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Asymmetric Catalysis Using Chiral, Enantiopure Disulfonimides

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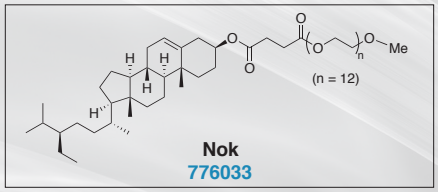
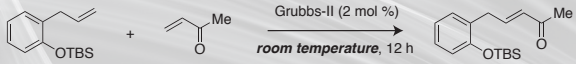



**Nok**
776033

### *Comparable Reactivity*




| surfactant (2 wt % aq.) | conversion (determined by $^1$H NMR) |
|---|---|
| PTS (698717) | 71% |
| TPGS-750-M (733857) | 77% |
| Nok (776033) | 76% |

### *Sustainable Solvent*


| cycle | conversion (determined by $^1$H NMR) |
|---|---|
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| 2 | >99% |
| 3 | >99% |
| 4 | >99% |
| 5 | >99% |
| 6 | >99% |

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|---|---|---|
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## ABOUT OUR COVER

Detail from ***Moonlight on the Yare.*** Photo courtesy National Gallery of Art, Washington, DC.

***Moonlight on the Yare*** (oil on canvas, 98.4 x 125.7 cm) was painted ca. 1816/1817 by John Crome (1768–1821), and is considered one of his most important works. Crome had a limited formal education, and his artistic training consisted of a seven-year apprenticeship with a house and sign painter and a few lessons in London with Sir William Beechey. Save for a few short visits to London and his friendship with Robert Ladbrooke and John Opie, he had little or no contact with the great artists of his time. Crome supplemented his painting and sketching career by lifelong work teaching drawing in schools and to children of the wealthy.

Crome was a founding member and later president of the Norwich School of Painters. While he did not enjoy great or wide fame during his life, his works became much more appreciated after his death, and have earned him a spot among England's prominent landscape painters. As with most of his landscapes, which are noted for their exquisite and realistic rendering of trees and their fidelity to nature, this painting is a romantic depiction of a rustic and tranquil nocturnal scene with a full moon rising into the cloudy sky over the River Yare in the Norwich area where Crome spent all his life. It is reminiscent of landscapes by seventeenth- and eighteenth-century Dutch and English masters,* which Crome greatly admired and copied early in his life as a way to hone his painting skills.

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

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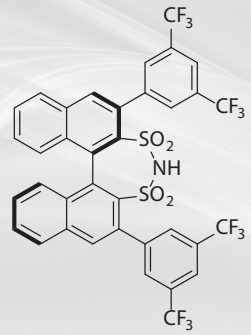


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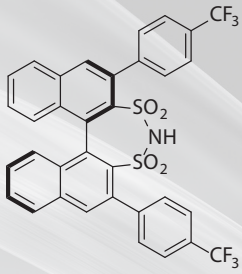


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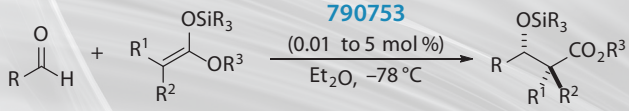


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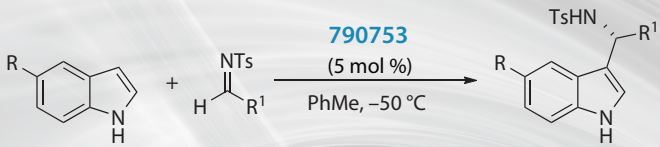


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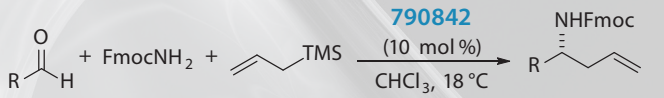


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# Asymmetric Catalysis Using Chiral, Enantiopure Disulfonimides


Mr. M. van Gemmeren


Mr. F. Lay


Prof. Dr. B. List

**Manuel van Gemmeren, Frank Lay, and Benjamin List***

Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1
45470 Mülheim an der Ruhr, Germany
Email: list@mpi-muelheim.mpg.de

**Keywords.** disulfonimide catalysis; asymmetric counteranion-directed catalysis (ACDC); Lewis acid organocatalysis; chiral Brønsted acid catalysis; asymmetric catalysis.

**Abstract.** Disulfonimides have recently emerged as powerful (pre)-catalysts, especially in Lewis acid organocatalysis. Herein, we survey the development of these catalysts, their application in asymmetric catalysis using the concept of asymmetric counteranion-directed catalysis (ACDC), and mechanistic studies that aim to elucidate the catalytic cycle and the intermediates involved.

## Outline



## 1. Introduction

Organocatalysts function by donating or removing electrons or protons, defining four distinct activation modes: (i) Brønsted base catalysis, (ii) Brønsted acid catalysis, (iii) Lewis base catalysis, and (iv) Lewis acid catalysis.[1] While the vast majority of organocatalysts, including amines, carbenes, and phosphines, act as Lewis bases, Brønsted acid and base organocatalysts are also growing strongly in importance and applications. Remarkably though, the one area that has been left almost completely unexplored is that of organic Lewis acid catalysis. This is understandable considering how few organic functional groups are Lewis acidic, and how many inorganic, typically metal-based, asymmetric Lewis acid catalysts have already been described.[2] Despite being widely known, such inorganic Lewis acids are often not very active catalysts for reasons to be discussed later on in this review; in contrast, their organic counterparts have not even been known for a long time. Recently, the concept of Asymmetric Counteranion-Directed Catalysis (ACDC) has evolved into a new, powerful tool for the development of asymmetric transformations in organocatalysis and transition-metal catalysis.[3] The application of this concept to Lewis acid catalysis utilizing disulfonimides (DSIs) as stereoinducing counteranions has enabled asymmetric transformations that circumvent traditional difficulties in Lewis acid catalysis.[4] The development of disulfonimides as Lewis acid organocatalysts and their potential in Brønsted acid catalysis are surveyed in this review.

### *1.1. Inherent Problems and Limitations of Traditional Lewis Acid Catalysis*

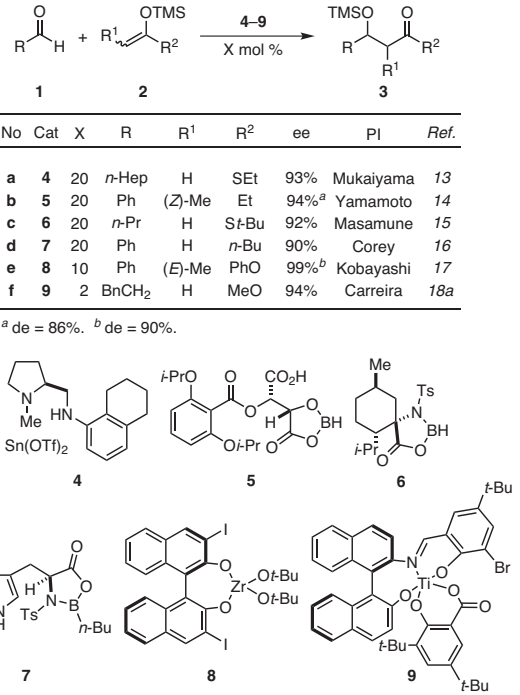
Ever since the description of electron (pair) acceptors and donors as acids and bases by G. N. Lewis[5]—thus expanding the concept of acids and bases beyond processes involving proton transfers—Lewis acid catalysts have found increasing applications for example in such industrially important but nonstereoselective reactions as the Friedel–Crafts[6] and Diels–Alder reactions[7] and the Ziegler–Natta polymerization.[8] In addition to the impact of Lewis acid catalysts on nonstereoselective

processes, the application of metal-based Lewis acids bearing chiral, enantiopure ligands in asymmetric catalysis has also gained considerable attention. In the decades following Yamamoto's pioneering work in the 1980s, a plethora of reactions have been catalyzed enantioselectively by using a large number of different catalyst systems based on metals and metalloids such as boron, aluminum, scandium, copper, tin, and many others.[2] However, a serious drawback of many Lewis acid catalysts in both nonstereoselective and asymmetric catalyses is that large catalyst loadings, sometimes even (super)stoichiometric amounts, are required to effect the transformation. This is especially the case for highly engineered ligands employed in enantioselective methodologies, where this limitation is sufficient to prevent the application of these methods on a large scale. Considering the high electron deficiency of many metal-based Lewis acid catalysts, the frequently observed low turnover numbers (TONs) may seem surprising. However, this can be understood, when the high Lewis basicity of typical products and/or byproducts in Lewis acid catalyzed processes is taken into account. Under the reaction conditions, the catalyst can promote the first reaction step but remains coordinated to the product, thus making subsequent catalyst regeneration rate-determining. The resulting low turnover frequencies (TOFs), together with the often-encountered sensitivity of the ligands or complexes employed to hydrolysis and/or oxidative decomposition, lead to the observed requirement for high catalyst loadings.[9,10] Furthermore, many catalytic systems intended for metal-based asymmetric Lewis acid catalysis encounter problems that are related to the transformation under consideration (vide infra).

### *1.2. Mukaiyama Aldol Reaction: A Showcase Example of the Challenges in Asymmetric Lewis Acid Catalysis*

The Mukaiyama aldol reaction and its asymmetric variants are among the most extensively studied Lewis acid catalyzed processes, and have traditionally been employed to evaluate the state of the art in asymmetric Lewis acid catalysis.[11] In 1974, Mukaiyama et al. discovered that the reaction between an aldehyde or ketone and a silyl enol ether or silyl ketene acetal can be catalyzed by Lewis acids.[12] Subsequently, a variety of metal-based Lewis acids (**5–9**, **eq 1**) were developed for the asymmetric catalysis of the reaction of aldehydes **1** with different silicon-containing nucleophiles, **2**. Some of the most prominent systems come from the groups of Mukaiyama (a),[13] Yamamoto (b),[14] Masamune (c),[15] Corey (d),[16] Kobayashi (e),[17] and Carreira (f).[18a] As an alternative approach, the use of chiral Lewis base catalysts has been developed, for example, by Denmark's group.[19] While these catalytic systems represent significant progress in the development of asymmetric Lewis acid catalysis, some of the typical drawbacks still have not been fully overcome. Importantly, catalyst loadings are still high in all of these cases (usually 20 mol %), with the exception of Carreira's system, which tolerates low catalyst loadings by incorporating a carboxylate group that acts as a so-called silyl shuttle. This shuttle aids the transfer of the silyl group from the reactant nucleophile to the aldolate oxygen. This way, catalyst liberation is accelerated, and a competing non-enantioselective pathway effectively suppressed. This non-enantioselective pathway is inherent in metal-based Lewis acid catalyzed Mukaiyama aldol reactions and is responsible for the strong detrimental effect of lowered catalyst loadings observed in many catalyst systems used in this transformation (**Scheme 1**).[18b,c]

While the mechanism of the Mukaiyama aldol reaction has not been fully elucidated and may vary depending on the reaction conditions, three steps are required in a simplified catalytic cycle: (i) The Lewis acidic metal **12** coordinates aldehyde **1**, giving an activated complex **10**. (ii) This complex is then attacked by silyl ketene acetal **2f** to give an aldolate adduct, **11**. (iii) Release of product **3** and concomitant regeneration of the catalyst conclude the catalytic cycle. However, if this last step is relatively slow, an alternative reaction can occur, whereby aldolate **11** liberates an achiral, highly active silicon Lewis acid catalyst **14**, while the chiral metal complex remains trapped in a catalytically inactive aldolate complex **13**.[18b,c] In order to minimize this non-enantioselective background catalysis, most metal-based chiral Lewis acid systems have required high catalyst loadings. In contrast, Carreira's system[18a] (see eq 1, entry f) was designed to accelerate the final step of the desired catalytic cycle, thus favoring the regeneration of the catalytically active metal species.

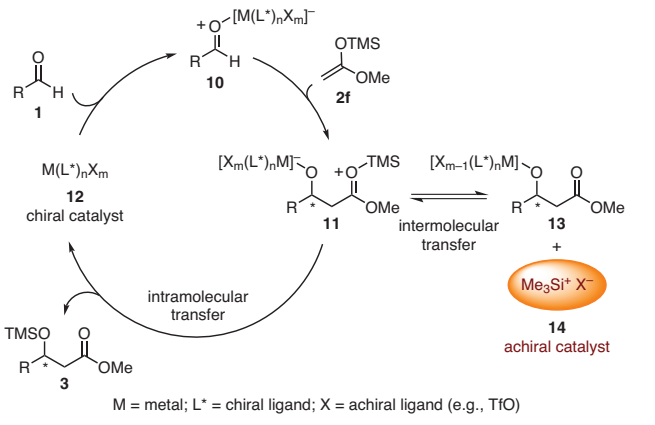



| No | Cat | X | R | $R^1$ | $R^2$ | ee | Pl | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| **a** | **4** | 20 | *n*-Hep | H | SEt | 93% | Mukaiyama | *13* |
| **b** | **5** | 20 | Ph | (*Z*)-Me | Et | 94%[a] | Yamamoto | *14* |
| **c** | **6** | 20 | *n*-Pr | H | S*t*-Bu | 92% | Masamune | *15* |
| **d** | **7** | 20 | Ph | H | *n*-Bu | 90% | Corey | *16* |
| **e** | **8** | 10 | Ph | (*E*)-Me | PhO | 99%[b] | Kobayashi | *17* |
| **f** | **9** | 2 | $BnCH_2$ | H | MeO | 94% | Carreira | *18a* |

[a] de = 86%. [b] de = 90%.




**eq 1**




**Scheme 1.** Competition between Enantioselective and Non-Enantioselective Pathways in the Mukaiyama Aldol Reaction. *(Ref. 18 b,c)*

### 1.3. Asymmetric Counteranion-Directed Catalysis (ACDC) as a Strategy for the Development of Enantioselective Reactions

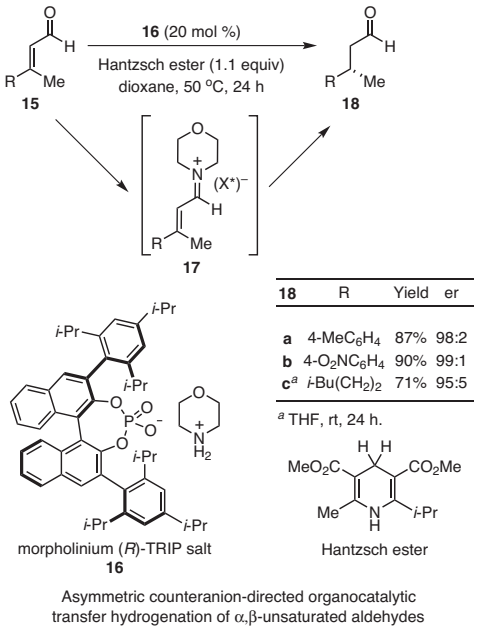
As a new strategy for the design of asymmetric catalysis, "Asymmetric counteranion-directed catalysis refers to the induction of enantioselectivity in a reaction proceeding through a cationic intermediate by means of ion pairing with a chiral, enantiomerically pure anion provided by the catalyst."[3b] Our group coined the term when we provided the proof of concept in 2006 in the enantioselective transfer hydrogenation of α,β-unsaturated aldehydes **15** (**eq 2**).[20] Morpholinium (*R*)-TRIP salt (**16**) activated the aldehyde by converting it to the iminium ion, **17**. The stereoinduction in the reaction of this cationic intermediate originated from the chiral, enantiopure counteranion incorporated in ion pair **17**. High yields and enantioselectivities were achieved for a variety of substrates, including the highest values to date for the asymmetric transfer hydrogenation of citral to (*R*)-citronellal (**18c**). Shortly thereafter, the use of ACDC was expanded to transition-metal catalysis through the pioneering work of Toste's group and ours.[21] Since then, a variety of applications have been developed in both areas of asymmetric catalysis.[3]

## 2. Development of Disulfonimide Catalysts

Since the Mukaiyama aldol reaction and other reactions involving Si-containing nucleophiles are often catalyzed in a non-enantioselective way by a silylium ion, we reasoned that this (normally undesired) pathway could potentially be rendered enantioselective by applying ACDC. A survey of achiral organic catalysts known to promote this reaction revealed silylated sulfonates[22] and disulfonimides[23] as promising lead structures. A comparison of their known Brønsted and Lewis acidities showed that HOTf (p*K*a = –5.9) is a stronger Brønsted acid than $HNTf_2$ (p*K*a = 1.7).[24] The situation is reversed for the Lewis acidities of the corresponding silylated species, where $Me_3SiNTf_2$ is much more acidic than $Me_3SiOTf$.[25] We thus concluded that disulfonimides were the most promising candidates for the development of an asymmetric counteranion-directed Mukaiyama aldol reaction.

The BINOL motif is known to be a privileged scaffold in asymmetric catalysis.[26] We, therefore, decided to develop a new class of disulfonimides based on this backbone. After developing the first synthesis of the 3,3'-unsubstituted motif,[27] we then described the first synthesis of substituted disulfonimide catalysts starting from enantiopure 3,3'-substituted BINOL derivatives (**Scheme 2**, Part (a)).[4] The introduction of sulfur at the 2 and 2' positions of (*R*)-**19** was achieved by conversion to the bis(*O*-aryl thiocarbamate) and subsequent Newman–Kwart rearrangement to the bis(*S*-aryl thiocarbamate) (*R*)-**20**.[28] Oxidative cleavage of the carbamate groups gave the corresponding disulfonic acid,[29] which was activated to the disulfonyl chloride using catalytic amounts of DMF in thionyl chloride. Cyclization of the disulfonyl chloride with ammonia in methanol and a final acid wash after column chromatography led to the desired free acid (*R*)-**21**.[30]

The following year, Lee and co-workers disclosed a synthesis of (*R*)-**21**, whereby the late stage introduction of the 3,3'-diaryl substituents enables the faster generation of a catalyst library (**Scheme 2**, Part (b)).[31] Starting from racemic, unsubstituted BINOL, *rac*-**22**, Lee's group generated bis(*O*-aryl thiocarbamate) *rac*-**23** in a manner similar to the conversion of (*R*)-**19** to (*R*)-**20**. Cleavage of *rac*-**23** with $LiAlH_4$, followed by oxidation with $Me_3SiCl$ and $KNO_3$ gave the disulfonyl chloride in higher yields than a direct oxidation of *rac*-**23** with *N*-chlorosuccinimide, in analogy to the results reported by Nishiguchi and co-workers.[32] The disulfonyl chloride was cyclized using (*S*)-(–)-α-methylbenzylamine to give the two chromatographically separable diastereomers, (*R*,*S*)- and (*S*,*S*)-**24**, in 41% and 47%, respectively. Hydrogenative cleavage of the methylbenzyl group in (*R*,*S*)-**24** gave the unsubstituted (*R*)-disulfonimide enantiomer, which was doubly *ortho*-metallated and reacted with molecular iodine to give the corresponding 3,3'-diiodinated disulfonimide**.** Cross-coupling of the latter with

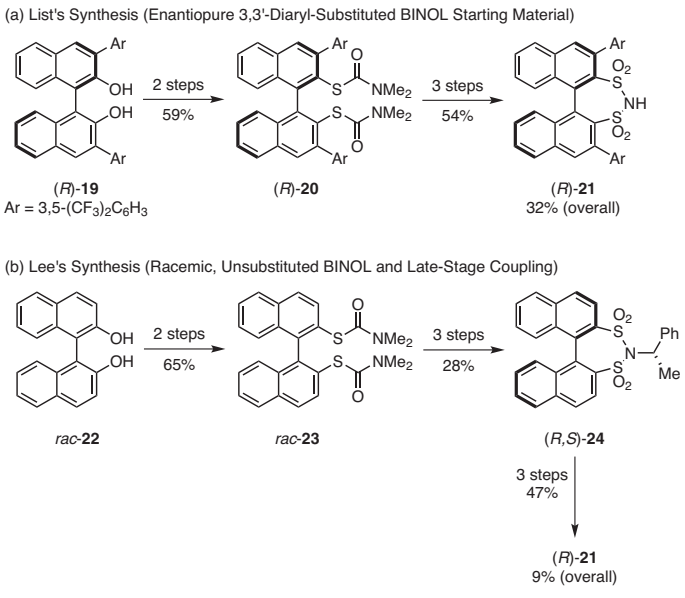



| 18 | R | Yield | er |
|---|---|---|---|
| **a** | 4-$MeC_6H_4$ | 87% | 98:2 |
| **b** | 4-$O_2NC_6H_4$ | 90% | 99:1 |
| **c**[a] | *i*-Bu$(CH_2)_2$ | 71% | 95:5 |

[a] THF, rt, 24 h.

Asymmetric counteranion-directed organocatalytic transfer hydrogenation of α,β-unsaturated aldehydes

**eq 2** *(Ref. 20)*




**Scheme 2.** Synthesis of Disulfonimide *(R)*-**21** by (a) List's Group and (b) Lee and Co-workers. *(Ref. 4,31)*

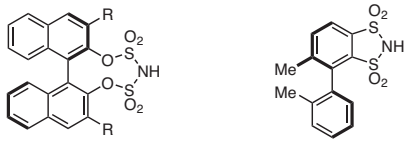
3,5-$(CF_3)_2C_6H_3B(OH)_2$ generated the desired free acid (*R*)-**21**. Importantly, this approach allowed for the large-scale preparation of the 3,3'-diiodinated disulfonimide coupling precursor and differentiation at the last step, where different 3,3'-substituents could be introduced.

In 2010, Berkessel et al. disclosed the synthesis of a series of BINOL-derived catalysts containing a disulfurylimide moiety.[33] These catalysts could be prepared from the corresponding BINOL derivatives in one step, giving the potential catalysts **25** in medium-to-good yields. Dughera, Ghigo, and co-workers have reported the five-step synthesis of **26**,[34] which was obtained in enantiopure form by using a separation of diastereomers analogous to the one reported above by Lee and co-workers. Although representing intriguing variants of the BINOL-derived disulfonimide motif, compounds **25** and **26** have not yet found application in highly stereoselective catalysis (**Figure 1**).[33,34a]

## 3. Disulfonimide-Based Enantioselective Lewis Acid Organocatalysis

### 3.1. Mukaiyama Aldol Reaction

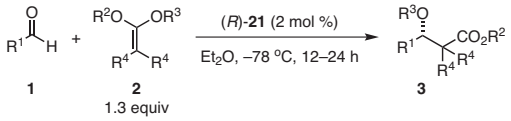
The Mukaiyama aldol reaction is arguably one of the most important chiral Lewis acid catalyzed processes.[11] To date, the development of enantioselective variants remains challenging, and catalytic asymmetric Mukaiyama aldol reactions have traditionally defined the state of the art in Lewis acid catalysis. Hence, we were delighted to discover that different chiral 3,3'-diaryl-substituted BINOL-derived disulfonimides show high catalytic activity in the reaction. After a brief catalyst screening and optimization of the reaction conditions, we found that the $CF_3$-substituted disulfonimide (*R*)-**21** gave the highest enantioselectivities in diethyl ether at −78 °C (**eq 3**).[4] The reaction is well suited for isobutyrate-derived silyl ketene acetals such as **2g**, which reacts with various aromatic aldehydes **1** to give the corresponding aldol products **3g–j** in high yields and enantioselectivities. An α,β-unsaturated aldehyde could also be employed with the same nucleophile, giving the desired product **3j** in good yield and a high enantiomeric ratio. Even the more challenging acetate-derived silyl ketene acetal **2h** was utilized and, upon reaction with different aromatic and α,β-unsaturated aldehydes, it gave rise to the corresponding aldol products, **3k–m**, in excellent yields and high enantioselectivities. In these cases, we also investigated the effect of lowering the catalyst loading on the outcome of the reaction. An amount of only 0.1 mol % turned out to be sufficient to give the desired products in good-to-excellent yields, while maintaining high enantioselectivity. In some cases, even lower catalyst amounts could be used with good results: (*E*)-α-methylcinnamaldehyde-derived aldol product, **3m**, was obtained in 88% yield and an enantiomeric ratio of 88:12 with a remarkably low catalyst loading of 0.01 mol % corresponding to a turnover number of 8,800. Such high turnover numbers are rare in organocatalysis and, to the best of our knowledge, unprecedented in enantioselective Mukaiyama aldol reactions, highlighting the potential of this catalyst type for high-performance asymmetric catalysis. Finally, aliphatic aldehydes were tested and, in the case of pivaldehyde, provided the corresponding aldol product, **3n**, in moderate yield and enantioselectivity.




(*R*)-**25**
R = H, Me, Ar

(*R*)-**26**

**Figure 1**. Related Scaffolds as Potential Catalysts. *(Ref. 33,34a)*




**1** **2** 1.3 equiv **3**

**2g** ($R^2$ = Me, $R^3$ = $Me_3Si$, $R^4$ = Me); **2h** ($R^2$ = *i*-Pr, $R^3$ = *t*-$BuMe_2Si$, $R^4$ = H)

| $R^1$ | 2 | 3 | Yield | er |
|---|---|---|---|---|
| 2-Np | **g** | **g** | 98% | 97:3 |
| 3,5-$Me_2C_6H_3$ | **g** | **h** | 78% | 95:5 |
| 3,5-$(MeO)_2C_6H_3$ | **g** | **i** | 98% | 96:4 |
| (*E*)-PhCH=CH | **g** | **j** | 82% | 97:3 |
| 2-Np | **h** | **k** | 92% | 96:4 |
| 2-Np[a] | **h** | **k** | 70% | 90:10 |
| 3,5-$Me_2C_6H_3$ | **h** | **l** | 93% | 92:8 |
| 3,5-$Me_2C_6H_3$[b] | **h** | **l** | 80% | 90:10 |
| (*E*)-PhCH=C(Me) | **h** | **m** | 95% | 93:7 |
| (*E*)-PhCH=C(Me)[c] | **h** | **m** | 88% | 88:12 |
| *t*-Bu | **h** | **n** | 46% | 91:9 |

[a] (*R*)-**21** (0.1 mol %). [b] (*R*)-**21** (0.1 mol %), –45 °C, 112 h. [c] (*R*)-**21** (0.01 mol %), 0 °C, 72 h.

**eq 3** *(Ref. 4)*

### 3.2. Vinylogous and Bisvinylogous Mukaiyama Aldol Reactions

We have successfully extended the application of our catalytic system to the vinylogous Mukaiyama aldol[12,35] reaction. The term "vinylogy" was introduced over 75 years ago by Fuson and describes the unique ability of π systems to transfer electron density and reactivity along conjugated bonds.[36] Vinylogous Mukaiyama aldol reactions exploit these remote reactivities for the highly γ-selective formation of C–C bonds between carbonyl compounds and dienol silanes, leading to structural subunits commonly found in natural products.[37] Even though several catalytic asymmetric versions had been developed,[38] general and highly stereoselective methods that tolerate a wide range of unactivated substrates were still needed. Disulfonimide catalysts proved to be compatible with a wide range of nucleophiles bearing different silyl groups and ester substituents. The reactions generally gave high γ/α ratios (>50:1), yields, and enantioselectivities. In terms of yield and stereoselectivity, ketene acetal **27** proved to be ideal (**eq 4**).[39] Electron-rich or neutral aromatic aldehydes provided superior results, while electron-poor aldehydes still enabled the reaction to occur with good yields and enantioselectivities. Despite lower yields and enantioselectivities, branched and unbranched aliphatic aldehydes can be employed as well.

