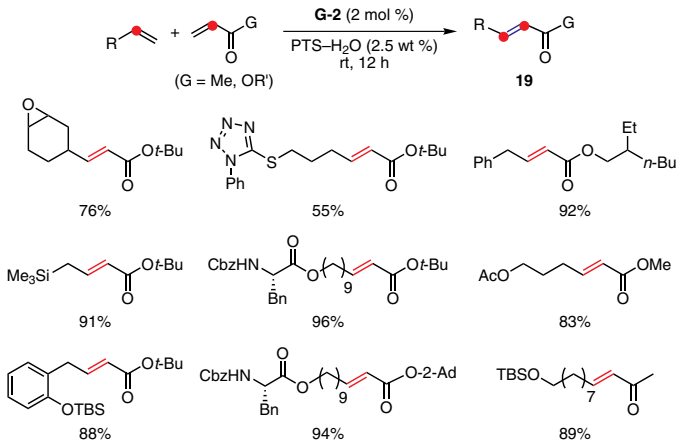
Ring-closing-metathesis (RCM) reactions in water have been of interest for over a decade.[52,71] Most approaches rely on ruthenium complexes that bear ligands modified to ensure water solubility (see Figure 10). An amphiphilic catalyst consisting of a block co-polymer based on poly(2-oxazoline) also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




**eq 18** *(Ref. 65,67)*

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

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

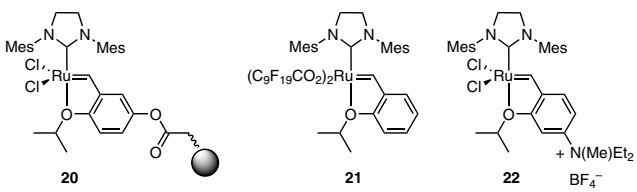



**eq 19** *(Ref. 70)*

**Table 2.** Literature Reports on RCM Reactions in Water

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

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



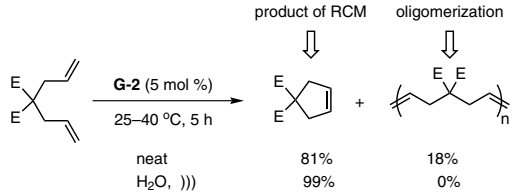

leads to *consistently* high conversions and hence, isolated yields.[77] RCM reactions in neutral PTS micelles take high place fairly quickly (1–3 hours), including the formation of seven-membered rings and trisubstituted arrays, mediated by the Grubbs 2nd-generation or Grubbs–Hoveyda 2nd-generation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

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

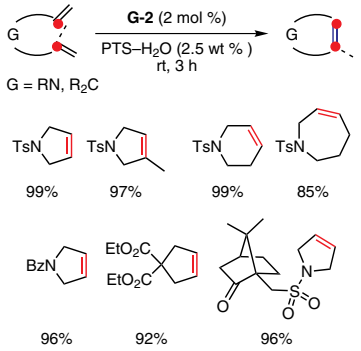
So, what about "seawater", rather than water out of the bottle, as the solvent for these cross-couplings using PTS? The answer is "yes"; at least insofar as CM and RCM reactions go, they work equally well in this medium (**Scheme 4**).[79] Of course, we can only make this claim for water taken from the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

## 5. Summary and Outlook

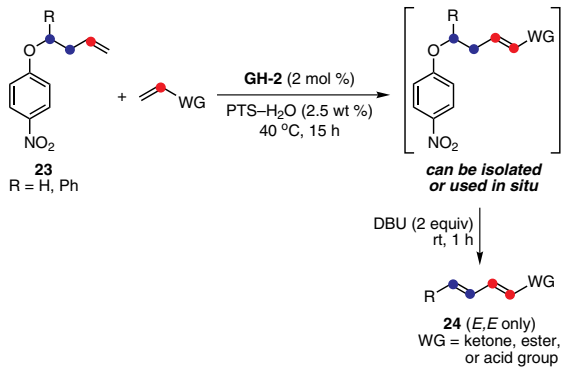
Studies to date on Heck and Suzuki–Miyaura couplings, as well as olefin metathesis reactions, in pure water at room temperature have been very encouraging. The presence of the nanometer-micelle-forming amphiphile PTS may provide the foundation for these aqueous conditions, but the catalysis is still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



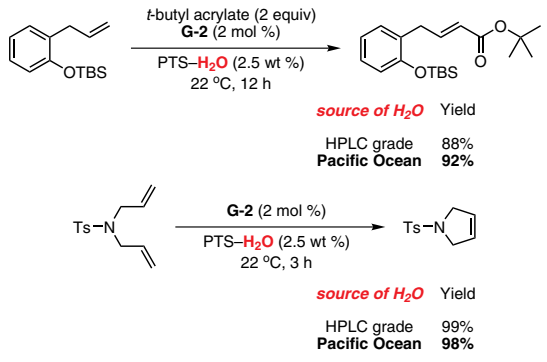

**eq 20** *(Ref. 74)*




**eq 21** *(Ref. 77)*




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




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

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

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

## 6. Acknowledgements

We are extremely appreciative of the financial support of our programs in green chemistry provided by Zymes, LLC (Hasbrouck Heights, NJ). Our sincere appreciation and gratitude are extended to our co-workers in the group, especially Benjamin Taft for initiating this project, and to Tue Petersen, Alex Abela, Grant Aguinaldo, David Chung, and Brian Rich, who have so skillfully developed these new technologies in water based on PTS. We thank Prof. R. W. Hoffmann (University of Marburg), and Drs. G. Paddon-Jones, S. Weinstock, R. Fain, and V. Berl for critical comments. Catalysts were generously supplied by Dr. Tom Colacot (Johnson Matthey; [Pd(dtbpf)$Cl_2$], CAS Registry No. 95408-45-0), Dr. Richard Pederson (Materia), Ms. Astrid Metzger (Umicore AG & Co. KG; NEOLYST® CX31, CAS Registry No. 884879-23-6), and Dr. Takao Saito, Mr. Hideo Shimizu, and Mr. Izuru Nagasaki (Takasago; (*R*)-(–)-DTBM-SEGPHOS®).

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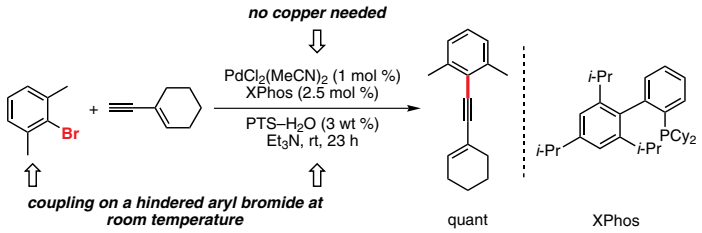
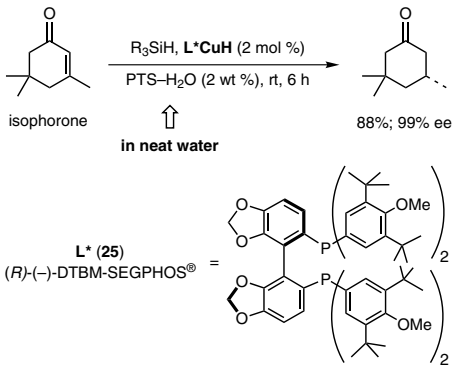



**Representative Sonogashira coupling in PTS–$H_2O$. Preparation of 2-(cyclohexen-1-ylethynyl)-1,3-dimethylbenzene.**[80a] $Pd(CH_3CN)_2Cl_2$(1.8 mg, 0.007 mmol) and XPhos (6.9 mg, 0.014 mmol) were introduced under argon into a 5-mL, round-bottom flask equipped with a stir bar. The following were then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

**eq 22** *(Ref. 80a)*




**eq 23** *(Ref. 82)*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**Keywords:** cross-couplings; green chemistry; micellar catalysis; designer surfactants; PTS.

## About the Authors

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

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

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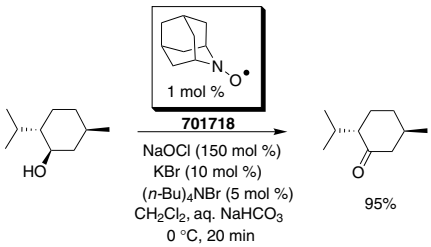
# Accelerate Organic Synthesis

## Organocatalyst for the Oxidation of Hindered Alcohols

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

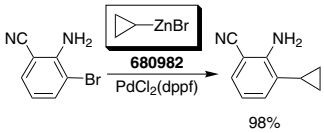



Shibuya, M. et al. *J. Am. Chem. Soc.* **2006**, *128*, 8412.

**701718**

## Cyclopropylzinc Bromide for the Negishi Coupling

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

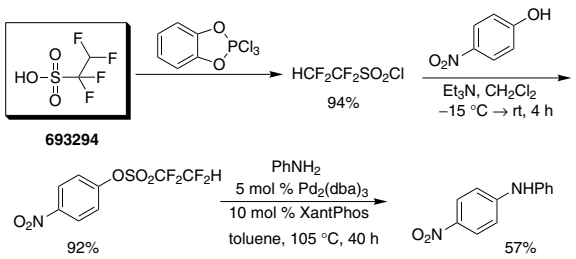



Campbell, J. B. et al. *Synth. Commun.* **1989**, *19*, 2265.


**680982**

## TFESA as an Alternative to Triflic Acid

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

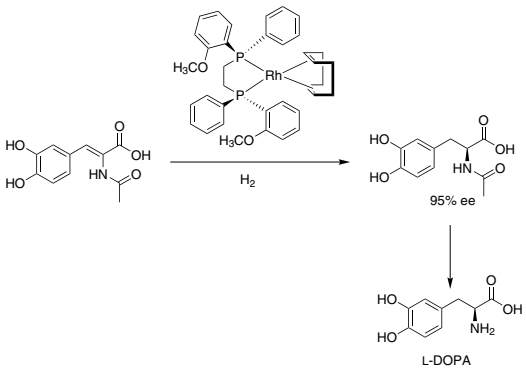



Rostovtsev, V. V. et al. *J. Org. Chem.* **2008**, *73*, 711

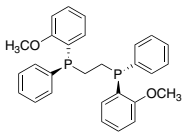
**693294**

## New DIPAMP Ligands for Enantioselective Hydrogenation

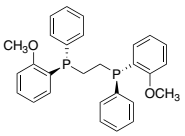
Rewarded by a Nobel Prize in 2001 for his pioneering work in asymmetric synthesis, Knowles was the first to develop a chiral transition-metal catalyst based on a chiral diphosphine ligand, DIPAMP, that could transfer chirality to a prochiral substrate with high enantiomeric excesses. He demonstrated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




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



(*S,S*)-DIPAMP
**697753**



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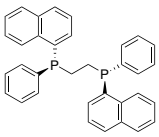
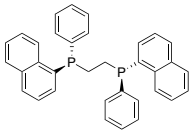
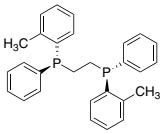
**697761**



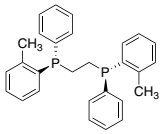
(*S,S*)-1-Naphthyl-DIPAMP
**697788**



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



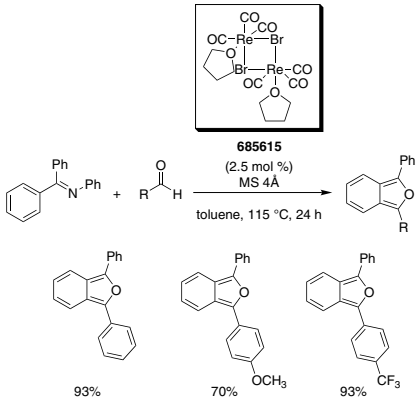
(*S,S*)-*o*-Tolyl-DIPAMP
**697818**



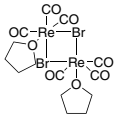
(*R,R*)-*o*-Tolyl-DIPAMP
**697826**

## Insertion of Aldehyde into a C–H Bond

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




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



**685615**

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

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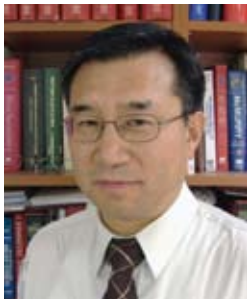

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## Outline

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## 1. Introduction

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

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

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

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

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

## 2.1. Diaryl Vicinal Diamines

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

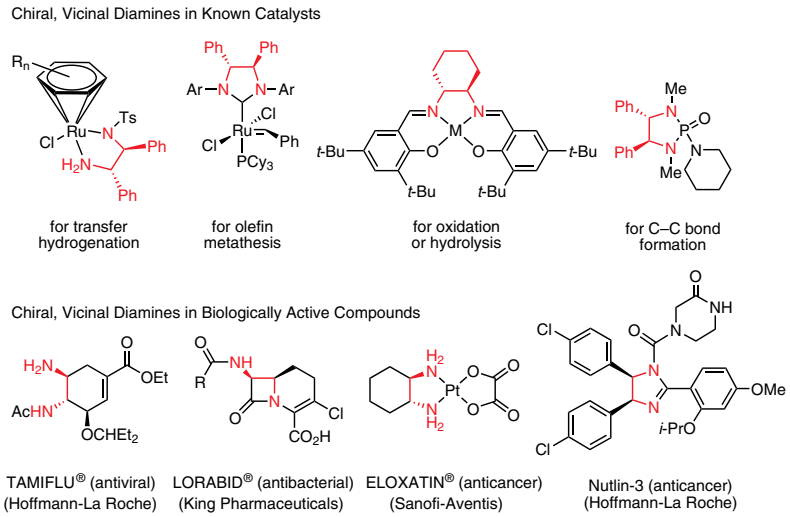
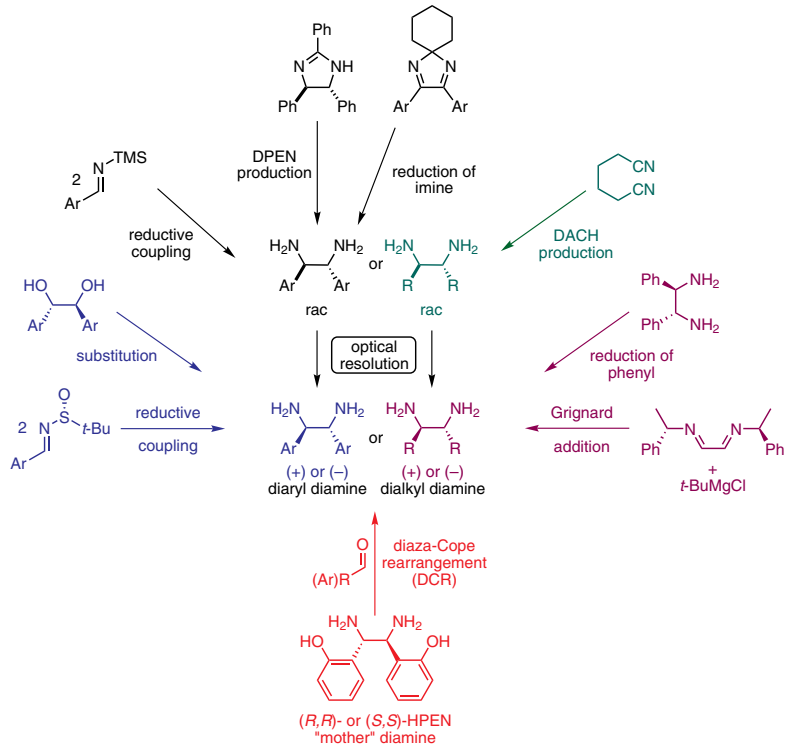
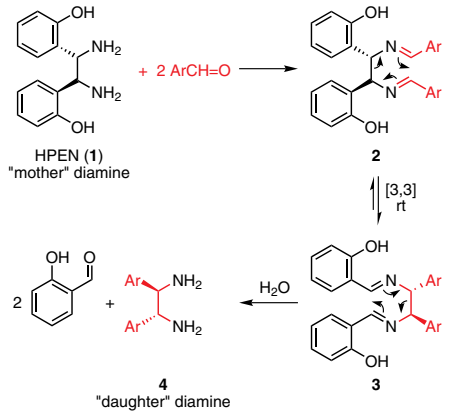



**Figure 1.** Vicinal-Diamine-Based Catalysts and Bioactive Compounds.




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




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

ee >99% in all cases.

