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VOL. 43, NO. 1 • 2010

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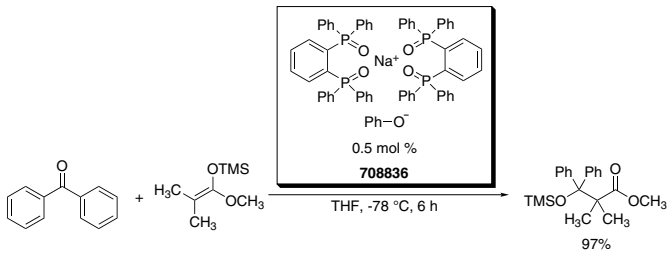
Efficient Lewis Base for Mukaiyama Aldol Reaction with Ketones

There have been few reported methods for the synthesis of tertiary aldols, due to the low reactivity of the starting ketones and the rapid retro-aldol reaction, even at low temperatures. Ishihara and coworkers recently reported the Lewis base catalyzed Mukaiyama aldol reaction using a simple, mixed sodium phenoxide–phosphine oxide catalyst. The catalyst was effective with a wide variety of TMS enolates and ketones, providing the aldol adducts in generally good-to-excellent yields. Additionally, the catalyst was also effective in Mannich-type reactions when benzyl-, Boc-, or Cbz-protected aldimines were used as substrates.



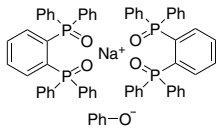
Hatano, M. et al. *Org. Lett.* **2007**, *9*, 4527.

Bis[1,2-bis(diphenylphosphine oxide)benzene] sodium phenoxide, 95%

708836 1 g

$C_{66}H_{53}NaO_5P_4$

FW: 1073.01



Indoles and Azaindoles

The indole subunit is a near-ubiquitous component of biologically active natural products, and the study of indoles has been a major focus of research for generations. Substituted indoles have frequently been referred to as privileged structures,[1] since they are capable of binding to multiple receptors with high affinity, and thus have applications across a wide range of therapeutic areas. Due to this activity, it is not surprising that the indole ring system has become an important structural motif in many pharmaceutical agents.

The azaindole moiety differs only by the presence of an additional ring nitrogen and, thus, it exhibits excellent potential as a bioisostere of the indole ring system. Although considerably more rare in nature, azaindoles still constitute essential subunits in many pharmaceutically important compounds, and have been very valuable to synthetic and medicinal chemists. 7-Azaindoles are of particular interest because of their ability to mimic purine in its role as a hydrogen-bonding partner.[2]

(1) Horton, D. A. et al. *Chem. Rev.* **2003**, *103*, 893 and references therein. (2) (a) Popowycz, F. et al. *Tetrahedron* **2007**, *63*, 1031. (b) Popowycz, F. et al. *Tetrahedron* **2007**, *63*, 8689. (c) Song, J. J. et al. *Chem. Soc. Rev.* **2007**, *36*, 1120.

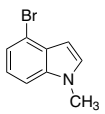
4-Bromo-1-methylindole, 95%

720860 500 mg

[*590417-55-3*]

C_9H_8BrN

FW: 210.07



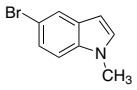
5-Bromo-1-methylindole, 97%

718300 5 g

[*10075-52-2*]

C_9H_8BrN

FW: 210.07

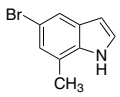


5-Bromo-7-methylindole, 97%

710822 1 g

C_9H_8BrN

FW: 210.07

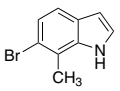


6-Bromo-7-methylindole, 97%

707155 250 mg

C_9H_8BrN

FW: 210.07



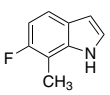
6-Fluoro-7-methylindole, 97%

707147 250 mg

[*57817-10-4*]

C_9H_8FN

FW: 149.16



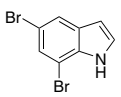
5,7-Dibromoindole, 97%

708798 1 g

[*36132-08-8*]

$C_8H_5Br_2N$

FW: 274.94

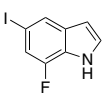


7-Fluoro-5-iodoindole, 97%

707058 500 mg

C_8H_5FIN

FW: 261.03



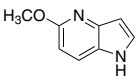
5-Methoxy-4-azaindole, 95%

707953 250 mg

[*17288-40-3*]

$C_8H_8N_2O$

FW: 148.16



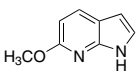
6-Methoxy-7-azaindole, 97%

702838 250 mg

[*896722-53-5*]

$C_8H_8N_2O$

FW: 148.16



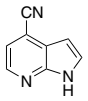
7-Azaindole-4-carbonitrile, 97%

706426 250 mg

[*344327-11-3*]

$C_8H_5N_3$

FW: 143.15



Aldrichimica Acta

VOL. 43, NO. 1 • 2010

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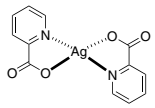
"PLEASE BOTHER US."

Joe Porwoll, President
Aldrich Chemical Co., Inc.

Professor Phil Baran of The Scripps Research Institute kindly suggested that we make silver picolinate. Baran and coworkers recently utilized silver picolinate to effect a chemoselective oxidation of the guanidine ring en route to their notable total synthesis of palau'amine.[1] This approach avoids overoxidation and laborious protecting group chemistry. Silver picolinate was also employed in the total synthesis of (±)-axinellamines A and B.[2,3]

(1) Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1095. (2) O'Malley, D. P.; Yamaguchi, J.; Young, I. S.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3581. (3) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854.



718157

718157 **Silver(II) picolinate, 97%** 5 g, 25 g

Naturally, we made this useful oxidation 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 back cover.

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ABOUT OUR COVER

The Grand Canal (oil on canvas, 23.0 × 33.0 cm) is one of twenty works of art by the British artist Richard Parkes Bonington (1802–1828) in the collection of the National Gallery of Art, and was painted in1826/1827. At the age of 16, Bonington moved to Paris with his parents and studied there at the French National Art School, the École des Beaux-Arts. During his brief career as an artist, he adopted the ideals of the Romantic Movement, and was influenced by the French artists Antoine-Jean Gros and Eugène Delacroix and by his fellow Englishman, John Constable.

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

Bonington was greatly admired for his exceptional ability to capture the effects of daylight and atmosphere with unerring assurance. In this work, the lovely play of sunlight on the building facades, the delicate reflections on the water, and the sweep of the clouds across the sky entice the eye and can be appreciated independently of the subject and its imitative appeal.

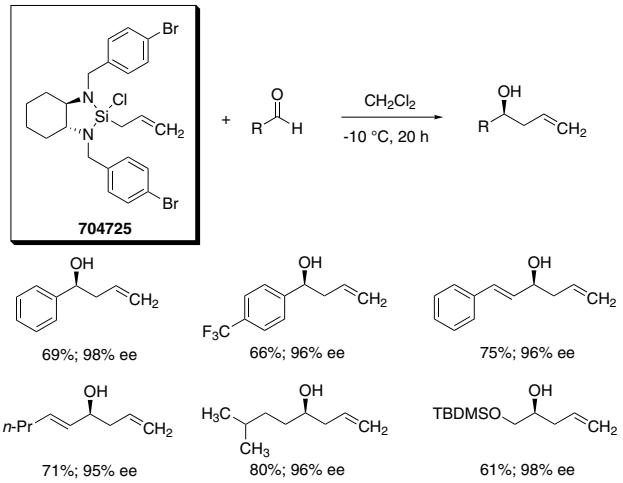
In the nineteenth century, painted scenes of Venice were very popular with the "Grand Tour" set, as post cards or photographs are today. Bonington produced many studies of this most beautiful city on the Adriatic while visiting Italy in 1826. He turned his sketches into some of his finest paintings, like the one seen here, which further enhanced his flourishing reputation as a landscape painter in London and Paris.

This painting is a gift of Roger and Victoria Sant to the National Gallery of Art, Washington, DC.

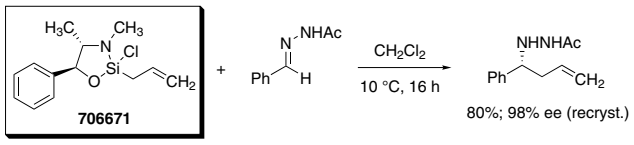
Leighton's Chiral Silane Reagents

The asymmetric allylation of carbonyl compounds remains one of the most important and fundamental addition reactions for the synthesis of optically active chiral building blocks.

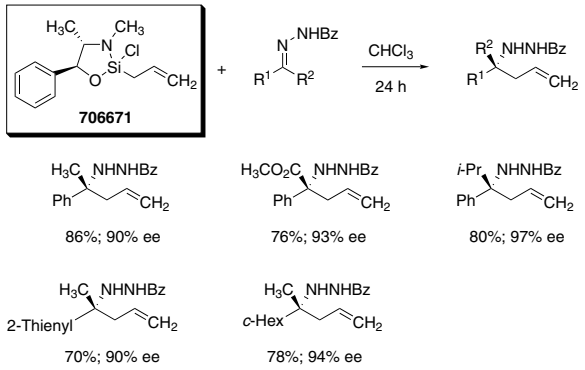
In 2002, Leighton and co-workers developed strained silacycle compounds as versatile reagents for the practical enantioselective allylation of aldehydes.[1] A newly developed chiral auxiliary based on the cyclohexane-1,2-diamine scaffold successfully allylated a broad range of aldehydes highly enantioselectively.[2]



The development of practical enantioselective syntheses of chiral amines is of great importance to synthetic organic and medicinal chemists. In 2003, Leighton and co-workers successfully used a pseudoephedrine-derived, five-membered-ring, strained silacycle reagent for the enantioselective allylation of acylhydrazones.[3]

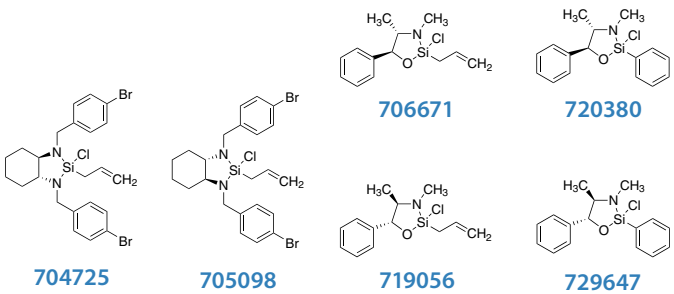


The reaction scope of these silacycles was extended to a practical method for the enantioselective synthesis of tertiary carbinamines based on the addition of this chiral allylsilane reagent to a structurally diverse array of ketone-derived benzoylhydrazones.[4] While many methods for the synthesis of quaternary α-amino acids have been published, far fewer reports have dealt with the synthesis of tertiary carbinamines. The free amines are easily accessed in good yields by treating the product hydrazides with SmI_2.



The reagents are effective with other types of imine electrophiles, and may be derivatized efficiently using cross-metathesis reactions. In addition, the corresponding phenylsilanes are effective general Lewis acids for a variety of enantioselective (nonallylation) nucleophilic addition reactions with acylhydrazones and other imine electrophiles.

References:
(1) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920. (2) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946. (3) Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9596. (4) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686.



For more information on the applications of the Leighton silacycle reagents, please see Professor Leighton's review in this issue or visit ***sigma-aldrich.com***

Powerful and Versatile Silicon Lewis Acids for Asymmetric Chemical Synthesis

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Department of Chemistry
Columbia University
3000 Broadway, MC 3117
New York, NY 10027, USA
Email: leighton@chem.columbia.edu

Professor James L. Leighton

Outline

1. Introduction

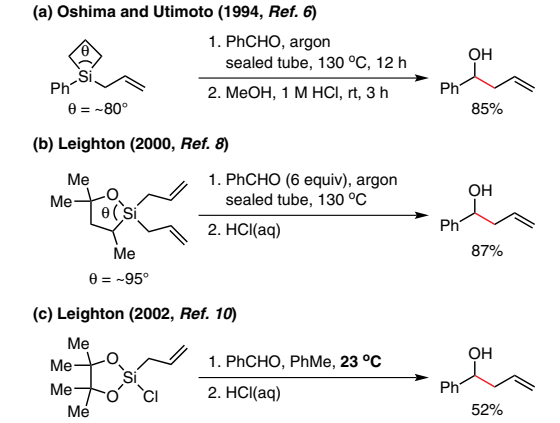
Nucleophilic addition to aldehydes, ketones, aldimines, and ketimines with activation by a chiral Lewis acid is one of the most important and fundamental reaction types in all of asymmetric chemical synthesis. If one were to ask what is the "ideal" element to serve as the Lewis acid from the standpoint of practicality, an extremely strong case could be made for silicon. It is abundant and inexpensive; it typically presents no significant issues in terms of toxicity and waste stream; and, if highly enantioselective reactions promoted by chiral silicon Lewis acids could be developed, they would possibly, if not likely, be readily adaptable for use in large-scale applications.

Such considerations, as well as the formidable and intriguing conceptual challenge, have inspired decades-long efforts to develop effective silicon Lewis acids for asymmetric synthesis. The arena of aldehyde allylation reactions has been the proving ground for many of these efforts. Three approaches have emerged for devising Type I[1] Lewis acidic allylsilanes that react with aldehydes through a closed transition state without the need for an exogenous Lewis acid: (i) the nucleophile-promoted addition of allylSiX_3 (X = F, OR) species, pioneered by Kira and Sakurai[2] and by Hosomi;[3] (ii) the related, but mechanistically distinct, Lewis base catalyzed addition of allyl$SiCl_3$, pioneered and developed into an effective asymmetric method by Denmark[4] following a report from Kobayashi;[5] and (iii) the addition of allylsilacyclobutanes disclosed by Oshima and Utimoto (**Scheme 1**, Part (a)),[6] based on a seminal report from Myers[7] who employed enoxysilacyclobutanes in Type I Mukaiyama aldol reactions.

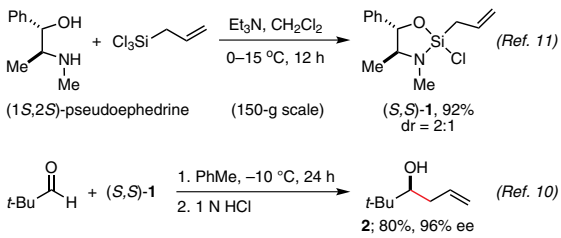
In this latter approach, the Lewis acidity of the silicon is derived from the ring strain in the silacyclobutane, which favors the rehybridization to a five-coordinate trigonal bipyramidal silane that accompanies the binding of the aldehyde. While mechanistically intriguing, this approach did not evolve into a broadly applicable asymmetric method due both to the lack of convenient synthetic access to silacyclobutanes and to the impractical conditions (130 °C in a sealed tube) of the allylation reaction. In 2000, Zacuto and Leighton provided the first unambiguous demonstration of the same phenomenon with the silicon constrained within a five-membered ring (**Scheme 1**, Part (b)).[8,9] The discovery that a similar reactivity could be realized with five-membered silacycles had profound practical implications in that one might simply constrain allylsilanes in a five-membered ring with 1,2-diols, diamines, or amino alcohols, and benefit from a boost in reactivity due to the attachment of more highly electronegative elements to the silicon. Indeed, in 2002, our group showed that the allylsilane derived from pinacol and allyltrichlorosilane smoothly allylated benzaldehyde *at ambient temperature* (**Scheme 1**, Part (c)).[10] This reaction set the stage for the development of a family of versatile and highly practical chiral silane Lewis acids for asymmetric synthesis.

2. Enantioselective Allylation of Aldehydes and Acylhydrazones—Same Allylsilane, Different Mechanisms

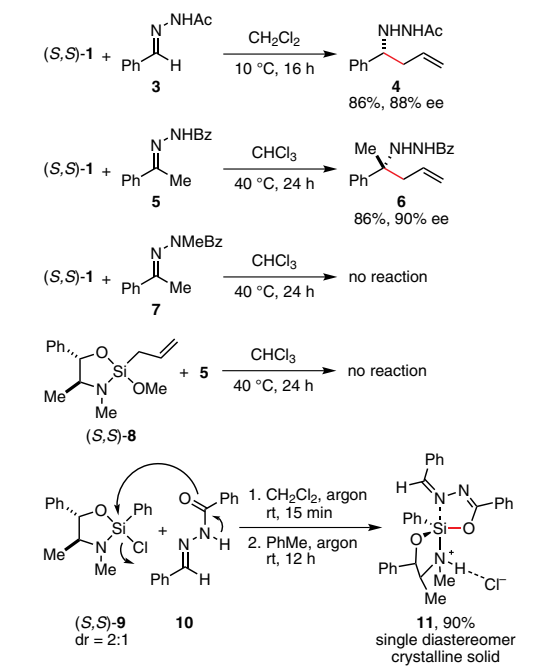
Following the discovery that allyl(chloro)dioxasilacyclopentanes react with aldehydes at ambient temperature, our group began a search for effective chiral diols, diamines, and amino alcohols. Considerations of practicality (economic and otherwise) led us to consider compounds such as pseudoephedrine: it is ready for use as is, and both enantiomers are commercially available and inexpensive. Thus, reaction of allyltrichlorosilane (also commercially available) with (1*S*,2*S*)-pseudoephedrine in the



Scheme 1. Milestones in the Development of Type I (Lewis Acidic) Allylsilanes Whose Activity Is Derived from Ring Strain.



Scheme 2. Synthesis of Chiral Allylsilane **1** and "Proof-of-Concept" Allylation of Pivalaldehyde.



Scheme 3. Discovery and Mechanistic Elucidation of the Enantioselective Allylation of Acylhydrazones. *(Ref. 11,12)*

presence of triethylamine leads to the synthesis (150-g scale) of (*S*,*S*)-**1** in 92% yield (**Scheme 2**).[11] It is important to note that the silicon atom is a stereogenic center and that **1** is isolated as a ~2:1 mixture of (unassigned) diastereomers. Despite this potentially complicating feature, **1** was found to react with pivalaldehyde to give alcohol **2** in 96% ee.[10] With less hindered aliphatic aldehydes and with aromatic and α,β-unsaturated aldehydes, however, **1** was found to be less effective, providing enantioselectivities in the 78–88% range. Nevertheless, this study served as a convincing proof of concept of the remarkably simple and yet previously unrecognized fact that one could simply react allyltrichlorosilane with a chiral amino alcohol, and thereby prepare an effective chiral allylsilane that reacts in a Type I sense. As described in Section 2.1, a highly enantioselective and more general second-generation, diamine-derived silacycle was developed for aldehyde allylation and crotylation.

The performance of allylsilane **1** in imine allylation reactions was also examined, but it quickly became clear that **1** is *not* competent to allylate a variety of imine derivatives (PhCH=N-R; where R = Bn, Ph, $SiMe_3$, OH, OMe, SO_2Ar).[11] Acylhydrazones, however, were found to react smoothly with **1**, and upon optimization, reaction of (*S*,*S*)-**1** with acetylhydrazone **3** gave hydrazide **4** in 86% yield and 88% ee.[11] Similarly, reaction of (*S*,*S*)-**1** with ketone-derived benzoylhydrazone **5** gave hydrazide **6** in 86% yield and 90% ee (**Scheme 3**).[12,13] It was subsequently determined that *N*-methylbenzoylhydrazone **7** was completely inert to the action of (*S*,*S*)-**1**, and that methoxysilane (*S*,*S*)-**8** was unreactive with hydrazone **5**. These data strongly implied that the unique reactivity of acylhydrazones among the imine derivatives examined was due to the amide-like portion of the acylhydrazone acting as an oxygen nucleophile and displacing the chloride from the silane, and the liberated HCl protonating the amino group of the bound pseudoephedrine. *It is this protonation that is the key to the reactivity of the system*, as it would be expected to dramatically increase the Lewis acidity of the silicon center.[14] To secure evidence for this proposal, phenylsilane (*S*,*S*)-**9** was prepared (and was isolated as a ~2:1 mixture of diastereomers, as was the case with allylsilane **1**) and treated with hydrazone **10**. When this reaction was carried out in toluene, a precipitate formed and was isolated in 90% yield. The ^{1}H NMR spectrum of this material is that of a single species, and is consistent with structure **11**—most notably, the NMe signal is a doublet. Recrystallization of the precipitate from CH_2Cl_2–hexanes provided X-ray quality crystals and the resulting X-ray data confirmed the structure of **11**.[12] That a single species, **11**, is formed in 90% yield is significant, because it provides compelling evidence that, in the reaction of **1** with acylhydrazones, the two diastereomers of the starting silane converge on a common complex prior to transfer of the allyl group.

The same allylsilane, **1**, thus reacts with aldehydes and acylhydrazones by distinct mechanisms. While the ring strain alone is sufficient for reactivity with aldehydes, it is insufficient for reactivity with ketones, aldimines, and ketimines. For these substrates, a suitably disposed directing and activating group (a protic nucleophile that can displace the chloride from the silane and generate an equivalent of HCl in situ) is required. As described below, a significant variety of effective directing/activating groups have been found, and significant advantages in terms of reactivity and selectivity accrue from employing this strategy. Finally, it is important to emphasize again that the fact that the pseudoephedrine-derived silane Lewis acids discussed herein are produced as mixtures of diastereomers is irrelevant for all of the chemistry described below. In the chloride displacement–HCl

activation manifold (all reactions other than aldehyde allylation), the two diastereomers converge on a common intermediate prior to the nucleophilic addition event.

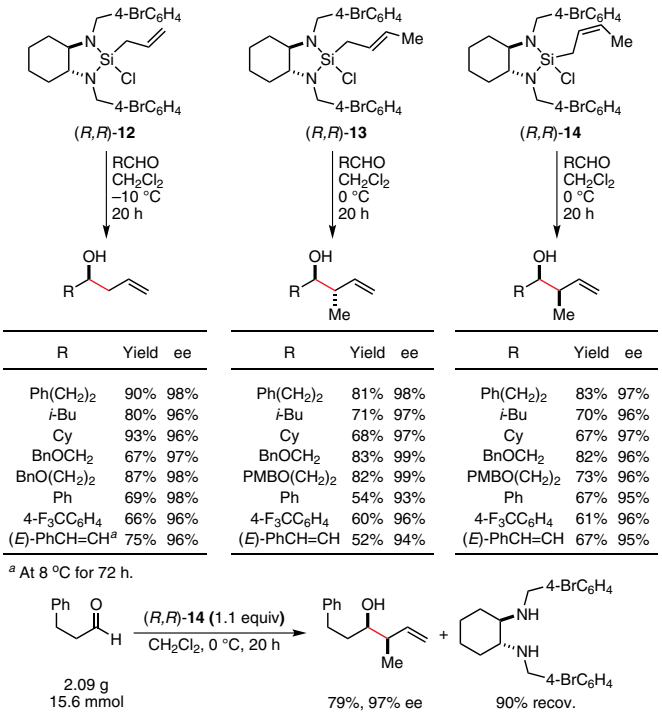
2.1. Allylation and Crotylation of Aldehydes

Because allylsilane **1** provided only moderate levels of enantioselectivity with many different classes of aldehydes, and because there was evidence that the two diastereomers of **1** were reacting independently and with different enantioselectivities, a second-generation reagent based on a C_2-symmetric chiral controller was developed. We quickly found that *N*,*N*'-dialkylcyclohexanediamine-derived allylchlorosilanes provided superior levels of enantioselectivity in aldehyde allylation reactions, and eventually settled on *p*-bromobenzyl groups because they—uniquely among the *N*-alkyl groups examined—rendered the allylsilane reagent, (*R*,*R*)-**12**, crystalline (**Scheme 4**).[15–17] As shown, **12** reacts with a variety of aldehydes to provide the homoallylic alcohol products in 96–98% ee.[15] The *trans*-crotylsilane (*R*,*R*)-**13** and the *cis*-crotylsilane (*R*,*R*)-**14** were also prepared, and were also crystalline solids.[17] These silanes crotylate a variety of aldehydes with uniformly excellent enantioselectivities (93–99% ee). From a practical standpoint, it is noteworthy that these reactions are carried out under highly convenient and scalable conditions: the crotylsilane is simply added to a cooled (0 °C) solution of the aldehyde in CH_2Cl_2.[17] As shown, a larger-scale crotylation reaction (2.09 g, 15.6 mmol of aldehyde) was demonstrated, wherein the chiral diamine was recovered in 90% yield.

2.2. Allylation and Crotylation of Ketones

In principle, the enantioselective allylation of ketones provides convenient access to chiral tertiary carbinols, but in practice this has proven a significantly more difficult problem than the corresponding allylation of aldehydes. Recently, there have been several enantioselective ketone allylation methods reported that employ allylboranes or allylboronates,[18] and one report that employs allylsilanes.[19] Despite these successes, the substrate scope remains limited for the most part to ketones wherein one side must be a methyl or linear alkyl group.

While allylsilanes **1** and **12** do not possess sufficient reactivity to allylate acetophenone, the mechanism of the acylhydrazone allylation reaction discussed above suggested an opportunity to install a directing/activating group on the ketone substrate. While this would limit the reaction scope in a different way, we wondered whether it might also allow the enantioselective allylation of aryl *branched*-alkyl ketones, as well as aryl aryl ketones—two important classes of ketone for which there had not been an effective solution. We found that allylsilane **12** smoothly allylates 2'-hydroxyacetophenone and, upon optimization, the product could be obtained in 75% yield and 83% ee (**eq 1**).[20] When the substrate scope was examined, it was found that not only could 2'-hydroxy-isobutyrophenone be smoothly allylated (88% ee), but also, remarkably, could the corresponding *tert*-butyl ketone (93% ee). A series of 2'-hydroxybenzophenones and related diaryl ketones could be allylated as well, including those with ortho substitution. The last two examples also demonstrate the highly diastereoselective and enantioselective crotylation of 2'-hydroxybenzophenone. Complex/transition state **15** represents a reasonable model for how these reactions proceed, with the key point being the highly significant boost in the reactivity of the silane that derives from the protonation of one of the amino groups attached to silicon, a protonation that attends the reaction of the hydroxyl group with the chlorosilane.



R	Yield	ee
$Ph(CH_2)_2$	90%	98%
i-Bu	80%	96%
Cy	93%	96%
$BnOCH_2$	67%	97%
$BnO(CH_2)_2$	87%	98%
Ph	69%	98%
4-$F_3CC_6H_4$	66%	96%
(*E*)-PhCH=CH[a]	75%	96%

R	Yield	ee
$Ph(CH_2)_2$	81%	98%
i-Bu	71%	97%
Cy	68%	97%
$BnOCH_2$	83%	99%
$PMBO(CH_2)_2$	82%	99%
Ph	54%	93%
4-$F_3CC_6H_4$	60%	96%
(*E*)-PhCH=CH	52%	94%

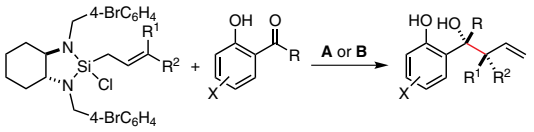
R	Yield	ee
$Ph(CH_2)_2$	83%	97%
i-Bu	70%	96%
Cy	67%	97%
$BnOCH_2$	82%	96%
$PMBO(CH_2)_2$	73%	96%
Ph	67%	95%
4-$F_3CC_6H_4$	61%	96%
(*E*)-PhCH=CH	67%	95%

[a] At 8 °C for 72 h.

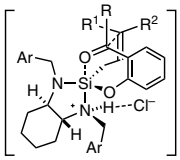
Scheme 4. Chiral Allyl- and Crotylsilanes for Highly Enantioselective Aldehyde Allylation and Crotylation Reactions. *(Ref. 15,17)*

2.3. Allylation of Aldehyde- and Ketone-Derived Acylhydrazones

As described above, allylsilane **1** is effective for the enantioselective allylation of aldehyde- *and* ketone-derived acylhydrazones. A full account of the substrate scope for both reactions is provided in **Scheme 5**.[11,12] For aldehyde-derived substrates, *acetyl*hydrazones proved most effective in terms of enantioselectivity,[11] while *benzoyl*hydrazones provided superior results for ketone-derived substrates.[12] Other than the pivalaldehyde-derived hydrazone, hydrazones of aliphatic aldehydes provided poor results. In contrast, in the ketone-derived hydrazone series, substrates derived from aryl alkyl and alkyl alkyl ketones gave useful levels of enantioselectivity. While in some cases the enantioselectivities observed were only moderately good (e.g., 83% or 85% ee) this need not be of concern from a practical point of view: we have demonstrated several of the reactions on a 5-g scale, wherein the products were isolated (without chromatography) by recrystallization, leading to a significant enhancement in their enantiomeric purity.[11] In one of these cases, the reductive cleavage of the N–N bond with SmI_2 was demonstrated, as was the recovery of pseudoephedrine (by extraction and without chromatography) in near-quantitative yield (98%).[12]



(*R,R*)-**12**; $R^1 = R^2 = H$
(*R,R*)-**13**; $R^1 = H$, $R^2 = Me$
(*R,R*)-**14**; $R^1 = Me$, $R^2 = H$



15

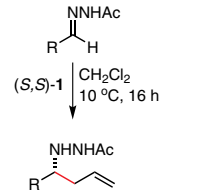
Silane	R	X	Method[a]	Yield	ee
12	Me	H	**A**	75%	83%
12	Me	4-Cl	**A**	65%	81%
12	*i*-Pr	H	**A**[b]	67%	88%
12	*t*-Bu	H	**A**[b]	63%	93%
12	Ph	H	**B**	62%	93%
12	2-MeC_6H_4	H	**B**	75%	94%
12	furan-2-yl	H	**B**	76%	88%
12	MeN-indol-2-yl	H	**B**	69%	95%
12	4-NC-2-$MOMOCH_2C_6H_3$	5-F	**B**[c]	90%	90%
13	Ph	H	**B**[d]	58%	92%
14	Ph	H	**B**[d]	63%	95%

[a] Method **A**: PhMe, 40 °C, 24 h; Method **B**: CH_2Cl_2, 23 °C, 48 h. [b] Reaction time = 48 h. [c] (*S,S*)-**12** was used at 0 °C, giving the opposite configuration at the benzylic carbon. [d] dr >20:1; ee is of the major diastereomer.

eq 1 *(Ref. 20)*

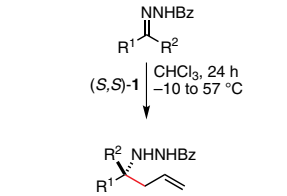
2.4. Allylation and Crotylation of Aldimines and Ketimines

While, as mentioned above, *N*-phenylimines were unreactive towards allylsilane **1**, the mechanism of the acylhydrazone allylation suggested that placement of a hydroxyl group at the ortho position of the *N*-phenyl ring of the imine might lead to successful reactions, wherein the phenol functionality would direct the chloride displacement–protonation steps.[21] Indeed, this strategy proved successful, leading to highly enantioselective reactions that are carried out at ambient temperature (**Scheme 6**).[22] This approach provided a solution to the problem of aliphatic aldimines, and allowed highly diastereoselective and enantioselective crotylation reactions with crotylsilanes **16** and **17** as well. Alternatively, the phenol functionality can be a

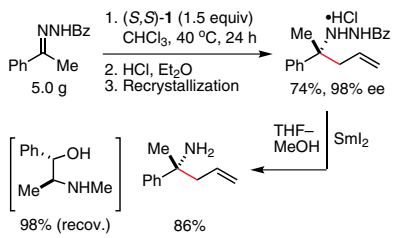


R	Yield	ee
Ph[a]	86%	88%
2-MeC_6H_4	75%	85%
4-BrC_6H_4	88%	85%
4-$MeOC_6H_4$	82%	86%
1,3-benzodioxol-5-yl	93%	83%
2-Np	85%	87%
furan-2-yl	89%	88%
furan-3-yl	78%	86%
thien-2-yl	76%	89%
BocN-indol-3-yl	96%	83%
BocN-pyrrol-2-yl[b]	49%	92%
t-Bu	88%	97%

[a] When this reaction was run on a 5-g scale, the recrystallized product was isolated in 80% yield and 98% ee. [b] 40% of unreacted starting material was also isolated.



R^1	R^2	Yield	ee
Ph	Me	86%	90%
Ph	Et	91%	89%
Ph	Bn	95%	84%
Ph	CO_2Me	76%	93%
Ph	*i*-Pr	80%	97%
4-BrC_6H_4	Me	92%	89%
4-$MeOC_6H_4$	Me	70%	85%
3-$O_2NC_6H_4$	Me	79%	88%
2-Np	Me	80%	89%
furan-2-yl	Me	46%	88%
thien-2-yl	Me	70%	90%
BocN-indol-3-yl	Me	64%	86%
$Ph(CH_2)_2$	Me	86%	87%
Cy	Me	78%	94%



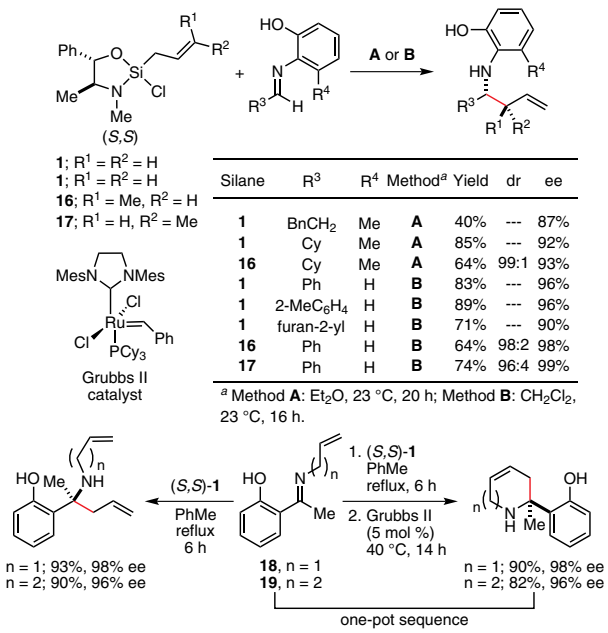
Scheme 5. Scope of the Enantioselective Allylation of Aldehyde- and Ketone-Derived Acylhydrazones. *(Ref. 11,12)*

part of the substrate, as in ketimines **18** and **19**, leading to the successful reaction of these. Despite the fact that these are more sluggish reactions (they are carried out in refluxing toluene), the enantioselectivities are remarkably high. Because the directing/activating group is already part of the ketone or aldehyde structure in these cases, there is flexibility in the choice of the imine N-substituent, which may then be thought of as part of a desired target structure and not as a protecting group to be removed later. As one example of this strategy, allylation of **18** and **19** may be followed by in situ ring-closing metathesis (RCM) to give the illustrated piperidine and azepine derivatives in a single-pot operation.[22]

The success with the phenol moiety as the directing/activating group inspired further inquiries into what other groups—especially those that might have relevance to medicinal chemistry—could successfully direct and activate reactions with allylsilane **1**. Among the groups considered was imidazole, and, indeed, it was found that the *N*-allylimine derived from 2-formylimidazole reacted smoothly with **1**. Unfortunately, the enantioselectivity of this reaction was very low (< 20% ee), and we began a search for more effective chiral controllers. Eventually the aminoindanol-derived allylsilane (1*S*,2*R*)-**20** was found to give good results (**Scheme 7**).[23] As shown, **20** is effective for the enantioselective allylation of a variety of 2-imidazolyl aldimines *and* ketimines, and crotylsilanes **21** and **22** may be employed for the diastereoselective and enantioselective crotylation of 2-imidazolylaldimines. The convenience of these reaction conditions, the fact that unprotected imidazoles may be employed (indeed, it is necessary that they be unprotected), and the flexibility in the choice of the imine N-substituent all combine to render this a reaction of significant potential utility in medicinal chemistry. As in Scheme 6, in situ ring-closing metathesis may be employed, following allylation of 2-acetylbenzimidazole-derived ketimines **23** and **24**, to provide access to stereochemically and functionally complex heterocycles in a simple one-pot procedure. From a strategy or reaction design perspective, it is noteworthy that the metathesis is unsuccessful when attempted on the isolated allylation products, presumably due to binding of the imidazole to the Grubbs II catalyst. Thus, the allylation reaction requires the use of unprotected imidazoles, and produces unprotected imidazoles, but the in situ silylation of the imidazole in the course of the allylation may be leveraged to allow the RCM to occur.

2.5. Tandem Cross-Metathesis–Diastereodivergent Cinnamylation of Aldimines

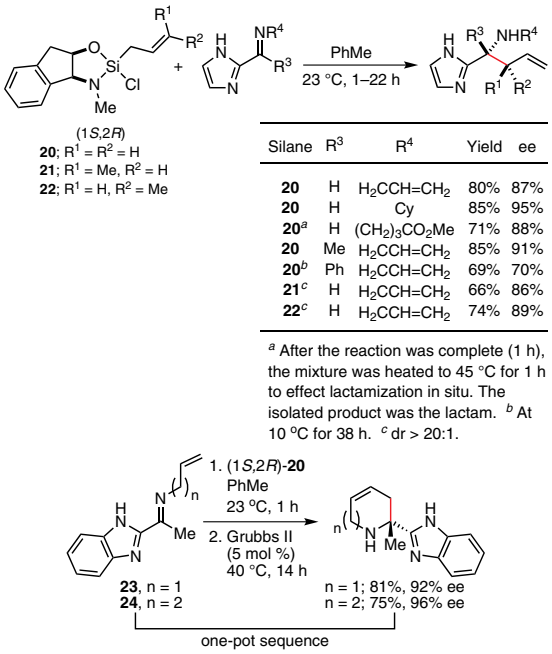
Because of the success observed with the crotylation reactions described in Schemes 6 and 7, we wondered whether substitution of the allylsilane with groups other than methyl might be tolerated as well. Indeed, in the arena of imine allylation (as opposed to aldehyde allylation) there is no particular reason for an emphasis on crotylation. The incorporation of aryl groups into the allylic position of the products by way of cinnamylation reactions might be expected to be far more important, especially from a medicinal chemistry perspective. Gratifyingly, cinnamylsilane **25** smoothly cinnamylated the benzaldimine derived from 2-aminophenol to give the syn product as the major diastereomer (**Scheme 8**).[24] Remarkably, the product was produced in 99% ee despite the fact that, to achieve a reasonable reaction rate, the cinnamylation had to be carried out in refluxing 1,2-dichloroethane (DCE). Furthermore, when the same reaction was carried out with the related benzaldimine derived from 2-(aminomethyl)phenol, the corresponding anti diastereomer was obtained exclusively in 97% ee. Both diastereomers of the product amines are thus accessible *from the same trans cinnamylsilane* based only on the absence or presence of a methylene group between the imine nitrogen and the phenol ring. Such a "diastereochemical switch" based on a seemingly trivial change to the structure of the imine is unprecedented and has significant practical implications, not least of all that it obviates the traditional necessity of synthesizing both the trans



Silane	R^3	R^4	Method[a]	Yield	dr	ee
1	$BnCH_2$	Me	**A**	40%	---	87%
1	Cy	Me	**A**	85%	---	92%
16	Cy	Me	**A**	64%	99:1	93%
1	Ph	H	**B**	83%	---	96%
1	2-MeC_6H_4	H	**B**	89%	---	96%
1	furan-2-yl	H	**B**	71%	---	90%
16	Ph	H	**B**	64%	98:2	98%
17	Ph	H	**B**	74%	96:4	99%

[a] Method **A**: Et_2O, 23 °C, 20 h; Method **B**: CH_2Cl_2, 23 °C, 16 h.

Scheme 6. Phenol-Directed/Activated Enantioselective Allylation and Crotylation of Aldimines and Ketimines. *(Ref. 22)*



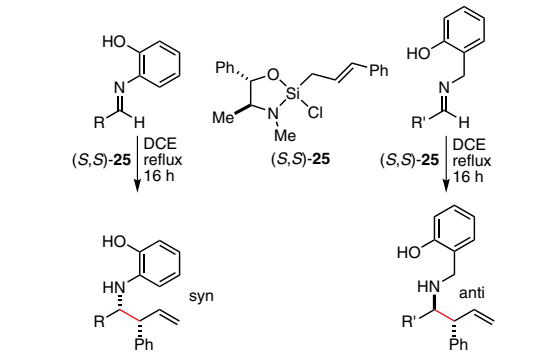
Silane	R^3	R^4	Yield	ee
20	H	$H_2CCH{=}CH_2$	80%	87%
20	H	Cy	85%	95%
20[a]	H	$(CH_2)_3CO_2Me$	71%	88%
20	Me	$H_2CCH{=}CH_2$	85%	91%
20[b]	Ph	$H_2CCH{=}CH_2$	69%	70%
21[c]	H	$H_2CCH{=}CH_2$	66%	86%
22[c]	H	$H_2CCH{=}CH_2$	74%	89%

[a] After the reaction was complete (1 h), the mixture was heated to 45 °C for 1 h to effect lactamization in situ. The isolated product was the lactam. [b] At 10 °C for 38 h. [c] dr > 20:1.

Scheme 7. Imidazole-Directed/Activated Allylation of Aldimines and Ketimines. *(Ref. 23)*

and cis cinnamylsilanes in order to access both diastereomers of the cinnamylated product.

As synthetically powerful as this methodology may be, its broad use in medicinal chemistry still faced a significant obstacle in that each different aryl group to be incorporated in this fashion would require a de novo synthesis of the corresponding cinnamylsilane. We therefore sought a method by which a collection of simple and readily available arene building blocks might be employed in this chemistry in easy-to-perform one-pot operations. Cross metathesis (CM) between allylsilane **1** (which can easily and inexpensively be prepared in multikilogram quantities) and vinylarenes seemed a direct and potentially straightforward solution, and indeed the second-generation Grubbs catalyst (Grubbs II) smoothly catalyzed a highly trans-selective CM between allylsilane **1** and vinylarenes.[25,26] The imine of choice may be added to the reaction pot upon completion of the CM reaction, and several examples of this simple one-pot procedure are summarized (**Scheme 9**). Stereochemically and functionally complex homoallylamines may thus be assembled in a single step from (*S*,*S*)-**1**, an imine, and a vinylarene. The example with 2-chloro-3-vinylpyridine makes clear the excellent functional group tolerance of the process, and the one-pot hydroformylation–reductive amination of the CM–cinnamylation product into the corresponding piperidine derivative illustrates the power of this method to deliver complex heterocyclic structures in just two operationally simple steps.



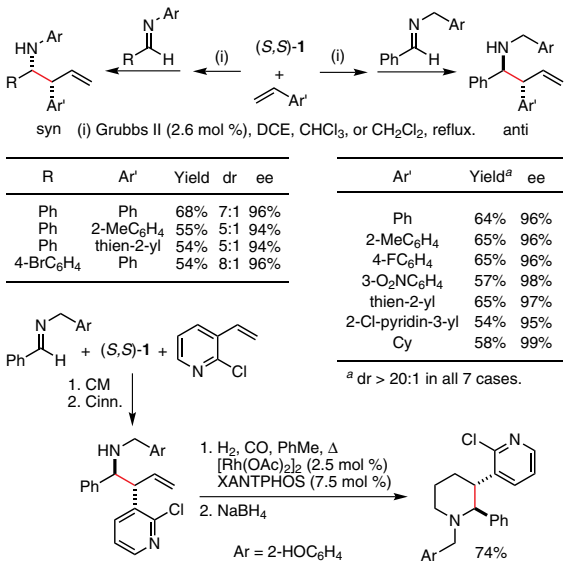
R	Yield	dr	ee
Ph	87%	7:1	99%
4-BrC$_6$H$_4$	79%[a]	13:1	97%
4-NCC$_6$H$_4$	66%	18:1	90%
4-MeOC$_6$H$_4$	53%	5:1	96%
thien-2-yl	69%	11:1	96%
Cy	60%[b,c]	>20:1	95%
BnCH$_2$	53%[b,d]	>20:1	98%

[a] At 60 °C. [b] The N-substituent was 2-HO-6-MeC$_6$H$_3$ instead of 2-HOC$_6$H$_4$. [c] In $CHCl_3$ at 50 °C. [d] In CH_2Cl_2 at reflux.

R'	Yield[a]	ee
Ph	91%	97%
4-O$_2$NC$_6$H$_4$	70%	95%
4-NCC$_6$H$_4$	73%	96%
4-MeOC$_6$H$_4$	89%	94%
thien-2-yl	77%	93%
2-MeOC$_6$H$_4$	77%	99%
BocN-indol-3-yl	51%[b]	98%

[a] In all cases, dr > 20:1. [b] At 60 °C.

Scheme 8. Diastereodivergent Cinnamylation of Aldimines. *(Ref. 24)*



R	Ar'	Yield	dr	ee
Ph	Ph	68%	7:1	96%
Ph	2-MeC$_6$H$_4$	55%	5:1	94%
Ph	thien-2-yl	54%	5:1	94%
4-BrC$_6$H$_4$	Ph	54%	8:1	96%

Ar'	Yield[a]	ee
Ph	64%	96%
2-MeC$_6$H$_4$	65%	96%
4-FC$_6$H$_4$	65%	96%
3-O$_2$NC$_6$H$_4$	57%	98%
thien-2-yl	65%	97%
2-Cl-pyridin-3-yl	54%	95%
Cy	58%	99%

[a] dr > 20:1 in all 7 cases.

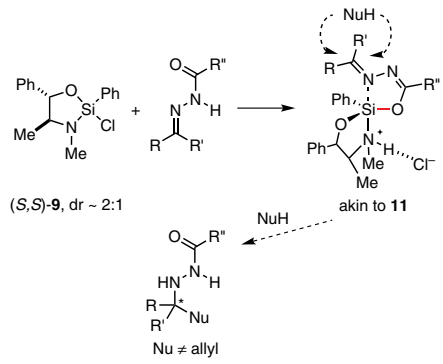
Scheme 9. Tandem Cross-Metathesis–Cinnamylation of Aldimines. *(Ref. 25)*

3. Nucleophilic Additions to Acylhydrazones Activated with Silane Lewis Acids

Encouraged by the remarkable synthetic power and generality of allylsilane **1**, and informed by the X-ray crystal structure of **11** (see Scheme 3), it was natural to wonder whether the related phenylsilane **9** might serve as a general Lewis acid for the activation of acylhydrazones towards non-allyl nucleophiles (**Scheme 10**).[27] We were particularly intrigued by the notion of devising a "universal" Lewis acid—one that can activate any member of a given class of electrophile (acylhydrazones, in this case) towards a variety of different nucleophilic addition reactions—and we were further hopeful that this approach might facilitate otherwise difficult transformations. As will be described below, silane **9** is not only generally effective for the activation of acylhydrazones towards a variety of different nucleophilic addition reactions, but is also effective for the activation of other imine derivatives as well.

3.1. Friedel–Crafts Alkylations with Acylhydrazones

The addition of electron-rich arenes to glyoxylate-derived imines, in an overall Friedel–Crafts-like alkylation reaction, provides access to valuable arylglycine derivatives.[28] We have found that silane **9** smoothly promotes the addition of anilines to the benzoylhydrazone of isopropyl glyoxylate (**Scheme 11**).[27] Ortho substitution on the arene nucleophile is well tolerated, as is the use of heteroaromatic nucleophiles, and the products are obtained with good-to-excellent levels of enantioselectivity. The reaction is easily scaled as the illustrated example (5-g scale) documents, and pseudoephedrine is recovered in essentially quantitative yield. Conversion of the hydrazide functionality into the more generally useful Boc-protected amine was straightforward and proceeded without racemization.



Scheme 10. Proposed Enantioselective Nucleophilic Additions to Silane–Acylhydrazone Complexes. *(Ref. 27)*

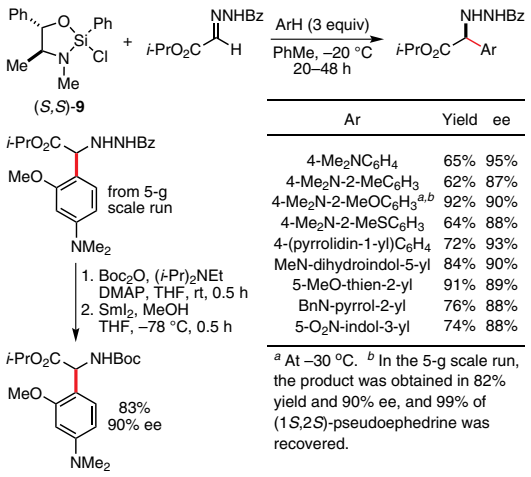
3.2. Acylhydrazone–Alkene [3 + 2] Cycloaddition Reactions

Silane **9** is also competent to activate acylhydrazones towards nucleophilic attack by electron-rich olefins, such as enol ethers. In contrast to the Friedel–Crafts chemistry, the oxocarbenium ion intermediate that results from attack of an enol ether on the silane-acylhydrazone complex persists long enough to be trapped by the acylated nitrogen atom, and a (stepwise) [3 + 2] cycloaddition reaction is the result. A variety of aliphatic and aromatic aldehyde-derived benzoylhydrazones may be reacted with *tert*-butyl vinyl ether to give pyrazolidines with excellent levels of enantioselectivity (**eq 2**).[29,30] Larger-scale (5 g of hydrazone) reactions of two substrates were carried out in order to demonstrate the true practicality and scalability of the method. These are "dump-and-stir" reactions that are carried out in toluene at ambient temperature, and the products may be isolated by recrystallization as single diastereomers in high yield and 99% ee. In both cases, pseudoephedrine was recovered in essentially quantitative yield as well.

3.3. Tandem Aza-Darzens–Ring-Opening Reactions

Silane **9** is effective in the promotion of aza-Darzens reactions[31,32] of acylhydrazones with the stabilized sulfonium ylide derived from the rhodium-catalyzed reaction of ethyl diazoacetate and diphenyl sulfide.[33] Rather than the aziridine products, however, it is the ring-opened β-chloro-α-hydrazido esters that are isolated as single diastereomers with good-to-excellent levels of enantioselectivity, albeit with varying levels of regioselectivity (**eq 3**).[34] The chloride ion is liberated in the silane–acylhydrazone complexation event and is competent to open the initially formed aziridine products. Thus, it is important to note that the silane Lewis acid not only activates the hydrazone toward attack by the ylide, but also activates the aziridine toward nucleophilic ring opening by the chloride ion.