Gratifyingly, the disulfonimide system effected the first catalytic, highly enantioselective bisvinylogous Mukaiyama aldol addition (**eq 5**).[39] A 1,6-selective addition of trienol silane **29** to aldehyde **1** directly elongated the carbonyl compound chain by six carbon atoms. As predicted by our DFT calculations,[39] the observed terminal ε-selectivity was inferior to the previously observed γ-selectivity in this type of transformation; nevertheless, significant ε/α ratios were still obtained. The system was particularly suited for aromatic

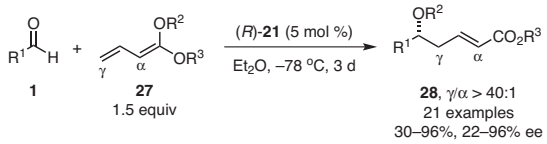
aldehydes and cinnamaldehyde derivatives (**30**). Aliphatic aldehydes could also be used with promising regioselectivity and yield, but poor enantioselectivity. To highlight the synthetic utility of this methodology, deprotected **30** ($R^1$ = 2-Np, $R^2$ = H, $R^3$ = *t*-BuMe$_2$Si, $R^4$ = Me) was converted into an eight-membered-ring lactone in reasonable yield by a straightforward sequence of hydrogenation, ester cleavage, and Yamaguchi lactonization.[39]

### 3.3. Hetero-Diels–Alder Reaction

In spite of all the advances in the development of catalytic systems for the Hetero-Diels–Alder reaction (HDA), the transformation is still largely limited to the originally introduced dienes,[40] and both substituted and functionalized dienes have been highly challenging substrates.[41] Only a few catalytic asymmetric syntheses of 2,6-disubstituted dihydropyrones via HDA have been reported, while the enantioselective synthesis of 2,5,6-trisubstituted dihydropyrones is entirely unknown.[42,43] Substituted 1,3-bis(silyloxy)-1,3-dienes, which are readily synthesized in one step from commercially available and inexpensive 1,3-diketones, are desirable dienes to accomplish these asymmetric HDA reactions. To our surprise, these dienes had not been previously employed in asymmetric catalysis[44]—conceivably due to a competing achiral silylium ion catalyzed background reaction—making them ideal model substrates to use to test our catalytic system. Indeed, we found that the perfluoroisopropyl variant, (*R*)-**32**, of disulfonimide (*R*)-**21** catalyzed a highly enantioselective HDA of aldehydes **1** and substituted 1,3-bis(silyloxy)-1,3-dienes (**31**) (**eq 6**).[45] A variety of 1,3-bis(silyloxy)-1,3-dienes could be employed with 2-naphthaldehyde, delivering the products in good-to-excellent enantioselectivities. Disulfonimide system (*R*)-**32** is also capable of converting tetrasubstituted dienes into 2,5,6-trisubstituted dihydropyrones **33a–c** in high yields and excellent enantioselectivities. Moreover, using the so-called inner-outer-ring 1,3-bis(silyloxy)-1,3-dienes, tricyclic dihydropyrone **33d** was obtained.[46] Again, electron-rich, neutral aromatic, and cinnamaldehyde-derived aldehydes provided excellent results (**33e–g**). Significantly, product **33h**, which is derived from an electron-deficient aromatic aldehyde, was formed in high yield and enantioselectivity by this catalytic system. The utility of our methodology was further demonstrated by the first asymmetric synthesis of a potent aromatase inhibitor.

### 3.4. Hosomi–Sakurai Reaction

In 2012, we expanded the application of enantioselective disulfonimide catalysis to the Hosomi–Sakurai reaction, which is the acid-catalyzed reaction between an aldehyde and an allyltrimethylsilane derivative.[47] We were interested in this reaction, as it furnishes aldehyde allylation products that are highly valuable in synthesis.[48] At the same time, the reaction shares a number of mechanistic features as well as the typical challenges found in metal-based Lewis acid catalyzed Mukaiyama aldol reactions.[22a] Additionally, only a limited number of enantioselective methodologies were known for this reaction at the time.[49] After extensive screening efforts, we succeeded in effecting the catalytic asymmetric methallylation of aldehydes (**eq 7**).[50] A variety of aldehydes, **1**, and allylsilane nucleophiles, **34**, were employed, giving the allylation products **36** in high yields and enantioselectivities. Unfortunately, simple allyltrimethylsilane was beyond the scope of this method, due to the dramatically reduced reactivity of this nucleophile.[51] This limitation also exists in the most successful metal-based systems to date. Apart from catalyst (*R*)-**35**, the optimized reaction conditions also included catalytic amounts of silyl ketene acetal **2g**, which accelerated the silylation of the precatalyst to give the catalytically active species (vide infra).



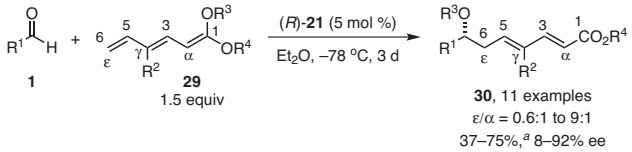

**1** **27** 1.5 equiv

**28**, γ/α > 40:1
21 examples
30–96%, 22–96% ee

Noteworthy Examples ($R^2$ = *t*-BuMe$_2$Si, $R^3$ = Me):

| $R^1$ | Yield | er |
|---|---|---|
| 6-MeO-2-Np | 80% | 98:2 |
| (*E*)-PhCH=C(Me) | 89% | 92:8 |
| 3,5-Me$_2$C$_6$H$_3$ | 81% | 96:4 |

**eq 4** *(Ref. 39)*




**1** **29** 1.5 equiv

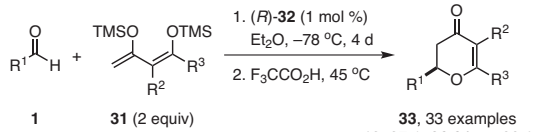
**30**, 11 examples
ε/α = 0.6:1 to 9:1
37–75%,[a] 8–92% ee

Noteworthy Examples ($R^2$ = H, $R^3$ = *t*-BuMe$_2$Si, $R^4$ = Me):

| $R^1$ | Yield[a] | er |
|---|---|---|
| 2-Np | 75% | 95:5 |
| (*E*)-PhCH=C(Me) | 65% | 89:11 |
| 4-Br-3,5-(MeO)$_2$C$_6$H$_2$ | 49% | 91:9 |

[a] Yield is of the isolated ε regioisomer.

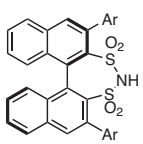
**eq 5** *(Ref. 39)*




**1** **31** (2 equiv)

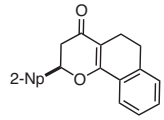
**33**, 33 examples
19–97%, 36:64 to >99:1 er

Noteworthy Examples:



(*R*)-**32**
Ar = 3,5-[(F$_3$C)$_2$CF]$_2$C$_6$H$_3$

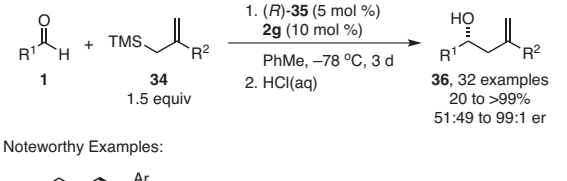
| **33** | $R^1$ | $R^2$ | $R^3$ | Yield | er |
|---|---|---|---|---|---|
| **a** | 2-Np | Me | Me | 95% | 99:1 |
| **b** | 2-Np | Ph | Me | 87% | 98:2 |
| **c** | 2-Np | Cl | Me | 88% | 96:4 |
| **d** | *a* | *a* | a | 95% | >99:1 |
| **e** | 3,5-(MeO$_2$)C$_6$H$_3$ | Me | Me | 97% | 99:1 |
| **f** | 3-MeC$_6$H$_4$ | H | *t*-Bu | 95% | 98:2 |
| **g** | (*Z*)-PhCH=CBr | H | *t*-Bu | 88% | 97:3 |
| **h** | 4-FC$_6$H$_4$ | H | *t*-Bu | 84% | 93.5:6.5 |

[a] **33d** = 

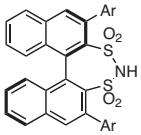

**eq 6** *(Ref. 45)*

### 3.5. Three-Component Aminoallylation of Aldehydes

Chiral enantiopure homoallylic amines are valuable intermediates in the synthesis of natural products and pharmaceutically active compounds.[52] However, their synthesis through direct, asymmetric three-component reactions of aldehydes, carbamates or amines, and allyltrimethylsilanes were unknown prior to our studies. The corresponding homoallylic amines were usually accessed by stereoselective addition reactions to preformed imines, or by other indirect methods.[53] The investigation of potential catalysts, nitrogen sources, and reaction conditions has allowed us to develop a highly enantioselective aminoallylation of aldehydes (**Scheme 3**).[54] The reaction between aldehydes **1**, allyltrimethylsilane (**34**, $R^2$ = H), and 9-fluorenylmethyl carbamate ($FmocNH_2$) was catalyzed by disulfonimide (*R*)-**37** under mild conditions. Remarkably, this catalytic system proved suitable for both aromatic (**38a** and **38b**) and aliphatic (**38c** and **38d**) aldehydes as substrates. The synthetic utility of this methodology was further highlighted by converting product **38b** into the corresponding β-amino acid derivative by oxidative cleavage of the double bond. In contrast to the previously discussed reactions, one equivalent of water is released in the catalytic cycle of this three-component reaction. Since silylium ion equivalents are highly sensitive to water, the differentiation between a Brønsted acid catalyzed pathway and a Lewis acid catalyzed one is not as straightforward as before.




Noteworthy Examples:

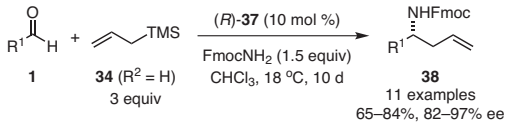


(*R*)-**35**
Ar = 3,5-$(O_2N)_2$-4-$MeC_6H_2$

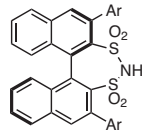
| 36 | $R^1$ | $R^2$ | Yield | er |
|---|---|---|---|---|
| **a** | 3,5-$Me_2C_6H_3$ | Me | 96% | 98:2 |
| **b** | 1-Np | Me | 93% | 96.5:3.5 |
| **c** | 2-Np | *n*-Hep | 97% | 97:3 |
| **d** | Ph | 4-$MeC_6H_4$ | 95% | 93.5:6.5 |

**eq 7** *(Ref. 50)*

(a) Three-Component Aminoallylation of Aldehydes




Noteworthy Examples:

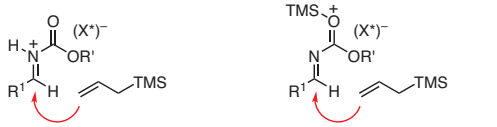


(*R*)-**37**
Ar = 4-$F_3CC_6H_4$

| 38 | $R^1$ | Yield | er |
|---|---|---|---|
| **a** | 4-MeO-3,5-$Me_2C_6H_2$ | 84% | 92:8 |
| **b** | 2-Np | 80% | 96:4 |
| **c** | $BnCH_2$[a] | 71% | 96:4 |
| **d** | *i*-Bu[b] | 83% | 92.5:7.5 |

[a] $TMSCH_2CH{=}CH_2$ (6 equiv), $FmocNH_2$ (3 equiv). [b] $TMSCH_2CH{=}CH_2$ (6 equiv), reaction time = 12 days.

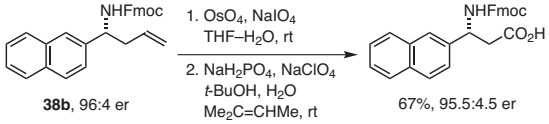
(b) Possible Pathways (R' = 9-fluorenyl-$CH_2$):



**Brønsted acid catalysis**
(Disulfonimide acts as a Brønsted acid, protonating and activating the in situ generated imine.)

**Lewis acid catalysis**
*(more likely)*
(First, catalyst is silylated in situ by allylsilane; then the silylated catalyst activates the imine by silicon-based Lewis acid catalysis.)

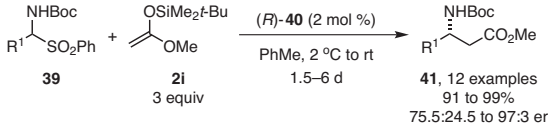
(c) Application to the Synthesis of Fmoc-protected $\beta^3$-Amino Acids



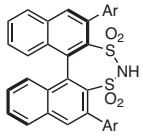

**Scheme 3.** The Catalytic, Asymmetric Three-Component Aminoallylation of Aldehydes. *(Ref. 54)*

### 3.6. Asymmetric Synthesis of $\beta^3$-Amino Esters from N-Boc-Amino Sulfones

The $\beta^3$-amino ester moiety is present in a large number of synthetically valuable intermediates and pharmacologically relevant compounds, and a considerable number of methods have been developed for the synthesis of such molecules.[55] Amongst these methods, the enantioselective Mannich reaction between an ester enolate equivalent and an imine can be considered particularly attractive, as it combines a C–C bond-forming event with the generation of a stereocenter.[56] However, these methods often suffer from the instability of the imine substrates. As these imines are often prepared from amino sulfones by an elimination reaction, we reasoned that it should be possible to combine the desired Mannich reaction with the in situ generation of the imine by using Lewis acid organocatalysis. Indeed, we found that the sterically demanding disulfonimide (*R*)-**40** successfully catalyzes the reaction of α-*N*-Boc-amino sulfones **39** with commercially available silyl ketene acetal **2i** to give $\beta^3$-amino esters **41** in excellent yields and high enantioselectivities (**eq 8**).[57] Aromatic substrates bearing different substitution patterns gave excellent results under the optimized reaction conditions. For example the phenyl-substituted product **41a** was obtained in 99% yield and an enantiomeric ratio of 95:5. Even better results were obtained with an extended aromatic system (**41b**, 97% yield, 97:3 er) or substituted aromatics (**41c**, 99% yield, 96.5:3.5 er). Additionally, the methodology was found to be potentially expandable to substrates bearing aliphatic substituents, which are normally challenging since the corresponding imines are even less stable than their aromatic counterparts. The




Noteworthy Examples:



(*R*)-**40**
Ar = 3,5-[3,5-$(F_3C)_2C_6H_3]_2C_6H_3$

| 41 | $R^1$ | Yield | er |
|---|---|---|---|
| **a** | Ph | 99% | 95:5 |
| **b** | 1-Np | 97% | 97:3 |
| **c** | 3-$MeOC_6H_4$ | 99% | 96.5:3.5 |
| **d** | $BnCH_2$ | 91% | 75.5:24.5 |

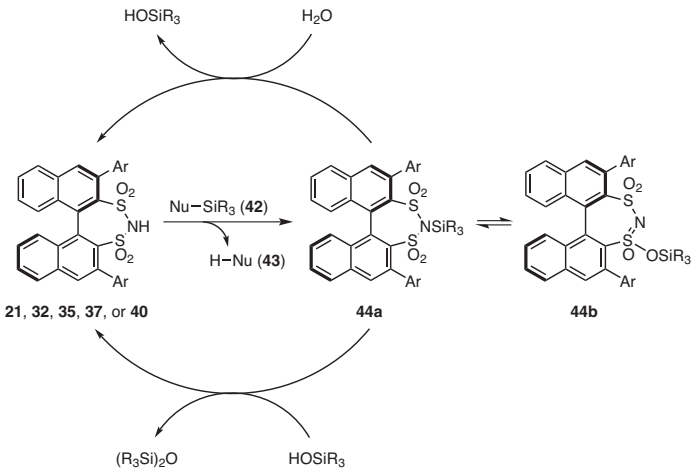
**eq 8** *(Ref. 57)*

aliphatic imine derived product, **41d**, was obtained in high yield and promising enantioselectivity. This constitutes the first example of an asymmetric Mannich reaction of a silyl ketene acetal, which affords *N*-Boc-protected aliphatic $\beta^3$-amino acid derivatives.

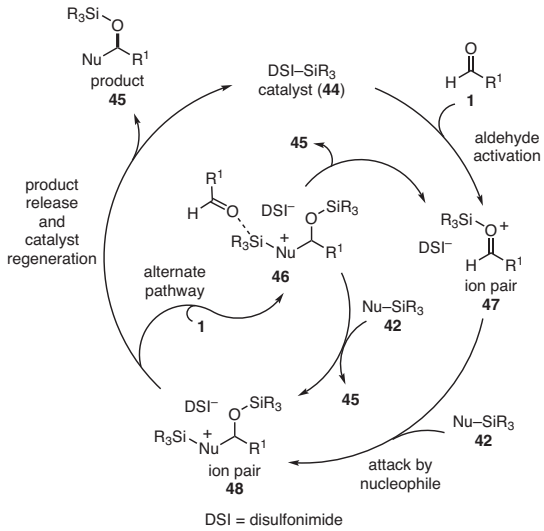
## 4. Mechanistic Aspects of Lewis Acid Organocatalysis Employing Chiral Enantiopure Disulfonimides

Mechanistic studies on the reactions described above, as well as studies performed with analogous achiral catalysts, provide basic insights into the detailed processes of the disulfonimide-catalyzed reactions. At the onset of our studies, we confirmed the unique ability of our chiral disulfonimides, in contrast to other typical Brønsted acids, to catalyze Mukaiyama-style reactions.[4] Whereas a phosphoric acid and an *N*-triflyl phosphoramide derived from 3,3'-diaryl-substituted BINOL, as well as a highly acidic 3,3'-diaryl-substituted binaphthyl-2,2'-disulfonic acid, gave no detectable conversion under the reaction conditions; disulfonimide (*R*)-**21** gave complete conversion and a promising enantioselectivity of 90:10 er under the same unoptimized reaction conditions. Mechanistic studies conducted in our laboratory indicate that the reactions commence by in situ activation of the Brønsted acid precatalyst to its silylated, active form by reaction with the nucleophile employed (**Scheme 4**).[4,58] When silicon-containing nucleophiles **42**, such as the silyl ketene acetals employed in the Mukaiyama aldol reaction, are combined with a disulfonimide catalyst, a rapid protodesilylation of the nucleophile occurs. This generates the corresponding protonated form of the nucleophile, **43**, and leads to the formation of the silylated catalyst, **44**. It had previously been shown that silylated disulfonimides can exist as a mixture of *N*- and *O*-silylated tautomers, which is also what we observe with catalyst **44**.[59] As described above, many Lewis acids suffer from a high sensitivity towards hydrolysis. The catalytically active species **44** also rapidly hydrolyzes, regenerating the disulfonimide precatalyst and a silanol as byproduct. These silanols can also hydrolyze catalyst **44**, resulting in the formation of disilyl ethers. One can thus conclude that one molecule of water leads to the quenching of two equivalents of active catalyst **44**. However, in sharp contrast to metal-based Lewis acid catalysts, the hydrolyzed catalyst (i.e., the disulfonimide) is not lost for catalysis, as it can simply undergo activation again. Thus, employing a slight excess of sacrificial nucleophile, a self-healing catalytic system is obtained. Similar self-healing pathways have also been observed in non-enantioselective catalysis using triflimide.[23b,60] The reduced sensitivity of the disulfonimide catalysts towards water makes their use more practical when compared to metal-based Lewis acid catalysts, as rigorous exclusion of water is not required to obtain high catalytic efficiency and selectivity. In the disulfonimide-catalyzed Hosomi–Sakurai reaction, the addition of catalytic quantities of silyl ketene acetal **2g** improved the efficiency. In light of the required in situ activation of the catalyst and the aforementioned lower nucleophilicity of allyltrimethylsilane derivatives when compared to silyl ketene acetals, this effect can easily be rationalized. The silyl ketene acetal accelerates the generation of active catalyst **44** and removal of potentially present traces of water, thus allowing the desired catalytic cycle to proceed without a significant induction period. This induction period has been observed in the allylation reaction in the absence of this additive.

Once the catalytically active species **44** is present in a dry reaction medium, the main catalytic cycle starts by coordination of the aldehyde or imine substrate with the trialkylsilyl group of the activated disulfonimide (**Scheme 5**).[4] The resulting ion pair, **47**, is attacked by the silylated nucleophile **42**, leading to a new ion pair, **48,** that contains a cationic, disilylated form of the product and the disulfonimide anion. From ion pair **48**, several possible scenarios can be considered. The simplest consists in the liberation of product **45** alongside catalyst regeneration. Alternatively, an additional molecule of aldehyde **1** can be coordinated to **48**, giving complex **46**. This species can liberate the product, regenerating the activated ion pair, **47**, without the free active catalyst **44** as intermediate. Another possibility is that complex **46** can itself react as an activated species and be attacked by nucleophile **42**. Subsequent liberation of the product would also close the catalytic cycle by regenerating ion pair **48**.



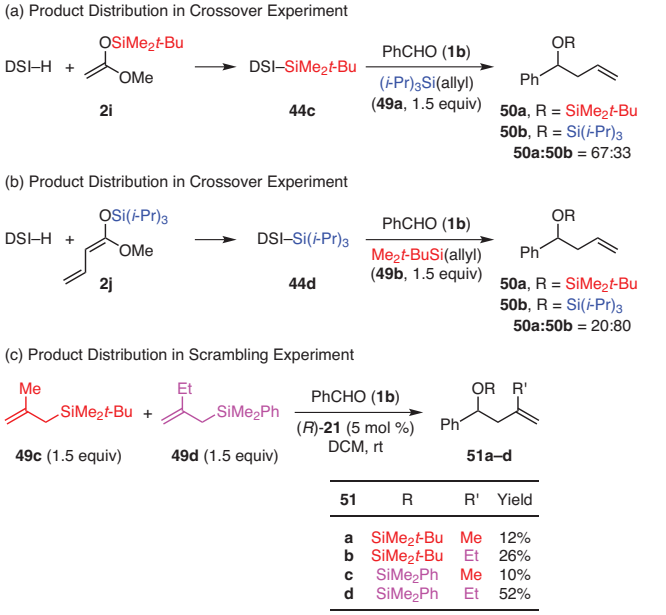

**Scheme 4.** DSI Catalyst Activation and Self-Healing. *(Ref. 4,58,59)*




**Scheme 5.** Generalized Catalytic Cycle for Reactions of Aldehydes with Alkenes Catalyzed by Chiral, Enantiopure Disulfonimides. *(Ref. 4)*

While none of the abovementioned scenarios can be established with certainty, some experimental evidence is available that points to the complex nature of the reaction systems. First, we confirmed that the silylated species **44** is indeed responsible for catalysis, as opposed to traces of the Brønsted acidic form (DSI–H). This was demonstrated by preactivating the catalyst in the presence of the nucleophile, adding the proton scavenger 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), followed by addition of the aldehyde substrate. Since the catalytic system could function equally well in the presence of a proton scavenger, we exclude catalysis by traces of Brønsted acid. Moreover, NMR experiments indicated that the reaction between *stoichiometric* amounts of DSI–H and silyl ketene acetal at room temperature instantaneously provides the silylated species (DSI–$SiR_3$, **44**). This indicates that, in the presence of a large excess of nucleophile as exists in the actual catalytic systems, any traces of Brønsted acid (DSI–H) should directly be reactivated to the Lewis acid (DSI–$SiR_3$, **44**).[4] Further insight into the complexity of the catalytic cycle was obtained in the course of our studies on the Hosomi–Sakurai reaction. Being aware of the studies by Yamamoto's group on the counteranion effects in non-asymmetric Mukaiyama aldol and, to some extent Hosomi–Sakurai, reactions, we were interested in how our system would behave in analogous experiments.[61] We combined stoichiometric amounts of preformed **44c** or **44d** (obtained by titrating DSI–H with silyl ketene acetal **2i** or **2j**) with benzaldehyde (**1b**) and a nucleophile containing a different silyl group, **49a** and **49b,** respectively. In these experiments, we could show that both the silyl group originally on the catalyst and that of the nucleophile can in principle be incorporated in the final product. However, we observed a slight preference for the transfer of the silyl group originally on the catalyst (**Scheme 6**, Parts (a) and (b)).[50]

In a scrambling experiment (Scheme 6, Part (c)), we combined benzaldehyde (**1b**) with two allylsilanes, differing both in their allyl group and their silyl group (**49c** and **49d**), and a catalytic amount of (*R*)-**21**.[50] The fact that the product consisted of a mixture of all four permutations between allyl groups and silyl groups, **51a–d**, also confirmed that the silyl group in the final product is not necessarily the one from the nucleophile that attacks the activated aldehyde. While these findings do not allow for a clear differentiation between the scenarios presented in Scheme 5, they clearly show that a significant dissociation occurs between the disulfonimide anion and the cationic intermediates involved in the catalytic cycle. This detachment supports our interpretation that the disulfonimides act as counteranions and that their reactions are thus examples of ACDC.




| 51 | R | R' | Yield |
|---|---|---|---|
| a | $SiMe_2t$-Bu | Me | 12% |
| b | $SiMe_2t$-Bu | Et | 26% |
| c | $SiMe_2Ph$ | Me | 10% |
| d | $SiMe_2Ph$ | Et | 52% |

**Scheme 6.** Crossover and Scrambling Experiments Using Different Silyl Groups. *(Ref. 50)*

In the case of the three-component aminoallylation of aldehydes, we reconsidered the issue of Lewis vs Brønsted acid catalysis, since one molecule of water is liberated during the condensation of the aldehyde with $H_2NFmoc$, thus leading to hydrolysis of the Lewis acidic catalyst. Even though we could not completely exclude Brønsted acid catalysis in this case, several experimental observations again pointed towards Lewis acid catalysis. Most importantly, when presilylated catalyst and preformed imine were reacted under conditions analogous to the ones of the three-component reaction, almost identical enantioselectivity was observed. Additionally, the fact that the reaction requires three equivalents of the nucleophile corroborates this interpretation: Because each molecule of water consumes two molecules of nucleophile, this causes three equivalents of the nucleophile to be the theoretical minimum required for the three-component aminoallylation reaction.

In the course of our studies on the asymmetric synthesis of $\beta^3$-amino esters using the Mukaiyama–Mannich reaction, we became interested in better understanding the catalytic cycle of this two-step process. We found that elimination of $ArSO_2SiR_3$ from the *N*-Boc amino sulfone to give the proposed imine substrate is rate-limiting, since the reaction of a preformed imine (PhCH=NBoc) under identical conditions proceeded significantly faster albeit with nearly identical selectivity (**Scheme 7**, Part (a)).[57] Another indication that imine formation is the rate-limiting step was obtained from NMR-based kinetic studies. Imine formation (Scheme 7, Part (b)) proceeds through a mechanism consisting of the catalyst activation step, followed by reaction of the silylated catalyst **44** with substrate **39a** to give silylated *N*-Boc amino sulfone **52**. This species was shown to accumulate at the beginning of the reaction and remains present until full completion of the reaction. In contrast, only minute amounts of PhCH=NBoc were present, which indicates that the imine is consumed at a faster rate than it is generated. Once generated, PhCH=NBoc reacts through a mechanism analogous to the reaction of aldehydes (Scheme 7, Part (c)).[57] Silylated catalyst **44** activates PhCH=NBoc to ion pair **53**, which is then attacked by silyl ketene acetal **2i** through a reactive complex **54**. As the silylium ion in **53** and **54** interacts with both the nitrogen and oxygen atoms of the *N*-Boc functionality, two products, **55a** and **55b**, are generated. These two intermediates remain present until hydrolytic workup, which delivers the final product, **41a,** from both intermediates.