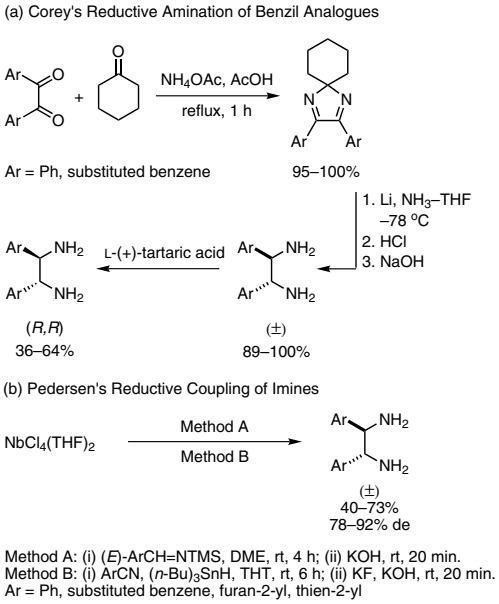
**Scheme 2.** "Mother-to-Daughter" Diamine by DCR. *(Ref. 7,8)*

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

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

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

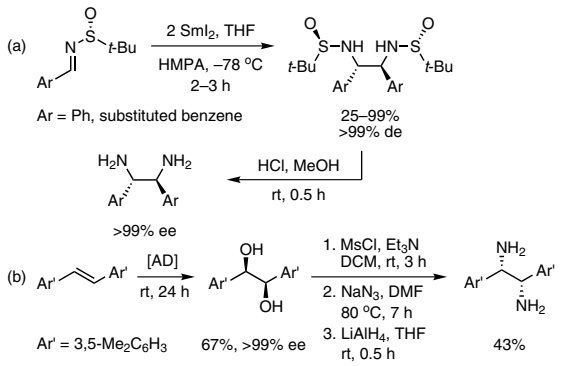
One obvious way to avoid the tedious resolution of racemic diamines is to synthesize the diamine enantiomers stereoselectively. Recently, the samarium-mediated reductive coupling of chiral sulfinyl imines has been reported by Xu and



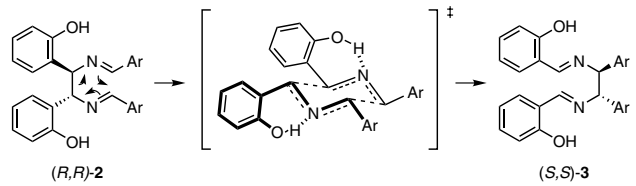

**Scheme 3.** Two of the Most Used Syntheses of Racemic Diaryl Vicinal Diamines. *(Ref. 10,11)*

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

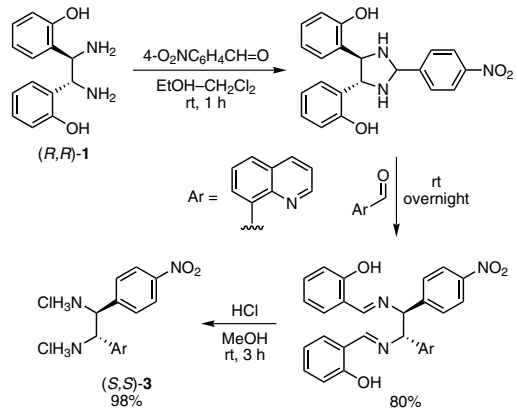
DFT computation is useful for predicting the equilibrium constant for the DCR reaction. The progress of the rearrangement reaction can be conveniently monitored by the appearance of the $^1$H NMR signal from the resonance-assisted hydrogen bond that is highly downfield-shifted away from other signals.[8]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



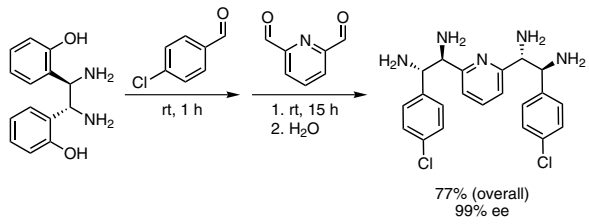

**Scheme 4.** Known Enantioselective Syntheses of Diaryl Vicinal Diamines. *(Ref. 17,19)*



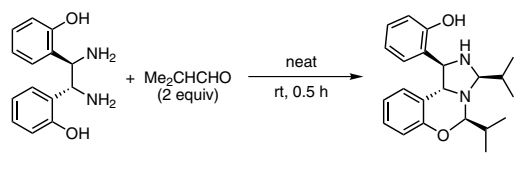

**eq 1** *(Ref. 8a)*




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




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




**eq 2** *(Ref. 8c)*

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

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

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

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

## 2.2. Dialkyl Vicinal Diamines

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

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

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

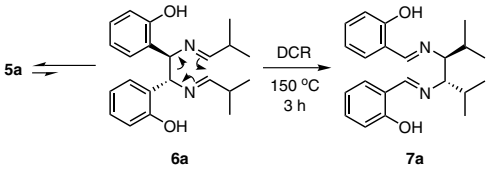
equilibrium with the initial diimine, **6a**, which rearranges to give the product diimine, **7a**. Monitoring of the reaction by $^1$H NMR spectrometry shows that the concentration of diimine intermediate **6a** does not accumulate to any observable extent during the conversion of **5a** to **7a**.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

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

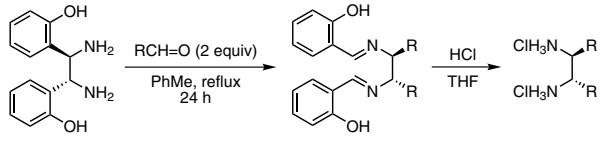
Some of the diamines in Scheme 7 were previously synthesized by other methods (**Scheme 8**).[23,24] Diamines **8a** and **8c** were synthesized by addition of Grignard reagents to chiral bisimines for the purpose of preparing NHE3 inhibitors.[25] However, the observed diastereoselectivity for this reaction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

## 2.3. Alkyl–Aryl Vicinal Diamines

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



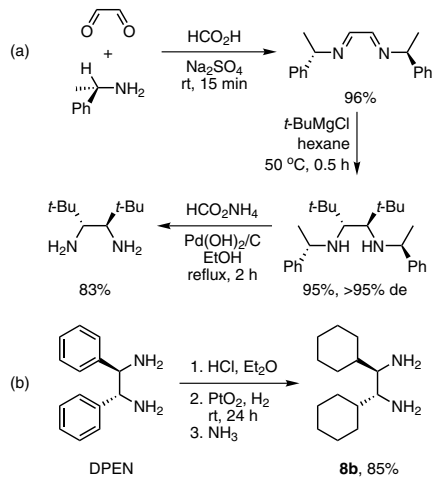

**eq 3** *(Ref. 8c)*



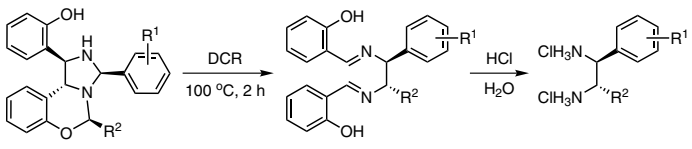

| R | No. | Yield 7 | Yield 8 |
|---|---|---|---|
| *i*-Pr | **a** | 85% | 91% |
| Cy | **b** | 80% | 95% |
| *c*-Pr | **c** | 73% | 90% |
| Et | **d** | 71% | 94% |

>99% ee in all cases.

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




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



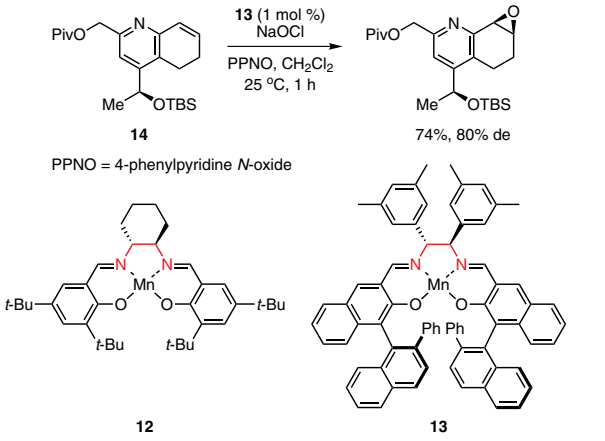

| 11 | a | b | c | d | e |
|---|---|---|---|---|---|
| $R^1$ | 2-F | 2-F | 2-F | 4-F | 4-Cl |
| $R^2$ | *i*-Pr | Cy | *n*-$C_5H_{11}$ | Et | Et |

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

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

## 3. Vicinal-Diamine-Based Catalysts

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




**eq 4** *(Ref. 42)*

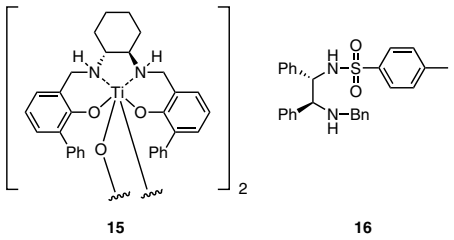



**Figure 2.** Oxidation Catalysts That Use Hydrogen Peroxide.
*(Ref. 43,44)*

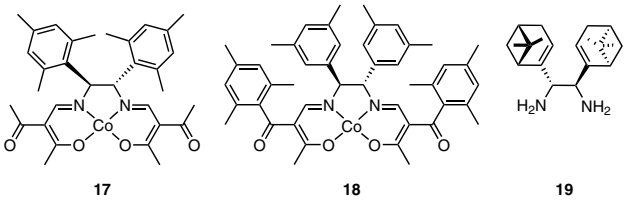



**Figure 3.** Catalysts Based on Sterically Bulky Vicinal Diamines.
*(Ref. 45–49)*

### 3.1. Steric and Electronic Tuning of Catalyst Structure

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

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

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

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

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

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

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

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

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

### 3.2. New Diamine Designs

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

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

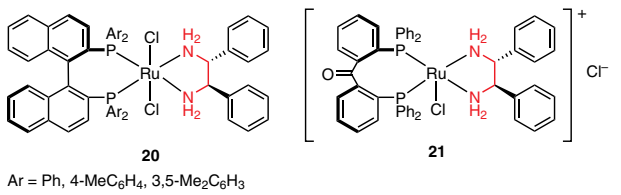
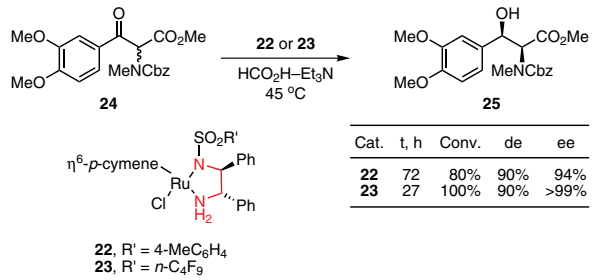
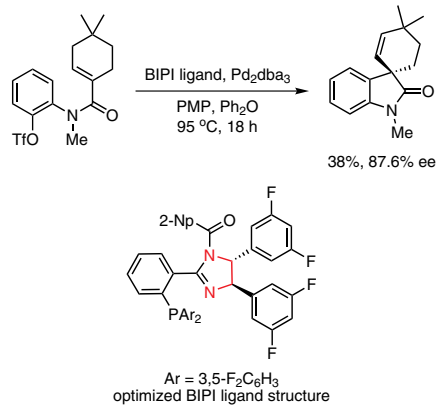


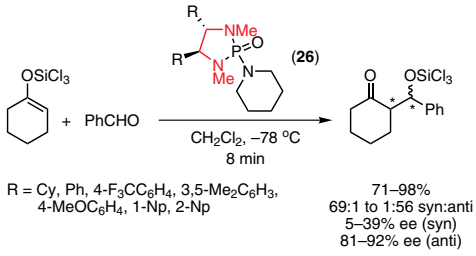

**Figure 4.** Vicinal-Diamine-Based Catalysts for the Hydrogenation of Prochiral Ketones. *(Ref. 50)*



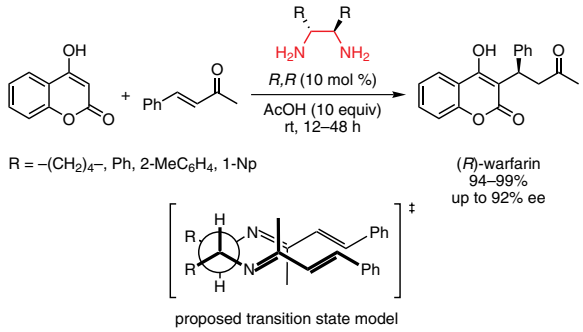

**eq 5** *(Ref. 52)*



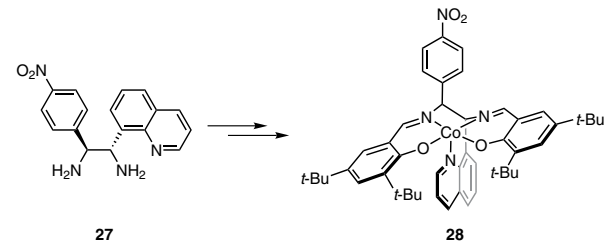

**eq 6** *(Ref. 12)*



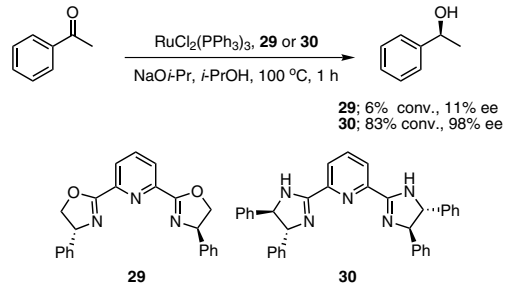

**eq 7** *(Ref. 13)*



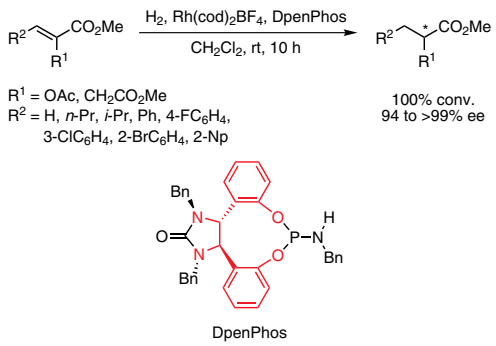

**eq 8** *(Ref. 53)*




**eq 9** *(Ref. 8b)*




**eq 10** *(Ref. 56,57)*




**eq 11** *(Ref. 61b)*

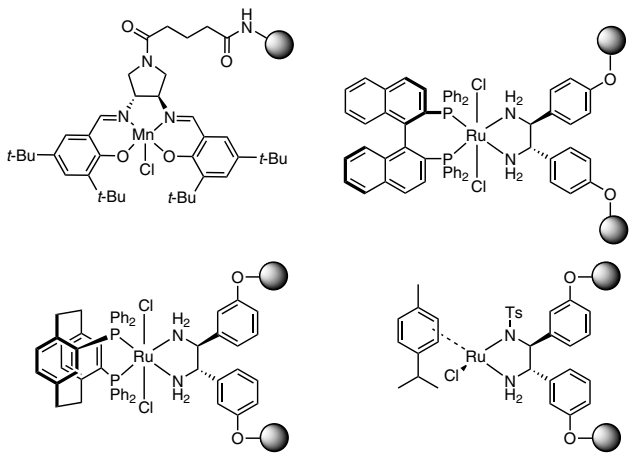



**Figure 5.** Chiral, Vicinal-Diamine-Based Catalysts on Solid Support. *(Ref. 63)*

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

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

### 3.3. Diamines on Solid Support

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

### 3.4. Water-Soluble Diamine Catalysts

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

## 4. Diamine Drugs

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

### 4.1. Acyclic Diamines

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

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

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

## 4.2. Imidazolines

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

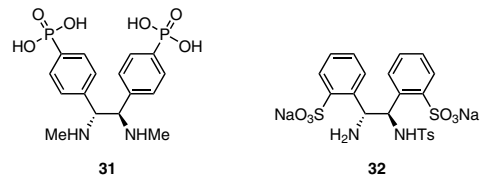
## 4.3. Piperazines

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

## 4.4. Other Diamines

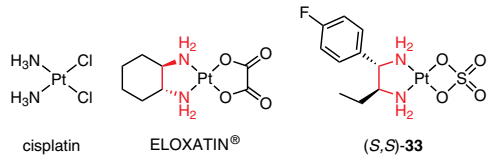
α,β-Diamino acids are a special class of chiral vicinal diamines that have potent biological activities.[75] For example, viomycin is an inhibitor of protein synthesis, and capreomycin IA, used for the treatment of tuberculosis, contain L-capreomycidine[76] as a key structural element. In addition, the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

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



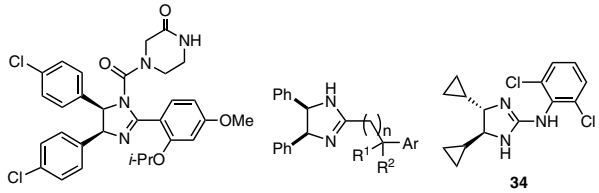
**31** **32**

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



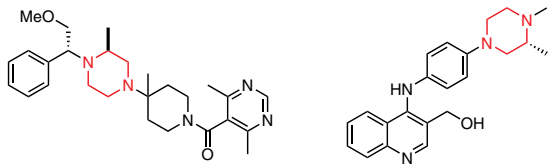
cisplatin ELOXATIN® (*S,S*)-**33**

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



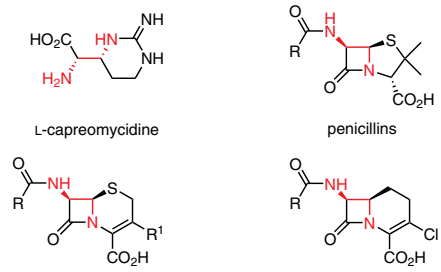
**34**

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



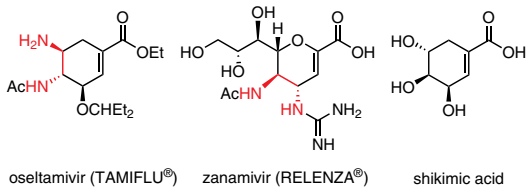
CCR5 antagonist **35** $\alpha_{2C}$-adrenoceptor antagonist

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



L-capreomycidine penicillins cephalosporins LORABID®

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



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

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

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

## 5. Conclusions

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

## 6. Acknowledgements

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

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

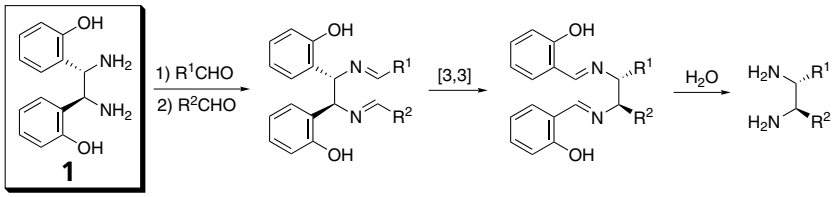
**Jik Chin** received his B.Sc. degree in chemistry and biochemistry (1977) from the University of Toronto. He worked on physical organic and bio-organic projects (ketophosphonate and maleamic acid hydrolysis; thiamine mechanisms) with Professor Ron Kluger for his M.Sc. (1978) and Ph.D. (1981) degrees.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

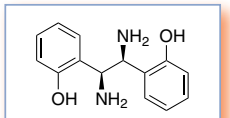
**B. Moon Kim** obtained his B.S. and M.S. degrees from the Department of Chemistry, Seoul National University. In 1983, he began his Ph.D. level research in the laboratory of the late Professor Satoru Masamune at M.I.T., where he studied asymmetric synthesis using organoboron compounds. Five years later,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

# NEW Chiral Vicinal Diamines for Asymmetric Synthesis

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

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

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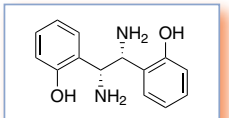


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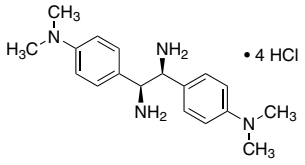
## Other NEW Chiral Vicinal Diamines

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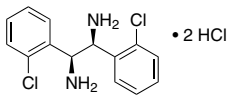


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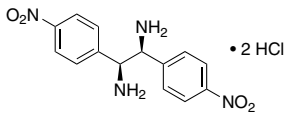


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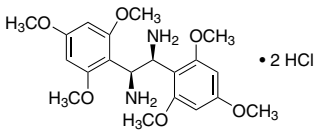


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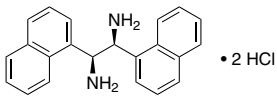


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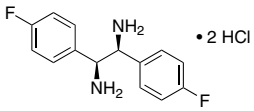


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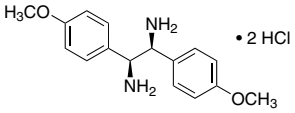


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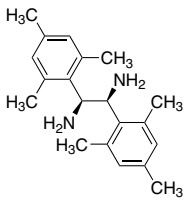


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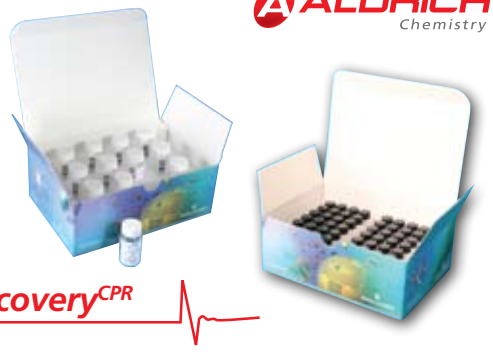

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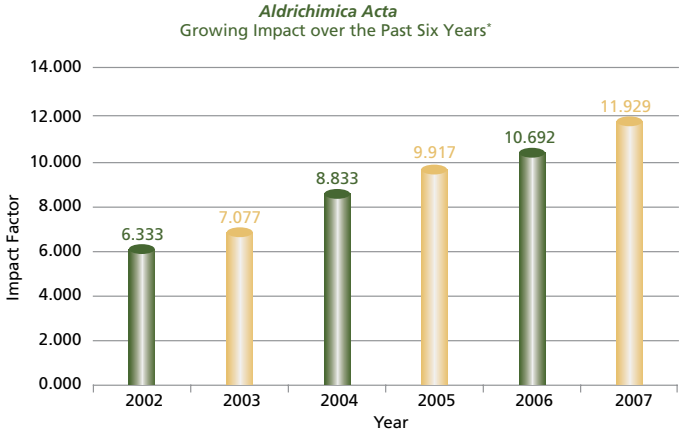


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CARBONYL COMPOUNDS: STILL CENTRAL TO ORGANIC SYNTHESIS

# Aldrichimica ACTA

VOL. 41, NO. 4 • 2008

ALDRICH Chemistry

Formation of C–C Bonds via Catalytic Hydrogenation and Transfer Hydrogenation: Vinylation, Allylation, and Enolate Addition

Amino Carbonyl Compounds in Organic Synthesis

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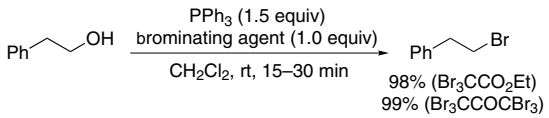
# New Products from Aldrich R&D

## *Aldrich Is Pleased to Offer Cutting-Edge Tools for Organic Synthesis*

### *Reagents for the Bromination of Alcohols*

There are various methods for the conversion of alcohols to bromides; however, commonly employed methods either use or generate toxic HBr gas. The use of hexabromoacetone ($Br_3CCOCBr_3$) and ethyl tribromoacetate ($Br_3CCO_2Et$) as less toxic, milder bromination reagents has recently been reported. Both reagents provide the desired alkyl bromide in excellent yield.