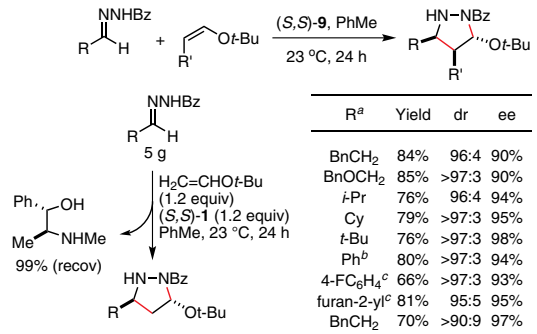
If the same reaction is carried out and a nucleophilic arene and $ZnCl_2$ are added prior to workup, the products formed are diarylalanine derivatives (**Scheme 12**).[34] The products are produced and isolated as single diastereomers and single regioisomers in 91–94% ee. The two-step conversion of one of the products into a trifluoroacetamide-protected α-amino ester was demonstrated as well. The role of $ZnCl_2$ appears to be to accelerate the reversion of the initially produced β-chloro-α-hydrazido esters back to the aziridines, which, activated by the silane Lewis acid, undergo nucleophilic attack by the arene. Stereochemically and functionally complex diarylalanine derivatives may thus be assembled from an acylhydrazone, ethyl diazoacetate, and an arene in a one-pot operation, in which silane Lewis acid **9** performs two distinct functions.



Ar	Yield	ee
4-$Me_2NC_6H_4$	65%	95%
4-Me_2N-2-MeC_6H_3	62%	87%
4-Me_2N-2-$MeOC_6H_3$[a,b]	92%	90%
4-Me_2N-2-$MeSC_6H_3$	64%	88%
4-(pyrrolidin-1-yl)C_6H_4	72%	93%
MeN-dihydroindol-5-yl	84%	90%
5-MeO-thien-2-yl	91%	89%
BnN-pyrrol-2-yl	76%	88%
5-O_2N-indol-3-yl	74%	88%

[a] At –30 °C. [b] In the 5-g scale run, the product was obtained in 82% yield and 90% ee, and 99% of (1*S*,2*S*)-pseudoephedrine was recovered.

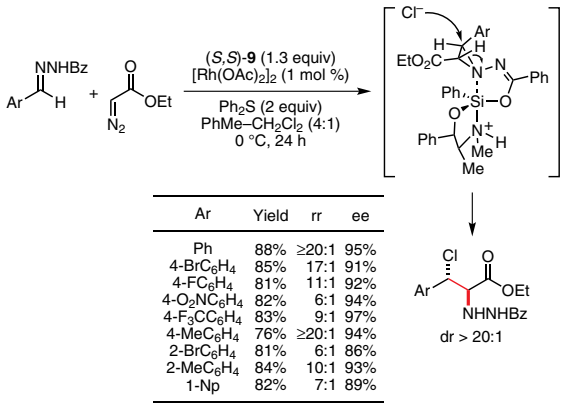
Scheme 11. Enantioselective Friedel–Crafts Alkylations with Acylhydrazones. *(Ref. 27)*



R^a	Yield	dr	ee
$BnCH_2$	84%	96:4	90%
$BnOCH_2$	85%	>97:3	90%
i-Pr	76%	96:4	94%
Cy	79%	>97:3	95%
t-Bu	76%	>97:3	98%
Ph[b]	80%	>97:3	94%
4-FC_6H_4[c]	66%	>97:3	93%
furan-2-yl[c]	81%	95:5	95%
$BnCH_2$	70%	>90:9	97%

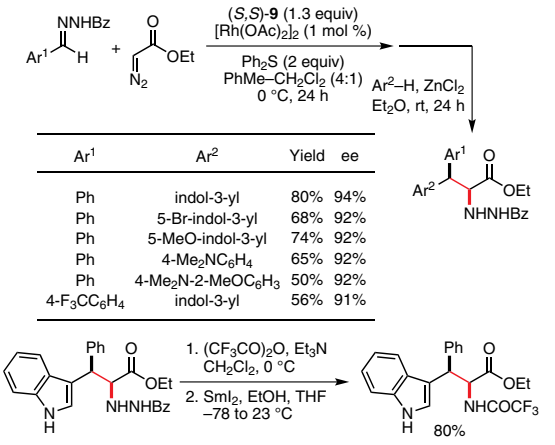
[a] R' = H, except for the last entry where R' = Me. [b] At 40 °C for 50 h. [c] At 40 °C.

eq 2 *(Ref. 29)*



Ar	Yield	rr	ee
Ph	88%	≥20:1	95%
4-BrC_6H_4	85%	17:1	91%
4-FC_6H_4	81%	11:1	92%
4-$O_2NC_6H_4$	82%	6:1	94%
4-$F_3CC_6H_4$	83%	9:1	97%
4-MeC_6H_4	76%	≥20:1	94%
2-BrC_6H_4	81%	6:1	86%
2-MeC_6H_4	84%	10:1	93%
1-Np	82%	7:1	89%

eq 3 *(Ref. 34)*



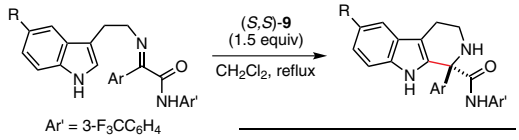
Ar^1	Ar^2	Yield	ee
Ph	indol-3-yl	80%	94%
Ph	5-Br-indol-3-yl	68%	92%
Ph	5-MeO-indol-3-yl	74%	92%
Ph	4-$Me_2NC_6H_4$	65%	92%
Ph	4-Me_2N-2-$MeOC_6H_3$	50%	92%
4-$F_3CC_6H_4$	indol-3-yl	56%	91%

Scheme 12. Enantioselective Tandem Aza-Darzens–Ring-Opening Reactions. *(Ref. 34)*

4. Pictet–Spengler Reactions with α-Ketoamide-Derived Ketimines

We have recently sought to explore the possibility that silane **9** might effectively activate imine types other than acylhydrazones. This effort was inspired by consideration of the Pictet–Spengler reaction, since the imine N-substituent must, by definition, be a two-carbon chain and cannot therefore perform the requisite directing/activating function. From a synthetic perspective, we hoped to provide a solution to the challenging problem of enantioselective *ketimine* Pictet–Spengler reactions, as there have only been a few examples of this reported to date.[35,36] It was found that ketimines prepared from α-ketoamides and tryptamines were indeed subject to smooth promotion of Pictet–Spengler reactions by silane **9**, wherein it is the amide functionality that, in analogy to the acylhydrazones, displaces the chloride from the silane Lewis acid and generates the activating equivalent of HCl.[37] Upon optimization, a very straightforward procedure was developed, a range of aryl ketone derived substrates were employed, and the corresponding tetrahydro-β-carboline products isolated with good-to-excellent levels of enantioselectivity (**eq 4**).[37] A larger-scale (5 mmol of substrate) example was also performed, wherein the product was isolated without chromatography in 79% yield and 99% ee (after recrystallization), and with quantitative recovery of pseudoephedrine.

It was further found that α-ketoamide-derived imines with aliphatic substituents also perform well in the asymmetric Pictet–Spengler reaction promoted by silane **9**. A reoptimization of the amide-directing group was necessary, as was a reoptimization of the reaction conditions. Eventually, a convenient one-pot procedure was developed, wherein the tryptamine and ketone are heated at reflux in toluene with a Dean–Stark trap, and then silane **9** is simply added (**eq 5**).[37] Using this procedure, 1-alkyl-1-carboxamide-substituted tetrahydro-β-carbolines were prepared with good-to-excellent levels of enantioselectivity.

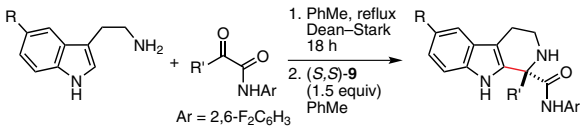


Ar' = 3-$F_3CC_6H_4$

R	Ar	Time	Yield	ee
H	Ph	48 h	93%	93%
H[a]	Ph	48 h	79%	99%
Br[b]	Ph	70 h	68%	89%
MeO	Ph	27 h	93%	82%
H	4-BrC_6H_4	48 h	85%	90%
H	4-$F_3CC_6H_4$	48 h	89%	90%
H[b]	4-$MeOC_6H_4$	20 h	94%	87%
H	2-Np	46 h	82%	91%
H	pyridin-3-yl	42 h	77%	87%
H[c]	1-Np	60 h	50%	87%
H[c]	2,4-$Cl_2C_6H_3$	60 h	86%	90%

[a] 5-mmol scale run: product was isolated by recrystallization and pure (1*S*,2*S*)-pseudoephedrine was recovered in quantitative yield. [b] $CHCl_3$ employed instead of CH_2Cl_2. [c] 2 equiv of (*S*,*S*)-**9** utilized, and DCE used instead of CH_2Cl_2.

eq 4 *(Ref. 37)*



R	R'	Temp	Time	Yield	ee
H	Me	50 °C	36 h	78%	89%
Br	Me	80 °C	48 h	67%	86%
MeO	Me	50 °C	48 h	86%	81%
H	*i*-Bu	50 °C	26 h	81%	90%
H	*i*-Pr	55 °C	25 h	83%	94%

eq 5 *(Ref. 37)*

5. Conclusions and Outlook

The chemistry described herein represents a significant advance in the effective use of silicon as a Lewis acid. The deceptively simple notion that launched this program was that synthetically useful levels of Lewis acidity may be induced in silanes merely by constraining them within 5-membered rings with 1,2-diols, amino alcohols, or diamines. It also led to the discovery of the chloride displacement–HCl activation mechanism, which provided the boost in reactivity that was essential for the development of almost all of the chemistry discussed in this review. Among the noteworthy features of the silane Lewis acid motif that we have developed is the remarkable generality of pseudoephedrine as the chiral controller. Whether the directing/activating group is an acylhydrazone, an aminophenol, an aminomethylphenol, or an *N*-arylamide; and whether the directing/activating functionality is the imine N-substituent or is contained within the substrate; silanes **1** and **9** provide consistently high levels of enantioselectivity for a wide range of substrates in both allylation and non-allylation nucleophilic addition reactions. While they are a long way from being truly "universal" Lewis acids, they can lay a strong claim to a high degree of versatility.

The use of silanes **1** and **9** in stoichiometric amounts (a consequence of the mechanism by which they act) may cause consternation to the extent that it cuts against current dogma in asymmetric reaction design, but the fact remains that, by any criteria that can be measured, the use of pseudoephedrine in stoichiometric amounts is, in practical and economic terms, competitive with most chiral ligands employed in sub-stoichiometric quantities. The considerable practical advantages that accrue to the use of silicon as the Lewis acidic element; the ease of recovery of pseudoephedrine by extraction, as demonstrated in several gram-scale reactions; and, most importantly, the fact that this strategy has led to the development of practical and scalable solutions to several otherwise difficult asymmetric transformations (e.g., ketimine allylations and Pictet–Spengler reactions) all strongly support claims of practicality and justify the development of this methodology. We anticipate that there will be many other effective directing/activating groups discovered, and many other important and otherwise challenging transformations that may be effectively addressed by silanes **1** and **9**. We are confident that these extraordinarily simple, yet highly effective, Lewis acids will find widespread utility, particularly in the arena of pharmaceutical chemistry.

6. Acknowledgments

This work was supported by grants from NIH-NIGMS (R01 GM58133) and NSF (CHE-04-53853 and CHE-08-09659), and by a Johnson & Johnson Focused Funding Award. Generous unrestricted support from Merck Research Laboratories, Amgen, and Bristol-Myers Squibb is acknowledged as well.

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Keywords: silicon Lewis acid; strained silacycles; allylsilane; asymmetric synthesis; chiral carbinamines.

About the Author

James L. Leighton was born in 1964 in New Haven, Connecticut. He received a B.S. degree in chemistry in 1987 from Yale University, where he worked in the laboratory of Professor Samuel Danishefsky. After a year and a half as a research chemist with the

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		200	7	Z569313-5EA
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		400	8	Z569356-5EA
		500	7	Z569364-5EA
		500	8	Z569372-5EA
		600	7	Z569380-5EA
		600	8	Z569399-5EA
		800	7	Z569402-5EA
		800	8	Z569410-5EA
Thrift	Yellow	200	7	Z569216-5EA
		200	8	Z569224-5EA
		300	7	Z569232-5EA
		300	8	Z569240-5EA
		400	7	Z569259-5EA
		400	8	Z569267-5EA
		500	7	Z569275-5EA
		500	8	Z569283-5EA
Disposable	Blue	200	7	Z569194-50EA
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Copper-Free Click Chemistry: Bioorthogonal Reagents for Tagging Azides

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Outline

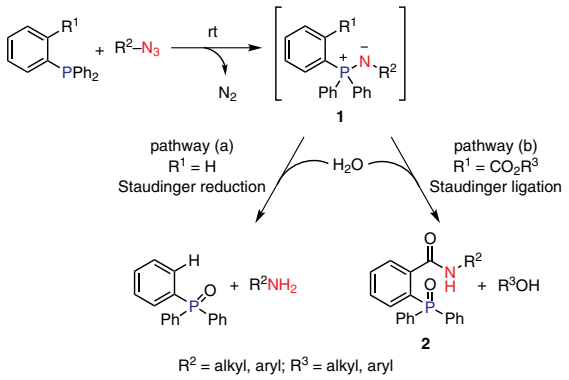
1. Introduction

In the 20th century, the azide functional group was widely used in the synthesis of nitrogen-containing natural products and medicinal agents. For example, the azide is one of the most popular amine precursors, and its ability to undergo 1,3-dipolar cycloadditions and diazo-transfer reactions has been capitalized on in many transformations. In biological settings, however, the azide played a relatively minor role during the same period of time. Sodium azide is a familiar metabolic poison and preservative, and aryl azides are well-known photoactivated cross-linkers; but, otherwise, azides were of little consequence to chemical biologists.[1,2] In the last decade, however, the azide has emerged as a rising star in bioconjugation chemistry, as numerous research groups have capitalized on its dual nature as a soft electrophile and a 1,3-dipole to develop highly selective, water-compatible reactions that employ the azide as a coupling partner. These "azido ligation" reactions have opened the door to applications beyond organic synthesis in fields as diverse as molecular imaging and biomaterials synthesis. These reactions are now at the leading edge of the emerging field of bioorthogonal chemistry (vide infra).

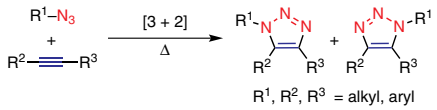
The first reported ligation strategy involving azides was a modification of the classical Staudinger reduction with phosphines. In the traditional Staudinger reduction,[3] attack of the nucleophilic phosphine on the γ position of the azide generates aza-ylide intermediate **1**, which undergoes hydrolysis to produce an amine and a phosphine oxide (**Scheme 1**, pathway (a)). We realized that under the right circumstances, the nucleophilic character of the aza-ylide intermediate could be harnessed for selective acylation of the α-nitrogen atom.[3] This feat was accomplished by installing an ester at a position on triphenylphosphine that would facilitate rapid intramolecular reaction with the aza-ylide. After hydrolysis, an amide bond was formed, and the phosphine oxide was part of the final ligation product, **2**. The overall transformation was named the Staudinger ligation (**Scheme 1**, pathway (b)).[3]

This reaction displays exquisite chemoselectivity. Not only does it proceed with no observable aza-ylide hydrolysis in aqueous solution, but the reaction can occur in the presence of numerous nucleophiles and electrophiles that are present within complex biological systems.[3] Importantly, the triarylphosphine reagents are not toxic to cultured mammalian cells or laboratory mice, setting the stage for numerous biological applications.[4] As a second-order chemical reaction, however, the Staudinger ligation possesses modest kinetic parameters ($k = 2.4 \times 10^{-3}$ $M^{-1}s^{-1}$ for reaction with benzyl azide ($PhCH_2N_3$) in 9:1 CD_3CN–H_2O).[5] Attempts to increase the intrinsic rate constant, which would enable more efficient ligation under circumstances where reaction time or reagent concentration are limiting, have thus far proven futile, in part due to the unfortunate side reaction of phosphine oxidation.[5]

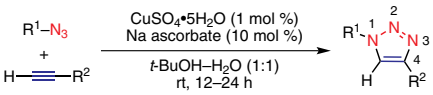
Thus, some chemists have turned to another of the azide's modes of reactivity, its 1,3-dipolar character. Again, the classic organic chemistry literature provided a starting point: in this case, studies of [3 + 2] cycloadditions between azides and alkynes to form 1,2,3-triazoles, first observed in 1893 by Michael and examined thoroughly by Huisgen seventy years later (**eq 1**).[6,7] The reaction intrigued physical organic chemists, but its high activation barrier, which could only be overcome by elevated temperatures or pressures, deterred synthetic organic chemists from using the reaction. In 2002, Sharpless and Meldal independently discovered that copper catalysis dramatically accelerates the rate of formal cycloaddition between azides and terminal alkynes.[8,9] This variant of the Huisgen cycloaddition, termed CuAAC for Cu-catalyzed azide–alkyne cycloaddition, proceeds rapidly at ambient temperatures and pressures to form 1,4-disubstituted 1,2,3-triazoles exclusively (**eq 2**).[8] CuAAC is an exceptional example of "click chemistry", a term coined by Sharpless and co-workers to describe a set of chemical reactions that efficiently link two components in high yield and with minimal byproducts.[10]



Scheme 1. The Staudinger Reduction and Staudinger Ligation. (For more details, see the entry for reference 3 in Section 6.)

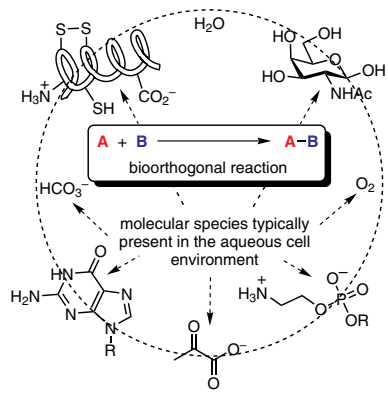


eq 1 *(Ref. 6,7)*



R^1	R^2	Yield
$BnOC(O)CH_2$	Ph	92%
$[(HO)CH_2]_2C(CH_2)_2$	Ph	93%
2-HO-cyclohexyl	Ph	82%
1-Ad	Ph	84%
$3\text{-}H_2NO_2SC_6H_4$	$H_2NC(=NH)NHCH_2$	91%
3-(tetrazol-5-yl)$C_6H_3CH_2$	$H_2NC(=NH)NHCH_2$	88%
$BnOCH_2$	CO_2H	88%
Bn	(*E*)-$HOCH_2CH{=}C(Me)$	84%
Bn	phthalimide-*N*-CH_2	88%
Bn	Et_2NCH_2	90%
(*S*)-$HOCH_2CH(OH)CH_2$	estradiol-17-yl	94%

eq 2 *(Ref. 8)*



eq 3 *(Ref. 14,15)*

The applications of CuAAC have grown tremendously since the reaction was first reported in 2002. In fact, its popularity as the archetypal "click" reaction has led many to simply refer to it as click chemistry. Some applications of CuAAC include the synthesis of small-molecule libraries for drug discovery,[11] the creation of novel supramolecular assemblies such as polymers and dendrimers,[12] and the selective labeling of biological molecules.[13] Though the technological breakthrough of Cu catalysis has enabled these and countless other applications, CuAAC is not without its limitations. Most problematic is the toxic nature of the requisite metal catalyst, which precludes many applications of CuAAC in living biological systems (e.g., imaging proteins and other biomolecules within live cells and animals).

Inspired by the ability of a simple copper catalyst to dramatically improve the kinetics of the Huisgen 1,3-dipolar azide–alkyne cycloaddition, we sought to identify an alternate means of alkyne activation that avoided the use of a toxic catalyst. Such a copper-free, [3 + 2] cycloaddition would, in theory, combine the desirable characteristics of CuAAC and the Staudinger ligation: rapid kinetics and biocompatibility.

This review describes our and others' efforts in developing "copper-free click chemistry", as well as selected applications in chemical biology and materials science. Central to the development of new reagents for this type of chemistry is the concept of bioorthogonality (**eq 3**).[14,15] For a chemical reaction to be useful for labeling applications within a biological system, the reagents must (i) not cross-react with any of the functional groups present in cells, (ii) selectively form covalent bonds in aqueous media at ambient temperatures and pressures, and (iii) be nontoxic to the biological system. In short, the reagents must be bioorthogonal, i.e., noninteracting with biology.

2. Development of Copper-Free Click Chemistry

2.1. Strain-Promoted [3 + 2] Cycloaddition of Cyclooctynes with Azides

The introduction of strain into organic molecules can raise their ground state energies and hence lower reaction barriers in cycloaddition reactions. Classic examples include the use of strained alkenes such as norbornene in Diels–Alder [4 + 2] cycloadditions. We reasoned that an alkyne constrained in a medium-size ring might display enhanced reactivity toward azides in a 1,3-dipolar cycloaddition. In fact, Wittig and Krebs observed in 1961 that cyclooctyne, the smallest stable cycloalkyne, reacted "like an explosion" when mixed with phenyl azide to produce a single triazole product.[16] The enhanced reactivity in the [3 + 2] cycloaddition of cyclooctyne, as compared to a linear, unstrained alkyne, likely derives from the roughly 18 kcal/mol of ring-strain energy present in cyclooctyne, a portion of which is released during the reaction.[17]

Motivated by these studies, we set out to synthesize a derivative of cyclooctyne containing a readily functionalizable side chain, in this case a carboxylic acid.[18] The installation of such a side chain enabled the facile conjugation of the cyclooctyne nucleus to molecular probes (e.g., fluorophores or affinity agents) or supramolecular scaffolds (e.g., polymers, cross-linking agents, resins, etc.). We termed this first-generation reagent OCT, for cyclooctyne, and synthesized it using a modification of the route of Reese and Shaw,[19] via a *trans*-1-bromocyclooctene intermediate. We first determined the stability, selectivity, and reaction kinetics of the new reagent. Fortunately, OCT was stable in water and to model nucleophiles (e.g., 2-mercaptoethanol). Kinetic studies of model [3 + 2] cycloadditions performed with a variety of organic azides (e.g., benzyl azide, 2-azidoethanol,

and *N*-butyl-α-azidoacetamide) revealed efficient formation of two regioisomeric 1,2,3-triazoles (**eq 4**) with second-order rate constants of 1.1–2.4 × 10^{-3} $M^{-1}s^{-1}$, comparable to those measured for model Staudinger ligations.[18]

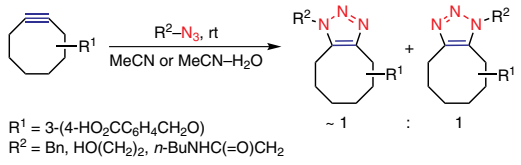
To evaluate the ability of this "strain-promoted" cyclooctyne–azide [3 + 2] cycloaddition to occur selectively within a biological system, we metabolically installed azides into cell-surface glycans using a synthetic azidosugar precursor and then reacted the cells with a biotinylated OCT derivative (OCT-biotin). In this case, we first treated Jurkat T cells with peracetylated *N*-azidoacetylmannosamine (Ac_4ManNAz), which is biosynthetically converted into an azido sialic acid residue (SiaNAz) within cell-surface glycans.[20] We then treated the cells with OCT-biotin and detected the extent of [3 + 2] cycloaddition at the cell surface by staining the cells with a fluorescent avidin conjugate and analyzing them by flow cytometry. Through these studies, we demonstrated that OCT-biotin has no cellular toxicity and displays similar reaction kinetics to the Staudinger ligation in the context of cell-surface labeling.[18]

At this point, we were keen to improve the sensitivity of the cyclooctyne reagents for detecting azides, with an eye toward biological imaging applications (i.e., using cyclooctyne-fluorophore conjugates). To accomplish this, we needed to enhance the kinetics of the [3 + 2] cycloaddition, which would require either an increase in (i) reagent concentration, (ii) reaction temperature, or (iii) reaction time; or else (iv) an improvement in the intrinsic second-order rate constant. Among the items on that list, the first two risk generating toxicity problems, as well as potential background fluorescence arising from the inability to rinse away unreacted cyclooctyne-fluorophore conjugate in the case of (i). While increased reaction time can afford higher yields and therefore greater sensitivity, biological systems are inherently dynamic and, therefore, to image rapid biological processes that occur on the second and minute timescales, increasing the reaction time is not an ideal solution. Thus, we set out to improve the intrinsic kinetics of the strain-promoted cycloaddition by synthesizing cyclooctynes that would be more reactive toward azides.

2.2. Improving [3 + 2] Cycloaddition Kinetics by Using Fluorinated Cyclooctynes

Our initial efforts to improve the kinetics of the [3 + 2] cycloaddition centered on the installation of electron-withdrawing groups (EWGs) adjacent to the triple bond in the cyclooctyne ring. This approach—appending EWGs to the 2π component in a [4π + 2π] cycloaddition—has been highly successful both in Diels–Alder and 1,3-dipolar cycloadditions.[7] Among the various options, we elected to attach fluorine atoms, which are strongly electron-withdrawing through σ bonds, to the cyclooctyne ring. Importantly, this choice avoided the use of a π-based electron-withdrawing group such as a carbonyl, which could have created a Michael acceptor capable of alkylating biological nucleophiles.

In the design of a monofluorinated cyclooctyne, termed MOFO (**Figure 1**),[18,21–23] we eliminated the propargylic ether linkage present in OCT, which exhibited slow decomposition, even at –20 °C.[21] These changes necessitated an entirely different synthetic route, starting with cyclooctanone and principally employing enolate chemistry. Kinetic studies of model [3 + 2] cycloadditions with benzyl azide revealed that MOFO (k = 4.3 × 10^{-3} $M^{-1}s^{-1}$) reacted more rapidly than OCT (k = 2.4 × 10^{-3} $M^{-1}s^{-1}$), suggesting that substitution of the cyclooctyne moiety with a fluorine atom did increase the rate of the strain-promoted cycloaddition (**eq 5**).[21] To quantify the precise effect of fluorine,



eq 4 *(Ref. 18)*

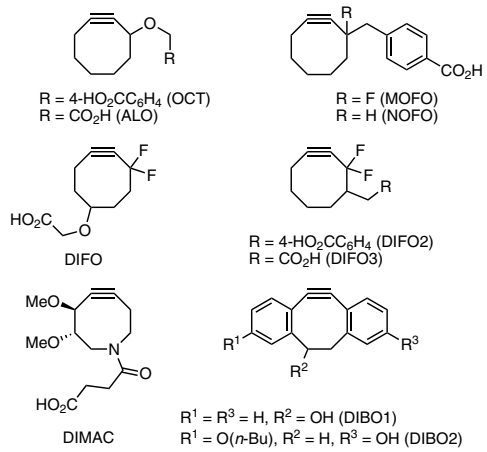
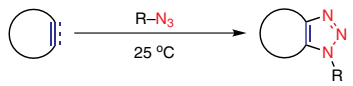


Figure 1. Cyclooctyne Reagents for Copper-Free Click Chemistry. *(Ref. 18,21–23,30–32)*



Alkyne	R[a]	Solvent	k (x 10^{-3} $M^{-1}s^{-1}$)	*Ref.*
OCT	Bn	CD_3CN	2.4	*18*
OCT	*n*-BuNHC(=O)CH_2	CD_3CN	1.9	*18*
OCT	$HO(CH_2)_2$	CD_3CN	1.1	*18*
OCT	$HO(CH_2)_2$	CD_3CN:D_2O[b]	2.0	*18*
MOFO	Bn	CD_3CN	4.3	*21*
NOFO	Bn	CD_3CN	1.2	*21*
DIFO	Bn	CD_3CN	76	*22*
DIFO2	Bn	CD_3CN	42	*23*
DIFO3	Bn	CD_3CN	52	*23*
ALO	Bn	CD_3CN	1.3	*21*
DIMAC	Bn	CD_3CN	3.0	*32*
DIBO1	Bn	CH_3OH	57	*31*
DIBO2[c]	Bn	CH_3OH	76	*31*
DIBO2[c]	*n*-Bu	CH_3OH	59	*31*
DIBO2[c]	Bn(Me)CH	CH_3OH	34	*31*
DIBO2[c]	Ph	CH_3OH	16	*31*
DIBO2[c]	*d*	CH_3OH	44	*31*
Oxanorbornadiene[e]	Bn	CD_3OD	0.85	*34*
Oxanorbornadiene[e]	$H_2N(CH_2)_3$	D_2O	0.70	*34*
Oxanorbornadiene[e]	HO_2CCH_2	D_2O	1.1[f]	*34*

[a] The product triazoles were obtained as ~1:1 mixtures of regioisomers. [b] CD_3CN–D_2O (55:45). [c] In this case, the DIBO2 employed had R^1 = R^3 = O(*n*-Bu) and R^2 = H. [d] *N*-Azidoacetylmannosamine used. [e] 2-Trifluoromethyl-oxanorbornadiene-3-carboxylic acid. [f] Only one regioisomer was observed.

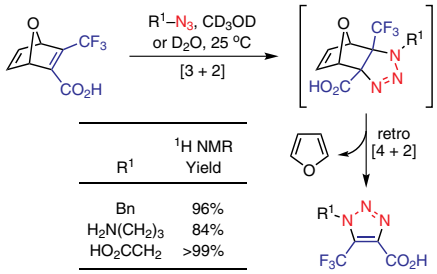
eq 5

we synthesized a nonfluorinated analogue of MOFO termed NOFO (see Figure 1); the rate constant for its reaction with benzyl azide is 1.2×10^{-3} $M^{-1}s^{-1}$, leading us to conclude that a single fluorine atom at the propargylic position increases the reaction rate by almost four-fold (see eq 5).[21]

We then immediately set out to further increase the rate constant by synthesizing difluorinated cyclooctyne reagents, selecting the 3,3-difluorocyclooctyne skeleton, rather than the 3,8-difluorocyclooctyne one, because of the ease of synthesis of the former. The first such difluorinated cyclooctyne reagent, termed DIFO (see Figure 1), was synthesized in nine linear steps and 1% overall yield.[22] Subsequent second-generation reagents, DIFO2 and DIFO3 (see Figure 1), retained the 3,3-difluorocyclooctyne core but contained different linkers and were generated by using vastly simplified synthetic routes.[23] Again, model [3 + 2] cycloaddition reactions with benzyl azide were employed to determine the kinetic parameters, with second-order rate constants in the range of $4.2–7.6 \times 10^{-2}$ $M^{-1}s^{-1}$ (see eq 5).[22,23]

Based on the results of the kinetic studies of the [3 + 2] cycloadditions of NOFO and MOFO with BnN_3, we had anticipated that DIFO would be roughly four-fold faster than MOFO. However, these estimates had assumed a linear relationship between the number of fluorine atoms and reaction kinetics. It is possible that the two fluorine atoms in the CF_2 group act synergistically in terms of their electron-withdrawing power. Indeed, an examination of mean C–F bond lengths in monofluorinated and difluorinated alkanes supports this claim. The mean C–F bond length in all reported small-molecule structures as determined by X-ray and neutron diffraction in monofluoromethine groups (R_3Csp^3–F, where R is an alkyl group) is 1.428 ± 0.009 Å, while that for difluoromethylene groups (R_2Csp^3–F_2) is 1.349 ± 0.012 Å, a difference of 0.08 Å.[24] Based on the simple inverse relationship between force and distance, therefore, the shorter bond lengths in difluoromethylene groups imply that the fluorine-bound carbon is more electropositive than would be predicted from simply doubling the effect of two isolated C–F bonds.

This line of reasoning offers a qualitative explanation for why the DIFO reagents are more than four times faster in model reactions with benzyl azide than MOFO is. In a series of computational studies of 1,3-dipolar cycloadditions between azides and cyclooctynes, Houk and others have proposed that the origin of the observed rate enhancements lies in an evaluation of two energy terms: (a) the distortion energy required to achieve the transition state, and (b) the interaction energies within the transition state.[25–27] More specifically, the rate enhancement using



R^1	^1H NMR Yield
Bn	96%
$H_2N(CH_2)_3$	84%
HO_2CCH_2	>99%

Scheme 2. Rutjes's Tandem [3 + 2] Cycloaddition–Retro-Diels–Alder Reaction of Azides with Electron-Deficient Oxanorbornadiene Derivatives. *(Ref. 34)*

cyclooctyne relative to an unstrained, linear alkyne is attributable to a decrease in distortion energy, while the rapid kinetics utilizing difluorinated relative to nonfluorinated cyclooctynes is explained by an increase in interaction energies.

Studies using live cells whose cell-surface glycans had been metabolically labeled using Ac_4ManNAz revealed that the efficiency of cell-surface labeling amongst the family of cyclooctyne and phosphine reagents mirrored the rate constants determined in model [3 + 2] cycloadditions and Staudinger ligations.[21–23] Applications of these reagents will be discussed in Section 3.

2.3. Other Strained Alkynes and Alkenes for Copper-Free Click Chemistry

Numerous other approaches for improving cyclooctyne kinetics have been taken in the quest for an optimal bioorthogonal reagent for detecting azides. An obvious choice would be to further increase ring strain. While cycloheptynes and cyclooctenynes are isolable but unstable at room temperature, dibenzocyclooctyne, containing two fused benzene rings formally in conjugation with the alkyne, has long been known to be an unexpectedly stable molecule.[28,29] Boons and co-workers recently synthesized dibenzocyclooctynol (DIBO) reagents (DIBO1 and DIBO2; see Figure 1) that can be easily functionalized, and they demonstrated that these compounds underwent rapid copper-free [3 + 2] cycloaddition with azides.[30] Kinetic measurements by Boons, Popik, and co-workers of model reactions of the two DIBO probes with various azides yielded second-order rate constants of $1.6–7.6 \times 10^{-2}$ $M^{-1}s^{-1}$, similar to those of reactions involving DIFO reagents (see eq 5).[31] In comparative biological labeling studies—in which Jurkat cells displaying SiaNAz residues in their cell-surface glycans were incubated with biotin derivatives of either DIBO1, DIFO, DIFO2, or DIFO3—we have determined that the labeling efficiency of DIBO1 is slightly better than that of DIFO2 or DIFO3 but slightly worse than that of DIFO, consistent with the rates measured in model reactions (see eq 5).[22,31] Further electronic and steric modifications to the dibenzocyclooctyne scaffold represent a fruitful area for reagent optimization. Additionally, Boons, Popik, and co-workers demonstrated that the dibenzocyclooctyne functionality could be masked as a cyclopropenone, enabling the light-triggered unveiling of the alkyne with spatial and temporal control.[31]

Beyond improved reaction kinetics, we had recognized early on that the hydrophobicity of the cyclooctyne probes could present problems in terms of limited water solubility and nonspecific adhesion to membranes and other hydrophobic surfaces in biological systems. To address these concerns, we designed two compounds with increased hydrophilicity, an arylless cyclooctyne analogue of OCT termed ALO and a heterocyclic dimethoxyazacyclooctyne termed DIMAC (see Figure 1).[21,32] Though these compounds lack the difluoromethylene moiety, which we later determined dramatically increases the rate of the 1,3-dipolar cycloaddition with azides, our motivation for the design of these compounds was to minimize lipophilic interactions in complex in vivo settings (e.g., adhesion to membranes or serum proteins in mammals). Indeed, both ALO and DIMAC outperform OCT in their ability to detect azidoglycans on cell surfaces within living mice.[33]

Lastly, Rutjes and co-workers have reported a tandem [3 + 2] cycloaddition–retro-Diels–Alder reaction between azides and electron-poor oxanorbornadienes to yield stable triazoles (**Scheme 2**).[34] The tandem reaction ensures that the unstable triazolene, the initial [3 + 2] cycloadduct between the azide and

the alkene, is converted into the stable, aromatic triazole product. While this reaction has been employed for protein bioconjugation in vitro, its sluggish kinetics ($k \approx 10^{-4}$ to 10^{-3} $M^{-1}s^{-1}$) has limited the use of oxanorbornadiene reagents for in vivo applications, in which extended reaction times are not ideal and toxicity concerns limit the concentration of reagent that can be utilized (see eq 5).[34]

3. Applications of Copper-Free Click Chemistry

In a broad sense, copper-free click chemistry has been applied in two fields of study: chemical biology and materials science. Biological applications range from imaging experiments in live cells and whole organisms to proteomic strategies to identify metabolically labeled biomolecules by mass spectrometry. In materials science, copper-free click chemistry has contributed to the growing area of biocompatible hydrogel development.

3.1. Chemical Biology Applications

Many different approaches have been employed in chemical biology to install the azide functional group as a bioorthogonal handle onto a variety of biological molecules. Within the area of glycobiology, we and others have utilized numerous azidosugars as metabolic labels of cell-surface and intracellular glycans, and we have used copper-free click chemistry to image glycan dynamics in biological systems.[20,22] In particular, fluorophore conjugates of DIFO have proven valuable in this regard, as we have successfully employed these probes to track glycans in cultured cells and in live zebrafish embryos, a useful model for studying vertebrate development (**Figure 2**).[22,35] We have also shown that copper-free click chemistry proceeds in mice, setting the stage for future imaging studies in this valuable model organism for human disease.[22,33]

In addition to glycans, other biomolecules have been imaged within live cells using copper-free click chemistry. Ting and co-workers utilized cyclooctyne probes as part of a method for site-specific protein labeling in mammalian cells. In their approach, the bacterial enzyme lipoic acid ligase (LplA) directs the attachment of an azido lipoic acid analogue to recombinant proteins bearing a consensus sequence termed the lipoate acceptor peptide (**Figure 3**).[36] In a second step, azide-labeled proteins were reacted with MOFO-fluorophore conjugates, enabling the imaging of the trafficking patterns of various cell-surface proteins, including the low-density lipoprotein and epidermal growth factor receptors.[36,37] Cyclooctyne-containing phospholipids have been used to visualize plasma membranes in live cells using copper-free click chemistry.[38] In this case, because the cyclooctyne was first incorporated into the biomolecule, a "fluorogenic" azide—one which only becomes fluorescent upon [3 + 2] cycloaddition—could be used, resulting in very low background due to unreacted fluorescent probe.[39]

Beyond molecular imaging, copper-free click chemistry has seen other applications within chemical biology. Tirrell and co-workers have utilized OCT-biotin to label a library of unnatural proteins displayed on *E. coli* cell surfaces in order to help select for mutant tRNA-synthetase activities.[40] Along a similar vein, Zou and Yin employed a DIFO-biotin derivative to select for adenylase activities in nonribosomal peptide synthase (NRPS) enzymes using a phage display approach.[41] Burkart and co-workers also used copper-free click chemistry to probe the biochemistry of an NRPS system.[42] In

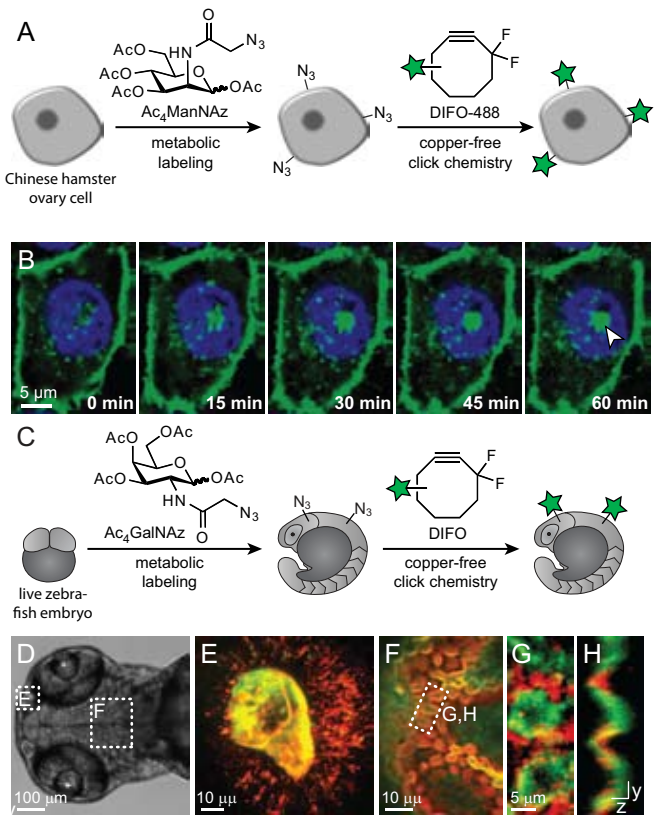


Figure 2. In Vivo Imaging of Glycans in Cultured Cells and Developing Zebrafish Using Copper-Free Click Chemistry. (Parts A and B are reproduced with permission from reference 22. Copyright (2007) National Academy of Sciences U.S.A. Parts C–H are reproduced from reference 35. Copyright (2008) American Association for the Advancement of Science. For more details, see the entries for references 22 and 35 in Section 6.)

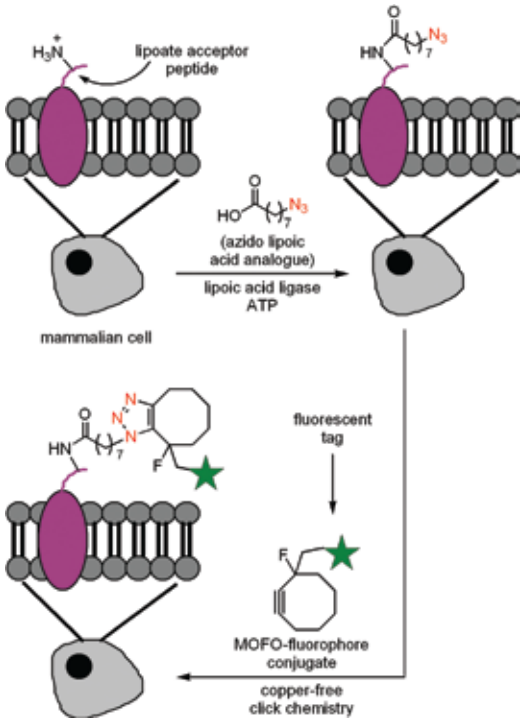


Figure 3. Site-Specific Labeling of Membrane-Resident Proteins Using Lipoic Acid Ligase and Copper-Free Click Chemistry. (For more details, see the entry for reference 36 in Section 6.)

their work, azido and DIFO derivatives of the cofactor pantetheine, which occurs as a posttranslational modification of certain NRPS domains, were utilized to study the assembly of NRPS enzymes. A successful protein–protein interaction between two cognate communication-mediating (COM) domains put the azide and DIFO moieties in close proximity, leading to triazole formation and, hence, NRPS subunit cross-linking, which was easily visualized by polyacrylamide gel electrophoresis (**Figure 4**). In this manner, copper-free click chemistry enabled a simple readout of otherwise difficult-to-observe noncovalent macromolecular interactions.

De Koster and co-workers have recently applied copper-free click chemistry to the area of proteomics.[43] In this work, an azide-reactive cyclooctyne resin containing disulfide-linked NOFO molecules was synthesized and used to capture azidopeptides from whole-cell lysates in which newly synthesized proteins had been metabolically labeled using an azido amino acid. Release of the captured peptides was accomplished by treatment with an alkyl phosphine reagent to reduce the disulfide; subsequent mass spectrometric analysis of the purified peptides enabled the identification of the de novo biosynthesized proteome. Lastly, Wolfbeis and co-workers demonstrated that copper-free click chemistry and CuAAC could be employed sequentially for dual labeling of proteins and nanoparticles, confirming the orthogonality of these two reactions.[44] Furthermore, the same research group monitored matrix metalloproteinase activity in vitro by utilizing a FRET-based silica nanoparticle probe (FRET = Fluorescence Resonance Energy Transfer) that was assembled by using sequential click reactions.[45]

3.2. Materials Science Applications

Copper-free click chemistry has become a valuable tool for materials science applications as well. In some instances, the requirement for a copper-free approach arises from a desire to

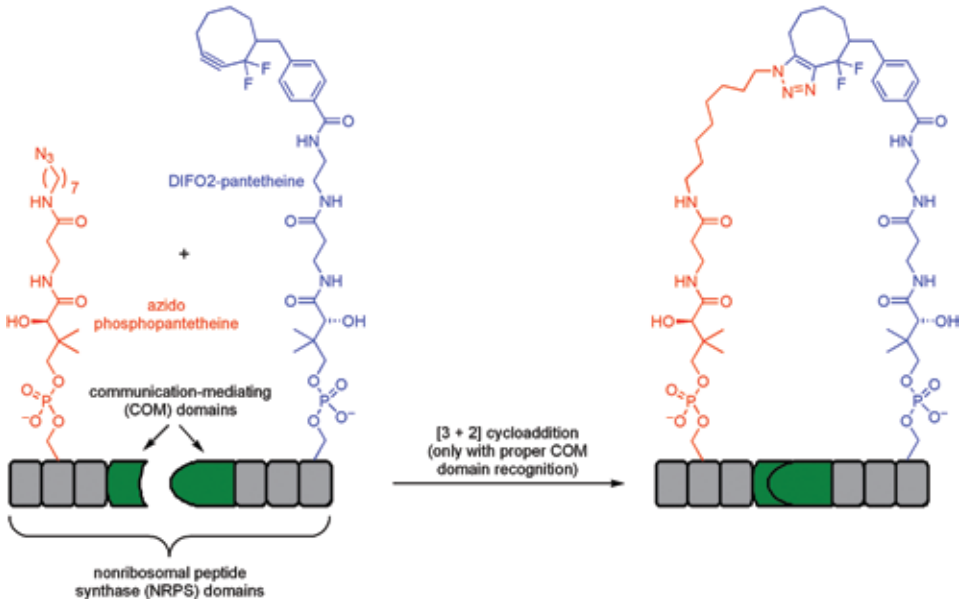


Figure 4. Probing Protein–Protein Interactions Among Nonribosomal Peptide Synthase (NRPS) Family Members Using Unnatural Pantetheine Analogues and Copper-Free Click Chemistry. (For more details, see the entry for reference 42 in Section 6.)

create materials that can interface with biological systems in a nontoxic manner (e.g., synthesis of hydrogels for encapsulation of live cells in 3D). Beyond these biological applications, though, other scenarios exist where utilizing copper is detrimental, necessitating the use of copper-free click chemistry. For example, Fernandez-Megia, Riguera, and co-workers reported that the use of CuAAC to functionalize chitosan–polyethylene glycol (PEG) nanostructures with fluorophores and other probes led to depolymerization of the polysaccharide-based chitosan polymers, presumably through the action of hydroxyl radicals generated by Fenton chemistry in the presence of Cu(I).[46] The same research group discovered that the use of cyclooctyne-functionalized fluorophores, monosaccharides, and even antibodies enabled efficient decoration of the chitosan–PEG nanostructures without any depolymerization.[46]

In addition to the functionalization of traditional nanomaterials, copper-free click chemistry has been utilized to create novel materials (**Figure 5**). Turro and co-workers created photodegradable gels by using a biscyclooctyne compound to cross-link tetraazido "star" polymers containing *ortho*-nitrobenzyl groups, which decompose under UV light.[47] The use of either MOFO or DIFO in the cross-linker enabled the tuning of the gelation kinetics. While these studies employed organic-soluble gels, they set an important precedent that the nontoxic copper-free click chemistry could be utilized to initiate a gelation process. Anseth and co-workers recently reported the generation of biologically compatible hydrogels by using copper-free click chemistry with DIFO3-based peptides to cross-link macromolecular precursors.[48] They encapsulated live cells within the hydrogel with no observed cellular toxicity. Additionally, they incorporated alkene groups into the precursors, allowing further functionalization of the intact hydrogel, with spatial control, by using a photochemically induced thiol–ene coupling reaction.

4. Summary and Outlook

In the six years since the original report that a cyclooctyne reagent could selectively tag azides in a nontoxic reaction,[18] copper-free click chemistry has emerged as a popular bioorthogonal ligation strategy. This reaction has been employed to solve many problems in chemical biology and materials science, and it will undoubtedly have additional applications in these and other areas in the future.[49] Moreover, the methodology itself is ripe for future development. Beyond the strain energy inherent in the cyclooctyne reagent, the second-generation reagents described in this review demonstrate that improved reaction kinetics can be achieved through the fluorination and fusion of benzene rings to the cyclooctyne. Other factors, such as hydrophilicity and synthetic tractability, have also driven methodology development. In the future, entirely novel azide-reactive scaffolds, exemplified by the oxanorbornadiene system, may yield useful reagents. Lastly, chemists have begun to develop new bioorthogonal reactions that do not employ the azide. These include inverse-electron-demand [4 + 2] Diels–Alder cycloadditions of tetrazines with alkenes[50–53] and 1,3-dipolar cycloadditions of nitrile oxides with strained alkenes.[54] Moreover, light-catalyzed processes are gaining in popularity, including thiol–ene reactions[55] and "photoclick" chemistry between in situ generated nitrile imines and alkenes.[56–58] The combination of methodology development and an expanding set of applications underscores the reach of copper-free click chemistry into many areas of science.

5. Acknowledgments

Work in C. R. B.'s laboratory was supported by a grant from the National Institutes of Health (GM058867). J. M. B. was supported by National Science Foundation and National Defense Science and Engineering predoctoral fellowships. We thank Ellen Sletten and Karen Dehnert for a critical reading of the manuscript.

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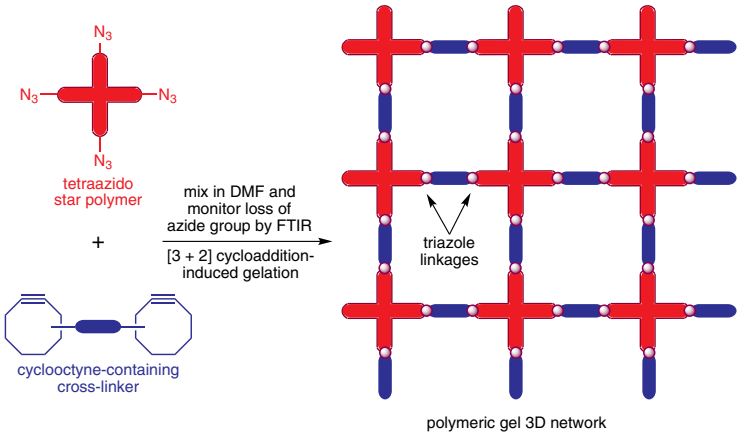

Figure 5. Generation of Novel Gels Using Copper-Free Click Chemistry. (For more details, see the entry for reference 47 in Section 6.)

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of soluble tetraazido star polymers (red) and biscyclooctyne-containing cross-linkers (blue) causes the formation of a 3D gel network (triazole linkages are shown in purple). The use of different star polymers and cross-linkers enables the modulation of gel properties (e.g., solubility, ability to be degraded by UV light, ability to be further functionalized post-gelation with imaging agents, drugs, or other probes). Incorporation of different cyclooctynes into the cross-linker (e.g., MOFO vs DIFO) allows for the tuning of gelation kinetics. See also reference 48.

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Keywords: click chemistry; [3 + 2] cycloaddition; bioorthogonal reagent; cyclooctynes; azides.