## 5. Application of Disulfonimides as Brønsted Acid Catalysts

Although our mechanistic studies indicated that the disulfonimide-catalyzed reactions developed in our group so far are silylium Lewis acid catalyzed, the potential of the disulfonimide anion motif in other areas of ACDC, such as asymmetric Brønsted acid catalysis, was anticipated from the outset of our studies.[4] For example, Lee's group recently reported a disulfonimide-catalyzed Friedel–Crafts alkylation that clearly involves only Brønsted acid catalysis (**eq 9**).[62] Their preliminary studies confirmed that the known necessity to perform an acid wash with phosphoric acid catalysts after column chromatography,[30,63] which had

prompted our group to treat all (pre)catalysts in this way from the outset of our studies, is indeed also required for disulfonimides. When they employed the disulfonimides as obtained from column chromatography, the results were disappointing; in contrast, they obtained satisfactory results by using the acid-washed catalysts. Employing the acid-washed catalyst and optimized reaction conditions, the authors obtained good enantioselectivities and yields of addition products **58**. As this reaction does not involve a silicon-based nucleophile, the issue of competing Lewis and Brønsted acid catalyses does not arise, and the reaction thus represents the first clear-cut application of the disulfonimide catalysts as Brønsted acid catalysts.

## 6. Conclusion and Outlook

Disulfonimides; such as *(R)*-**21**, *(R)*-**32**, *(R)*-**35**, *(R)*-**37**, and *(R)*-**40**; have recently been developed as powerful (pre)catalysts for a variety of reactions. In recent years, advances have been made in the application of disulfonimides as precatalysts for reactions involving silicon-containing nucleophiles; these are then rendered enantioselective based on the concept of Asymmetric Counteranion-Directed Catalysis (ACDC). These disulfonimide catalyst systems offer a general solution to the problems in Lewis acid catalysis, which arise from the non-asymmetric background catalysis by $R_3Si^+$ cations paired with achiral counteranions. In light of the high Brønsted acidity of disulfonimides,[64] which should enable milder and thus more selective reaction conditions, further applications in Brønsted acid catalysis are highly anticipated. Finally, the use of disulfonimide anions as chiral, enantiopure counteranions in transition-metal catalysis remains unexplored to date and seems highly promising, considering the large number of reactions known to be catalyzed by transition metals bearing a triflimide counteranion.[65] Further mechanistic studies of these catalysts are expected to broaden our understanding of Lewis acid catalyzed reactions in general, which are often far from being fully understood, even in the case of metal-based Lewis acid catalysts.

## 7. Acknowledgments

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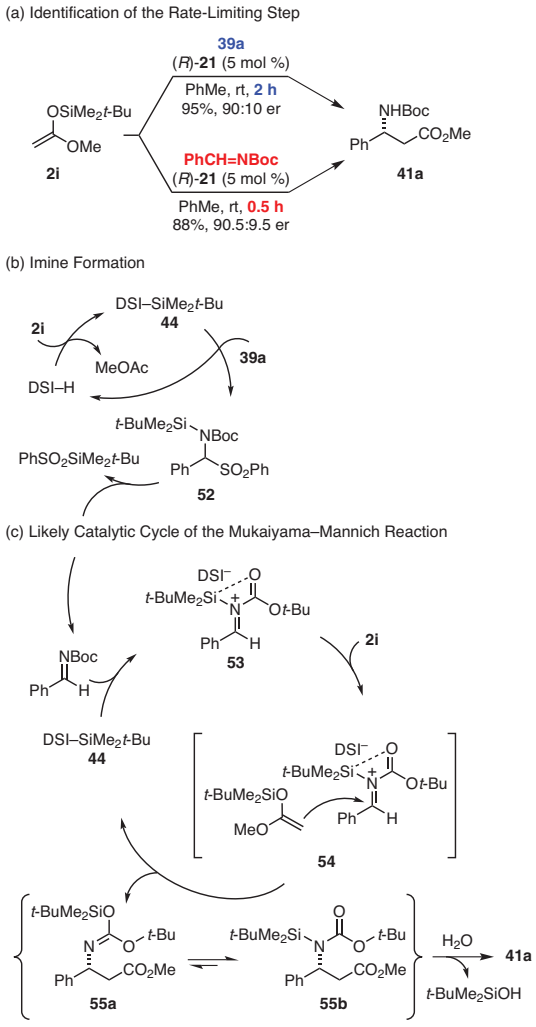
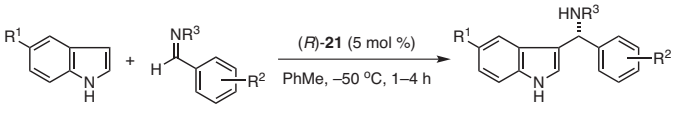



**Scheme 7.** Proposed Mechanism of the Disulfonimide-Catalyzed Asymmetric Mukaiyama–Mannich Reaction. *(Ref. 57)*




Noteworthy Examples ($R^3$ = Ts):

| $R^1$ | $R^2$ | Yield | ee |
|---|---|---|---|
| Me | H | 88% | 95% |
| H | 4-Me | 87% | 92% |
| H | 4-Cl | 65% | 93% |
| H | 3-MeO | 91% | 87% |

**eq 9** *(Ref. 62)*

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## About the Authors

**Manuel van Gemmeren** was born in 1985 in Madrid, Spain. He studied chemistry at the Albert-Ludwigs-Universität Freiburg, where he received in 2010 his diploma in chemistry with distinction for thesis work carried out under the supervision of Prof. Dr. Reinhard Brückner. In early 2011, he joined the group of Prof. Dr. Benjamin List as a Kekulé fellow of the Fonds der Chemischen Industrie, where he is currently working towards his Ph.D. degree by investigating new applications of the ACDC concept in Lewis acid catalysis.

**Frank Lay** was born in 1978 in Breisach am Rhein, Germany. He got a first glimpse of modern chemical research during his apprenticeship as lab technician in the group of the late Prof. Dr. Horst Prinzbach at the Albert-Ludwigs-Universität Freiburg. He then studied chemistry at Eberhard Karls Universität Tübingen, where he received his chemistry diploma in 2006 for research in the field of natural product synthesis under the supervision of Prof. Dr. Martin E. Maier. In early 2007, he began his postgraduate studies and joined the group of Prof. Dr. Benjamin List, where he has established different synthetic routes to enantiopure disulfonimides and explored their first applications in stereoselective catalysis.

**Benjamin List** was born in 1968 in Frankfurt, Germany. He studied undergraduate chemistry at the Freie Universität Berlin, and received his Ph.D. degree in 1997 with Prof. Dr. Johann Mulzer at the University of Frankfurt for developing a new synthetic strategy towards vitamin $B_{12}$. After postdoctoral studies at the Scripps Research Institute, he became Assistant Professor at the same institute in 1999. In 2003, he moved back to Germany to take a position as group leader at the Max-Planck-Institut für Kohlenforschung in Mülheim, and, in 2004, he became Honorary Professor at the University of Cologne. In 2005, he was promoted to Director at the Max-Planck-Institut für Kohlenforschung. His group is mostly interested in developing new strategies for organic synthesis.

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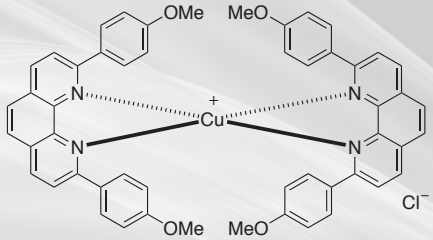


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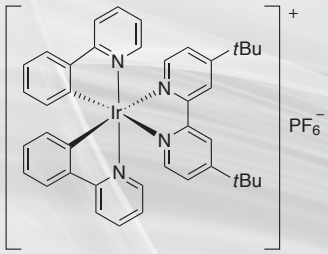


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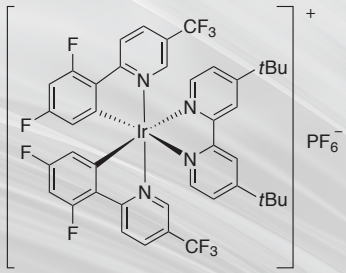


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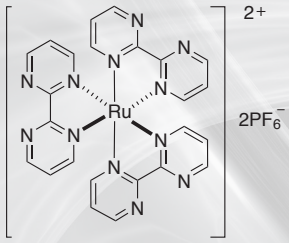


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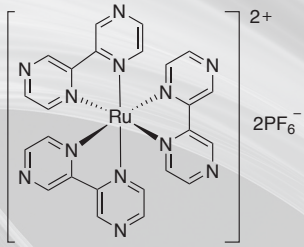


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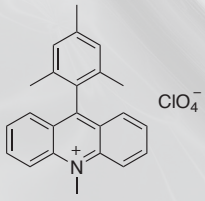


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# Enabling Novel Photoredox Reactivity via Photocatalyst Selection


Dr. J. J. Douglas


Mr. J. D. Nguyen


Dr. K. P. Cole


Prof. C. R. J. Stephenson

**James J. Douglas,[a,b] John D. Nguyen,[a] Kevin P. Cole,[b] and Corey R. J. Stephenson*[,a]**

[a] Department of Chemistry
University of Michigan
930 N. University Avenue
Ann Arbor, MI 48109, USA
Email: crjsteph@umich.edu

[b] Process Design and Development
Lilly Research Laboratories
Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285, USA

**Keywords.** photocatalysis; radical; visible light; reductive quenching; oxidative quenching.

**Abstract.** The following conspectus serves as a personal account of the research in the Stephenson group pertaining to photoredox catalysis. Relevant literature precedent as well as influential and related work from other research groups will also be discussed. We have structured this review according to the two modes of single-electron-transfer quenching (reductive and oxidative quenching) that the excited state of the photocatalyst can undergo and to the important applications that can result from these quenching pathways.

## Outline



## 1. Introduction

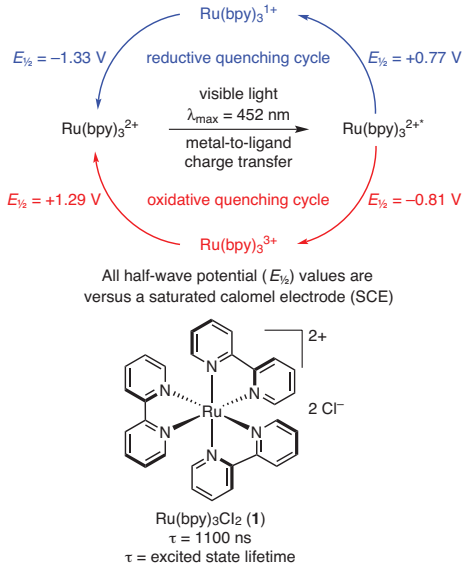
Visible-light-active metal complexes have been extensively studied in numerous contexts since the first reported synthesis of tris(bipyridine)-ruthenium(II) chloride ($Ru(bpy)_3Cl_2$) in 1936.[1] The optical and redox properties[2] of $Ru(bpy)_3Cl_2$ and related complexes have allowed for their use in the development of such fields as photochemistry, electrochemistry, and photocatalysis.[3] For decades, with few exceptions, studies into the visible-light-induced redox properties of these catalysts were conducted by inorganic and physical chemists for applications that included water splitting,[4] photovoltaic cells,[5] and energy storage.[6] Complexes of this type have attracted the attention of synthetic chemists due in large part to the extended excited state lifetime of $Ru(bpy)_3Cl_2$ and related complexes. This property confers the ability to undergo electron- or energy-transfer processes, allowing reactivity from the visible-light-induced excited state.

The same properties that render $Ru(bpy)_3Cl_2$ and related complexes valuable in materials chemistry make them also desirable in organic synthesis. $Ru(bpy)_3Cl_2$ absorbs at 452 nm with a high molar extinction coefficient ($\varepsilon = 14{,}600\ M^{-1}cm^{-1}$),[3a] which has been assigned to a metal–ligand charge transfer (MLCT). The efficiency of the intersystem crossing is such that the quantum yield ($\Phi$) is effectively unity for the $*Ru(bpy)_3^{2+}$ $^3MLCT_1$ state,[7] which has a long lifetime ($\tau$) of 1100 ns. As a result, fluorescence and internal conversion from $^1MLCT_1$ of $*Ru(bpy)_3^{2+}$ are minor deactivation pathways. The efficient energy transfer of visible light and the long excited-state lifetime allow for efficient bimolecular quenching of the excited state and provide access to single-electron redox chemistry.

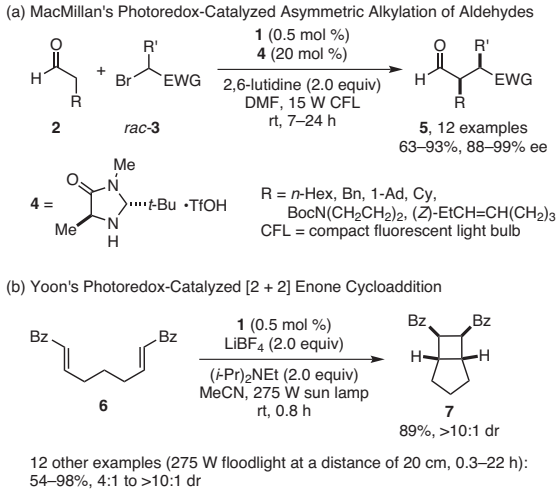
The detailed photochemical processes relating to the excited-state species have been thoroughly investigated, with a synopsis designed for the organic chemist available.[8] In basic terms, upon absorption

of visible light, MLCT generates an excited-state species that is "bipolar" in nature. This species can undergo either a single-electron reduction [reductive quenching; e.g., $Ru(bpy)_3^{2+*} \rightarrow Ru(bpy)_3^{+}$] or a single-electron oxidation [oxidative quenching; e.g., $Ru(bpy)_3^{2+*} \rightarrow Ru(bpy)_3^{3+}$] (**Scheme 1**).[2,3a,8] It is also important to note that the species resulting from either oxidative or reductive quenching [$Ru(bpy)_3^{3+}$ or $Ru(bpy)_3^{+}$] are themselves strong oxidants and reductants, respectively; thus, the possibility of single-electron transfer (SET) from multiple species must be considered.

Pioneering research prior to 2008 by the groups of Deronzier,[9] Oda and Okada,[10] Kellogg,[11] and Fukuzumi[12] identified some of the key reactivities of $Ru(bpy)_3Cl_2$ that could be applied to organic synthesis. They demonstrated the ability of $Ru(bpy)_3Cl_2$ to successfully reduce a variety of C–X bonds, N–O bonds, diazonium salts, and nitroarenes. However, these were often limited to isolated and sporadic examples, with the wider utility of $Ru(bpy)_3Cl_2$ and related complexes predominantly overlooked by the broader synthetic chemistry community.




**Scheme 1.** Photocatalytic Cycles of $Ru(bpy)_3^{2+}$. *(Ref. 2,3a,8)*




**Scheme 2.** Recent Reports on Photoredox Catalysis That Have Reinvigorated Interest in the Field. *(Ref. 13,14)*

Two publications in 2008 initiated continued and directed interest in photoredox catalysis, primarily through novel applications of known modes of reactivity of $Ru(bpy)_3Cl_2$. Nicewicz and MacMillan reported an efficient merger of photoredox and organocatalysis to overcome the barriers associated with traditional two-electron strategies for the asymmetric alkylation of aldehydes. They elegantly harnessed the ability of $Ru(bpy)_3Cl_2$ to reduce C–Br bonds (such as in **3**) to create an electron-deficient radical that may add to a chiral enamine. This transformation proceeded in typically excellent yield and ee for a range of alkyl aldehydes and activated alkyl bromides (**Scheme 2**, Part (a)).[13]

Independently, Yoon's group demonstrated the ability to perform [2 + 2] cycloadditions, traditionally the realm of high-energy UV light, with a photoredox catalyst harnessing visible light. In this methodology, a radical anion is generated from reduction of an activated enone by $Ru(bpy)_3^{+}$, leading to intramolecular cyclization and ultimately the cycloaddition products such as **7** (Scheme 2, Part (b)).[14] Following the preceding disclosures by MacMillan's and Yoon's groups, the synthetic community began to appreciate the wider applicability of $Ru(bpy)_3Cl_2$ and related complexes, leading to an exponential increase in the quantity and diversity of related reports. This renewed focus has transformed photoredox catalysis from a series of independent publications into a definable field of research.

Recent comprehensive reviews[15] and numerous perspective articles[16] on this topic have already appeared and can serve as excellent resource texts. This review will provide a personal account, with other relevant examples, of a portion of the development of photoredox catalysis in the Stephenson group over the last five years. The aim of this narrative approach, organized according to the mode of quenching of the photocatalyst excited state, is to impart the reader with a greater understanding of the journey that led to our current position within the research area. Specifically, how the choice of photocatalyst, and how it is employed within the catalytic cycle, drove the discovery and optimization of a wide range of photoredox-mediated processes.

## 2. Reductive Quenching

### *2.1. Reductive Dehalogenation*

Our endeavors in the field of photoredox catalysis were initiated during investigations aimed at the functionalization of bromopyrroloindolines such as **8**, and their subsequent use in complex-molecule synthesis. We were drawn to the possibility of a radical dehalogenation mediated by $Ru(bpy)_3Cl_2$, initially focusing on the reduction of activated C–Br bonds and reporting a generalized protocol to accompany pioneering initial studies by Fukuzumi and Tanaka,[12,17] Kellogg,[11] and Kern and Sauvage.[18] This method allows the tin-free reductive dehalogenation of a range of activated alkyl chlorides and bromides, and proceeds with typical yields of 70–99%.[19] Importantly, this approach displays excellent chemoselectivity, with aryl and alkenyl bromides and iodides being tolerated without competing reduction. Two complementary sets of reaction conditions (**Scheme 3**, Parts (a) and (b)) were developed for this transformation, with the second set, Part (b), being particularly effective for substrates (such as **10**) that are prone to undergoing competing displacement of the activated halogen with formate.

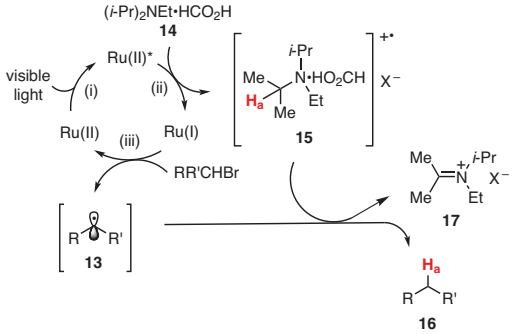
We propose a catalytic cycle initiated by SET from the ammonium formate complex **14** to the excited Ru(II)*. The resulting Ru(I) complex selectively reduces the carbon–halogen bond of the substrate and is oxidized back to the initial Ru(II) photoactive ground state. Deuterium labeling studies showed that the hydrogen atom abstracted by alkyl radical **13** is primarily from one of the methine carbons of **15**, the radical cation of $(i\text{-Pr})_2$NEt (**Scheme 4**).[19]

We had initially chosen $Ru(bpy)_3Cl_2$ ($E_{½}^{II/I} = -1.33$ V vs SCE) as the photocatalyst due to its commercial availability and previously demonstrated versatility. Our somewhat limited experience in the field rendered us initially slow to fully appreciate the number of well described transition-metal photocatalysts, which are, to this date, still mainly used in inorganic chemistry and materials science. Recently, our research group and others have shown how a considered selection of photocatalysts has allowed the rapid expansion of methods that operate via the reductive and oxidative quenching cycles (vide infra).

## 2.2. Intramolecular Radical Additions

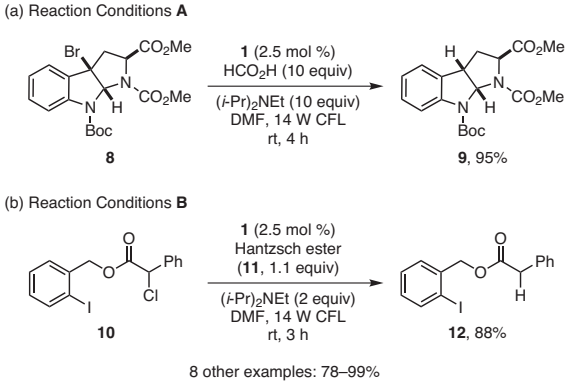
We followed our initial report on the dehalogenation reaction with the disclosure that the radical formed from the carbon–halogen bond reduction could efficiently participate in carbon–carbon bond-forming processes.[20] By employing slightly modified conditions to those of the reductive dehalogenation, a range of bromomalonates (such as **18**) were efficiently reduced and intramolecularly coupled to either indoles or pyrroles in good yields (typically >60%) (**eq 1**).[20] This approach provides an alternative to previous oxidative free-radical cyclizations[21] such as the stoichiometric $Mn(OAc)_3$-mediated oxidative cyclization reported by Kerr and co-workers.[22] Formation of the reductive dehalogenation product, e.g. **20**, from premature hydrogen-atom abstraction by the alkyl radical was minimized by use of $Et_3N$ as the reductive quencher. Other amine quenchers such as DABCO®, $Me_3N$, and $(HOCH_2CH_2)_3N$ were efficient in generating the alkyl radical, but resulted primarily in the formation of reduced starting material **20**. Furthermore, while $Ph_3N$ was completely selective for the desired cyclization product, **19**, it resulted in consistently low conversions (60%), even after prolonged reaction times (>48 h). This is presumably due to triphenylamine's increased oxidation potential, which limits access to the $Ru(bpy)_3^{+}$ reductant, when compared to trialkylamines.

We successfully applied the reaction conditions developed for the intramolecular radical coupling of electron-rich heterocycles to the analogous intramolecular addition to alkynes and alkenes.[23] A range of 5- or 6-exo cyclizations (**Scheme 5**, Part (a)) were realized in good-to-excellent yields (69–100%) through initial reduction of the activated C–Br bond. Consistent with MacMillan's report,[13] we found that the use of inexpensive, commercially available blue LEDs (1 W, $\lambda_{max}$ = 435 nm) greatly accelerated the reaction when $Ru(bpy)_3Cl_2$ was employed as the photocatalyst.[23b] Although this method features milder initiation and greater functional group tolerance than typical radical processes, attempts to further improve the utility of the reaction by expanding the substrate scope to less activated bromides, such as α-bromo esters, typically led only to recovery of starting material. Reasoning that a more strongly reducing photocatalyst was required, we explored $Ir(ppy)_2(dtbbpy)$-$PF_6$ (**24**) ($E_{½}^{III/II} = -1.51$ V vs SCE,[24] compared to $E_{½}^{II/I} = -1.33$ V for $Ru(bpy)_3Cl_2$), and were able to efficiently cyclize α-bromo esters (such as **23**, Scheme 5, Part (b)) and dibrominated cyclopropane substrates.[23] This was our first demonstration that the judicious choice of photocatalyst can allow for altered reactivity and a broader substrate scope.

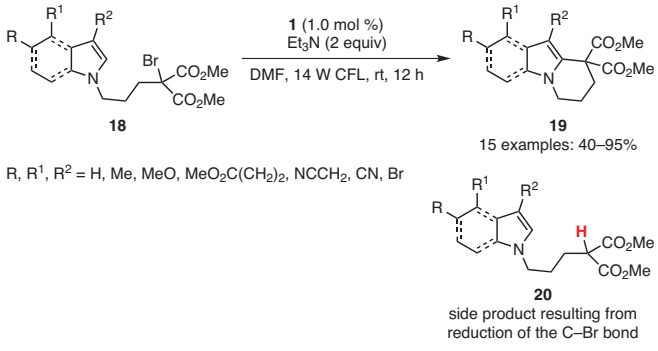



R = alkyl, aryl; R' = aryl, EWG
(i) Light activation of photoactive complex; (ii) single-electron transfer from **14** and reduction of Ru(II)*; (iii) reduction of C–Br bond and re-oxidation of catalyst to the photoactive ground state.

**Scheme 4.** Proposed Catalytic Cycle for the Photoredox-Catalyzed Reductive Dehalogenation. *(Ref. 19)*




**Scheme 3.** Reductive Dehalogenation of Activated Carbon–Halogen Bonds. *(Ref. 19)*



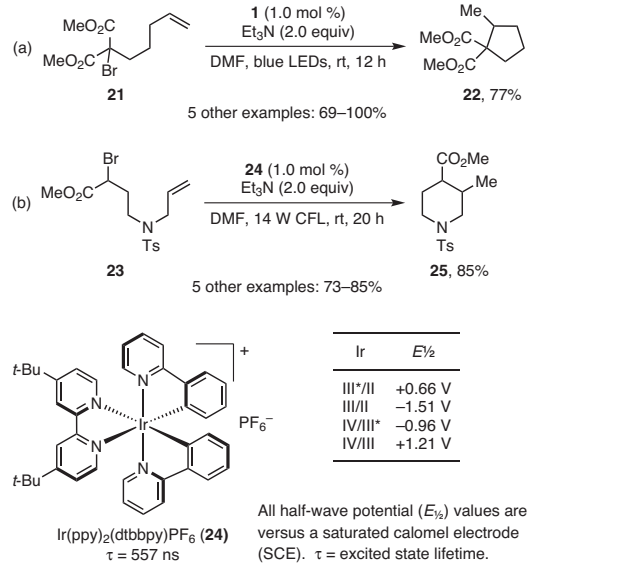

**eq 1** *(Ref. 20)*

### 2.3. Intermolecular Radical Additions

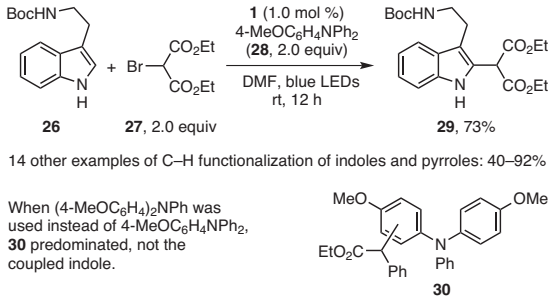
Our attempts to apply this method to intermolecular couplings were consistently hampered by competitive hydrogen-atom abstraction from the trialkylamine by the malonyl radical, forming the reduced malonate. This pathway also leads to further reactive components derived from the amine, such as iminium ions and enamines, that, while detrimental to the desired intermolecular coupling, could be effectively utilized as discrete intermediates in other photochemical transformations (see Section 2.4). We were able to overcome this challenge by using *N*,*N*-diphenyl-4-methoxyaniline (**28**) as a reductive quencher that cannot function as an efficient H-atom donor, showcasing the ability to drive selective reactivity by independently varying the photocatalyst or the quencher. Under the optimized conditions, a range of electron-rich heterocycles, such as Boc-protected tryptamine **26**, were efficiently coupled to diethyl bromomalonate in good-to-excellent yields (typically 60–90%) (**eq 2**).[25] However, significant challenges still remained as this methodology could not be applied to less activated C–Br bonds, such as methyl 2-bromo-2-phenylacetate, where typically only starting material was recovered. In this case, we postulated that charge recombination between the triarylamine radical cation and the Ru(I) outcompetes C–Br bond reduction. Employing a more electron-rich triarylamine [$(4\text{-MeOC}_6H_4)_2$NPh] successfully reactivated the reduction cycle. However, addition to the electron-rich amine, resulting in **30** rather than the desired indole, dominated—highlighting the need for further development of efficient photocatalyst quenchers. Ultimately, the reduction of unactivated carbon–halogen bonds was accomplished by switching the photocatalyst to *fac*-Ir(ppy)$_3$,[3e,26] a strong excited-state reductant ($E_{1/2}^{IV/III*} = -1.73$ V vs SCE), thus eliminating the requirement for an amine quencher (see Section 3.5).