Tongkate, P. et al. *Tetrahedron Lett.* **2008**, *49*, 1146.

**Ethyl tribromoacetate, 97%**

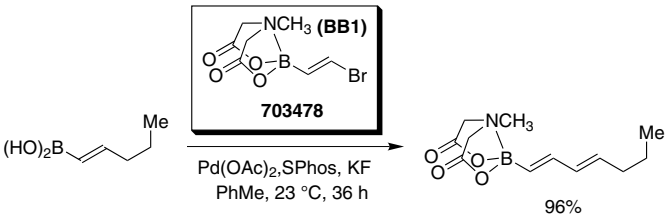
**704679** 1 g, 5 g
*[599-99-5]*
$C_4H_5Br_3O_2$
FW: 324.79

**1,1,1,3,3,3-Hexabromoacetone, 97%**

**702404** 5 g, 25 g
*[23162-64-3]*
$C_3Br_6O$
FW: 531.46

### *New Boronic Acid Surrogates for Iterative Cross-Coupling*

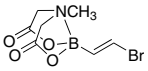
Professor Martin Burke and co-workers at the University of Illinois (Urbana-Champaign) have recently disclosed a technology employing boronic acid surrogates (termed "MIDA boronates") for use in iterative Suzuki cross-coupling reactions. The air-stable, chromatography-compatible, and easily deprotected boron building blocks permit difficult couplings through the attenuation of transmetallation via pyramidalization of the boron atom. The chemistry has been applied to the preparation of polyenyl MIDA boronates, for which the boronic acid counterpart is unstable. This subsequently led to the efficient synthesis of the left half of amphotericin B.




Lee, S. J. et al. *J. Am. Chem. Soc.* **2008**, *130*, 466.

**trans-2-Bromovinylboronic acid MIDA ester**

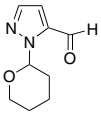
**703478** 500 mg, 1 g
$C_7H_9BBrNO_4$
FW: 261.87



### *New Aldehydes from Aldrich R&D*

**1-(2-Tetrahydropyranyl)-1*H*-pyrazole-5-carboxaldehyde**

**699365** 1 g
*[957483-88-4]*
$C_9H_{12}N_2O_2$
FW: 180.20

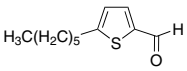


**3-Methylpyridine-2-carboxaldehyde, 97%**

**699071** 1 g
*[55589-47-4]*
$C_7H_7NO$
FW: 121.14

**5-Hexylthiophene-2-carboxaldehyde, 97%**

**699187** 1 g
*[100943-46-2]*
$C_{11}H_{16}OS$
FW: 196.31

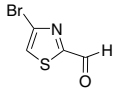


**4-Oxazolecarboxaldehyde, 97%**

**697915** 250 mg, 1 g
*[118994-84-6]*
$C_4H_3NO_2$
FW: 97.07

**4-Bromothiazole-2-carboxaldehyde, 96%**

**699284** 1 g
*[167366-05-4]*
$C_4H_2BrNOS$
FW: 192.03



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## "PLEASE BOTHER US."

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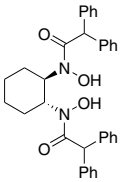
Professor Hisashi Yamamoto of The University of Chicago kindly suggested that we make bis(hydroxamic acid) based ligands, which, in combination with $VO(O\textit{i}\text{-}Pr)_3$, generate highly active catalysts for the asymmetric epoxidation of allylic alcohols. Good-to-excellent yields and enantioselectivities of up to 97% ee have been reported.



Zhang, W. et al. *Angew. Chem., Int. Ed.* **2005**, *44*, 4389.

**700592 (1*R*,2*R*)-*N*,*N*′-Dihydroxy-*N*,*N*′-bis(diphenylacetyl)-1,2-cyclohexanediamine, 97%** 50 mg
(*R*)-CBHA-DPA

**700576 (1*S*,2*S*)-*N*,*N*′-Dihydroxy-*N*,*N*′-bis(diphenylacetyl)-1,2-cyclohexanediamine, 97%** 50 mg
(*S*)-CBHA-DPA

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

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

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*Sivaraj Baktharaman, Ryan Hili, and Andrei K. Yudin,** University of Toronto


## ABOUT OUR COVER

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

***Pont Neuf, Paris*** (oil on canvas, 75.3 × 93.7 cm), was painted by the French Impressionist painter, Pierre Auguste Renoir (1841–1919), on a gloriously sunny and warm summer's day in 1872. While Renoir's paintings of women and children are better known, his landscapes resonate with a vigor and freshness new to the art scene at the time.

In this painting, Renoir uses a bright, light palette to emphasize an intense midday sun, but he deliberately suppresses incidental detail and clarity, displaying the basic tenets central to the development of Impressionism. Although Renoir presents us with an impressionistic view of the scene, the bridge and buildings in the background are accurate enough to be identifiable, then and now.

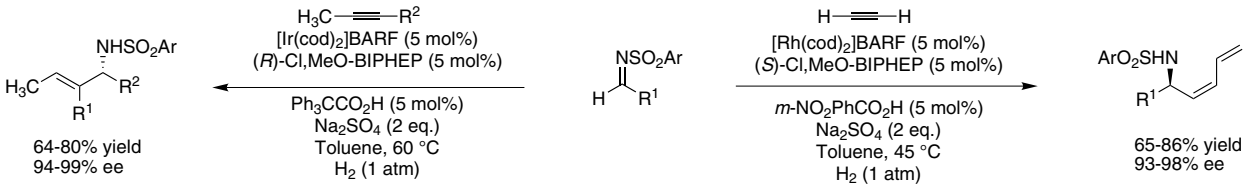
Renoir occupied an upper floor of a café on the left bank of the Seine to depict this famous view of the ninth bridge. Pont Neuf connects the Île de la Cité with the rest of Paris. Edmond Renoir, the artist's younger brother and novice journalist in 1872, later recounted in an interview that he helped his brother by periodically delaying a Parisian on the bridge long enough for the artist to record their appearance. Renoir captures Edmond, walking stick in hand, wearing a light-colored straw hat and slacks and a dark jacket in at least two locations. Can you find him?

**This painting is part of the Ailsa Mellon Bruce Collection at the National Gallery of Art, Washington, DC.**

# Metal Complexes and Ligands for Enantioselective Reductive Coupling

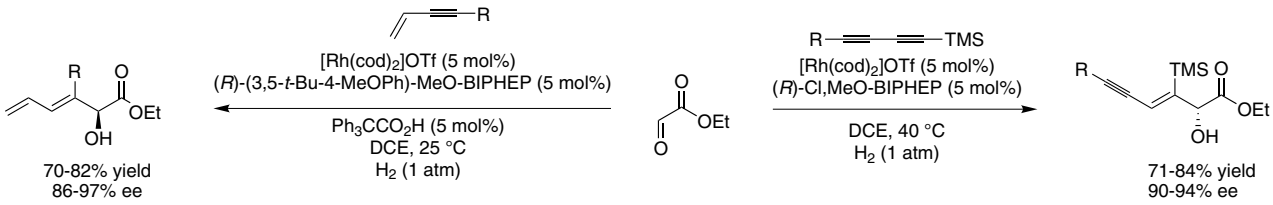
Asymmetric hydrogenation is one of the most utilized reactions to induce chirality in a molecule. It is currently widely used in industry. Krische and co-workers have developed a new type of transformation based on the enantioselective reductive C–C bond formation mediated by hydrogen. Utilizing a rhodium-, iridium-, or ruthenium-based complex with a variety of ligands, Krische and co-workers demonstrated the potency of this reaction for the reductive coupling of conjugated enones, dienes, imines, enynes, and carbonyls. Aldrich is offering a series of complexes and ligands for enantioselective reductive coupling.

## *Enantioselective Imine Vinylation*

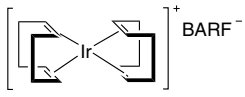



Ngai, M.-Y. et al. *J. Am. Chem. Soc.* **2007**, *129*, 12644. Skucas, E. et al. *J. Am. Chem. Soc.* **2007**, *129*, 7242.

## *Enantioselective Reductive Coupling of Alkynes with Glyoxalates*




Hong, Y.-T. et al. *Org. Lett.* **2007**, *9*, 3745. Cho, C.-W.; Krische, M. J. *Org. Lett.* **2006**, *8*, 3873.

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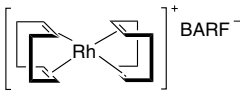


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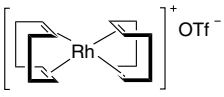


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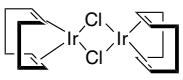


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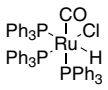
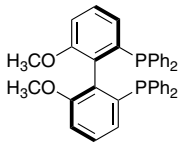
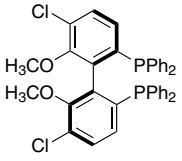



**334995**



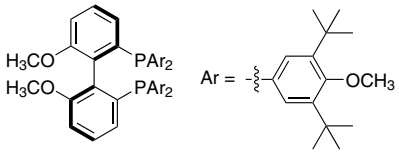

*(R)*-(+)-MeO-BIPHEP **29510**

*(S)*-(–)-MeO-BIPHEP **29511**



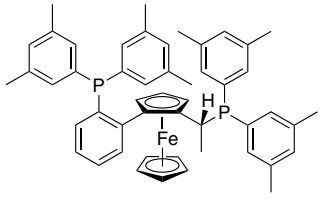

*(R)*-(–)-Cl,MeO-BIPHEP **76854**

*(S)*-(+)-Cl,MeO-BIPHEP **96738**




*(R)*-(3,5-*t*-Bu-4-MeOPh)-MeO-BIPHEP **29512**

*(S)*-(3,5-*t*-Bu-4-MeOPh)-MeO-BIPHEP **29513**




*(R)*-Xylyl-WALPHOS **65683**

*(S)*-Xylyl-WALPHOS **65684**

# Formation of C–C Bonds via Catalytic Hydrogenation and Transfer Hydrogenation: Vinylation, Allylation, and Enolate Addition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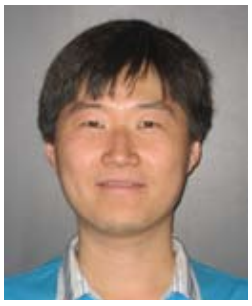
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## Outline

1. Introduction
2. Vinylation of Carbonyl Compounds and Imines
3. Allylation and Propargylation of Carbonyl Compounds
4. Hydrogenative Aldol and Mannich Additions
5. Future Directions
6. Acknowledgments
7. References and Notes

## 1. Introduction

A fundamental challenge in organic chemistry resides in the development of efficient protocols for carbon–carbon-bond formation. The ideal C–C-bond forming processes should be applicable to both petrochemical and renewable feedstocks and should be aligned with the economic and aesthetic ideals of atom-economy,[1] step-economy,[2] and Green Chemistry.[3] Ultimately, chemical production should be sustainable, that is, it should not compromise human health, the environment, or the economy.

Hydrogen is vastly abundant, constituting roughly 90% of the atoms present in the Universe. Catalytic additions of elemental hydrogen, termed "hydrogenations," are of enormous socioeconomic importance. For example, the catalytic hydrogenation of atmospheric nitrogen to produce ammonia, the Haber–Bosch process,[4] is used to produce over $10^7$ metric tons of ammonia annually. Nitrogenous fertilizer obtained from the Haber–Bosch process is estimated to sustain one-third of the Earth's population.[5] The asymmetric hydrogenation of C=X π bonds (X = O, NR) is estimated to account for over half of the chiral drugs manufactured industrially, not including those prepared via physical and enzymatic resolution.[6]

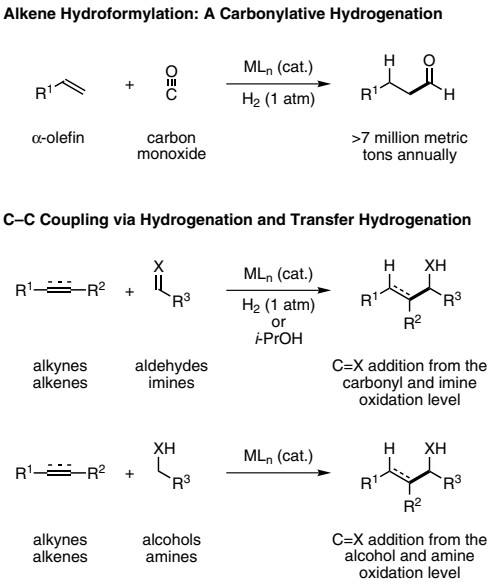
The Fischer–Tropsch reaction[7] and alkene hydroformylation[8] may be viewed as the prototypical C–C-bond forming hydrogenations. Hydroformylation combines basic feedstocks (α-olefins, carbon monoxide, and hydrogen) with perfect atom-economy, and accounts for the production of over 7 million metric tons of aldehyde annually, making it the largest-volume application of homogeneous metal catalysis.[9] Given the impact of hydroformylation, it is surprising that the field of "hydrogenative C–C-bond formation" lay fallow for over 70 years.[10,11]

As described herein, we have discovered that hydrogenation and transfer hydrogenation may be used to couple diverse π-unsaturated reactants to carbonyl compounds and imines.[12] Such hydrogenative C–C couplings define a departure from the use of preformed organometallic reagents in classical C=X (X = O, NR) addition reactions, in many cases enabling completely byproduct-free C=X addition processes. Furthermore, under transfer-hydrogenative coupling conditions, carbonyl addition can be achieved from the alcohol or aldehyde oxidation level,[12e,f] circumventing the redox manipulations typically required to adjust oxidation level (**Scheme 1**).

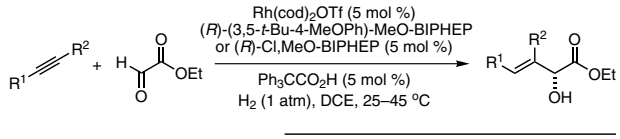
## 2. Vinylation of Carbonyl Compounds and Imines

Numerous methods exist for the preparation of allylic alcohols and allylic amines.[13,14] For example, metal-catalyzed allylic substitution employing oxygen and nitrogen nucleophiles is a powerful protocol for the synthesis of chiral nonracemic allylic alcohols and allylic amines.[15] Another approach, though less developed, involves catalytic enantioselective aldehyde vinylation.[16–19] Catalytic enantioselective vinyl transfer to imines had not been achieved prior to our work (vide infra).[20,21]

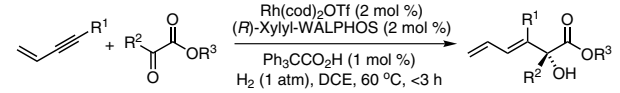
Limitations associated with the use of preformed vinyl metal reagents are potentially overcome through direct metal-catalyzed alkyne–carbonyl reductive couplings. The first catalytic process of this type, a rhodium-catalyzed reductive cyclization of acetylenic aldehydes mediated by silane, was reported in 1994 by Ojima et al.[22] In 1995, Crowe and Rachita disclosed related titanium-catalyzed cyclizations mediated by



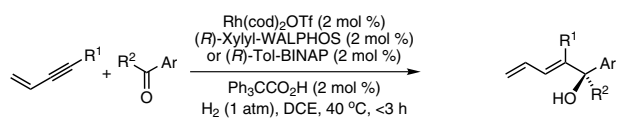

**Scheme 1.** Catalytic C–C Coupling via Hydrogenation and Transfer Hydrogenation.




| $R^1$ | $R^2$ | Yield | ee |
|---|---|---|---|
| $TBSOCH_2C{\equiv}C$ | TMS | 72% | 90% |
| $PhC{\equiv}C$ | TMS | 84% | 91% |
| $H_2C{=}CH$ | thien-2-yl | 72% | 92% |
| $H_2C{=}CH$ | $TESOCH_2CH_2$ | 70% | 90% |




| $R^1$ | $R^2$ | $R^3$ | Yield | ee |
|---|---|---|---|---|
| $BocNHCH_2$ | Me | Me | 88% | 90% |
| $AcOCH_2$ | Me | Me | 98% | 90% |
| $AcOCH_2$ | *c*-Pr | Me | 85% | 88% |
| *n*-Pent | Me | Et | 96% | 91% |




| $R^1$ | $R^2$ | Ar | Yield | ee |
|---|---|---|---|---|
| $BocNHCH_2$ | *c*-Pr | pyridin-2-yl | 89% | 97% |
| $AcOCH_2CH_2$ | H | 1,5-$Ph_2$-pyrazol-3-yl | 76% | 92% |
| $BocNHCH_2$ | Me | pyrazin-2-yl | 92% | 98% |
| Ph | H | 5-Me-isoxazol-3-yl | 73% | 94% |

**Scheme 2.** Direct, Byproduct-Free Hydrogenative Coupling of Conjugated Alkynes to Activated Carbonyl Compounds and Imines Employing Cationic Rhodium Catalysts. *(Ref. 27)*

silane.[23] Corresponding nickel-catalyzed cyclizations were first reported in 1997 by Montgomery and co-workers.[24a–c,e] Based on Montgomery's finding, nickel-catalyzed intermolecular alkyne–aldehyde reductive coupling was achieved by Jamison in 2000.[25] Improved nickel-based catalysts were developed later by Takai[26] and Montgomery.[24d] While reductive couplings of this type signal a departure from the use of preformed organometallic reagents, these methods employ terminal reductants such as hydrosilanes, hydrostannanes, organozinc reagents, organoboron reagents, or chromium(II) chloride and, hence, produce molar equivalents of metallic byproducts.