About the Authors

Jeremy M. Baskin was born in Montreal, Canada. He received his B.S. degree in chemistry in 2004 from the Massachusetts Institute of Technology (M.I.T.), with minors in biology and music. While at M.I.T., he performed research in the laboratories of Professor Stephen L. Buchwald and Professor Alice Y. Ting. In 2004, Jeremy began graduate studies in the laboratory of Professor Carolyn R. Bertozzi at the University of California, Berkeley. As a graduate student, Jeremy's research focused on the development of fluorinated cyclooctyne reagents for copper-free click chemistry and their application to imaging glycans in vivo. He earned his Ph.D. degree in 2009 and is currently conducting postdoctoral research under the guidance of Professor Pietro De Camilli at the Yale School of Medicine.

Carolyn R. Bertozzi is the T. Z. and Irmgard Chu Distinguished Professor of Chemistry and Professor of Molecular and Cell Biology at UC Berkeley; an Investigator of the Howard Hughes Medical Institute; and Director of the Molecular Foundry, a DOE Nanoscale Science and Research Center at the Lawrence Berkeley National Laboratory. She received her undergraduate degree in chemistry from Harvard University in 1988 and her Ph.D. degree in chemistry from UC Berkeley in 1993. After postdoctoral work at UC San Francisco in the field of cellular immunology, she joined the UC Berkeley faculty in 1996.

Professor Bertozzi's research interests span the disciplines of chemistry and biology with an emphasis on studies of cell surface glycosylation pertinent to disease states. Her lab focuses on profiling changes in cell surface glycosylation associated with cancer, inflammation, and bacterial infection, and on exploiting this information for the development of diagnostic and therapeutic approaches. In addition, her group develops nanoscience-based technologies for probing cell function and for medical diagnostics.

Professor Bertozzi has been recognized with many honors and awards for both her research and teaching accomplishments. She is an elected member of the National Academy of Sciences, the American Academy of Arts and Sciences, and the German Academy of Sciences Leopoldina. She has been awarded the Whistler Award, the Ernst Schering Prize, a MacArthur Foundation Fellowship, the ACS Award in Pure Chemistry, a Presidential Early Career Award in Science and Engineering, and the Irving Sigal Young Investigator Award of the Protein Society, among many others. Her efforts in undergraduate education have earned her a UC Berkeley Distinguished Teaching Award and the Donald Sterling Noyce Prize for Excellence in Undergraduate Teaching. Professor Bertozzi participates in high-school outreach programs such as the Catalyst Program sponsored by the Camille and Henry Dreyfus Foundation, as well as programs that promote the participation of women in science. She was recently presented with the Li Ka Shing Award for Women in Science in recognition of these efforts.

New Catalysis Products from Aldrich R&D

Palladium(II) Acetate, Recrystallized

It has been shown that in some applications recrystallized palladium(II) acetate, $Pd(OAc)_2$, performs better than typical grades. White and Overman have both independently demonstrated that in some applications a particular grade of $Pd(OAc)_2$ is necessary. In particular, the preparation of the White catalyst as well as the preparation of the COP catalysts-$[COP\text{-}OAc]_2$ and $[COP\text{-}Cl]_2$ by Overman successfully employ and require recrystallized $Pd(OAc)_2$.

720070

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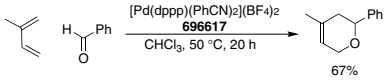
Cationic Palladium Complexes, $[Pd(dppp)(PhCN)_2](BF_4)_2$

Cationic palladium(II) complexes are utilized in a variety of reactions. $[Pd(dppp)(PhCN)_2](BF_4)_2$ catalyzes the hetero-Diels–Alder reaction of dienes with aldehydes. The reaction yields substituted 5,6-dihydro-2*H*-pyrans without the use of Lewis acids and is believed to proceed through a stepwise mechanism.



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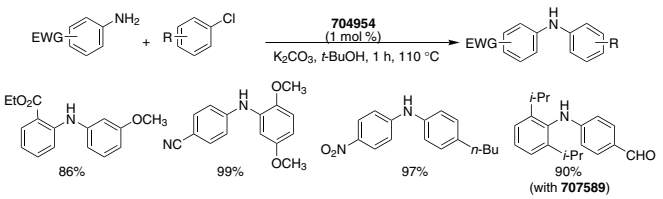
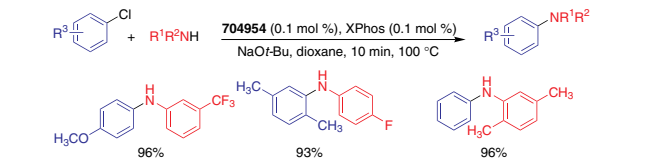
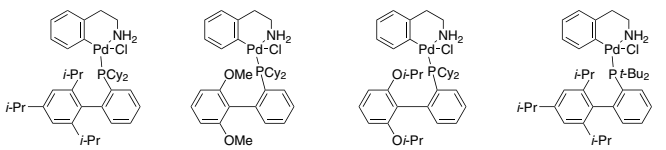
Air-Stable Precatalysts for Amination

C–N-bond-forming cross-coupling reactions typically require a palladium source along with associated ligands. Most Pd(0) sources are not air-stable, while the commonly employed air-stable Pd(0) source, $Pd_2(dba)_3$, contains associated ligands which could impede the reaction in some cases. Stable Pd(II) precursors require reduction under the reaction conditions. In either case, a ligand must be added to the reaction in order to lead to the active Pd species. Buchwald and coworkers recently reported the use of highly active air- and moisture-stable precatalysts, which, under the standard reaction conditions, form the active monoligated Pd species. These precatalysts are exceptionally efficient even under challenging conditions, such as coupling electron-poor anilines with deactivated aryl chlorides. The catalyst precursors also offer other advantages including low catalyst loadings and short reaction times.







704954 (from XPhos) **704946** (from SPhos) **707589** (from RuPhos) **708739** (from *t*-BuXphos)

Reference: Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686.

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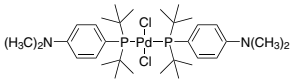
Nonproprietary Catalysts for Cross-Coupling Reactions

The cross-coupling reaction of heteroaryl halides is of particular interest to the pharmaceutical industry since many biologically active compounds are accessed through use of the Suzuki–Miyaura reaction. However, the efficient coupling of boronic acids with five-membered-ring heteroaryl halides or six-membered-ring heteroaryl chlorides bearing heteroatom substituents has not been well-developed. Catalysts are thought to form inactive complexes with many of these types of substrates, and thus, they typically require high catalyst loadings in order to achieve good yields. Guram's group at Amgen has recently reported the development of an air-stable palladium complex, $(A^{ta}Phos)_2PdCl_2$, for Suzuki–Miyaura cross-coupling reactions. The catalyst is very effective at coupling a wide range of substrates with arylboronic acids, including amino-substituted 2-chloropyridines and five-membered-ring heteroaryl halides. The products are obtained in excellent yields and high turnover numbers (up to 10,000 TON) are typically achieved. A series of new $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ catalysts were developed with various reactivities.



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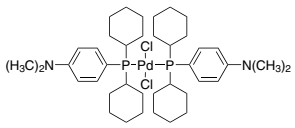

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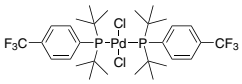

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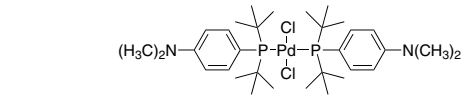

678740

(1 mol %)

K_2CO_3, toluene–water, reflux, 12 h

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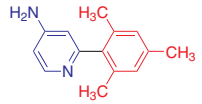
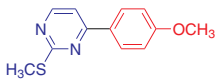
2		98
3		95

References: (1) Singer, R. A. et al. *Tetrahedron Lett.* **2006**, *47*, 3727. (2) Singer, R. A. et al. *Synthesis* **2003**, 1727. (3) Guram, A. S. et al. *Org. Lett.* **2006**, *8*, 1787.

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Palladium(II) [1,3-bis(diphenylphosphino)propane]bis(benzonitrile) bis(tetrafluoroborate)

696617 250 mg

[*175079-12-6*]

$C_{41}H_{36}B_2F_8N_2P_2Pd$

FW: 898.71

(XPhos) palladium(II) phenethylamine chloride

704954 250 mg, 1 g

$C_{41}H_{59}ClNPPd$

FW: 738.76

(SPhos) palladium(II) phenethylamine chloride (1:1 MTBE solvate)

704946 250 mg, 1 g

$C_{39}H_{57}ClNO_3PPd$

FW: 760.72

RuPhos palladium(II) phenethylamine chloride

707589 250 mg

$C_{30}H_{43}O_2P{\cdot}C_8H_{10}ClNPd$

FW: 728.68

***t*-BuXPhos palladium(II) phenethylamine chloride**

708739 250 mg

$C_{37}H_{55}ClNPPd$

FW: 686.69

Bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine) dichloropalladium(II)

678740 1 g, 5 g

[*887919-35-9*]

$C_{32}H_{56}Cl_2N_2P_2Pd$

FW: 708.07

Bis[(dicyclohexyl)(4-dimethylaminophenyl)phosphine]palladium(II) chloride

692913 250 mg, 1 g

$C_{40}H_{64}Cl_2N_2P_2Pd$

FW: 812.22

Bis[(di-*tert*-butyl)(4-trifluoromethylphenyl)phosphine]palladium(II) chloride

692921 250 mg, 1 g

$C_{30}H_{44}Cl_2F_6P_2Pd$

FW: 757.93

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THE COMING OF AGE OF GOLD CATALYSIS

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ALDRICH Chemistry

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Copper-, Silver-, and Gold-Catalyzed Migratory Cycloisomerizations Leading to Heterocyclic Five-Membered Rings

Enantioselective Synthesis Based on Catalysis by Chiral Oxazaborolidinium Cations

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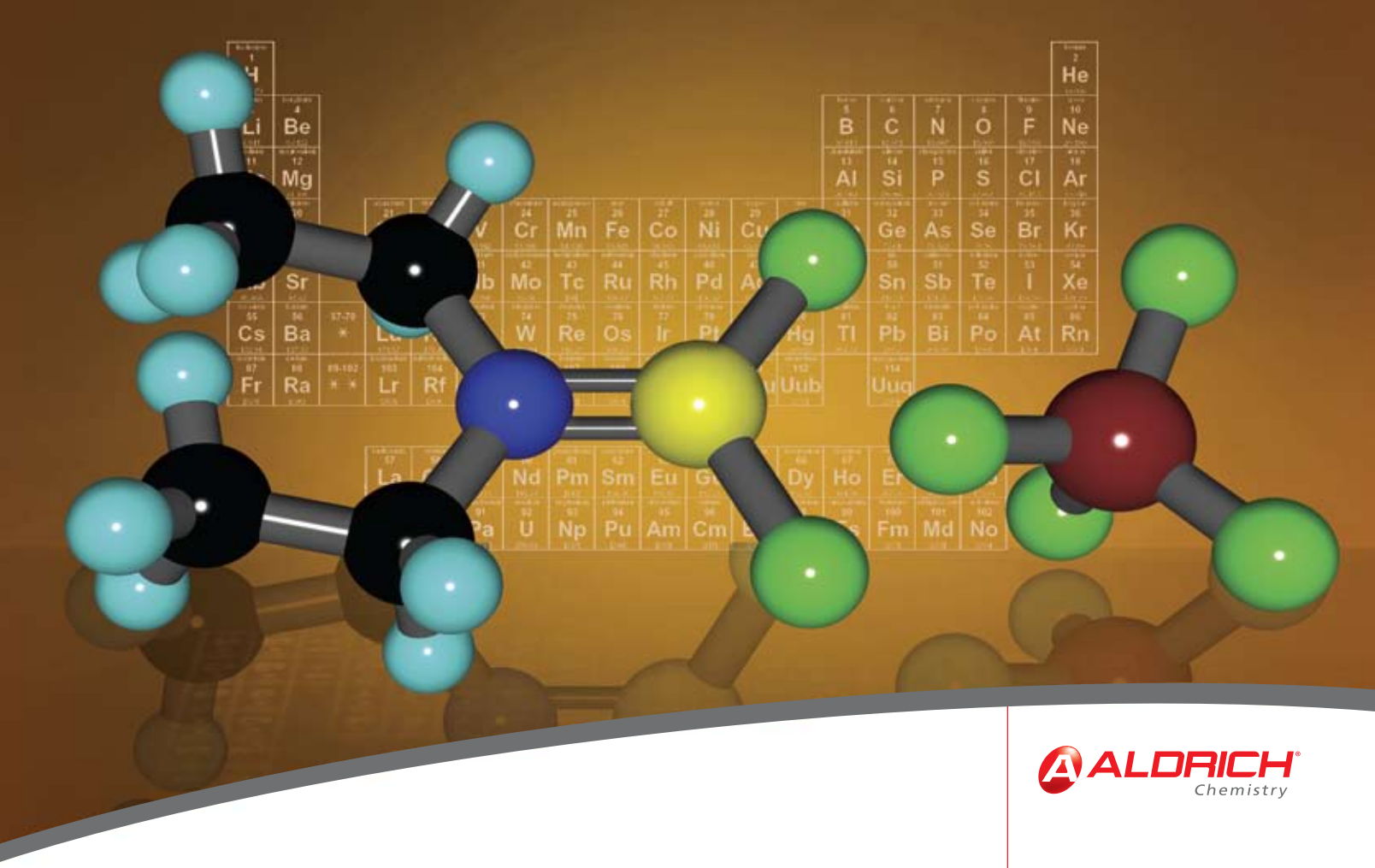

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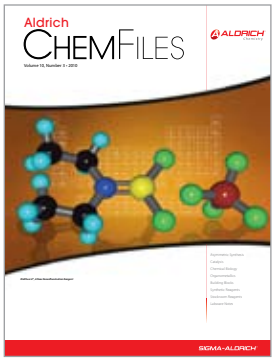

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"PLEASE BOTHER US."

Joe Porwoll

Joe Porwoll, President
Aldrich Chemical Co., Inc.

Professor Bruce Lipshutz from the University of California, Santa Barbara, kindly suggested that we make copper-in-charcoal. This useful heterogeneous catalyst promotes a variety of catalytic transformations such as asymmetric hydrosilylations, click reactions, and is also used in the preparation of diaryl ethers.

(1) Lipshutz, B. H.; Frieman, B. A.; Tomaso, A. E., Jr. *Angew. Chem., Int. Ed.* **2006**, *45*, 1259. (2) Lipshutz, B. H.; Taft, B. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 8235. (3) Lipshutz, B. H.; Unger, J. B.; Taft, B. R. *Org. Lett.* **2007**, *9*, 1089.

Cu/C
709107

709107 Copper-in-charcoal, 3 wt. % 5 g

Naturally, we made this useful heterogeneous catalyst. 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 back cover.

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Detail from *Travellers near the Edge of a Wood*. Photograph © Alfred Bader.

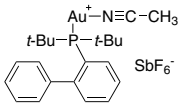
Detail from ***Travellers near the Edge of a Wood*** (oil on panel, 51.5 × 67.2 cm) was painted ca. 1638 by Jacob van Geel (ca.1585–1638), the seventeenth-century Dutch painter. Born in Middelburg, Zeeland Province, he became a member of the guild of St. Luke (Middelburg) at about age 30, and later joined the painters' guilds of Delft and Dordrecht, and seems to have led a private life dominated by debt and conflict.

Having been influenced by the painting styles of Jan Brueghel the Elder (1568–1625) and Hercules Seghers (ca. 1589–1638), he specialized in painting fantasy landscapes often dominated by a large cluster of trees, as is the case here. In this complex composition, the viewer is drawn to at least three scenes featuring travellers at various stages of their journey. The bright daylight penetrates from the left side and illuminates the twisted and bulging trees that fill the composition and attract the viewer's eyes to the center of this work.

This painting is part of the Bader Collection of Dutch and Flemish Paintings, whose future home will be the Agnes Etherington Art Centre of Queen's University, Kingston, ON, Canada.

Gold Catalysts from Sigma-Aldrich

Gold Catalysts



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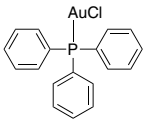

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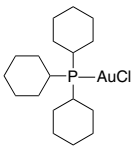

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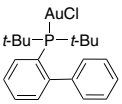

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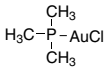

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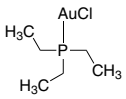

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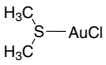

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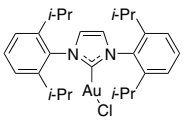

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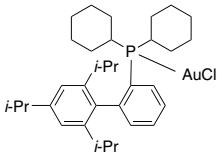

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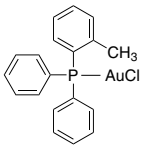

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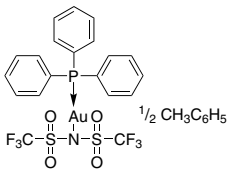


677922

$NaAuCl_4 \cdot 2H_2O$

298174

$AuBr_3$

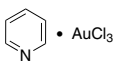
398470

AuCl

481130

$AuCl_3$

334049



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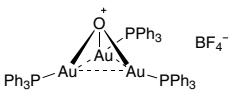

665142

$AgNTf_2$

668001

AgOTs

176427

$AgSbF_6$

227730

$AgBF_4$

208361

$AgPF_6$

227722

AgOTf

176435

For more information, please visit *aldrich.com/gold*

Gold-Catalyzed Addition of X–H Bonds to C–C Multiple Bonds

Professor Dr. A. S. K. Hashmi

Ms. Miriam Bührle

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Outline

1. Introduction

Homogeneous gold catalysis had found only limited use in organic synthesis up until the year 2000,[1] when the advantages of gold complexes as catalysts were first recognized. Intense research activity in this area of catalysis followed, as documented by a number of reviews that have since been published.[2] After much work on methodology, an increasing number of applications in the synthesis of natural products have been reported in recent years.[3]

One of the early reactions in this rapidly developing field was the gold-catalyzed addition of water and alcohols to alkynes[4]—a reaction previously dominated by mercury(II) and strongly acidic conditions[5] or, according to Reppe,[6] the direct nucleophilic addition of alcohols to alkynes under strongly basic conditions. This reaction not only showed the benefits of gold catalysis, it has also guided the selection of the reaction types to be covered in this review, namely the addition of an X–H bond to a C–C multiple bond, with X being an electronegative heteroatom. The literature up to the early part of 2010 is covered. By extension, the intramolecular addition of X–H to C–C multiple bonds has become a very effective tool in the synthesis of heterocyclic compounds from easily available starting materials.

2. Gold-Catalyzed Addition of X–H Bonds to Alkynes

Alkynes are more reactive than allenes or alkenes when activated by a gold catalyst, and have thus been the most studied of the three. A theoretical understanding of this strong reactivity has been difficult to achieve, and most of the theoretical calculations published do not properly address the effects specific to gold. Only recently, has a full computational study of gold–alkyne complexes been published.[7]

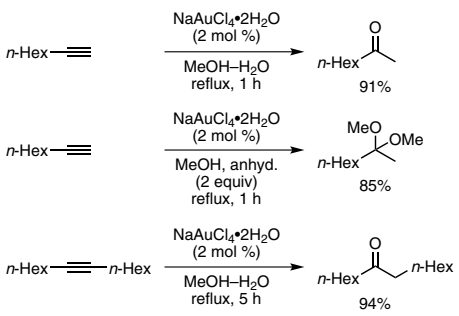
2.1. Addition of Water, Alcohols, and Sulfonic Acids

As mentioned in Section 1, the first reactions were conducted with water and alcohols as the nucleophiles and gold(III) in the form of $NaAuCl_4$ as the catalyst. In this pioneering work, Utimoto and co-workers observed a Markovnikov addition to the alkyne: with terminal alkynes, water delivered methyl ketones while methanol gave ketals (**Scheme 1**).[4] Internal alkynes did not react regioselectively, and, therefore, symmetrical alkynes had to be employed to obtain a single addition product.

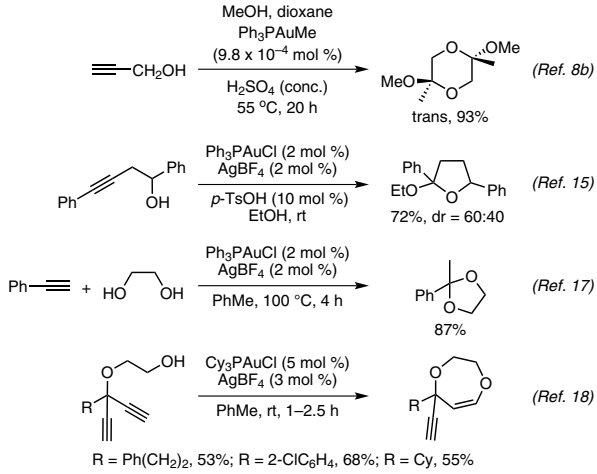
Teles and co-workers subsequently reported that cationic gold(I) phosphine, phosphite, and arsine complexes are extremely efficient catalysts for these conversions, achieving turnover numbers (TONs) of up to 10^5 moles of product per mole of catalyst and turnover frequencies (TOFs) of up to 5,400/h.[8] Herrmann's group reported successful conversions too by employing NHC–gold(I) complexes.[9] Nolan and co-workers observed TONs similar to those reported by Teles and TOFs of up to 4,700/h for the addition of water to alkynes, also catalyzed by NHC–gold(I) complexes.[10] Other systems with fluorinated[11] or water-soluble[12] counterions have been investigated. Nevertheless, phosphines and the weakly coordinating BF_4^- and TfO^- have been the most used ligands and counterions, respectively.[13]

Apart from the intermolecular ketal formation, select mixed intra- and intermolecular examples have been reported (**Scheme 2**).[8,14–18] Propargyl alcohol can dimerize and combine with two molecules of methanol as an external nucleophile to form a cyclic bisketal,[8] a pathway that can be avoided in the presence of other nucleophiles in the substrate.[14] A homopropargylic alcohol first closes to a dihydrofuran, which subsequently adds ethanol as the external nucleophile.[15] This cyclization is dependent on the presence of an activating aryl group on the alkyne and is slow or does not proceed in the case of alkyl-substituted or terminal alkynes.[16] A reversed sequence is observed with diols as external nucleophiles: ethylene glycol first reacts with phenylacetylene in an intermolecular addition, then the second hydroxyl group undergoes an intramolecular addition to form the cyclic ketal.[17] The last example in Scheme 2 features a case in which the absence of a second nucleophile leads to monohydroalkoxylation and the formation of seven-membered rings.[18]

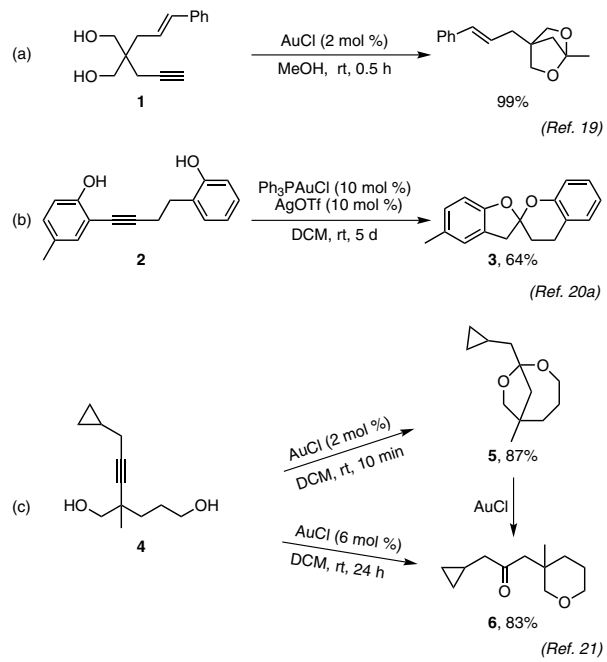
Completely intramolecular additions automatically lead to polycyclic ketals (**Scheme 3**).[19–21] In the 1,6-enynediol **1**, alcohol addition to the alkyne is the more efficient process, delivering the



Scheme 1. Gold(III)-Catalyzed Hydration and Hydroalkoxylation of Alkynes. *(Ref. 4c)*



Scheme 2. Intra- and Intermolecular Hydroalkoxylation of Alkynes.



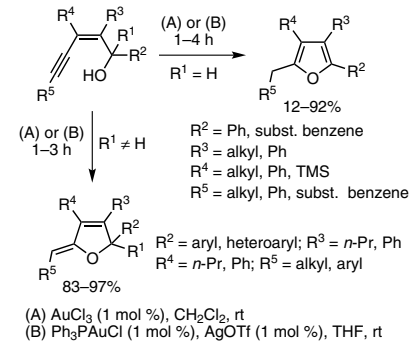
Scheme 3. Intramolecular Hydroalkoxylation of Alkynes.

bicyclic ketal; enyne cycloisomerization or alcohol addition to the activated alkene is not observed.[19] The bisbenzannelated spiroketal core, **3**, of the rubromycin family is a prospective intermediate, which is obtained in 64% yield by the intramolecular addition of two phenolic hydroxyl groups tethered to the carbon–carbon triple bond in **2**.[20] In some cases, the observed product depended on the reaction time and catalyst loading (see Scheme 3, Part (c)): the substituted, unsaturated pentanediol **4** gives bicyclic ketal **5** after a short reaction time and low catalyst loading (2 mol %), but leads to tetrahydropyranyl ketone **6** after a longer reaction time and a higher catalyst loading (6 mol %).[21]

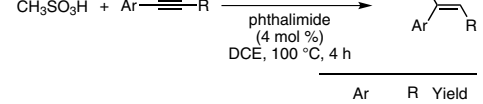
Aromatic heterocycles can be obtained from secondary enyne alcohols by an intramolecular hydroalkoxylation followed by a double bond isomerization (**Scheme 4**).[22] The initial hydroalkoxylation product is believed to be the exocyclic olefin, as indicated by the isolation of such a compound in the reaction of the corresponding tertiary enyne alcohols. In the latter case, the double bond geometry indicates that the 5-*exo-trig* cyclization is an *anti*-oxyauration step.

Gold(I) catalyzes not only the addition of alcohols, but also of the weakly nucleophilic sulfonic acids to C–C triple bonds (**eq 1**).[23] Activated arylalkynes are suitable addition partners for these weak nucleophiles.

A number of reactions not only involve the overall addition of the O–H bond to the alkyne, but also subsequent isomerization. Examples of these reactions are: the isomerization of 2-en-3-ynols to furans[22a] and the formation of furans from alkynyl epoxides.[24] The latter example was shown to proceed by initial ring-opening of the oxirane and subsequent addition and isomerization.[25] In the 6-*exo-dig* cyclization of 5-ynols to six-membered-ring oxygen heterocycles, isomerization of the initially formed exocyclic double bond to an endocyclic one is also observed.[26] Another kind of isomerization involves the nucleophile: in the cyclization of *N*-propargylcarboxamides, the oxygen atom of the amide can attack in a 5-*exo-dig* or a 6-*endo-dig* mode.[27] This is followed by proton elimination from the amide nitrogen and rearrangement of the amide structure to an imidate-like structure. The related



Scheme 4. Aromatic Heterocycles from Secondary Enyne Alcohols by an Intramolecular Hydroalkoxylation–Double-Bond Isomerization. *(Ref. 22b)*



Ar	R	Yield
4-EtC$_6$H$_4$	H	82%
Ph	Ph	73%

eq 1 *(Ref. 23)*

carboxylic acids can also be added to alkynes in an inter- or intramolecular manner.[11,28]

2.2. Hydroamination

Nitrogen nucleophiles were the second type of nucleophiles explored. Again, Fukuda and Utimoto provided one of the first examples, an intramolecular addition (**Scheme 5**),[29] in which the imine originates from the isomerization of the initially formed enamine. In the presence of an acidic co-catalyst, such as $H_3PW_{12}O_{40}$ or AgOTf, even intermolecular additions are possible with low catalyst loadings.[30] Because of the high functional-group tolerance of gold catalysis, oxygen and humidity do not have to be excluded from the reaction medium, and aryl halides such as aryl iodides are tolerated.[31] This means that these gold-catalyzed isomerizations and, for example, the palladium-catalyzed cross-coupling reaction are orthogonal in a synthetic sense. With diamino compounds, cyclic aminals are obtained.[32]

Selective intramolecular monohydroamination is observed in a number of cases, in which the initially formed enamine cannot isomerize to the corresponding imine (**Scheme 6**).[18,34–37] Imidates,[33,34] carbamates,[35] secondary amines,[18,36] and even primary amines[37] exhibit this reactivity pattern and give rise to a number of useful heterocyclic enamines.

2.3. Hydrothiolation

Here, only one type of addition is known. The two-fold addition of ethylenedithiol and related dithiols to phenylacetylene delivers the corresponding dithioketals in low-to-moderate yields (**eq 2**).[17]

2.4. Hydrohalogenation

The first reaction of this type is the addition of hydrogen chloride to acetylene, catalyzed by tetrachloroauric acid **(Scheme 7)**.[38,39] Even a weak nucleophile such as fluoride can be added to the C–C triple bond: the reaction is catalyzed by an NHC complex of gold(I) and proceeds with excellent regioselectivity even with a thiophene derivative.[40]

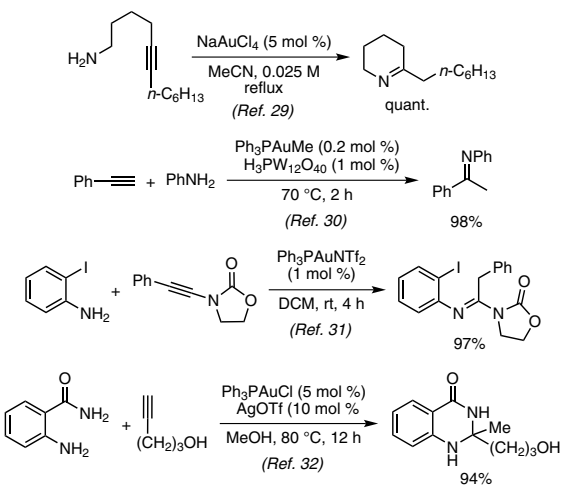
3. Gold-Catalyzed Addition of X–H Bonds to Allenes

Allenes are isomers of alkynes, but are generally less thermodynamically stable than alkynes. Even though their gold-catalyzed reactions are the second most studied after those of alkynes, far fewer examples have been reported than for alkynes. This is probably a result of the fact that allenes are synthetically less accessible than alkynes. Nevertheless, the first gold-catalyzed addition of thiols, which usually poison a transition-metal catalyst, has been reported for allenes (see Section 3.3).

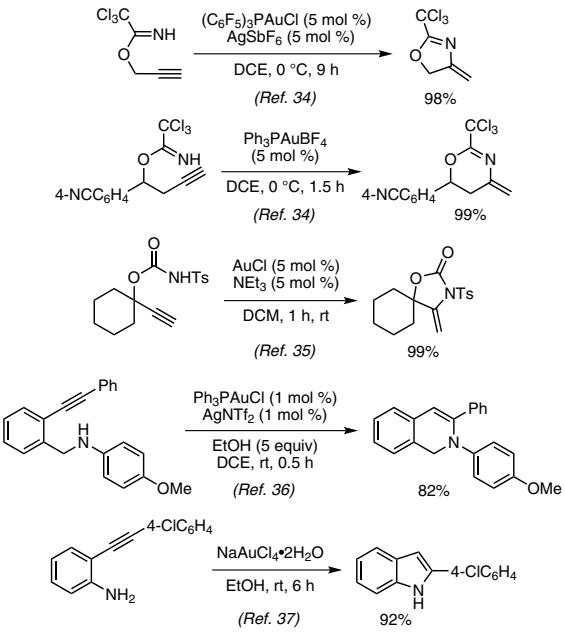
3.1. Hydroalkoxylation

A number of intramolecular gold-catalyzed additions of alcohols to allenes have been reported (**Scheme 8**). These lead to five- and six-membered rings[41] and, in special cases such as that of the β-lactam derivative, even to seven-membered rings.[42]

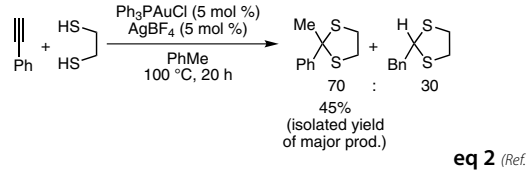
The intermolecular variants include the addition of water and primary and secondary alcohols (**Scheme 9**).[43,44] In all of these examples, the nucleophile adds to one of the terminal carbon atoms of the allene, which is the usual mode of nucleophilic attack for allenes. In the examples of intramolecular additions (Schemes 8, 10, and eq 3), the preferred formation of five- and six-membered rings directs the nucleophiles to the terminal



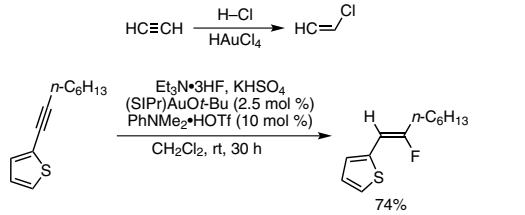
Scheme 5. Formation of Imines and Aminals by the Hydroamination of Alkynes.



Scheme 6. Formation of Stable, Heterocyclic Enamines by the Intramolecular Hydroamination of Alkynes.



eq 2 *(Ref. 17)*

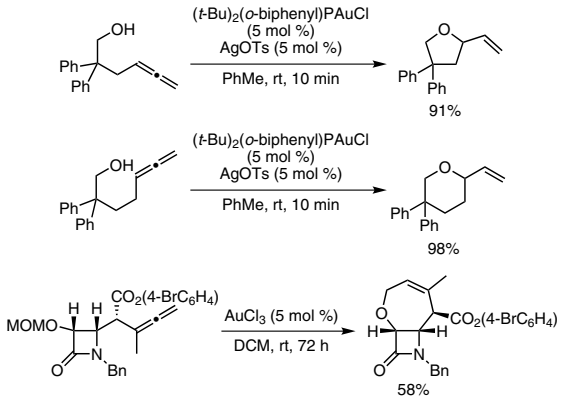


Scheme 7. Intermolecular Hydrohalogenations of Alkynes. *(Ref. 38–40)*

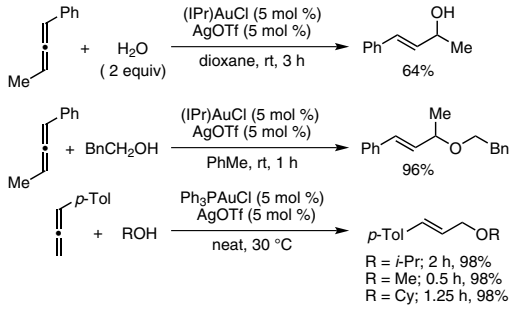
position of the allenes. The regioselectivity of the additions in Scheme 9 can either be directed by a faster reaction of the less sterically hindered double bond of the allene, or be directed by the formation of the thermodynamically more stable conjugated product.

The most remarkable example in this field is the catalytic asymmetric intramolecular hydroalkoxylation using achiral gold complexes and chiral counterions (**eq 3**).[45] This has opened new perspectives for asymmetric synthesis, since prior efforts employing other transition metals had generally delivered unsatisfactory results.[2] Presumably, the linear coordination geometry of the gold(I) complexes is an important factor in these successful conversions with the chiral counterions.

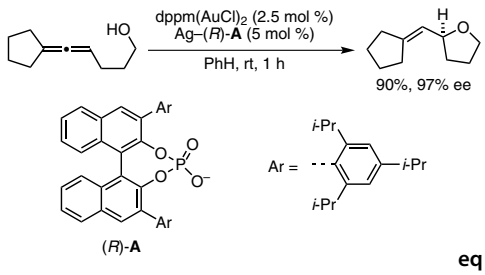
Mechanistic studies have demonstrated that the formation of dimers by oxidative (dehydrogenative) coupling in gold(III)-mediated reactions of allenyl carbinols is an indication that gold(III) is reduced in situ by the substrate.[46] A number of reactions combine a rearrangement of a gold-catalyzed propargylic derivative to an allene with a subsequent gold-catalyzed intramolecular alcohol addition.[47] Moreover, carboxylic acids have also been used as nucleophiles in hydroxycarboxylation reactions.[45]



Scheme 8. Intramolecular Hydroalkoxylation of Allenes. *(Ref. 41,42)*



Scheme 9. Intermolecular Hydroalkoxylation of Allenes. *(Ref. 43,44)*



eq 3 *(Ref. 45a)*

3.2. Hydroamination

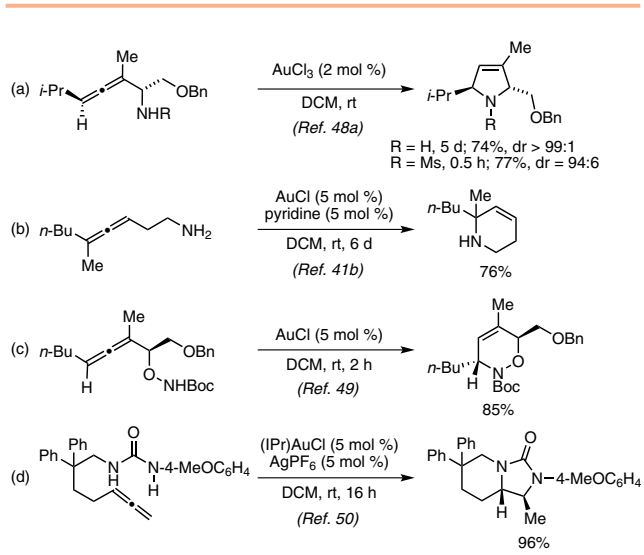
In analogy to the hydroalkoxylation reaction, the intramolecular hydroamination of allenes leading to five-[48] and six-membered[41b] rings is known (**Scheme 10**). Even hydroxylamine derivatives have been used.[49] Derivatives of urea have led to an interesting 1,2-diamination of the allene functional group by a bis(hydroamination).[50]

In the intermolecular hydroamination counterparts, the nucleophile only adds to the terminal carbon atom of the allene. Fmoc-protected ammonia[51] and aniline[52] undergo the reaction, yielding the corresponding allylamines (**Scheme 11**).

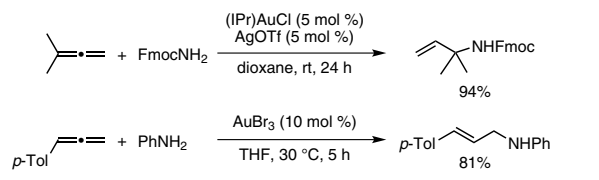
The enantioselective addition of nucleophiles to allenes induced by chiral counterions (see eq 3) was extended to the intramolecular addition of amines (**eq 4**).[45,53]

3.3. Hydrothiolation

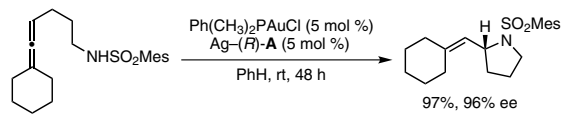
In their pioneering work, Morita and Krause successfully carried out a diastereoselective intramolecular hydrothiolation of allenes (**eq 5**).[54] In general, the transfer of axial to central chirality is successful with allenic substrates.



Scheme 10. Intramolecular Hydroamination of Allenes.



Scheme 11. Intermolecular Hydroamination of Allenes. *(Ref. 51,52a)*



eq 4 *(Ref. 45a)*

4. Gold-Catalyzed Addition of X–H Bonds to Alkenes

Among substrates with C–C multiple bonds, alkenes react most sluggishly in gold-catalyzed reactions, and typically require noncoordinating solvents of low polarity for successful conversion.

4.1. Hydroalkoxylation

Because of the reduced reactivity of olefin–gold complexes, it is not surprising that some of the alkenes used have been the strained, and thus activated, ones. One example is norbornene, which adds 3-chloroethanol at elevated temperatures in the presence of a gold(I) complex that is activated in situ by silver triflate (**Scheme 12**).[55] Styrene also reacts with the expected Markovnikov selectivity in the presence of gold(III) chloride at even higher temperatures.[56] These conditions have also proved suitable for the addition of methanol to monoalkyl-substituted terminal alkenes. Most remarkably, even the weak nucleophile *p*-nitrophenol reacts with alkenes, providing the addition product in good yield.[57] An intramolecular variant is the formation of a spiro compound by a combined hydroalkoxylation and hydroamination of a bisolefin.[58]

4.2. Hydroamination

Because of the low reactivity of the alkenes, the stronger nitrogen nucleophiles have found more widespread use than their oxygen counterparts (e.g., alcohols). In most cases, the nitrogen atom has a protecting group since the free amine appears to compete with the olefin for the coordination site on the catalyst. Many examples of the intramolecular variant have been reported, delivering nitrogen heterocycles with the preferred formation of five-membered rings (**Scheme 13**).[58–62] Of these examples, the cyclization to benzo-anelated heterocycles with a tosyl group on nitrogen is noteworthy.[58] Other nitrogen protecting groups have also been successfully employed.[59] A decent diastereoselectivity is observed when a urea group is used as the nucleophile,[60] and when 1,3-dienes are utilized as substrates, leading to the products of 1,4 addition.[61] The successful reactions of unprotected primary or secondary amines under acidic conditions have also been reported.[62]

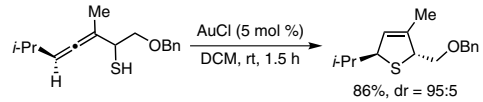
Examples of the intermolecular variants of the hydroamination of alkenes are shown in **Scheme 14**.[58b,63,64] When an imidazolidinone is utilized as the nitrogen nucleophile, the cyclic urea even adds to a number of simple, unactivated alkenes including ethylene.[63] In the next two examples, a two-fold hydroamination of a 1,5-hexadiene delivers the expected, highly substituted pyrrolidine,[58b] and a disubstituted 1,3-diene undergoes selective Markovnikov addition to the less substituted double bond.[64]

4.3. Hydrothiolation

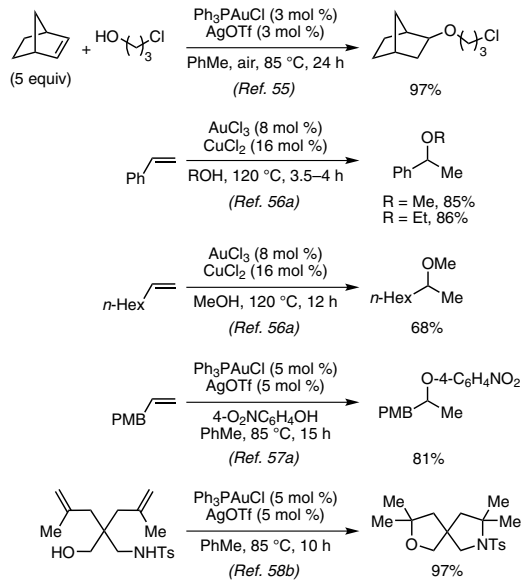
We are aware of only one publication that has reported the addition of S–H to an olefin, a 1,3-diene. Here, too, the less substituted double bond is attacked regioselectively, this time by a thiocarboxylic acid as the nucleophile (**eq 6**).[65]

5. Conclusions and Outlook

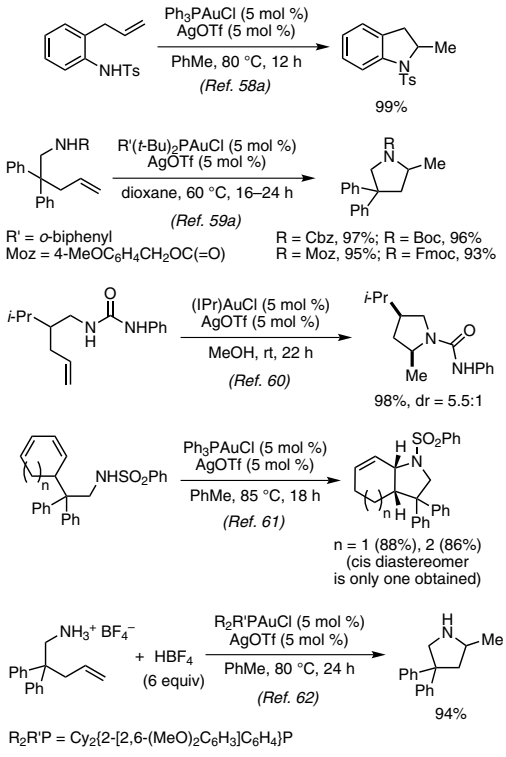
The gold-catalyzed intramolecular addition of alcohols and amines to C–C multiple bonds has proven to be a very innovative synthetic tool in heterocyclic chemistry.[66] One significant advantage of gold catalysis over other hydroamination catalysts is that the gold-catalyzed reactions do not have to be conducted in a glove box. The intermolecular reactions are also very useful in organic synthesis, as exemplified by the synthesis of products such as allylamines. Nevertheless, significant research is still needed in this area, since catalyst loadings are still high and the most conveniently accessible unsaturated substrates, the alkenes, have yet to be investigated in more detail. This is the case since alkenes clearly



eq 5 *(Ref. 54)*



Scheme 12. Hydroalkoxylation of Alkenes.



Scheme 13. The Preferred Formation of Pyrrolidines in the Intramolecular Hydroamination of Alkenes.

are the most important class of unsaturated substrates in terms of their industrial applications.

6. Acknowledgements

We gratefully acknowledge the continued financial support of our work in the area of gold catalysis by the Deutsche Forschungsgemeinschaft (DFG) and Umicore AG & Co. KG.

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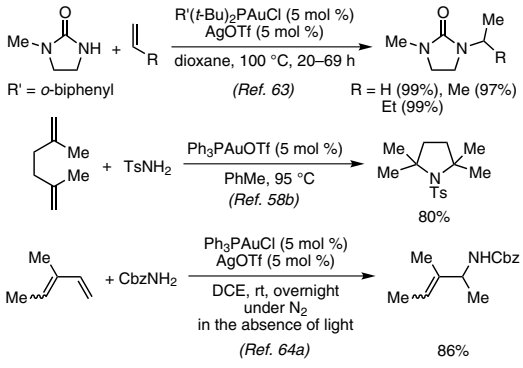
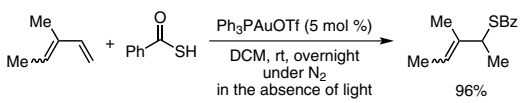


Scheme 14. Intermolecular Hydroamination of Alkenes.



eq 6 *(Ref. 65)*

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Keywords: alkenes; alkynes; allenes; gold; heterocycles; phosphines; N-heterocyclic carbenes.

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A. Stephen K. Hashmi was born in 1963 in Munich, Germany. He studied chemistry at Ludwig-Maximilians-Universität München (LMU Munich), where he obtained his diploma and Ph.D. degree working under the direction of Prof. G. Szeimies. After a stint as a postdoctoral associate with Prof. B. M. Trost at Stanford University, he did his "Habilitation" with Prof. J. Mulzer at the Free University of Berlin, the University of Frankfurt, and the University of Vienna. He was then a visiting scientist at the University of Tasmania, and, after positions at Marburg University and Stuttgart University, he now holds a chair in organic chemistry at Ruprecht-Karls University in Heidelberg. His group has been involved in gold catalysis research for more than a decade.

Miriam Bührle was born in Blaubeuren, Germany. She started to study chemistry in 2002 at Stuttgart University, where she joined Prof. Hashmi's group in 2007. She then moved with the group to Heidelberg University, where she is currently completing her Ph.D. dissertation, which she expects to defend later on this year.

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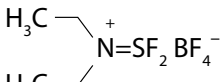

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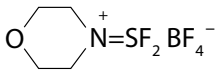

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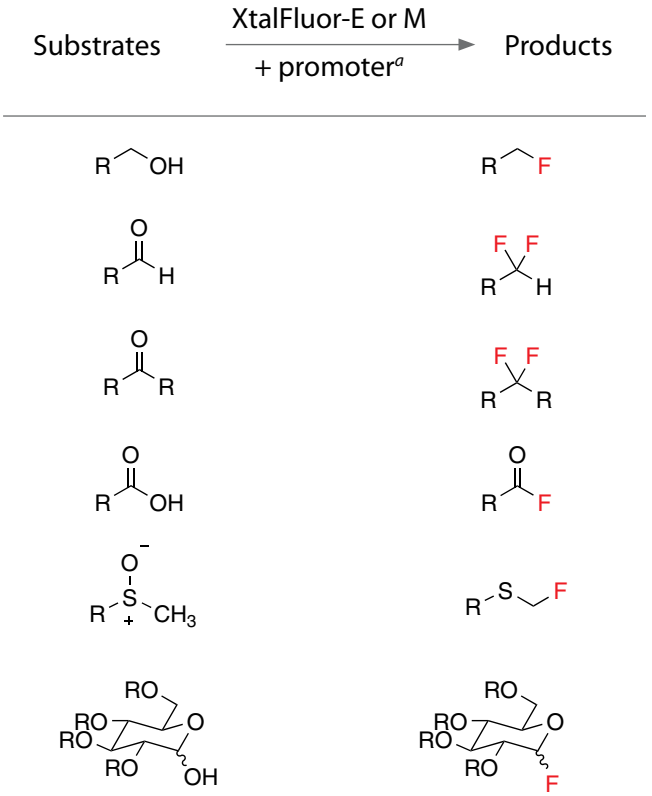

[a] Promoters: DBU, $Et_3N{\bullet}3HF$, or $Et_3N{\bullet}2HF$

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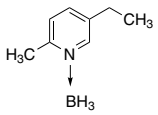

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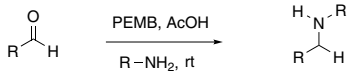
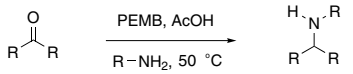
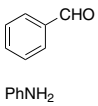
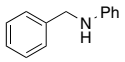
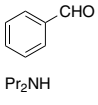
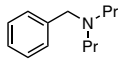
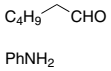
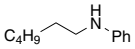
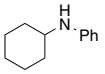
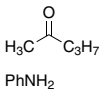
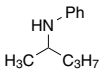




Examples

Aldehyde and Amine	Conditions	Product	% Yield in MeOH (% Yield Neat)
	PEMB, AcOH, MeOH, 25 °C		72 (80)
	PEMB, AcOH, MeOH, 25 °C		0 (96)
	PEMB, MeOH, 25 °C		92 (94)
	PEMB, AcOH, MeOH, 25 °C		92 (93)
	PEMB, AcOH, MeOH, 50 °C		74 (94)

For more examples and experimental details, please see: Burkhardt, E. R.; Coleridge, B. M. *Tetrahedron Lett.* **2008**, *49*, 5152.