### 2.4. Nucleophilic Addition to Iminium Ions Derived from Tetrahydroisoquinolines

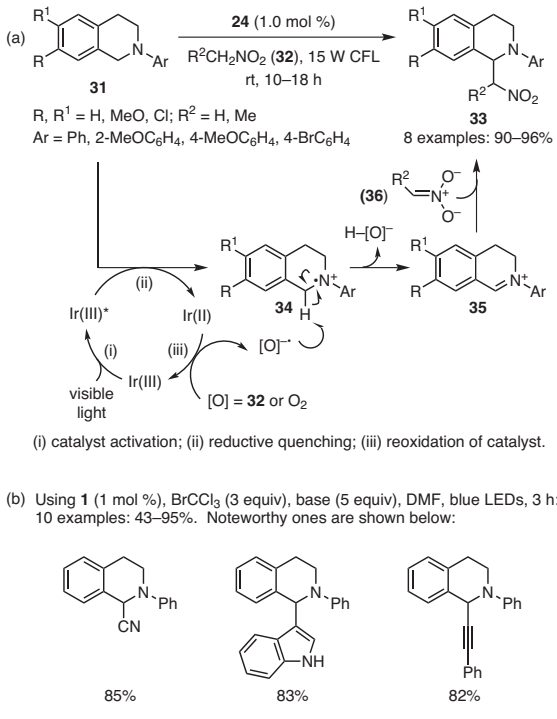
Seeking to exploit the synthetic potential of iminium ions analogous to **17**, which was postulated as a detrimental side product in the debromination methodologies described above, we investigated the competency of such iminium ions as reactive species in the oxidative aza-Henry reaction with nitroalkanes (**Scheme 6**, Part (a)).[27] In this reaction manifold, the excited state of the photocatalyst, **1** or **24**, undergoes reductive quenching with a tetrahydroisoquinoline to generate the radical cation **34** and the reduced catalyst. Photocatalyst turnover is mediated by either adventitious oxygen and/or nitromethane to provide the ground state catalyst and a radical anion, $[O]^{-\bullet}$, that may abstract a H-atom from the amine radical cation, **34**, to form the desired iminium ion, **35**. Addition of the nitromethane-derived nitronate **36** to




**Scheme 5.** Expanding the Substrate Scope of the Intramolecular Radical Cyclization by the Judicious Choice of Photocatalyst. *(Ref. 23)*




**eq 2** *(Ref. 25)*




(b) Using **1** (1 mol %), $BrCCl_3$ (3 equiv), base (5 equiv), DMF, blue LEDs, 3 h: 10 examples: 43–95%. Noteworthy ones are shown below:




**Scheme 6.** Photoredox Catalysis in the Aza-Henry Reaction and Its Subsequent Expansion to Include the Addition of Other Nucleophiles to Iminium Ions. *(Ref. 27,29a)*

this iminium ion forms the observed nitroalkylated product in 90–96% yields, demonstrating that this method is comparable in efficiency to the analogous Cu-mediated process by Li and Li.[28] The general utility of this photoredox approach was subsequently demonstrated by our research group[29] and others[30] by expanding it to include the efficient addition of various nucleophiles such as cyanide, indole, and alkynes (Scheme 6, Part (b)).

### 2.5. Radical Cation Diels–Alder Reactions

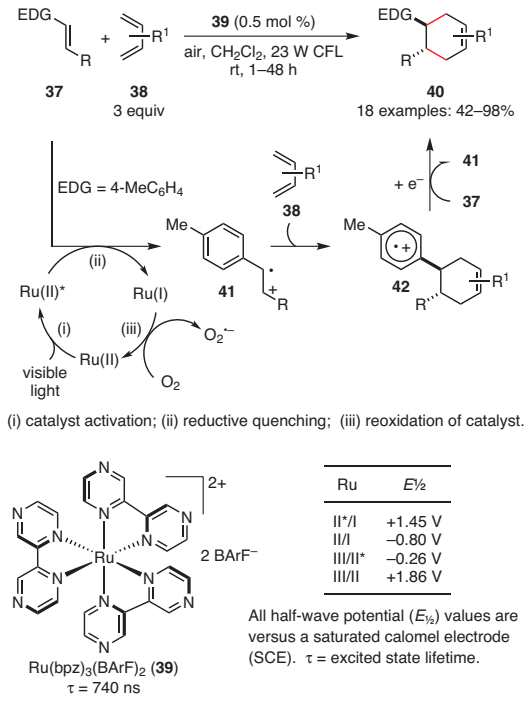
Yoon's research group has also studied the reactivity of tetrahydroisoquinolines under photoredox conditions, albeit in a formal reversal of polarity whereby an α-amino radical adds efficiently to a range of α,β-unsaturated ketones.[31] This report provides two notable conclusions: (i) the reaction is greatly enhanced by Brønsted acids, and (ii) the primary mechanism is through radical propagation rather than photocatalyst turnover. The same group has also made significant contributions to the field by developing a range of visible-light-mediated cycloadditons,[32] perhaps the most striking example being the radical cation Diels–Alder cycloaddition.[33] In this methodology, $Ru(bpz)_3^{2+}$ ($E_{½}^{II*/I}$ = +1.45 V vs SCE)[34] was employed since, unlike $Ru(bpy)_3Cl_2$ ($E_{½}^{II*/I}$ = +0.77 V vs SCE), it can directly oxidize **37** (+1.1 V) to the radical cation, **41**, from its excited state ($Ru^{II}$*). This important realization, coupled with the correct choice of counterion ($BArF^-$ vs $PF_6^-$) to allow solvation in less polar solvents, permitted a range of [4 + 2] cycloadditions to occur with low catalyst loadings (typically 0.5 mol %) and in good yields (typically 60–98%) (**Scheme 7**).[33] The mechanism is postulated to begin with promotion of $Ru(bpz)_3^{2+}$ ($\lambda_{max}$ = 440 nm) to its excited state, which is capable of oxidizing **37** to its radical cation **41**. This species can then undergo intermolecular [4 + 2] cycloaddition, followed by abstraction of an electron from **37** in a chain propagation sequence. Finally, $Ru(bpz)_3^+$ is returned to the photoactive ground state, $Ru(bpz)_3^{2+}$, by oxidation with molecular oxygen. This elegant methodology displays both reversed intrinsic dienophile electronics, as well as overall regiochemical preference when compared to the traditional Diels–Alder reaction, making it highly complementary to previously reported methods. Equally impressive is the demonstration of how the judicious selection of photocatalyst and subsequent tuning of physical properties make such a valuable method possible.

### 2.6. Formal [3 + 2] Cycloaddition of Aminocyclopropanes

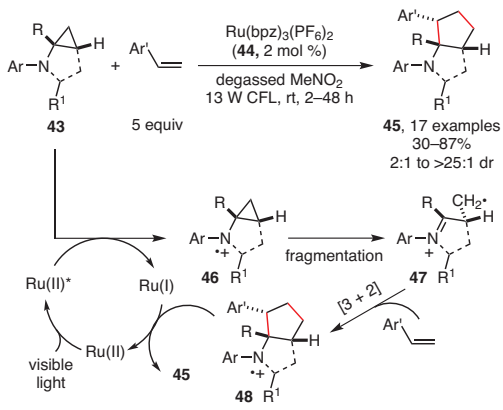
Another methodology that successfully utilizes the strongly oxidizing $Ru(bpz)_3^{2+}$ excited state was recently reported by Zheng and co-workers for the intramolecular [3 + 2] cycloaddition of cyclopropylamines with alkenes.[35] In agreement with the pathway of the tetrahydroisoquinoline methodology, the amine serves in the present system as the reactive species rather than the sacrificial quencher. The excited state photocatalyst initiates a cyclopropane ring opening by amine N-oxidation, generating a β-carbon radical iminium ion, **47**, that is competent in a formal [3 + 2] cycloaddition with a range of predominantly styrenyl alkenes (**Scheme 8**).[35] The authors postulate that the product following cycloaddition, **48**, is reduced by Ru(I), returning the photocatalyst to the parent oxidation state and furnishing a range of cyclopentanes and fused bicyclic systems in good yields (typically >70%). The reaction scope with respect to the amine is limited to either secondary or tertiary amines bearing at least one aryl substituent. This method further showcases the ability to tune the reaction conditions by the choice of photocatalyst. The yield correlated well with the excited state oxidation potential of the phtotocatalyst, with the weaker oxidants $Ru(bpy)_3Cl_2$ (**1**) ($E_{½}^{II*/I}$ = +0.77 V vs SCE) and $Ir(ppy)_2(dtbbpy)PF_6$ (**24**) ($E_{½}^{III*/II}$ = +0.66 V vs SCE) performing less efficiently than $Ru(bpz)_3^{2+}$ ($E_{½}^{II*/I}$ = +1.45 V vs SCE).

### 2.7. Application of Reductive Quenching in Total Synthesis

The reductive quenching cycle returned to its origins in complex-molecule synthesis when we successfully applied it to the synthesis of (+)-gliocladin C.[36] The key carbon–carbon bond was forged between the C-3 position of indole **50** and the elaborated bromopyrroloindoline radical generated by reductive dehalogenation of **49**. $Ru(bpy)_3Cl_2$ (**1**) was identified as the optimal photocatalyst in combination with $(n\text{-}Bu)_3N$ as the reductive quencher. Competing hydrogen-atom



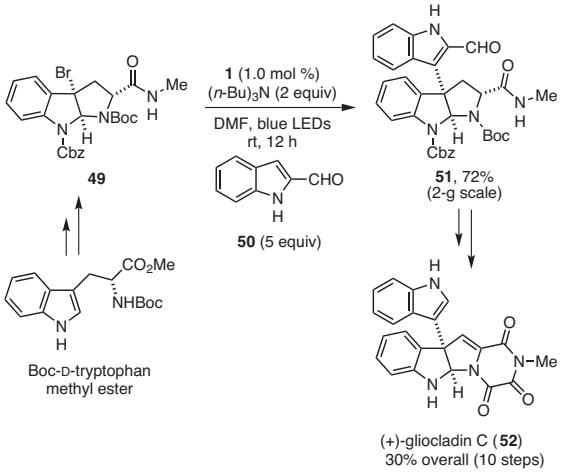

**Scheme 7.** Yoon's Radical Cation Diels–Alder Reaction. *(Ref. 33)*



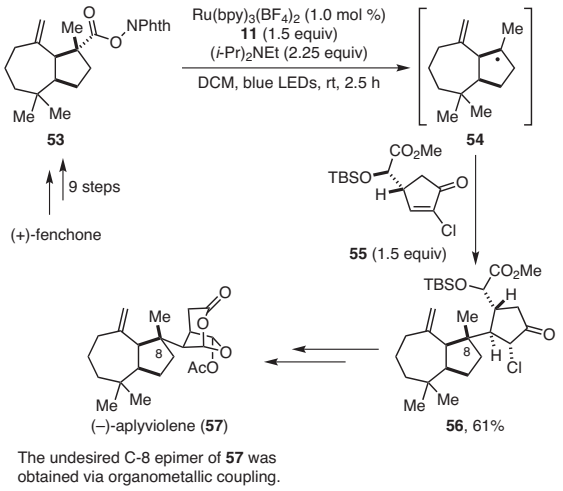

**Scheme 8.** Formal [3 + 2] Cycloaddition of Aminocyclopropanes. *(Ref. 35)*

abstraction by the tertiary radical was minimized by the use of 5 equivalents of the readily available indole **50**, allowing the reaction to successfully operate on a multigram scale in good yield (72%) with only 1 mol % of the photocatalyst (**Scheme 9**).[36] The efficiency of this reaction allowed the total synthesis of (+)-gliocladin C in 10 steps from commercially available Boc-D-tryptophan methyl ester in 30% overall yield, and highlights the viability of photoredox catalysis for facilitating complex molecular synthesis.

A similar strategy was elegantly employed by Schnermann and Overman in their concise, second-generation formal synthesis of (−)-aplyviolene.[37] The key transformation, relying on the seminal work of Okada and Oda,[10] accomplishes the coupling of tertiary radical **54**—generated by decarboxylative reduction of **53**—to




**Scheme 9.** Photocatalytic Radical Reductive Coupling as a Key Reaction Step en Route to (+)-Gliocladin C. *(Ref. 36)*




**Scheme 10.** Photocatalytic Radical Reductive Coupling as a Key Reaction Step in a Formal Total Synthesis of (–)-Aplyviolene. *(Ref. 37)*

α-chlorocyclopentenone **55** to furnish adjacent quaternary and tertiary centers with high stereoselectivity. Optimization of this challenging transformation led to conditions reported by Gagné and co-workers for the reduction of glycosyl halides under anhydrous conditions.[38] Accordingly, 1 mol % of $Ru(bpy)_3(BF_4)_2$ with $(i\text{-}Pr)_2NEt$ (2.25 equiv) and Hantzsch ester **11** (1.5 equiv) in DCM provided **56** in 61% yield and, importantly, the opposite stereoselectivity to that obtained by an analogous organometallic coupling reaction (**Scheme 10**).[37] This method was later expanded to a general process for the synthesis of quaternary carbons from tertiary alcohols, with a range of electron-deficient alkenes employed as the coupling partners.[39]

## 3. Oxidative Quenching

### 3.1. Atom-Transfer Radical Addition (ATRA)

Our ability to efficiently utilize the oxidative quenching cycle was initially slower to develop than the corresponding reductive quenching pathway. During our investigation of reductive radical cyclizations (Section 2.2), we discovered that replacing terminal alkenes and alkynes with tethered cyclopentene **58** or cyclohexene **59** provided atom-transfer products (**Scheme 11**, Part (a)).[40] We found that, by removal of $Et_3N$, which acts as both a reductive quencher and H-atom donor, the exclusive atom-transfer product could be obtained.[41] Further optimization of this protocol, including the use of $[Ir\{dF(CF_3)\text{-}ppy\}_2(dtbbpy)]PF_6$ (**63**) as the photocatalyst,[24b] greatly increased the reaction efficiency (Scheme 11, Part (b)).[41] It is postulated that **63** is optimal due to its extended excited-state lifetime ($\tau = 2300$ ns) compared to $Ru(bpy)_3Cl_2$ ($\tau = 1100$ ns), given their similar excited-state reduction potentials: $E_{1/2}^{IV/III*} = -0.89$ V vs SCE compared to $E_{1/2}^{III/II*} = -0.81$ V for $Ru(bpy)_3Cl_2$.

This optimized process proceeds exclusively via oxidative quenching, whereby the excited state of the catalyst directly reduces the carbon–halogen bond of the bromomalonate substrate, **27**, to produce the desired radical. Interestingly, mechanistic studies have indicated that the process may proceed further—via propagation in a radical polar crossover and/or via catalyst turnover—to generate the same product, **64** (Scheme 11, Part (c)).[41] This mode of reactivity eliminates the requirement for a stoichiometric quencher, and allows the atom-transfer radical addition (ATRA) coupling of a range of halogenated compounds to olefins under mild conditions in typically excellent yields (Scheme 11, Part (b)).[41]

Although this methodology generally performed effectively for a range of halogenated substrates, it was not efficient for the addition of perfluoroalkyl iodides (such as **69**), a system designed to achieve fluorous tagging. We, therefore, returned to the reductive quenching of $Ru(bpy)_3Cl_2$ approach, but with sodium ascorbate as an electron donor instead of a tertiary amine. This effectively prevents the premature reduction of the perfluoroalkyl radical, and allows the efficient ATRA tagging of a range of alkenes and alkynes such as **68** (**eq 3**).[40]

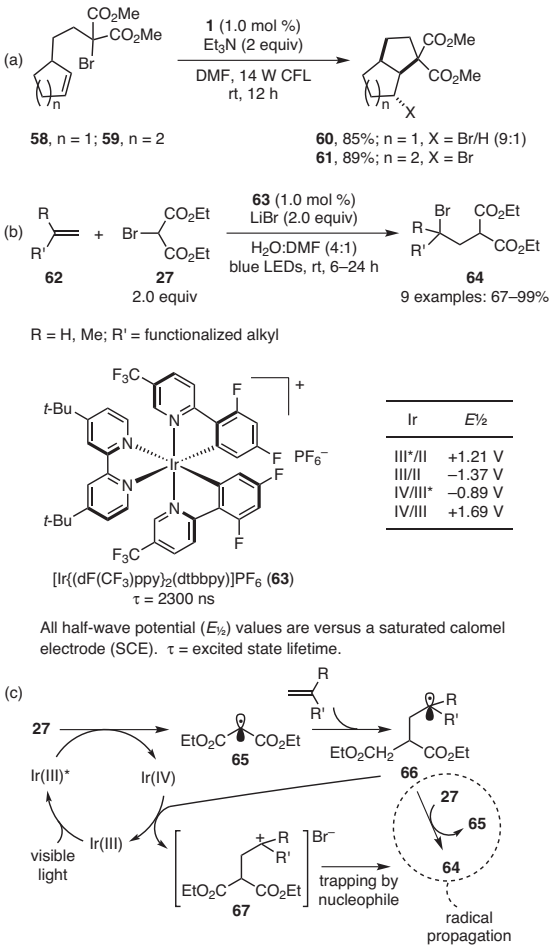
### 3.2. Oxytrifluoromethylation of Alkenes

Yasu, Koike, and Akita recently published an elegant advancement of the ATRA methodology to oxytrifluoromethylation.[42] In this protocol, Umemoto's reagent is reduced by the excited state of the photocatalyst to generate the active $CF_3$ radical. Following radical addition and either oxidation or chain propagation, the carbocation intermediate (analogous to **67**) is trapped by a nucleophilic additive. The use of *fac*-$Ir(ppy_3)$ (**73**),[3e] the strongest excited-state reductant ($E_{1/2}^{IV/III*} = -1.73$ V vs SCE) of the commonly employed photocatalysts, in combination with Umemoto's reagent (−0.25 V vs SCE)[43] proved critical for good reactivity. A range of styrenyl alkenes were efficiently trapped in good yields (typically

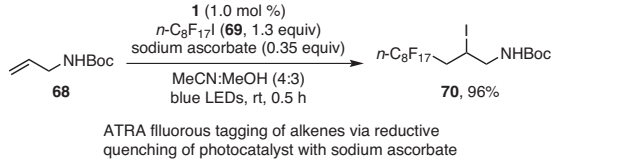
>75%) by a range of alcohols, carboxylic acids, or water (**eq 4**).[42] Preliminary studies indicated moderate levels of diastereocontrol in the addition of simple alcohols to *trans*-stilbene (typically 5:1 dr), while the application of this methodology to the synthesis of the antiestrogen drug Panomifene showcased its potential synthetic utility.

### 3.3. Trifluoromethylation of Arenes and Heteroarenes

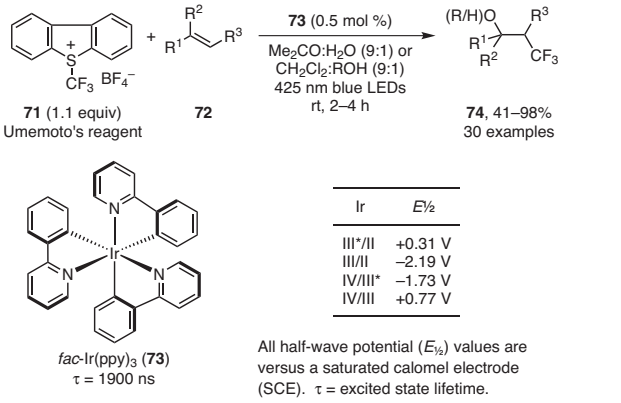
Nagib and MacMillan developed an alternate method for the generation of the $CF_3$ radical via photoredox catalysis, in this instance for the trifluoromethylation of arenes and heteroarenes.[44] Triflyl chloride ($F_3CSO_2Cl$ or TfCl, −0.18 V vs SCE) represents a comparatively cost-effective and easily handled material when compared to other $CF_3$ sources. In this protocol, the $CF_3$ radical is generated by reduction of TfCl with the excited state of the photoredox catalyst and fragmentation. Selective addition of this electron-deficient radical to the most electron-rich position of a range of arenes and heteroarenes provides, following rearomatization, pharmaceutically relevant building blocks in typically good yields (>30 examples with >70% yield) and regiocontrol (**Scheme 12**). Ru(phen)$_3$Cl$_2$ ($E_{½}^{III/II*}$ = −0.87 V vs SCE)[3a,45] provided an optimal mix of reactivity and selectivity for electron-rich heteroarenes, whereas Ir(Fppy)$_3$ (Fppy = 2-(2',4'-difluorophenyl)pyridine)[46,47] was



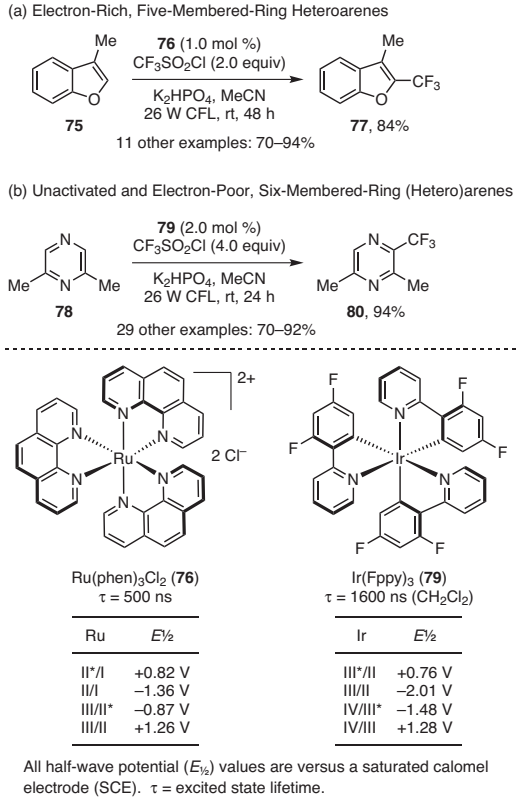

**Scheme 11.** Atom-Transfer Radical Addition (ATRA): (a) Discovery, (b) Optimization, and (c) Possible Mechanisms. *(Ref. 40,41)*



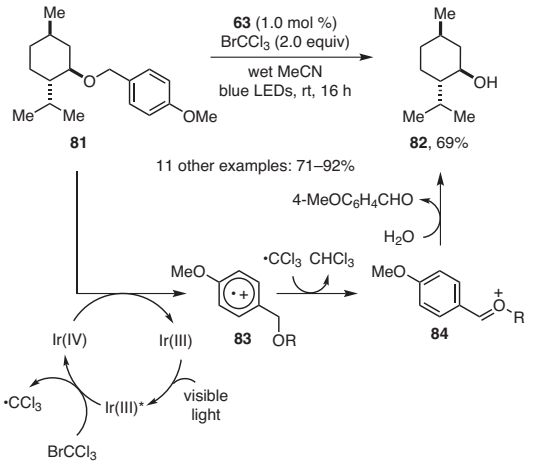

**eq 3** *(Ref. 40)*



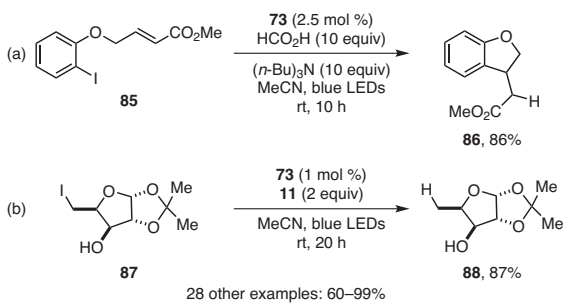

**eq 4** *(Ref. 42)*



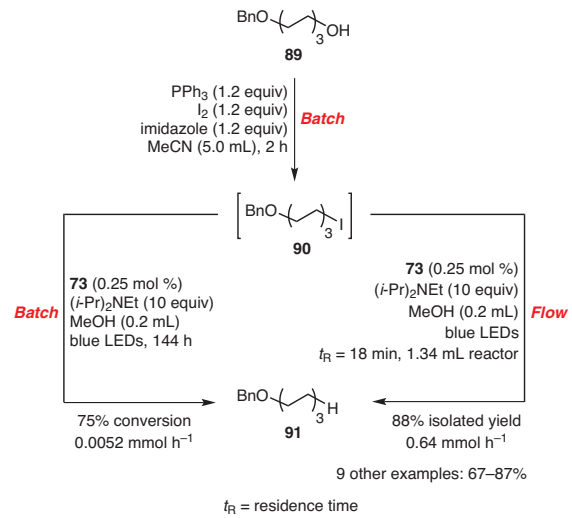

**Scheme 12.** Trifluoromethylation of (a) Electron-Rich and (b) Electron-Poor Heteroarenes. *(Ref. 44)*




**Scheme 13.** Selective, Photocatalytic Oxidative Radical Deprotection of PMB Ethers. *(Ref. 48)*




**Scheme 14.** Dehalogenation of Unactivated C–I Bonds. *(Ref. 49)*




**Scheme 15.** Efficiency Comparison of Batch and Batch-to-Flow Deoxygenations of Primary and Secondary Alkyl Alcohols. *(Ref. 56)*

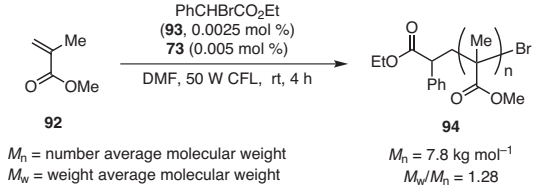
employed for more difficult substrates such as arenes and electron-poor heteroarenes (e.g, **78**). The authors propose that the higher reactivity of $Ir(Fppy)_3$ is due to increased excited-state lifetime when compared to $Ru(phen)_3$.

### 3.4. Deprotection of PMB Ethers

During the course of investigations into the functional group tolerance of the ATRA methodology (Section 3.1) we discovered that PMB ethers (PMB = *para*-methoxybenzyl) were unstable to the reaction conditions, undergoing partial deprotection. Following optimization of reactions conditions, most notably running the reactions in wet acetonitrile with bromotrichloromethane, a range of PMB ethers could be selectivity deprotected (**Scheme 13**).[48] Functional group tolerance includes pivalate esters, substituted olefins, THP acetals, and Fmoc and Cbz groups. This mild, catalytic PMB deprotection serves as an excellent alternative to typical methods that employ DDQ, CAN, $SnCl_4$, AcOH, or Lewis acids. In analogy to the mechanism for the photoredox-catalyzed-ATRA reaction, $BrCCl_3$ oxidatively quenches Ir(III)* to generate Ir(IV) and the trichloromethyl radical ($•CCl_3$). Ir(IV) then oxidizes the PMB ether to generate radical cation **83** and regenerate the ground state of the catalyst. The trichloromethyl radical ($•CCl_3$) may then abstract a benzylic hydrogen from **83** to produce oxonium intermediate **84**, which is hydrolyzed by water to the free alcohol and anisaldehyde (Scheme 13).[48]

### 3.5. Dehalogenation of Unactivated Alkyl, Alkenyl, and Aryl Iodides

The strong reductive power of *fac*-$Ir(ppy)_3$ (**73**) from the excited state ($E_{½}^{IV/III*} = -1.73$ V vs SCE) returned us to our earlier studies on reductive dehalogenation and to consider the possibility of further expanding the scope to unactivated C–I bond reduction. By utilizing conditions similar to those employed in our initial entry into the area of photoredox catalysis, but harnessing the oxidative quenching cycle of **73**, a range of unactivated alkyl, alkenyl, and aryl iodides could be successfully reduced (**Scheme 14**).[49] Consistent with the full suite of reductive protocols developed within our group, the reaction displays excellent functional group compatibility and operational simplicity, and proceeds in typically high yields. It is important to note that the reduction potentials of many of the substrates that are effectively reduced lie outside the effective range of **73**. This observation is of merit as it indicates that reduction potentials are an effective guide to available reactivity, but are by no means the only defining factor. In this, and other instances,[50] we believe the reaction to be driven by the rapid and irreversible C–H abstraction by the radical following C–I bond reduction.