Under hydrogenation conditions, alkynes engage in completely byproduct-free reductive couplings to both carbonyl compounds and imines.[12d] First-generation catalytic systems based on rhodium promote the highly enantioselective coupling of conjugated alkynes to activated aldehydes and ketones in the form of vicinal dicarbonyl compounds.[27a–c] Heterocyclic aromatic aldehydes and ketones couple to conjugated alkynes under closely related conditions, providing access to heteroaryl-substituted carbinols.[27d] Notably, the diene- and enyne-containing products are not subject to over-reduction under the hydrogenative coupling conditions. Presumably, upon consumption of the electrophile (the limiting reagent) excess alkyne unproductively coordinates rhodium and so impedes the rate of further conventional hydrogenation (**Scheme 2**).[27]

The coupling of conjugated enynes or diynes to ethyl (*N*-sulfinyl)iminoacetates proceeds efficiently under the conditions of rhodium-catalyzed hydrogenation (**Scheme 3**).[28] Using appropriately substituted (*N*-sulfinyl)iminoacetates, one generates the corresponding β,γ-unsaturated α-amino acid esters as single diastereomers. A second hydrogenation of the unsaturated side chain of the coupling product provides access to β-substituted α-amino acids.

Gaseous acetylene couples to aldehydes and imines under hydrogenation conditions to furnish products of (*Z*)-butadienylation.[29] Using chirally modified rhodium catalysts, allylic alcohols and allylic amines are formed in highly optically enriched form (**Scheme 4**).[29,30] These byproduct-free couplings combine acetylene, an abundant feedstock,[31] with carbonyl compounds or imines to furnish chiral adducts in the absence of any preformed vinyl metal reagents.

Using second-generation catalysts based on iridium, highly enantioselective hydrogenative coupling of 1,2-dialkyl-substituted alkynes to *N*-arylsulfonyl imines is achieved (**Scheme 5**).[32] The trisubstituted allylic amine products are formed with complete levels of *E*:*Z* selectivity (≥95:5), and excellent regiocontrol is observed using nonsymmetric alkynes. This byproduct-free coupling provides trisubstituted allylic amines that are not accessible via metal-catalyzed asymmetric allylic alkylation.[15]

Finally, intramolecular coupling of alkynes to tethered aldehydes occurs readily in the rhodium-catalyzed hydrogenation. Using chirally modified catalysts, products of reductive carbocyclization are formed with uniformly high levels of optical enrichment.[33] Using an achiral rhodium catalyst, chiral racemic acetylenic aldehydes engage in highly *syn*-diastereoselective reductive cyclizations to furnish cyclic allylic alcohols (**Scheme 6**).

## 3. Allylation and Propargylation of Carbonyl Compounds

Carbonyl allylation is employed routinely in synthetic organic chemistry.[34] Asymmetric allylation has been achieved using chirally modified allyl metal reagents,[35] chiral Lewis acid catalysts, or chiral Lewis base catalysts.[36] These methods

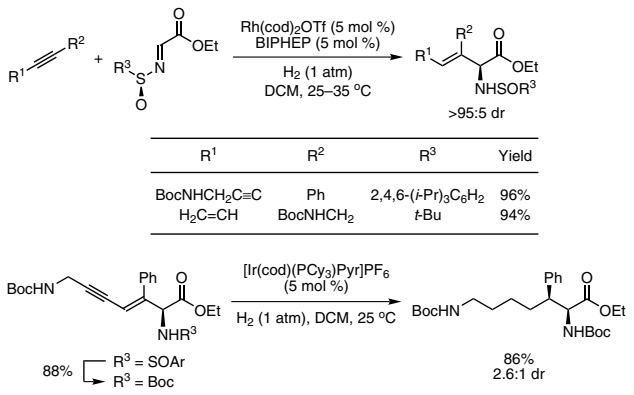
invariably employ preformed allyl metal reagents, such as allyl stannanes or trichlorosilanes, which generate stoichiometric quantities of metallic byproducts. Other methods for catalytic carbonyl allylation include the reduction of metallo-π-allyls derived from allylic alcohols and allylic carboxylates,[37] which require stoichiometric quantities of metal-based terminal reductants for catalytic turnover.[38]

We find that allyl metal species arising transiently in the course of allene hydrogenation may be captured by exogenous carbonyl electrophiles, thus enabling byproduct-free carbonyl allylation. For example, iridium-catalyzed hydrogenation of dimethylallene in the presence of activated aldehydes or ketones delivers products of reverse prenylation.[39a] Under the conditions of iridium-catalyzed transfer hydrogenation employing isopropanol as the terminal reductant, dimethylallene also couples to aldehydes.[39b] Finally, hydrogen embedded within an alcohol substrate can be redistributed among reactants to generate nucleophile–electrophile pairs, enabling byproduct-free carbonyl reverse prenylation *from the alcohol oxidation level* (**Scheme 7**).[39b]

These results prompted efforts toward general catalytic protocols for alcohol–unsaturate transfer-hydrogenative coupling.[40] Under iridium-catalyzed transfer-hydrogenation conditions employing isopropanol as terminal reductant, 1,3-cyclohexadiene reductively couples to aldehydes. By exploiting alcohols as both hydrogen donors and aldehyde precursors, an identical set of carbonyl addition products is accessible from the alcohol oxidation level under nearly identical conditions (**Scheme 8**).[41] In the ruthenium-catalyzed transfer hydrogenation employing $RuHCl(CO)(PPh_3)_3$ as precatalyst, simple acyclic dienes (butadiene, isoprene, and 2,3-dimethylbutadiene) couple to diverse alcohols (**Scheme 9**).[42] Again, coupling is possible from the alcohol or aldehyde oxidation level. In the latter case, isopropanol or formic acid may be employed as terminal reductants.

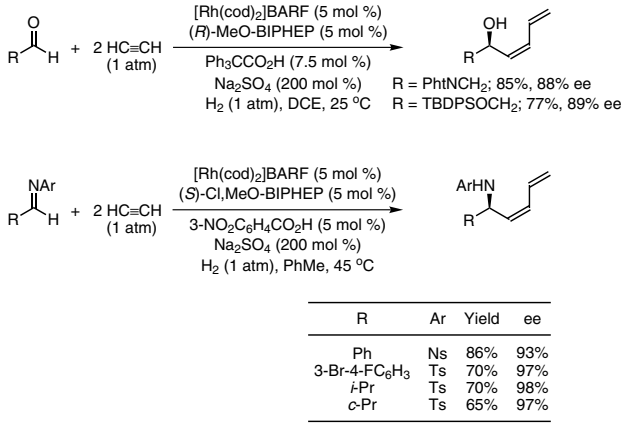
Under the conditions of ruthenium-catalyzed transfer hydrogenation employing isopropanol as terminal reductant, conjugated enynes couple to aldehydes to furnish products of carbonyl propargylation (**Scheme 10**).[43–45] Under nearly identical conditions, the very same set of adducts is obtained directly from the corresponding benzylic, allylic, and aliphatic alcohols, which serve as both hydrogen donors and aldehyde precursors. Thus, carbonyl propargylation is achieved from the alcohol or the aldehyde oxidation level in the absence of preformed allenyl metal reagents. Stereocontrolled variants of these newly developed allene, diene, and enyne couplings are currently under investigation.

An especially powerful application of transfer hydrogenative C–C coupling involves iridium-catalyzed carbonyl allylation from the aldehyde or alcohol oxidation level employing allyl acetate as the allyl donor.[46a] Exposure of allyl acetate to benzylic alcohols in the presence of commercially available $[Ir(cod)Cl]_2$ and (*R*)-BINAP delivers products of *C*-allylation in good-to-excellent yields and with high levels of asymmetric induction. Allylation from the aldehyde oxidation level is achieved by employing isopropyl alcohol as the terminal reductant. In this case, (–)-TMBTP is used as the chiral phosphine ligand to generate identical allylation adducts with high degrees of enantioselectivity. Thus, asymmetric allylation is achieved from the alcohol or aldehyde oxidation level in the absense of preformed allyl metal reagents. More recently, this asymmetric allylation protocol has been extended to allylic alcohols and aliphatic alcohols (**Scheme 11**).[46b]



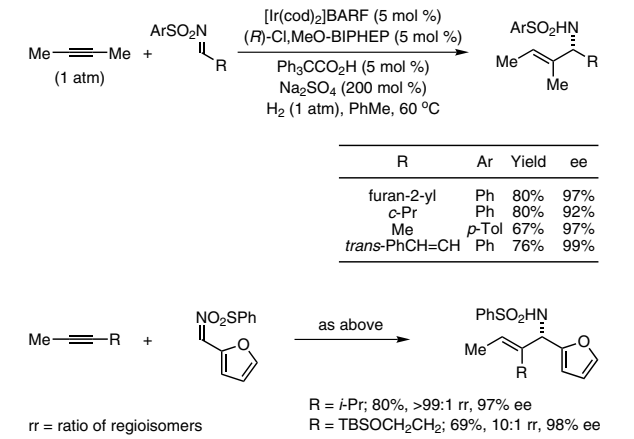

| $R^1$ | $R^2$ | $R^3$ | Yield |
|---|---|---|---|
| $BocNHCH_2C{\equiv}C$ | Ph | $2,4,6\text{-}(i\text{-}Pr)_3C_6H_2$ | 96% |
| $H_2C{=}CH$ | $BocNHCH_2$ | *t*-Bu | 94% |

**Scheme 3.** Unnatural α-Amino Acids via C–C-Bond-Forming Hydrogenation. *(Ref. 28)*



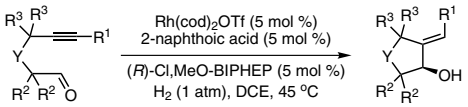

| R | Ar | Yield | ee |
|---|---|---|---|
| Ph | Ns | 86% | 93% |
| 3-Br-4-$FC_6H_3$ | Ts | 70% | 97% |
| *i*-Pr | Ts | 70% | 98% |
| *c*-Pr | Ts | 65% | 97% |

**Scheme 4.** Enantioselective Carbonyl and Imine (*Z*)-Butadienylation via Rhodium-Catalyzed Hydrogenative Coupling of Acetylene. *(Ref. 29,30)*

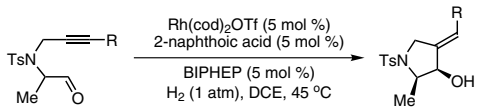



| R | Ar | Yield | ee |
|---|---|---|---|
| furan-2-yl | Ph | 80% | 97% |
| *c*-Pr | Ph | 80% | 92% |
| Me | *p*-Tol | 67% | 97% |
| *trans*-PhCH=CH | Ph | 76% | 99% |

**Scheme 5.** Enantioselective Imine Vinylation via Iridium-Catalyzed Hydrogenative Coupling of Unconjugated Alkynes. *(Ref. 32b)*



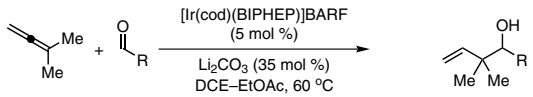

| Y | $R^1$ | $R^2$ | $R^3$ | Yield | ee |
|---|---|---|---|---|---|
| BnN | Me | H | =O | 83% | 99% |
| O | *n*-Hex | Me | H | 86% | 99% |
| TsN | Me | H | Me | 63% | 98% |
| TsN | H | Me | H | 76% | 96% |



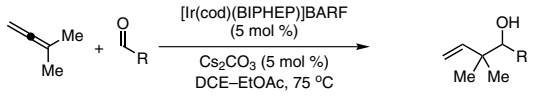

racemic

R = Ph; 95%, 8.3:1 dr
R = Me; 83%, >20:1 dr

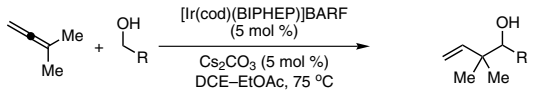
**Scheme 6.** Enantio- and Diastereoselective Carbocyclizations of Acetylenic Aldehydes via Rhodium-Catalyzed Asymmetric Hydrogenation. *(Ref. 33)*




| R | Yield |
|---|---|
| $BnOCH_2$ | 80% |
| 4-Br-3-$O_2NC_6H_3$ | 92% |
| Cbz | 78% |
| 6-Br-pyridin-2-yl | 84% |

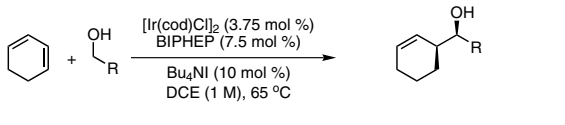



| R | Yield |
|---|---|
| $PhtNCH_2$ | 57% |
| 3-$MeOC_6H_4$ | 70% |
| Ph | 81% |
| thien-2-yl | 81% |



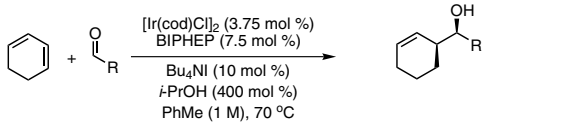

| R | Yield |
|---|---|
| $PhtNCH_2$ | 84% |
| 3-$MeOC_6H_4$ | 76% |
| Ph | 90% |
| thien-2-yl | 68% |

**Scheme 7.** Catalytic Carbonyl Addition via Iridium-Catalyzed Hydrogenative Coupling of Dimethylallene. *(Ref. 39)*




| R | Yield | 1,4:1,5 |
|---|---|---|
| 3-$MeOC_6H_4$ | 95% | 9:1 |
| 4-Br-3-$O_2NC_6H_3$ | 63% | 15:1 |
| 1-Me-indol-2-yl | 64% | 8:1 |
| thien-2-yl | 85% | 6:1 |

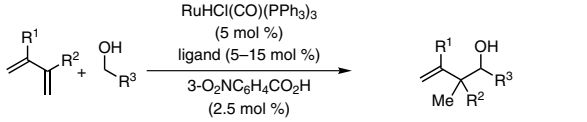
dr >95:5 in all cases. 1,4:1,5 is the ratio of the 1,4- to the 1,5-olefinic alcohol.




| R | Yield | 1,4:1,5 |
|---|---|---|
| 3-$MeOC_6H_4$ | 88% | 17:1 |
| 4-Br-3-$O_2NC_6H_3$ | 73% | 33:1 |
| 1-Me-indol-2-yl | 77% | 7:1 |
| thien-2-yl | 89% | 10:1 |

dr >95:5 in all cases. 1,4:1,5 is the ratio of the 1,4- to the 1,5-olefinic alcohol.

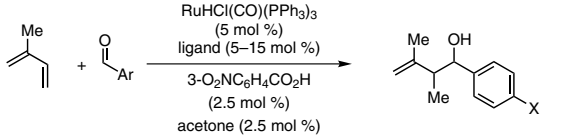
**Scheme 8.** Coupling of Dienes to Alcohols or Aldehydes via Iridium-Catalyzed Transfer Hydrogenation. *(Ref. 41)*




Ligand = P(4-$MeOC_6H_4$)$_3$ or *rac*-BINAP

| $R^1$ | $R^2$ | $R^3$ | Yield | dr |
|---|---|---|---|---|
| Me | H | *n*-Oct | 65% | 3:1 |
| Me | H | *a* | 75% | 2:1 |
| Me | Me | Ph | 91% | — |
| H | H | thien-2-yl | 87% | 1.5:1 |

[a] $R^3$ = $Me_2C$=CH($CH_2$)$_2$C(Me)=CH.




Ligand = P(4-$MeOC_6H_4$)$_3$ or *rac*-BINAP

| Terminal Reductant | X | Yield | dr |
|---|---|---|---|
| *i*-PrOH | $NO_2$ | 84% | 2:1 |
| *i*-PrOH | H | 82% | 2:1 |
| *i*-PrOH | MeO | 68% | 1:1 |
| $HCO_2H$ | $NO_2$ | 89% | 3:1 |
| $HCO_2H$ | H | 64% | 2:1 |
| $HCO_2H$ | MeO | 68% | 1:1 |

*i*-PrOH (400 mol %); $HCO_2H$ (200 mol %).

**Scheme 9.** Coupling of Dienes to Alcohols or Aldehydes via Ruthenium-Catalyzed Transfer Hydrogenation. *(Ref. 42a)*

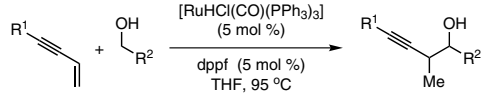
## 4. Hydrogenative Aldol and Mannich Additions

For well over a century, the aldol reaction has served as a core method in organic synthesis.[47] Intensive efforts have led to the realization of aldol addition protocols that enable excellent levels of diastereo- and enantiocontrol.[48] A particularly significant advance involves the refinement of methods for the direct asymmetric aldol additions of unmodified ketones employing metallic[49] or organic[50] catalysts. These byproduct-free processes herald a departure from the use of chiral auxiliaries and preformed enol(ate) derivatives. A significant limitation of these nascent technologies resides in the issue of regiocontrolled enolization. For example, direct catalytic asymmetric aldol additions of unsymmetrical ketones, such as 2-butanone, typically result in coupling at the less substituted enolizable position to furnish linear aldol adducts.[51]

The challenge of regiocontrolled enolization is overcome via enone reduction. Pioneering work by Stork demonstrates that dissolving metal reduction of enones enables regiospecific generation and capture of enolate isomers that cannot be prepared exclusively under standard conditions for base-mediated deprotonation.[52] Subsequently, catalytic reductive couplings of enones to aldehydes emerged.[53] To date, myriad metallic catalysts for "reductive aldol coupling" have been devised, including those based on rhodium,[54] cobalt,[55] iridium,[56] ruthenium,[57] palladium,[58] copper,[59,60] nickel,[61] and indium.[62,63] These protocols invariably employ metallic terminal reductants, such as stannanes, silanes, and organozinc reagents, which mandate the generation of stoichiometric byproducts. Inspired by the prospect of developing completely byproduct-free processes, catalytic reductive aldol additions employing elemental hydrogen as the terminal reductant were investigated.[64]

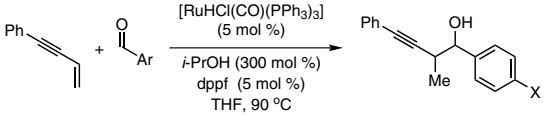
Our initial efforts centered on developing intramolecular reductive aldol couplings of tethered enone-aldehydes under hydrogenative conditions (**Scheme 12**).[64a] It was found that upon exposure to catalytic quantities of phosphine-modified cationic rhodium complexes under ambient pressures of hydrogen, a range of enone-aldehydes engage in highly diastereoselective cyclization to deliver five- and six-membered-ring products. In a similar fashion, enone-ketones cyclize to furnish *syn*-aldol adducts as single diastereomers.[64b] However, in these cases, the diminished electrophilicity of the ketone leads to substantial quantities of simple enone reduction product. Extension of this method to enone-diketone substrates provides a powerful desymmetrization strategy for the stereocontrolled generation of bicyclic frameworks bearing three contiguous stereocenters. The addition of aldehyde enolates to ketones, for which a single stoichiometric variant is known,[65] represents a highly challenging type of aldol addition. Under hydrogenative conditions, enal-ketones cyclize with a high degree of efficiency to provide products of aldehyde enolate-ketone addition, although competitive 1,4-reduction also is observed (**Scheme 13**).[64c]

Intermolecular hydrogenative aldol couplings also are possible. Under an atmosphere of hydrogen, cationic rhodium complexes catalyze the coupling of vinyl ketones to diverse aldehydes.[64a] Whereas the catalyst derived from $Rh(cod)_2OTf$ and triphenylphosphine provides aldol adducts as diastereomeric mixtures, high *syn*-diastereoselectivity is achieved using tri(2-furyl)phosphine as ligand.[64e,66] Under these modified conditions, a wide range of aldehydes couple to methyl or ethyl vinyl ketone with exceptional levels of *syn*-diastereoselectivity. Of note is the wide range of potentially "hydrogen-labile" functionality that is tolerated, thus enabling the use of substrates containing alkynes, alkenes, benzylic ethers, nitroarenes, and aryl bromides.