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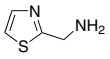
2-(Aminomethyl)thiazole

721522 1 g

[*55661-33-1*]

$C_4H_6N_2S$

FW: 114.17



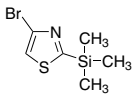
4-Bromo-2-(trimethylsilyl)thiazole

717029 1 g

[*108306-53-2*]

$C_6H_{10}BrNSSi$

FW: 236.20



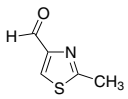
2-Methylthiazole-4-carboxaldehyde

717231 500 mg

[*20949-84-2*]

C_5H_5NOS

FW: 127.16



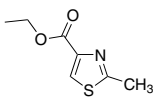
Ethyl 2-methylthiazole-4-carboxylate

716308 1 g, 5 g

[*6436-59-5*]

$C_7H_9NO_2S$

FW: 171.22



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New Iodinated Building Blocks

Iodine-containing substrates are valuable building blocks for a diverse array of synthetic methodologies. They have the ability to participate in various cross-coupling reactions for the generation of carbon–carbon, carbon–nitrogen, and carbon–oxygen bonds and are often preferred to the brominated analogues. They are also handy precursors for the formation of organolithium, organozinc, or organomagnesium reagents.

3-Chloro-4-iodopyridine

724114 1 g

[*77332-79-7*]

C_5H_3ClIN

FW: 239.44

2,4-Dichloro-3-iodopyridine

721069 1 g

[*343781-36-2*]

$C_5H_2Cl_2IN$

FW: 273.89

2-Chloro-4-iodopyridine-3-carboxaldehyde

722596 1 g

[*153034-90-3*]

C_6H_3ClINO

FW: 267.45

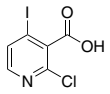
2-Chloro-4-iodopyridine-3-carboxylic acid

723290 1 g

[*544671-78-5*]

$C_6H_3ClINO_2$

FW: 283.45



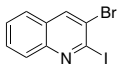
3-Bromo-2-iodoquinoline

707260 1 g

[*898559-23-4*]

C_9H_5BrIN

FW: 333.95



1-Iodoisoquinoline

720879 1 g

[*19658-77-6*]

C_9H_6IN

FW: 255.06

Other New Building Blocks

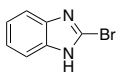
2-Bromo-1*H*-benzimidazole

703826 1 g

[*54624-57-6*]

$C_7H_5BrN_2$

FW: 197.03



3-Bromo-2-bromomethyl-1-propene

721581 1 g

[*15378-31-1*]

$C_4H_6Br_2$

FW: 213.90

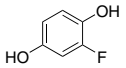
Fluorohydroquinone

722677 1 g

[*55660-73-6*]

$C_6H_5FO_2$

FW: 128.10



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Copper-, Silver-, and Gold-Catalyzed Migratory Cycloisomerizations Leading to Heterocyclic Five-Membered Rings


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Prof. Vladimir Gevorgyan

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Outline

1. Introduction

Aromatic heterocycles are highly important structural units that are found in a vast number of biologically active natural compounds, pharmaceuticals, and materials.[1] Aromatic heterocycles are important intermediates in organic synthesis, often providing access to other highly desirable structures.[2] A myriad of methodologies and protocols have been developed for their synthesis,[1] and, although generally high efficiencies and selectivities can be achieved, a large number of these methodologies are limited to the preparation of heterocycles with particular substitution patterns. Thus, there is a compelling need to develop novel and more general methods for the synthesis of heterocycles.

In recent years, the use of transition-metal-catalyzed transformations truly revolutionized the area of heterocyclic chemistry.[3–15] Many research groups have focused on the development of general methods that utilize readily accessible starting materials under mild reaction conditions for the synthesis of densely functionalized heterocyclic cores to achieve better functional group compatibilities and greater levels of molecular complexity. A particularly attractive approach toward this goal involves the incorporation of molecular rearrangement steps into the transition-metal-catalyzed cycloisomerization cascade reactions. In most cases, this approach provides a significant advantage over alternative routes in the convergent preparation of heterocycles with new substitution patterns. This review covers the most important recent advances in the Cu-,[11,16–19] Ag-,[12] and Au-catalyzed[20–27] syntheses of five-membered aromatic heterocycles proceeding with 1,*n* migrations of various groups during the assembly of the heterocyclic ring. The main organization of this review is based on the type of migrating group, and the discussion of a particular migrating group is structured by the type of its 1,*n* shift. The concepts underlying a given transformation and the synthetic applicability of the corresponding method are emphasized. A brief discussion of the mechanism is given where needed to shed some light on possible reaction intermediates in the catalytic transformation.

2. Synthesis of Heterocycles via Migratory Cycloisomerizations

2.1. Formal Hydrogen Migration

Among a variety of transition-metal-catalyzed syntheses of aromatic heterocycles containing five-membered rings, the cycloisomerization of *single-component* acyclic precursors represents the most versatile, atom-economical, and direct approach.[15,21,28] Moreover, a major fraction of the corresponding *multicomponent* syntheses[10,29,30] also relies on the fundamental reactivities of these key acyclic precursors. Extensive research on the synthesis of aromatic heterocycles through transition-metal-catalyzed cycloisomerizations has been stimulated by the pioneering work of Heilbron (1947; Hg, 2-en-4-yne-1-ols),[31] Castro (1966; Cu, *ortho*-alkynyl anilines),[32] Miller (1969; Hg, alkynyl epoxides),[33] Huang (1986 and 1987; Pd, alkynyl ketones[34] and propargyl ketones[35]), and Marshall (1990; Ag, Rh, allenyl ketones).[36] The cycloisomerizations of allenyl- or alkynyl-containing substrates, catalyzed by Ag, Cu, or Au complexes,[11–13,28] have been extensively utilized in the construction of heterocyclic cores (**Figure 1**). Mechanistically, these reactions proceed via formal 1,2- or 1,3-hydrogen migrations (prototropic isomerizations, G = H), which limit these methodologies to the preparation of heterocyclic frameworks with at least one unsubstituted position. In recent years, researchers have sought to develop novel strategies that might help overcome this limitation. One of the possible solutions involves the introduction of a migrating group other than hydrogen into the transition-metal-catalyzed cascade cycloisomerizations of allenes and alkynes. Subsequent sections of this review describe advances in this exciting and growing area.

2.2. Sulfur and Selenium Migrations

In 2003, our group discovered that the Cu(I)-catalyzed cycloisomerization of 4-thio-substituted allenone **1** proceeded

very efficiently with a 1,2 migration of the phenylsulfanyl group,[37,38] providing 3-thio-substituted furan[39] **2** in high yield.[40] This discovery led us to formulate a general concept of transition-metal-catalyzed cascade cycloisomerizations of alkynyl and allenyl systems involving the formal 1,2 migration of different functional groups as the key step in a rapid assembly of densely functionalized heterocyclic cores (vide infra).

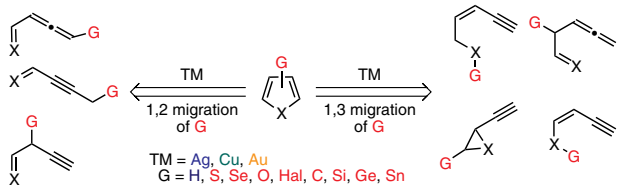
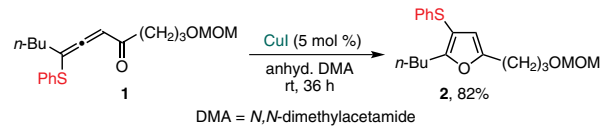
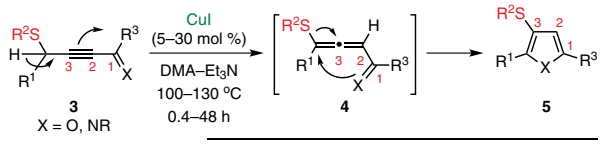


Figure 1. Retrosynthetic Analysis of Traditional Transition-Metal-Catalyzed Cycloisomerizations Leading to Aromatic Heterocycles. *(Ref. 11–13, 28)*



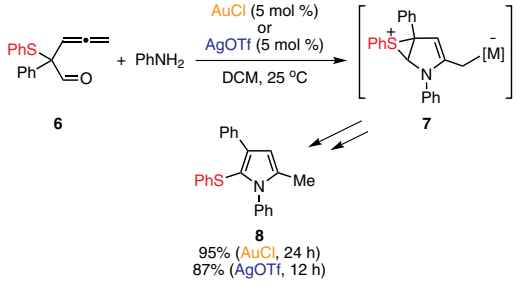
eq 1 *(Ref. 40)*



X[a]	R^1	R^2	R^3	Yield
O	*n*-Bu	Ph	Ph	91%
O	*n*-Bu	Ph	Me	76%
O	*n*-Bu	Ph	*t*-Bu	89%
O	*n*-Bu	Ph	Me_2C=CH	95%
O	*n*-Bu	Ph	H	71%
O	Me	Ph	$MeO_2C(CH_2)_2$	71%
O	$THPO(CH_2)_3$	Ph	Me	93%
O	*n*-Bu	*n*-dodecyl	Me	72%
N*t*-Bu	*n*-Bu	Ph	H	78%
NTr	*n*-Bu	Ph	H	85%
NEB	*n*-Bu	Ph	H	74%
N*t*-Bu	*n*-Bu	*n*-dodecyl	H	86%
NEB	$THPO(CH_2)_3$	Ph	H	78%
NEB	*n*-Bu	*n*-dodecyl	H	67%
b,c	*n*-Bu	Ph	*c*	53%

[a] Tr = Ph_3C; EB = $CH(Me)CH_2CO_2Et$; THP = tetrahydropyran-2-yl. [b] Reaction carried out with CuBr (50 mol %) at 150 °C for 12 h. [c] 3-*n*-Butyl-5-methyl-2-phenylthioindolizine was isolated.

eq 2 *(Ref. 40,46)*



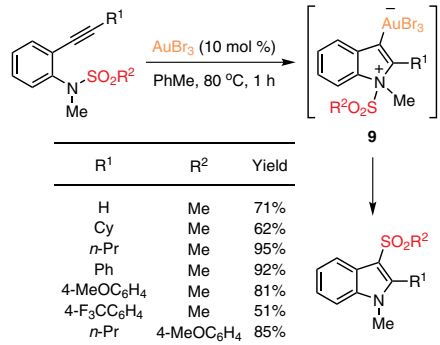
eq 3 *(Ref. 48)*

This report had been preceded by our disclosure in 2001 and 2002 that alkynyl imines and ketones (see Figure 1; G = H, X = NR or O) could be transformed highly efficiently into pyrroles[41,42] and furans[43] via the Cu(I)-catalyzed cycloisomerization. In this way, the alkynyl imines and ketones serve as surrogates of reactive allenyl intermediates generated in situ by the base-assisted propargyl–allenyl isomerization. In light of these findings from 2001–2003, our group next attempted a migratory cycloisomerization of substituted propargyl sulfides **3**, undoubtedly superior precursors when compared with their allenyl sulfide analogues from a synthetic point of view. We found that 3-sulfanyl-substituted furans, pyrroles,[44] and even indolizines[45] **5** are efficiently accessed via the Cu(I)-catalyzed migratory cycloisomerization of the corresponding propargyl sulfides (**eq 2**).[40,46] The alkylsulfanyl group migrates with efficiency comparable to that of its phenylsulfanyl analogue, and a variety of functional groups are perfectly tolerated under these reaction conditions. It is believed that, mechanistically, this transformation proceeds through the Cu(I)-catalyzed cycloisomerization of reactive allenyl sulfide **4**, wherein a 1,2 migration of an alkylthio or arylthio group[47] occurs via a thiirenium intermediate (vide infra). This transformation represents the first example of 1,2 migration of the sulfanyl group from an olefinic sp^2 carbon to an sp center.[37]

Recently, Wang and co-workers reported another example of a 1,2-sulfur migration that was utilized in the assembly of polysubstituted pyrroles **8** via an acid-catalyzed cascade reaction sequence of skipped allenyl aldehydes **6** and anilines. They also demonstrated that this reaction could be catalyzed by Au(I) or Ag salts, wherein the 1,2 migration of the sulfanyl group occurs intramolecularly via the proposed thiiranium intermediate **7** (**eq 3**).[48]

In 2007, Yamamoto's group showed that cycloisomerization of *ortho*-alkynylsulfonanilides in the presence of a Au(III) catalyst produces 3-sulfonylindoles via a 1,3 migration of a sulfonyl group (**eq 4**).[49,50] This reaction is compatible with a variety of alkyl, aryl, and terminal alkynes and provides the indole products in generally high yields. The proposed mechanism involves Au-catalyzed 5-*endo*-*dig* cyclization of *ortho*-alkynylsulfonamides to the zwitterionic indolyl–gold intermediate **9**, in which the 1,3 migration of the sulfonyl group occurs intramolecularly.

Our group recently extended the 1,2-sulfur migration approach (see eq 2) to the related 1,2-selenium migration in the Cu(I)-catalyzed cycloisomerization cascade of propargyl selenides into polysubstituted 3-selenylfurans and pyrroles (**eq 5**).[46] Remarkably,



R^1	R^2	Yield
H	Me	71%
Cy	Me	62%
n-Pr	Me	95%
Ph	Me	92%
4-$MeOC_6H_4$	Me	81%
4-$F_3CC_6H_4$	Me	51%
n-Pr	4-$MeOC_6H_4$	85%
n-Pr	4-AcC_6H_4	80%
n-Pr	Me[a]	60%

[a] N(*i*-Pr) instead of NMe.

eq 4 *(Ref. 50)*

the 1,2 migration of the seleno group is more facile than that of the thio groups; this fact permits such cycloisomerizations to be carried out under significantly milder reaction conditions. The proposed mechanism for selenium migration is analogous to that suggested for the Cu(I)-catalyzed cycloisomerization of propargyl sulfides and involves formation of the reactive allenyl intermediate **10** via the initial prototropic rearrangement.

2.3. Halogen Migration

In 2005, our group reported a very efficient and regiodivergent Au-catalyzed haloallenyl ketone cycloisomerization that proceeds with a 1,2 migration of iodine, bromine, or chlorine atoms,[51] and leads to 3-halofurans with 1–4 substituents (**eq 6**).[52] Remarkably, in the presence of the Au(III) catalyst, 1,2 migrations of bromine and iodine are more facile than 1,2-alkyl and even 1,2-hydrogen shifts in these allenyl ketones. In contrast, employment of a Au(I) catalyst, Et_3PAuCl, for the cycloisomerization of ambident C-4 monohalo-substituted allenones (see eq 6, R^1 = H) furnishes 2-halofuran products via exclusive 1,2-hydrogen migration. It was demonstrated that various functionalities, including alkene and free hydroxyl groups, are tolerated under the reaction conditions. Iodo- and bromo-substituted substrates were shown to be more efficient in this cycloisomerization than their chloro-substituted analogues. The 3-halofurans thus obtained can easily be further functionalized at the C-3 position via cross-coupling protocols.[53]

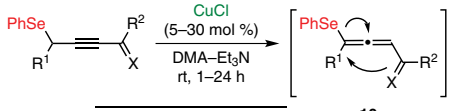
Thorough mechanistic studies, including high-level Density Functional Theory (DFT) calculations, have indicated that activation of the distal double bond of the allene with either a Au(I) or Au(III) catalyst leads to the formation of the gold–carbene intermediate **11**, wherein a kinetically favored 1,2-halogen migration gives 3-halofuran **12** (**Scheme 1**).[54] However, the use of $Au(PR_3)L$ (L = Cl, OTf; R = Et, Ph) catalysts in the case of ambident haloallenones triggers the stepwise counterion- or ligand-assisted[55] hydrogen shift, leading to 2-halofurans **13**. This observation indicates that, in these Au-catalyzed processes, whether hydrogen or bromine migrates is determined by the nature of the ligand on Au.[52,54] In addition, switching the reaction solvent from toluene to THF, which is capable of assisting the stepwise 1,2-hydrogen migration, provides the regiodivergent formation of 2-halofurans **13**.[52]

2.4. Carbon Migration

The first example of a 1,2-alkyl shift[56,57] in the Au-catalyzed synthesis of heterocycles was reported by Toste and co-workers in 2005.[58] In the presence of a cationic Au(I) catalyst, homopropargylic azides possessing cyclobutyl or cyclopentyl substituents undergo an acetylenic Schmidt reaction leading to C-3–C-4-fused pyrroles in good yields (**eq 7**).[58] This protocol allows for the rapid assembly of N-unprotected pyrroles possessing 1–4 substituents. According to the mechanistic hypothesis, the Au(I) catalyst activates the alkyne moiety toward nucleophilic attack by the azide to produce gold–carbene **14** with loss of dinitrogen. A subsequent 1,2 migration of a CH_2 group in the cyclobutyl or cyclopentyl ring to the gold–carbene center furnishes the pyrrole product after tautomerization.

Aiming to incorporate various 1,2-migratory groups into the cycloisomerization cascade, we developed an efficient synthesis of furans with 1–4 substituents. The synthesis proceeds by a 1,2 migration of alkyl or aryl groups in allenyl ketones in the presence of π-philic Au(I), Ag, Cu(I), or Cu(II) catalysts (**eq 8**).[59] Based on studies of the migratory aptitude of various groups, we proposed this cycloisomerization to occur via metal–oxonium ion intermediate **15**. The latter can be viewed as a resonance form of a metal–carbene intermediate analogous to **11**, but with the carbon atom attached to the metal possessing more cationic than carbene-like character.[46,59]

In 2006, Iwasawa and co-workers established an efficient Au(III)-catalyzed protocol for the construction of N-1–C-2-fused polycyclic indole skeletons via a cycloisomerization–

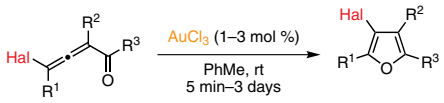


X	R^1	R^2	Yield
N(*t*-Bu)	*n*-Bu	H	74%
N(EB)	*n*-Bu	H	57%
NTr[a]	*n*-Bu	H	54%
O	*n*-Bu	H	74%
O	*n*-Bu	Me	71%
O	*n*-Bu	Ph	84%
O	Bn	*t*-Bu	71%
O	Bn	H	53%

[a] At 110 °C.

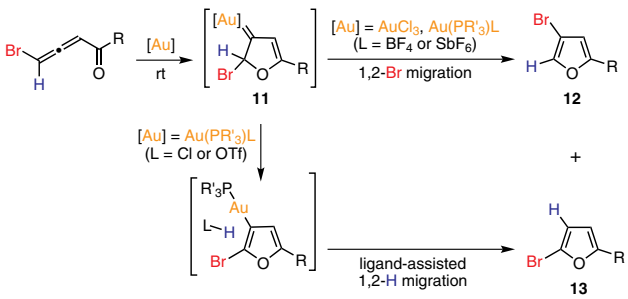
DMA = *N*,*N*-dimethylacetamide
Tr = trityl (Ph_3C)
EB = ethyl butyryl or $CH(Me)CH_2CO_2Et$

eq 5 *(Ref. 46)*



Hal	R^1	R^2	R^3	Yield
Br	H	H	*n*-Oct	86%
I	H	H	*n*-Oct	97%
Br	*n*-Bu	Ph	Ph	75%
I	*n*-Bu	Ph	Ph	73%
Br	*n*-Hep	Me	H	73%
I	H	H	Ph	71%
Br	$TBSO(CH_2)_2$	Ph	Ph	73%
Br	$HOCH_2$	Ph	Ph	61%
Cl	$TBSO(CH_2)_2$	Ph	Ph	48%
Br	$H_2C{=}CHCH_2CH(Ph)$	Ph	Ph	88%

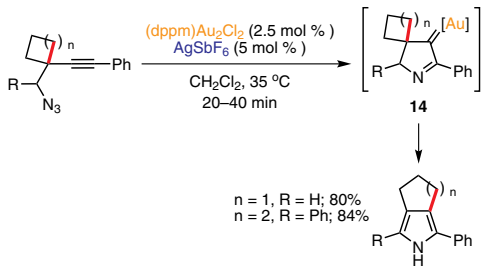
eq 6 *(Ref. 52)*



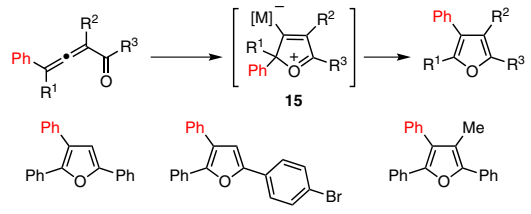
R	[Au][a]	Solvent	**12:13**
n-Oct	$AuCl_3$	THF	5:95
n-Oct	Et_3PAuCl	PhMe	<1:99
Me	$AuCl_3$	PhMe	96:4
Me	Ph_3PAuBF_4	PhMe	>98:2
Me	$Ph_3PAuOTf$	PhMe	0:100
Me	$Ph_3PAuSbF_6$	PhMe	100:0

[a] 1–5 mol %.

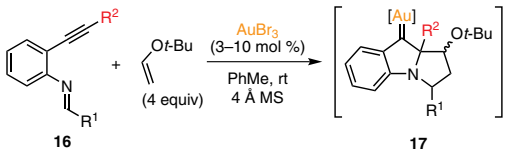
Scheme 1. Ligand-Controlled Hydrogen vs Bromine 1,2 Migration. *(Ref. 52,54)*



eq 7 *(Ref. 58)*



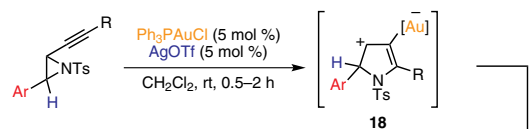
eq 8 *(Ref. 46,59)*



R^1	R^2	Hours	Yield
Ph	*n*-Pr	2.5	80%
Ph	Me	22	81%
Ph	Cy	2	89%
Ph	Ph	0.5	62%
i-PrO[a]	*n*-Pr	1	60%

[a] 10 equiv of H_2C=CHO*t*-Bu was used.

eq 9 *(Ref. 60)*



Ar	R	Yield[a]	19:20
Ph	*n*-Bu	60%	7.6:1
4-MeC_6H_4	*n*-Bu	32%	50:1
Ph	Ph	98%	6:1
4-MeC_6H_4	Ph	65%	*b*
4-BrC_6H_4	*n*-Bu	74%	1.1:1

[a] Isolated yield of **19** + **20**.
[b] Only **19** was observed.

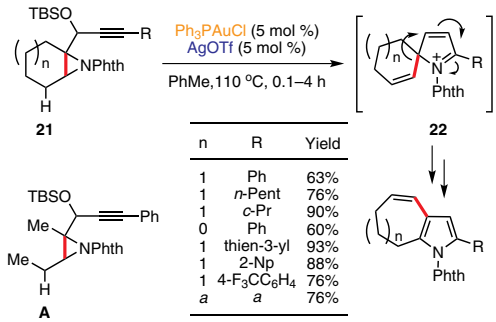
eq 10 *(Ref. 62)*

cycloaddition reaction sequence of alkene enol ethers with *ortho*-alkynylphenylanilides **16**.[60] Iwasawa's group showed that the latter substrates (i.e., *ortho*-alkynylphenylanilides), upon activation with the Au(III) catalyst, generate reactive azomethine ylides.[61] Interception of such ylides with *tert*-butyl vinyl ether via a [3 + 2] cycloaddition leads to the formation of the key gold–carbene intermediates. 1,2-Alkyl migration to the Au-stabilized carbene center in the latter intermediates affords fused indole products in moderate-to-high yields (**eq 9**).[60]

Very recently, another example of the synthesis of heterocycles via a 1,2-aryl group migration to a cationic center was reported by Davies and Martin.[62] In this study, alkynyl aziridines were shown to undergo the Au(I)-catalyzed cycloisomerization, providing mixtures of regioisomeric pyrroles **19** and **20** (**eq 10**). According to the proposed mechanism, ring-opening of the aziridine and subsequent nucleophilic attack of the nitrogen atom at the distal position of the alkyne, activated by the Au(I) catalyst, affords the metal-substituted intermediate **18**. Interestingly, 1,2 migration of the phenyl group is preferred in this intermediate over the generally facile proton elimination, leading to pyrrole **19** as the major product. Introduction of electron-rich aryl groups provides **19** exclusively, whereas the isomerization of substrates with electron-deficient aryl substituents (e.g., 4-bromo) exhibits poor selectivity. The authors also demonstrated that the use of a more basic tosylate-containing, instead of triflate-containing, Au(I) catalyst[55] favors the proton elimination pathway, furnishing pyrroles **20** as the sole regioisomers in excellent yields.

The utility of aziridines in the synthesis of pyrroles was further demonstrated by Tu and co-workers, who reported that cycloisomerization of skipped alkynyl aziridines **21** in the presence of a Au(I) catalyst affords polysubstituted 3-vinylpyrroles via a formal 1,2-alkenyl shift (**eq 11**).[63] Various alkyl-, aryl-, and heteroaryl-substituted alkynes were easily transformed into pyrrole products in good yields. A mechanistic hypothesis for this transformation cascade features the 1,2-alkenyl migration in the spirocyclic iminium intermediate **22**, while formation of the alkenyl unit in the latter arises from the prior proton elimination step. The authors showed that this reaction could equally efficiently proceed with a ring expansion of the five- and six-membered rings fused to the aziridine moiety, as well as with a 1,2-propenyl shift in the case of acyclic substrates.

Besides migratory cycloisomerizations proceeding by 1,2 shifts, several groups have recently reported examples of Au- and Ag-catalyzed counterparts taking place by 1,3 migrations of alkyl,



n	R	Yield
1	Ph	63%
1	*n*-Pent	76%
1	*c*-Pr	90%
0	Ph	60%
1	thien-3-yl	93%
1	2-Np	88%
1	4-$F_3CC_6H_4$	76%
a	*a*	76%

[a] **A** was used as starting material.

eq 11 *(Ref. 63)*

alkenyl, and carbonyl groups. Similarly to the Pt(II)-catalyzed migratory cycloisomerizations leading to benzofuran[64–68] and indole[64,68,69] cores, Yamamoto's group disclosed the Au(I)-catalyzed cycloisomerization of *ortho*-alkynylthiophenol alkyl ethers into 2,3-disubstituted benzothiophenes in excellent yields. This transformation is believed to occur by an intramolecular 1,3 migration of the alkyl group attached to sulfur in intermediate **23** (**eq 12**).[70] Remarkably, a variety of 1,3-migrating groups, including Si-containing and cyclic tetrahydropyranyl ones, were easily incorporated into this transformation cascade. Other sulfur substituents capable of stabilizing the incipient positive charge, such as allyl and *para*-methoxybenzyl,[71,72] were also efficiently employed, leading to 3-allyl- or 3-benzylbenzothiophenes, respectively. According to the proposed mechanism, this reaction cascade begins with the Au-catalyzed 5-*endo*-*dig* cyclization of the *ortho*-alkynylthiophenol alkyl ether to give the gold-substituted benzothiophenium intermediate **23**, which subsequently undergoes intramolecular 1,3-alkyl migration to give the rearranged final product.

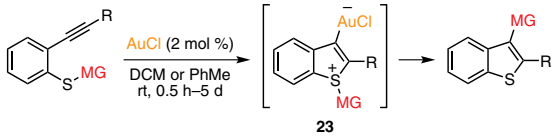
Following this report, the same group later disclosed that the Au(I)-catalyzed carbothiolation reaction of optically active *ortho*-alkynylphenyl 1-phenylethyl sulfides proceeded with predominant retention of the configuration in the 1-phenylethyl migrating group (see eq 12, last two entries).[73] This observation indicates that, at least in the case of 1-arylethyl groups, 1,3-alkyl migration proceeds through formation of a contact ion pair during the migration process.

Oh and co-workers have very recently demonstrated that a variety of 3-vinylindoles, possessing different alkyl and aryl substituents at C-2, can be accessed efficiently through a 1,3-alkenyl shift in a Ag-catalyzed cascade reaction (**eq 13**).[74] The authors have proposed that the initial condensation of *N*-(alkynylphenyl)formimidate **24** with malonate derivative **25**, and subsequent cyclization in the presence of the silver catalyst, provide *N*-alkenyl intermediate **26**. The 1,3 shift of the alkenyl group in this intermediate from N to C-3 gives indole derivative **27**. However, the exact mechanism and nature of this interesting 1,3 migration remain unknown.

In 2007, Istrate and Gagosz reported that *N*,*N*-disubstituted (*Z*)-(2-en-4-ynyl)amines, with a second allyl group attached to the nitrogen atom, undergo a Au(I)-catalyzed cycloisomerization with a 1,3-allyl shift to afford tri- and tetrasubstituted pyrroles (**eq 14**, conditions A).[75] This transformation allows for the synthesis of homoallyl-substituted pyrroles bearing various functional groups in good-to-excellent yields. The proposed mechanism involves, in the first step, activation of the alkyne moiety toward 5-*exo*-*dig* cyclization to give the cyclic vinyl–gold intermediate **28**. A subsequent 1,3-allyl shift[64,76] occurs via a Au(I)-catalyzed aza-Claisen-type rearrangement, furnishing the corresponding pyrrole. More recently, Heugebaert and Stevens applied the same concept to the synthesis of isoindoles from *N*-allyl-benzylamine derivatives (see eq 14, conditions B).[77]

Zhang and co-workers recently synthesized a variety of tri- and tetrasubstituted N–C-2-fused pyrroles by the Au(I)-catalyzed cycloisomerization of (*Z*)-(2-en-4-ynyl)lactams **29** (**eq 15**).[78] This interesting synthesis proceeds by a formal ring expansion of the β-lactam moiety via a 1,3-carbonyl migration.[79] Similarly to Gagosz's rationale, the Au(I)-catalyzed 5-*exo*-*dig* cyclization is followed by lactam ring opening, which leads to the formation of nucleophilic vinyl–Au species **30**. A subsequent 1,2 addition of the latter functional group to the activated carbonyl function produces the fused pyrrole product.

Finally, several migratory cycloisomerizations involving a Claisen-type rearrangement of the carbon skeleton of the substrate prior to the heterocyclization step have been reported. Kirsch and co-workers first reported that vinyl propargyl ethers **31** could be converted into densely substituted furans via a Au(I)-catalyzed cycloisomerization reaction (**Scheme 2**, **Part (a)**)[80,81] Thus, a variety of tetrasubstituted alkyl, aryl, and heteroarylfurans possessing a carbonyl group at C-3 were obtained under very mild reaction conditions. It is believed that this cascade process begins

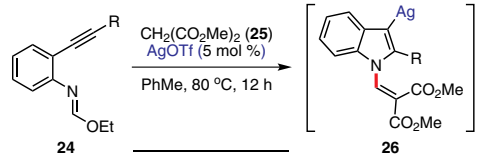


23

R	MG[a]	Yield
n-Pr	$MeOCH_2$	93%
4-$F_3CC_6H_4$	$MeOCH_2$	100%
4-$MeOC_6H_4$	$MeOCH_2$	96%
EtO_2C	$MeOCH_2$	85%
Ph	$TBSOCH_2$	99%
Ph	2-THP	93%
Ph	allyl	93%
Ph	PMB	98%
4-$MeOC_6H_4$	(*R*)-MeCH(Ph) (97% ee)	98% (88% ee)
4-$F_3CC_6H_4$	(*R*)-MeCH(Ph) (95% ee)	87% (72% ee)

[a] MG = migrating group.

eq 12 *(Ref. 70,73)*

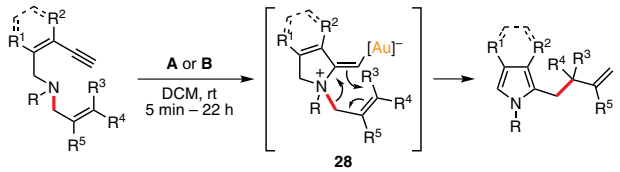


24 **26** **27**

R	Yield
Ph	91%
Cy	72%
$TBSO(CH_2)_2$	53%
n-Bu	62%
t-Bu	77%
1-Np	75%
Ph[a]	69%
Cy[a]	73%

[a] $CH_2(CN)_2$ was used.

eq 13 *(Ref. 74)*



28

R^1	R^2	R^3	R^4	R^5	Yield[a]
H	Ph	H	H	H	72%
H	Me	H	H	Me	89%
Cl	Me	H	Ph	H	98%
H	Me	Me	Me	H	90%
H	Me	Me	HC≡C	H	84%

[a] **A** = (4-$F_3CC_6H_4)_3PAuNTf_2$ (2 mol %); R = Ts.

R	R^3	R^4	R^5	Yield[a]
allyl	H	H	H	98%
Bn	Me	Me	H	72%
n-Pr	Ph	H	H	98%
n-Pr	Ph	H	Cl	76%

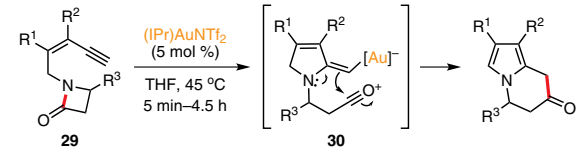
[a] **B**: $AuCl_3$ (1 mol %); R^1,R^2 = HC=CH-CH=CH.

eq 14 *(Ref. 75,77)*

with a Au(I)-catalyzed Claisen-type rearrangement[82] and leads to the formation of the reactive skipped allenyl ketone intermediate **32**, which undergoes a Au(I)-catalyzed 5-*exo*-*dig* cyclization to produce the furan ring.

The same group later disclosed that vinyl propargyl ethers **31** could also be employed in a very efficient synthesis of densely substituted pyrroles via the Ag–Au(I)-catalyzed condensation–cycloisomerization reaction sequence (see Scheme 2, Part (b))[83] Thus, skipped allenyl ketones **32**, formed by the Ag-catalyzed Claisen rearrangement, were intercepted by the amination reaction with various anilines and the resulting imines underwent the Au(I)-catalyzed 5-*exo*-*dig* cyclization to furnish the corresponding pyrroles. The authors demonstrated that a variety of pyrroles possessing different labile groups could be rapidly obtained in moderate-to-high yields under mild reaction conditions. In addition, the reaction was quite general with respect to the aromatic amine component, whereas aliphatic amines (R^5 = Me, *i*-Pr, Bn) did not undergo this transformation at all.

More recently, Saito et al. applied the above methodology to the direct synthesis of pyrroles from vinyl propargyl amines **31** (X = Y = NTs) in the presence of an (NHC)Au(I) catalyst[84] (see Scheme 2, Part (c)).[85] Furthermore, this new catalytic system was shown to be highly efficient for the cycloisomerization of ether analogues as well (X = Y = O, see Scheme 2, Part (c), conditions (ii)).

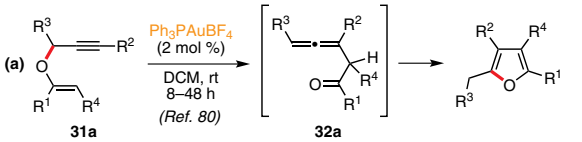


29 30

R^1	R^2	R^3	Yield
H	H	*n*-Pr	78%
H	$BnO(CH_2)_2$	Me	74%
Ph	H	Me	90%
H	*n*-Pr	Bn	66%
a	*a*	Me	70%

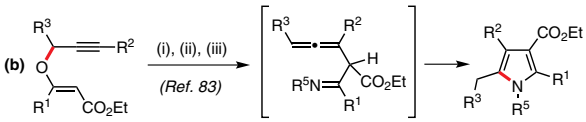
[a] R^1,R^2 = $-(CH_2)_5-$

eq 15 *(Ref. 78)*



31a 32a

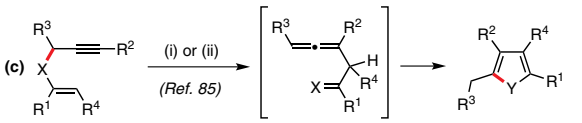
R^1	R^2	R^3	R^4	Yield
n-Pent	Me	H	CO_2Me	97%
Ph	Me	H	C(O)Ph	72%
Ph	Me	Me	CO_2Et	45%
Ph	2-Py	H	CO_2Et	82%



31b 32b

(i) $AgSbF_6$ (2–5 mol %), DCM, rt
(ii) R^5NH_2 (1.5 equiv)
(iii) Ph_3PAuCl (2–5 mol %)
DCM, 38 °C, 0.5–2 h

R^1	R^2	R^3	R^5	Yield
Ph	Me	H	4-$MeOC_6H_4$	75%
Ph	Me	H	3-$O_2NC_6H_4$	55%
Ph	Me	Me	Ph	38%
Me	Ph	H	Ph	75%
Ph	$CyCH_2$	H	Ph	90%
Ph	TBS	H	Ph	77%



31c 32c

(i) X = Y = NTs
[(IPr)Au(MeCN)]BF_4
(5 mol %)
DCM–HFIP, rt, 1–22 h
(ii) X = Y = O
[(IPr)Au(MeCN)]BF_4
(5 mol %), DCM, rt, 1 h

HFIP = hexafluoroisopropanol

X	R^1	R^2	R^3	R^4	Yield
TsN	CO_2Et	H	H	CO_2Et	68%
TsN	Me	H	*n*-Pent	CO_2Et	87%
O	Me	Ph	H	CO_2Et	99%
O	Ph	Me	H	C(O)Ph	89%

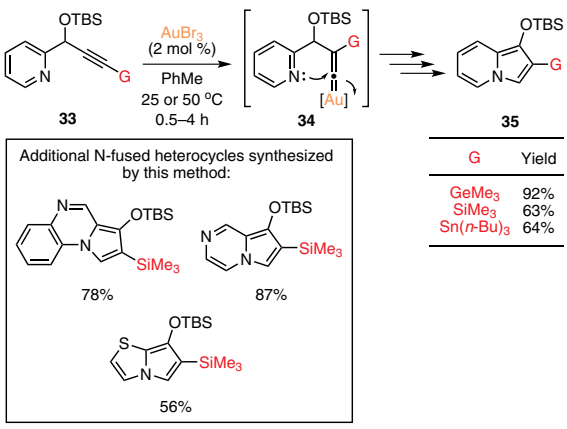
Scheme 2. Migratory Cycloisomerizations Involving a Claisen-Type Rearrangement Prior to Heterocyclization.

More recently, Saito et al. applied the above methodology to the direct synthesis of pyrroles from vinyl propargyl amines **31** (X = Y = NTs) in the presence of an (NHC)Au(I) catalyst[84] (see Scheme 2, Part (c)).[85] Furthermore, this new catalytic system was shown to be highly efficient for the cycloisomerization of ether analogues as well (X = Y = O, see Scheme 2, Part (c), conditions (ii)).

2.5. Silicon, Germanium, and Tin Migrations

Aiming at the efficient synthesis of not-so-easily accessible C-2-substituted indolizines, our group developed a highly efficient, Au(III)-catalyzed cascade cycloisomerization of skipped propargylpyridines **33** into indolizines **35** (**eq 16**).[86,87] This cascade is proposed to occur with a facile 1,2 migration of a silyl, stannyl, and even germyl group via an alkyne–vinylidene isomerization[88] of propargyl substrate **33** to give the reactive organogold species **34**. A subsequent cyclization of the intermediate, **34**, followed by a series of 1,2-hydride shifts, furnishes the corresponding indolizine. We have further demonstrated the synthetic utility of this methodology by carrying out the facile synthesis of various N-fused heterocycles, including pyrrolo[1,2-*a*]quinoxaline, pyrrolo[1,2-*a*]pyrazine, and pyrrolo[2,1-*b*]thiazole.

Yamamoto's group has developed the Au(I)-catalyzed, high-yield synthesis of 3-silyl-substituted benzothiophenes through a 1,3-silyl group migration during the cycloisomerization cascade of *ortho*-alkynylthiophenol silyl ethers (**eq 17**).[89] However, lower yields were obtained for substrates bearing very bulky or strong electron-withdrawing substituents, or containing less nucleophilic silyl migrating groups. In contrast to the intramolecular nature of the 1,3-alkyl-group migration in the analogous system (see eq 12), the observed crossover of two different silyl groups during the cycloisomerization of two different substrates indicated that the 1,3 migration of the silyl group proceeds intermolecularly. The observed crossover was rationalized by the suggested longer



33 34 35

G	Yield
$GeMe_3$	92%
$SiMe_3$	63%
$Sn(n\text{-}Bu)_3$	64%

eq 16 *(Ref. 86)*

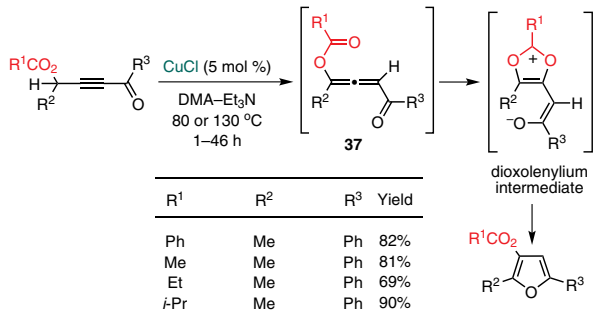
lifetime of the gold–silylsulfonium ion intermediate **36** due to the lower migratory ability of a silyl group relative to that of an alkyl group.

2.6. Acyloxy, Phosphatyloxy, and Sulfonyloxy Migrations

In 2004, our group envisioned that highly reactive allenyl substrates could be accessed via a formal 1,3 migration in propargyl acetates,[90-92] phosphates, or sulfonates.[93] This early concept later evolved into a series of highly efficient, practical, and general methodologies for the assembly of polysubstituted furans and indolizines. Accordingly, we demonstrated that an array of densely functionalized 3-acyloxyfurans could be synthesized via a Cu(I)-catalyzed cycloisomerization cascade of conjugated alkynyl ketone acetates proceeding through a formal 1,2-acyloxy-group migration (**eq 18**).[93] The nature of the base required for the selective formation of the 3-acyloxy regioisomer supported possible involvement of allene intermediate **37**, which is generated upon initial prototropic rearrangement of the substrate. Based on further mechanistic studies involving ^{17}O-labeled substrates, we proposed that this formal 1,2-acyloxy-group migration[94,95] likely occurs through the involvement of a dioxolenylium intermediate.[96]

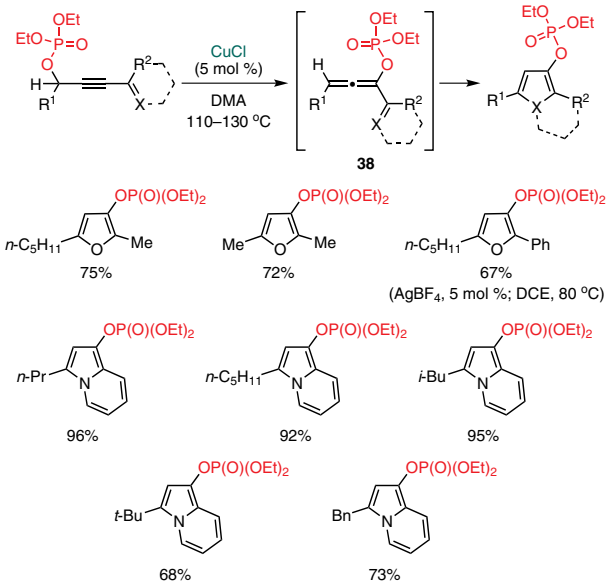
Our group also investigated the Cu(I)-catalyzed cycloisomerization of conjugated keto or pyridino propargyl phosphates in the absence of a base (**eq 19**).[96] This transformation allowed for a highly efficient synthesis of 3-phosphatyloxy furans and indolizines[97] via a formal 1,3-phosphatyloxy group migration.[96] Thorough mechanistic studies of this transformation with the aid of ^{17}O-labeled substrates revealed that the cycloisomerization proceeds via an initial formal [3,3]-sigmatropic rearrangement of propargyl phosphates into the reactive allenyl phosphates **38**. It should be noted that the phosphatyloxy-containing furans and indolizines represent versatile synthons, as the phosphatyloxy group can efficiently be substituted with various alkyl and aryl groups by the Kumada cross-coupling reaction.[96]

Next, we developed an alternative route to tetrasubstituted and even to fused furans via a transition-metal-catalyzed migratory cycloisomerization of skipped propargylic substrates. Thus, alkynyl acetates **39** underwent, in the presence of a silver catalyst at room temperature, a formal 1,2-acyloxy-group migration furnishing fully substituted 3-acyloxyfurans in high yields (**eq 20**).[93,96] The

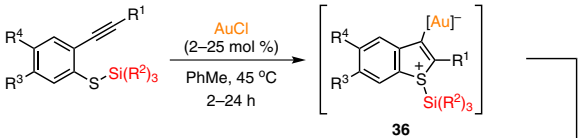


R^1	R^2	R^3	Yield
Ph	Me	Ph	82%
Me	Me	Ph	81%
Et	Me	Ph	69%
i-Pr	Me	Ph	90%
t-Bu	Me	Ph	86%
Ph	*n*-Pent	Ph	80%
Ph	(*S*)-TBSOC(Me)H	Ph	83%
Piv	*n*-Pent	*t*-Bu	80%

eq 18 *(Ref. 93,96)*



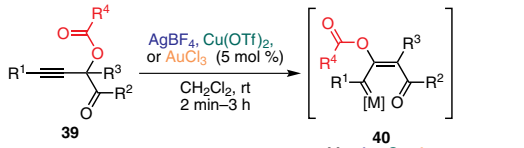
eq 19 *(Ref. 96)*



R^1	R^2	R^3	R^4	Yield
n-Pr	*i*-Pr	H	H	98%
2,4-$(MeO)_2C_6H_3$	*i*-Pr	H	H	99%
4-$MeOC_6H_4$	*i*-Pr	H	H	99%
4-$F_3CC_6H_4$	*i*-Pr	H	H	60%
4-$MeOC_6H_4$	*i*-Pr	*a*	*a*	72%
n-Pr	Ph	H	H	40%
4-$MeOC_6H_4$	*i*-Pr	F	H	88%
n-Hex	*b*	H	H	100%
4-$MeOC_6H_4$	*i*-Pr	F	H	51%

[a] $R^3,R^4 = OCH_2O$. [b] $Si(R^2)_3 = Si(s\text{-}Bu)(i\text{-}Pr)_2$.

eq 17 *(Ref. 89)*



R^1	R^2	R^3	R^4	Yield
n-Bu	Ph	Ph	Me	60%
n-Bu	Ph	Ph	*t*-Bu	81%
Ph	Ph	Ph	Me	91%
TMS[a]	Ph	Ph	Me	78%
t-Bu	Ph	Ph	Me	>99%
t-Bu	Ph	Ph	*t*-Bu	73%
t-Bu	Ph	Me	Me	84%
t-Bu	Me	Ph	Me	73%
t-Bu	Me	Me	Me	90%
t-Bu	*b*	*b*	Me	86%

[a] In PhMe. [b] $R^2,R^3 = (CH_2)_4$

eq 20 *(Ref. 93,96)*

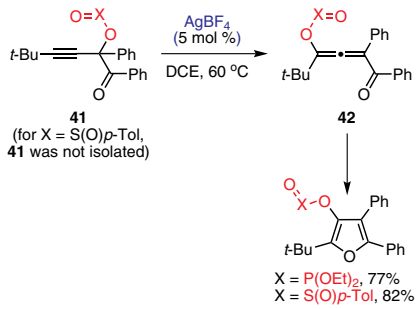
mechanism for the cycloisomerization of skipped alkynyl ketones **39** is suggested to follow a Rautenstrauch-type 1,2 migration,[98] resulting in intermediate **40**, and subsequent cycloisomerization to the furan ring.[96] Several other transition-metal complexes, including Cu(II) and Au(III), also catalyzed this transformation. Furthermore, phosphatyloxy and tosyloxy groups underwent an analogous 1,2 migration from propargyl (**41**) and allenyl (**42**) substrates, providing 3-phosphatyloxy- and 3-tosyloxyfurans, respectively (**Scheme 3**). In the case of skipped phosphatyloxy alkynyl ketones, **41**, cycloisomerization proceeds via two consecutive 1,2 migrations leading to the formation of allene intermediate **42** and a formal 1,3 shift. Subsequent 1,2 migration gives rise to the final product, 3-phosphatyloxy- or 3-tosyloxyfuran.

3. Conclusions and Outlook

This review highlighted a growing interest in the development of novel cascade transformations that incorporate various molecular rearrangements and functional-group migrations. Recent reports featuring this approach established new, general, highly efficient, and atom-economical transformations that lead to complex and densely functionalized aromatic heterocycles with diverse substitution patterns. These heterocycles are not easily available via alternative routes. A variety of functional groups—including S-, Se-, Hal-, C-, Si-, Ge-, Sn-, and O-containing functionalities—undergo various types of 1,*n* migrations during these heterocycle syntheses. In recent years, in addition to the continuing interest in the traditional Ag and Cu catalysts, the focus of many research groups has shifted to the remarkably efficient and mild gold catalysis. Although further development of novel, more general, and efficient migratory methodologies is certainly highly warranted, the progress achieved so far in this area bodes well for broad application in organic synthesis.

4. Acknowledgements

We thank the National Institutes of Health (GM-64444) and National Science Foundation (CHE-0710749) for financial support of this work. A. S. D. is grateful to the University of Illinois at Chicago Graduate College for a Dean's Scholar Award. N. C. thanks the Department of Chemistry of the University of Illinois at Chicago for the Moriarty Graduate Fellowship.



Scheme 3. Tetrasubstituted Furans by the Migratory Cycloisomerization of Skipped Propargylic Substrates. *(Ref. 93,96)*

5. References and Notes

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Keywords: copper; silver; gold; migration; cyclization.

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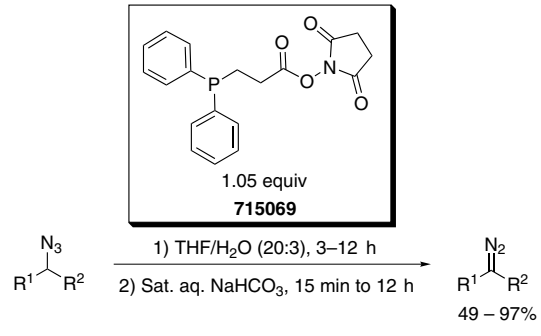
Alexander S. Dudnik was born in Krasnodar, Russia. He received his B.S. degree in 2005 from the M. V. Lomonosov Moscow State University. Between 2003 and 2005, he worked as a visiting researcher at the Zelinsky Institute of Organic Chemistry of the Russian Academy of Sciences. He is currently a fifth-year graduate student in Professor Gevorgyan's group at the University of Illinois at Chicago. A major part of his research in Prof. Gevorgyan's group is devoted to the development of new Lewis acid and gold-, copper-, and silver-catalyzed methodologies involving C–C or C–heteroatom bond-forming reactions and molecular rearrangements leading to carbo- and heterocycles. Alexander has recently received a University of Illinois Graduate College Dean's Scholar Award. After completion of his Ph.D. requirements, he will join the laboratory of Professor Gregory C. Fu at the Massachusetts Institute of Technology as a postdoctoral associate.