Control of Living Radical Polymerization of Methacrylates by Use of Visible-Light-Mediated ATRA

**eq 5** *(Ref. 58)*

### 3.6. Batch-to-Flow Deoxygenation

The efficiency of the dehalogenation described above, along with many other photoredox transformations, can be greatly improved by running the reaction in continuous flow mode. Seminal publications from our collaboration with Jamison,[51] and those from the research groups of Seeberger[52] and Gagné[53], have demonstrated that conducting photoredox reactions in a flow rather than in a batch setting generally leads to shorter reaction times, improved yields, and lower catalyst loadings. This is simplistically attributed to greater light penetration, owing to the increased surface-to-volume ratio within a typical flow reactor when compared to a batch reaction.[54]

Attempts to merge our own photoredox method for the conversion of alcohols to halides[55] with the updated dehydroiodination protocol have, to this date, been largely unsuccessful. However, we have recently reported a batch-to-flow method for the efficient reduction of a range of primary and secondary alcohols.[56] This protocol proceeds by utilizing the Garegg–Samuelsson reaction[57] in batch, transforming the alcohol functionality into an iodide, which can then be reduced in flow by the photocatalyst. The use of a flow system allows reduced loadings (0.25–0.5 mol % compared to 2.5 mol % in batch) of the catalyst, *fac*-Ir(ppy)$_3$ (**73**), and provides an overall method that is competitive with deoxygenation strategies such as those of Barton–McCombie and others that typically employ tributyltin hydride or samarium diiodide (**Scheme 15**).[56]

### 3.7. Control of Living Polymerization

An excellent application of the visible-light-mediated ATRA reaction to living radical polymerization has recently been reported by Fors and Hawker.[58] In this system, atom-transfer radical polymerization (ATRP) is initiated and controlled[59] by using *fac*-Ir(ppy)$_3$ (**73**). Reduction of the alkyl bromide initiator, **93**, by the excited state of the photocatalyst, and subsequent ATRA reaction with the monomer, **92**, provide an overall cyclic process that can be turned on or off using visible light. This important feature allows excellent control over molecular weight, displaying low polydispersity while employing only between 0.005 and 0.13 mol % of **73** (**eq 5**).[58] When compared to other traditional copper-based ATRP processes, this system displays excellent functional group tolerance as exemplified by the use of a free carboxylic acid monomer.

## 4. Conclusions and Outlook

Building upon the pioneering investigations into the use of transition-metal photoredox catalysts, our group and many others have successfully demonstrated their broader applicability in organic synthesis. While considerable research effort has been directed towards applications of previously reported transformations, many new modes of reactivity have also been outlined. This has been facilitated in part by leveraging the large number of reported transition-metal photoredox catalysts, whose origins lie outside their direct use in organic synthesis. Concurrent with driving new reaction discovery, this review has emphasized that the breadth of available photocatalysts allows for astute reaction optimization on the basis of known photophysical properties. The ability of these photocatalysts to potentially operate as either strong oxidants or reductants, combined with the relatively large range of accessible potentials, is key to their expanded use in organic synthesis. This is particularly well illustrated by our group's continued research into the reduction of carbon–halogen bonds, where both modulation of the photocatalyst and mode of quenching have allowed the reduction of increasingly more challenging substrates.

As the field continues to expand and mature, we will likely see further novel applications that harness the versatile nature of this mode of single-electron chemistry. Equally important will be endeavors aimed at addressing some of the current limitations such as the transition from one- to two-electron processes. Other areas with potential for development include the further design and synthesis of catalysts with a similar range of electronic potentials, excited-state lifetimes, and chemical stability, which do not rely on costly transition metals such as iridium and ruthenium. Another strategy to alleviate some of the cost pressures precluding wider use on scale may be analysis of catalyst recovery and re-use systems, particularly when coupled to the growing combination of photoredox and continuous processing methods. Given the frequent ambiguity over the precise mechanistic pathway for visible-light-mediated reactions, in-depth mechanistic studies are also warranted, potentially providing insights into previous processes or directing new avenues for investigation.

## 5. Acknowledgments

We gratefully acknowledge financial support from the University of Michigan. Our research was also supported in part by a Lilly Innovation Fellowship Award to J. D. from Eli Lilly and Company. J. D. N. thanks the Division of Organic Chemistry of the American Chemical Society and Amgen for a graduate fellowship.

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## About the Authors

**James J. Douglas** was born in Cambridge (U.K.). He obtained an MChem degree from the University of York in 2008, which included a one-year placement at GlaxoSmithKline in Stevenage (U.K.). In 2012, he completed his Ph.D. degree under the supervision of Professor Andrew Smith at the University of St Andrews (U.K.) and was jointly funded by AstraZeneca and the EPSRC. His research focused on the application of N-Heterocyclic Carbenes (NHCs) to novel asymmetric organocatalytic processes. He is currently a Lilly Innovation Fellowship Award (LIFA) postdoctoral scientist based jointly with the Eli Lilly Process Design and Development group and the research group of Prof. Corey Stephenson at the University of Michigan. His research is directed towards the application of visible-light photochemical processes to pharmaceutical development.

**John D. Nguyen** earned his B.S. degree in chemistry with a concentration in education in 2007 from the University of California, Irvine. From 2007 to 2009, he was a junior research assistant to Prof. Christopher D. Vanderwal at UC Irvine, where he worked on the synthesis of chlorosulfolipid natural products. He then began graduate studies in organic chemistry at Boston University, and is currently continuing his studies at the University of Michigan with Prof. Corey R. J. Stephenson. His work has focused on the use of visible-light-active photocatalysts for the radical-based reduction of carbon–halogen bonds for hydrodehalogenations, intramolecular cyclizations, and intermolecular couplings. John was the recipient of the 2012 AstraZeneca Graduate Fellowship in Organic Chemistry and the 2012/2013 ACS Division of Organic Chemistry Graduate Fellowship sponsored by Amgen.

**Kevin P. Cole** was born in St. Paul, Minnesota. He obtained his Ph.D. degree in chemistry in 2005 from the University of Minnesota

Twin Cities campus, and worked in the laboratory of Prof. Richard Hsung. In 2007, he completed postdoctoral studies in the laboratory of Prof. K. C. Nicolaou at The Scripps Research Institute in San Diego, CA. In the same year, Kevin joined Eli Lilly and Company in Indianapolis, IN, and was promoted to Sr. Research Scientist in 2010. He is currently working as a process chemist in Lilly's continuous processing group.

**Corey R. J. Stephenson** received an Honours B.Sc. degree in 1998 from the University of Waterloo and a Ph.D. degree in 2005 from the University of Pittsburgh, where he worked under the direction of Prof. Peter Wipf. After carrying out postdoctoral research in the laboratory of Prof. Erick M. Carreira at ETH Zürich, Switzerland, he joined the Department of Chemistry at Boston University in 2007 as Assistant Professor and co-Principal Investigator in the Center for Chemical Methodology and Library Development (CMLD-BU). He was granted tenure and promoted to Associate Professor in February 2013. As of July 2013, he has been Associate Professor at the University of Michigan, Ann Arbor, where his research group focuses on catalysis, natural product synthesis, and continuous flow chemistry.

Photo courtesy of Alfred R. Bader

Dr. Bader, 2005

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*For more than 60 years,* Dr. Alfred Bader has been a significant influence in the world of chemistry, business, art and philanthropy. As a tangible manifestation of his vision and dedication to chemistry, he co-founded Aldrich Chemical Company in 1951. Through his contributions, Dr. Bader helped make Sigma-Aldrich the leading Life Science and High Technology company it is today.

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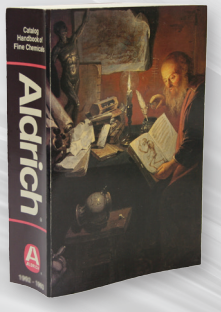


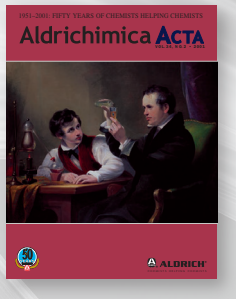


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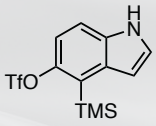


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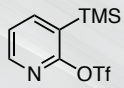


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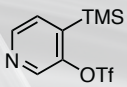


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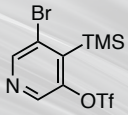


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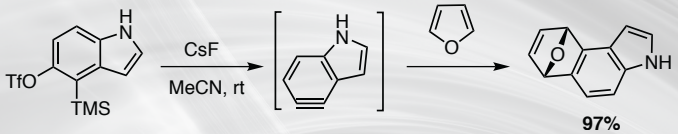


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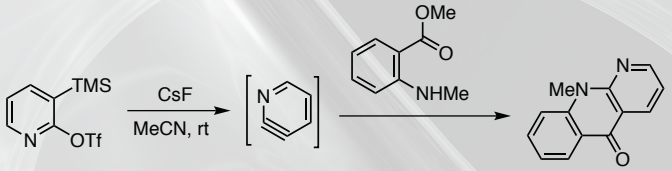


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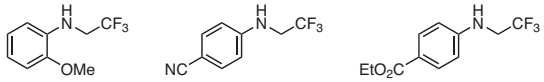


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## ABOUT OUR COVER

Detail from ***Lake Albano***. Photo courtesy National Gallery of Art, Washington, DC.

***Lake Albano*** (oil on canvas, 121.9 x 170.4 cm) was completed in 1762 by Richard Wilson (1712/1714–1782). Born and raised in Wales, Wilson left for London at about age 15 to study portraiture under Thomas Wright. After about six years of training, he struck out on his own as a portraitist for almost two decades, but without attaining the recognition and financial success he had hoped for. In 1752, he made a trip to Italy that proved to be a turning point in his career as an artist. In Rome, he came to admire and was heavily influenced by the works of celebrated landscape painters, such as Claude Lorrain and Gaspard Dughet, who had lived and worked in the city a century earlier. In 1757 or 1758, he returned to Britain, where he devoted himself to painting primarily Welsh and Italian (often idealized) sceneries and to training a new generation of artists. The fame and success that eluded him as a portrait artist he attained as a landscape painter. Considered by many to be a pioneer of British landscape painting, Wilson has been an acknowledged strong influence on later British landscapists, in particular John Constable and Joseph Turner.

***Lake Albano**** embodies many of the elements that characterize Wilson's landscapes: small human figures; a body of water; a building or two, often in the middle ground of the painting; bright and generally clear skies; and delicate trees and foliage, often more prominent in the foreground. His landscapes, whether actual or idealized, depict charming and serene scenes, with human and animal figures inserted to give depth and scale but not distract from the beauty or majesty of the surroundings. While his landscapes tend to capture the general appearances of nature, his rendering of light and distance validate his keen and delicate observations of the natural world.

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

** Actual Lake Albano was a favorite setting for a number of landscape artists of the 18th and 19th centuries. To find out who else has painted it, visit* ***Aldrich.com/acta472***

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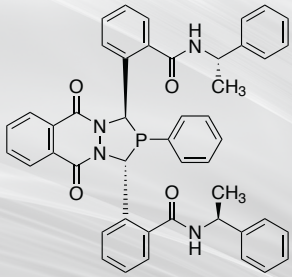

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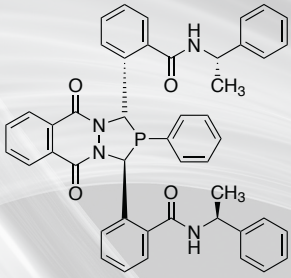

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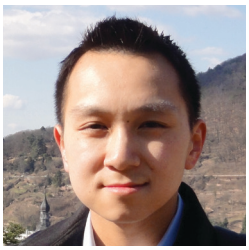
82087-b

# Highly Enantioselective Hydroformylation of Alkenes by Rhodium-Diazaphospholane Catalysts



Dr. Gene W. Wong
(Deceased)

Prof. Clark R. Landis

**Gene W. Wong and Clark R. Landis***

Department of Chemistry
University of Wisconsin-Madison
1101 University Avenue
Madison, WI 53706-1322, USA
Email: landis@chem.wisc.edu

**Keywords.** asymmetric catalysis; hydroformylation; rhodium; chiral phosphines; organic synthesis.

**Abstract.** Rhodium-diazaphospholane complexes catalyze the highly enantioselective hydroformylation of aryl alkenes, vinyl acetates and carboxamides, functionalized allylic substrates, heterocycles, and 1,3-dienes at fast rates and high turnover numbers. The state of the art (≥ 90% ee) in enantioselective hydroformylation is reviewed and highlighted with applications to organic synthesis.

## Outline



## 1. Introduction

Chiral aldehydes are versatile intermediates for the construction of complex molecules with applications as fragrances, agrochemicals, pharmaceuticals, natural products, and others. The importance of chiral aldehydes to target-oriented synthesis has long been recognized by organic chemists, and is best summarized in the following statement:[1] "The aldehyde is arguably the most versatile carbonyl functionality…. This unique combination of functional versatility and activity renders chiral aldehydes highly valuable intermediates in asymmetric synthesis". However, chiral aldehydes constitute a synthetically challenging class of building blocks. Common routes to chiral aldehydes include: aldol condensations;[2–6] α-functionalization of aldehydes[7–11] or carbonyl compounds (requires reduction to a formyl group);[12–16] conjugate additions;[17–19] cycloaddition reactions;[20] Friedel–Crafts alkylations;[21] and Mannich condensations.[6] Many of these methods lead to structurally diverse aldehydes, but suffer from drawbacks associated with organocatalysis or the use of stoichiometric chiral auxiliaries: atom-inefficiency, low reaction temperatures and long reaction times, aldehyde side reactions (aldol condensation, epimerization, etc.) especially at non-neutral pHs, and low catalytic activity (<100 turnover numbers (TON); TON = moles of product/moles of catalyst). Perfect atom-economy, inexpensive reactants, neutral reaction conditions, simple purification, fast rates, and high TONs make the rhodium-catalyzed enantioselective hydroformylation an attractive alternative for the scalable synthesis of chiral aldehydes.

Hydroformylation is a large-scale commodity process yielding millions of pounds of linear aldehydes per year from inexpensive alkenes and synthesis gas (carbon monoxide and dihydrogen). In contrast, the rhodium-catalyzed *asymmetric* hydroformylation (AHF) is underutilized due to the limited number of ligands that preferentially form the branched aldehyde with high yield and enantioselectivity. Although the rhodium-catalyzed asymmetric hydroformylation has rapidly advanced in recent years, there are unmet challenges with the current state-of-the-art ligands; these include AHF of substrates such as multisubstituted alkenes; modular ligands for substrate optimization; catalyst-controlled chemo-, regio-, and enantioselectivities; and highly active and robust catalysts.

The catalytic asymmetric *hydrogenation* of C=C and C=X (where X = O or N) with dihydrogen is well established as a powerful method in organic synthesis. Noyori has described asymmetric catalysis as four-dimensional chemistry: Not only is perfect stereochemistry for a molecule (x, y, z) a requisite, but attaining optically active materials in a reasonable amount of time (t) is also paramount.[22] Similar challenges apply to the catalytic AHF. AHF is operationally similar to the asymmetric hydrogenation in that both reactions use gaseous reagents under pressurized conditions. Hydroformylations are commonly performed in autoclaves (150–5000 psi) or glass bottles (15–150 psi). The demand for higher gas pressures in these reactions arises from two factors: (i) the generation of active hydroformylation catalysts, and (ii) the desire to achieve high reaction rates and selectivities. Both of these factors depend on efficient gas–liquid mixing and, for very active catalysts, mass transport of gas is among the limiting factors of the reaction rate. For these reasons, AHF procedures do not commonly use balloons of $H_2$ and CO. Thus, an important consideration in the application of AHF by a synthetic chemist is the cost and sophistication of the equipment needed. Rhodium-diazaphospholane complexes are highly active and robust enantioselective hydroformylation catalysts that typically operate at mild reaction temperatures and pressures.

Hydroformylation has been thoroughly reviewed.[23–34] This survey offers an in-depth look at the effect of diazaphospholane ligands[35,36] in rhodium-catalyzed enantioselective hydroformylations of structurally

diverse alkenes and comparison to that of existing state-of-the-art ligands (**Figures 1** and **2**). We limit our treatment to reactions that yield >90% enantiomeric excess, that is, reactions of potential interest to modern synthetic chemists. We de-emphasize other important criteria in the evaluation of enantioselective hydroformylation catalysts such as chemoselectivity, regioselectivity, substrate scope, syngas pressure and temperature effects, catalyst activity and speciation, and scalability.

Given the precedent of chiral phosphorus-containing ligands being effectively employed in asymmetric *hydrogenation* catalysis, it is surprising how challenging enantioselective rhodium-catalyzed AHF remained until Takaya, Nozaki, and co-workers reported the ligand (*R*,*S*)-BinaPhos (**1a**) in 1993.[37] The use of enantioselective hydroformylation in organic synthesis has remained sparse due to the small number of ligands that exhibit desirable selectivity for many alkenes. Herein, a sampling of exceptional results is presented for several substrate classes: aryl alkenes, vinyl acetates and amides, functionalized allylic alkenes, heterocycles, 1,3-dienes, and miscellaneous alkenes. Relevant synthetic applications of enantioselective hydroformylation using diazaphospholane ligands are included throughout this review.

## 2. Enantioselective Hydroformylation of Alkenes

The relative rates of reactivity of rhodium-catalyzed hydroformylations generally decrease with increased substitution of the alkene (**Figure 3**).[38–40] Terminal alkenes are the most common substrates employed in AHF due to their ease of hydroformylation under mild conditions (low pressures and temperatures). 1,2-Disubstituted alkenes generally require higher temperatures for reasonable rates, resulting in fewer applications in enantioselective hydroformylation. Not surprisingly, higher temperatures are detrimental to the regio- and enantioselectivity of the hydroformylation for many catalyst systems. Few examples of AHF of 1,1-disubstituted alkenes (to β-chiral aldehydes or quaternary aldehydes) have been reported, and no reports of AHF of trisubstituted and tetrasubstituted alkenes have appeared.

### 2.1. Styrenes and Aromatic Alkenes

Styrenes are common substrates for AHF due to their potential application in the synthesis of pharmacologically active, anti-inflammatory analgesics (ibuprofen, ketoprofen, and naproxen). Takaya, Nozaki, and co-workers reported the earliest examples of rhodium-catalyzed enantioselective hydroformylation of styrene using (*R*,*S*)- and (*S*,*R*)-BinaPhos, with *ent*-**1a** providing the branched aldehyde, (*S*)-(+)-2-phenylpropionaldehyde, in 94% ee.[37] Zhang and Yan developed a related phosphine-phosphoramidite ligand (*R*,*S*)-YanPhos (**1d**) that led to 98% ee of (*R*)-(–)-2-phenylpropionaldehyde.[41] Ligand libraries derived from BinaPhos,[42–44] bisdiazaphospholanes (**12a–d**),[45,46] (*R*,*R*)-Ph-BPE (**14**),[47] and (*R*,*S*)-YanPhos (**1d**)[48] demonstrated stereoselectivities generally similar to those of the corresponding parent ligand—although superior results were observed for some specific substrates. Bisphosphites, such as (*2R*,*4R*)-chiraphite (**7**),[23,24,49,50] and a D-(+)-glucose-derived bisphosphite, **8**,[51] enabled highly regio- (up

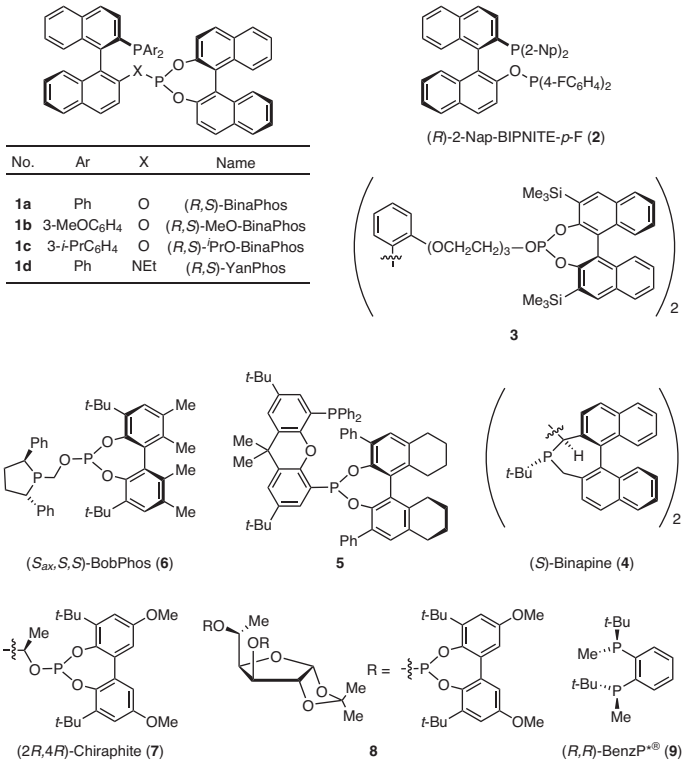



**Figure 1.** Chiral Phosphorus-Containing Ligands That Exhibit ≥90% ee in the Rhodium-Catalyzed Asymmetric Hydroformylation (AHF) of Various Alkenes.

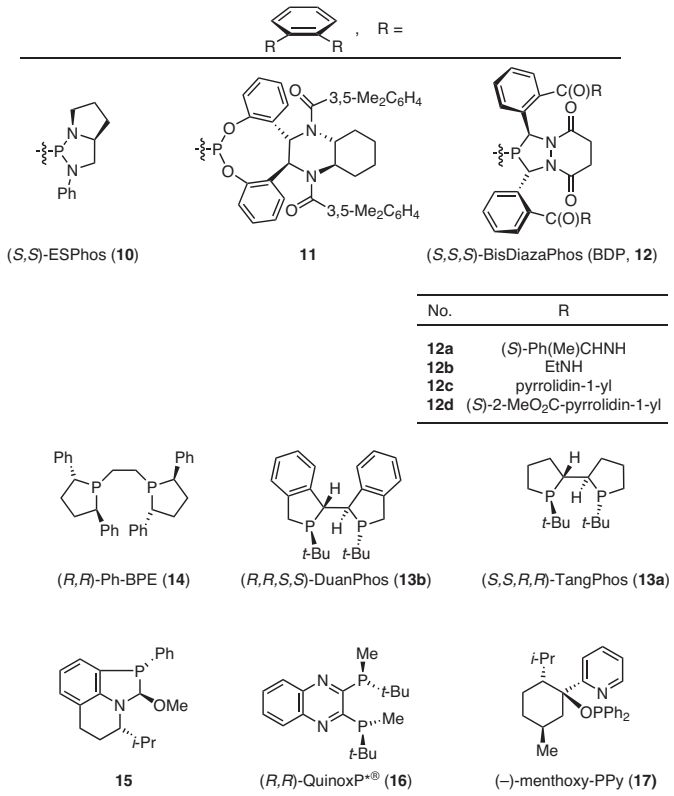



**Figure 2.** Chiral Phosphorus-Containing Ligands That Exhibit ≥90% ee in the Rhodium-Catalyzed Asymmetric Hydroformylation (AHF) of Various Alkenes.

to 99% branched aldehyde) and enantioselective hydroformylations (90% ee for both ligands) of styrene, albeit at low conversions due to the low reaction temperatures. Hydroformylation of styrene with bisphospholane **14** resulted in 57% conversion and 94% ee.[47,52] Other cyclic bisphosphines, such as (*S*,*S*,*R*,*R*)-TangPhos (**13a**) and Binapine (**4**), yielded less active hydroformylation catalysts (12% conversion in both cases and 90% and 94% ee, respectively).[53] Cobley, Clarke, and co-workers developed BobPhos (**6**), a hybrid phospholane-phosphite ligand, that effected a highly regioselective (98% α-aldehyde) and enantioselective hydroformylation (91% ee) of styrene.[54] AHF with partially optimized conditions using (*S*,*S*,*S*)-bisdiazaphospholane **12a** (bis[(*S*,*S*,*S*)-DiazaPhos]-SPE) achieved a highly regioselective and enantioselective hydroformylation of styrene (98% branched and 93% ee).[55] It is worth noting that carbon monoxide pressure and temperature effects on the regio- and enantioselectivity of the hydroformylation prompted our group to carry out mechanistic studies with rhodium-bisdiazaphospholane catalysts.[56–58]

Four ligands from this group have demonstrated effective enantioselective hydroformylation of substituted styrenes and 1,2-disubstituted aryl alkenes (**eq 1**). The highest reported enantioselectivities of various substituted styrenes occur with hybrid ligands: (*R*,*S*)-BinaPhos (**1a**), (*S*,*R*)-YanPhos (*ent*-**1d**), and ($S_{ax}$,*S*,*S*)-BobPhos (**6**). BinaPhos-based ligands gave 86–88% of the branched aldehyde for unfluorinated (entries 1, 3, 8) and 89–96% for fluorinated styrenes (entries 10, 12, and 14), while exhibiting high stereoselectivity (92–98% ee).[37,43] Zhang and co-workers reported >98% ee's for the AHF of various substituted styrenes using (*R*,*S*)-YanPhos (**1d**) (entries 2, 4, 6, 9, 11, and 13).[41,48] Cobley, Clarke, and co-workers achieved 86–90% ee's and >98:2 α:β ratios for three substituted styrenes (e.g., entry 7) and 2-methoxy-6-vinylnaphthalene by employing ($S_{ax}$,*S*,*S*)-BobPhos (**6**).[54] D-(+)-Glucose-derived bisphosphite (**8**) enabled 91% ee and 99:1 α:β regioselectivity at 20 °C (entry 5).[51] AHF of substituted styrenes with (*S*,*S*,*S*)-diazaphospholane ligand **12a** gave >95% regioselectivity for the α-aldehyde and 70–89% ee's (not shown in eq 1) under unoptimized conditions.[55] Hydroformylation of *para*-substituted styrenes using rhodium-diazaphospholane catalysts revealed branched selectivity increased with electron-withdrawing groups (up to 98.5% branched aldehyde). The Hammett-like plot of log(α:β) vs $\sigma_{para}$ is linear with a positive slope ($\sigma$ = +0.56, $R^2$ = 0.93), suggesting a negative charge buildup in the regioselectivity-determining transition state.[55]