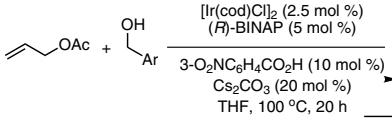

| $R^1$ | $R^2$ | Yield | dr |
|---|---|---|---|
| $TBSOCH_2$ | Ph | 78% | 1.5:1 |
| Ph | *a* | 63% | 1.5:1 |
| Ph | *n*-Pent | 72% | 2:1 |
| Ph | 1-Me-indol-2-yl | 94% | 1:1 |

[a] $R^2 = Me_2C{=}CH(CH_2)_2C(Me){=}CH$

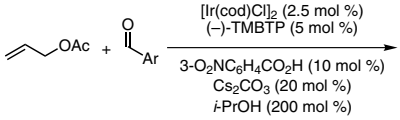



| X | Yield | dr |
|---|---|---|
| $NO_2$ | 61% | 1:1 |
| H | 74% | 1:1 |
| MeO | 91% | 1:1 |

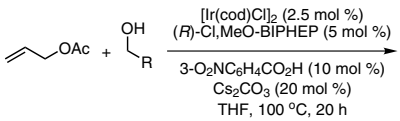
**Scheme 10.** Carbonyl Propargylation from the Alcohol or Aldehyde Oxidation Level via Ruthenium-Catalyzed Transfer-Hydrogenative Coupling of 1,3-Enynes. *(Ref. 43)*




| Ar | Yield | ee |
|---|---|---|
| $4\text{-}BrC_6H_4$ | 74% | 93% |
| 1-Me-indol-2-yl | 55% | 90% |
| $2\text{-}MeOC_6H_4$ | 80% | 92% |
| $3,4\text{-}(OCH_2O)C_6H_3$ | 76% | 91% |

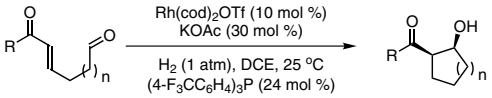



| Ar | Yield | ee |
|---|---|---|
| $4\text{-}BrC_6H_4$ | 77% | 97% |
| 1-Me-indol-2-yl | 82% | 94% |
| $2\text{-}MeOC_6H_4$ | 86% | 95% |
| $3,4\text{-}(OCH_2O)C_6H_3$ | 83% | 94% |



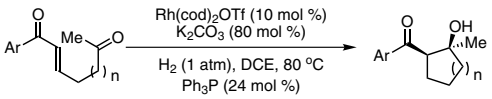

| R | Yield | ee |
|---|---|---|
| $BnO(CH_2)_3$ | 78% | 95% |
| $BnOCH_2C(Me_2)$ | 63% | 93% |
| *n*-Oct | 78% | 95% |
| *trans*-PhCH=CH | 72% | 91% |

**Scheme 11.** Enantioselective Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level via Iridium-Catalyzed Transfer-Hydrogenative Coupling of Allyl Acetate. *(Ref. 46b)*




| R | n | Yield | syn:anti | 1,4[a] |
|---|---|---|---|---|
| Ph | 1 | 71% | 24:1 | 1% |
| Ph | 2 | 89% | 10:1 | 0.1% |
| Me | 2 | 65% | 1:5 | — |
| thien-2-yl | 2 | 76% | 19:1 | 2% |

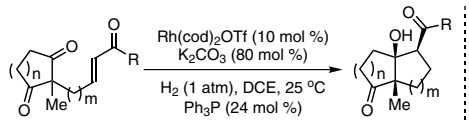
[a] Yield of the 1,4-reduction product.




| Ar | n | Yield[a] | 1,4[b] |
|---|---|---|---|
| 2-Np | 1 | 74% | 18% |
| 2-Np | 2 | 78% | 18% |
| thien-2-yl | 1 | 66% | 24% |
| thien-2-yl | 2 | 78% | 8% |

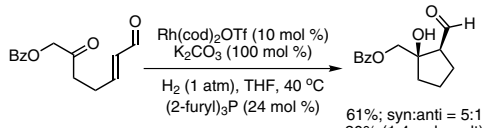
[a] In all cases, syn:anti >95:5. [b] Yield of the 1,4-reduction product.

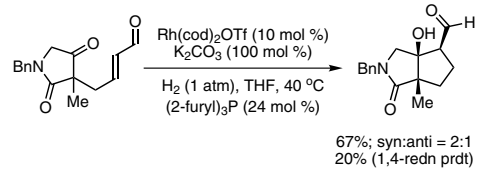
**Scheme 12.** Reductive Aldol Cyclization via Catalytic Hydrogenation. *(Ref. 64a,b)*




| m | n | R | Yield[a] |
|---|---|---|---|
| 1 | 1 | Ph | 84% |
| 2 | 1 | Ph | 86% |
| 2 | 2 | Ph | 65%[b] |
| 1 | 2 | Me | 73% |

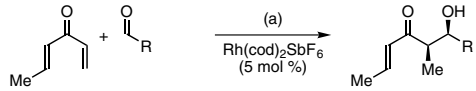
[a] In all cases, syn:anti aldol >95:5. [b] 15% of the 1,4-redn prdt observed.



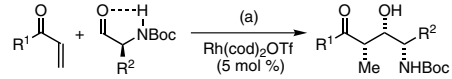




**Scheme 13.** Reductive Aldol Cyclization via Catalytic Hydrogenation. *(Ref. 64b,c)*


| R1 | R2 | Yield | syn:anti |
|---|---|---|---|
| Me | 4-O2NC6H4 | 91% | 16:1 |
| Et | 4-O2NC6H4 | 90% | 28:1 |
| Me | BnOCH2 | 90% | 17:1 |
| Et | BnOCH2 | 88% | 18:1 |
| Me | PhC≡C | 65% | 8:1 |
| Et | PhC≡C | 70% | 10:1 |
| Me | PhtNCH2 | 95% | 50:1 |
| Et | PhtNCH2 | 97% | >99:1 |




| R | Yield | syn:anti |
|---|---|---|
| 4-O2NC6H4 | 82% | 13:1 |
| BnOCH2 | 80% | 9:1 |
| 6-Br-pyridin-2-yl | 94% | 11:1 |
| PhtNCH2 | 85% | 13:1 |

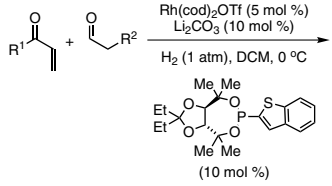



(a) $Li_2CO_3$ (10 mol %), $H_2$ (1 atm), DCM, 25 °C, $(2\text{-furyl})_3P$ (12 mol %)

| R1 | R2 | Yield |
|---|---|---|
| Et | Bn | 91% |
| Me | TBDPSOCH2 | 78% |
| Et | TBDPSOCH2 | 91% |
| Me | Bn | 84% |

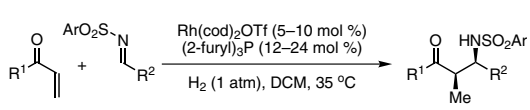
In all cases, dr ≥ 20:1.

**Scheme 14.** *syn*-Diastereoselective Hydrogen-Mediated Aldol Coupling Employing Cationic Rhodium Catalysts Ligated By Tri(2-furyl)phosphine. *(Ref. 64e–g)*




| R1 | R2 | Yield | syn:anti | ee (syn) |
|---|---|---|---|---|
| Me | BnO | 85% | 25:1 | 91% |
| Me | PhtN | 88% | 50:1 | 96% |
| Et | 1-Me-indol-3-yl | 97% | 25:1 | 90% |
| Et | Ph | 76% | 22:1 | 90% |

**eq 1** *(Ref. 64h)*




| R1 | R2 | Yield | syn:anti |
|---|---|---|---|
| Et | 4-O2NC6H4 | 80% | 7:1 |
| Me | 3,4-Cl2C6H3 | 67% | 9:1 |
| Et | 5-O2N-furan-2-yl | 83% | 4:1 |
| Me | 4-F3CC6H4 | 71% | 6:1 |

**eq 2** *(Ref. 67)*

Furthermore, functionalized enones also are tolerated, as demonstrated by the employment of crotyl vinyl ketone.[64f] Remarkably, the essentially neutral reaction conditions permit aldol coupling of configurationally sensitive *N*-Boc-α-amino aldehydes without racemization. Here, high levels of anti-Felkin–Anh control are achieved by taking advantage of hydrogen-bonded chelates, which arise in reaction media with low dielectric constants (**Scheme 14**).[64g]

The ability to access *syn*-aldol adducts relevant to polyketide synthesis inspired further efforts toward enantioselective variants. π-Acidic monodentate phosphine ligands are required to enforce high levels of diastereoselectivity and catalytic turnover. However, commercially available phosphines of this type (e.g., phosphoramidites and BINOL-derived phosphites) give rise to inactive rhodium complexes, suggesting a very narrow window in terms of ligand π acidity. Consequently, the design of an effective chiral monodentate phosphorus-based ligand was undertaken. The versatility of TADDOL-like phosphonites enabled the determination of key structure–selectivity trends, ultimately leading to the design of an effective ligand. Thus, by simply exposing methyl or ethyl vinyl ketone to aldehydes under an atmosphere of gaseous hydrogen in the presence of the rhodium phosphonite complex, aldol addition occurred with high levels of relative and absolute stereocontrol. This method generates optically enriched polyketide substructures and circumvents the stoichiometric generation of byproducts (**eq 1**).[64h]

Based on the preceding results, reductive Mannich couplings of vinyl ketones were explored.[67] Previously, reductive Mannich couplings had been accomplished using silane,[68] the Hantzsch ester,[69] or diethylzinc[70] as the terminal reductant. Under hydrogenative conditions employing a tri(2-furyl)phosphine-ligated rhodium catalyst, vinyl ketones couple to *N*-(*o*-nitrophenyl)sulfonyl aldimines to furnish the desired Mannich addition products with good levels of *syn*-diastereoselectivity (**eq 2**).[67] These preliminary studies suggest the feasibility of developing asymmetric variants of this transformation.

## 5. Future Directions

The stereoselective vinylation, allylation, and enolate addition of carbonyl compounds rank among the most broadly utilized methods in organic synthesis. Traditional protocols have relied upon the use of organometallic reagents, which are often basic, moisture sensitive, and give rise to stoichiometric quantities of metallic byproducts. Inspired by alkene hydroformylation and the parent Fischer–Tropsch reaction, hydrogenative variants of classical carbonyl addition processes are aimed at meeting the environmental, economic, and health and safety ideals set by Green Chemistry. For the hydrogenative protocols, carbonyl and imine addition occurs under essentially neutral conditions simply upon exposure of an unsaturate–electrophile pair to gaseous hydrogen in the presence of a metal catalyst. Accordingly, vinylation, allylation, and enolate addition are achieved without stoichiometric byproduct generation and with stereoselectivities often surpassing traditional methods. The discovery of related transfer-hydrogenative couplings not only evades the stoichiometric generation of metallic byproducts, but also the requirement for substrate oxidation level adjustment. The ability to perform carbonyl addition from either the aldehyde or alcohol oxidation level has broad implications for the field of organic synthesis. These nascent reactivity modes should serve as the basis for innumerable byproduct-free alcohol–unsaturate and amine–unsaturate coupling processes.

## 6. Acknowledgments

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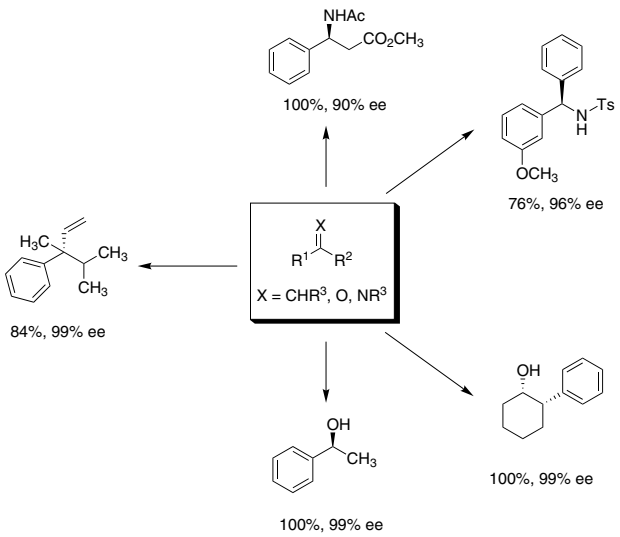
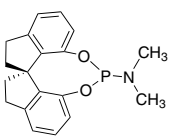
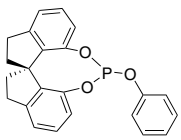
Asymmetric hydrogenation is playing a major role in the creation of chiral centers, and is widely used on a research and industrial production scale. Some of the most common ligands for asymmetric hydrogenation are $C_2$-symmetrical phosphines, of which the most notable ones are BINAP, DIPAMP, or TADDOL. Zhou and co-workers have developed a new type of $C_2$-symmetrical ligand with 1,1′-spirobi-indane as backbone, and which offers higher enantiocontrol. It has shown excellent reactivity and selectivity in a variety of asymmetric hydrogenations. Aldrich is pleased to offer a library of these new ligands.



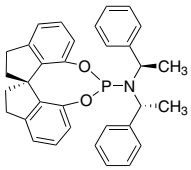

(1) Xie, J.–H. et al. *J. Am Chem. Soc.* **2003**, *125*, 4404. (2) Fu, Y. et al. *J. Org. Chem.* **2004**, *69*, 4648. (3) Xie, J.–H. et al. *J. Org. Chem.* **2005**, *70*, 2967. (4) Shi, W.–J. et al. *J. Am. Chem. Soc.* **2006**, *128*, 2780. (5) Duan, H.–F. et al. *Org. Lett.* **2006**, *8*, 1479. (6) Duan, H.–F. et al. *Org. Lett.* **2006**, *8*, 2567.



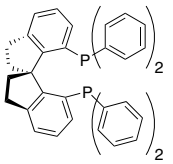
(*R*)-SIPHOS
**700797**
(*S*)-SIPHOS
**700789**



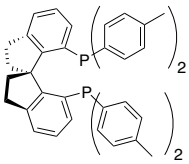
(*R*)-ShiP
**700800**
(*S*)-ShiP
**700819**



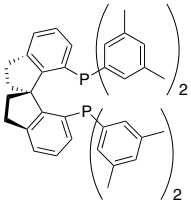
(*R*)-SIPHOS-PE
**700770**
(*S*)-SIPHOS-PE
**700762**



(*R*)-SDP
**700754**
(*S*)-SDP
**700746**



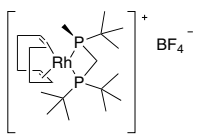
(*R*)-Tol-SDP
**700827**
(*S*)-Tol-SDP
**700835**



(*R*)-Xyl-SDP
**700843**
(*S*)-Xyl-SDP
**700851**

## *Asymmetric Hydrogenation of α-Acetamido Dehydroamino Acids*

The importance of asymmetric hydrogenation is highlighted by the everyday use of this transformation in industry. The most common chiral ligands used for these reactions have $C_2$-symmetry. Hoge et al. have developed a new chiral ligand with a $C_1$-symmetry and used it with rhodium for the asymmetric hydrogenation of α-acetamido dehydroamino acids. Excellent selectivity was observed in the hydrogenation of a variety of α-acetamido dehydroamino acids.

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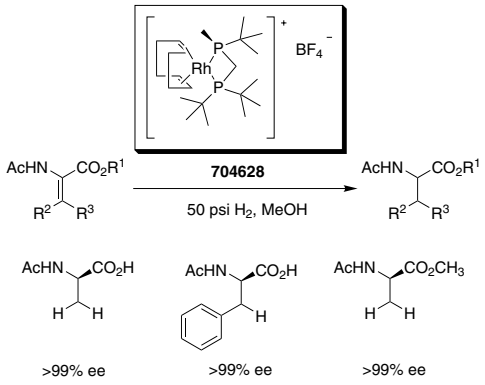
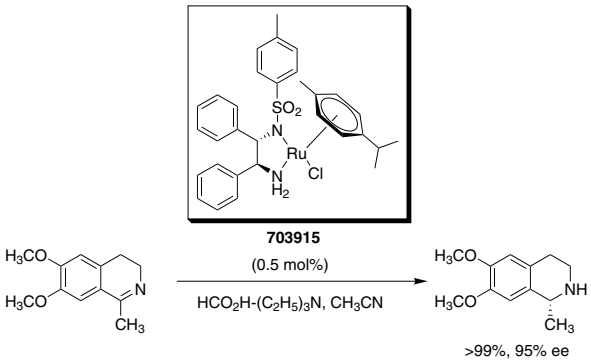


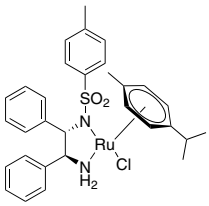

Hoge, G. et al. *J. Am. Chem. Soc.* **2004**, *126*, 5966.

## *Asymmetric Transfer Hydrogenation of Imines*

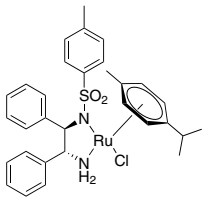
The use of transfer hydrogenation to reduce alkenes, carboxyl groups, or imines is becoming an increasingly attractive procedure. Uematsu et al. reported the asymmetric transfer hydrogenation of a variety of imines using a chiral diamine ligand complexed with ruthenium. A low loading of the catalyst is sufficient, and good yields and excellent stereoselectivities are observed.




Uematsu, N. et al. *J. Am. Chem. Soc.* **1996**, *118,* 4916.