Natalia Chernyak was born in Riga, Latvia. She received her B.S. degree in 2002 and M.S. degree in 2005 from Riga Technical University. Between 2000 and 2005, she worked as a researcher at the Latvian Institute of Organic Synthesis. In 2005, she joined the laboratory of Professor Gevorgyan at the University of Illinois at Chicago, where she is currently a fifth-year graduate student. Her dissertation research has focused on the development of novel Pd-catalyzed direct/directed CH-functionalization processes, C–C-bond-forming reactions proceeding via CH activation, and the Cu-catalyzed multicomponent synthesis of heterocycles. Recently, her research achievements were recognized with a Moriarty Graduate Fellowship. Upon graduation, she will join the laboratory of Professor Stephen L. Buchwald at the Massachusetts Institute of Technology, as a postdoctoral associate.

Vladimir Gevorgyan was born in Krasnodar, Russia. He received his B.S. degree in 1978 from Kuban State University and his Ph.D. degree in 1984 from the Latvian Institute of Organic Synthesis, where he was promoted to Group Leader in 1986. He spent two years (1992–1994) in Tohoku University in Sendai, Japan, the first as a Japan Society for the Promotion of Science (JSPS) Postdoctoral Fellow and the second as a Ciba-Geigy International Postdoctoral Fellow. The following year (1995), he was a Visiting Professor at Consiglio Nazionale delle Ricerche (CNR) in Bologna, Italy. He returned to Tohoku University in 1996 as an Assistant Professor and was promoted to Associate Professor in 1997. In 1999, he moved to the University of Illinois at Chicago as an Associate Professor, and was promoted to the rank of Professor in 2003. Prof. Gevorgyan's current research interests cover four main areas: (i) highly selective Pd-catalyzed benzannulations, (ii) novel transition-metal-catalyzed reactions for the synthesis of heterocyclic and naturally occurring compounds, (iii) selective Lewis acid catalyzed bond formation and cleavage reactions, and (iv) the chemistry of strained-ring systems. In 2008, his contributions to the field of organic chemistry were recognized with the University of Illinois at Chicago Researcher of the Year Award.

Phosphine for the Conversion of Azides into Diazo Compounds

Due to difficulties with their preparation, especially when sensitive functional groups are present, diazo compounds are often overlooked in synthesis despite their synthetic versatility. Myers and Raines have developed a mild method to convert an azido group with delicate functional groups into a diazo compound by using the phosphine reagent featured here. Formally, this reaction is a reductive fragmentation of the azide, like the venerable Staudinger reaction, and is highly selective in most chemical environments.



Myers, E. L; Raines, R. T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2359.

ALDRICH Chemistry

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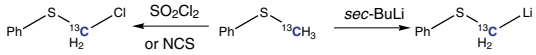
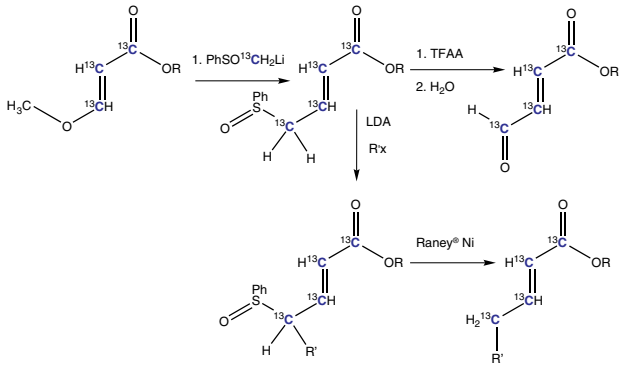
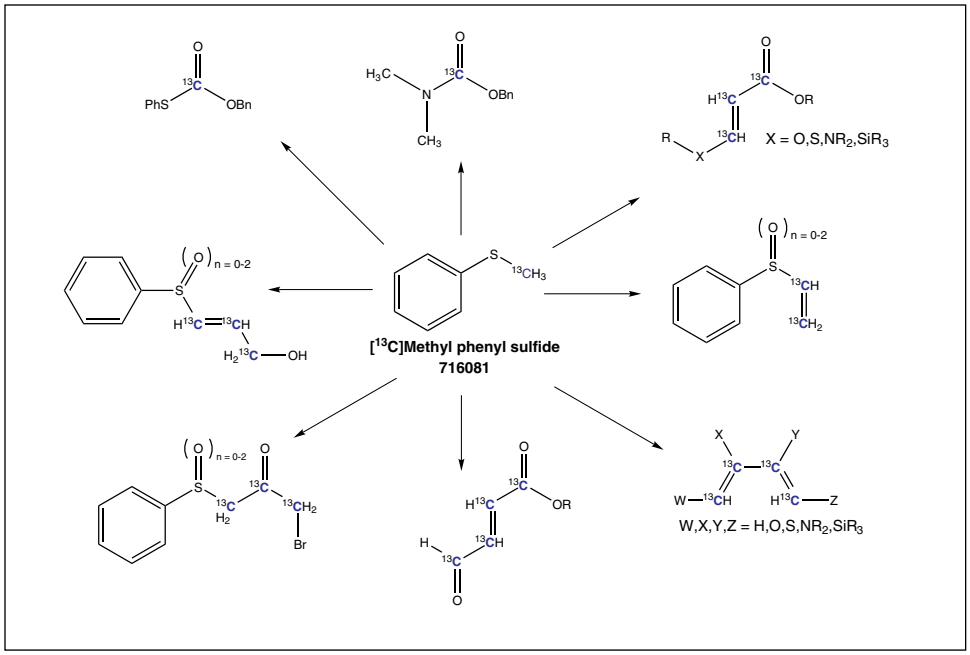
Reference: Martinez, R. A.; Alvarez, M. A.; Velarde, S. P.; Silks, L. A. P.; Stotter, P. L.; Schmidt, J. G.; Unkefer, C. J. Large-Scale Preparation of [^{13}C]-Methyl Phenyl Sulfide from [^{13}C]Methanol by a One-Step Process. *Org. Process Res. Dev.* **2002**, *6*, 851.

Some of the most versatile compounds in the collection include the methyl addition reagents of which methyl-^{13}C phenyl sulfide (**716081**) is a notable example. Methyl phenyl sulfide has a rich chemistry and, if prepared with carbon and deuterium labels in the methyl group, would be a versatile labeling precursor that could be easily converted into a nucleophilic or an electrophilic synthon.



The labeled methyl phenyl sulfide can be oxidized, adjusting the pK_a and allowing for subsequent modifications. A Raney® Ni mediated desulfurization can be used to remove the sulfur, leaving a labeled methylene group. Alternatively, a ^{13}C-labeled aldehyde, carboxylic acid, or carboxylic ester can be prepared directly.





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CBS Oxazaborolidine Reagents

Since 1987, the chiral oxazaborolidines known as CBS catalysts (after the work of Corey, Bakshi, and Shibata) have been used for the catalytic reduction of prochiral ketones, imines, and oximes to produce chiral alcohols, amines, and amino alcohols in excellent yields and ee's. A recent example is the total synthesis of the structurally complex *Lycopodium* alkaloid (+)-Lyconadin A shown in **Scheme 1**.[1]

The chiral oxazaborolidines can also be used to generate a new class of powerful Lewis acids by activation with a strong protic or Lewis acid. Such activated cationic oxazaborolidines are extremely effective catalysts for a wide range of asymmetric transformations, from cycloaddition reactions to the asymmetric synthesis of a wide variety of complex natural products and other molecular structures. The usefulness of cationic oxazaborolidines is demonstrated in a recent total synthesis of Aflatoxin B_2 via an asymmetric [3 + 2] cycloaddition reaction (**Scheme 2**).[2]

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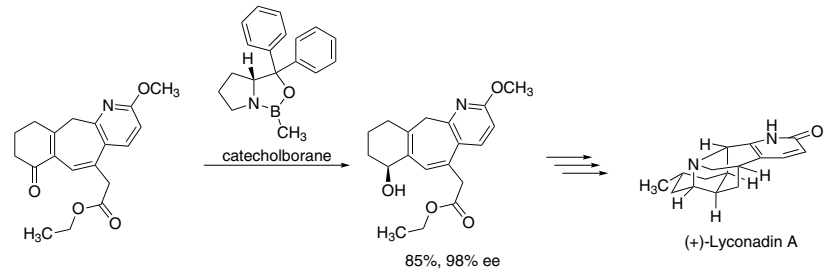
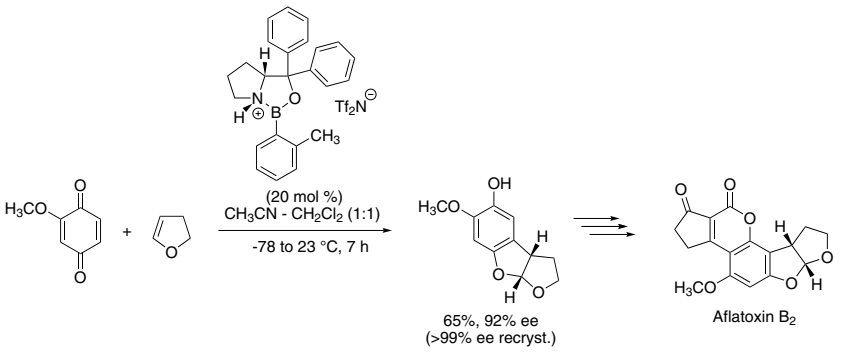
For more information on the applications of the CBS catalysts, please see Prof. Corey's review in this issue or visit ***sigma-aldrich.com***

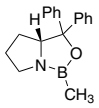


Scheme 1

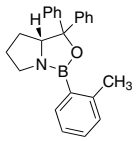


Scheme 2

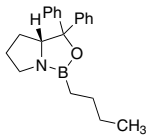
Product Section:



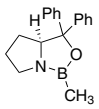
649317
457698: 1 M in toluene
674656: 1 M in THF



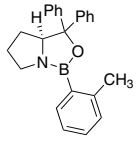
654299:
0.5 M in toluene



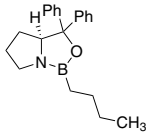
715956:
1 M in toluene



649309
457701: 1 M in toluene
674648: 1 M in THF



654302:
0.5 M in toluene



720607:
1 M in toluene

Cat. No.	Name
649317	(*R*)-(+)-2-Methyl-CBS-oxazaborolidine
649309	(*S*)-(–)-2-Methyl-CBS-oxazaborolidine
457698	(*R*)-(+)-2-Methyl-CBS-oxazaborolidine solution, 1 M in toluene
457701	(*S*)-(–)-2-Methyl-CBS-oxazaborolidine solution, 1 M in toluene
654299	(*R*)-(+)-*o*-Tolyl-CBS-oxazaborolidine solution, 0.5 M in toluene
654302	(*S*)-(–)-*o*-Tolyl-CBS-oxazaborolidine solution, 0.5 M in toluene
674656	(*R*)-(+)-2-Methyl-CBS-oxazaborolidine solution, 1 M in THF
674648	(*S*)-(–)-2-Methyl-CBS-oxazaborolidine solution, 1 M in THF
715956	(*R*)-(+)-2-Butyl-CBS-oxazaborolidine solution, 1 M in toluene
720607	(*S*)-(–)-2-Butyl-CBS-oxazaborolidine solution, 1 M in toluene

Enantioselective Synthesis Based on Catalysis by Chiral Oxazaborolidinium Cations

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Outline

1. Introduction

During the 1980s, proline-derived chiral oxazaborolidines of general structure **1** (**Figure 1**) were introduced as catalysts for enantioselective reduction of prochiral ketones. This process, sometimes referred to as the CBS (Corey-Bakshi-Shibata) reduction,[1] has subsequently been applied to a wide range of ketonic substrates. A useful feature of the CBS reduction methodology is the availability of a well-defined stereochemical model for reduction (**2** in Figure 1). The application of this methodology for the asymmetric synthesis of a wealth of natural products and non-natural molecules has been reviewed previously.[2]

The chiral oxazaborolidines represented by **1** can also be used to generate a new class of powerful Lewis acids by activation with a strong protic or Lewis acid.[3] Such activated cationic oxazaborolidines are extremely effective catalysts for a wide range of asymmetric transformations. In this review, we provide an overview of the formation and utility of cationic oxazaborolidines as chiral catalysts and their application to the asymmetric synthesis of a wide variety of complex natural products and non-natural structures, especially by Diels-Alder addition.

2. Proton-Activation of Oxazaborolidines

Although various Lewis acids (e.g. BF_3, $SnCl_4$, $ZnCl_4$, $AlCl_3$) were found not to be useful for the coordinative activation of **1**, the strong protic acid, triflic acid (TfOH), turned out to be a powerful activator of **1a**: ^{1}H NMR measurement of a 1:1 mixture of **1a** and TfOH in $CDCl_3$ at -80 °C revealed the presence of two protonated species **3** and **4**, in a ratio of ca. 1.5:1 at about 0.05M concentration (**Scheme 1**).[4] Complete protonation required a very strong protic acid; acids such as methanesulfonic or benzenesulfonic acids were too weak. The Lewis acidity of **4**, expected to be high from the fact that a very strong protic acid is required to produce it from **1a**, was fully confirmed by subsequent studies. The equilibrium between **3** and **4** is facile (although slow on ^{1}H NMR timescale at -80 °C) and so the mixture is equivalent to the cation **4**.

2.1. Diels-Alder Reactions of α,β-Enals

The protonated oxazaborolidine **4** was first found to be an extremely powerful catalyst for the Diels-Alder reaction of 2-methacrolein or 2-bromoacrolein with a variety of dienes of quite different reactivity as shown in **Table 1**.[4] Optimization of the catalyst structure in terms of yield and enantioselectivity of this reaction revealed an *o*-tolyl group on boron to be the substituent of choice.[4] The C-aryl substituent 3,5-dimethylphenyl (*m*-xylyl or mexyl) was somewhat superior to phenyl (see Table 1), likely because of its greater basicity as a neighboring π-rich aromatic group.[4]

The highly enantioselective formation of the Diels-Alder adducts shown in Table 1 is considered to result from the preferred pre-transition-state assembly **6** (Figure 2), for which there is considerable precedent in our previous work.[5-7] The complex of the catalyst with 2-substituted acrolein has been proposed to involve an electrostatic interaction between the formyl hydrogen and the oxygen on boron that is synergistic with the coordination of formyl oxygen to boron. In the pre-transition-state assembly **6** the formyl carbon, rendered more positive due to the carbonyl coordination to boron, lies at Van der Waals contact distance (3.5 Å) above an *ortho*-carbon of the nearby mexyl group. This attractive interaction of the coordinated C=O and the neighboring π-rich benzenoid ring

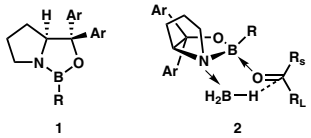
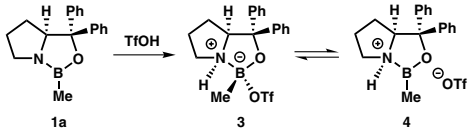
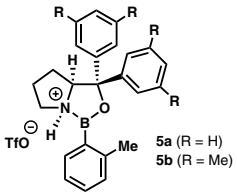


Figure 1. Chiral Oxazaborolidine **1** and the Stereochemical Model for CBS-Reduction. *(Ref. 2)*

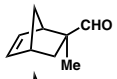
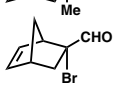
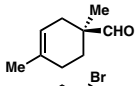
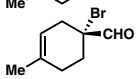
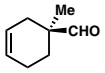
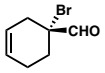
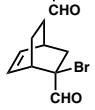


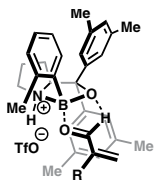
Scheme 1. Protonation of Oxazaborolidine **1a** with Triflic Acid. *(Ref. 4)*

Table 1. Diels-Alder Reactions of 1,3-Dienes with 2-Methacrolein or 2-Bromoacrolein Catalyzed by Proton-Activated Oxazaborolidines **5a** or **5b**. *(Ref. 4)*



5a (R = H)
5b (R = Me)

Product	Catalyst (mol %)	Temp (°C) Time (h)	Yield (%) (*exo*/*endo*)	*ee* (%)
	**5a** (6)	-95, 1	99 (91:9)	91
	5b (6)	-95, 1	97 (91:9)	96
	**5a** (6)	-95, 1	99 (91:9)	92
	5b (6)	-95, 1	99 (91:9)	96
	**5b** (6)	-78, 13	96	97
	**5a** (6)	-95, 1	98	97
	5b (6)	-95, 1	98	97
	**5b** (20)	-78, 24	85	94
	**5a** (6)	-95, 2	95	96
	5b (6)	-95, 2	97	96
	**5a** (20)	-78, 24	91 (5:95)	92
	5b (20)	-78, 24	58 (6:94)	92
	**5a** (6)	-95, 2	81 (6:94)	92
	5b (6)	-95, 2	85 (7:93)	92



6

Figure 2. Pre-transition-state Assembly for Enantioselective Diels-Alder Reactions of 2-Substituted α,β-Enals. *(Ref. 4)*

is maintained in the transition state even as the diene addition takes place to the α,β-bond of the enal. That π-π attractive interaction screens the rear face of the complexed *s-trans* α,β-enal and directs addition to the front face of the dienophile as shown in **6**. The mechanistic model exemplified by **6** is a reliable predictor of the absolute stereochemical course of Diels-Alder reactions of α,β-enals under catalysis by cationic oxazaborolidines.

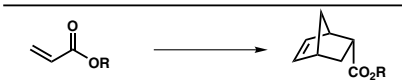
2.2. Diels-Alder Reactions of Other α,β-Unsaturated Carbonyl Compounds

The application of proton-activated oxazaborolidines **5a-b** was found not to be limited to α,β-enals as dienophiles and extended to a variety of α,β-unsaturated carbonyl compounds including α,β-unsaturated esters, lactones, ketones and especially quinones.[8] Our initial studies demonstrated that acrylate and crotonate esters are satisfactory dienophiles when cyclopentadiene was used as the diene (**Table 2**). However, due to the lower reactivity of crotonates relative to the corresponding acrylates, it is advantageous to use more reactive trifluoroethyl ester rather than methyl and ethyl ester.

The dienophile face selectivity for Diels-Alder addition to acrylate and crotonate esters was found to be opposite to that for α,β-enals. A likely reason for this divergent behavior emerged from X-ray crystallographic studies of BF_3-complexes of α,β-unsaturated esters and enones. As summarized in **Figure 3**, one of the fluorines on boron and the α-C-H of the unsaturated carbonyl compounds is in close proximity and within Van der Waals contact distance (2.67 Å).

These data suggest the possibility that the face selectivity observed for α,β-unsaturated esters and enones that possess an α-C-H group may be due to a pre-transition-state assembly of type **7** (**Figure 4**), which clearly would lead to opposite face-selectivity than the corresponding formyl C-H···catalyst interaction as in **6**.

Table 2. Diels-Alder Reactions of Acrylates and Crotonates with Cyclopentadiene Catalyzed by **5a-b**. *(Ref. 8)*

Dienophile R	Cat (mol %)	Temp (°C) Time (h)	Yield (%) (*endo*/*exo*)	*ee* (%)
				
H	**5a** (20)	-35, 1.5	99 (95:5)	98
Et	**5b** (20)	-20, 16	96 (97:3)	>99
				
Et	**5b** (13)	+4, 72	46 (91:9)	>98
CH_2CF_3	**5a** (20)	-20, 16	93 (95:5)	>98

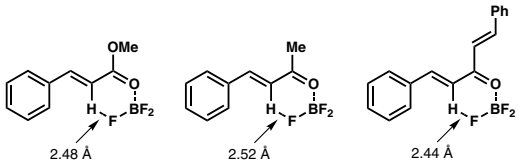


Figure 3. α-C-H to Fluorine Distances in BF_3 Complexes of α,β-Unsaturated Carbonyl Compounds as Determined by X-Ray Crystallography. *(Ref. 8)*

The generality of the catalytic enantioselective Diels-Alder reaction mediated by **5a** and **5b** and the α-CH···catalyst binding mode of reaction are further supported by the results summarized in **Figure 5**, which shows the products derived from cyclopentadiene and a variety of α,β-unsaturated carbonyl compounds. The utility of cyclic α,β-enones and quinone monoketals in the catalytic Diels-Alder processes is noteworthy, not only because of the good yields and enantioselectivities, but also because other chiral Lewis acids are ineffective for these substrate classes.

One limitation of the triflic acid-activated oxazaborolidines stems from their instability at temperatures above 4 °C, which significantly limits the scope of the Diels-Alder reactions within reactive dienes and/or dienophiles. Consequently, triflimide, $(CF_3SO_2)_2NH$ (known to be comparable in acid strength[9] to triflic acid), was investigated as activating agent. Fortunately, protonated triflimide catalysts were found to be sufficiently stable to be useful at 25-40 °C.[10] The development of triflimide-activated catalysts **8a-b** (**Figure 6**) has broadened the scope of the Diels-Alder reaction to include many less reactive partners and to allow shorter reaction times.

An instructive comparison of triflic acid- and triflimide-activated catalysts is shown in **Table 3**. The order of reactivity of α,β-unsaturated esters as dienophiles with **5a** or **8a** is acrylate > crotonate > cinnamate and for a given acid the trifluoroacetate ester is markedly more reactive then the methyl or ethyl ester.

The power of triflimide-activated catalysts **8a-b** in promoting asymmetric Diels-Alder reactions with less reactive dienes was further exemplified by using diethyl fumarate and trifluoroethyl acrylate as dienophiles (**Figure 7**).

The development of triflimide-activated catalysts has enabled the formation of cycloaddition products derived from less reactive 2,3-dimethylbutadiene (**Figure 8**). Even though products were obtained with somewhat reduced enantioselectivity, this is a real advance in extending the scope of the asymmetric Diels-Alder reaction toward less reactive dienophiles.

The effective range of the catalysts **5** or **8** also extends to heterodienes such as those in the furan series.[11] The use of furans as dienes for Diels-Alder reactions had been restricted due to their low reactivity and the reversibility of addition which has resulted in poor conversions and/or undesirable side reactions. Excellent results were obtained for the Diels-Alder reactions of a number of furan derivatives with trifluoroethyl acrylate using proton-activated catalysts **5a** and **8a**, as summarized in **Figure 9**.[11]

2.3. Diels-Alder Reactions of Quinones

Compared to other α,β-unsaturated carbonyl compounds, quinones are even better partners in these catalytic Diels-Alder

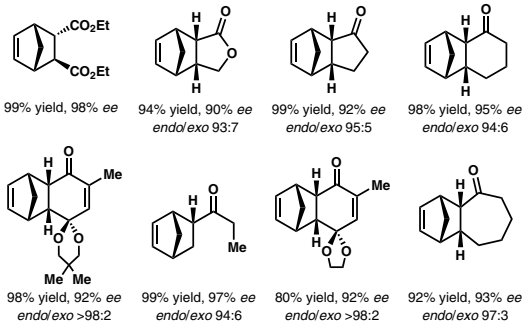


Figure 5. Examples of Diels-Alder Adducts from Reactions which Proceed Through α-CH•••Catalyst Binding. *(Ref. 8)*

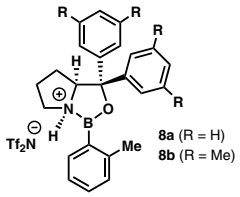
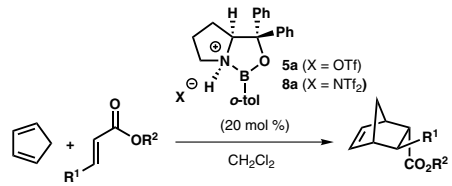


Figure 6. Triflimide-Activated Oxazaborolidines **8a** and **8b.** *(Ref. 10)*

Table 3. Comparison of Triflic Acid and Triflimide-Activated Catalysts in Diels-Alder Reactions. *(Ref. 10)*



R^1	R^2	Cat	Temp (°C) Time (h)	Yield (%) (*endo*/*exo*)	*ee* (%)
Me	Et	**5a**	4, 72	46 (91:9)	>98 (*endo*)
Me	Et	**8a**	20, 16	94 (89:11)	97 (*endo*)
Ph	CF_3CH_2	**5a**	4, 72	27 (85:15)	95 (*endo*), 94 (*exo*)
Ph	CF_3CH_2	**8a**	20, 16	79 (83:17)	93 (*endo*), 96 (*exo*)
Ph	CF_3CH_2	$EtAlCl_2$	20, 16	86 (88:12)	-

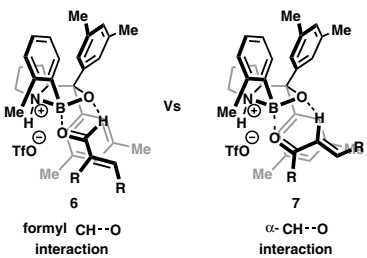


Figure 4. Difference in Stereochemical Model for the Diels-Alder Reaction of α,β-Enals and Other α,β-Unsaturated Carbonyl Compounds with Catalyst **5b.** *(Ref. 8)*

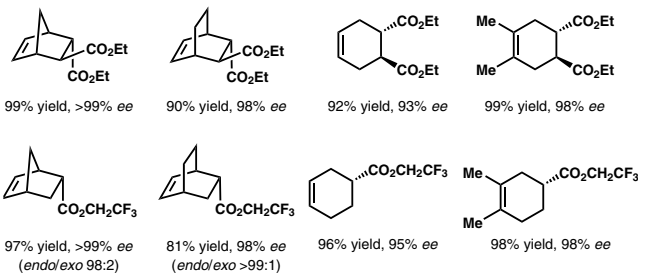


Figure 7. Assorted Examples of Diels-Alder Products Derived from Diethyl Fumarate and Trifluoroethyl Acrylate Using Triflimide-Activated Catalysts **8a** or **8b.** *(Ref. 10)*

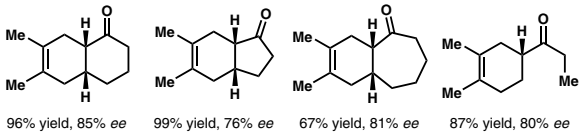


Figure 8. Diels-Alder Products Derived from α,β-Enones and 2,3-Dimethylbutadiene Catalyzed by Triflimide-Activated Catalysts **8a** or **8b**. *(Ref. 10)*

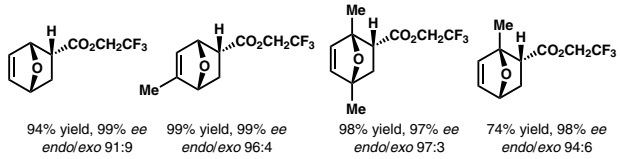


Figure 9. Products of Diels-Alder Reactions between Trifluoroethyl Acrylate and Furans Using Catalyst **5a** or **8a.** *(Ref. 11)*

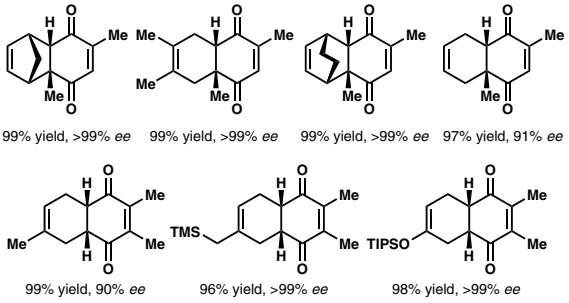
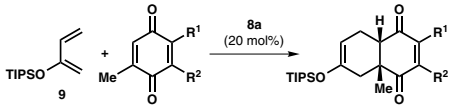
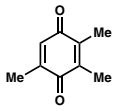
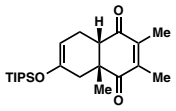
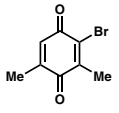
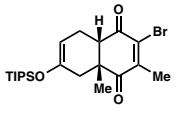
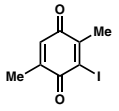
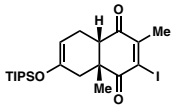
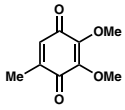
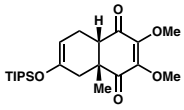
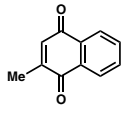
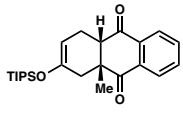


Figure 10. Diels-Alder Products Derived from 2,5- and 2,3-Dimethyl 1,4-Benzoquinones with Various Dienes Obtained Using Triflimide-Activated Catalysts **8a.** *(Ref. 10)*

Table 4. Enantioselective Diels-Alder Reactions of Trisubstituted 1,4-Benzoquinones with 2-Triisopropylsilyloxybutadiene Catalyzed by **8a.** *(Ref. 16)*



Quinone	Product	Temp (°C) Time (h)	Yield (%), *ee* (%)
		-78, 12	98, 99
		-78, 3	96, 97
		-78, 16	99, >99
		-50, 48	85, 95
		-60, 36	96, 91

reactions with various dienes. In general, quinones are highly reactive substrates and so the scope of the reaction is broad and the yields and enantioselectivities are excellent. These factors are quite significant, since the quinone-Diels-Alder subtype is a very powerful construction that is highly useful for the synthesis of many natural products and other complex molecules. Despite their synthetic value, enantioselective quinone-Diels-Alder reactions were elusive until it was discovered[12-15] that the use of Mikami's BINOL-$Cl_2Ti(O\textit{i}\text{-}Pr)_2$ catalyst can give adducts with good enantioselectivity. The scope of this catalysis, however, was restricted to a very limited set of reactants such as naphthoquinone and quinone monoketals. As shown in Figure 5, the triflic acid-activated catalyst **5a** is an efficient and very general catalyst for Diels-Alder reactions of quinone monoketals as dienophiles.

Because of the synthetic importance for the asymmetric Diels-Alder reactions of quinones, the scope of this process was evaluated in detail. The triflimide activated catalyst **8a** was found to be an excellent catalyst for Diels-Alder reactions of 2,3- and 2,5-dimethyl-1,4-benzoquinones with a variety of dienes as depicted in **Figure 10**.[10] Diels-Alder reactions between unsymmetrical dienes and 2,5-dimethyl-1,4-benzoquinones, which involve regioselectivity as well as enantioselectivity issues, were also tested using catalyst **8a**. Although the position selectivity was found to be rather nominal, both regioisomers were formed in excellent enantioselectivities.[10]

The high yields and enantioselectivities of these reactions extend to a wide range of other quinones, including mono-, di- and trisubstituted quinones.[16] Catalyst **8a** was once again found to be the most efficient. The results obtained for the unsymmetrical test diene 2-triisopropylsilyloxybutadiene (**9**) and five different trisubstituted quinones are displayed in **Table 4**. Excellent yields, enantioselectivities and position selectivities were realized.

The products in each case are as expected from the pre-transition-state assembly shown in **Figure 11** with the help of the following additional information: (a) the diene attaches to the less substituted double bond; (b) C-1 of triisopropylsilyloxybutadiene is more nucleophilic than C-4 and its bonding to quinone is stronger than that of C-4 in the transition state (concerted, asynchronous pathway); (c) C-1 of diene attaches preferentially to the carbon of the quinone which is β to the catalyst coordinated carbonyl group; and (d) an *endo*, suprafacial addition occurs at sterically unshielded face of the α,β-double bond to form the Diels-Alder adduct.[16]

Similar levels with respect to yield and enantioselectivity were observed for the Diels-Alder reactions of di- and monosubstituted quinones with 2-triisopropylsilyloxybutadiene as exemplified in **Table 5** and **Table 6**, respectively. In these cases also, one positional isomer predominates even when more than one is theoretically possible.

Based on the observation of the results summarized in Figure 10 and Tables 4-6, the following set of selection rules for the prediction of structure and absolute configuration of the products

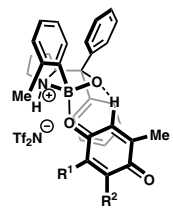


Figure 11. Pre-transition-state Assembly for Enantioselective Diels-Alder Reactions of 1,4-Benzoquinones. *(Ref. 16)*

obtained in Diels-Alder reactions of quinones using catalyst **8a** was proposed:

(1) For a quinone carbonyl flanked by C_α-H and C_α-R, the major product will result from catalyst coordination preferentially at the oxygen lone pair on the C-H side *a* rather than the C-R side *b* because *a* is sterically more accessible than *b* (see **Figure 12a**).

(2) Catalyst coordination at the more basic of the two 1,4-quinone oxygens will predominate, and this mode will lead to the preferred Diels–Alder adduct (see **Figure 12b**).

(3) If a double bond of the quinone in 1,3-diene addition bears two hydrogens, it will be more reactive than that bearing substituent(s), especially one or two π-electron donor groups.

(4) For monosubstituted 1,4-quinones (or *p*-benzoquinone itself), the major product pathway will involve coordination of catalyst at C=O *syn* to the HC=CH subunit that undergoes [4+2]-cycloaddition (see **Figure 12c**).

(5) C(1) of 2-triisopropylsilyloxy-1,3-butadiene (**9**), the more nucleophilic end of the diene, will attach to the carbon β to the carbonyl group that coordinates with the catalyst, i.e., the more electrophilic carbon.

(6) The preferred three-dimensional transition state corresponds to the *endo* arrangement of diene and catalyst-coordinated quinone.

2.4. Enantioselective [3+2]-Cycloaddition: Synthesis of Aflatoxin B_2

The very positive results obtained with the chiral oxazaborolidinium cations **8a-b** as catalysts for enantioselective Diels–Alder reactions encouraged the study of their application to [3+2]-cycloaddition processes. The possibility of such reactions was successfully investigated in the context of developing a simple enantioselective route to the microbial toxin aflatoxin B_2 (**10**). As outlined in **Scheme 2**, addition of 2,3-dihydrofuran (just over 1 equiv) to a solution of triflimide catalyst *ent*-**8a** and 2-methoxy-1,4-benzoquinone in a mixture of CH_2Cl_2 and CH_3CN at -78 °C and subsequent reaction at -78 °C to 23 °C gave the [3+2] cycloadduct **11** in 65% yield.[17] This was converted in several steps to the isomeric phenol **12**, which upon condensation with 2-ethoxycarbonyl-3-bromo-2-cyclopentenone gave aflatoxin B_2 (**10**), as shown in Scheme 2. This is by far the simplest known enantioselective route to **10**.

Strong evidence that the [3+2] cycloaddition reaction that produced adduct **11** is actually a two step process was obtained from a simple experiment in which a reactive intermediate was trapped. When the [3+2]-cycloaddition was carried out with a ten-fold excess of 2,3-dihydrofuran over 2-methoxybenzoquinone, the formation of cycloadduct **11** was suppressed and a new product was formed in an approximately equal amount. The structure of the product was shown unequivocally to be **13** (**Scheme 3**) by X-ray crystallographic analysis. Since it is likely that **13** arose by trapping of the intermediate **15**, a reaction pathway for the formation of **13** that involved **15** as an intermediate was proposed. It is reasonable that both the 1:1 cycloadduct **11** and the 2:1 adduct **13** are formed via the pre-transition-state assembly **14** and intermediate **15**.[17] This [3+2] cycloaddition reaction, even though limited in scope, could be extended to a few different quinones, and adducts were obtained with high enantioselectivity.[17]

2.5. Asymmetric Michael Addition to α,β-Unsaturated Enones

The reaction of α,β-enones with silyl enol ethers of esters using proton-activated chiral oxazaborolidines follows a Michael addition

Table 5. Enantioselective Diels-Alder Reactions of 2,3- or 2,6-Disubstituted 1,4-Benzoquinones with 2-Triisopropylsilyloxybutadiene Catalyzed by **8a**. *(Ref. 16)*

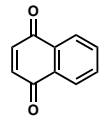
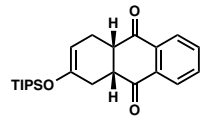
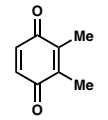
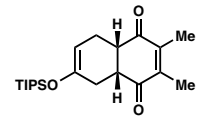
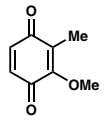
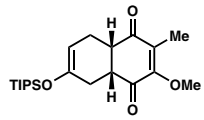
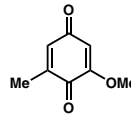
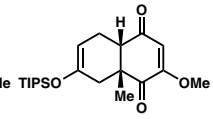
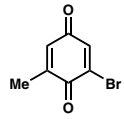
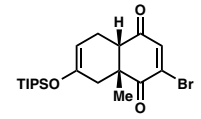
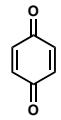
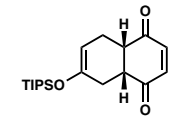
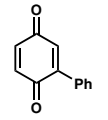
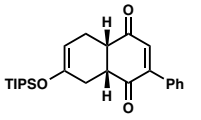
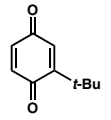
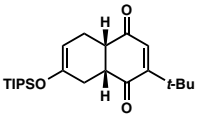
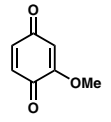
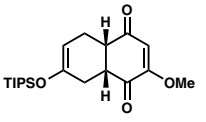
Quinone	Product	Temp (°C) Time (h)	Yield (%), *ee* (%)
		-78, 2	98, 97
		-95, 2	98, >99
		-78, 12	84, 90
		-50, 96	98, 92
		-78, 4	95, 91

Table 6. Enantioselective Diels-Alder Reactions of Unsubstituted or Monosubstituted 1,4-Benzoquinones with 2-Triisopropylsilyloxybutadiene Catalyzed by **8a**. *(Ref. 16)*

Quinone	Product	Temp (°C) Time (h)	Yield (%), *ee* (%)
		-78, 6	85, 88
		-78, 24	87, 94
		-78, 12	92, 91
		-78, 16	95, 91

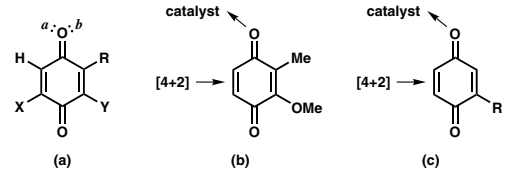
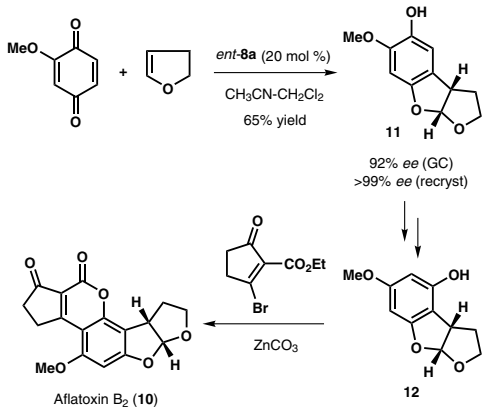
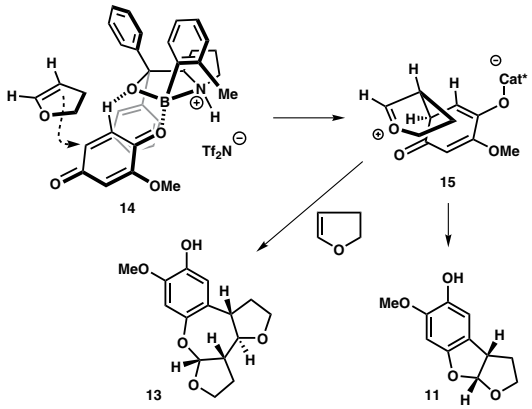


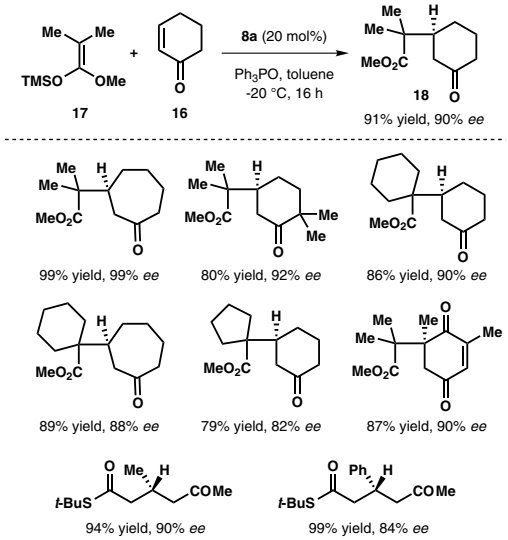
Figure 12. Catalyst Binding and Diene Approach to Quinones. *(Ref. 16)*



Scheme 2. Asymmetric [3+2]-Cycloaddition Reaction and its Application to the Enantioselective Synthesis of Aflatoxin B_2. *(Ref. 17)*



Scheme 3. Rational Pathway for the Formation of **11** and **13** via **15** with Catalyst **8a**. *(Ref. 17)*



Scheme 4. Catalytic Enantioselective Michael Addition: the Reaction and Substrate Scope. *(Ref. 18)*

pathway rather than the [2+2]-cycloaddition route (see Section 3.3). The Michael addition process is exemplified in **Scheme 4** using 2-cyclohexenone (**16**) and the trimethylsilyl enol ether of methyl isobutyrate (**17**) as substrates. The reaction proceeds efficiently (91% yield) and the product (**18**) is obtained with 90% *ee* when a catalytic amount of triphenylphosphine oxide is used as a trap for transiently formed Me_3Si^+ (or equivalent).[18] A fairly general substrate scope (see Scheme 4) for this reaction could be achieved under slightly modified reaction conditions and Michael adducts were obtained with high enantioselectivity.[18] As in the case of cycloaddition reactions, the absolute configuration of the Michael adduct can be predicted using an analogous stereochemical model (see Figure 4).

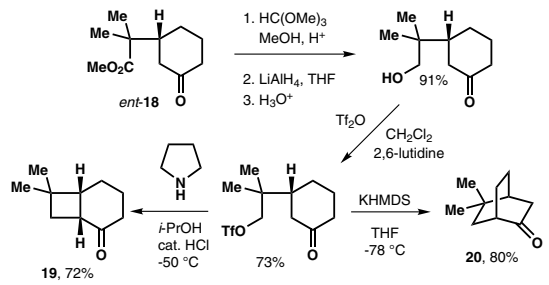
The Michael adduct *ent*-**18**, obtained using *ent*-**8a** as the catalyst, could be converted either to the fused-ring bicyclic product **19** or the bridged-ring isomer **20** as shown in **Scheme 5**.[18] The chiral bicyclo[4.2.0]octanone **19** is an intermediate for the enantioselective synthesis of the unique sesquiterpene β-caryophyllene.[19]

2.6. Enantioselective Cyanosilylation of Carbonyl Compounds

Considering the activation of aldehydes by protonated oxazaborolidines and the resulting highly enantioselective Diels-Alder reactions of enals (see Section 2.1), it is not surprising that these catalysts can be effective in promoting enantioselective nucleophilic addition to aldehydes.

Cyanosilylation was chosen as the model reaction and was indeed found to proceed highly enantioselectively with 10 mol % **8b** (Figure 6) when trimethylsilyl cyanide (TMSCN) was used as the reagent and catalytic amount (20 mol %) of triphenylphosphine oxide (Ph_3PO) as additive.[20] A variety of aromatic and aliphatic aldehydes underwent efficient cyanosilylation and the corresponding cyanohydrins were obtained after acidic work-up with >90% ee in all cases (**Table 7**). Data from a number of NMR and IR experiments suggested the possible formation of phosphine oxide bound isocyanide [Ph_3P(OTMS)(N=C:)] as the active nucleophile in this reaction.[20] The absolute configuration of these products is in agreement with the stereochemical model (**Figure 13a**).

The catalytic oxazaborolidine method has also been extended to include ketonic substrates.[21] Catalyst **5b** was found to be superior in this case and the products were obtained with the same face selectivity as for aldehydes. A pre-transition-state assembly (**Figure 13b**) analogous to the one for aldehyde cyanosilylation



Scheme 5. Synthesis of Chiral Fused or Bridged-ring Ketones from a Michael Adduct. *(Ref. 18)*

but involving α-C-H···O hydrogen bonding instead of formyl C-H···O hydrogen bonding could be invoked to explain the same face selectivity.[21]

3. Aluminum Bromide-Activated Oxazaborolidines

The discovery of the high efficiency and utility of proton-activated oxazaborolidines prompted the reinvestigation of the earliest approach to the activation of oxazaborolidines by Lewis acids. The original negative findings for BF_3, $SnCl_4$, $ZnCl_2$, $MeAlCl_2$ were confirmed. In contrast, the very strong Lewis acids BBr_3 and $AlBr_3$ (the latter is available from Aldrich as a 1.0M solution in CH_2Br_2) provided viable catalysts. It was found that activation by $AlBr_3$ afforded a complex that was comparably effective as TfOH- or Tf_2NH-activated oxazaboroline as a catalyst for enantioselective Diels–Alder reactions.[22] BBr_3-activation was definitely inferior to $AlBr_3$-activation, although better than that observed for the other Lewis acids mentioned above. The $AlBr_3$-activated oxazaborolidine is stable in the temperature range -78 °C to -20 °C in CH_2Cl_2 solution. The ^1H NMR spectrum is very similar to that for the proton-activated catalysts **5a** and **8a** and fully consistent with the analogous structure **21** (**Figure 14**).

3.1. Diels-Alder Reactions of Various Dienophiles

A comparison of the Diels–Alder reactions catalyzed by $AlBr_3$-activated oxazaborolidine **21** with those catalyzed by the proton-activated oxazaborolidines **5a** and **8a** revealed generally similar results in terms of reaction yield and enantioselectivity. One advantage of the $AlBr_3$-activated **21** was that the reaction proceeds well even with only 4 mol % of catalyst, as compared to ca. 10 mol % for **5a** and **8a** in most instances (possibly the result of less serious product inhibition of the catalytic process).[22] Catalyst **21** can be generated both conveniently and reproducibly using a solution of $AlBr_3$ in CH_2Br_2. The results for the reactions of a variety of dienophiles with cyclopentadiene, isoprene and less reactive heterodienes such as furans are shown in **Figure 15**.[22]

Excellent results were also obtained for catalyst **21** in Diels-Alder reactions of quinones with various dienes (**Figure 16**).[22]

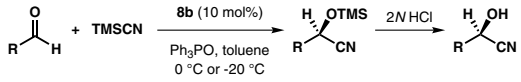
3.2. Diels-Alder Reactions of Maleimides

Maleimides are an interesting class of dienophiles that have been utilized successfully for diastereoselective Diels-Alder reactions with a number of chiral dienes.[23-24] However, despite the usefulness of the products obtained via Diels-Alder reactions using maleimide dienophile, the range of catalytic enantioselective versions of this reaction has been rather limited.[25-27] Very recently we have developed a catalytic asymmetric Diels-Alder reaction of maleimides using activated oxazaborolidines **8a** and **21**, which showed broad scope both in terms of dienes and maleimides.[28] *Endo*-adducts were obtained exclusively (*dr* >99:1) in very high yield and with excellent enantioselectivity as indicated by the examples in **Figure 17**.[28]

3.3. Enantioselective [2+2]-Cycloaddition Reactions

A process for enantioselective [3+2]-cycloaddition reactions involving the π-electron rich vinylic ether 2,3-dihydrofuran using as chiral catalyst the triflimide **8a** was described in Section 2.4. It was surmised that vinyl ethers might also participate in enantioselective [2+2]-cycloadditions using the same catalyst. Such a result was first realized with the test reaction of 2,3-dihydrofuran with trifluoroethyl acrylate in the presence of a catalytic amount of the $AlBr_3$-activated oxazaborolidine **21**, as outlined in **Scheme 6**.[29] The *exo*-cycloadduct **22** was produced with near perfect diastereo- and enantioselectivity in 87% yield.