The asymmetric hydroformylation of 2-substituted styrenes has been successfully carried out using (*R*,*S*)-BinaPhos (**1a**)[59] and (*S*,*S*,*S*)-diazaphospholane (**12a**)[55] ligands (**eq 2**). Preference for the α-aryl-substituted aldehyde ranged from 92 to 97%, while the stereoselectivity of the major aldehyde was high, in the 92–96% range. Hydroformylation of indene (not shown) gave 88% ee by using (*S*,*R*)-BiphemPhos, a BinaPhos analogue.[42,44] Nozaki and co-workers explored the hydroformylation of vinyl-substituted heteroaromatic alkenes with (*R*,*S*)-MeO-BinaPhos (**1b**). Hydroformylation of 3-vinylfuran[60] and 3-vinylthiophene[61] resulted in 99% and 91% ee, respectively, with good regioselectivity (92% α-aldehyde) for both substrates. AHF of 2-vinylthiophene and 5-methyl-2-vinylthiophene also exhibited high enantio- (93% and 95% ee) and regioselectivity (94% and 95% α-aldehyde) with the same ligand.[61]

## 2.2. Vinyl Acetate and N-Vinyl Carboxamides

The asymmetric hydroformylation of vinyl acetate and related enols yields protected α-hydroxy aldehydes, which have numerous applications in synthesis. A handful of ligand classes have achieved the rhodium-catalyzed hydroformylation of vinyl acetate with greater than 90% ee (**eq 3**). These ligands include (*R*,*S*)-BinaPhos (**1a**),[37] (*S*,*S*,*S*)-diazaphospholane ligand **12a**[45] {which generates a highly active catalyst (TOF 19,400 $h^{-1}$) in the presence of [Rh(acac)$(CO)_2$]},[62] (*R*,*S*)-YanPhos (**1d**)[41] and analogues.[48] It is worth noting that changing the steric bulk of the substituent R had a minimal effect on the selectivity of the hydroformylation, as demonstrated with (*R*,*S*)-BinaPhos (**1a**)[43]

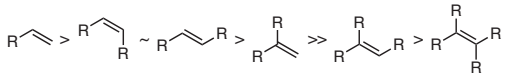
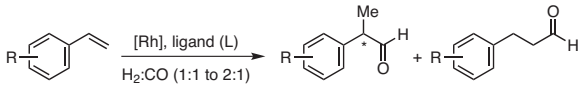


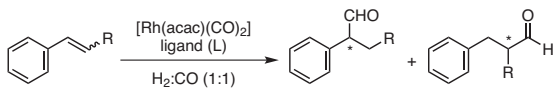
**Figure 3.** Decreasing Relative Rates of Reactivity of Various Substituted Alkenes in the Rhodium-Catalyzed Hydroformylation. *(Ref. 38–40)*




| Entry | R | L | b:l | *R/S* | ee | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | 4-Me | *ent*-**1a** | 86:14 | (+) | 95% | *37* |
| 2 | 4-Me | **1d** | 87:13 | *R* | 99% | *41* |
| 3 | 4-*i*-Bu | *ent*-**1a** | 88:12 | *S* | 92% | *43* |
| 4 | 4-*i*-Bu | **1d** | 89:11 | *R* | 98% | *41* |
| 5 | 4-MeO | **8** | 99:1 | (–) | 91% | *51* |
| 6 | 4-MeO | **1d** | 86:14 | *R* | 98% | *41* |
| 7 | 4-MeO | **6** | 98:2 | ---- | 90% | *54* |
| 8 | 4-Cl | *ent*-**1a** | 87:13 | (+) | 93% | *43* |
| 9 | 4-Cl | **1d** | 87:13 | *R* | 98% | *41* |
| 10 | 4-F | **1a** | 89:11 | (–) | 92% | *43* |
| 11 | 4-F | **1d** | 88:12 | *R* | 98% | *41* |
| 12 | 2-F | **1a** | 91:9 | (–) | 95% | *43* |
| 13 | 2-F | **1d** | 91:9 | *R* | 98% | *41* |
| 14 | (i) | **1a** | 96:4 | *R* | 98% | *43* |
| 15 | (ii) | **1c** | 94:6 | *R* | 95% | *44* |
| 16 | (ii) | **12a** | 98:2 | *R* | 94% | *55* |
| 17 | (iii) | **12a** | 98:2 | *R* | 96% | *55* |

[Rh] = [Rh(acac)$(CO)_2$]
(i) = $F_5CCH{=}CH_2$
(ii) = 2-NpCH=$CH_2$
(iii) = 2-MeO-6-(CH=$CH_2$)Np

**eq 1**



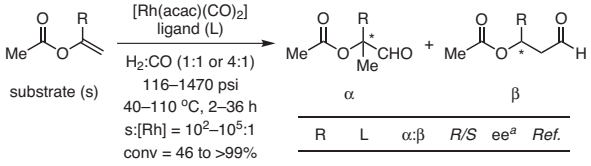

| R | L | α:β | *R/S* | ee[a] | *Ref.* |
|---|---|---|---|---|---|
| *trans*-Me | **1a** | >97:3 | *R* | 92% | *59* |
| *cis*-Me | **12a** | 92:8 | *R* | 92% | *55* |
| *cis*-Ph | **12a** | ----- | *R* | 93% | *55* |
| *b* | **1a** | 96:4 | (–) | 96% | *59* |

[a] ee of the α isomer. [b] s = dihydronaphthalene.

**eq 2**

and (*R*,*S*)-YanPhos (**1d**)[48] (85–96% regioselectivity for the branched aldehyde and 90–98% ee's). Additional ligands successfully employed in the AHF of vinyl acetate include the diazaphospholidine ESPhos (**10**),[63] the $C_2$-symmetric bisphosphonite ligand **11**,[64] and supramolecular bisphosphite ligand **3** possessing a long polyether bridge.[65] Buchwald and Wang have demonstrated the effective asymmetric hydroformylation of a 1,1-disubstituted vinyl acetate (where R = $CF_3$) using ligands **16** and **13b**, and isolated, after oxidation, the corresponding carboxylic acid, 2-trifluoromethyllactic acid, with 99% ee.[66]

Thomas, Klosin, and co-workers have reported 150–180-gram-scale hydroformylations of vinyl acetate using rhodium-diazaphospholane catalysts, whereby remarkable TONs of up to 100,000 and TOFs approaching 20,000 $h^{-1}$ were achieved.[62] Both enantiomers of the α-aldehyde were obtained in excellent purity (>99.0% regioselectivity and 94–96% ee) and utilized in the synthesis of an amino alcohol, an imidazole, and isoxazolines. These syntheses demonstrate that α-hydroxy aldehydes obtained by AHF can be utilized for the synthesis of enantioenriched heterocycles without racemization of the stereocenter.




| R | L | α:β | *R/S* | ee[a] | *Ref.* |
|---|---|---|---|---|---|
| H | **1a** | 86:14 | *S* | 92% | *37* |
| H | **12a** | 96:4 | *S* | 96% | *62* |
| H | **1d** | 93:7 | *S* | 96% | *48* |
| H | **10** | 94:6 | *S* | 90% | *63* |
| H | **11** | 98:2 | *S* | 91% | *64* |
| H | **3**[b] | >99:1 | *S* | 90% | *65* |
| $F_3C$[c] | **16** | ---- | ---- | >99% | *66* |
| $F_3C$[c] | **13b** | ---- | ---- | >99% | *66* |

[a] ee of the α isomer. [b] Cs[B(3,5-$(F_3C)_2C_6H_3)_4$] or CsBArF was used as additive. [c] ee is of the corresponding acid, 2-trifluoromethyllactic acid.

**eq 3**

Burke and Risi have employed bisdiazaphospholane **12a** for the asymmetric hydroformylation of a 1,2-disubstituted (*Z*)-vinyl ester, derived from (*2R*)-8-nonyn-2-ol, for the synthesis of (+)-patulolide C (**Scheme 1**).[67] The enantiomerically enriched α-hydroxy aldehyde obtained from the AHF was treated with Bestmann's ylide to give acetylated (+)-patulolide C. Enzymatic ester hydrolysis completed the synthesis, which was thus effected in three steps and 49% overall yield from (*2R*)-8-nonyn-2-ol. We have demonstrated one-pot AHF and Wittig olefination (WO) sequences for the synthesis of γ-chiral α,β-unsaturated carbonyl compounds. Importantly, olefination with stabilized Wittig reagents proceeds without erosion of the aldehyde enantiopurity.[68] Polyester oligomers and other complex products that contain various functionalities, multiple C–C double bonds, and multiple stereocenters can be made by iterative AHF–WO reactions that employ only a single loading of robust rhodium-diazaphospholane catalysts.

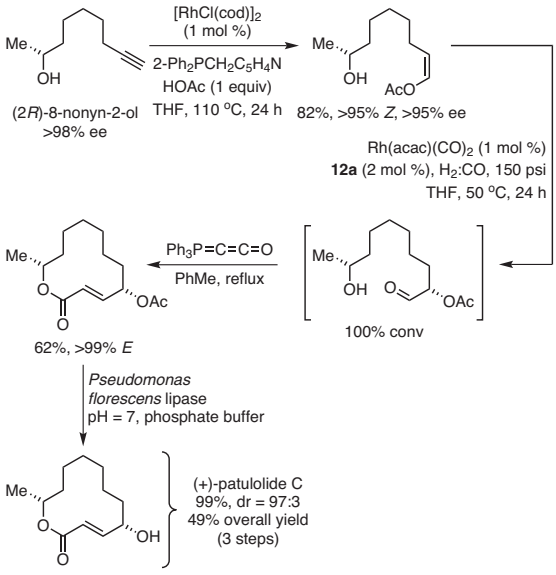
The enantioselective hydroformylation of *N*-vinyl amides in the presence of (*S*,*S*,*S*)-bisdiazaphospholane **12a** and [Rh(acac)$(CO)_2$] leads to the formation of 1,2-amino aldehydes with quantitative conversion and high enantioselectivity (**eq 4**).[69] As was observed in the AHF of vinyl carboxylates, the steric bulk of the carboxamide group had a minimal effect on the regio- and enantioselectivity of the reaction. The hydroformylation of (*Z*)-1-acetamido-1-propene, a 1,2-disubstituted alkene (a commonly difficult substrate class in AHF), yields the corresponding 1,2-amino aldehyde in 90% ee under mild conditions. In contrast, AHF of the (*E*)-1,2-disubstituted alkene (not shown) resulted in poor regio- (α:β ratio = 82:18) and enantioselectivities (32% ee).

## 2.3. Functionalized Allylic Substrates

Enantioselective hydroformylation of functionalized allylic substrates yields aldehydes that constitute useful building blocks for organic synthesis. Control of the regioselectivity in the hydroformylation of this substrate class has been a challenge for rhodium-coordinated ligands. Approaches that have been employed to mitigate this challenge include the use of substrate-tethered ligands (i.e., "directing groups" and "scaffolding ligands")[70,71] or taking advantage of supramolecular interactions (or secondary coordination sphere interactions) between a substrate and a metal complex outside of primary coordination sphere,[72] which overrides the intrinsic regioselectivity.

A particular aim in this area has been the hydroformylation of allyl cyanide to yield the corresponding α-aldehyde, which is a key building block[73,74] in the synthesis of two important, pharmacologically active targets: a gonadotropin releasing hormone (GnRH) antagonist[75] and a tachykinin $NK_1$ receptor antagonist.[76,77] A number of the ligands shown in Figures 1 and 2 have proven effective (>90% ee) in the hydroformylation of allyl cyanide: (*R*,*R*)-Ph-BPE (**14**) (96% conv, 90% ee),[52] **13a** (61% conv, 88:12 α:β ratio, and 93% ee),[53] Binapine (**4**) (87% regioselectivity and 94% ee),[53] YanPhos (**1d**) (>99% conv, 96% ee),[48] and **12a** (87% ee, unoptimized conditions).[52]

Zhang and co-workers have investigated the AHF of a series of *N*-allylamides (*N*-allyl carbamates, benzamide, sulfonamides, phthalimide), and obtained modest-to-good regioselectivities (66–

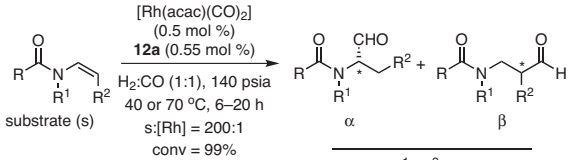



**Scheme 1.** Concise, Three-Step Synthesis of (+)-Patulolide C with AHF of a 1,2-Disubstituted (*Z*)-Vinyl Ester as the Key Step. *(Ref. 67)*

84% of the α-aldehyde) and high enantioselectivities (92–99% ee's) with YanPhos (**1d**).[78] By comparison, AHF of $CbzNHCH_2CH{=}CH_2$ with (*S*,*S*,*S*)-bisdiazaphospholane (**12a**) resulted in 86% ee for the α-aldehyde (82% regioselectivity).[69] Nozaki et al. have achieved the AHF of a chiral 4-vinyl β-lactam using (*R*)-2-Nap-BIPNITE-*p*-F (**2**)[79] in an effort to develop a new synthetic route toward 1*β*-methylcarbapenem antibiotics.[80–84] Specialized approaches such as those employing directing groups[70,85–87] and catalytic amounts of scaffolding ligands[71,88–90] have been developed to control the regioselectivity of hydroformylation in organic synthesis. Tan and co-workers have developed a labile, chiral scaffolding ligand, **15**, containing a hemiaminal functional group, for the enantioselective hydroformylation of substituted allylamines (73–93% ee).[91,92] Zhang's group has recently reported the asymmetric hydroformylation of 1,1-disubstituted allylphthalimides to $\beta^3$-amino aldehydes in 55–95% ee's by using bisphospholane (*S*,*S*)-Ph-BPE (*ent*-**14**).[93]

The enantioselective hydroformylation of allyl alcohols, ethers, silyl ethers, and esters (**eq 5**) has been demonstrated with (*S*,*S*,*S*)-BisDiazaPhos **12a**[69] and (*R*,*S*)-YanPhos (**1d**)[78] following Nozaki's work using (*R*,*S*)-BinaPhos (**1a**) (not shown).[94] Allyl alcohol hydroformylation with **12a** yields predominantly (77%) the achiral linear aldehyde, while the branched aldehyde (23%) is obtained highly enantioselectively (95% ee).[69] Allyl silyl ethers and allyl phenyl ether undergo effective hydroformylation, yielding the α-aldehyde with excellent enantioselectivity (92–96% ee) and improved regioselectivity (64–72% α-aldehyde). Zhang's group disclosed that the hydroformylation of allyl phenyl ether and allyl acetate with **1d** leads to 94% ee of the branched α-aldehyde in both cases.[78] 1,3-alkoxy aldehydes and 1,3-silyloxy aldehydes (protected Roche aldehydes) are useful in polyketide total synthesis. Common methods for Roche aldehyde synthesis typically involve functional group manipulation of the Roche ester through protection, reduction to the primary alcohol, and oxidation to the aldehyde. In contrast, enantioselective hydroformylation using diazaphospholane ligands offers an alternative, scalable method for accessing Roche aldehydes from protected allyl alcohols (**Scheme 2**).[69,95] For example, rhodium-diazaphospholane catalysts enable 5,000 turnovers in the hydroformylation of allyl *tert*-butyldimethylsilyl ether on a gram scale (3.24−3.43 g) to give the desired aldehyde in 55–58% isolated yields.[95] The hydroformylation of TMS-protected Z-crotyl alcohol (α:β = 74:26, 94% ee) and cinnamyl alcohol (α:β <2:98, 90% ee) proceeds in reasonable 15- and 16-hour reaction times with (*S*,*S*,*S*)-BisDiazaPhos **12a**.[69]

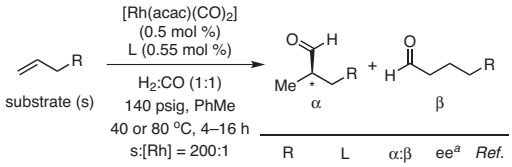
The enantioselective hydroformylation of α,β-unsaturated carbonyl substrates is not common because the branched dicarbonyl product can undergo rapid racemization via enolization. Faraone and co-workers reported the hydroformylation, in 95% conversion and 92% ee, of methyl acrylate to the branched aldehyde by using a (−)-menthol-derived phosphonite-pyridinyl bidentate ligand, **17** (**eq 6**, entry 1).[96] Clarke's group utilized (*S*,*S*,*S*)-bisdiazaphospholane **12a** in the AHF of *N*,*N*-dialkylacrylamides (not shown) and observed up to 82% ee.[97] Buchwald and Wang demonstrated the effective AHF of 1,1-disubstituted alkenes (α-alkylacrylates) to yield β-substituted aldehydes in 54–91% isolated yields and 81–94% ee's (eq 6, entries 2–4).[98] The α regioisomer was not observed in appreciable amounts in accordance with Keulemans' rule for 1,1-disubstituted alkenes.[99,100] Hydroformylation of α-alkylacrylates provides a synthetic route to 1,4-dicarbonyl structures that are present in pharmacologically active ingredients and biologically relevant molecules. Because the hydroformylation products of α,β-unsaturated carbonyls can undergo side reactions, protected analogues provide increased stability for the corresponding hydroformylation products. AHF with **12a** of acrolein derivatives protected as a 1,3-dioxolane (entry 5) or diacetoxy acetal (entry 7) yielded modest regio- (81% and 88% α:β ratio) and high enantioselectivities (92% and 93% ee, respectively).[69] Analogously,




| R | $R^1$ | $R^2$ | α:β | ee[a] |
|---|---|---|---|---|
| *b* | *b* | H | 98:2 | 95% |
| BnO | H | H | 98:2 | 94% |
| *t*-BuO | H | H | 97:3 | 99% |
| $F_3C$ | H | H | 98:2 | 99% |
| Me | H | Me | 97:3 | 90% |

[a] ee of the α isomer.
[b] $R,R^1 = C_6H_4$-1,2-$(CO)_2$.

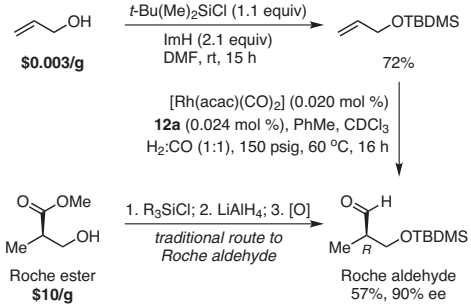
**eq 4** *(Ref. 69)*




| R | L | α:β | ee[a] | *Ref.* |
|---|---|---|---|---|
| HO | **12a** | 23:77 | 95% | *69* |
| TMSO | **12a** | 67:33 | 97% | *69* |
| TBSO | **12a** | 67:33 | 96% | *69* |
| TBSO | **12a** | 64:36 | 92% | *69* |
| PhO | **12a** | 72:28 | 96% | *69* |
| PhO | *ent*-**1d** | 71:29 | 94% | *78* |
| AcO | *ent*-**1d** | 30:70 | 94% | *78* |
| *b* | **12a** | 74:26 | 94% | *69* |
| *c* | **12a** | <2:98 | 90% | *69* |

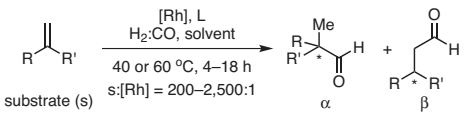
[a] ee of the α isomer. [b] Substrate = *cis*-$MeCH{=}CHCH_2OTMS$. [c] Substrate = *trans*-$PhCH{=}CHCH_2OH$.

**eq 5**




**Scheme 2.** AHF of Allyl Alcohol as an Alternative Route to Roche Aldehyde. *(Ref. 69,95)*

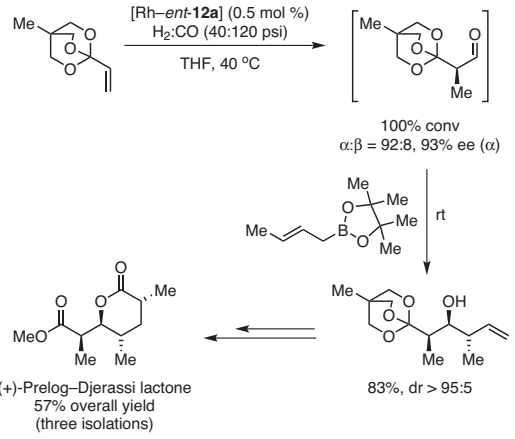
AHF of methyl vinyl ketone, protected as 2-methyl-2-vinyl-1,3-dioxolane, provided the α-aldehyde in 96% ee (entry 6). Burke and Risi employed *ent*-**12a** for the hydroformylation of a vinyl orthoester with improved regioselectivity (α:β = 92:8), while maintaining high enantioselectivity (93% ee). This same reaction was employed as the first step in the synthesis of the Prelog–Djerassi lactone (**Scheme 3**).[101] Leighton and co-workers have demonstrated the power of enantioselective hydroformylation in the total synthesis of dictyostatin.[102] Scalable syntheses of stereotriads C12−C14 and C20−C22 in fragments **A** and **B** (**Figure 4**) were accessed by hydroformylation of 2-vinyl-1,3-dioxolane and 2-methyl-2-vinyl-1,3-dioxolane at substrate:catalyst loadings of 6,667:1 and 3,333:1, respectively, and in the presence of rhodium-diazaphospholane catalyst *ent*-**12a** (**Scheme 4**).[102] One-pot, asymmetric, and Felkin-selective crotylation reactions of the branched aldehyde isolated from these hydroformylations yielded more than a gram of each of the stereotriads C12−C14 and C20−C22, using just 2 and 4 milligrams of ligand *ent*-**12a**! This unrivalled step-economical total synthesis of dictyostatin was achieved with a linear sequence of only 14 steps.




| Entry | R | R' | L | α:β | ee[a] | *Ref.* |
|---|---|---|---|---|---|---|
| 1 | H | $MeO_2C$ | **17** | 97:3 | 92% | *96* |
| 2 | *i*-Pr | $EtO_2C$ | **9** | only β | 92% | *98* |
| 3 | Cy | $EtO_2C$ | **9** | only β | 94% | *98* |
| 4 | *c*-Pent | $EtO_2C$ | **9** | only β | 93% | *98* |
| 5 | H | $(H_2CO)_2CH$ | **12a** | 81:19 | 92% | *69* |
| 6 | H | $(H_2CO)_2CMe$ | **12a** | 70:30 | 96% | *69* |
| 7 | H | $(AcO)_2CH$ | **12a** | 88:12 | 93% | *69* |
| 8 | H | $MeC(H_2CO)_3C$ | *ent*-**12a** | 92:8 | 93% | *101* |

[a] ee of the major isomer.

**eq 6**




**Scheme 3.** Application of the AHF of a Vinyl Orthoester in the Synthesis of Prelog–Djerassi Lactone. *(Ref. 101)*

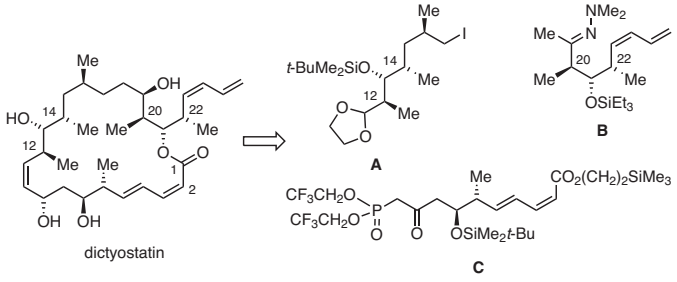
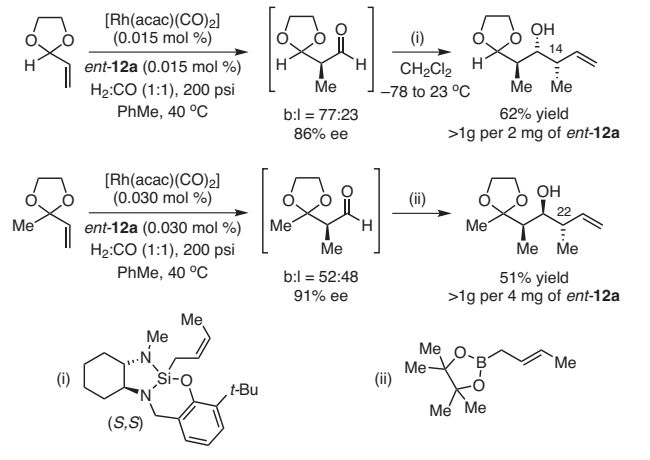



**Figure 4.** Leighton's Retrosynthetic Analysis of Dictyostatin. *(Ref. 102)*

## 2.4. Heterocycles

Chiral heterocycles such as pyrrolidines and tetrahydropyrans are common structural components of natural products. The asymmetric hydroformylation of 2,3-dihydropyrrole in the presence of (*R*,*S*)-BinaPhos (**1a**)[103] and (*S*,*S*,*S*)-BisdiazaPhos **12a**[69] gives 97% ee of the α-formyl product (a precursor of proline) in both cases (**eq 7**, entries 1 and 2). Conversely, the β-formyl isomer (a precursor of the β-amino acid) is accessible in 94% regioselectivity and 91% ee by hydroformylation of 2,5-dihydropyrrole with ligand **12a** (entry 3).[69] Reek and co-workers have effected the hydroformylation of 2,5-dihydrofuran using the phosphine–phosphite ligand **5** to give only the corresponding β-formyl regioisomer in 90% ee (entry 6).[104,105] Isomerization–hydroformylation of 2,3-dihydrofuran can be accomplished with ligand **5** to give the β-formyl aldehyde in high enantioselectivity (91% ee) but low conversion. In contrast, hydroformylation of 2,3-dihydrofuran using bisdiazaphospholane ligands *ent*-**12c** and *ent*-**12d** yields the α-formyl product in 78–79% regioselectivity and 90% ee (entries 4 and 5), while the 2,5-dihydrofuran preferentially gives the β-formyl product (entries 7 and 8; 97% regioselectivity and 95% ee for both ligands).[46] Burke and Clemens have reported the hydroformylation of *N*-Boc-2,2-dimethyl-3-oxazolidine to the synthetically useful Garner's aldehyde in high regio- (95%) and enantioselectivity (97%) using bisdiazaphospholane *ent*-**12a** (entry 9).[106]




**Scheme 4.** Leighton's Scalable, One-Pot, AHF Reactions in the Synthesis of the C12–C14 and C20–C22 Stereotriads of Dictyostatin. *(Ref. 102)*

### 2.5. 1,3-Dienes

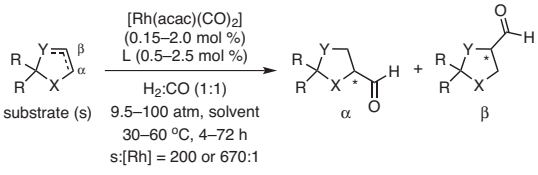
The hydroformylation of 1,3-dienes provides β,γ-unsaturated chiral aldehydes—key intermediates in polyketide synthesis. For example, Jacobsen and Lui have demonstrated the usefulness of the hydroformylation of 1,3-dienes [(*S*,*R*)-BinaPhos (*ent*-**1a**); b:l = 91:9, dr = 96:4] in setting the stereocenter at C15 in the total synthesis of (+)-ambruticin.[107] Similarly, Smith and co-workers have validated the use of (*R*,*S*)- and (*S*,*R*)-BinaPhos (**1a** and *ent*-**1a**) in the AHF of a diene intermediate in controlling the stereochemistry (dr > 95:5) at C10 of the C1–C12 fragment of tedanolide C.[108]

The hydroformylation of 1,3-butadienes can lead to 1-formyl, 2-formyl, and 4-formyl products, as well as products from alkene isomerization (**eq 8**). Hydroformylation of (*E*)-1-phenyl-1,3-butadiene, in the presence of (*R*,*S*)-BinaPhos (**1a**)[109] or (*S*,*S*,*S*)-bisdiazaphospholane (**12a**),[110] yields the 2-formyl product (**A**) (entries 1 and 2) in high regio- 92% and 99%) and enantioselectivities (90% and 91% ee). AHF of (*E*)-1-(2-furyl)-1,3-butadiene with **12a** enables the selective formation of the 2-formyl product (**A**) in 99% regioselectivity and 97% ee (entry 3). (*E*)-1-Methoxy- (entry 4), (*E*)-1-acetoxy- (entry 5), and (*E*)-1-triisopropylsilyloxy-1,3-butadienes (entry 6) all undergo effective AHF with high enantioselectivity [94%, 91%, and 90%, respectively, for the (*E*)-β,γ-unsaturated aldehyde]. Interestingly, hydroformylation of (*Z*)-1-triisopropylsilyloxy-1,3-butadiene (**Scheme 5**) results in the opposite absolute configuration of the aldehyde (70% ee) using the same enantiomer of the ligand (**12a**).[110] For this reason, stereochemically pure samples of (3*E*)-1,3-dienes are required to achieve highly enantioenriched aldehydes.