RuCl(*p*-cymene)[(*S,S*)-Ts-DPEN]
**703915**



RuCl(*p*-cymene)[(*R,R*)-Ts-DPEN]
**703907**

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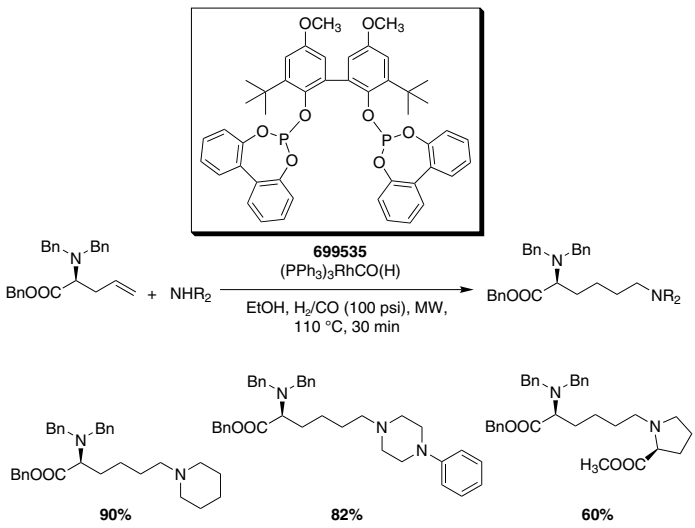
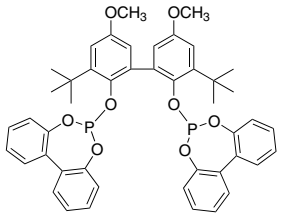
## *Hydroaminomethylation of Alkenes*

The direct hydroamination of terminal alkenes is an interesting reaction due to its atom economy. However, only a few groups have taken advantage of this reaction. Petricci et al. reported the hydroamination of alkenes using BiPhePhos with a rhodium complex under microwave irradiation. Using this technique resulted in high conversion and selectivity, and reduced the reaction time.



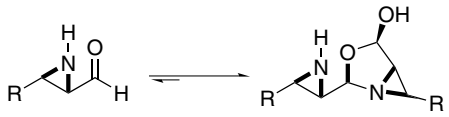

Petricci, E. et al. *Tetrahedron Lett.* **2008**, *48*, 8501.



BiPhePhos
**699535**

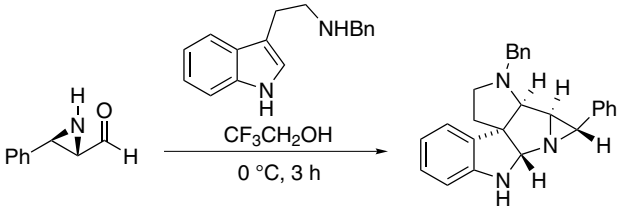
# Discover Unprotected Amino Aldehydes from Professor Yudin

Professor Andrei Yudin and co-workers have recently described the preparation of bench-stable, unprotected α-amino aldehydes.[1] These kinetically amphoteric molecules exist as dimers, and due to the strain of the aziridine ring, resist inter- and intramolecular iminium ion formation. Furthermore, the two functionalities remain orthogonal to each other throughout their transformations, allowing for the reaction of the aldehyde without the requirement of an additional protecting group.



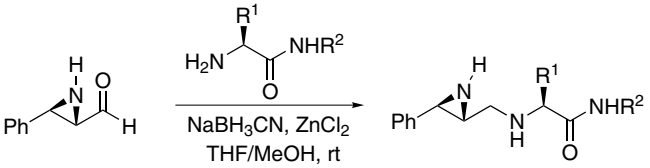
Whereas the reductive amination of protected amino aldehydes has significant limitations due to epimerization or overalkylation, these Yudin amino aldehyde dimers do not suffer from either limitation, due to a negligible concentration of free aldehyde during the reaction. This allows the researcher facile access to a method for the creation of complex polycyclic skeletons[2] or peptidomimetic conjugates[3] with a high degree of stereocontrol. Nucleophilic additions,[4] Wittig and related olefination reactions can be carried out with high selectivities and yields. Sigma-Aldrich is pleased to offer these useful Yudin amino aldehydes for your research.

## *Cascade Polycyclizations*



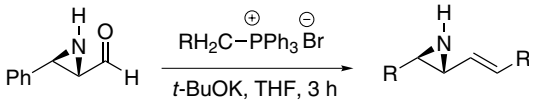

97%

## *Synthesis of Peptidomimetic Conjugates Without Protecting Groups*



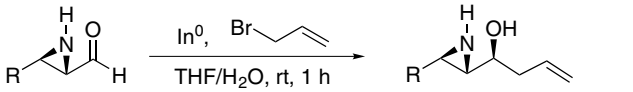

75 - 86%

## *Unprotected Vinyl Aziridines via Olefination*

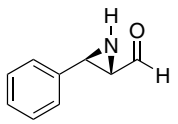



70-95%

## *Unprotected Vicinal 1,2-Amino Alcohols via Allylation with Indium Reagents*




81-96%
>99% diastereoselectivity



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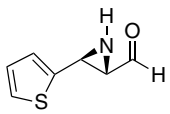

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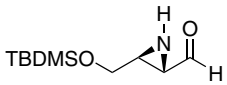


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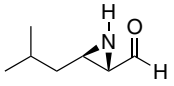

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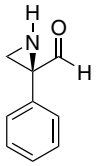

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(1) Hili, R.; Yudin, A. K. *J. Am. Chem. Soc.* **2006**, *128*, 14772. (2) Yudin, A. K.; Hili, R. *Chem.—Eur. J.* **2007**, *13*, 6538. (3) Li, X.; Yudin, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 14152. (4) Hili, R.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 4188.

# Amino Carbonyl Compounds in Organic Synthesis


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Mr. Ryan Hili


Professor Andrei K. Yudin

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## Outline

1. Introduction
   1.1. Involvement of Amino Carbonyl Compounds in Biosynthesis
   1.2. Physical Properties of Amino Carbonyl Compounds
2. Preparation of Amino Aldehydes and Amino Ketones
   2.1. α-Amino Aldehydes and Ketones
   2.2. β-Amino Aldehydes and Ketones
   2.3. γ-Amino Aldehydes and Ketones
   2.4. Miscellaneous Amino Aldehydes and Ketones
3. Applications of Amino Carbonyl Compounds in Organic Synthesis
   3.1. Selected Examples from Natural Product Synthesis
   3.2. Applications as Building Blocks in the Pharmaceutical Industry
   3.3. Applications in Biochemistry and Chemical Biology
4. Conclusions
5. References
6. Notes Added in Proof

## 1. Introduction

Amino aldehydes and amino ketones, $R^1C(=O)(CH_2)_nCHR^2NHR^3$, are versatile building blocks that are indispensable in the synthesis of natural products and pharmaceuticals. Their utility stems from the broad scope of synthetic transformations available to both the amino and carbonyl functional groups. However, the utility of amino aldehydes and ketones is not without shortcomings, as nitrogen- or carbon-protecting groups are usually needed in order to prevent undesired inter- and intramolecular self-condensation reactions. While serving to prevent these undesired processes, nitrogen protection can also have a detrimental effect on subsequent transformations of the carbonyl group. This review focuses on recent advances in the field of amino carbonyl chemistry.

### *1.1. Involvement of Amino Carbonyl Compounds in Biosynthesis*

The versatility of amino carbonyl compounds is amply represented in complex alkaloid biosynthesis. Exquisitely tuned enzymatic cascades have evolved to handle the chemically incompatible carbonyl and amine functionalities. The biosynthesis of retronecine[1] is an instructive case: at least two points in its biosynthetic cascade incorporate transiently formed intermediates with a 1,5-aldehyde–amine relationship. Another well-known case is that of morphine (**1**), an archetypal opioid exhibiting potent analgesic effects on the central nervous system (**Figure 1, Part A**). The biosynthetic pathway to morphine involves stable amino carbonyl compounds such as neopinone and codeinone. The semi-synthetic opioid noroxymorphone (**2**), which contains a demethylated nitrogen, is also stable and has been used as an intermediate in the synthesis of other opioid receptor agonists.[2] Amino sugars belong to yet another class of naturally occurring amino carbonyl compounds. These molecules are important constituents of glycoproteins and glycolipids and are implicated in a vast range of cellular recognition events. Among the most commonly encountered monoaminosaccharides are glucosamine, *N*-acetylglucosamine, galactosamine, and *N*-acetylgalactosamine (**Figure 1, Part B**). Some of the most widely used antibiotics including vancomycin, erythromycin, and streptomycin contain amino sugar substituents.

### *1.2. Physical Properties of Amino Carbonyl Compounds*

The first documented attempt at a chemical synthesis of an unprotected α-amino aldehyde was made by Fischer and Leuchs in 1903 when they reported the synthesis of *d*-glucosamine.[3] Although the aldehyde functionality in this molecule is masked as a hemiacetal, the equilibrium with an open-chain form predisposes glucosamine to self-condensation reactions. Therefore, this molecule is only stable in the salt form. Fischer later attempted to synthesize glycinal, which could not be isolated and was characterized through degradation studies. Almost a century later, Myers and co-workers demonstrated that α-amino aldehydes are autoprotective at acidic pH, whereby the amine group is present as the strongly electron-withdrawing ammonium ion and the aldehyde group exists as its tetrahedral solvent adduct.[4]

In chemical synthesis, the innate incompatibility between amine and aldehyde functionalities has been circumvented through the use of protecting groups. Protected α-amino aldehydes are relatively unstable, both chemically and configurationally, particularly in solution or in the course of chromatographic purification. The enantiomeric integrity of α-amino aldehydes largely depends on their structure, especially in terms of inter- or intramolecular stabilization.[5] Ito et al. undertook a comprehensive study of the loss of enantiomeric purity of N-protected α-amino aldehydes during chromatography on silica gel.[5] The

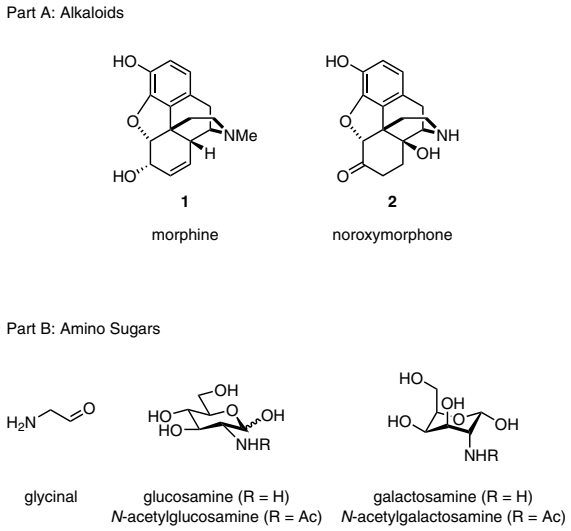
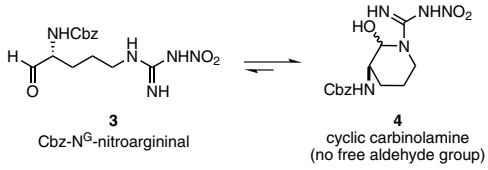
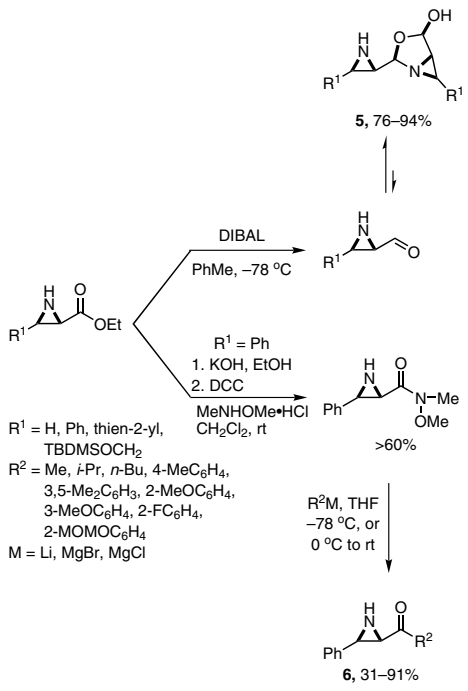



**Figure 1.** Alkaloids (Part A) and Amino Sugars (Part B) That Are Available Biosynthetically from Amino Carbonyl Compounds. *(Ref. 2,3)*




**eq 1** *(Ref. 5)*




**Scheme 1.** Preparation of Unprotected α-Amino Carbonyl Compounds from Aziridine-2-carboxylates. *(Ref. 10)*

configurational stability of α-amino aldehydes on silica gel decreases in the following order: Cbz-*S*-Bzl-L-cysteinal >> Cbz-phenylalaninal > Cbz-leucinal >> Cbz-N$^G$-nitroargininal. The capacity of **3** to cyclize into hemiaminal **4** significantly impedes the racemization process (**eq 1**).[5] It is by this cyclization that the configurational stability of *Z*-*N*-nitro-L-argininal is maintained. The enantiomeric integrity of α-amino aldehydes can also be preserved by masking the aldehyde in either imidazolidine or acetal form.[6] These valuable intermediates can be purified by chromatography. In some cases, low temperatures may suffice for brief storage of unstabilized N-protected amino aldehydes.[7]

C-Protected amino aldehydes in which the amino group is free and the aldehyde is masked have been much less explored.[8] The carbonyl group of amino aldehydes can be protected as an acetal or an amino nitrile. C-Protected amino aldehydes have served as strategic precursors in the synthesis of saframycin A and its analogues.[9]

## 2. Preparation of Amino Aldehydes and Amino Ketones

The development of stable, unprotected amino carbonyl compounds has been a challenge in organic synthesis, not only from the standpoint of atom economy, but also from the standpoint of avoiding racemization. A few recent examples of stable, unprotected amino carbonyl compounds have been disclosed. Our group has described the preparation of unprotected α-amino aldehydes and ketones such as **5** and **6** from aziridine-2-carboxylate esters.[10] The α-amino aldehydes exist as dimers, whereas the corresponding ketones are monomeric compounds. Their stability is attributed to the increase in ring strain that would have accompanied self-condensation via iminium ion formation. For a similar reason, the α center of aziridine carbonyl compounds is not epimerizable (**Scheme 1**).

### *2.1. α-Amino Aldehydes and Ketones*

Garner's aldehyde,[11] Reetz's *N,N*-dibenzyl and *N*-benzyl aldehydes,[12] as well as N-monoprotected and N,N-diprotected amino aldehydes are among the most widely utilized amino aldehyde derivatives.[13] Their general synthesis is outlined in **Scheme 2**. The most commonly used method is the reduction of carboxylic acid esters by diisobutylaluminum hydride (DIBAL), but in many cases over-reduction to the respective alcohol has been observed. In a few cases, the reduction with DIBAL can lead to erosion of enantiomeric purity by as much as 15%. However, DIBAL reduction of *N*-Boc amino acids, commonly used in peptide chemistry, gives the corresponding aldehydes without appreciable racemization. The alcohol is generally obtained through initial reduction of the corresponding α-amino acid or ester, which is then followed by oxidation. The final step can be carried out using a wide range of methods including Swern, Dess–Martin, or Parikh–Doering oxidations.

Weinreb amides are very useful in the preparation of α-amino aldehydes and ketones due to the fact that over-reduction and racemization are not observed (**Scheme 3**). These intermediates can be reduced to the aldehydes[14] in the presence of $LiAlH_4$, $LiAl(t\text{-}BuO)_3H$, or lithium tris[(3-ethyl-3-pentyl)oxy]aluminum hydride (LTEPA). A wide range of N-protecting groups are stable under these conditions. A kilogram-scale preparation of an α-amino aldehyde was reported by Schwindt et al. using sodium bis(2-methoxyethoxy)aluminum hydride (Vitride® or Red-Al®).[14d] This is an attractive alternative to other methods of reduction and a useful way to synthesize ketones,[15] including pentafluoroethyl ketones,[15a] and β-ketophosphonates.[15b]

The catalytic enantioselective α amination of aldehydes is a recent approach to the synthesis of α-amino aldehydes.[16] The research groups of List[17] and Jørgensen[18] independently developed the enantioselective synthesis of α-amino aldehydes by using the L-proline-catalyzed α amination of aldehydes (**eq 2**). This direct C–N-bond-forming reaction affords high levels of enantioselectivity in the formation of a stereogenic α-carbon center. Thus, propanal (**7**, $R^1$ = Me) reacts with diethyl azodicarboxylate (**8**, $R^2$ = Et) in the presence of L-proline as catalyst to give the corresponding amination product, **9**, in 93% yield and 92% ee. The reaction proceeds with low catalyst loadings and can be performed on a gram scale with high yields and enantioselectivities. The main drawback to this approach is that the products formed by the direct α amination of aldehydes display a gradual decrease in enantiomeric purity because of the acidity of the α proton. In addition, cleavage of the N–N bond requires harsh conditions.

As previously mentioned, enantiopure α-amino ketones have been prepared by reaction of organolithium and Grignard reagents with suitably N-protected α-amino acid derivatives. Recently, the catalytic asymmetric amination of ketones has become prominent in the synthesis of α-amino ketones. Johnson and co-workers[19] reported an enantioselective addition of acylsilanes to nitrone electrophiles in the presence of metallophosphite ligands. The key requirement for this reaction is an energetically accessible pathway for silyl transfer (**eq 3**).

Hashimoto and co-workers have reported a catalytic, enantioselective amination of silyl enol ethers with [*N*-(2-nitrophenylsulfonyl)imino]phenyliodinane in the presence of dirhodium(II) catalyst **10**.[20] The chiral amino ketone obtained by this method has been employed in the formal synthesis of (–)-metazocine, a benzomorphan analgesic (**Scheme 4**). Osmium-catalyzed ketamination of alkenes was developed by Muñiz into an efficient route to α-amino ketones.[20b]

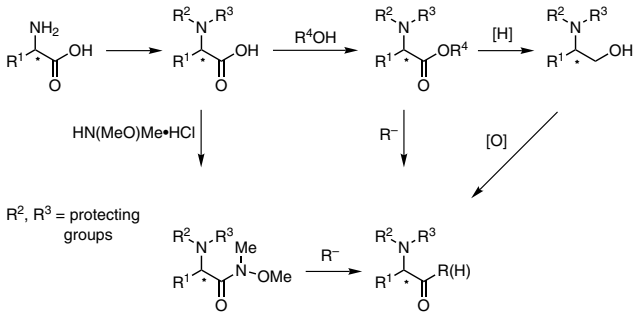
Mattson and Scheidt[21] have reported the synthesis of amino ketone **13** by reaction of acylsilanes **11** with imines **12** in the presence of carbene catalysts, which are generated in situ from readily available thiazolium salts. Furthermore, the authors showed that this method tolerates a wide range of acylsilanes and imines (**eq 4**).

Davis and co-workers[22] have described an effective way to synthesize C- and N-protected amino ketones from sulfinimines **14** with the aid of lithio-1,3-dithianes. α-Amino-1,3-dithioketals **16** and *N*-sulfinyl-α-amino ketones **17** were obtained after selective removal of the sulfinyl and thioketal groups, respectively (**Scheme 5**). This approach was employed in the asymmetric synthesis of (2*S*,3*R*)-(–)-3-hydroxy-3-methylproline (**18**), a poly-oxypeptin amino acid.