Table 7. Oxazaborolidinium-Catalyzed Cyanosilylation of Aldehydes. *(Ref. 20)*



R	Time (h)	Yield (%)	*ee* (%)
phenyl	40	94	95
2-tolyl	72	95	91
4-anisyl	40	91	90
4-cyanophenyl	144	98	97
cyclohexyl	40	97	90
tert-butyl	40	96	91
n-hexyl	48	96	91

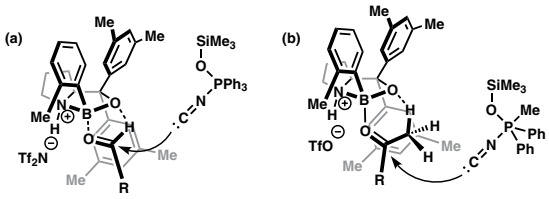


Figure 13. Pre-transition-state Assembly for Enantioselective Cyanosilylation of (a) Aldehydes and (b) Ketones. *(Ref. 21)*

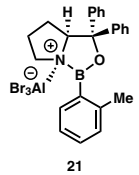


Figure 14. Oxazaborolidine–$AlBr_3$ Complex **21**. *(Ref. 22)*

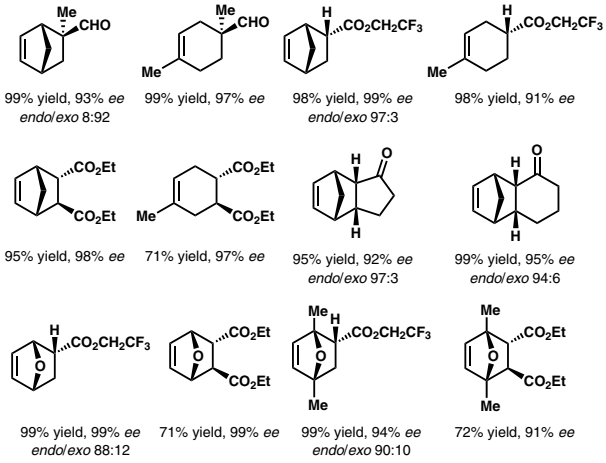


Figure 15. A Selection of Products Obtained by Enantioselective Diels-Alder Reactions in the Presence of $AlBr_3$-Activated Oxazaborolidine **21**. *(Ref. 22)*

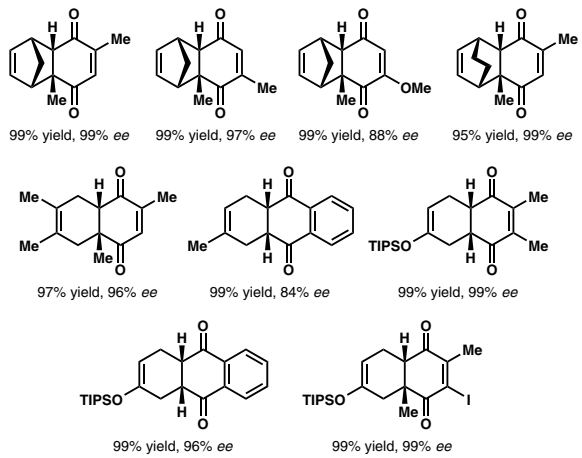


Figure 16. A Selection of Products Obtained via Diels-Alder Reactions of an Assortment of Quinones and Dienophiles Using **21** (4 mol %). *(Ref. 22)*

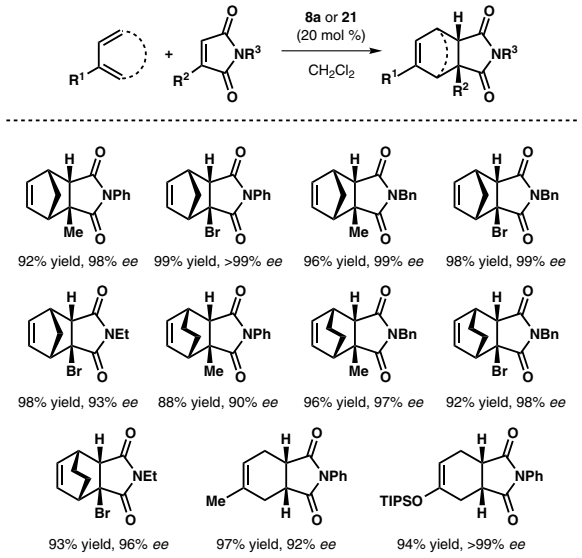
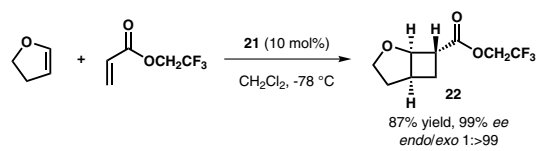


Figure 17. Diels-Alder Reaction of Maleimides as Dienophile: the Reaction and Substrate Scope. *(Ref. 28)*



Scheme 6. Asymmetric [2+2]-Cycloaddition Using Catalyst **21** for the Formation of Bicyclic Ester **22**. *(Ref. 29)*

Similar enantioselective [2+2]-cycloaddition reactions occur between trifluoroethyl acrylate and silyl enol ether derivatives of ketones as summarized in **Table 8**.[29]

It is noteworthy that the $AlBr_3$-activated catalyst **21** was found to be quite superior for [2+2]-cycloaddition reactions to the triflimide-activated catalyst **8a**. Also of interest is the fact that the predominating geometry, specifically *endo* vs *exo* $CO_2CH_2CF_3$ substitution, varies with the vinyl ether substrate.[29] It has been proposed that these reactions occur by non-concerted, two-step processes starting from complex **23** and proceeding via the pre-transition-state assembly **24** (**Scheme 7**), which explain the divergent stereoselectivities shown in Table 8.

4. Lewis-Acidic *N*-Methyl-oxazaborolidinium Cation

Another type of chiral Lewis acid with the oxazaborolidine core is the *N*-methylated oxazaborolidinium cation **25** (**Scheme 8**).[30] The cationic species **25** is an efficient chiral Lewis acid catalyst as shown by various Diels-Alder adducts summarized in Scheme 8.

A comparison of catalyst **25** with $AlBr_3$-activated oxazaborolidine **21** in the Diels-Alder reaction is outlined in **Table 9**.[30] Although higher levels of the *N*-methyl catalyst **25** are required in order to attain a convenient rate of reaction as compared to the $AlBr_3$-activated catalyst **21** (10 mol % vs 4 mol %), catalyst **25** afforded the adducts in similar or higher yield in most cases. Catalysts **5**, **8**, **21**, and **25** produce the same enantiomeric products from a wide range of substrates and appear to function by the same basic mechanism discussed above.

5. Application of Oxazaborolidinium Cations in Enantioselective Synthesis

Cationic chiral oxazaborolidines have been shown to be extremely useful and versatile catalysts for the synthesis of many biologically interesting complex molecules.[17,31-35] This utility has been demonstrated by applications some of which will be outlined in

Table 8. Enantioselective [2+2]-Cycloaddition Reactions of Trifluoroethyl Acrylate to Silyl Enol Ethers with 10 mol % Catalyst **21** in CH_2Cl_2 at –78 °C. *(Ref. 29)*

Enol ether	Product	Time (h)	Yield (%) (*endo*:*exo*)	*ee* (%)
OTBS	TBSO, H, $CO_2CH_2CF_3$, H; *endo*	6	97 (82:18)	92
OTIPS	TIPSO, H, $CO_2CH_2CF_3$, H; *endo*	12	99 (97:3)	92
OTIPS	TIPSO, H, $CO_2CH_2CF_3$, H; *endo*	6	99 (99:1)	99
OTBS, Me	TBSO, H, $CO_2CH_2CF_3$, Me; *exo*	0.5	99 (1:99)	98
OTBS, Me	TBSO, H, $CO_2CH_2CF_3$, Me; *exo*	16	99 (10:90)	98
OTBS, Me	TBSO, H, $CO_2CH_2CF_3$, Me; *endo*	4	91 (96:4)	98

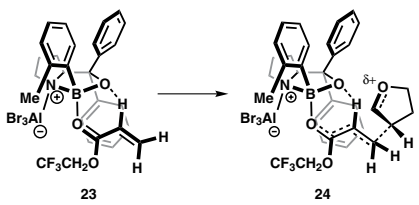
this section. The new catalysts enhance the power of synthesis not only because they enable enantioselective syntheses which have not previously been possible, but also because the mechanistic model is powerfully predictive and allows the selection of the appropriate enantiomer of the oxazaborolidine for a synthesis a priori.

5.1. Enantioselective Synthesis of Complex Targets

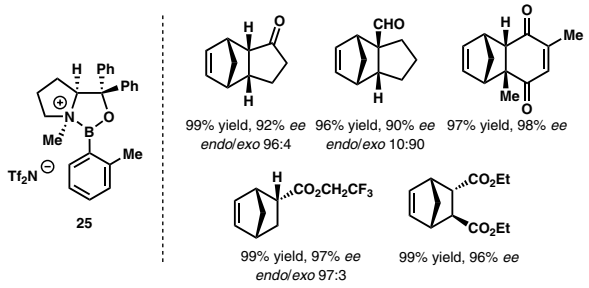
The application of the oxazaborolidinium-catalyzed asymmetric [3+2]-cycloaddition reaction in a short enantioselective synthesis of microbial toxin aflatoxin B_2 (**10**, Scheme 2)[17] was outlined above. Many other natural and non-natural complex molecules were synthesized using oxazaborolidinium-catalyzed Diels-Alder cycloaddition reactions. These include estrone,[30-31] desogestrel,[31] laurenditerpenol,[36] oseltamivir[35] and dolabellane-type marine natural products[33] as shown in **Figure 18**. Among these, particularly noteworthy is the enantioselective synthesis of oral antiflu drug oseltamivir (Tamiflu®, **29**), for which a short, scalable and simple route was developed starting with the Diels-Alder adduct prepared from 1,3-butadiene and trifluoroethyl acrylate.[35]

5.2. Conversion of Racemic Synthetic Routes into Enantioselective Pathway

The transformative role of chiral oxazaborolidinium cations can be gauged by the recent demonstration that several of the classic achievements of synthesis of racemic natural products from the period 1950 to 2000 can be elevated to the most modern enantioselective standards through their use.[32] These include Sarett's total synthesis of cortisone (**32**),[37] Kende's total synthesis of the alkaloid dendrobine (**33**),[38] Eschenmoser's photochemical route to vitamin B_{12},[39] Chu-Moyer/Danishefsky's synthesis of myrocin C (**38**),[40] Mehta's general approach to triquinanes[41] and several others. **Figure 19** illustrates some of these natural products.

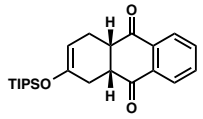
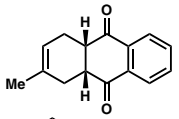
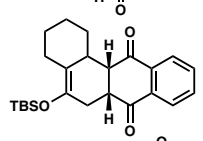
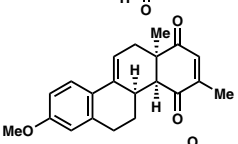
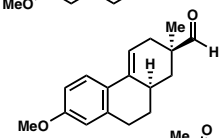
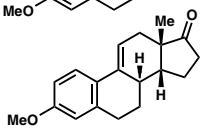


Scheme 7. Plausible Reaction Pathway for the [2+2]-Cycloaddition. *(Ref. 29)*



Scheme 8. *N*-Methyl-oxazaborolidinium Triflimide **25** and Some Diels-Alder Adducts Obtained by Using **25.** *(Ref. 30)*

Table 9. Comparative Studies of [4+2]-Cycloaddition Reactions Catalyzed by **21** and **25.** *(Ref. 30)*

Product	Cat	Temp (°C), Time (h)	Yield (%), *ee* (%)
	**21**	-78, 16	99, 96
	25	-78, 4	95, 96
	**21**	-78, 16	99, 84
	25	-78, 16	97, 84
	**21**	-78, 2	90, 12
	25	-78, 4	83, 96
	**21**	-78, 2	87, 84
	25	-78, 2.5	87, 98
	**21**	-78, 0.5	95, 98
	25	-78, 2.5	90, 98
	**21**	-20, 48	50, 75
	25	23, 24	98, 82

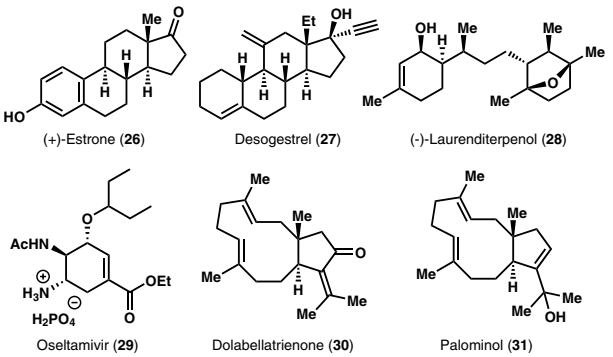


Figure 18. A selection of Complex Molecules Synthesized Using Enantioselective Diels-Alder Reactions. *(Ref. 31,33,35,36)*

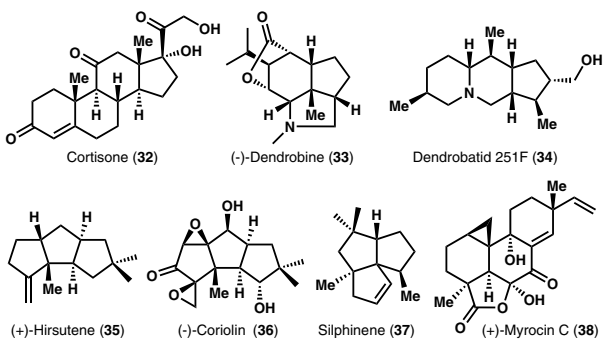


Figure 19. Examples of Natural Products Synthesized Enantioselectively Following their Classic Racemic Routes. *(Ref. 32)*

5.3. Other Applications

Besides the synthesis of natural and non-natural targets, protonated and $AlBr_3$-activated oxazaborolidine catalyzed Diels-Alder reactions have also been used for the stereoselective synthesis of woody fragrances like georgyone, arborone and their structural relatives.[34,42] In addition, very recently our lab has reported the enantioselective synthesis of chiral-bridged dienes, which, by coordination to Rh(I), can serve as excellent catalysts for the enantioselective conjugate addition of vinyl and aryl groups to α,β-unsaturated ketones.[43]

6. Conclusions

Chiral oxazaborolidines derived from 1,1-diphenylpyrrolidinomethanol can be activated by protonation (at N) using very strong proton acids [e.g., CF_3SO_3H or $(CF_3SO_2)_2NH$] or coordination with $AlBr_3$ (at N) to form very strong chiral Lewis acids. The efficiency of such Lewis acids as chiral catalysts for promoting different cycloadditions, Michael addition, cyanosilylation of carbonyl compounds is reviewed here. The application of these enantioselective reactions, especially the Diels-Alder reaction, for the synthesis of numerous complex natural products and non-natural compounds shows their utility. These reactions were developed only during the last decade and have not yet become standard tools of synthesis. However, the applicability of this class of chiral Lewis acids keeps increasing as evident from a number of reports by our group[43-46] as well as by other groups[47-52] which clearly indicate the potential for further development.

7. Acknowledgements

We are grateful to all the current and previous members of our research group for their scientific excellence, creativity and experimental skill which transformed the concepts of activated oxazaborolidines to reality.

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Trademarks: TAMIFLU (Hoffmann-La Roche, Inc.).

Keywords: asymmetric catalysis; oxazaborolidine; chiral Lewis acid; Diels-Alder reaction; natural product.

About the Authors

Santanu Mukherjee, born in 1980 in Hooghly, India, obtained his B.Sc. (Chemistry Honors) from Ramakrishna Mission Residential College, Narendrapur (2000) and M.Sc. (Chemistry) from the Indian Institute of Technology, Kanpur (2002). He then moved to Germany to join the research group of Professor Albrecht Berkessel at Universität zu Köln, where he completed his Ph.D. (*summa cum laude*) in February 2006. He worked as a postdoctoral fellow (2006-2008) in the group of Professor Benjamin List at Max-Planck Institut für Kohlenforschung in Mülheim an der Ruhr before joining Professor Corey's research group at Harvard University.

In 2010, Santanu returned to India and joined the Department of Organic Chemistry at the Indian Institute of Science, Bangalore as an Assistant Professor. His research interests revolve around developing new methods for asymmetric catalysis.

Elias J. Corey, born in 1928 in Methuen, 30 miles north of Boston, studied chemistry from 1945 to 1950 at the Massachusetts Institute of Technology, where he gained his doctorate for work on synthetic penicillins under the supervision of John C. Sheehan. In January 1951, he joined the University of Illinois at Urbana-Champaign as an Instructor in Chemistry and was promoted in 1956 to full Professor. Since 1959 he has been at Harvard University. He recently published with Barbara Czakó and László Kürti the interdisciplinary textbook *Molecules and Medicine*, voted by the American Association of Publishers as the best book in the Sciences for 2007.

ALDRICH Chemistry

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MIDA Boronate Building Blocks:
Towards a General Platform for Small-Molecule Synthesis

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Martin D. Burke, Ph.D.
Assistant Professor of Chemistry
University of Illinois
at Urbana-Champaign, U.S.A.

Moderator

Mitch Jacoby, Ph.D.
Senior Editor
Chemical & Engineering News

This Aldrich Chemistry Webinar discusses the many physical and chemical properties of MIDA boronates that underlie their widespread utility, including:

- Ease of preparation, purification, and storage and minimized environmental impact
- Reversibly attenuated boronic acid reactivity that enables small-molecule synthesis via iterative cross-coupling
- Capacity for slow-release cross-coupling that transforms even notoriously unstable 2-heterocyclic, vinyl, and cyclopropyl subunits into air-stable and highly effective cross-coupling partners
- Compatibility with a wide range of common reaction conditions, which enables the multistep synthesis of structurally complex boronic acids from simple B-containing starting materials

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ALDRICH Chemistry

Heterocyclic MIDA Boronates from Aldrich

Aldrich has prepared a series of 2-, 3-, and 4-heterocyclic MIDA boronates, including the notoriously unstable 2-pyridyl boron anion equivalent 2-pyridinylboronic acid MIDA ester (**719390**).

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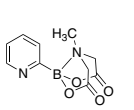
Figure 1. 2-Pyridinylboronic acid MIDA boronate, stable 2-pyridyl boron anion equivalent.

Benefits of MIDA Boronates:

- Bench- and air-stable
- Stable to anhydrous cross-couplings conditions
- Good solubility properties
- Monomeric composition
- Silica gel compatible
- Controlled release for in situ cross-coupling
- Straightforward surrogate to unstable boronates
- Simple, IP-included model

Aldrich has prepared a growing series of heterocyclic MIDA boronates, many of which are shown below.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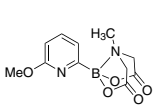
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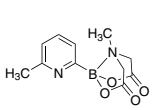
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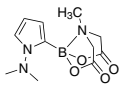
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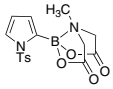
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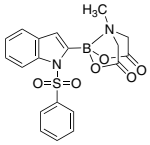
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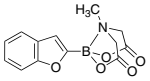
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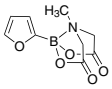
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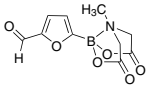
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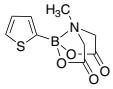
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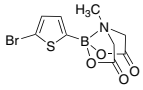
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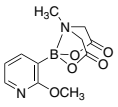
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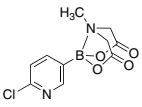
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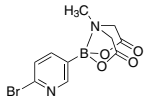
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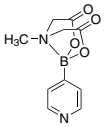
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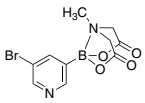
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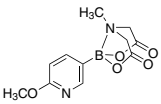
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DEDICATED TO DR. JAI P. NAGARKATTI

Aldrichimica ACTA

VOL. 43, NO. 3 • 2010

ALDRICH Chemistry

Remembering Dr. Jai P. Nagarkatti (1947–2010)

Recent Advances in the Application of α-Phenylethylamine (α-PEA) in the Preparation of Enantiopure Compounds

2-Iodoxybenzenesulfonic Acid (IBS) Catalyzed Oxidation of Alcohols

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Aldrich Congratulates the 2010 Winners of the Nobel Prize in Chemistry

Professors **Ei-ichi Negishi**, **Akira Suzuki**, and **Richard F. Heck** have been awarded the 2010 Nobel Prize in Chemistry by The Royal Swedish Academy of Sciences for their trailblazing contributions to the area of "palladium-catalyzed cross couplings in organic synthesis".

Photo courtesy of Purdue U./ Andrew Hancock

Distinguished Professor
Ei-ichi Negishi
Purdue University, U.S.A.

Photo courtesy of Hokkaido U.

Distinguished Professor Emeritus
Akira Suzuki
Hokkaido University, Japan

Photo courtesy of U. of Delaware

Professor Emeritus
Richard F. Heck
University of Delaware, U.S.A.

Aldrich congratulates these distinguished chemistry pioneers on this achievement and thanks them for their lasting contributions to organic synthesis. Our company is proud to have had close collaborations with Professors Negishi and Suzuki, two former associates of another Nobel laureate and longtime Aldrich collaborator and member of the Board of Directors, the late Professor H. C. Brown.

The *Aldrichimica Acta* has had the distinct privilege of publishing high-impact review articles by a number of chemistry Nobel laureates, such as Professors Derek H. R. Barton, Herbert C. Brown, Elias James Corey, Ei-ichi Negishi, George A. Olah, Charles J. Pedersen, Vladimir Prelog, and K. Barry Sharpless.

The tradition of supporting future scientific leaders is strong at Sigma-Aldrich. Throughout our history, we have acknowledged scientific excellence through sponsorship of awards, symposia, and graduate-level research in the fields of chemistry, life science, and materials science. A number of previous winners of Sigma-Aldrich sponsored American Chemical Society awards (e.g., Professors George A. Olah, K. Barry Sharpless, and Ei-ichi Negishi) have gone on to receive the ultimate recognition, the Nobel Prize in Chemistry.

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"PLEASE BOTHER US."

Joe Porwoll

Joe Porwoll, President
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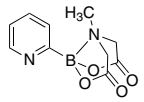
A number of customers have suggested that we produce 2-pyridinylboronic acid MIDA ester. This isolable, chromatographically and benchtop-stable reagent serves as a viable 2-pyridylboron anion equivalent, and is used as a versatile cross-coupling partner.

(1) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961.



719390

719390 2-Pyridinylboronic acid MIDA ester 1 g
5 g

Naturally, we made this useful boronic acid surrogate. 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 back cover.

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ABOUT OUR COVER

Photograph © Rosie Sandifer.

Taos Pueblo Snow (oil on canvas, 40.6 × 70.0 cm) was painted in 2009 by the American painter and sculptor Rosie Sandifer (b. 1946) following a visit to the Pueblo. It depicts the centuries-old, Native American village with the same name. Taos Pueblo is located about two miles north of the town of Taos, New Mexico, and is one of the longest continually inhabited places in the U.S.A. It has been designated a World Heritage Site by UNESCO and a National Historic Landmark by the U.S. Government.

Equally gifted at painting and sculpting, Sandifer paints her impressions of what she observes in nature by simplifying to the essentials the effects of fleeting light on the subject, as evidenced by the white, brown, and turquoise that dominate in this painting. While her subject matter has included landscapes, figures, and animals, she has tended to focus on Western landscapes. She has participated in numerous solo, group, and juried exhibitions, and her paintings and sculptures are on display in a number of museums and public places in the U.S. Currently a resident of Santa Fe, NM, Sandifer received her extensive art education and training most notably at the Froman Painting School in Cloudcroft, NM, and the Art Students League in Stowe, VT, where she was influenced by Frank Mason, a classical realist painter and one of the most acclaimed modern American painters and teachers.

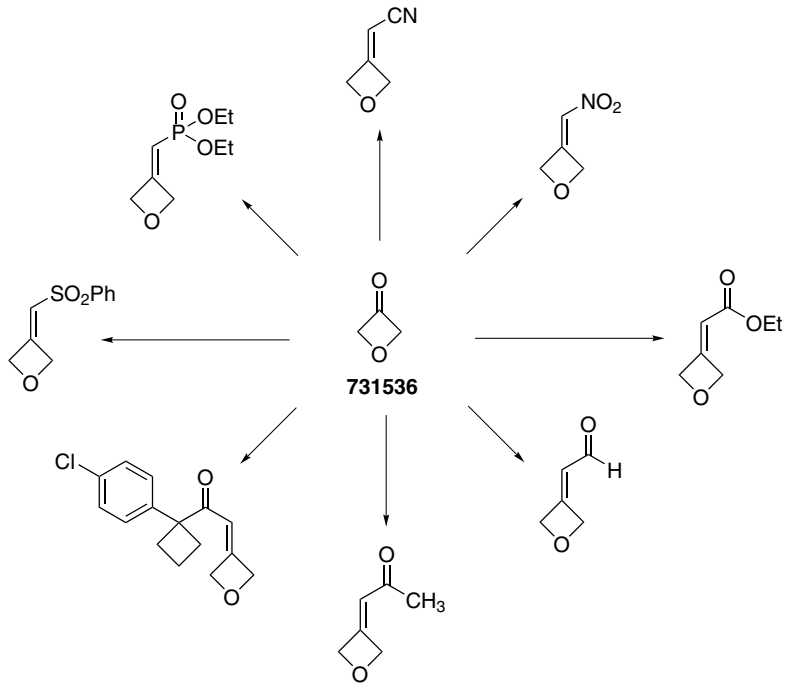
This painting is provided courtesy of the artist and is in her private collection.

New Oxetane Building Blocks

Oxetanes have historically been of modest interest to synthetic and medicinal chemists, perhaps with the natural product paclitaxel or TAXOL® being the best known example of an oxetane-containing substance. Presently, oxetanes are receiving greater attention as attractive modules for drug discovery, largely due to a series of reports from Rogers-Evans, Carreira, and coworkers. These reports have demonstrated the improved physico- and biochemical properties of a molecular scaffold when an oxetane unit replaces a *gem*-dimethyl unit[1] and the ability for an oxetane ring to function as a surrogate for a carbonyl group.[2,1b] Another recent report has disclosed the use of 1,6-substituted azaspiro[3.3]heptanes containing an oxetane ring as alternatives to unstable 1,3-heteroatom-substituted cyclohexanes.[3] In most cases, 3-oxetanone, **731536**, was the principal building block employed by the authors to install the oxetane unit (**Scheme 1**).

References: (1) (a) Wuitschik, G. et al. *Angew. Chem., Int. Ed.* **2006**, *45*, 7736. (b) Wuitschik, G. et al. *J. Med. Chem.* **2010**, *53*, 3227. (2) Wuitschik, G. et al. *Angew. Chem., Int. Ed.* **2008**, *47*, 4512. (3) Burkhard, J. A. et al. *Org. Lett.* **2010**, *12*, 1944.

For a complete list of available oxetanes, please visit *aldrich.com/oxetane*



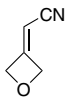
Scheme 1. Oxetane Derivatives Synthesized from 3-Oxetanone.

We are pleased to offer a wide selection of new oxetane building blocks for a variety of applications in synthetic and medicinal chemistry.


731536


733296


731560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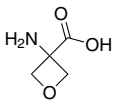
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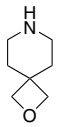
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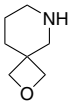
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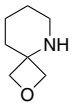
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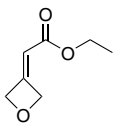
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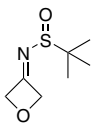
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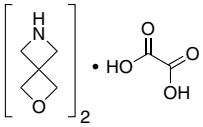
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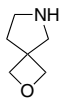
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Remembering Dr. Jai P. Nagarkatti (1947–2010)

Dr. Sharbil J. Firsan[1]
Editor, Aldrichimica Acta
Sigma-Aldrich Corp.

The *Aldrichimica Acta* has lost a dear friend, a lifelong staunch supporter, and a strong believer in its value and mission, both to the company and to the chemistry community. Dr. Jai P. Nagarkatti—the company's Chairman, CEO, and President—died suddenly on Saturday, November 13, 2010.[2–4] While his Sigma-Aldrich "family" has been devastated by his unexpected departure and mourn his loss, this editorial will not be about the facts and figures of Jai's career and accomplishments, nor about Sigma-Aldrich's growth under his tenure. Suffice it to say that he gave over 34 years of dedicated service to Aldrich and Sigma-Aldrich, the only employer he ever worked for after receiving his Ph.D. degree from Texas A&M University, Commerce, TX. Not that facts and figures are not important, but the intention here is to offer fond recollections that shed some light on the kind of man Jai really was.

It was during my first interview with the company that I met Jai. He was the president of Aldrich at the time, and came across as energetic, eager, engaged, and passionate about Aldrich and the business and science of chemistry. He was keen to find out from me what new ideas I was bringing in and what I, as a customer, thought of Aldrich. He took notes during our meeting. During the interview, I could tell he was very proud of working for Aldrich.

After joining the company, I became well acquainted with Jai, who consistently showed strong interest in the *Acta*: He eagerly anticipated each issue, kept copies in his office, and took a strong interest in what was published and what was advertised in it. He recommended authors, emailed thank-you letters to them, and never missed a chance to offer this editor sincere words of appreciation and encouragement. In fact, one little story sums him up in this regard: I sometimes would be crossing St. Paul Avenue in Milwaukee going from one Aldrich building to another, while Jai would be crossing the same street in the opposite direction. He, invariably, would stop me in the middle of the street to ask me about the *Acta*—totally oblivious to fast-moving traffic and the fact that both of us could be run over by an inattentive driver.

I wholeheartedly concur with one of Jai's longtime associates who related to me that he was always amazed at how eminently reachable Jai was, even after becoming the Chairman, President, and CEO of Sigma-Aldrich, a $2+ billion company, considering how incredibly busy and in demand he was. While he had administrative assistants, Jai never walled himself off; one could walk into his office anytime. He also did not hesitate to answer a phone call or an email himself, or walk into any area of the company and chat with anyone. When he wanted to talk to a subordinate, he preferred to walk over to his/her cube or office, rather than call him/her to come to his office. He did not hesitate, as this editor can attest to, to pick up the phone and call someone in the company to thank them for their efforts and offer words of encouragement. He was incredibly humble and had a knack for conversing with equal ease with a custodian at Sigma-Aldrich, a Wall Street analyst, or a highly regarded university professor. He made sure to attend and serve at as many of the company functions for employees as he could. He almost was a fixture at our Company's annual picnic and other events. That was his way of staying connected to the employees. As Dr. Alfred Bader put it, "[Jai] was inspirational for employees who appreciated his dedication and warmth. Jai was so very human...."

Jai P. Nagarkatti in 2007 at Sigma-Aldrich's Headquarters in St. Louis, MO.

By keeping a full schedule and working hard to the point of being a workaholic, Jai led by example and brought an excitement, and a depth of perception, to projects and tasks that went beyond the customary business reasons and logic: If you met with him to discuss a project, you learned not only about the project, but also about the deeper significance of the project to the company, to customers, and even to society. This, of course, meant that you also left his office with a lot more work to do than when you walked in.

Being focused on his work and responsibilities did not mean that he lacked a sense of humor. In fact, it wasn't unusual to overhear him being lighthearted. One noteworthy moment that I remember occurred at an Aldrich employee award dinner in Milwaukee, when he was introducing a longtime, distinguished associate, who was well-known for being outspoken. Jai said that, "when [name omitted] reported to me, I was never sure who reported to whom." Being as humble as he was, Jai was not afraid of making fun of his weaknesses, as when he picked up a set of golf clubs at a company outing and played a round of golf, never having swung a golf club before! Jai just wanted employees to see that he wasn't good at everything.

Farewell my friend, Jai. Your enthusiasm, dedication, thoughtfulness, humility, and kindness will be forever missed.

Notes

(1) I thank John Radke, Joe Porwoll, and Ali Ataei for sharing their recollections of Jai. Some of these recollections have been weaved into this article. I am also grateful to Ms. Melissa Jacobs of Sigma-Aldrich for reviewing this article and offering helpful suggestions.

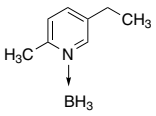
(2) A summary of Jai's career at Sigma-Aldrich is part of a press release issued by the company on November 14, 2010, announcing Jai's sudden death and the appointment of a successor. It can be accessed at *http://investor.sigmaaldrich.com/releasedetail.cfm?ReleaseID=530331*.

(3) The obituary released by Jai's family was published in the St. Louis Post-Dispatch of Monday, November 15, 2010, which can be accessed at *http://www.legacy.com/obituaries/stltoday/obituary.aspx?n=jai-nagarkatti&pid=146642609*.

(4) The St. Louis Post-Dispatch ran a story on Jai by Jim Doyle on Tuesday, November 16, 2010, which can be accessed at http://*www.stltoday.com/business/article_46d399bc-61e2-521a-9ff8-b7048bf6ab3b.html*.

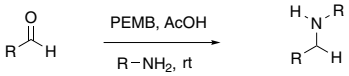
New Reductive Amination Reagent

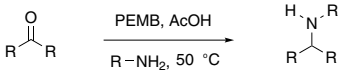
PEMB: A Stable, Liquid Pyridine Borane Complex



5-Ethyl-2-methylpyridine borane (PEMB)
725080

Select Substrate Scope

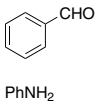
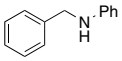
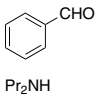
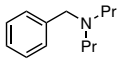
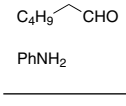
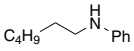
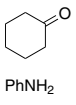
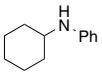
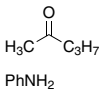
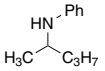




Advantageous Properties of PEMB:

- Excellent for reductive aminations
- Mild reducing agent for imines and oximes
- Reaction with protic solvents is very slow
- Soluble in aromatic hydrocarbons, alcohols, and ether solvents
- Can be used solvent-free for reductive aminations
- Chemically efficient: two of three hydrides are utilized

Examples

Aldehyde and Amine	Conditions	Product	% Yield in MeOH (% Yield Neat)
	PEMB, AcOH, MeOH, 25 °C		72 (80)
	PEMB, AcOH, MeOH, 25 °C		0 (96)
	PEMB, MeOH, 25 °C		92 (94)
	PEMB, AcOH, MeOH, 25 °C		92 (93)
	PEMB, AcOH, MeOH, 50 °C		74 (94)

For more examples and experimental details, please see: Burkhardt, E. R.; Coleridge, B. M. *Tetrahedron Lett.* **2008**, *49*, 5152.

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For research quantities under 500 grams, please contact Aldrich Chemistry.
For quantities over 500 grams, please contact BASF.

Recent Advances in the Application of α-Phenylethylamine (α-PEA) in the Preparation of Enantiopure Compounds

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Outline

1. Introduction

Mostly as a consequence of the increased interest in the production of enantiomerically pure compounds by the pharmaceutical and agrochemical industries, the chemistry community has intensified its efforts to develop more efficient ways to obtain chiral products with the desired configuration. In this regard, α-phenylethylamine (α-PEA, 1-phenylethylamine, 1-phenylethanamine, α-methylbenzenemethanamine, α-methylbenzylamine, α-aminoethylbenzene, $CH_3CH(Ph)NH_2$) has emerged as an important chiral reagent principally because of its low price, accessibility in both enantiomeric forms, and facile introduction and removal in most asymmetric syntheses. Two reviews appeared in the late 1990s on the use of α-PEA in the preparation of enantioenriched compounds.[1] However, a significant number of new developments have been reported in the last decade, which warrants an update on the more significant advances in the area that were reported between 2000 and early 2010. This review focuses on the applications of α-PEA as a chiral ligand for asymmetric catalysis, as a chiral auxiliary in the resolution of racemates, and as a chiral reagent in the stereodifferentiation of prochiral substrates, as well as on its incorporation into novel organocatalysts.

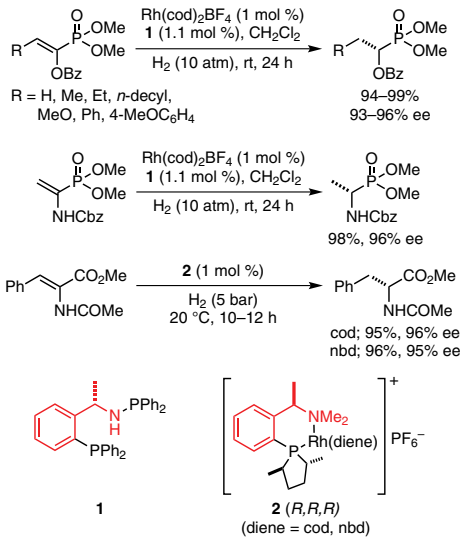
2. Incorporation of α-Phenylethylamine (α-PEA) in Chiral Ligands for Asymmetric Catalysis

A central development in asymmetric catalysis has been the design and preparation of enantiopure catalysts containing an active metal and a regulating chiral organic ligand and their application in the synthesis of enantioenriched building blocks from prochiral substrates. Following the great success of complexes of chiral phosphine ligands and transition metals in asymmetric synthesis,[2] intense research activity has been directed towards the development of comparable ligands containing nonracemic amines. In particular, catalysts incorporating ligands with the α-PEA moiety have been quite effective in several asymmetric transformations.

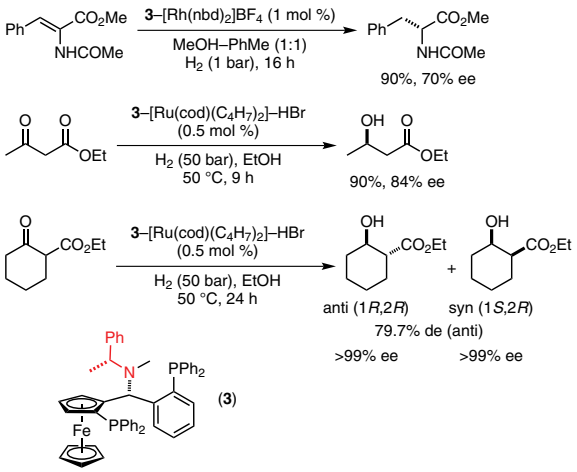
2.1. Enantioselective Reduction of Prochiral Unsaturated Double Bonds

Hu, Zheng, and co-workers[3] have described the use of chiral phosphine–aminophosphine ligand **1** (easily synthesized from (*S*)-α-PEA, *n*-BuLi, and Ph_2PCl), in combination with $Rh(cod)_2BF_4$, for the enantioselective hydrogenation of the C–C double bond in various α-enol ester phosphonates and α-enamido phosphonates. In particular, ligand **1** was utilized in the successful preparation of biologically important α-hydroxy and α-amino phosphonates in 94–99% yields and 93–97% ee's (**Scheme 1**). In the same way, optically active ligand **2** was developed by Brauer et al.[4] for the enantioselective hydrogenation of methyl acetamidocinnamate to the corresponding amido ester with 95% ee (see Scheme 1).

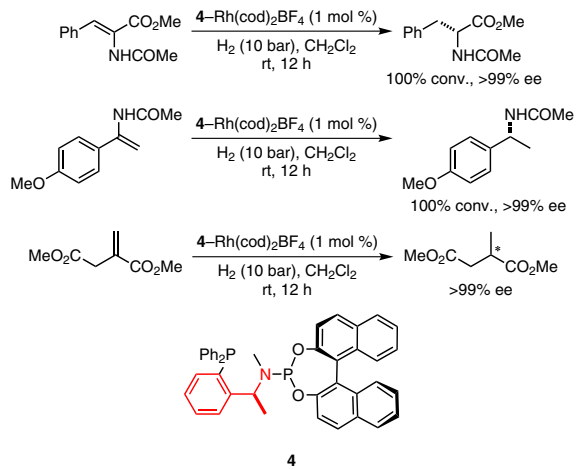
In a related development, Knochel and collaborators reported on the effectiveness of the nonracemic, ferrocene-based ligand **3** in



Scheme 1. Highly Enantioselective Hydrogenations of C–C Double Bonds in the Presence of Chiral Ligands Incorporating α-PEA. *(Ref. 3a,4)*



Scheme 2. Chiral Ferrocene Derivative **3** in the Ru- and Rh-Catalyzed Hydrogenation of C=C and C=O Bonds. *(Ref. 5)*



Scheme 3. Highly Enantioselective Hydrogenations Catalyzed by **4**–Rh(I) Complexes. *(Ref. 6)*

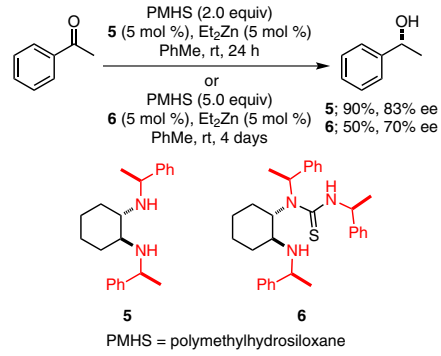
the enantioselective ruthenium- and rhodium-catalyzed hydrogen addition to prochiral substrates containing C=C or C=O bonds (**Scheme 2**).[5]

Similarly, Huang et al. prepared an interesting phosphine–phosphoramidite ligand, **4**, starting from (*S*)-α-PEA. Together with Rh(I), **4** efficiently catalyzes the reduction of α-dehydroamino esters, enamines, and dimethyl itaconate to afford the reduced products in ≥99% ee's. These results show that the central chirality of the α-phenylethylamine moiety in **4** dictates the absolute configuration of the hydrogenation product, regardless of the axial chirality of the binaphthyl moiety (**Scheme 3**).[6]

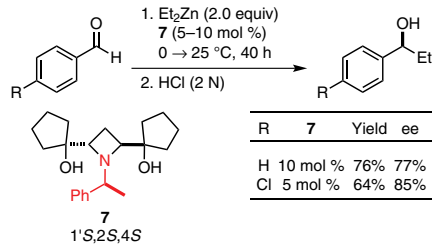
The asymmetric transfer hydrogenation of prochiral ketones can be carried out successfully by employing α-PEA derivatives. For example, the enantioselective hydrosilylation and reduction of prochiral ketones to alcohols has been effected by using polymethylhydrosiloxane (PMHS) as the hydride source and a set of *all-S*, α-PEA-containing, chiral diamines, **5**, and thioureas, **6**. This procedure afforded the respective secondary *R* alcohol (**eq 1**).[7] Along similar lines, Adolfsson and co-workers showed that the use of α-amino-acid-containing chiral thioamide ligands, *i*-PrOH as a hydride source, and Ru(II)- or Rh(III)-based catalyst complexes, led to several secondary alcohols derived from acetophenones in high yields and good enantioselectivities.[8]

2.2. Enantioselective Addition of Diethylzinc to Aromatic Aldehydes

Asymmetric organozinc addition to prochiral aldehydes and ketones allows the synthesis of chiral alcohols, which are ubiquitous features in the structures of natural products and pharmaceuticals. The reaction between diethylzinc (Et_2Zn) and benzaldehyde has become a benchmark reaction for testing newly designed ligands for catalytic enantioselective synthesis.[9] In this context, Wilken et al. have reported the use of several nonracemic tridentate azetidines in the enantiocontrolled catalytic addition of diethylzinc to several aromatic aldehydes, and demonstrated that the *all-S* chiral ligand, **7**, efficiently catalyzes this reaction in good yields and ee's (**eq 2**).[10] In a related development, Guofu Zi and collaborators prepared



eq 1 *(Ref. 7)*



eq 2 *(Ref. 10)*

various chiral azetidines by reaction of (*R*)- or (*S*)-α-PEA, benzaldehyde, and acetoxyacetyl chloride. These researchers observed that the resulting *R*,*R*,*R* azetidine ligand led to the *S* alcohols, while the *R*,*S*,*S* diastereomer gave rise to the *R* alcohols in 73–94% yields and 57–95% ee's.[11]

Moreover, Wang's group[12] has described the application of optically active ligand **8**—prepared by a one-pot condensation of the corresponding aldehyde with 2-naphthol and (*S*)-α-PEA—in the enantioselective addition of diethylzinc to aldehydes. Most interesting are the high ee values obtained at room temperature (>99% ee's for the *R* alcohols). Furthermore, Mikami and collaborators[13] have demonstrated that ligand **9** efficiently catalyzes diethylzinc addition to several aromatic aldehydes in good yields and high ee's (**eq 3**).

Based on the efficient opening of cyclohexene oxide by α-PEA,[14] Mastranzo et al. prepared a series of chiral ligands derived from *trans*-β-aminocyclohexanol. The versatility of this approach resulted in the preparation of a large number of optically active ligands that were successfully tested in the benchmark reaction of Et_2Zn with benzaldehyde (**eq 4**).[15]

2.3. α-PEA Derivatives as Ligands in Miscellaneous Enantioselective Reactions

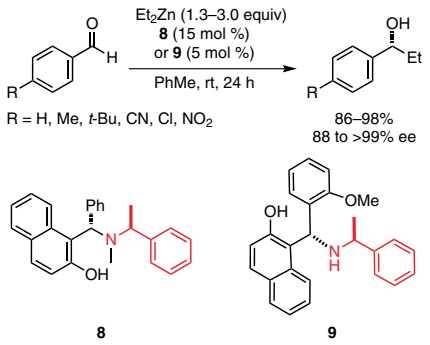
Recently, Isleyen and Dogan described the use of chiral ferrocenyl aziridinylmethanol **14,** which is prepared in three steps from an acryloylferrocene precursor and (*S*)-α-PEA. In particular, these authors showed that **14** can be employed in the catalytic, enantioselective conjugate addition of diethylzinc to enones to give β-ethylated ketones in up to 80% ee's, with the *R* enantiomer being favored in the majority of cases (**eq 5**).[16]

Another case of successful application of α-PEA derivatives as ligands in asymmetric synthesis is the palladium-catalyzed enantioselective allylic alkylation with dimethyl malonate in the presence of chiral ligands **15** and **16**. Ding and co-workers prepared chiral ligand **15** by the asymmetric aminoalkylation of 2-naphthol with (*R*)-α-PEA and benzaldehyde. Ligand **15** efficiently catalyzes the asymmetric substitution of the acetate group in 1,3-diphenylprop-2-en-1-yl substrates in 41–96% yields and with ee's as high as 70% in favor of the *S* product (**Scheme 4**).[17a] A few years later, Huang et al. employed a non-racemic imine, **16**, synthesized from (*S*)-α-PEA, to catalyze a similar reaction, achieving better yields and enantioselectivities (see Scheme 4).[17b] Furthermore, Tsogoeva and collaborators have recently obtained modest enantioselectivities in the allylation of aldimines and the reduction of ketimines with trichlorosilane by utilizing chiral proline–formamide derivatives.[18]

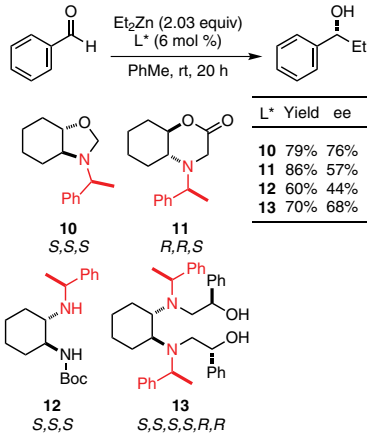
In a very recent elegant work, Alonso et al. examined a set of chiral phosphoramidite–gold(I) complexes, incorporating the bis(α-PEA) moiety, as catalysts in the intramolecular, enantioselective [4 + 2] cycloaddition reaction of allenes and dienes. In one example, Au–phosphoramidite complex **17** catalyzed the enantioselective allene and diene [4 + 2] cycloaddition over the [4 + 3] cycloaddition, giving rise to enantiomeric ratios greater than 95:5 (**eq 6**).[19]

Chiral, cyclic hydroxynaphthylphosphonodiamide **18**—synthesized from (*S*)-α-PEA, 1,2-dibromoethane, and *O*-aryl phosphorodichloridates—has been employed as a chiral ligand in the asymmetric cyanation of aromatic aldehydes catalyzed by Ti(*i*-PrO)$_4$. The corresponding cyanohydrins were obtained in good yields and ee's (**eq 7**).[20]

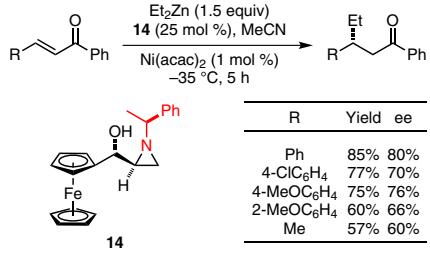
A remarkable application of a chiral ligand containing α-PEA was reported by Mikami's group, who prepared nonracemic ligand **19** from bis((*S*)-α-PEA), PCl_3, and 2,2'-methylenebis(4-



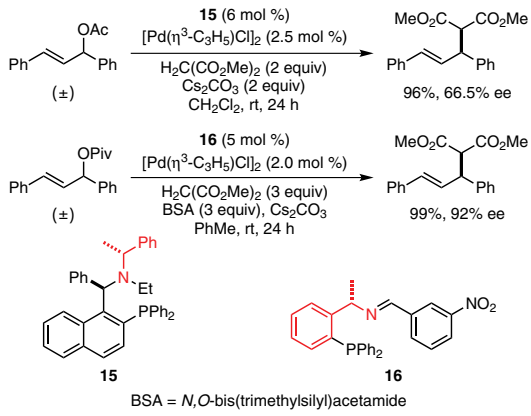
eq 3 *(Ref. 12,13)*



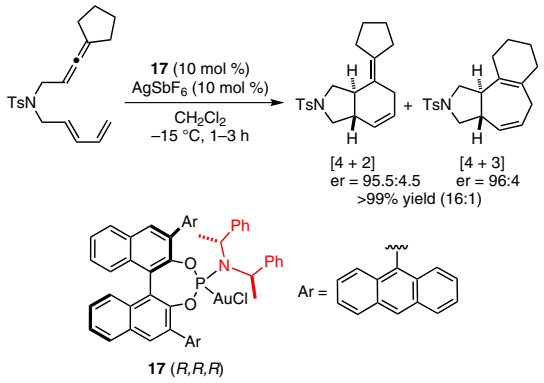
eq 4 *(Ref. 14,15)*



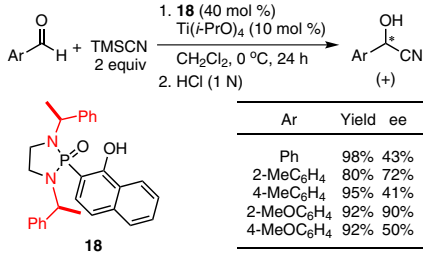
eq 5 *(Ref. 16)*



Scheme 4. Enantioselective Palladium-Catalyzed Allylic Alkylation of Allyl Acetates with Dimethyl Malonate in the Presence of **15** and **16.** *(Ref. 17)*

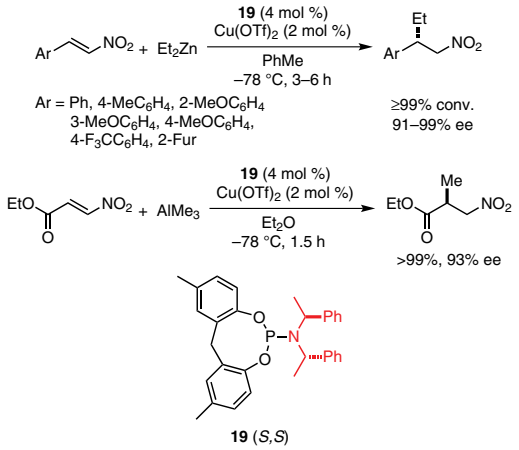


eq 6 *(Ref. 19)*

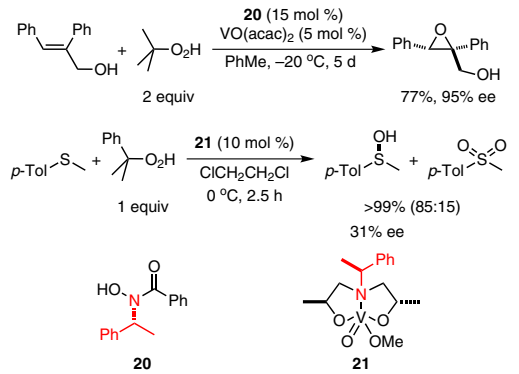


Ar	Yield	ee
Ph	98%	43%
2-MeC$_6$H$_4$	80%	72%
4-MeC$_6$H$_4$	95%	41%
2-MeOC$_6$H$_4$	92%	90%
4-MeOC$_6$H$_4$	92%	50%

eq 7 *(Ref. 20)*



Scheme 5. Asymmetric Cu-Catalyzed Conjugate Additions to Nitroalkenes and Nitroacrylates. *(Ref. 21)*



Scheme 6. Asymmetric Oxidations Catalyzed by Complexes of Vanadium and Chiral Ligands Incorporating α-PEA. *(Ref. 22,23)*

methylphenol) for use in copper-catalyzed conjugate additions of organometallics to nitroalkenes and nitroacrylates. In the case of copper-catalyzed addition of diethylzinc to nitroalkenes, metal complexes containing ligand **19** showed high catalytic activity and very good enantioinduction (>99%, 91–99% ee). Similarly, the conjugate addition of trimethylaluminum to nitroacrylate proceeded in high yield (>99%) and enantioselectivity (93% ee) (**Scheme 5**).[21] The product of this latter reaction was hydrogenated with palladium-on-charcoal to give the corresponding β^2-alanine ethyl ester.[21]

On the other hand, the asymmetric oxidation of prochiral olefins and thioethers, catalyzed by chiral vanadium complexes, has emerged as an important alternative to other standard oxidation procedures. Traber et al.[22] have described the application of a series of chiral hydroxamic acids as ligands for the vanadium-catalyzed asymmetric epoxidation of allylic alcohols. A noteworthy example is the preparation of the *S,S* epoxy alcohol in 77% yield and 95% ee by the asymmetric epoxidation of 2,3-diphenylallyl alcohol catalyzed by a vanadium complex with chiral ligand **20** (**Scheme 6**). In the same context, Rehder and co-workers[23] evaluated the catalytic properties of a series of chiral oxovanadium(V) complexes containing a chiral tridentate amino-bis(alcoholate) in the asymmetric oxidation of prochiral sulfides by organic hydroperoxides. (*S*)-Methyl *p*-tolyl sulfoxide was obtained with modest ee in the presence of catalyst **21** and cumyl hydroperoxide (CHP) as the oxidant (see Scheme 6).