The enantioselective hydroformylation of (*E*)-1-carboethoxy-1,3-butadiene (eq 8, entry 7; 91% ee)[110] with **12a** offers a shorter synthetic route to the same aldehyde intermediate employed in the total synthesis of iejimalide B.[111] Fürstner and co-workers utilized six steps to synthesize a β,γ-unsaturated aldehyde from the Roche ester; the same intermediate can be accessed in one step through AHF of an achiral 1,3-diene. The hydroformylation, in the presence of **12b**, of 1-phenyl- and 1-(2-furanyl)-1,3-dienes, with methyl substitution at C2 (eq 8, entries 8 and 9), leads to the β,γ-unsaturated aldehyde in 88% and 98% regioselectivity, respectively, and 93% ee in both cases. 1-Vinylcyclohexene hydroformylation with ligands **1a** or **12b** affords the 2-formyl product (**A**) in an 86% and 88% ratio and in 96% and 92% ee, respectively (eq 8, entries 10 and 11). *Z*-selective hydroformylation was accomplished in the presence of an *E* alkene in the course of the hydroformylation of (1*E*,3*Z*)-1-phenyl-1,3-pentadiene with *ent*-**12a**, and resulted in the 2-formyl product (**A**) in 99% regioselectivity and 91% ee (entry 12).[110]

### 2.6. Other Alkenes

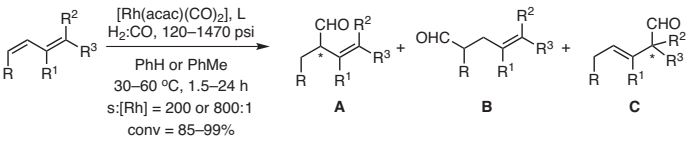
The industrial-scale hydroformylation of simple terminal alkenes, such as 1-hexene or 1-octene, has mainly aimed to optimize linear aldehyde formation. Reports of enantioselective hydroformylation of these substrates have been sparse, in part due to low selectivity for the branched aldehyde. Nozaki and co-workers have achieved the AHF of various aliphatic alkenes with (*R*,*S*)-BinaPhos (**1a**) and related ligands with varying levels of enantioselectivity (75–90% ee) and low-to-fair regioselectivity (8–30%).[44,112] Cobley, Clarke, and co-workers have utilized ($S_{ax}$,*S*,*S*)-BobPhos (**6**) for the asymmetric hydroformylation of 1-hexene and other alkyl alkenes in up to 93% ee and 71–86%




| X | Y | R | L | Conv | α:β | ee[a] | *R/S* | *Ref.* |
|---|---|---|---|---|---|---|---|---|
| NBoc | $CH_2$ | H | **1a** | 99% | 67:33 | 97% | *S* | *103* |
| NBoc | $CH_2$ | H | **12a** | 99% | 91:9 | 97% | ---- | *69* |
| NBoc | CH | H | **12a** | 99% | 6:94 | 91% | ---- | *69* |
| O | $CH_2$ | H | *ent*-**12c** | 45% | 79:21 | 90% | *R* | *46* |
| O | $CH_2$ | H | *ent*-**12d** | 27% | 78:22 | 90% | *R* | *46* |
| O | CH | H | **5** | 97% | 0:100 | 90% | *S* | *105* |
| O | CH | H | *ent*-**12c** | 94% | <3:97 | 95% | *S* | *46* |
| O | CH | H | *ent*-**12d** | 92% | <3:97 | 95% | *S* | *46* |
| NBoc | O | Me | *ent*-**12a** | 70%[b] | 95:5 | 97% | *S* | *106* |

[a] ee of the major regioisomer. [b] Isolated yield.

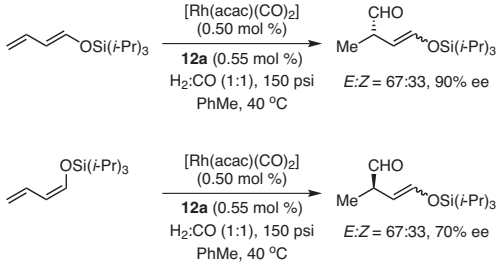
**eq 7**




| Entry | R | $R^1$ | $R^2$ | $R^3$ | **A**[a] | L | *E:Z* | *R/S*[b] | ee[b] | *Ref.* |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | H | H | Ph | 92% | **1a** | ---- | *R* | 90% | *109* |
| 2 | H | H | H | Ph | 99% | **12a** | >99:1 | *S* | 91% | *110* |
| 3 | H | H | H | 2-Fur | 99% | **12a** | >99:1 | *S* | 97% | *110* |
| 4 | H | H | H | MeO | 99% | **12a** | 1:1 | *S* | 94% | *110* |
| 5 | H | H | H | AcO | 60% | **12a** | 1:1 | *S* | 91% | *110* |
| 6 | H | H | H | TIPSO | 99% | **12a** | 2.4:1 | *S* | 90% | *110* |
| 7 | H | H | Me | $CO_2Et$ | 95% | **12a** | >99:1 | *S* | 91% | *110* |
| 8 | H | Me | H | Ph | 88% | **12b** | >99:1 | *S* | 93% | *110* |
| 9 | H | Me | H | 2-Fur | 98% | **12b** | >99:1 | *S* | 93% | *110* |
| 10 | H | *c* | H | *c* | 86% | **1a** | ---- | *R* | 96% | *109* |
| 11 | H | *c* | H | *c* | 88% | **12b** | >99:1 | *S* | 92% | *110* |
| 12 | Me | H | H | Ph | 99% | *ent*-**12a** | >99:1 | *S* | 91% | *110* |

[a] Percent of isomer A in the product. [b] Configuration and ee of the *E* isomer. [c] $R^1$,$R^3$ = $(CH_2)_4$.

**eq 8**




**Scheme 5.** Opposite Stereochemical Outcomes in the AHF of the *E* and *Z* Isomers of 1-Tri(isopropyl)silyloxy-1,3-diene with the Same Enantiomer of Ligand **12a**. *(Ref. 110)*

regioselectivity at 16 °C.[113] Zhang's group has employed (*R*,*S*)-YanPhos (**1d**) in the hydroformylation of allyltrimethylsilane and allylbenzene both in 94% ee (72 and 42% regioselectivity).[78] Nozaki et al. have accomplished the hydroformylation of 3,3,3-trifluoropropene, with (*R*,*S*)-BinaPhos (**1a**), giving the α-aldehyde in 95% regioselectivity and 93% ee.[43] Huang, Bunel, and co-workers have effected the enantioselective rhodium-catalyzed hydroformylation of norbornenes in up to 93% ee in the presence of (*R*,*R*,*S*,*S*)-TangPhos (*ent*-**13a**).[114]

## 3. Conclusions and Outlook

The enantioselective *hydroformylation* of alkenes using rhodium-bisdiazaphospholane catalysts offers a practical method for the synthesis of functionalized chiral building blocks that approach the efficiency found in the catalytic, asymmetric *hydrogenation*. AHF of styrenes yields precursors to pharmacologically active, anti-inflammatory analgesics such as ibuprofen and naproxen. The protected α-hydroxy aldehydes resulting from the hydroformylation of vinyl esters have been employed in the synthesis of chiral isoxazolines and imidazoles, and in the synthesis of (+)-patulolide C. The hydroformylation of vinyl amides provides access to protected α-amino aldehydes. Protected allyl alcohol, acroleins, acrylates, and related analogues undergo AHF to synthetically useful precursors (e.g., Roche aldehydes) for natural product synthesis (e.g., Prelog–Djerassi lactone and dictyostatin). Exploiting the high activity and selectivity of robust rhodium-diazaphospholane catalysts enables scalable and practical syntheses of useful chiral building blocks for more complex products. The enantioselective hydroformylation of heterocycles yields useful aldehydes such as Garner's aldehyde or precursors to proline or β-proline. AHF of 1,3-dienes yields chiral β,γ-unsaturated aldehydes that are useful intermediates for natural product synthesis (e.g., (+)-ambruticin and tedanolide C). Simple alkyl alkenes remain a challenge in hydroformylation because of the difficulty in controlling the regioselectivity, but high levels of enantioselectivity have recently been achieved with several hybrid ligands.

Enantioselective hydroformylation is an emerging technology for the atom-efficient synthesis of chiral aldehydes. It is anticipated that new chiral ligands will offer solutions to present challenges in hydroformylation. In particular, the hydroformylation of disubstituted and trisubstituted alkenes would enable the synthesis of products with more diverse branching substituents. Reaction sequences that couple hydroformylation with hydrogenation, oxidation, olefination, hydroaminomethylation, etc., could capitalize on the inherent advantages of hydroformylation (gaseous reagents, essentially neutral conditions, fast rates, and large turnover numbers). Newer reactor technologies, such as flow reactors, could be applied to hydroformylation and would simplify the translation of bench-top reactions into scalable processes in the pharmaceutical environment. For the bench chemist, the replacement of synthesis gas with more easily handled equivalents; such as formalin, paraformaldehyde, or polyols; would make hydroformylation more attractive. These challenges and opportunities will continue to drive research into, and applications of, the enantioselective hydroformylation.

## 4. Acknowledgments

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## About the Authors

**Gene W. Wong** received his undergraduate chemistry degree in 2007 from the University of Nevada, Reno, where he conducted undergraduate research with Professor Brian J. Frost on new water-soluble phosphine ligands. In 2012, he received his Ph.D. degree from the University of Wisconsin-Madison, working with Professor Clark R. Landis. His graduate studies focused on the synthesis of a library of bisdiazaphospholane ligands and their application in the rhodium-catalyzed asymmetric hydroformylation. Until his recent untimely death, Gene had been a research associate with Professor Karen I. Goldberg at the University of Washington.

**Clark R. Landis** is Helfaer Professor of Inorganic and Organic Chemistry at the University of Wisconsin-Madison. Born in 1956, he received a B.S. degree in chemistry from the University of Illinois at Urbana-Champaign and a Ph.D. in chemistry from the University of Chicago in 1983. His graduate work with Professor Jack Halpern concerned the mechanism of enantioselective catalytic hydrogenation reactions. After three years as a research scientist at Monsanto Corporation, Clark began his academic career at the University of Colorado Boulder. Since 1990, he has been at the University of Wisconsin-Madison. His current research interests include mechanisms of catalytic transformations, development of new instrumentation for fast kinetics, design of modular enantioselective catalysts, computational modeling, and bonding theory. Special recognitions include the 2010 ACS Award in Organometallic Chemistry, the UW Chancellor's Distinguished Teaching Award, AAAS Fellow, ACS Fellow, and numerous lectureships. Clark and Frank Weinhold are authors of the books *Valency and Bonding* (Cambridge University Press, 2005) and *Discovering Chemistry with Natural Bond Orbitals* (Wiley, 2012).

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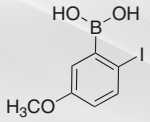


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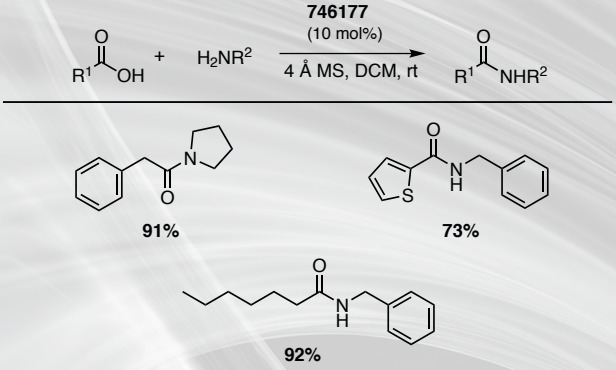


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# Boronic Acid Catalysis: an Atom-Economical Platform for Direct Activation and Functionalization of Carboxylic Acids and Alcohols

Dr. Hongchao Zheng

Prof. Dennis G. Hall

**Hongchao Zheng and Dennis G. Hall***

Department of Chemistry
University of Alberta
Edmonton, AB T6G 2G2, Canada
Email: dennis.hall@ualberta.ca

**Keywords.** catalysis; boronic acids; atom-economy; green chemistry; direct amidation; Friedel–Crafts alkylation; cycloadditions; Meyer–Schuster rearrangement; allylic alcohol transposition.

**Abstract.** Boronic Acid Catalysis (BAC) offers an alternative strategy for activating hydroxyl-containing substrates such as carboxylic acids, alcohols, and other functional groups in a mild and selective manner. In the past five years alone, the list of reactions shown amenable to BAC has increased significantly. By avoiding the need for stoichiometric activation associated with the use of halide leaving groups and complex reagents, BAC provides better atom- and step-economy.

## Outline



## 1. Introduction

Catalysis is ubiquitous to life and central to the chemical industry, where the discovery and development of sustainable processes rely heavily on advances in the field of catalysis. Indeed, catalysis, atom-economy, and reduction of derivatives constitute three of the *12 Principles of Green Chemistry*.[1] In this regard, the ACS Green Chemistry Institute Pharmaceutical Roundtable has identified a list of industrially relevant chemical reactions in need of greening, and fundamental transformations, such as amide formation from carboxylic acids and Friedel–Crafts alkylations, were ranked as top research priorities.[2] Over the past decade, catalysis of reactions by simple, metal-free organic compounds (organocatalysis) has also become an important area of research.[3] Compared with catalysts consisting of metal complexes, organocatalysts demonstrate many advantages including a lower sensitivity to moisture and oxygen, ease of preparation, low cost, and avoidance of drug regulatory issues for trace metals. Thus far, organocatalysis has been applied mainly to the activation of carbonyl-containing compounds (ketones, aldehydes) and imine derivatives.[3] Comparatively, very few strategies have been exploited for catalytically activating the hydroxyl group of carboxylic acids and alcohols via transient covalent-bond formation. A limited number of successful efforts to develop catalytic Mitsunobu-like and other reactions of secondary alcohols have been reported.[4] Strong Brønsted acids may be employed as catalysts and promoters of $S_N1$-type reactions of activated alcohols.[5] These conditions, however, often create issues of functional group incompatibilities. This review highlights an emerging, alternative strategy for activating hydroxyl-containing substrates such as carboxylic acids, alcohols, diols, and other functionalities in a mild and selective manner using boronic acids as catalysts.

## 2. Boronic Acid Catalysis (BAC)

Boronic acids are a particularly attractive class of synthetic intermediates because of their unique properties and reactivity as mild organic Lewis acids ($sp^2$-hybridized boron atom with a vacant orbital), combined with their stability and ease of handling.[6] Moreover, because of their low toxicity and their ultimate degradation into boric acid, boronic acids can be regarded as "green" (environmentally friendly) compounds. Most boronic acids exist as white crystalline solids, typically as mixtures of the free boronic acid together with its anhydride forms such as the 6-membered boroxine. Arylboronic acids, in particular, can be handled in air without special precautions, and most are chemically stable and display shelf-stability for long periods of time. Boronic acids can form covalent bonds with the hydroxyl groups of alcohols and carboxylic

acids in a reversible manner, providing a template upon which the reactants can be brought together and properly oriented in order to accelerate reactions (**Figure 1**). Faster reactions and unique selectivity are some of the main benefits provided by the synthetic strategy of "induced intramolecularity".[7]

The use of arylboronic acids as stoichiometric templates to enable chemical transformations has been demonstrated several decades ago. For instance, a boronic acid facilitated Diels–Alder cycloaddition was key to Nicolaou's total synthesis of Taxol® (**Scheme 1**, Part (a)),[8] and the Nagata hydroxyalkylation of phenols also requires boronic acids (Scheme 1, Part (b)).[9] The first reported use of boronic acids as reaction *catalysts* appears to date from 1963, when Letsinger and co-workers demonstrated that quinolin-8-ylboronic acid could promote the hydrolysis and alcoholysis of chlorine-substituted aliphatic alcohols in the presence of collidine to afford diols as the products (Scheme 1, Part (c)).[10] The boronic acid functionality serves as a template to hold the alcohol substrate through the formation of a covalent hemiester intermediate, and the nitrogen atom of the quinolin-8-ylboronic acid moiety assists chloride displacement presumably through a cooperative general base effect. Although this study had little practical value as a method to prepare glycols, it represents an important milestone for BAC as a type of organocatalysis.

Decades after Letsinger's seminal study, substituted arylboronic acids are emerging as a unique class of organocatalysts due to their Lewis acidity, which can be easily modulated by their substitution pattern (see Y in Figure 1, Part (a)).[11] Furthermore, *ortho*-substituted arylboronic acids can be regarded as bifunctional catalysts.[12] The boronic acid functionality can form temporary covalent bonds with alcohols, carboxylic acids, or amines that are readily cleaved in subsequent steps to allow catalytic recycling. These covalent intermediates can concomitantly activate the alcohol or carboxylic acid for a desired reaction. In this context, the *ortho*-substituent, X, can further activate the substrate, or serve as a handle or template for directing reagents via cooperative effects. The concept of BAC will be discussed and illustrated in the next sections with a review of the recent progress achieved with several different catalysts such as **1**–**12** (Figure 1, Part (b)).

## 3. Activation of Carboxylic Acids

Arylboronic acids react reversibly with carboxylic acids to generate a putative, monoacyl boronate species, which can provide electrophilic activation of the carboxylate group by an inductive effect that may be augmented through an intramolecular hydrogen bond. This mode of carboxyl activation has been successfully applied in several important organic reactions.

### 3.1. Direct Amidation of Carboxylic Acids

The first and most popular example of the boronic acid catalyzed activation of carboxylic acids is the preparation of amides. The amide bond is ubiquitous in naturally occurring compounds such as peptides and in synthetic commodity chemicals. In this respect, it has been reported that as much as 25% of all synthetic pharmaceutical drugs contain an amide unit.[13] A plethora of sophisticated and efficient methods

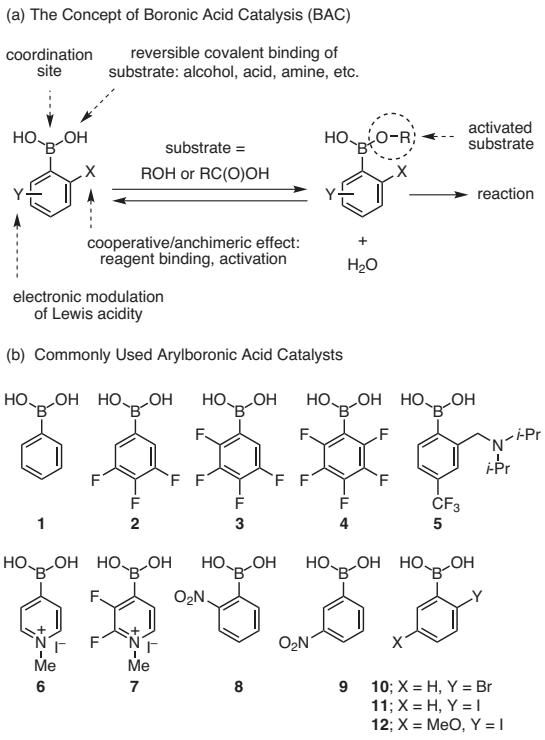
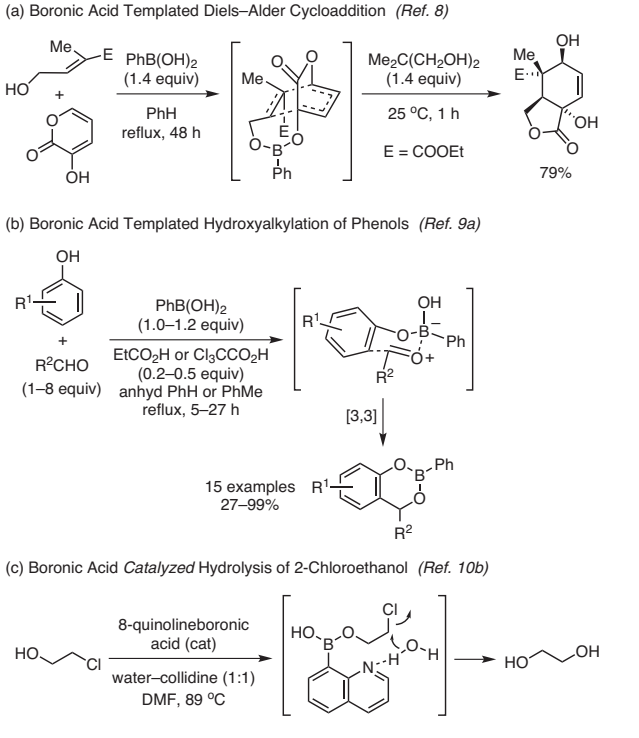



**Figure 1**. (a) Boronic Acid Catalysis, and (b) Common Arylboronic Acids Employed as Catalysts.




**Scheme 1.** Examples of Early Applications of Boronic Acids as Templates or Catalysts: (a) Diels–Alder Reaction, (b) Phenol Hydroxyalkylation, and (c) Boronic Acid Catalyzed Nucleophilic Hydrolysis.

employing dehydrating–activating reagents have been developed for the direct ("in situ") coupling of carboxylic acids and amines.[14] Common coupling reagents such as carbodiimides and phosphonium or uronium salts are expensive, often toxic, and provide poor atom-economy. These reagents and their associated co-reagents—including bases, supernucleophiles, and other additives—are required in stoichiometric excess and generate wasteful byproducts that complicate the isolation of the desired amide product. It is therefore not surprising that amide formation has been deemed the top-priority research area by the ACS Green Chemistry Institute Pharmaceutical Roundtable.[2] An ideal direct amidation reaction between carboxylic acids and amines would be a waste-free, catalytic, and operationally simple process occurring at ambient temperature. Despite the favorable thermodynamic stability of the resulting amide, the simple thermal dehydration between an amine and a carboxylic acid generally requires high temperatures, from 85 °C for some substrate combinations[15] to well over 150 °C for others.[16] These conditions may not be compatible with highly functionalized molecules, and this large energy barrier has made it very challenging to develop a direct amidation method between free carboxylic acids and amines at room temperature.[17]

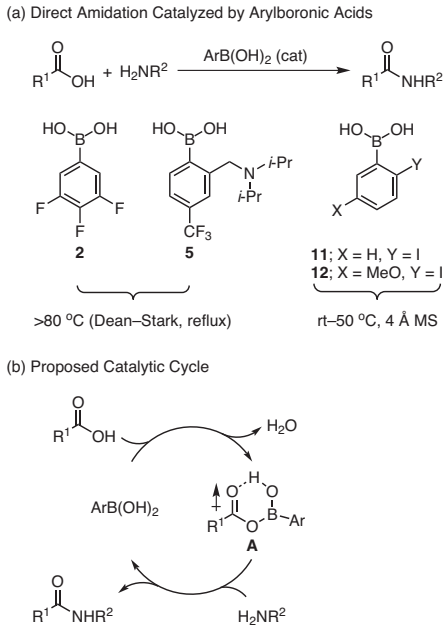
Boron compounds, used in a stoichiometric fashion, have long been known to promote direct amidation reactions.[18] In 1996, Yamamoto and co-workers described the first catalytic use of arylboronic acids for direct amidations,[19] and found electron-poor polyfluorinated arylboronic acids to be preferable. However, even the most efficient one, 3,4,5-trifluorophenylboronic acid (**2**), required reflux temperatures over 110 °C for several hours in nonpolar solvents. Other efficient arylboronic acids have been reported, such as Whiting's bifunctional 2-(diisopropylaminomethyl)-4-trifluoromethylphenylboronic acid (**5**)[20] and even boric acid.[21] All of these catalysts function at levated temperatures (**Scheme 2**, Part (a)). Following their initial discovery, Yamamoto and co-workers reported that the highly electron-deficient *N*-methyl-4-pyridiniumboronic acid (**6**, Figure 1) was more efficient than **2** in catalyzing direct amide formation,[22] and showed better thermal stability as compared to the 3-pyridinium isomer.[23] In both cases, the reaction needs to be realized under azeotropic reflux conditions (>110 °C). The superior catalytic activity of electron-deficient arylboronic acids is most likely the result of the enhanced Lewis acidity of the boron atom, which boosts the electrophilic activation of the carboxyl group in the proposed monoacyl boronate intermediate **A** (Scheme 2, Part (b)).

Soon after identifying catalyst **5**, Whiting and co-workers designed a chiral ferrocene-based bifunctional *ortho*-amino-substituted arylboronic acid for the kinetic asymmetric resolution of racemic α-substituted benzylamines with achiral carboxylic acids.[24] Although moderate yields and enantioselectivities (up to 41% ee) were obtained, this landmark study represented the first example of asymmetric direct amidation reactions, and opened up a new direction for the kinetic resolution of amines.