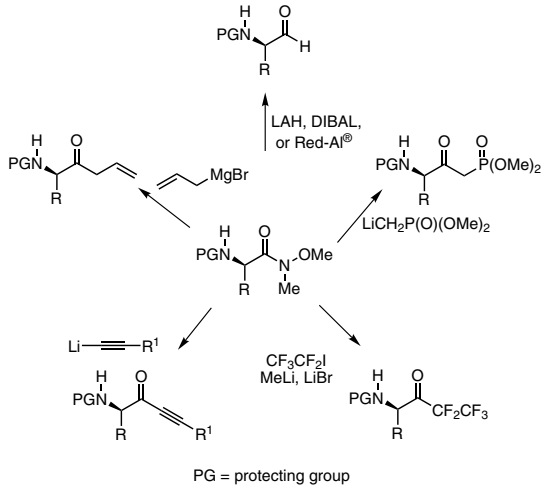
The organocatalytic asymmetric Mannich reaction is an efficient method for the synthesis of amino ketones. Recently, Barbas and co-workers[23] reported the synthesis of chiral 1,2- and 1,4-diamines **19** and **20** from azido ketones and phthalimido ketones, respectively, in the presence of an L-proline-derived tetrazole catalyst. Enantioselectivities of up to 99% have been achieved. The regioselectivity was found to depend on the nitrogen protecting group (**Scheme 6**).

## 2.2. β-Amino Aldehydes and Ketones

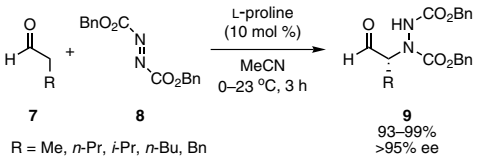
β-Amino acids are less abundant in nature than the corresponding α-amino acids. However, they do play important biological roles and have considerable potential for the stabilization of peptide-based drugs against proteolytic degradation. In general, β-amino aldehydes are not stable due to polymerization, self-condensation,



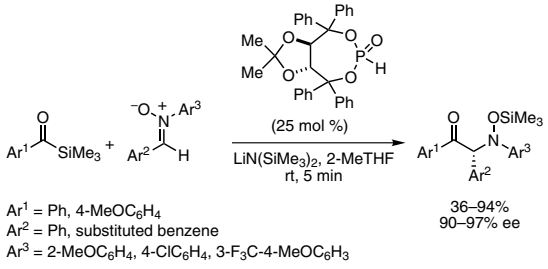

**Scheme 2.** General Synthesis of α-Amino Aldehydes and Ketones.



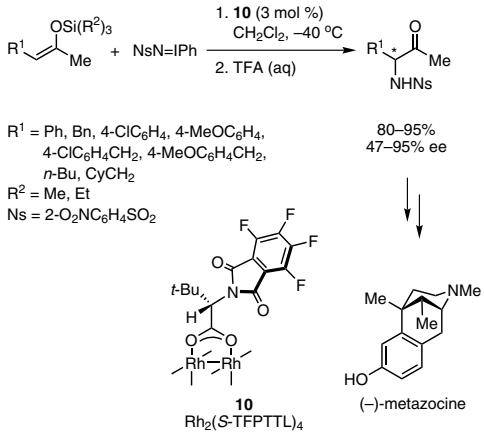

**Scheme 3.** α-Amino Carbonyl Compounds from Weinreb Amides. *(Ref. 14,15)*



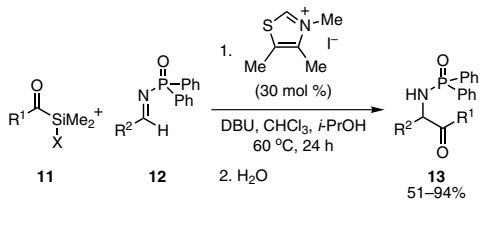

**eq 2** *(Ref. 17)*



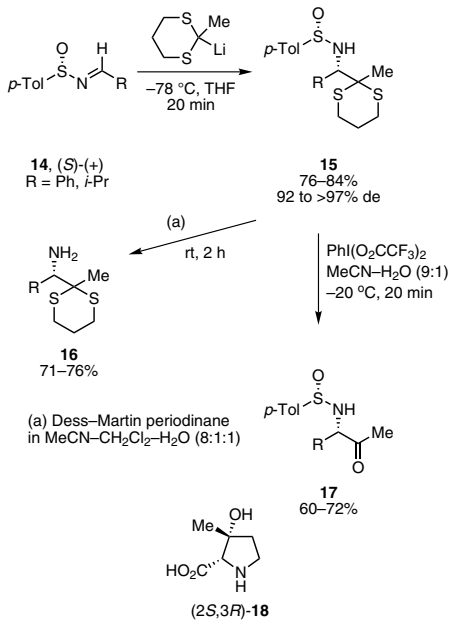

**eq 3** *(Ref. 19)*




**Scheme 4.** Chiral α-Amino Ketones by the Enantioselective Amination of Silyl Enol Ethers. *(Ref. 20)*




**eq 4** *(Ref. 21)*




**Scheme 5.** C- and N-Protected α-Amino Ketones from Sulfinimines. *(Ref. 22)*

or elimination of the β-amino group.[24] While one can obtain the β-amino carbonyl compounds from the corresponding α-amino acids, the most common approach toward their synthesis is to utilize Mannich-type reactions (**Scheme 7**).[25] This approach suffers from difficulties in controlling both the regio- and stereoselectivity. Some improvements have been made through the employment of Brønsted acids,[26] cinchona alkaloids,[27] phase-transfer catalysts,[28] metal catalysts,[29] and modified organocatalysts.[30]

List reported the proline-catalyzed asymmetric and diastereoselective Mannich reaction in 2000.[31] Recently, Barbas's[32] and Maruoka's[33] groups independently developed an efficient way to synthesize β-amino aldehydes through the direct, catalytic, and asymmetric anti-Mannich reaction. The reaction was catalyzed by chiral amino acids and amino sulfonamide ligands (**Scheme 8**). MacMillan and co-workers reported an efficient organocatalytic approach to β-amino aldehyde derivatives using the asymmetric conjugate addition of protected hydroxylamines to α,β-unsaturated aldehydes.[34]

3-Aminopropanoic acids bearing a single substituent at C-2 are classified as $\beta^2$-amino acids and are found in natural products exhibiting important biological activities.[35] Gellman and co-workers reported the synthesis of $\beta^2$-amino acids by the proline-catalyzed diastereoselective aminomethylation of aldehydes (**Scheme 9**).[36] A similar type of methodology has been described by Córdova's group.[37]

Recently, Davis and Song reported the synthesis of syn α-substituted β-amino ketones from chiral sulfinimines and prochiral Weinreb amide enolates, and highlighted their application in the synthesis of chiral amino acids, amino alcohols, ketones, and lactams (**eq 5**).[38]

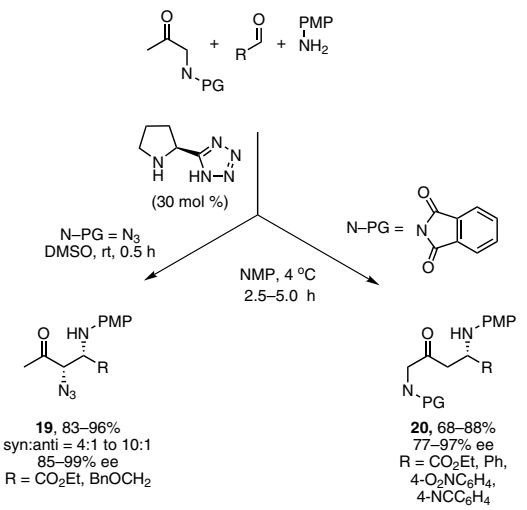
In 2000, Gomtsyan disclosed a direct synthesis of β-amino ketones.[39] Vinylmagnesium bromide was added to amides such as **21**, followed by addition of water to give β-amino ketones **22** in good yields. This procedure worked well for a variety of substituents such as aryl, heteroaryl, and alkyl groups, with the electronic nature of the substituents having little effect on the outcome of the reaction (**eq 6**).

Shibasaki's group reported that imines equipped with a diphenylphosphinoyl (dpp) group on nitrogen can selectively furnish either *anti*- or *syn*-β-amino alcohols.[29c] Similarly, Trost and co-workers have reported the synthesis of *anti*- or *syn*-α-hydroxy-β-amino ketones by a direct, catalytic asymmetric Mannich-type reaction using a dinuclear zinc catalyst, whereby the selectivity was governed by the judicious choice of the protecting group (**Scheme 10**).[40]

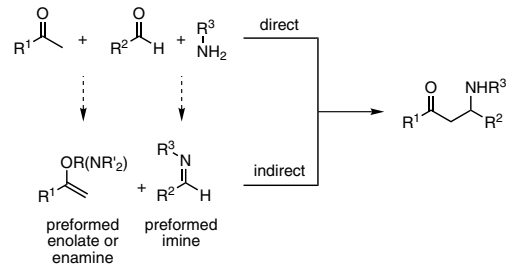
## 2.3. γ-Amino Aldehydes and Ketones

The synthesis of γ-amino ketones and aldehydes is not as developed as that of the corresponding α- and β-amino compounds. Nevertheless, γ-amino ketones are useful intermediates for the synthesis of five-membered-ring heterocycles.[41] Sato and co-workers[42] reported the synthesis of chiral γ-amino aldehydes and their application in the synthesis of γ-amino acids, pyrrolidinoisoquinolines, and a key intermediate in the synthesis of batzelladine D (**Scheme 11**). Carreira and co-workers developed an elegant approach to β-amino ketones via zinc-mediated reductive scission of 2,3-dihydroisoxazoles.[42b] A "redox-neutral" synthesis of β-amino aldehydes from imines by an alkynylation–hydration sequence was reported by Bolm and co-workers.[42c]

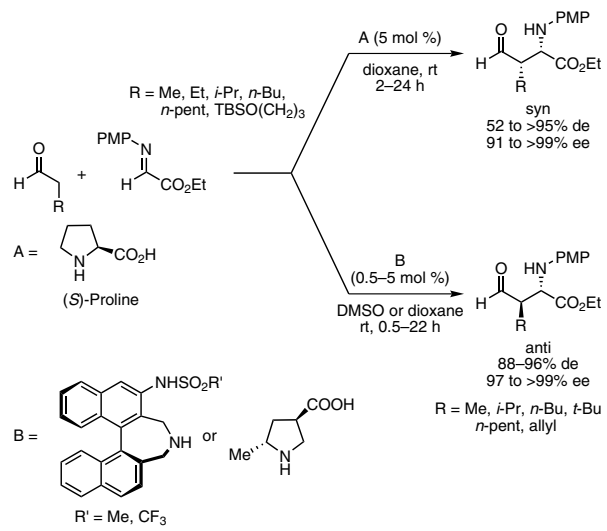
Ma and co-workers[43] outlined the synthesis of γ-amino-β-hydroxy-[44] and γ-amino-α,β-dihydroxy ketones in moderate-



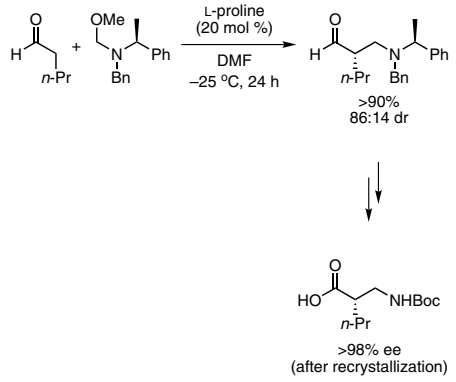

**Scheme 6.** Amino Ketones by the Organocatalytic Asymmetric Mannich Reaction. *(Ref. 23)*



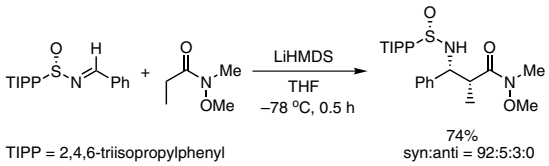

**Scheme 7.** Mannich-Type Reactions in the Synthesis of β-Amino Carbonyl Compounds. *(Ref. 25)*



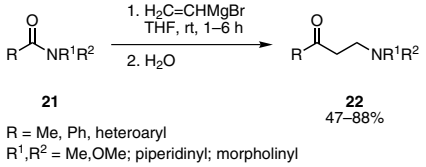

**Scheme 8.** Preparation of β-Amino Aldehydes by the Catalytic, Asymmetric anti-Mannich Reaction. *(Ref. 30g,32,33)*



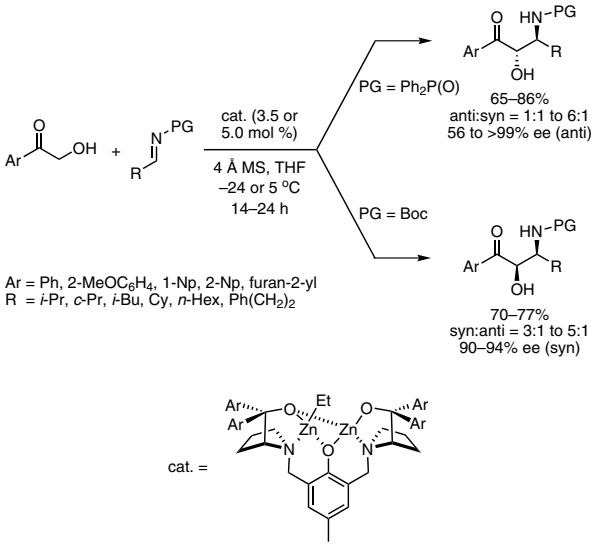

**Scheme 9.** β²-Amino Acids by the Diastereoselective Aminomethylation of Aldehydes. *(Ref. 36)*



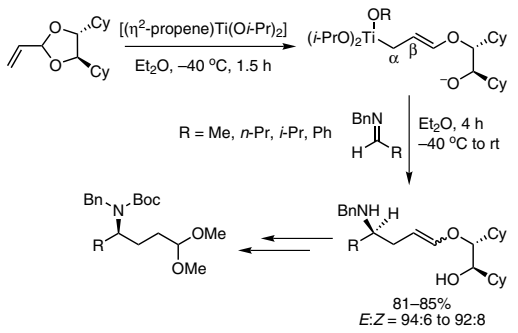

**eq 5** *(Ref. 38)*



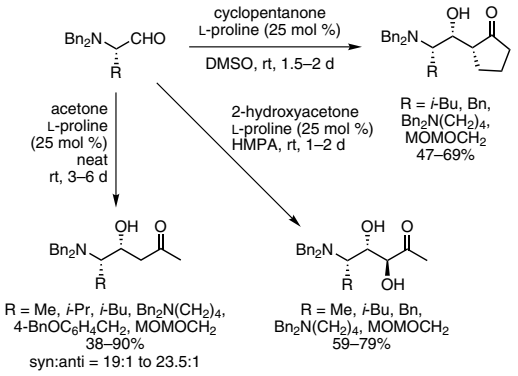

**eq 6** *(Ref. 39)*



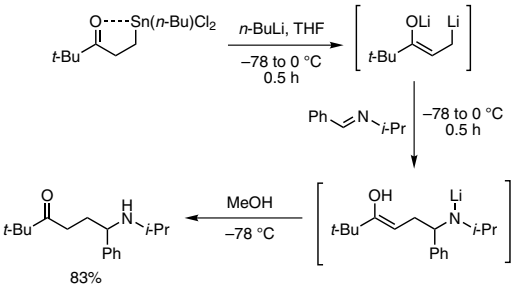

**Scheme 10.** Trost's Diastereoselective Synthesis of α-Hydroxy-β-amino Ketones. *(Ref. 40)*



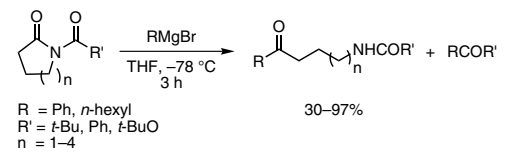

**Scheme 11.** Sato's Synthesis of Chiral γ-Amino Aldehydes. *(Ref. 42)*




**Scheme 12.** Ma's Synthesis of γ-Amino Ketones. *(Ref. 43)*




**Scheme 13.** Ryu's Synthesis of γ-Amino Ketones *(Ref. 45)*




**eq 7** *(Ref. 46)*

to-excellent yields and diastereoselectivities. The reaction was performed in the presence of L-proline to catalyze the direct aldol reaction of L-amino acid derived *N,N*-dibenzylamino aldehydes with ketones including acetone, cyclopentanone, and hydroxyacetone (**Scheme 12**).

Ryu[45] and co-workers reported a route to a variety of γ-amino ketones involving the reaction of ketone dilithio α,β-dianions with imines or hydrazones. The dianions were prepared from β-(dichloro(*n*-butyl)stannyl) ketones using excess *n*-BuLi. The enolates added to the imines to selectively form *Z* enolates containing a lithium amide. The *Z* enolates were then transformed into γ-amino ketones and related compounds through reaction with subsequently introduced electrophiles (**Scheme 13**).

### 2.4. Miscellaneous Amino Aldehydes and Ketones

Savoia and co-workers[46] reported the synthesis of ω-amino ketones[47] from the corresponding Boc-protected cyclic amides. The efficiency of ketone formation decreased with increasing ring size. They also described the use of other protecting groups including pivaloyl, Cbz, and benzoyl. Boc-protected amides were found to be optimal in this chemistry (**eq 7**).

In 1993, Asensio et al.[48] reported that tetrafluoroborate salts of primary, secondary, and tertiary alkylamines are resistant to nitrogen oxidation by methyl(trifluoromethyl)dioxirane (TFDO), which allows for the selective oxidation of aliphatic secondary and tertiary C–H bonds in the alkyl side chain. Thus, when amine **23** was subjected to oxidation by TFDO, the initially formed amino ketone **24** led to cyclic imine **25** as the final product. Alternatively, linear amine **26** furnished ε- and δ-amino ketones **27** and **28** (**Scheme 14**).

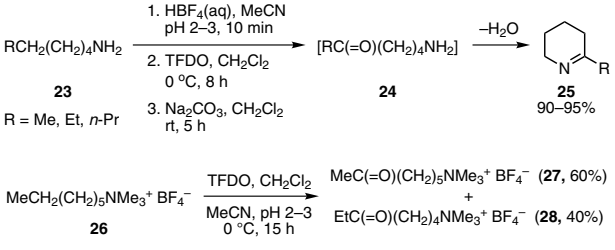
Porantherine, an alkaloid containing an ω-amino ketone subunit, was synthesized by Corey and Balanson.[49] The difference in acid lability between the ketal and acetal functionalities of compound **29** was exploited in performing selective amine-carbonyl condensation reactions. When compound **29** was treated with 10% HCl, acetal cleavage, followed by intramolecular condensation, furnished the porantherine skeleton **30**. Exposure of **30** to more acidic reaction conditions resulted in the cleavage of the ketal group and subsequent intramolecular Mannich reaction to yield **31**. Selective reduction of the ketone functionality using sodium borohydride, followed by dehydration, gave porantherine (**Scheme 15**).