Millward et al.[24] employed an optically active cyclopentadienylamido titanocene complex in the enantioselective ethylalumination of allylbenzene and styrene, which proceeded with modest yields and enantioselectivities. Bianchini and Lee[25] carried out the cyclopropanation of styrene with ethyl diazoacetate catalyzed by a chiral ruthenium 2,6-bis(imino)pyridyl complex in good yield but modest enantioselectivity.

3. α-Phenylethylamine as a Resolving Agent

The resolution of racemates through the formation of ionic or covalent diastereomeric derivatives is widely used in academic research as well as in industry, in particular for the manufacture of pharmaceuticals on an industrial scale.

3.1. Resolution via Diastereomeric Salt Formation

A variety of chiral racemic acids—mandelic,[26] organophosphorus,[27] acetic and benzoic acid derivatives,[28,29] and others[30]—have been resolved by separation of the diastereomeric salts that they form with α-PEA. Ma and co-workers[31] developed an elegant synthesis of enantiopure β-halobutenolides (*R*)- and (*S*)-**24** that relies on the resolution of racemic 2-methyl-4-phenyl-2,3-butadienoic acid with (*R*)- or (*S*)-α-PEA (**Scheme 7**).

Similarly, Kato and collaborators employed (*S*)-*N*-benzyl-α-PEA, ((*S*)-**26**) to form a mixture of diastereomeric salts with the key chiral carboxylic acid precursor to the cardioprotective drug (*S*)-**27** (**Scheme 8**).[32] Fractional crystallization of the diastereomeric salts and further elaboration of the precursor led to enantiopure (*S*)-**27**.

Another successful application of α-PEA as resolving agent in the pharmaceuticals area was disclosed by Trung et al.[33] In this work, fractional crystallization of the diastereomeric salts, prepared from (*R*)-α-PEA and racemic ibuprofen, was a key step in the preparation of (*R*)-ibuprofen, an effective analgesic and anti-inflammatory agent.

3.2. Resolution via Covalent Attachment of α-PEA to Racemic Substrates

Very recently, Aitken's group[34] carried out the preparation of the four possible stereoisomers of 2-aminocyclobutanecarboxylic acid starting with the condensation of the cis racemate with (*R*)-α-PEA to give a mixture of the corresponding diastereoisomeric amides. The amides were separated by column chromatography, (*R*)-α-PEA cleaved, and a controlled epimerization to the more stable trans isomers carried out, leading to the isolation of all four stereoisomers in enantiomerically pure form.

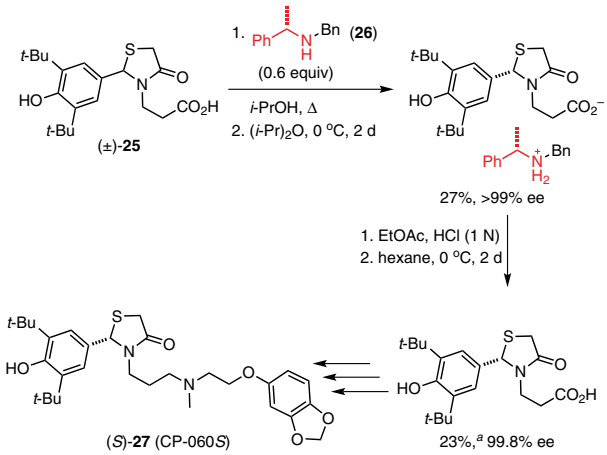
The 1,3-dipolar cycloaddition of a proline-derived, cyclic nitrone with acrylamide, followed by a reductive cleavage–cyclization domino process, afforded the racemic trans hydroxy ester **28**. Reaction of **28** with (*R*)-α-PEA led to two diastereomeric intermediates, which were separated and subjected to reductive cleavage of the α-PEA moiety to give enantiomerically pure, bicyclic pyrrolizidinones **30** (**Scheme 9**).[35] Pyrrolizidinones **30** were subsequently coupled to α-amino acids to give pseudotripeptides that induce β-turn peptidomimetic foldamers.

Recently, Morales-Ríos and co-workers further confirmed the efficiency of α-PEA in the enantioselective synthesis of natural products, by carrying out the preparation of debromoflustramine B (**31**). This approach involved reacting the racemic γ-lactone precursor with (*S*)-α-PEA and chromatographic separation of the resulting diastereomeric *N*-(α-phenylethyl)lactam intermediates, Subsequent hydrolytic cleavage of the α-PEA moiety regenerated the lactone; this was followed by formation of the *N*-methyllactam with $MeNH_2$ in methanol and reduction of the amide carbonyl to afford both enantiomers of **31** (**Scheme 10**).[36]

An efficient resolution of chiral, C_2-symmetric biphenols, e.g., **32**, was described by Delogu et al., who employed the α-PEA-containing reagent (*S*)-**33** to derivatize **32** into diastereomeric phosphorothioamidates **34**. Separation of the phosphorothioamidate intermediates by fractional crystallization and reductive cleavage with $LiAlH_4$ afforded biphenols (*M*)-**32** and (*P*)-**32** (**Scheme 11**).[37] A similar approach was employed by Rozenberg and collaborators in the resolution of 15-hydroxy[2.2]paracyclophane-4-carbaldehyde.[38] In another interesting development, Zakrzewski and co-workers reported the resolution of a racemic diphosphaferrocenecarboxylic acid by chromatographic separation of the corresponding diastereomeric amides formed by reaction of the acid with (*S*)-α-PEA.[39]

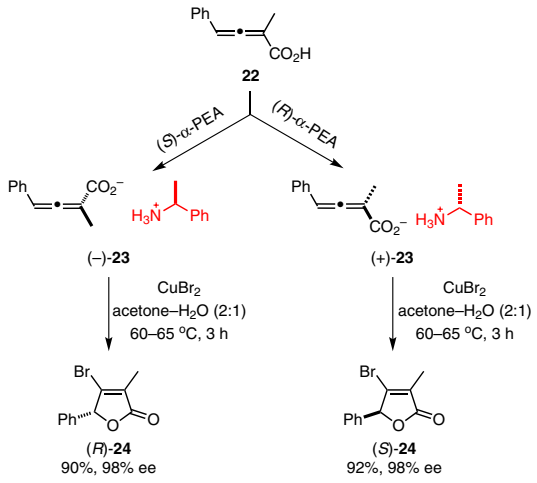
3.3. Chiral Solvating Agents Containing the α-PEA Fragment

One advantage of chiral recognition is that it can be easily evaluated spectroscopically, for example by NMR using chiral discriminating reagents. A variety of chiral solvating agents based on α-PEA are known; they efficiently differentiate the enantiomers of several types of molecules such as chiral Kemp's acid derivatives,[40] iminoboronate derivatives of chiral alcohols,[41] chiral phospholene oxides,[42] chiral unsaturated ethers,[41b,43] and chiral carboxylates.[44] In a relevant example, our group[44a] has demonstrated that simple chiral thiourea (*S*,*S*)-**35** (**Scheme 12**) is an efficient receptor for chiral carboxylates, such as α-amino

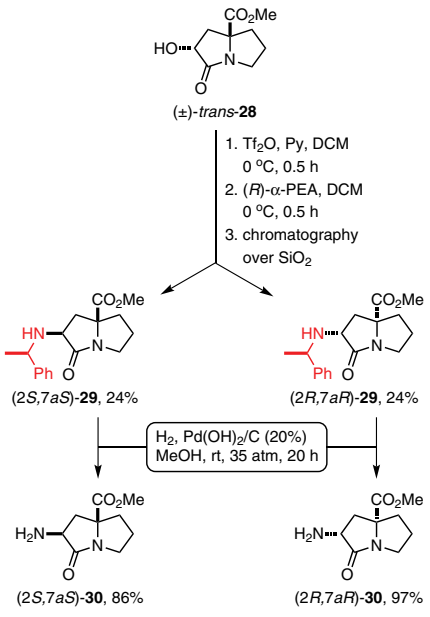


[a] The yield of the desired *S* acid was improved to ~70% after recovering the undesirable *R* isomer, racemizing it, and subjecting it to the resolution steps outlined here.

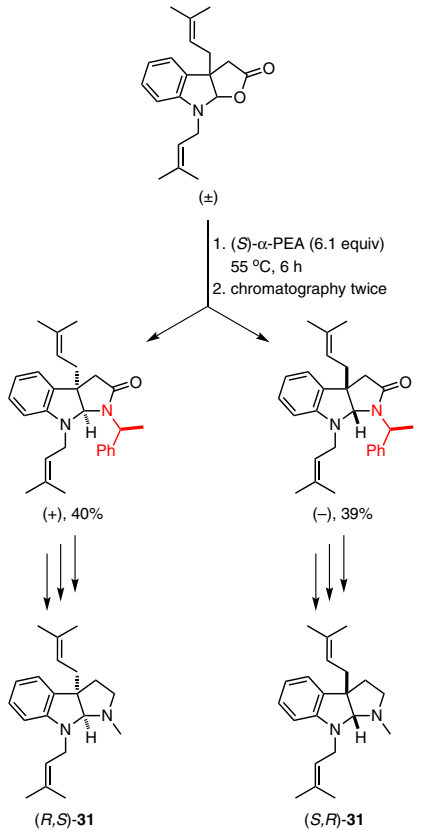
Scheme 8. Key Enantiomeric Separation in the Synthesis of the Cardioprotective Drug (*S*)-**27.** *(Ref. 32)*



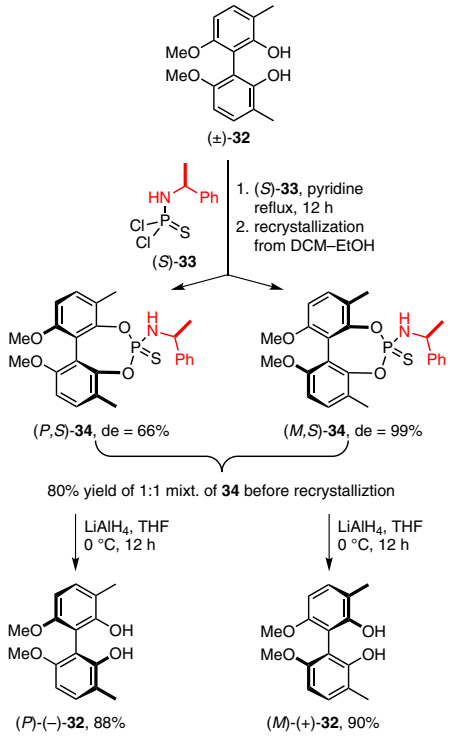
Scheme 7. Resolution of *rac*-2-Methyl-4-phenyl-2,3-butadienoic Acid (*rac*-**22**), and Subsequent Formation of Enantioenriched β-Halobutenolides. *(Ref. 31a)*



Scheme 9. Synthesis of Enantiopure **30** by Covalent Attachment of Enantiopure α-PEA to Racemic Substrates. *(Ref. 35a)*



Scheme 10. Synthesis of Enantiopure Debromoflustramine B, (*R*,*S*)- and (*S*,*R*)-**31**. *(Ref. 36a)*



Scheme 11. Resolution of C_2-Symmetric Biphenols **32**. *(Ref. 37a)*

and α-hydroxy acids. The diastereomeric complexes obtained from such complexation give rise to distinguishable signals in ^{1}H NMR spectra, which can be used for determining the optical purity. Furthermore, thiourea (*S*,*S*)-**35** has proved useful for assigning the absolute configuration of the carboxylic acids; indeed, it was observed that the *R* enantiomer of the carboxylate exhibits a C_α–H chemical shift at higher frequency.

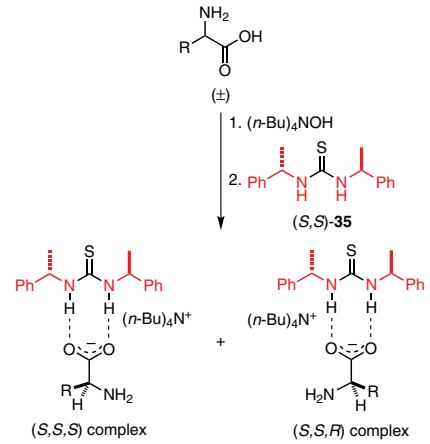
4. α-Phenylethylamine as Chiral Auxiliary

The ready availability of α-PEA and its facile incorporation in, and removal from, organic molecules have contributed to making α-PEA into an excellent auxiliary in asymmetric synthesis. Thus, α-PEA-controlled reactions have become an important tool in the preparation of enantioenriched products.

4.1. Diastereoselective Reactions of Chiral Imines Incorporating the α-Phenylethyl Moiety

The condensation of aldehydes and ketones with α-PEA provides the corresponding chiral imines, in which the difference in size between substituents at the stereogenic center helps to differentiate the diastereotopic faces at the prochiral C=N bond, especially in those cases where one conformation of the chiral auxiliary predominates in the transition state. This working hypothesis has been exploited in several methods, which are described below.

The apparent addition of hydride from the side of the less bulky group in the reduction of α-PEA imines has allowed the synthesis of several types of enantioenriched product such as ferrocenes,[45] amines,[46] glycosyl amino acids,[47] amino esters,[48] and spiro compounds.[49] Indeed, an excellent procedure for the preparation of chiral primary amines from both cyclic and acyclic dialkyl or aryl–alkyl prochiral ketones was described by Nugent and co-workers.[46e] The key step in this reaction consists of the asymmetric reductive amination of the ketone with (*R*)- or (*S*)-α-PEA in the presence of a Lewis acid and a conventional hydrogenation catalyst. The correct combination of hydrogenation catalyst, solvent, and temperature is essential for achieving high reaction yields and high diastereomeric excesses. In one example, the reduction of ethyl or hexyl methyl ketone afforded the corresponding amines in good yields and diastereoselectivities (**Scheme 13**, Part (a)). When Raney® Ni was employed as the hydrogenation catalyst in the reduction of ethyl methyl ketone, the product was formed with a 74% de, whereas the use of rhodium-on-charcoal led to a significantly



Scheme 12. Thiourea (*S*,*S*)-**35** and its Proposed Coordination in the Stereodifferentiation of Chiral α-Amino Carboxylates. *(Ref. 44a)*

lower diastereoselectivity (de = 36%, **Scheme 13**, Part (b)). Finally, the α-phenylethylimine derivative of hexyl methyl ketone was reduced with 72% diastereomeric excess in THF as solvent, and 49% de in DMSO (**Scheme 13**, Part (c)).

A variety of nucleophiles also add stereoselectively to α-PEA-containing imines. When the nucleophile is cyanide, this leads to enantioenriched non-natural amino acids (**Figure 1**).[50] An illustrative procedure for the enantioselective preparation of carbocyclic α-amino acids was described by Frahm's group.[51] Chiral ketimines were obtained by condensation of racemic 2-alkylcyclopentanones and (*S*)-α-PEA as chiral auxiliary. In the key stereodifferentiating step, cyanide addition provided diastereomeric mixtures of nitriles, whose composition is dramatically influenced by the nature of the solvent, the temperature, and the size of the substituents. Hydrolysis of the nitriles with conc. H_2SO_4 yielded diastereomeric mixtures of carboxamides, which were separated, hydrogenolyzed, and hydrolyzed to yield the pure stereoisomers of 1-amino-2-methoxycyclopentanecarboxylic acid.

In a similar fashion, the addition of allylmetal nucleophiles to imines provides a valuable route to homoallylic amines, which can undergo any number of transformations at the C=C bond of the allylic fragment.[52] Gálvez and co-workers[53] reported a good application of this approach in the synthesis of non-natural α-amino acid **37**. Thus, chiral *N*-phenylethylimines were prepared from (*R*)-2,3-di-*O*-benzylglyceraldehyde and (*S*)- or (*R*)-α-PEA and treated with allylmagnesium bromide or allyl-9-borabicyclo[3.3.1]nonane (allyl-9-BBN). Conversion of the resulting homoallylic amine into the corresponding syn or anti *N*-Boc-aminodiol was conveniently performed by hydrogenolysis with $Pd(OH)_2$ on charcoal in the presence of $(Boc)_2O$. Subsequent treatment with an excess of sodium periodate in the presence of ruthenium trichloride followed by acid hydrolysis, gave α-amino acid (*R*)- or (*S*)-**37**, depending on the nature of the starting material (**Scheme 14**).

4.2. Diastereoselective Reactions of Optically Active Enamines

The enantioselective reduction of enamines, is a useful tool for the synthesis of biologically important molecules such as β-amino acids, as demonstrated by Wright and collaborators.[54] These workers prepared diverse cyclic β-amino acids by amination of cyclic β-keto esters with (*R*)-α-PEA in the presence of acetic acid. The enamines were reduced with $NaBH_3CN$ in acetic acid, the resulting mixtures of diastereomers purified by chromatography, separated by recrystallization, and the chiral auxiliary cleaved by hydrogenation over Pd/C. Final saponification of the methyl ester and Fmoc protection of the amino group provided cyclic β-amino acids, e.g. (*S*,*S*)-**38**, that are suitable for peptide synthesis (**Scheme 15**).[54] Other remarkable examples that follow this strategy were reported by Lhommet's group[55] and by Jona

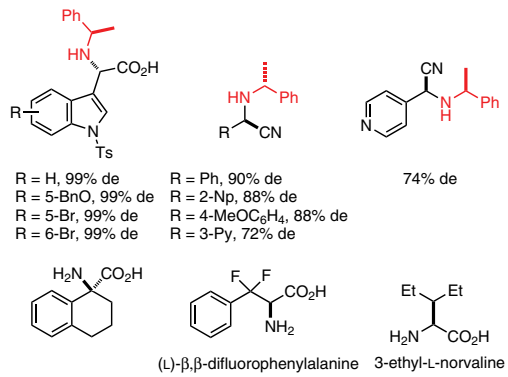
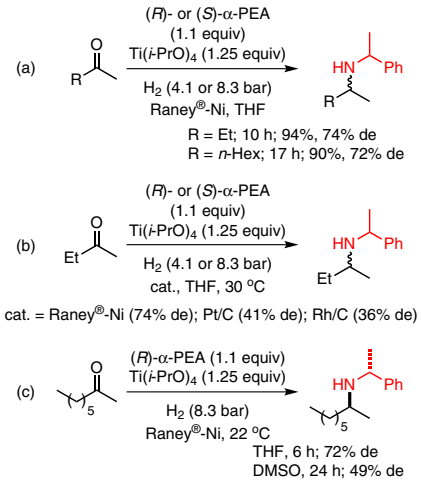
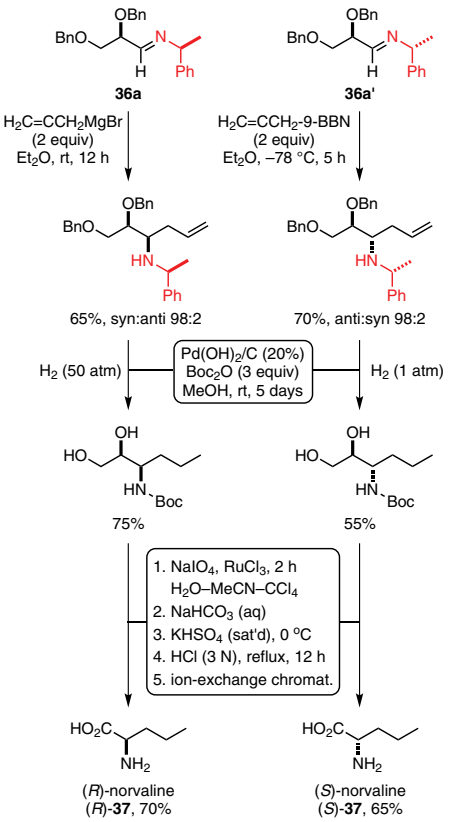


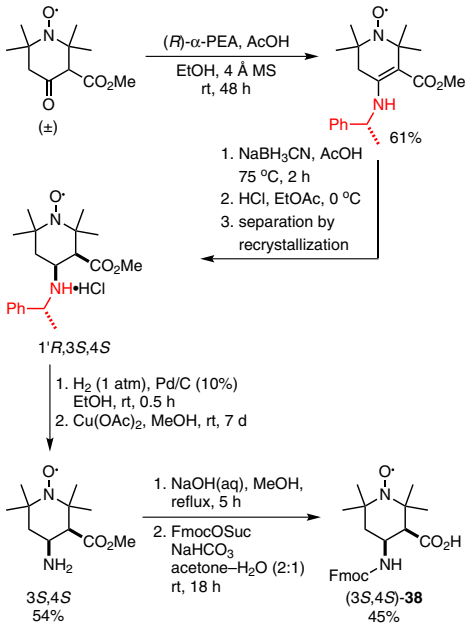
Figure 1. Select Intermediates and α-Amino Acids Obtained by the Diastereoselective Addition of Cyanide to Chiral Imines Containing the α-PEA Moiety. *(Ref. 50)*



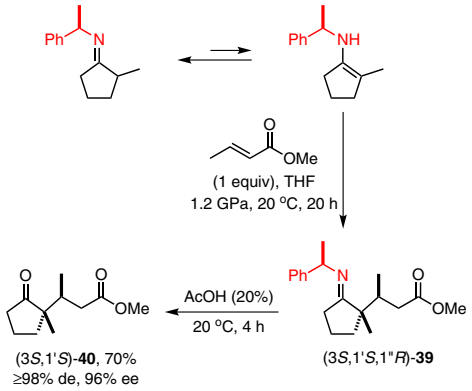
Scheme 13. The Asymmetric Reductive Amination of Prochiral Ketones Evaluated under a Variety of Conditions. *(Ref. 46e,h)*



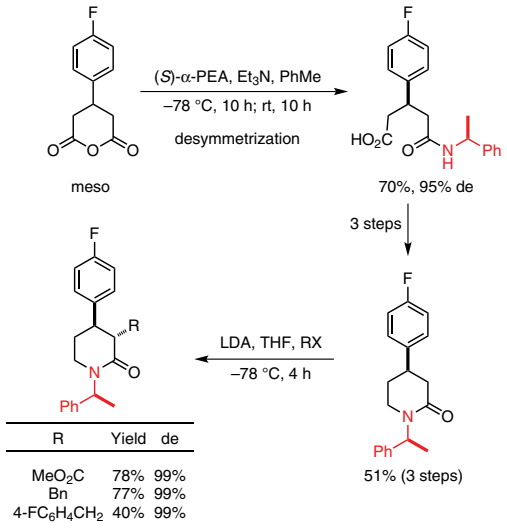
Scheme 14. The Diastereoselective Allylation of *N*-(α-Phenylethyl)imines in the Enantioselective Preparation of α-Amino Acids. *(Ref. 53)*



Scheme 15. Preparation of Cyclic β-Amino Acids (*S,S*)-**38** by Reduction of Enamines. *(Ref. 54a)*



Scheme 16. Michael Addition to Methyl Crotonate of Chiral Imines Derived from 2-Methylcyclopentanone and α-PEA. *(Ref. 58)*



Scheme 17. α-PEA as Chiral Auxiliary in the Desymmetrization and Alkylation or Acylation of an α-PEA-Containing 2-Piperidinone Enolate. *(Ref. 59)*

and co-workers[56] in the synthesis of chiral enamino lactones and dihydrobenzimidazolepiperidine-1,3-dicarboxylate, respectively, in good yields and ee's.

On the other hand, Michael addition of enamines to electron-deficient olefins has emerged as a simple and efficient tool for the stereocontrolled synthesis of quaternary stereocenters, as demonstrated in several recent reports.[57] A relevant example is the report by Dumas and co-workers[58] of the stereoselective addition to methyl crotonate of chiral imines derived from 2-methylcyclopentanone and enantiopure α-PEA to give, in the case of the *R* imine, product **39**. Hydrolysis of **39** afforded keto ester **40** in 70% yield, ≥98% de, and 96% ee (**Scheme 16**).

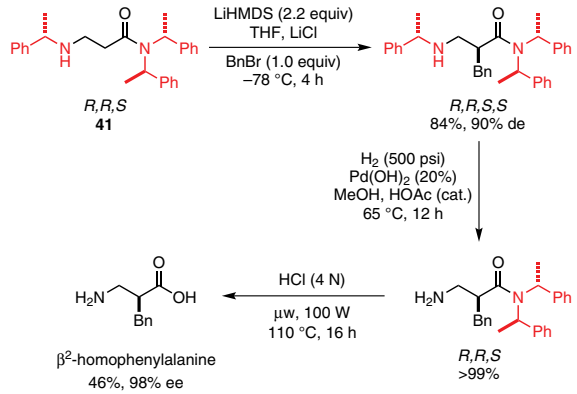
4.3. Diastereoselective Alkylation of α-PEA-Containing Enolates

The diastereoselective alkylation of enolates containing the α-phenylethylamino moiety has been employed in the synthesis of open-chain or cyclic enantioenriched compounds, notably piperidinones,[59] β-amino acids,[60] diamino dicarboxylic acids,[61] disubstituted phosphonopropanamides[62] or alkylcyclobutanones.[63] An illustrative example was described by Liu and co-workers, who prepared nonracemic disubstituted piperidinones and piperidines by alkylation or acylation of the enolate derived from α-PEA-containing 2-piperidinone (**Scheme 17**).[59]

Our group has successfully employed C_2-symmetric bis(α-PEA) and Evans-type hexahydrobenzoxazolidinone chiral auxiliaries in the asymmetric synthesis of β²-amino acids, such as (*R*)-β²-homoDopa, (*S*)-β²-homophenylalanine, (*S*)-β²-homovaline, (*S*)-β²-homoleucine, and (*S*)-β²-homotryptophan.[60] Thus, chiral amide **41** is conveniently metallated with lithium hexamethyldisilazide (LiHMDS) whose diastereotopic faces in the resulting enolate allow the stereoselective addition of benzyl bromide in 90% de. In this instance, hydrogenolysis of the benzylated product and hydrolysis under microwave (μw) irradiation result in the formation of (*S*)-β²-homophenylalanine with 98% ee (**Scheme 18**).[60b]

4.4. α-PEA in Diastereoselective Cyclization Reactions

Piperidine, pyrrolidine, and morpholine derivatives have received considerable attention because of their applications in organic, materials, and pharmaceutical chemistry. The use of α-PEA has permitted the preparation of several promising molecules in this class, such as tetrahydroisoquinolines (used in the treatment of Parkinson's disease);[64] benzodiazepines (sedatives);[65] oxazolidines,



Scheme 18. Enantioselective Synthesis of β²-Homophenylalanine. *(Ref. 60b)*

oxazolidinones, and lactams (antibiotics);[66] piperidine and pyrrolidine derivatives;[67] phthalides (enzyme inhibitors);[68] noranabasamine alkaloids (anti-inflammatory); and others.[69]

In this regard, Yamaguchi and collaborators[70] reported an interesting N-heterocyclization of primary amines with diols catalyzed by an iridium complex. When the reaction of (*R*)-α-PEA and 1-phenyl-1,5-pentanediol was carried out in the presence of a catalytic amount of $[Cp^*IrCl_2]_2$, a diastereoisomeric mixture of phenylpiperidines formed in 76% yield, 92% de, and good enantiomeric excess. Reduction of this mixture with Pd/C gave (*S*)-2-phenylpiperidine **42** in 96% yield and 78% ee (**Scheme 19**).

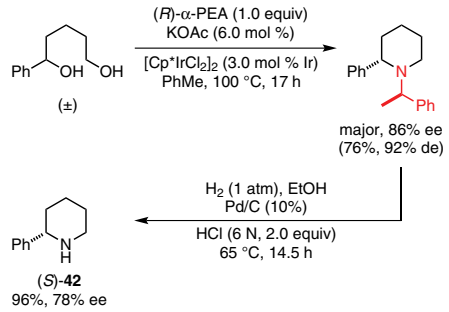
The potential of α-PEA as chiral auxiliary in diastereoselective Diels–Alder reactions was successfully demonstrated in recent years.[71] In a relevant example, Badorrey et al.[71a] employed a chiral imine dienophile prepared from (*S*)-2,3-di-*O*-benzylglyceraldehyde and (*R*)-α-PEA. In the presence of Danishefsky's diene and ZnI_2, this chiral imine underwent a hetero-Diels–Alder reaction leading to **43** (**Scheme 20**), which is a valuable intermediate in the synthesis of palinavir—a potent inhibitor of the human immunodeficiency virus (HIV-1 and HIV-2).

4.5. α-PEA as Chiral Auxiliary in Miscellaneous Procedures

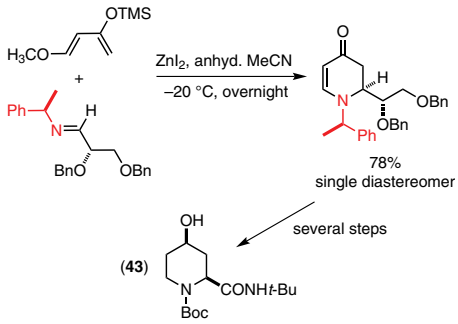
In addition to the processes described above, the applications of α-PEA as chiral auxiliary include several other kinds of reactions such as diastereoselective carbozincation of propargylic amines,[72] aldimine coupling of imines with methoxyketene methyltrimethylsilyl acetal in the synthesis of β-amino-α-hydroxy acids,[73] preparation of α,β-unsaturated amides from 2-phosphonamides via the Horner–Wadsworth–Emmons reaction,[74] preparation of imidazole derivatives by the thio-Ugi reaction,[75] synthesis of azabicyclooctane carboxylic acids,[76] α-pyridylation of amines through urea coupling, stereoselective lithiation and rearrangement,[77] development of amino vinyl cyclohexenes,[78] and synthesis of therapeutic agents such as DPC 961 (HIV non-nucleoside reverse transcriptase inhibitor).[79]

5. α-Phenylethylamine as Chiral Reagent in the Stereodifferentiation of Prochiral Substrates

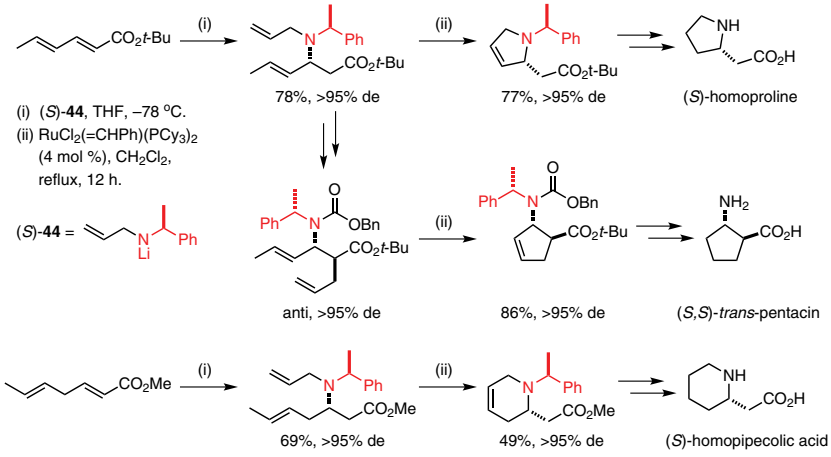
Conjugate addition of a nitrogen nucleophile to α,β-unsaturated carboxylic acid derivatives is one of the most useful and simplest methods for the formation of N–C bonds.[80] In particular, addition of "chiral ammonia" nucleophiles to the acceptor unsaturated carbonyl group produces a new stereogenic center at the β position. The diastereoselectivity of this reaction depends on the nature of the starting ester, the "chiral ammonia" equivalent, and on the particular reaction conditions. Davies, the recognized pioneer and leader of this methodology, has demonstrated the versatility of this approach in the synthesis of a large number of chiral β-amino acids.[81] In a striking example, Davies and co-workers[82] achieved the diastereoselective conjugate addition of lithium *N*-allyl-(*S*)-α-PEA, (*S*)-**44**, to a wide range of α,β-unsaturated esters (**Scheme 21**). Subsequent ring-closing metathesis (RCM) afforded a variety of substituted cyclic β-amino esters in high de's. Final reduction and



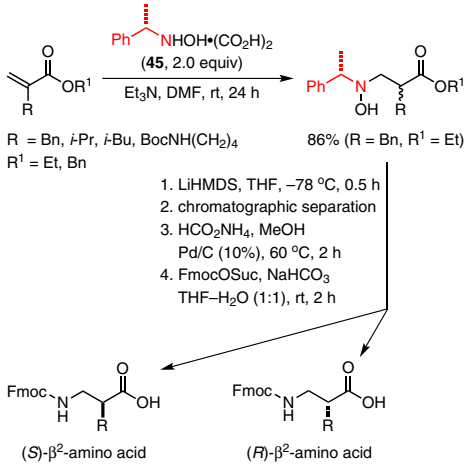
Scheme 19. Diastereoselective Cyclization in the Enantioselective Synthesis of (*S*)-2-Phenylpiperidine, (*S*)-**42.** *(Ref. 70a)*



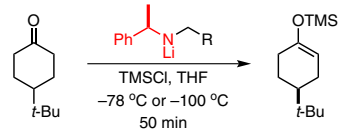
Scheme 20. Hetero-Diels–Alder Reaction in the Synthesis of **43**, an Intermediate in the Synthesis of Palinavir. *(Ref. 71a)*



Scheme 21. The Synthesis of β-Amino Acids by Addition of "Chiral Ammonia" Equivalent (*S*)-**44** to α,β-Unsaturated Esters Followed by RCM. *(Ref. 82)*

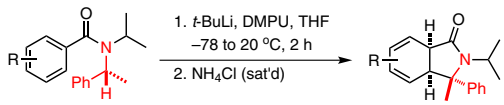


Scheme 22. Formation of β²-Amino Acids by Diastereoselective Michael Addition. *(Ref. 86)*



R	Yield	ee
Me	55%	41%
t-Bu	94%	32%
FCH_2	61%	43%
F_2CH	66%	59%
F_3C	**86%**	**92%**
CF_3CF_2	**92%**	**83%**
Me_2NCH_2	92%	18%

eq 8 *(Ref. 91)*



R[a]	Yield	ee
2-MeO	74%	>99%
3-MeO	66%	>99%
4-MeO	80%	>99%

[a] Position numbers are with respect to starting material.

eq 9 *(Ref. 92)*

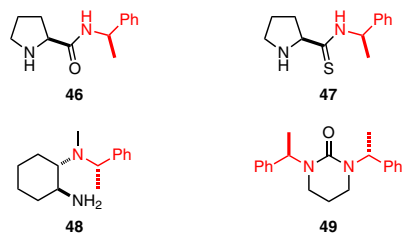


Figure 2. Chiral, α-PEA-Containing Organocatalysts Employed in Asymmetric Aldol Reactions. *(Ref. 94–97)*

hydrolysis generated the corresponding cyclic β-amino acids; i.e., (*S*)-homoproline, (*S*)-homopipecolic acid, and carbocyclic (*S*,*S*)-*trans*-pentacin.

A vast number of important molecules have been synthesized by applying this methodology. For example, Michael's group[83] prepared the optically active bicyclic compound (–)-indolizidine; Coleman and collaborators[84] synthesized nonracemic dihydrobenzofuran β-amino acids, which are aspartic acid mimetic that are structurally related to benzodioxole systems; and Podlech[85] reported the preparation of enantiomerically pure β-amino acids. Moreover, Gellman and co-workers described the enantioselective Michael addition of chiral hydroxylamine (*S*)-**45** to α-alkylacrylates followed by cyclization to give a diastereomeric mixture of α-substituted isoxazolidinones. A set of α-substituted β²-amino acids were obtained after separation, hydrogenation, and final Fmoc protection (**Scheme 22**).[86] Furthermore, Herrera et al.[87] reported the preparation of chiral α-hydroxy-β-amino acid derivatives based on the diastereoselective addition of (*R*)-α-PEA to representative captodative olefins, a strategy that Blanchet and co-workers[88] used later in the enantioselective synthesis of (*S*)-β-proline. Lhommet and collaborators[89] carried out a similar intramolecular Michael addition of (*S*)-α-PEA to chloroacetylenic esters in acetonitrile to form chiral piperidine enamino esters.

Several examples have been described in which α-PEA-lithium amide has been employed for the selective removal of one enantiotopic proton in symmetrical carbonyl compounds.[90] In a particularly interesting example, Aoki and Koga[91] reported an efficient procedure for the enantioselective deprotonation of 4-*tert*-butylcyclohexanone. These researchers utilized α-PEA-derived chiral lithium amides containing alkyl or fluoroalkyl substituents at the amide nitrogen. The resulting trapped enolates were obtained in yields as high as 94%, and enantiomeric excesses up to 92% (**eq 8**).[91] In a related study, Clayden and co-workers[92] reported a lithiation of chiral benzamides containing the α-PEA moiety, which triggered a stereospecific cyclization process (**eq 9**).

6. α-Phenylethylamine in Organocatalysts

The use of small organic molecules to accelerate chemical reactions, has been of great relevance in organic chemistry. The lack of sensitivity to moisture and oxygen, ready availability, low cost, and low toxicity confer high advantages to organocatalysts over metal catalysts in the production of drugs.[93] Several asymmetric organic reactions have made use of organocatalysts containing a chiral α-PEA fragment to induce chirality in the final products. In recent years, numerous reports have described the development of the asymmetric aldol reaction (**Figure 2**).[93–97] In an excellent example, Chimni and Mahajan[94] employed protonated chiral prolinamide derivative **46** as asymmetric organocatalyst for the enantioselective aldol reaction in water with good yields and moderate enantioselectivity. Gryko and co-workers[95] designed organocatalyst **47** by replacing the amide functionality in **46** with the thioamide group in order to increase the acidity of the N–H bond and, as a consequence, to increase yields and enantiomeric excesses (up to 99% ee). Recently, Singh and collaborators[96] utilized chiral primary and tertiary diamine **48** to catalyze the *syn*-aldol (with unprotected hydroxyacetone) and *anti*-aldol (with cyclic ketones) reactions in aqueous media with high diastereo- and enantioselectivities. Recently, our group described the synthesis of chiral urea **49**, which incorporates (*R*)- or (*S*)-α-PEA, and its application as a Lewis base in the asymmetric aldol reaction.[97]

In other relevant organocatalytic reactions, Tsogoeva and co-workers[98] have developed a group of chiral thiourea

derivatives, e.g. **50**, as bifunctional catalysts for the nitro-Michael addition (addition of acetone to nitroolefins), achieving higher enantioselectivities than with proline derivatives. Similarly, Kelleher et al.[99] synthesized spirolactam organocatalyst **51** for the asymmetric conjugate addition of aldehydes to nitroolefins in excellent yields, with good diastereoselectivity and enantioselectivity using low catalyst loadings (5 mol %). Our group demonstrated the potential of α-PEA derivatives such as **52**, in the enantioselective amination of α-substituted α-cyanoacetates with azodicarboxylates as electrophiles.[100] González-Olvera et al. described the preparation and use of chiral diazabicyclo[2.2.1]heptane **53** as organocatalyst for the enantioselective Biginelli reaction, giving rise to good yields and enantioselectivities.[101] On the other hand, Zhao, Zhou, and collaborators employed a chiral cyclic β-amino alcohol, **54**, as co-catalyst (in combination with L-proline) in the enantioselective Baylis–Hillman reaction between *o*-nitrobenzaldehyde and methyl vinyl ketone, obtaining the corresponding keto alkenyl alcohol with good selectivity.[102] In a preliminary study, Peris and Miller reported the desymmetrization of prochiral ketones through the Baeyer–Villiger oxidation by employing an α-PEA-containing peptide, **55**, to give the corresponding lactones with modest enantioselectivities.[103] Finally, Hansch et al.[104] prepared enantiomerically pure thiomorpholine **56**, which includes the α-PEA fragment, for application in sulfur ylide mediated asymmetric epoxidation of aldehydes with excellent yields, enantioselectivities, and diastereoselectivities (**Figure 3**).

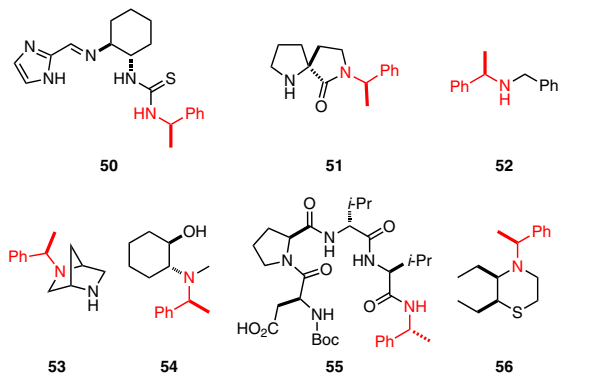


Figure 3. Remarkable, α-PEA-Containing Organocatalysts Utilized in Various Asymmetric Reactions. *(Ref. 98–104)*

7. Concluding Remarks

Because of its low price, accessibility in both enantiomeric forms, facile incorporation in starting materials, and easy removal from final products, α-phenylethylamine (α-PEA) continues to stand as an important chiral reagent in asymmetric synthesis. This is attested to by the great number of methodologies that are available for its application as chiral ligand, in the resolution of racemic mixtures, as chiral auxiliary, as chiral base, and in the development of new organocatalysts. The present review has described noteworthy recent developments in the chemistry of α-PEA, which may motivate chemists involved in enantioselective synthesis to take advantage of this versatile molecule.

8. Acknowledgements

The authors are grateful to the Consejo Nacional de Ciencia y Tecnología (CONACyT, México) for financial support. Y. Bandala is also indebted to CINVESTAV-IPN for a postdoctoral fellowship.

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Keywords: α-Phenylethylamine; chiral ligand; resolving agent; chiral auxiliary; chiral reagent; organocatalyst.

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Yamir Bandala was born in 1979 in Perote, México. He studied chemistry at the Centro de Investigación y de Estudios Avanzados (CINVESTAV), México, where he completed his doctoral thesis on the "Synthesis and Conformational Analysis of Cyclic and Open-Chain β- and α/β-Peptides" at the beginning of 2009 in Prof. Juaristi's research group. After one year of postdoctoral work with Prof. Juaristi, he moved in 2010 to a second postdoctoral position in Professor Gerardo Corzo's group at the Instituto de Biotecnología (UNAM), México, where he is working on the development of new β-amino acids and α/β-peptides.

Eusebio Juaristi was born in 1950 in Querétaro, México. He studied chemistry with Prof. E. L. Eliel at the University of North Carolina, Chapel Hill, where he received his Ph.D. degree in 1977. Following postdoctoral stays at UC Berkeley (with A. Streitwieser) and the Syntex Diagnostics Division (Palo Alto, CA), he returned to Mexico where he is now Professor of Chemistry at the Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional. He has also served as Visiting Professor at ETH-Zurich (1985–1986 and 1992–1993) and UC Berkeley (1999–2000). In 1998, he received the National Medal of Science and, in 2006, he became a member of El Colegio Nacional (highest academic honor in México).

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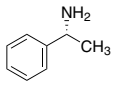

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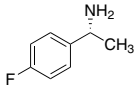

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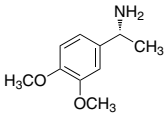

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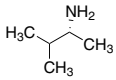

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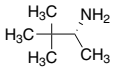

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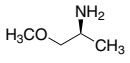

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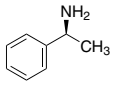

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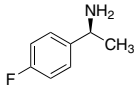

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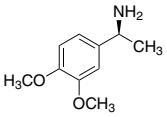

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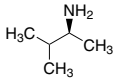

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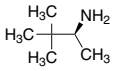

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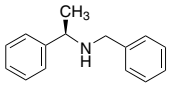

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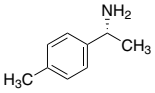

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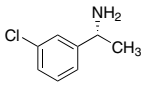

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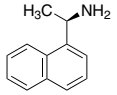

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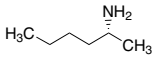

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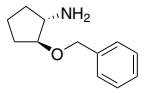

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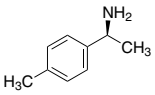

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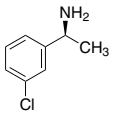

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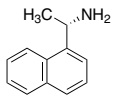

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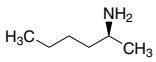

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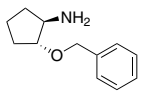

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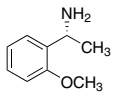

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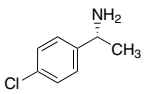

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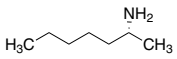

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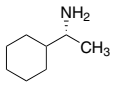

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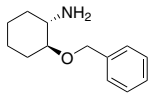

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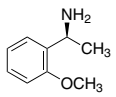

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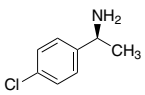

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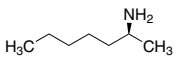

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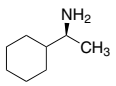

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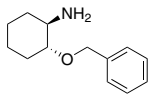

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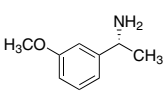

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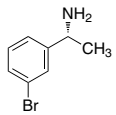

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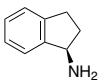

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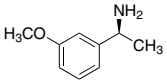
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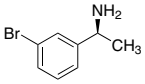
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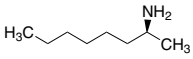
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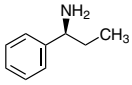
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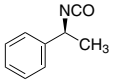
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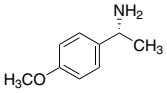
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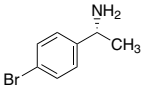
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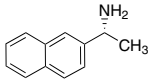
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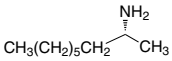
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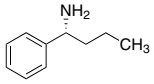
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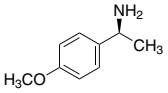
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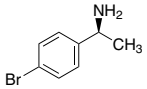
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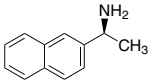
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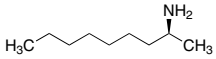
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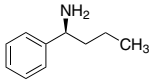
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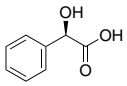
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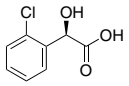
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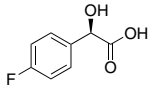
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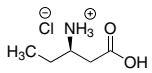
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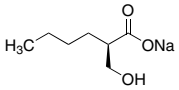
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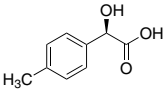
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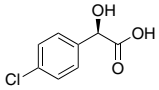
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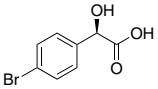
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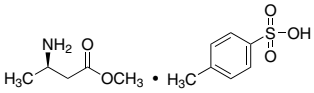
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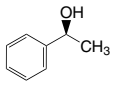
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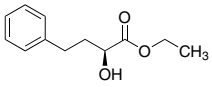
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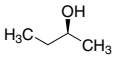
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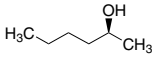
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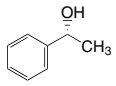
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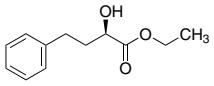
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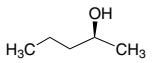
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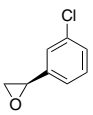
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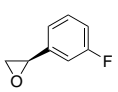
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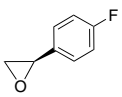
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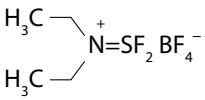

XtalFluor-E
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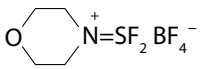

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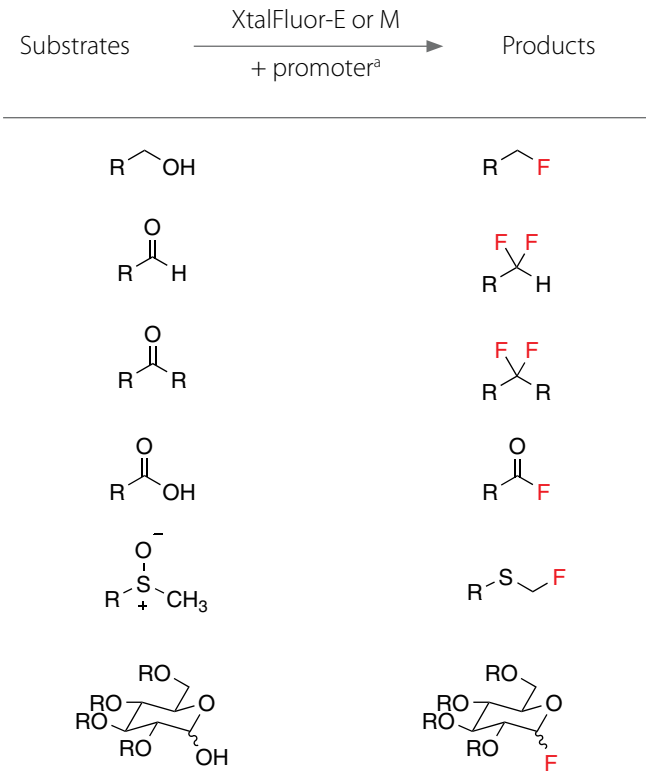
Representative Scope



[a] Promoters: DBU, $Et_3N{\bullet}3HF$, or $Et_3N{\bullet}2HF$

References: (1) Beaulieu, F. et al. *Org. Lett.* **2009**, *11*, 5050. (2) L'Heureux, A. et al. *J. Org. Chem.* **2010**, *75*, 3401.