## 3. Applications of Amino Carbonyl Compounds in Organic Synthesis

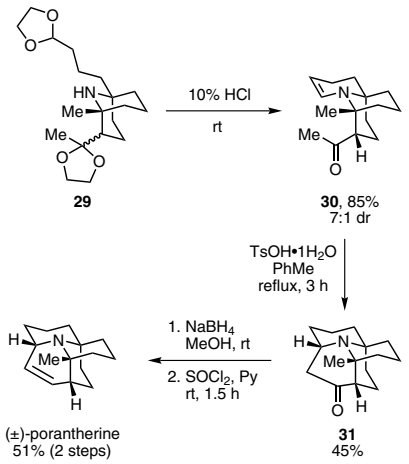
Amino carbonyl compounds are important building blocks in the synthesis of nitrogen-containing natural products, and are widely used in the pharmaceutical industry. Some of the transformations that amino carbonyl compounds undergo include: nucleophilic addition,[50] Wittig reaction,[51] aldol reaction, reductive amination,[52] [3 + 2] annulation,[53] [2 + 2] addition,[54] construction of aromatic and aliphatic cyclic compounds,[55] and formation of cyanohydrin adducts followed by hydrolysis.[50b]

Clive and co-workers synthesized a variety of protected amino aldehydes, and employed them in the Morita–Baylis–Hillman reaction. The resulting adducts were used for the preparation of hexahydroquinolizines, hexahydroindolizines, and related bicyclic structures with nitrogen at the bridgehead position.[56]

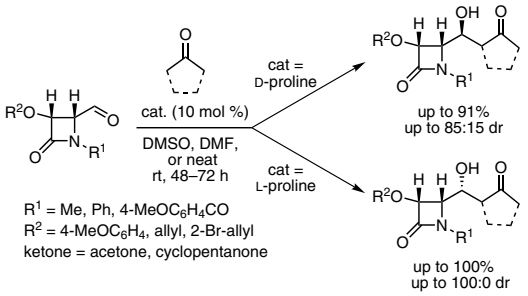
Alcaide et al.[57] recently reported a proline-catalyzed diastereoselective synthesis of γ-amino-β-hydroxy ketones in good yields by the direct aldol reaction between 4-oxoazetidine-2-carbaldehydes and unsubstituted ketones (**Scheme 16**).[57]



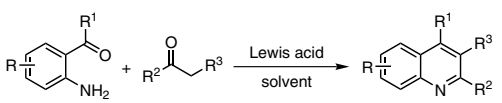

**Scheme 14.** Miscellaneous Amino Ketones by the TFDO Oxidation of Alkylammonium Tetrafluoroborates. *(Ref. 48)*



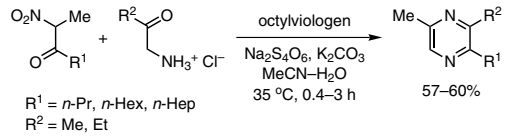

**Scheme 15.** Corey's Synthesis of (±)-Porantherine, a ω-Amino Ketone Containing Alkaloid. *(Ref. 49)*



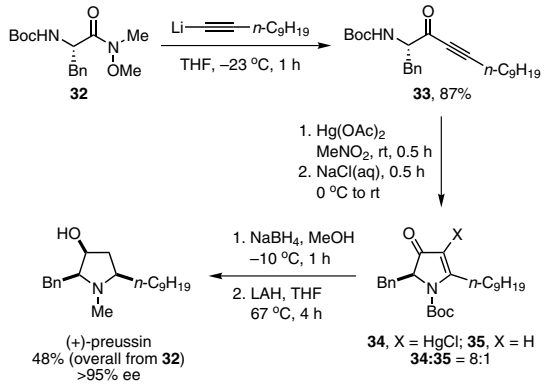

**Scheme 16.** Application of Amino Aldehydes in the Synthesis of γ-Amino-β-hydroxy Ketones. *(Ref. 57)*



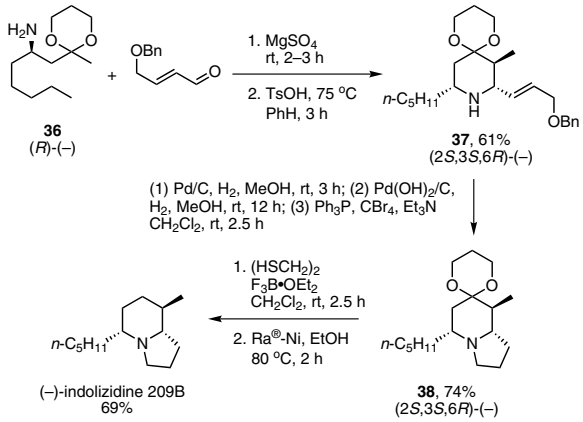

**eq 8** *(Ref. 59)*



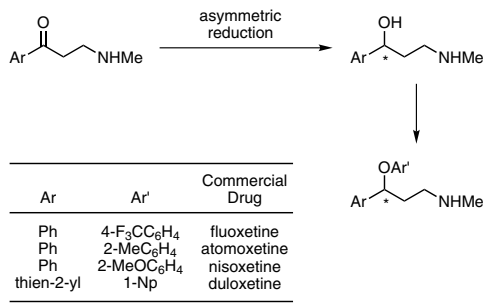

**eq 9** *(Ref. 61)*



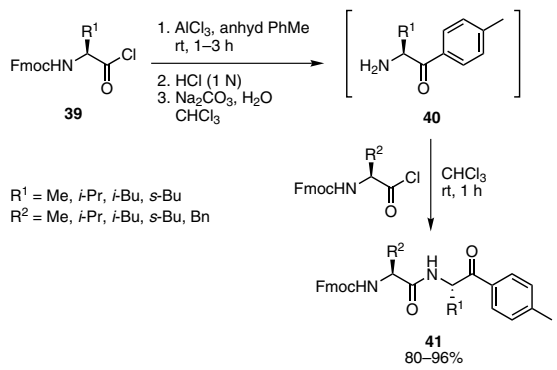

**Scheme 17.** Amino Carbonyl Compounds in the Synthesis of Natural Products. *(Ref. 62)*



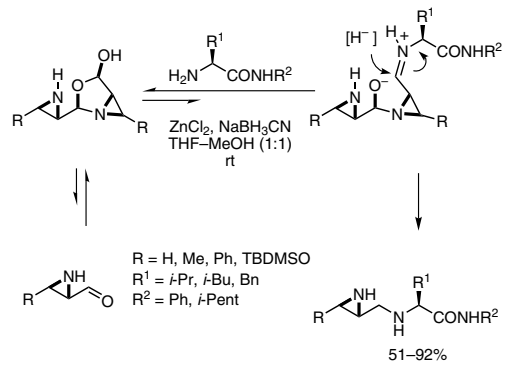

**Scheme 18.** β-Amino Ketones in the Synthesis of (–)-Indolizidine 209B. *(Ref. 63)*




**Scheme 19.** Some of the Pharmaceutically Relevant Compounds Synthesized from Amino Ketones. *(Ref. 64)*




**Scheme 20.** Liguori's Synthesis of Chiral Peptidyl Ketones. *(Ref. 68)*




**Scheme 21.** Protecting-Group-Free Strategy for Replacing Amide Bonds. *(Ref. 71)*

In general, β-lactams are important pharmacophores for the treatment of diseases caused by bacterial infections.[58]

An important use of amino ketones is in the synthesis of quinolines and their derivatives,[59] which have a wide range of biological activities including antimalarial, anti-inflammatory, antihypertensive, and antibacterial ones. Tyrosine kinase inhibitors and histamine $H_3$ receptor antagonists were prepared from amino carbonyl compounds.[60] In general, quinolines can be obtained using Skraup, Doebner–Von Miller, and Friedländer methods. Among these procedures, the Friedländer method is best for the synthesis of quinolines involving amino carbonyls as substrates (**eq 8**).

Elmaaty and Castle have reported a facile, regiocontrolled synthesis of trialkyl-substituted pyrazines.[61] α-Nitro ketones were reacted with α-amino ketones in the presence of hydrogen sulfite and octyl viologen as an electron-transfer reagent (**eq 9**). Alkylpyrazines have found utility as flavor components in food, as pheromones, and as versatile synthetic intermediates.

### 3.1. Selected Examples from Natural Product Synthesis

(+)-Preussin, an antifungal agent, was synthesized in five steps from *t*-Boc-(*S*)-phenylalanine via Weinreb amide **32** (**Scheme 17**).[62] When treated with undecynyllithium (THF, –23 ºC, 1 h), compound **32** furnished ynone **33** in 87% yield. Reaction of **33** with $Hg(OAc)_2$ induced 5-*endo*-*dig* cyclization to give pyrrolinones **34** and **35** in an 8:1 ratio. The mixture of **34** and **35** reacted directly with $NaBH_4$ in methanol at –10 ºC to give the Boc-protected preussin, which was reduced with LAH to afford preussin.

Davis and Yang reported the synthesis of indolizidine 209B via a β-amino ketone intermediate (**Scheme 18**).[63] The starting amino ketal **36** was obtained from a chiral sulfonamide in three steps and, upon stirring with anhydrous $MgSO_4$ and (*E*)-4-benzyloxy-2-butenal, gave an unstable imine intermediate. The Mannich product **37** was obtained as a single diastereoisomer by heating the intermediate imine in the presence of anhydrous TsOH. Debenzylation of **37** followed by hydrogenation provided bicyclic compound **38**. Treatment of **38** with ethanedithiol in the presence of $F_3B{\bullet}OEt_2$, followed by reduction with Raney®-Nickel led to indolizidine 209B.

### 3.2. Applications as Building Blocks in the Pharmaceutical Industry

Amino ketones have served as important building blocks in the synthesis of a variety of marketed pharmaceuticals. Through catalytic asymmetric hydrogenation, amino ketones can be converted into enantiomerically pure amino alcohols exhibiting various pharmacological activities. The pharmaceutical industry has implemented this strategy in the enantioselective preparation of several adrenergic receptor agonists including phenylephrine hydrochloride, etilefrine hydrochloride, salbutamol hydrochloride, and adrenaline sulfate.

(–)-Lobeline, an alkaloid isolated from *Lobelia inflate* (Indian tobacco), has been prepared by the asymmetric monoreduction of lobalanine. It is a known nicotinic agonist and has been employed as an antiasthmatic, expectorant, respiratory stimulant,[64] and smoking-cessation aid, with more recent applications in the treatment of psychostimulant abuse.[65]

The amino alcohols derived from the selective reduction of the corresponding amino ketones can also serve as chiral building blocks for the industrial-scale synthesis of other pharmaceutical compounds. In the preparation of the immunoregulating drug levamisole, the intermediate amino alcohol was obtained through selective reduction of the corresponding amino carbonyl.[66]

Fluoxetine (a selective serotonin-reuptake inhibitor), atomoxetine (a selective noradrenaline-reuptake inhibitor), nisoxetine (inhibitor of norepinephrine), and duloxetine hydrochloride (a dual inhibitor of serotonin and noradrenaline reuptake) are important pharmaceuticals, which have been obtained from the corresponding amino ketones by asymmetric reduction (**Scheme 19**).[64] Duloxetine was approved by the U.S. FDA in 2004 for the treatment of major depressive disorder.[67]

### 3.3. Applications in Biochemistry and Chemical Biology

Di Gioia et al. employed stable and enantiomerically pure Fmoc-protected acid chlorides **39** in a Friedel–Crafts-type reaction to generate chiral α-amino ketones **40**, which reacted in situ with another equivalent of **39** to yield peptidyl ketones **41** (**Scheme 20**).[68] Later, the authors extended this strategy to the preparation of various monopeptidyl ketones and dipeptidyl ketones.

The synthesis of peptidomimetic agents has been an active area of research for a number of years. Protected amino aldehydes have been utilized as aldehyde components in reductive aminations with amino acid containing partners, furnishing $CH_2NH_2$ linkages in place of selected amide bonds. The resulting reduced amide bond isosteres have received attention due to their propensity to bind at the protease active site.[69] This is possible due to close mimicry of the tetrahedral transition states involved in amide bond hydrolysis. An instructive example in the area of renin inhibition demonstrates that selective replacement of the amide bonds can lead to molecules with improved potency.[70] Although the reductive amination of protected amino aldehydes has been employed in numerous research- and industrial-scale applications, there are significant challenges that face this chemistry. The amino aldehydes as well as their immediate precursors are sensitive to epimerization. In addition, the imine–enamine equilibrium triggered during the reductive amination can lead to epimerization on both the amine and the aldehyde sides of the peptidomimetic fragment. A protecting-group-free strategy for replacing amide bonds with versatile aziridine-containing templates has been developed by Li and Yudin for the synthesis of peptidomimetic molecules (**Scheme 21**).[71] This chemistry is possible due to the dimeric nature of aziridine aldehyde derived intermediates. This feature prevents both overalkylation and epimerization in the course of the reductive amination.

## 4. Conclusions

Amino carbonyl compounds are versatile synthetic intermediates. Numerous studies have demonstrated their central role in organic synthesis. One can expect that further developments in this field will lead to many more examples where these fascinating molecules partake in strategically significant bond-forming processes.

## 5. References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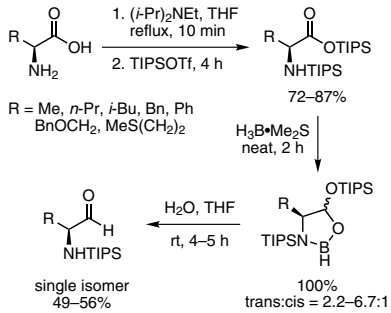
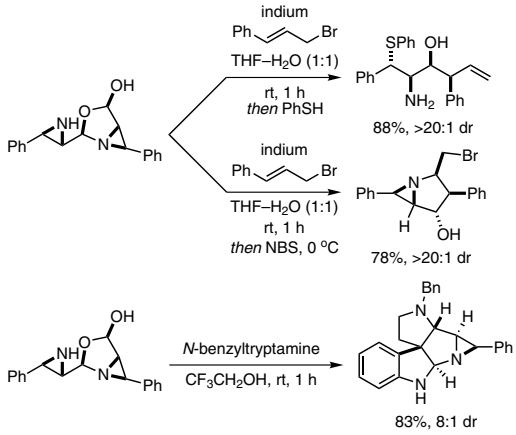
## 6. Notes Added in Proof

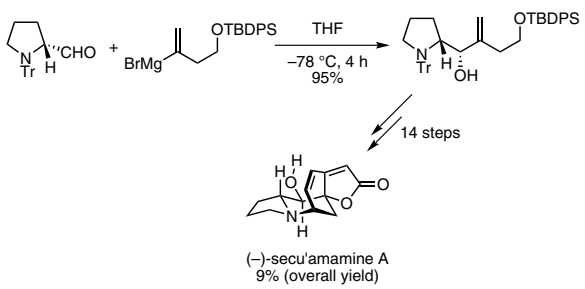
(a) Recently, Soderquist and co-workers have developed a novel borane-based approach to convert α-amino acids into *N*-TIPS-α-amino aldehydes, which were found to be resistant to both degradation and racemization. (Soto-Cairoli, B.; Justo de Pomar, J.; Soderquist, J. A. *Org. Lett.* **2008**, *10*, 333.)




(b) The amphoteric nature of unprotected amino aldehydes has been utilized in the rapid assembly of densely functionalized molecules. Indium-mediated allylation of aziridine aldehydes proceeds with full diastereocontrol, allowing for the one-pot synthesis of either tetrasubstituted pyrrolidines or γ-thio-α-amino alcohols. The nucleophilic nitrogen of the aziridine can also intercept reactive intermediates that are formed in an equilibrium process. Upon reaction of the aziridine aldehyde with *N*-benzyltryptamine, the Pictet–Spengler reaction is interrupted by nucleophilic attack of the aziridine on an iminium intermediate resulting in a complex pentacyclic product. (Hili, R.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 4256. Yudin, A. K.; Hili, R. *Chem.—Eur. J.* **2007**, *13*, 6538.)




(c) Weinreb and co-workers recently disclosed their total synthesis of the *Securinega* alkaloid (–)-secu'amamine A. The synthesis began with the Felkin–Anh addition of a vinylmagnesium bromide to *N*-tritylprolinal to produce the desired amino alcohol as a single diastereomer. With this approach, the complex tetracyclic natural product was reached in 15 steps with a 9% overall yield from the α-amino aldehyde. (Liu, P.; Hong, S.; Weinreb, S. M. *J. Am. Chem. Soc.* **2008**, *130*, 7526. Bejjani, J.; Chemla, F.; Audouin, M. *J. Org. Chem.* **2003**, *68*, 9747.)

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**Keywords:** amino aldehydes; amino ketones; orthogonal functional groups; aziridine aldehydes.

## About the Authors

**Sivaraj Baktharaman** was born in 1978 in Vellore, Tamil Nadu, India. He received a B.Sc. degree in chemistry from The New College and an M.Sc. degree in organic chemistry from the University of Madras, Chennai. He joined the research group of Professor Vinod K. Singh at the Indian Institute of Technology Kanpur, where he obtained his Ph.D. degree in 2007. In November 2006, he joined the research group of Professor Andrei K. Yudin as a postdoctoral fellow at the University of Toronto. Currently, his research is focused on the synthesis of bioactive natural products and on the development of new synthetic methodologies that are based on unprotected aziridines.

**Ryan Hili** was born in 1983 in Burlington, Canada. He received his H.B.Sc. degree, with a specialist in biological chemistry, in 2005 from the University of Toronto. As an undergraduate student, he worked in the area of nitrene-transfer reactions under the supervision of Professor Andrei. K. Yudin. He remained in the Yudin group to pursue a doctorate degree and is currently in his third year of study. His research is focused on the synthesis and applications of unprotected aziridine aldehydes in organic synthesis.

**Andrei K. Yudin** obtained his B.Sc. degree at Moscow State University and his Ph.D. degree at the University of Southern California under the direction of Professors G. K. Surya Prakash and George A. Olah. He subsequently took up a postdoctoral position in the laboratory of Professor K. Barry Sharpless at the Scripps Research Institute. In 1998, he started his independent career at the University of Toronto. He received early tenure in 2002, and became Full Professor in 2007. His research interests focus on the development and application of novel synthetic methods that enable the discovery of functionally significant molecules.

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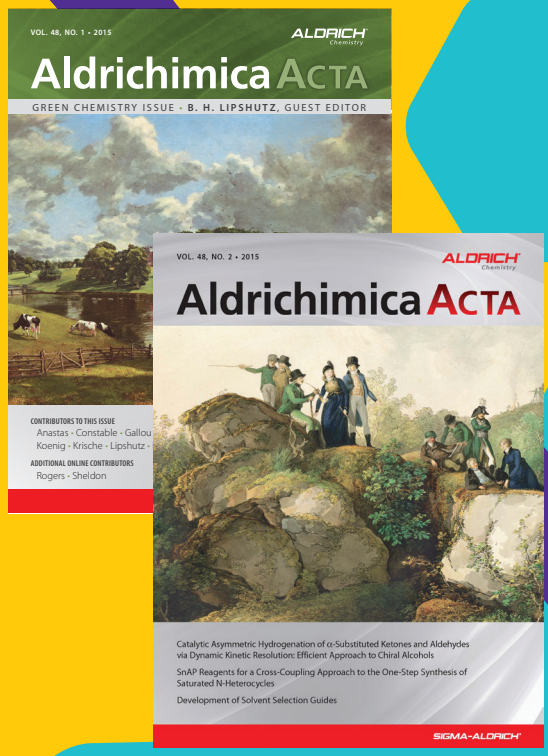


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