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2-Iodoxybenzenesulfonic Acid (IBS) Catalyzed Oxidation of Alcohols

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Outline

1. Introduction

The oxidation of alcohols to the corresponding carbonyl compounds is one of the most important transformations in synthetic organic chemistry.[1] Over the past two decades, hypervalent iodine compounds have received a great deal of attention due to their mild and chemoselective oxidizing properties and to the fact that, unlike toxic heavy-metal-based reagents, they are environmentally benign.[2] We recently published a review on the oxidation of alcohols with stoichiometric or catalytic hypervalent iodine compounds.[3] The present review focuses on the discovery and development of 2-iodoxybenzenesulfonic acid (IBS, **1**) and related hypervalent iodine compounds. It also covers advances in hypervalent iodine catalyzed alcohol oxidations and related transformations reported between 2005 and 2010.

2. Hypervalent Iodine Catalysts for Alcohol Oxidation

To date, various hypervalent iodine (λ³- and λ⁵-iodane) reagents have been developed as oxidants for alcohols.[3] 2-Iodoxybenzoic acid (IBX, **2**) and Dess–Martin periodinane (DMP, **3**) are the best known and most commonly used hypervalent iodine reagents (**Figure 1**). Dess and Martin used **2** as a precursor for **3**.[4] In the early studies, **2** was synthesized from 2-iodobenzoic acid (**4**) and potassium bromate ($KBrO_3$) in aqueous sulfuric acid.[4a] Although **2** was later reported to be explosive,[5] Dess and Martin subsequently speculated that some bromate or other impurity may have been included in samples that were found to be explosive, but that IBX (**2**) itself should be non-explosive.[4b] The first use of **2** for alcohol oxidation in DMSO was reported in 1994 by Frigerio and Santagostino.[6] The simple, one-step preparation of **2** from **4** with Oxone®, an environmentally safe oxidant, has made **2** a popular reagent (**eq 1**).[7] To date, **2** has been employed as a powerful and selective oxidant that mediates a variety of transformations such as the oxidation of alcohols, phenols, and amines; the dehydrogenation of ketones, aldehydes, and N-heterocycles; and the oxidative cleavage of dithioacetals.[2,3] Several research groups have attempted to improve on **2** by structurally modifying it, or by developing polymer-supported analogues.[3] Additionally, Quideau's group reported a stabilized formulation of IBX, SIBX, containing benzoic acid and isophthalic acid, which offered some advantages, such as safety and ease of workup.[8]

In 2005 and 2006, Vinod[9] and Giannis[10] independently reported the oxidation of alcohols catalyzed by **2**—generated in situ from **4** or 2-iodosobenzoic acid (IBA)—in the presence of Oxone® as co-oxidant (**Scheme 1**). Vinod's group employed 20–40 mol % of **4** in a water–acetonitrile biphasic solvent system, in which primary and secondary alcohols were oxidized to carboxylic acids and ketones, respectively (**eq 2**).[9] In contrast, Giannis's group utilized a water–ethyl acetate biphasic solvent system in the presence of 10 mol % each of **4** and tetrabutylammonium hydrogen sulfate [$(n\text{-Bu})_4NHSO_4$] as a phase-transfer catalyst. Under these conditions, primary benzylic alcohols were oxidized to the corresponding aldehydes, which did not undergo further oxidation (**eq 3**).[10] These two reports stated that it was not necessary to isolate beforehand the hypervalent iodine compounds, which are potentially shock-sensitive explosive oxidants.

Page and co-workers demonstrated that several primary and secondary alcohols can be oxidized to the respective aldehydes and ketones under reflux conditions in acetonitrile or dichloroethane in the presence of tetraphenylphosphonium monoperoxysulfate (TPPP, $Ph_4P^+HSO_5^-$) and a catalytic amount of **4** (**eq 4**).[11] TPPP was derived from Oxone® by simple counterion exchange with tetraphenylphosphonium chloride. This catalytic system enables the oxidation of primary alcohols to the corresponding aldehydes without further oxidation to the carboxylic acids.

The selective oxidation of benzylic C–H bonds to the corresponding carbonyl functionalities has been achieved using a catalytic amount of **4** and Oxone® in aqueous acetonitrile (**Scheme 2**).[12] The authors hypothesized that the active

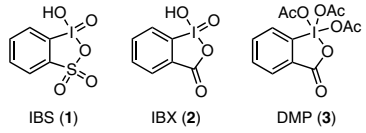
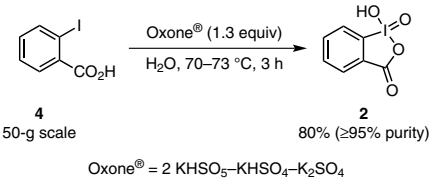
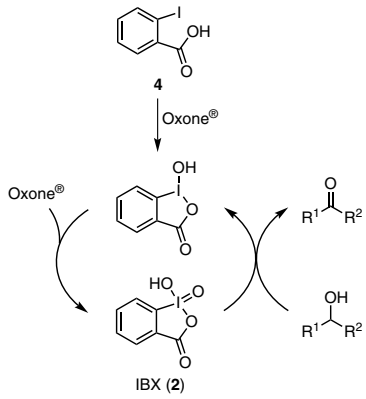


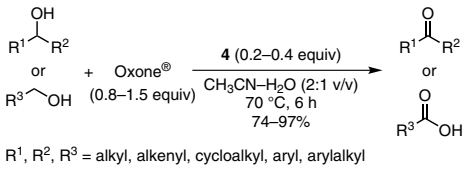
Figure 1. IBS (**1**), IBX (**2**), and DMP (**3**).



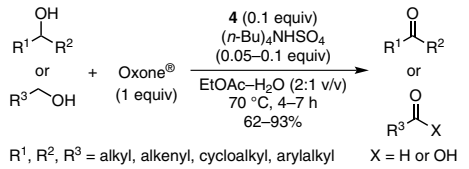
eq 1 *(Ref. 7)*



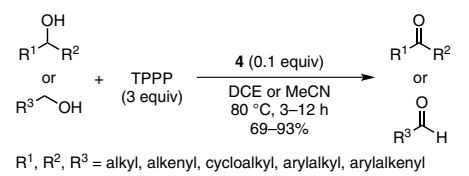
Scheme 1. The Oxidation of Alcohols Catalyzed by IBX (**2**) Generated in Situ. *(Ref. 9,10)*



eq 2 *(Ref. 9)*



eq 3 *(Ref. 10)*

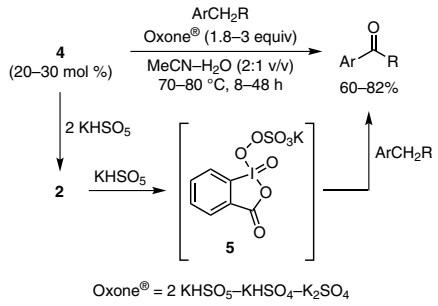


eq 4 *(Ref. 11)*

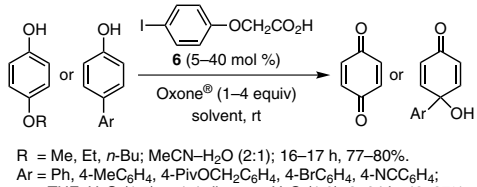
hypervalent iodine oxidant generated in situ might not be IBX (**2**), but a soluble derivative of IBX, **5**, incorporating a peroxy ligand ($KHSO_5$). This species is believed to oxidize a benzylic C–H bond via a single-electron-transfer (SET) mechanism.[12]

Yakura's group reported that *para*-alkoxyphenols and *para*-arylphenols are oxidized in excellent yields to the corresponding *para*-quinones and *para*-quinols, respectively, using catalytic amounts of 4-iodophenoxyacetic acid (**6**) with Oxone® as a co-oxidant in aqueous acetonitrile (**eq 5**).[13]

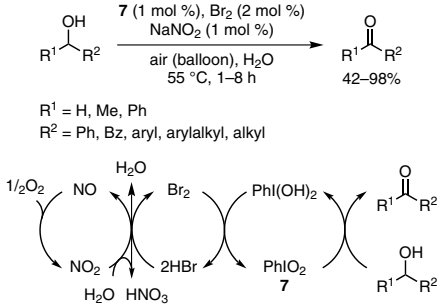
An efficient, catalytic aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones has been carried out by Liu and co-workers by using a mixture of iodoxybenzene ($PhIO_2$, **7**, 1 mol %), Br_2 (2 mol %), and $NaNO_2$ (1 mol %) in water (**Scheme 3**).[14] The proposed reaction mechanism includes three redox cycles. In the first redox cycle, **7** is the active species that oxidizes the alcohol to the corresponding carbonyl compound, and is reduced to dihydroxyiodobenzene ($PhI(OH)_2$). In the second cycle, $PhI(OH)_2$ is reoxidized to **7** with Br_2, which is reduced to HBr. In the third and final cycle, the oxidation of NO with O_2 produces NO_2, which reoxidizes HBr to Br_2. However, we were not able to effect the oxidation of alcohols under Liu's



Scheme 2. The Oxidation of Benzylic C–H Bonds with Oxone® Catalyzed by **5** Generated in Situ. *(Ref. 12)*



eq 5 *(Ref. 13)*



Scheme 3. Liu's Aerobic Oxidation of Alcohols Catalyzed by $PhIO_2$ (**7**). *(Ref. 14)*

conditions,[15] which led us to suggest, on the basis of several control experiments, that the actual oxidant of the alcohols in this case is Br_2 rather than $PhIO_2$.[15]

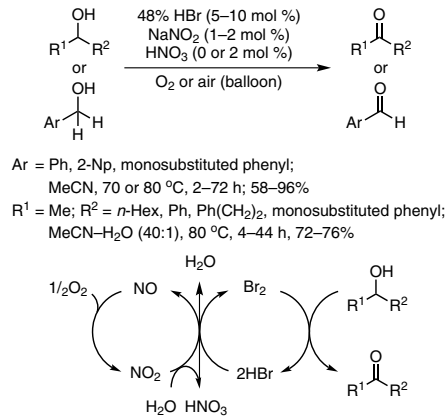
Moreover, our group disclosed that the simple and environmentally benign catalytic system consisting of HBr and $NaNO_2$ is very effective for the aerobic oxidation of alcohols (**Scheme 4**).[15] Primary benzylic alcohols are selectively oxidized to the corresponding aldehydes in acetonitrile under a balloon pressure of O_2. Secondary alcohols are oxidized to the corresponding ketones in the presence of a small amount of water. Furthermore, the aerobic oxidation of alcohols can also be achieved under a balloon pressure of air instead of pure O_2 with the HBr–$NaNO_2$–HNO_3 catalytic system.[15]

Li and co-workers developed an effective system for the oxidation of alcohols under an atmosphere of oxygen, without the need for any additional solvent or transition-metal catalyst, by using catalytic amounts of phenyliodine diacetate (PIDA (**8**))–TEMPO–KNO_2 (**Scheme 5**).[16]

In 2009, Yusubov, Zagulyaeva, and Zhdankin reported an efficient tandem catalytic system, based on a Ru(V)-catalyzed reoxidation of iodosobenzene (PhIO, **9**) to $PhIO_2$ (**7**), for the oxidation of alcohols and hydrocarbons to carbonyl compounds by employing stoichiometric amounts of Oxone® at room temperature (**Scheme 6**).[17]

Very recently, Nemykin, Zhdankin, and co-workers reported the room temperature, Fe(III)–porphyrin-catalyzed oxygenation of the anthracene ring to the anthraquinone system in the presence of a substoichiometric amount of iodobenzene and an excess of Oxone® (**Scheme 7**).[18] The proposed reaction mechanism includes two catalytic redox cycles. Accordingly, the active λ^3-iodane species, generated in solution by treatment of iodobenzene with Oxone®, is responsible for the oxidation of the Fe(III)–porphyrin to the oxo-Fe(IV)$^+$–porphyrin complex, which then acts as the actual oxygenating agent.

The same year, a catalytic, room-temperature oxidation of alcohols was effected with *meta*-chloroperbenzoic acid (*m*-CPBA) or potassium peroxodisulfate ($K_2S_2O_8$) in the presence of a catalytic amount of iodobenzene and *N*-hydroxyphthalimide (NHPI) or TEMPO in aqueous acetonitrile (**Scheme 8**).[19] In both cases, iodobenzene was oxidized by *m*-CPBA or $K_2S_2O_8$ in situ to a λ^3-iodane species, a reoxidant of NHPI or TEMPOH to phthalimide-*N*-oxyl radical (PINO) or TEMPO, which then oxidizes the alcohols.



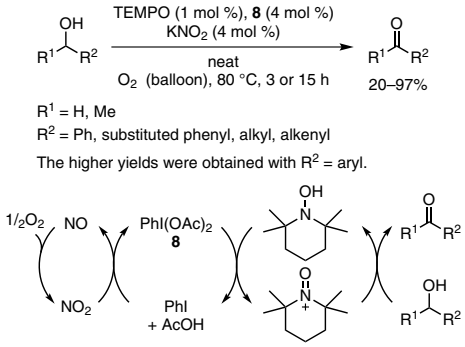
Scheme 4. Ishihara's Bromine-Catalyzed Aerobic Oxidation of Alcohols. *(Ref. 15)*

3. 2-Iodoxybenzenesulfonic Acid (IBS)

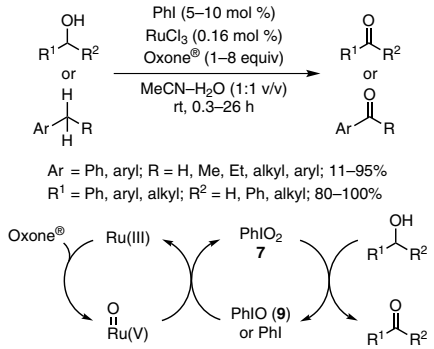
3.1. Related Hypervalent Iodine Reagents

3.1.1. HMBI and λ^3-Iodane Derivatives

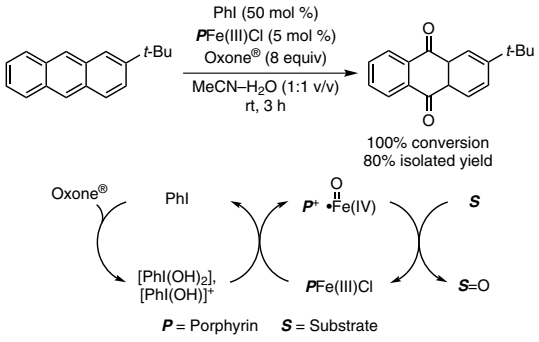
In 1993, Koser and co-workers first reported that the oxidation of 2-iodo-5-methylbenzenesulfonic acid (**10**) with peracetic acid leads to 1*H*-1-hydroxy-5-methyl-1,2,3-benziodoxathiole 3,3-dioxide (HMBI, **11**) (**Scheme 9**).[20] In 2007, Justik reported that the sodium salt (**10**•Na) could be directly oxidized to **11** through in situ protonation with a small amount of concentrated sulfuric acid (see Scheme 9).[21] HMBI (**11**) was utilized to



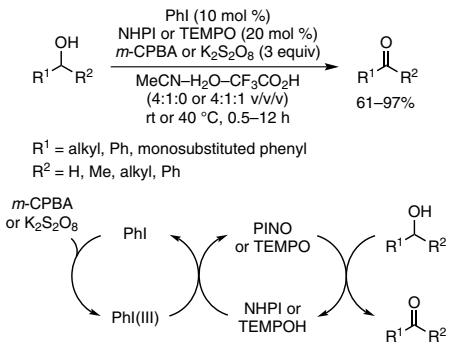
Scheme 5. TEMPO–PIDA (**8**) Co-catalyzed Aerobic Oxidation of Alcohols. *(Ref. 16)*



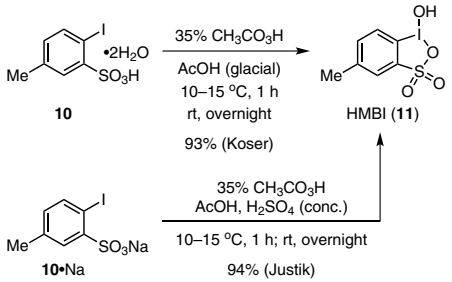
Scheme 6. Ru(III)–$PhIO_2$ (**7**) Co-catalyzed Oxidations with Oxone®. *(Ref. 17)*



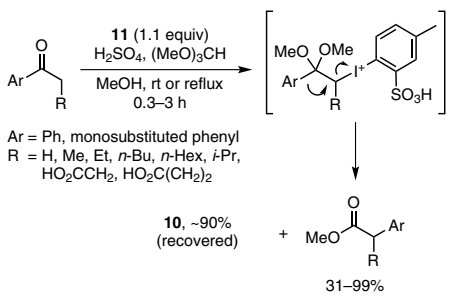
Scheme 7. Fe(III)–Porphyrin–Iodine(III) Co-catalyzed Oxidation of the Anthracene Nucleus. *(Ref. 18)*



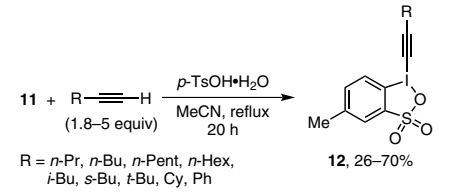
Scheme 8. Nitroxyl Radical–Iodine(III) Co-catalyzed Oxidation of Alcohols with *m*-CPBA or $K_2S_2O_8$. *(Ref. 19)*



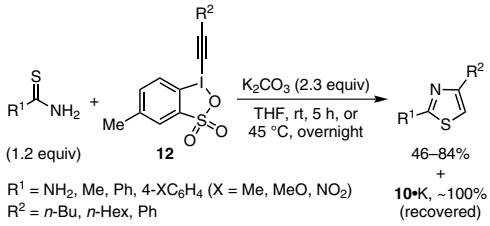
Scheme 9. Koser's and Justik's Syntheses of HMBI. *(Ref. 20,21)*



eq 6 *(Ref. 21)*



eq 7 *(Ref. 20)*



eq 8 *(Ref. 22)*

convert alkanophenones to alkyl esters of 2-arylalkanoic acids by oxidative rearrangement (**eq 6**).[21] The use of **11** offers several advantages over other similar oxidizing agents, including facile workup of the reaction mixture and recovery of the reduced iodine reagent.

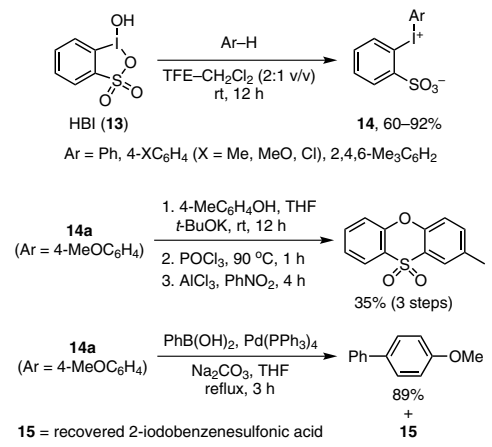
In the same 1993 report, Koser also disclosed the synthesis of 1*H*-1-(1-alkynyl)-5-methyl-1,2,3-benziodoxathiole 3,3-dioxides (AMBIs, **12**) from **11** and the corresponding terminal alkynes in low-to-good yields (**eq 7**).[20] Such AMBIs were later employed by Ishiwata and Togo to prepare thiazoles from the corresponding thioamides (**eq 8**).[22] The reduced iodo compound **10**•K was recovered quantitatively by simple filtration of the reaction mixture, and could be converted to **12** to be reused for the preparation of thiazoles.[22]

In a subsequent report, Justik's group disclosed that the reaction of 1*H*-1-hydroxy-1,2,3-benziodoxathiole 3,3-dioxide (HBI, **13**) with arenes produces 2-[(aryl)iodonio]benzenesulfonates (**14**) in moderate-to-high yields (**Scheme 10**).[23] HBI (**13**) was prepared from sodium 2-iodobenzenesulfonate (**15**•Na) similarly to the way its methyl analogue, **11**, was prepared (see Scheme 9). The zwitterionic sulfonates, **14**, were employed in the synthesis of 2-sulfonyloxyarenes and as potential recyclable aryl-transfer reagents in transition-metal-catalyzed cross-coupling reactions (see Scheme 10).[23]

3.1.2. IBS and λ⁵-Iodane Derivatives

Zhdankin and co-workers first reported in 2006 the preparation and full characterization of IBS (**1**), a λ⁵-iodane and a thia analogue of IBX (**2**).[24] IBS (**1**)—which is the cyclic tautomeric form of 1*H*-1-hydroxy-1,2,3-benziodoxathiole 1,3,3-trioxide—was synthesized by two different methods: (i) the direct oxidation of 2-iodobenzenesulfonic acid (**15**) with Oxone® (Method **A**) or (ii) by hydrolysis of the methyl ester of IBS, **16**, (Method **B**)[25] (**Scheme 11**). Method **A** results in a low-purity IBS, while Method **B** yields IBS of a high purity. IBS (**1**) is thermally unstable and highly reactive toward organic solvents such as acetonitrile, DMSO, and methanol.[24] Because of this instability (reductive decomposition to the corresponding λ³-iodane) and reactivity, these researchers did not investigate its oxidative ability.[24]

The pseudocyclic λ⁵-iodanes, IBS ester (**16**)[25] and amides (**17**),[26] have been prepared by oxidation of the corresponding 2-iodobenzenesulfonic ester and 2-iodobenzenesulfonamide with dimethyldioxirane (**Scheme 12**).[26] The starting material



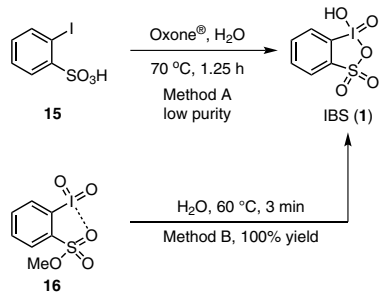
Scheme 10. Preparation and Application of 2-[(Aryl)iodonio]-benzenesulfonates (**14**). *(Ref. 23)*

for these monovalent iodines, 2-iodobenzenesulfonyl chloride, was synthesized from **15**•Na (see Scheme 12).[25] IBS amides **17** can selectively oxidize benzyl alcohols to aldehydes.[26] While IBS esters **16** could not oxidize alcohols, they are useful for the oxidation of other organic functional groups, such as sulfides and secondary amines to the respective sulfoxides and imines (**Scheme 13**).[25]

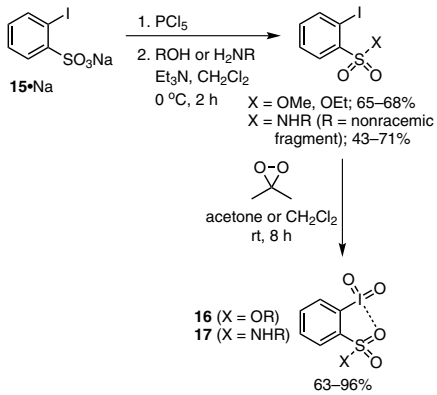
3.2. Discovery of IBS as a Catalyst for Alcohol Oxidation with Oxone®

To develop a more powerful hypervalent iodine catalyst for selective alcohol oxidation, we became interested in modifying the arene moiety of IBX (**2**) (**Figure 2**).[27] We discovered that electron-donating groups in the benzene ring, as in **18** and **19**, resulted in λ⁵-iodanes that were superior to **2** as catalysts for the oxidation of alcohols with Oxone® under nonaqueous conditions, even though Oxone® was almost insoluble in most organic solvents. In contrast, electron-withdrawing groups, as in **20**, resulted in λ⁵-iodanes with lower reactivity than **2**. The stability of these IBX catalysts was strongly influenced by solvents and the substituents; for instance, the 3-methyl- and 4,5-dimethoxy-substituted IBXs, **21** and **22**, decomposed under both aqueous and nonaqueous oxidation conditions.[27]

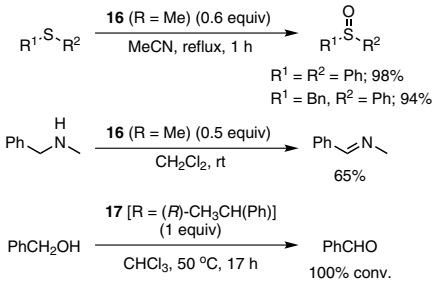
We then turned our attention to IBS (**1**) for the purpose of developing an even more powerful catalyst for alcohol oxidation. Our reasoning was that the Lewis acidity of the iodine(V) atom in **1** would be higher than that in **2** due to the strong electron-withdrawing sulfonate group in **1**.[27,28] Although **1** is not stable enough to isolate in pure form and examine in stoichiometric reactions, it can be prepared in situ in the presence of the alcohol substrate from **15**, **15**•Na, or **15**•K and Oxone®. We compared the catalytic efficiencies of in situ generated **1** and **2** in the oxidation of 5-nonanol (**Figure 3**, **1** in red and **2** in blue).[27] In nonaqueous nitromethane and acetonitrile, **1** was superior to **2** (red square and circle vs blue open-square and open circle; in nitromethane, TOF ≥ 50 h^{-1} vs 16 h^{-1}, respectively). In sharp contrast, **2** was superior to **1** in aqueous media (red diamond vs blue open diamond).



Scheme 11. Zhdankin's First Reported Synthesis of IBS (**1**). *(Ref 24)*



Scheme 12. Synthesis of Pseudocyclic λ⁵-Iodanes **16** and **17**. *(Ref. 25)*



Scheme 13. Facile Oxidations with IBS Ester **16** and IBS Amide **17**. *(Ref. 25,26)*

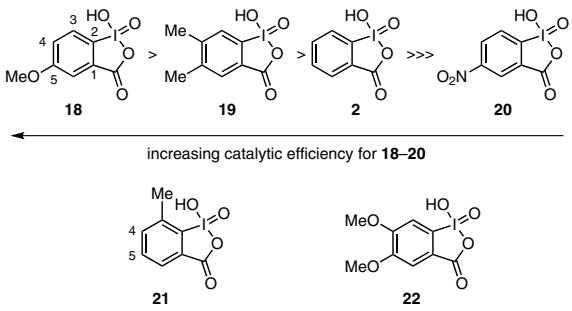


Figure 2. Catalytic Efficiencies of Arene-Substituted IBXs. *(Ref. 27)*

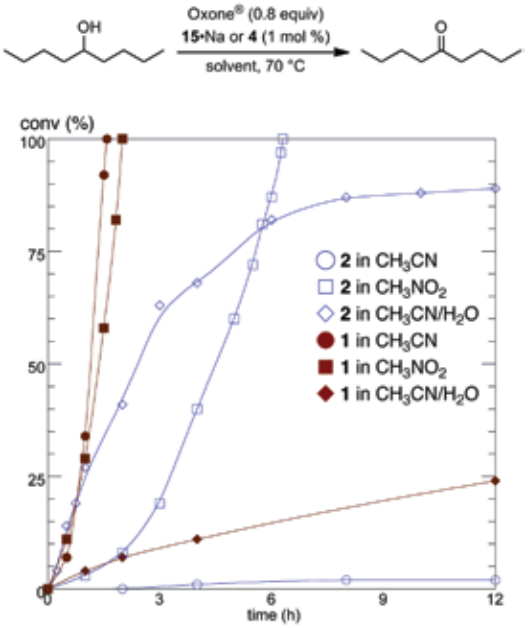


Figure 3. The Catalytic Efficiencies, in Aqueous or Nonaqueous Media, of IBS (**1**) and IBX (**2**) Generated in Situ from **15**•Na and **4**, Respectively. *(Ref. 27)*

Moreover, **1** was sufficiently active in less polar, but more environmentally benign, ethyl acetate; while the **2**-catalyzed oxidation of alcohols was very slow in nonaqueous solvents such as ethyl acetate or acetonitrile. We investigated the substituent effect on the IBS-catalyzed oxidation of alcohols: IBS derivatives substituted with electron-donating groups, as in 5-Me-IBS (**23**) and 4,5-Me_2-IBS (**24**) (**Figure 4**), were superior to **1**, although the differences in the catalytic efficiencies were not large. The oxidation rates of reactions catalyzed by IBS were further accelerated by the use of powdered Oxone® due to its increased surface area. Additionally, vigorous stirring of the heterogeneous reaction mixture is essential for the efficient grinding of Oxone® and efficient alcohol oxidation. In a nonaqueous solvent system, the desired carbonyl products were obtained in nearly pure form by simple filtration of most wastes derived from Oxone® and washing with water to remove catalyst derivatives.[27]

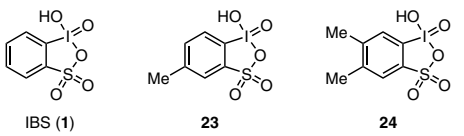
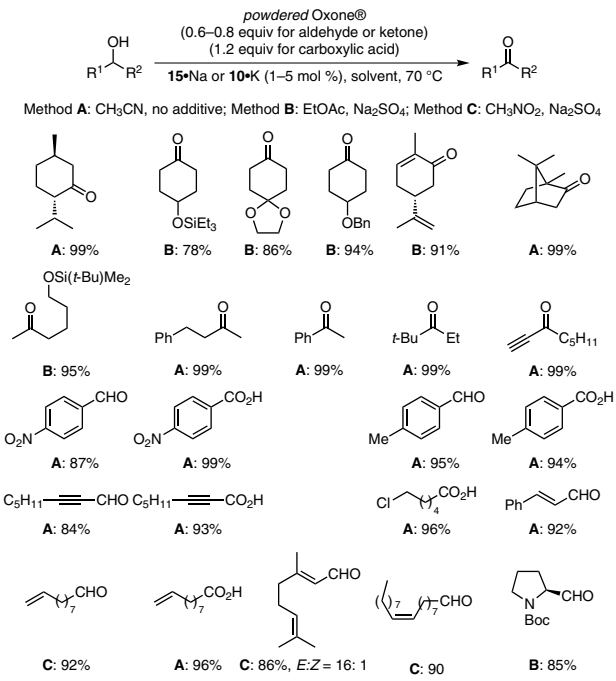


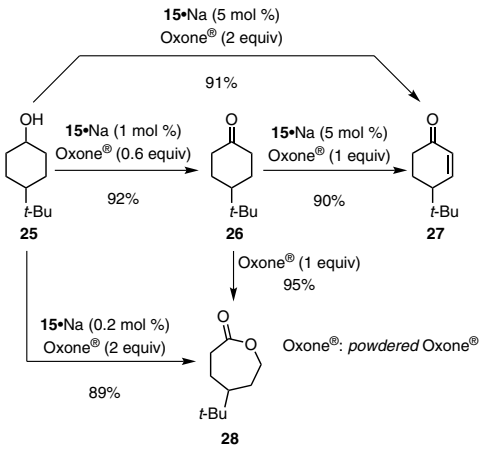
Figure 4. IBS Derivatives Substituted with Electron-Donating Groups. *(Ref. 27)*



eq 9 *(Ref. 27)*

Structurally diverse primary and secondary alcohols were oxidized with **1** or **23** under optimized conditions (**eq 9**).[27] Not only primary, α,β-unsaturated alcohols—such as allylic, propargylic, and benzylic alcohols—but also aliphatic alcohols were selectively oxidized to the corresponding aldehydes and carboxylic acids in excellent yields by controlling the amount of Oxone® added in the presence of **15**•Na or **10**•K. In particular, Methods **B** and **C** were effective for the selective oxidation of acid-sensitive alcohols and primary aliphatic alcohols to the corresponding aldehydes, respectively. This protocol was also applied to the chemoselective oxidation of alcohols bearing several functional or protective groups such as silyloxy, benzyloxy, ketal, alkenyl, alkynyl, and halo groups (see eq 9).[27]

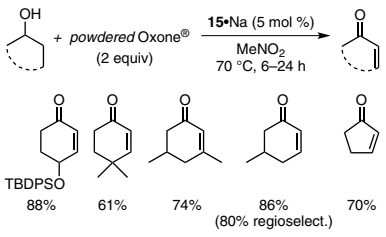
In 2000, Nicolaou and co-workers reported the direct oxidative dehydrogenation, via a single-electron-transfer (SET) mechanism, of saturated alcohols and carbonyl compounds by using stoichiometric amounts of IBX (**2**) in DMSO.[29,30] During the course of our research on the oxidation of cycloalkanols, we found that the selective oxidation of 4-*tert*-butylcyclohexanol (**25**) to 4-*tert*-butylcyclohexanone (**26**) and the subsequent oxidation of **26** to 4-*tert*-butyl-2-cyclohexenone (**27**) and 5-*tert*-butyl-2-oxepanone (**28**) proceeded in excellent yields by controlling the amounts of **15**•Na and Oxone® (**Scheme 14**).[27] Five- and six-membered cycloalkanols were transformed into the corresponding enones in good yields (**eq 10**).[27]



Scheme 14. The IBS-Catalyzed Selective Oxidation of **25** to **26** or **27**. *(Ref. 27)*

3.3. Large-Scale Oxidations

The selective oxidation of primary alcohols to the corresponding aldehydes or carboxylic acids would be a powerful tool in organic synthesis. The transition-metal- or nitroxyl-radical-catalyzed oxidation of alcohols to ketones or aldehydes has attracted a lot of attention because aqueous H_2O_2 or gaseous O_2 can be used as a stoichiometric oxidant.[1] However, it is technically difficult to control the amount of gaseous O_2 added as an oxidant. Moreover, while aqueous H_2O_2 and gaseous O_2 are often concentrated under evaporation and high pressure, respectively, to increase their reactivity, such treatments are dangerous because these materials can be explosive. Although aqueous H_2O_2 and gaseous O_2 are more atom-economical than Oxone®, the latter offers several advantages for selective large-scale oxidations such as stability, simple handling, controllable addition, and nontoxic nature.



eq 10 *(Ref. 27)*

4-Bromobenzyl alcohol (6 g) was selectively oxidized to the corresponding aldehyde and carboxylic acid in excellent yield by controlling the amount of Oxone® added in the presence of **10**•K (1 mol %): 0.65 equiv was used for selective oxidation to the aldehyde, while 1.3 equiv was employed for oxidation to 4-bromobenzoic acid (**eq 11**).[31]

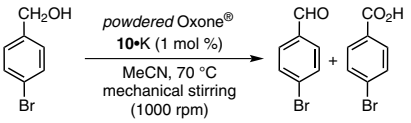
3.4. Application to the Oxidative Rearrangement of Tertiary Allylic Alcohols

The oxidative rearrangement of tertiary allylic alcohols to β-disubstituted α,β-unsaturated ketones or aldehydes using oxochromium(VI)-based reagents (Collins reagent, PCC, PDC) has been widely used in synthetic organic chemistry.[32] In 2004, Iwabuchi and co-workers reported that IBX (**2**) could be used instead of hazardous Cr(VI) for the oxidative rearrangement of tertiary allylic alcohols.[33] In 2008, the same research group reported that TEMPO-derived oxoammonium salts ($TEMPO^+ BF_4^-$ and $TEMPO^+ SbF_6^-$) were more effective as stoichiometric reagents for this transformation of acyclic tertiary allylic alcohols in acetonitrile.[34] In that same year, Iwabuchi[35] and Vatèle[36] independently reported the first *catalytic* oxidative rearrangement of tertiary allylic alcohols. Iwabuchi's group utilized catalytic amounts of TEMPO with $NaIO_4$–SiO_2 as co-oxidant in dichloromethane to convert several cyclic and acyclic tertiary allylic alcohols into the corresponding enones in good yields.[35] In contrast, Vatèle developed a Lewis acid [$Bi(OTf)_3$ or Re_2O_7] promoted oxidative rearrangement using catalytic amounts of TEMPO with PhIO (**9**) as co-oxidant.[36] As part of our continuing interest in the use of IBS/Oxone® catalytic oxidation systems in organic synthesis, we reported the development of an oxidative rearrangement of tertiary allylic alcohols to enones with powdered Oxone® promoted by catalytic quantities of **10**•Na (**Scheme 15**).[37] 5-Me-IBS (**23**) is generated in situ and serves as the actual catalyst for the oxidation. Interestingly, **1** was less effective than **23** as catalyst in this case. The addition of inorganic bases, such as K_2CO_3, and a phase-transfer catalyst, such as tetra-*n*-butylammonium hydrogen sulfate [$(n\text{-Bu})_4NHSO_4$], extended the substrate scope for oxidative rearrangement reactions (see Scheme 15). Cyclic and acyclic substrates gave the corresponding enones in moderate to high yields. Notably, sterically demanding steroid alcohol **29** was converted into the desired enone **30** in 69% yield (see Scheme 15). In contrast, Iwabuchi's group reported that **29** was rearranged to allylic alcohol **31**, which was not oxidized to **30** under TEMPO-mediated conditions, due to considerable steric hindrance.[34,35] Our protocol should be recognized as a practical method for the oxidative rearrangement of tertiary alcohols, since it does not require any toxic, dangerous, or expensive reagents.[37]

3.5. Theoretical Calculations and Reaction Mechanism

The oxidation of alcohols with IBS consists of two steps, which are essentially identical to those of the IBX oxidation proposed by Santagostino:[38] a fast pre-equilibrium step and a rate-determining disproportionation step. The catalytic cycle of **1**, which is prepared in situ from **15**, can be accomplished by regenerating **1** through the oxidation of **15** with Oxone® (**Scheme 16**).

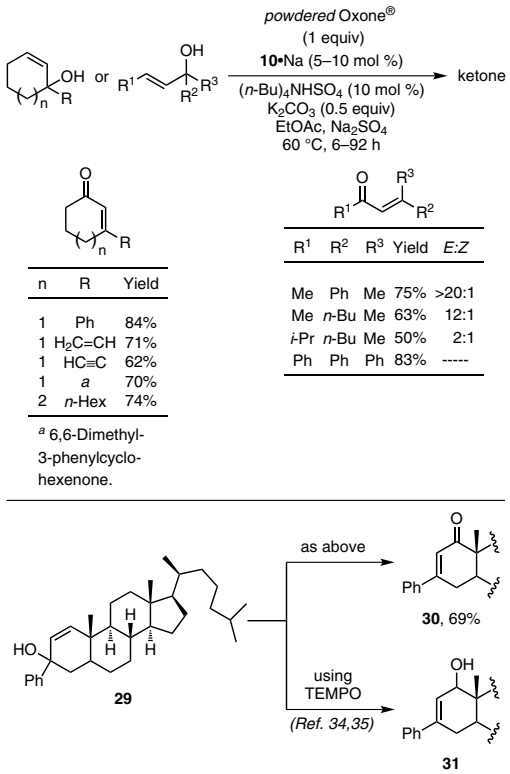
Based on the theoretical study by Su and Goddard on the oxidation of alcohols with IBX (**2**),[39] we also determined that the twisting of alkoxyperiodinanes **32-A** to the intermediates **32-B** was the rate-limiting step (**Scheme 17**).[27] Interestingly, **32** has a much lower twisting barrier than **33** (**33-A**→**33-B**: 10.3 kcal/mol vs **32-A**→**32-B**: 6.5 kcal/mol).[27] The I(V)–OCO and I(V)–OSO_2 distances in **33-A** and **32-A** are correlated with the twisting barriers: 2.252 Å for **32-A** > 2.193 Å for **33-A**. Based



0.65 equiv	5 h	91%	≤5%
1.3 equiv	9 h[a]	≤2%	93%

[a] After 4 h, H_2O (100 mL) was added.

eq 11 *(Ref. 31)*

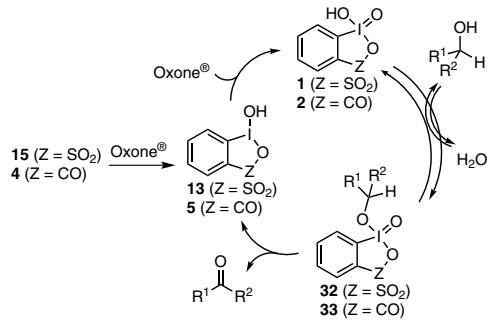


n	R	Yield
1	Ph	84%
1	H_2C=CH	71%
1	HC≡C	62%
1	*a*	70%
2	*n*-Hex	74%

[a] 6,6-Dimethyl-3-phenylcyclohexenone.

R^1	R^2	R^3	Yield	*E:Z*
Me	Ph	Me	75%	>20:1
Me	*n*-Bu	Me	63%	12:1
i-Pr	*n*-Bu	Me	50%	2:1
Ph	Ph	Ph	83%	-----

Scheme 15. IBS-Catalyzed Oxidative Rearrangement of Tertiary Allylic Alcohols. *(Ref. 37)*



Scheme 16. Proposed Catalytic Cycle for IBS- and IBX-Catalyzed Oxidations. *(Ref. 27)*

on theoretical calculations, we assumed that the relatively ionic character of the intramolecular hypervalent iodine–OSO_2 bond of IBS might lower the twisting barrier of the alkoxyperiodinane intermediate **32-A**. We are able to confirm that Goddard's *hypervalent twisting* would be the rate-determining step for the *stoichiometric oxidation* of alcohols with not only IBX (**2**) but also IBS (**1**). In contrast, it was reasonable to assume that the rate-determining step of *I(V)-catalyzed oxidations* might be the regeneration of I(V) species because: (i) the catalytic oxidation of alcohols was accelerated with powdered Oxone®, and (ii) control experiments indicated that the 5-methyl substituent of 5-Me-IBX had no influence on the oxidation of alcohols, while the 5-methyl substituent of 5-Me-IBS (**23**) accelerated the oxidation from I(III) to I(V).[27]

4. Conclusion

Over the past two decades, IBX (**2**) and other hypervalent iodine compounds have received considerable attention because of their mild and chemoselective oxidizing properties and because they are environmentally benign in contrast to the well-known but highly toxic heavy metal oxidants.[2] However, the stoichiometric use of **2** has been limited because it is potentially shock-sensitive and weakly soluble in common organic solvents.[2] Over the past five years, several research groups have reported alcohol oxidation reactions catalyzed by in situ generated IBX or related hypervalent iodines. These developments have been highlighted in this review.[9–19] Although IBS (**1**) is not stable enough to isolate in pure form and examine in stoichiometric reactions, we have reported that IBS's **1** and **23** can be prepared in situ from pre-IBS **15**•Na and **10**•K and Oxone® in the presence of an alcohol substrate. We have also disclosed that **1** and **23** show greater catalytic activity than IBX (**2**) under nonaqueous conditions.[27] Consequently, we have developed a highly efficient and chemoselective oxidation of various alcohols to carbonyl compounds with powdered Oxone® in the presence of catalytic amounts of IBS. Our findings could lead to new possibilities in hypervalent-iodine-catalyzed oxidative transformations.

5. Acknowledgement

We gratefully acknowledge support from Nissan Chemical Industries, Ltd. Financial support for this project was partially provided by JSPS.KAKENHI (20245022), the GSC Project of METI, the Toray Science Foundation, Kyowa Hakko Chemical Co., Ltd. (The 1st Seeds Contest), and the Global COE Program of MEXT.

6. References and Notes

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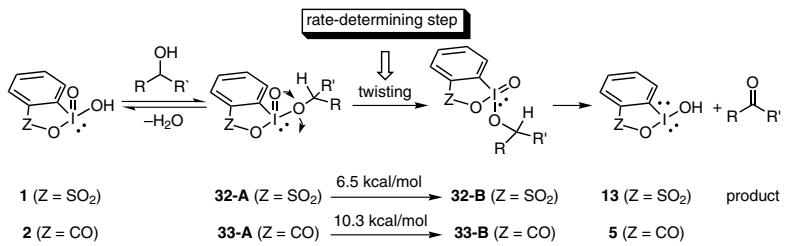

Scheme 17. Goddard's Hypervalent Twisting Mechanism of I(V)-Mediated Alcohol Oxidation. *(Ref. 27,39)*

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Keywords: λ^5-Iodanes; IBS; Oxone®; alcohol oxidation; chemoselective oxidation; catalytic oxidation.

About the Authors

Muhammet Uyanik was born in 1981 in Samsun, Turkey, and received his Ph.D. degree in 2007 from Nagoya University under the direction of Professor Kazuaki Ishihara. He was appointed Assistant Professor at Nagoya University in 2007. In 2009, Dr. Uyanik received the Shionogi Award in Synthetic Organic Chemistry, Japan, and, in 2010, an Incentive Award for Young Scientists from the Tokai Branch of The Society of Synthetic Organic Chemistry, Japan. His research interests include oxidation reactions and asymmetric catalysis.

Kazuaki Ishihara was born in 1963 in Aichi, Japan, and received his Ph.D. degree in 1991 from Nagoya University under the direction of Professor Hisashi Yamamoto. He had the opportunity to work under the direction of Professor Clayton H. Heathcock at the University of California, Berkeley, as a visiting graduate student for three months in 1988. From 1989 to 1991, he was a Japan Society for the Promotion of Science (JSPS) Fellow under the Japanese Junior Scientists Program. Beginning in 1991, he spent 15 months carrying out postdoctoral studies with Professor E. J. Corey at Harvard University. In 1992, Dr. Ishihara returned to Japan to join Professor Hisashi Yamamoto's group at Nagoya University as an assistant professor. In 1997, he was promoted to the rank of associate professor and, in 2002, he was appointed to his current position as a full professor at Nagoya University. Dr. Ishihara received the Inoue Research Award for Young Scientists (1994); the Chemical Society of Japan Award for Young Chemists (1996); the Thieme Chemistry Journal Award (2001); the Green and Sustainable Chemistry Award from the Ministry of Education, Culture, Sports, Science and Technology (2003); the JSPS Prize (2005); the BCSJ Award (2005); the International Conference on Cutting-Edge Organic Chemistry in Asia Lectureship Award (2006); a Japan/UK GSC Symposium Lectureship (2007); the IBM Japan Science Prize (2007); and the Mukaiyama Award (2009). His research interests include asymmetric catalysis, biomimetic catalysis induced by artificial enzymes, dehydrative condensation catalysis towards green and sustainable chemistry, and acid–base combination chemistry.

Boronic Acid Surrogates

The use boronic acids and esters for Suzuki–Miyaura cross-coupling reactions is an invaluable tool for the construction of complex molecules. However, complications associated with the purification and handling of these sensitive organometallic reagents have detracted from the use of this method. To address these issues, two new classes of stable boron anion equivalents have been developed and are now available from Aldrich: MIDA boronates and trifluoroborate salts.

New MIDA Boronates from Aldrich

Benefits of MIDA Boronates

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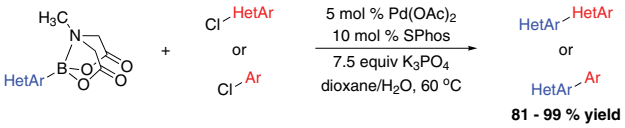
- Good solubility properties and monomeric in nature
- Controlled release for in situ cross-couplings



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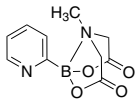
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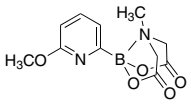
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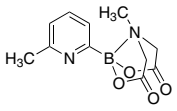
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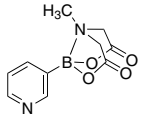
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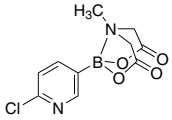
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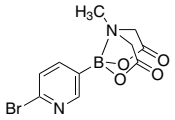
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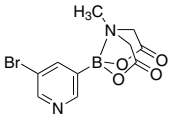
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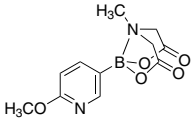
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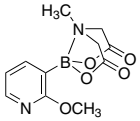
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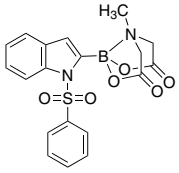
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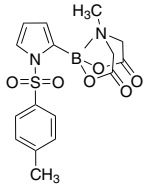
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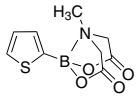
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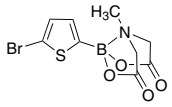
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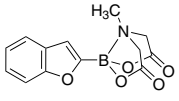
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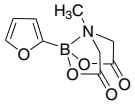
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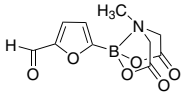
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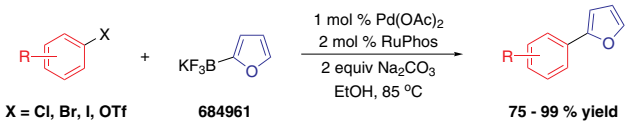
- Tetracoordinated monomeric species
- Less prone to protodeborylation



X = Cl, Br, I, OTf **684961** **75 - 99 % yield**

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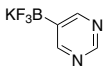

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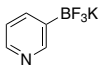

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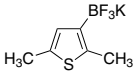

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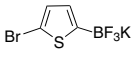

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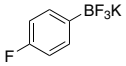

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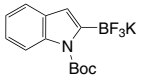

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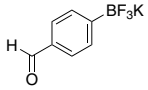

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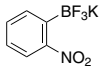

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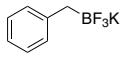

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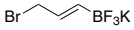

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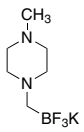

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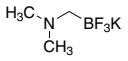

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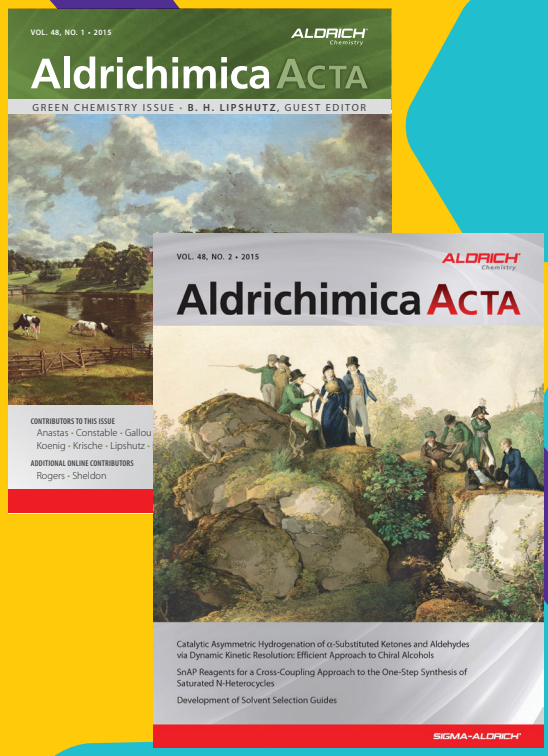

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