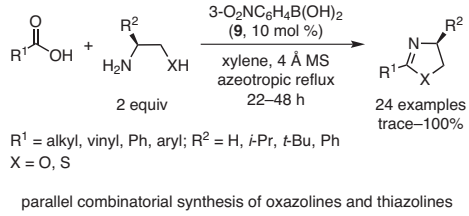
Wipf and Wang have exploited Yamamoto's direct amidation protocol in developing a method for the preparation of a combinatorial library of biologically active oxazolines and thiazolines (**eq 1**).[25] In this process, electron-deficient 3-nitrophenylboronic acid (**9**) was employed as catalyst to promote a tandem condensation–cyclodehydration of carboxylic acids with amino alcohols or amino thiols.[25]

In 2008, our group disclosed that *ortho*-iodophenylboronic acid (**11**) possesses superior catalytic activity for the direct amidation of carboxylic acids, and is effective at room temperature in the presence of molecular sieves.[26] Boronic acid **11** showed better catalytic efficiency than its analogues with a bromo or chloro substituent under the same reaction conditions. After carefully optimizing the arene core of the *ortho*-haloarylboronic acid with regards to the steric and electronic effects of ring substitution, 5-methoxy-2-iodophenylboronic acid (MIBA, **12**) was recently identified as the optimal new catalyst.[27] MIBA is kinetically more active than the parent, des-methoxy catalyst **11**, and provides higher yields of amide products in shorter reaction times under mild conditions at ambient temperature (**Scheme 3**).[26,27]

A thorough optimization of reaction conditions identified 4 Å molecular sieves as the optimal dehydrating agent, and methylene chloride, toluene, or 2-Me-THF as the optimal solvents with a substrate concentration of 0.07–0.1 M.[27] Because excess amine slows down the amidation, it is preferable to use a slight excess of the carboxylic acid. Moreover, the order of addition is critical. It is essential to premix the carboxylic acid and the catalyst in the presence of molecular sieves for several minutes prior to addition of the amine. All of the examples with the optimal MIBA catalyst (**12**) provided faster reactions and higher product yields when compared under identical conditions to the first-generation catalyst **11**.[27] The amidation reaction gives excellent yields within two hours at room temperature for most aliphatic substrates, and,

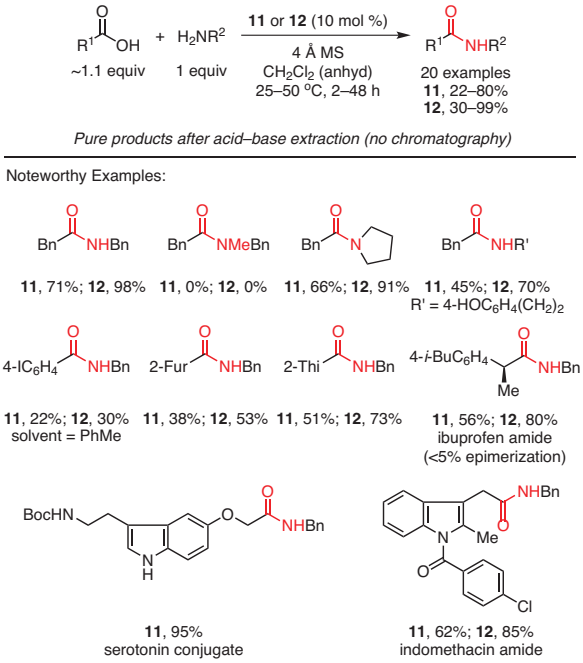



**Scheme 2.** The Boronic Acid Catalyzed Direct Amidation of Carboxylic Acids. *(Ref. 19,20,26,27)*




**eq 1** *(Ref. 25)*

although an acyclic secondary amine failed to undergo the reaction, cyclic amines provided high yields of the desired amides. Aromatic amines (not shown) were unreactive, and aromatic carboxylic acids were found to require a higher reaction temperature to afford low yields after 48 hours. On the other hand, heteroaromatic carboxylic acids provided amide products in moderate-to-good yields in reactions performed at 50 °C. Highly functionalized substrates containing phenol, pyridine, and indole units were successfully employed to make biologically relevant amide products. One such amide that was prepared with ease using catalyst **12** is a derivative of the drug indomethacin known to inhibit COX-2 enzymes.[28] This method is in sharp contrast to a previously reported synthesis of the same amide that employs excess coupling reagents and a chromatographic purification.[28] The amidation of optically active (*S*)-ibuprofen with benzylamine led to the corresponding amide with less than 5% racemization. Given the propensity of ibuprofen and its amides to racemize,[29] this result demonstrates the mildness of these ambient conditions. These direct catalytic amidations are operationally simple, employ quasi-equimolar amounts of acid and amine, require no or low heating, and generate no byproducts. In many cases, pure amide products are isolated after a simple filtration and acid–base extractions to remove any unreacted substrates. It is noteworthy that, when the synthesis of BnCONHBn was repeated on a larger scale (5 mmol), the boronic acid catalyst was successfully recovered in high yield (90%) by simple acidification and extraction of the basic aqueous phase. When re-subjected to the same amidation reaction, the recovered catalyst afforded the same yield of product. Furthermore, our group has recently prepared a solid-supported prototype of the MIBA catalyst, and showed it to be competent in amidations of primary amines.[30]




**Scheme 3.** Direct Amidation Catalzyed by *ortho*-Iodoarylboronic Acids **11** and **12**. *(Ref. 26,27)*

## 3.2. Mechanistic Studies of the Boronic Acid Catalyzed Direct Amidation

The mechanism of the boronic acid catalyzed amidations, as proposed by Yamamoto and co-workers, was supported by the apparent observation of a monoacyl boronate intermediate (**A** in Scheme 2).[19] In our system, we ruled out the intermediacy of carboxylic acid anhydrides based on the observation that no acetic anhydride was observed when acetic acid and **11** were mixed alone under the direct amidation conditions.[26] Concerning the role of the ortho-iodide substituent, we established that the acidity of **11** is not abnormal (i.e, p$K_a$ of 8.9 vs 8.8 for $PhB(OH)_2$)[26] and thus cannot explain its exceptional catalytic activity. Not only is the iodide substituent preferred, its ortho position is crucial. Indeed, both the para isomer and a naphthyl derivative are significantly less effective.[27] Other reaction variables play an intriguing role in this amidation reaction, and point towards a complicated reaction process. For instance, it was suggested that molecular sieves act both as a dehydrating agent and as a reversible reservoir of trace water. Although the detailed mechanism is uncertain at present, preliminary experiments by us suggest that the free boronic acid is the active catalyst (not the boroxine), and DFT calculations by Marcelli[31] suggest that the catalytic activity of *ortho*-haloarylboronic acids results from the Lewis basic character of the halogen atom. The latter would be implicated as an H-bond acceptor to facilitate the elimination of water from the orthoaminal intermediate proposed in the rate-determining step. Marcelli's DFT calculations imply the formation of an acylborate intermediate en route to the orthoaminal transition state (**TS**) shown in **Scheme 4**.[27,31] The catalyst accelerates the orthoaminal formation step (**A**•$H_2O$ to **B**) by activating the acyl group for nucleophilic attack by the amine. Elimination of water from the orthoaminal intermediate (**B**), as depicted in the transition state (**TS**), becomes the rate-limiting step.[31] This step was proposed to be facilitated by a halogen–hydrogen bond that decreases the overall degrees of freedom while rendering the boron more electrophilic to ease the required shuffling of B–O bonds. In this scenario, compared to **11**, the optimal catalyst **12**, with a slightly more basic iodide, forms a stronger I···H bond that consequently leads to a lower activation energy. According to Marcelli's DFT calculations, the iodide substituent possesses the right size, geometry, and basicity to support the mechanism shown in Scheme 4.[31]

## 3.3. Esterification and Anhydride Formation

The electron-deficient *N*-methyl-4-pyridiniumboronic acid (**6**) catalyzes the esterification of hydroxycarboxylic acids with excess alcohols.[32] A hydroxyl group at the α or β position of the carboxylic acid is essential for the success of the reaction since it can participate in the formation of a tetrahedral acyloxyborate in the proposed intermediate.[32] A similar concept was recently applied to a dehydrative amidation of α-hydroxycarboxylic acids using alkylboronic acids as catalysts.[33] In light of the ability of Whiting's bifunctional *ortho*-aminomethyl-substituted arylboronic acid **5** to accelerate direct amidations, Ishihara and co-workers developed a similar bis(*ortho*-aminomethyl)-substituted arylboronic acid **13** to effectively catalyze the dehydrative intramolecular condensation of dicarboxylic acids to afford cyclic anhydrides at significantly milder temperatures as compared to the thermal variant (**eq 2**).[34] The authors claimed that boronic acid **13** works as a bifunctional catalyst, with the amine substituent serving as a Brønsted base to deprotonate the first carboxylic acid, thus increasing the nucleophilicity of the corresponding carboxylate functionality in the proposed monoacyl boronate intermediate.[34] Moreover, the second protonated amine substituent could act as a Brønsted acid to further activate the second (acceptor) carbonyl group through a relay of two hydrogen bonding interactions.

## 4. Activation of Unsaturated Carboxylic Acids

Because of the potential chemical incompatibility of the carboxylic acid group with other functional groups, the former is usually handled in a masked form, such as the ester, which in turn requires additional synthetic steps to prepare and remove. In this regard, a direct method for electrophilic (or LUMO-lowering) activation of unsaturated carboxylic acids towards cycloadditions would be very advantageous in terms of atom- and step-economy. Such a concept, employing boronic acids as catalysts, would mirror the strategy of iminium activation for unsaturated aldehydes and ketones.[3] We first demonstrated its application in [4 + 2] cycloadditions of acrylic acid with acyclic and cyclic 1,3-dienes catalyzed by arylboronic acids.[26]

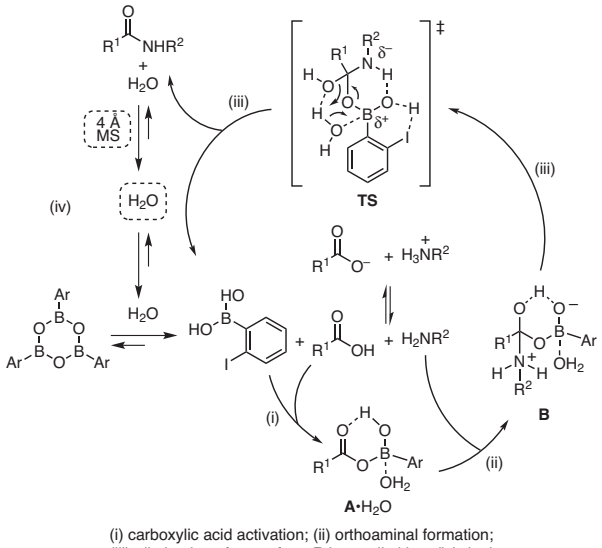
### 4.1. Diels–Alder Cycloadditions

Upon optimizing the boronic acid catalyzed [4 + 2] cycloaddition of acrylic acid and simple 1,3-dienes, it quickly became apparent to us that electron-poor boronic acids such as *ortho*-nitro- and *ortho*-bromophenylboronic acids **8** and **10** provide faster reaction rates (**Scheme 5**, Part (a)).[26,27] Moreover, the cycloaddition failed to proceed appreciably in the absence of catalyst, and there was no need for molecular sieves in these reactions (in fact, some water was required for catalyst turnover). This method was recently employed by Roussi and co-workers to prepare a complex bicyclic bridgehead carboxylic acid required in a biomimetic total synthesis of meiogynin A.[35] Alkynoic acids are suitable partners, and as with alkenoic acids, a remarkable increase in regioselectivity can be observed in the boronic acid catalyzed manifold (Scheme 5, Part (b)).[36]

### 4.2. Dipolar Cycloadditions: Huisgen Cycloaddition with Azides

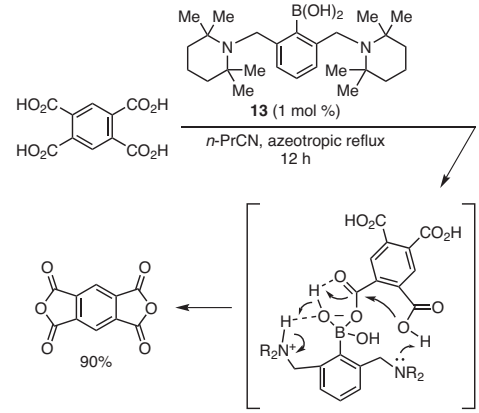
Our group extended the concept of BAC to the activation of unsaturated carboxylic acids in several classic dipolar [3 + 2] cycloadditions involving azides, nitrile oxides, and nitrones.[37] These cycloadditions produce pharmaceutically interesting small heterocyclic products such as triazoles, isoxazoles, and isoxazolidines. BAC allows these cycloadducts to be formed directly from the free carboxylic acid group (obviating the need for masking and unmasking the carboxylate through esterification steps), which can then be employed for further transformation. With optimal conditions in hand (2–20 mol % 2-$O_2NC_6H_4B(OH)_2$ (**8**) in $ClCH_2CH_2Cl$ at 25 °C), the scope of azide and alkyne substrates was examined for the Huisgen [3 + 2] cycloaddition (**Scheme 6**).[37] A wide variety of aliphatic and aromatic azides could be employed. Not only did the boronic acid catalyzed variant give greatly improved yields of 1,2,3-triazole products over the uncatalyzed reaction, but the regioselectivity was also significantly improved to the point of avoiding the need to separate regioisomers in most cases. Satisfactorily, it was found that 3-substituted 2-alkynoic acids can be successfully utilized provided a slightly elevated temperature or a longer reaction time is used. Alkenoic acids are not suitable substrates as indicated by the failure of acrylic acid to react with benzyl azide (not shown).

The boronic acid catalyzed Huisgen cycloaddition of acetylenic carboxylic acids does not only display an interesting substrate scope, it also circumvents the decarboxylation side reaction that plagues the thermal uncatalyzed variant.[38] For example, when run under typical conditions in refluxing 1,2-dichloroethane for just four hours,

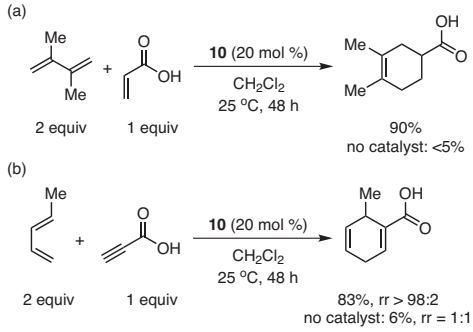



(i) carboxylic acid activation; (ii) orthoaminal formation; (iii) elimination of water from **B** is rate-limiting; (iv) dual role of molecular sieves as a reversible dehydrating agent.

**Scheme 4.** Proposed Catalytic Cycle for the Ambient, Direct Amidation Catalyzed by *ortho*-Iodoarylboronic Acids. *(Ref. 27,31)*



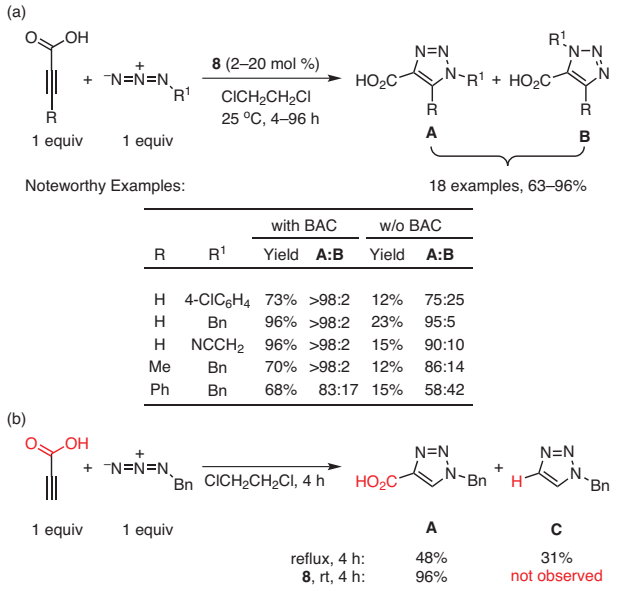

**eq 2** *(Ref. 34)*




regioisomer ratio (rr) is for the 2-Me vs 3-Me product

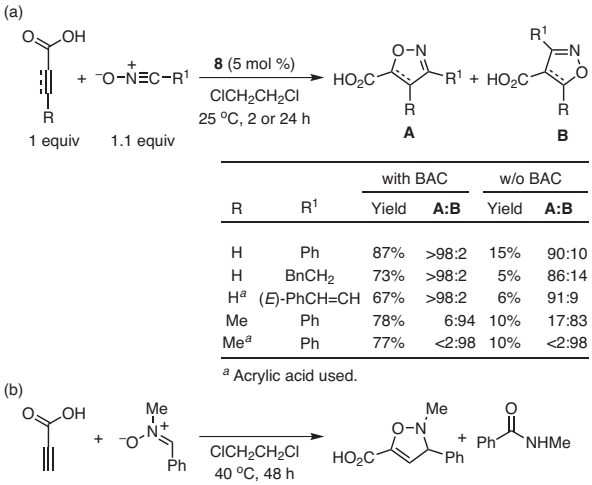
**Scheme 5.** Boronic Acid Catalyzed Diels–Alder Cycloadditions. *(Ref. 26,36)*

the product of cycloaddition of benzyl azide and propiolic acid was accompanied by as much as 31% of the corresponding decarboxylated adduct (Scheme 6, Part (b)). The BAC variant (**8**, rt, 4 h) completely suppressed this undesired pathway. This method was recently applied in the preparation of triazole-based prodrugs of novel acyclic nucleoside phosphonates.[39]




| | | with BAC | | w/o BAC | |
|---|---|---|---|---|---|
| R | $R^1$ | Yield | A:B | Yield | A:B |
| H | 4-$ClC_6H_4$ | 73% | >98:2 | 12% | 75:25 |
| H | Bn | 96% | >98:2 | 23% | 95:5 |
| H | $NCCH_2$ | 96% | >98:2 | 15% | 90:10 |
| Me | Bn | 70% | >98:2 | 12% | 86:14 |
| Ph | Bn | 68% | 83:17 | 15% | 58:42 |

**Scheme 6.** Boronic Acid Catalyzed Dipolar Cycloadditions between Alkynoic Acids and Azides to Produce 1,2,3-Triazoles. *(Ref. 37)*




| | | with BAC | | w/o BAC | |
|---|---|---|---|---|---|
| R | $R^1$ | Yield | A:B | Yield | A:B |
| H | Ph | 87% | >98:2 | 15% | 90:10 |
| H | $BnCH_2$ | 73% | >98:2 | 5% | 86:14 |
| H[a] | (*E*)-PhCH=CH | 67% | >98:2 | 6% | 91:9 |
| Me | Ph | 78% | 6:94 | 10% | 17:83 |
| Me[a] | Ph | 77% | <2:98 | 10% | <2:98 |

[a] Acrylic acid used.

**Scheme 7.** Boronic Acid Catalyzed Dipolar Cycloadditions between Unsaturated Carboxylic Acids and Nitrile Oxides and Nitrones. *(Ref. 37)*

### 4.3. Cycloadditions with Nitrile Oxides and Other Dipoles

The generality of this activation concept was assessed in other types of [3 + 2] cycloadditions that afford valuable heterocyclic products. Remarkably, nitrile oxides and nitrones added to both alkynoic and alkenoic acids in the presence of 2-$O_2NC_6H_4B(OH)_2$ (**8**) as catalyst to give the corresponding isoxazoles and isoxazolines in much improved yields and regioselectivity when compared to the thermal, uncatalyzed reactions (**Scheme 7**, Part (a)).[37] Interestingly, in the cycloadditions of nitrile oxides, (unsubstituted) propiolic and acrylic acids tended to provide the sterically favored isomers, while 3-substituted alkynoic and alkenoic acids generated the opposite regioisomers as a result of electronic control. With nitrones, it was necessary to employ a special procedure to minimize the formation of the undesired amide, which can arise from the protic-acid-catalyzed Beckmann rearrangement of nitrones. Thus, the unsaturated carboxylic acid substrate was added slowly to the reaction mixture containing the catalyst so as to form the acylborate intermediate stoichiometrically, thus keeping the concentration of free carboxylic acid to a minimum (Scheme 7, Part (b)).

### 4.4. Mechanistic Studies of Boronic Acid Catalyzed Cycloadditions

Employing Childs's method,[40] we conducted NMR spectroscopic measurements whereby a large increase of 6.9 ppm was recorded for the $^{13}C$ NMR chemical shift of the β carbon (C3) of the monoacylated boronate of (*E*)-crotonic acid.[37] The extent of this chemical shift increase is comparable to the effect achieved in the complexation of methyl crotonate with moderate Lewis acids such as $SnCl_4$.[40] According to these results, 2-$O_2NC_6H_4B(OH)_2$ (**8**) catalyzes the cycloadditions through a powerful LUMO-lowering activation of the dienophile/dipolarophile by formation of a monoacylated covalent adduct **A** (see also Scheme 2) with the unsaturated carboxylic acid. Combined with the role of water in recycling the catalyst, this preliminary mechanistic study led to the catalytic cycle proposed in **Figure 2**.[37]

## 5. Activation of Alcohols

Arylboronic acids can provide electrophilic activation of the hydroxyl group of alcohols by facilitating the complete (or partial) ionization of the C–O bond to generate a carbocation intermediate. When applied to activated substrates such as allylic alcohols, regioselectivity becomes an issue as the reaction can proceed via two possible pathways depending on the degree of ionization of the C–O bond.

### 5.1. Friedel–Crafts Alkylations

In a landmark paper, McCubbin and co-workers reported that the highly Lewis acidic pentafluorophenylboronic acid (**4**) showed excellent catalytic activity in the regioselective Friedel–Crafts reaction of allylic alcohols at room temperature and in the presence of molecular sieves (**eq 3**).[41] When compared with other catalysts such as *p*-TsOH, $BF_3$, and $FeCl_3$, catalyst **4** provided a higher yield of product with one set of model substrates. However, only the most electron-rich arenes or heteroarenes are suitable substrates; for instance, even anisole is not reactive enough under these conditions. Nonetheless, a variety of highly substituted arenes and heteroarenes was prepared in this manner, and the Friedel–Crafts alkylation reaction was presumed to proceed through an $S_N1'$ pathway involving an allylic carbocation with the regioselectivity being controlled by steric effects. Benzylic alcohols were also suitable substrates, but higher reaction temperatures were required (see eq 3, last example).[42] Later, the same group extended this catalytic system to propargylic alcohols, developing a highly effective and selective methodology for the propargylation and allenylation of electron-rich

aromatics.[43] Although the substrate scope is limited to highly electron-rich aromatic nucleophiles, these methodologies provide a milder and more environmentally friendly means for alcohol activation compared to existing strategies using Lewis acids, Brønsted acids, or transition-metal catalysts. Recently, our group identified improved Friedel–Crafts alkylation conditions by employing catalyst **7** (see structure in Figure 1) in nitromethane, which allowed less activated arenes to participate as substrates (**eq 4**).[44]

### 5.2. Intramolecular Trapping (Cyclization) of Alcohols

Our research group applied the BAC concept to the cyclization of allylic alcohols embedded with a pendent nucleophile.[45] Optimization studies identified catalysts that were notably superior to **4**, namely tetrafluorophenyl- and hexafluoronaphthylboronic acids, **3** and **14**, along with the most active catalyst, *N*-methyl-2,3-difluoropyridiniumboronic acid (**7**, Figure 1). Reaction optimization also identified nitromethane as the preferred solvent. Using these mild conditions at ambient temperature, or at 50 °C for the most difficult substrates, a variety of substrates were cyclized to provide carbocycles and heterocycles such as piperidines, pyrans, pyrrolidines, and tetrahydrofurans (**Scheme 8**).[45] It is notable that Brønsted acids, such as *p*-TsOH, provided much lower product yields, while BAC provided milder and cleaner reactions that are compatible with the use of acid-sensitive functional groups such as phenolic silyl ethers. Benzylic alcohols and tertiary alcohols are suitable substrates, although they require the most active catalyst **7** and a higher reaction temperature.

### 5.3. Nazarov Cyclization of Pentadienols

The Nazarov cyclization is a widely employed chemical transformation for the synthesis of substituted cyclopentenones. In its classical variant, a Lewis or Brønsted acid activates a divinyl ketone to generate a hydroxyl-substituted pentadienyl cation as a key intermediate, which then undergoes a 4π-electrocyclic ring closure to furnish the desired cyclopentenone product.[46] Although the Nazarov reaction of divinyl ketones has been studied extensively, there are only sporadic reports of divinyl alcohols being employed as starting materials.[47] Moreover, nearly all published methods require strongly acidic catalysts. We envisioned that a pentadienyl cation could be generated from divinyl alcohols under the mild conditions of boronic acid catalysis. This idea was validated when the resulting pentadienyl cations were shown to undergo the Nazarov cyclization to provide synthetically useful cyclic dienes by hydrogen elimination from the cyclopentenyl cations (**eq 5**).[48]

### 5.4. Transposition of Allylic and Propargylic Alcohols

The 1,3-transposition of allylic alcohols[49] and the related Meyer–Schuster rearrangement of propargylic alcohols[50] are synthetically useful processes. Although these isomerizations can be promoted in various ways, several methods require stoichiometric activation

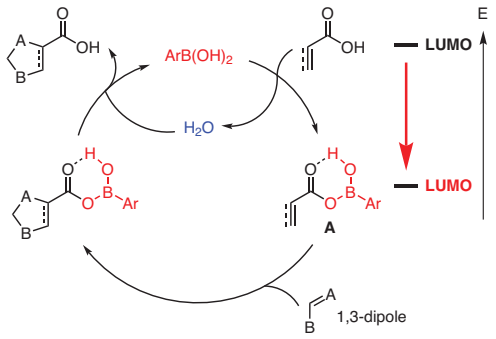
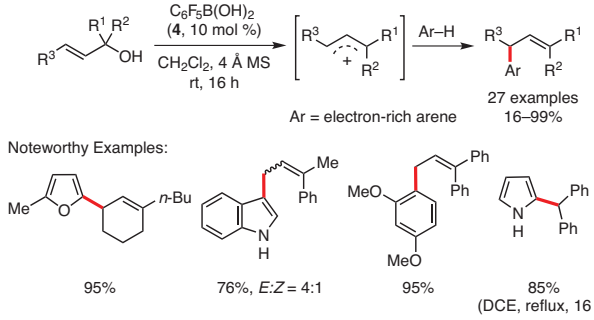
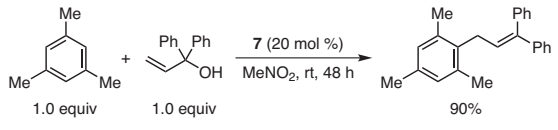


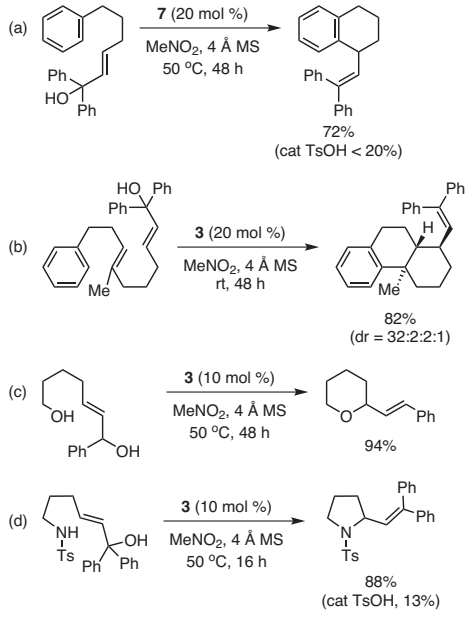

**Figure 2.** Proposed Mechanistic Cycle for the Boronic Acid Catalyzed Cycloadditions of Unsaturated Carboxylic Acids. *(Ref. 37)*




**eq 3** *(Ref. 41,42)*




**eq 4** *(Ref. 44)*



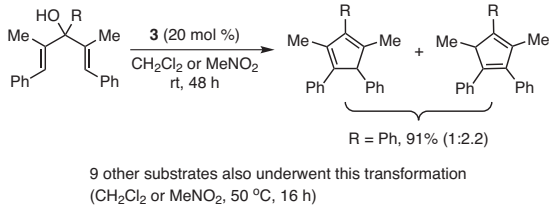

**Scheme 8.** Examples of Carbo- and Heterocyclizations of Allylic Alcohols Catalyzed by Boronic Acids. *(Ref. 45)*

of the hydroxyl group, while others employ transition metals or strong protic acid catalysts often under harsh conditions such as high temperatures.[49,50] Although rhenium(VII) oxo complexes are generally effective catalysts for allylic alcohols,[49] these complexes must be stored and used under strictly anhydrous conditions. Based on the mild Friedel–Crafts alkylations reported by McCubbin to take place by activation of allylic and benzylic alcohols with air-stable boronic acids,[41] we reasoned that allylic alcohols should rearrange selectively in the absence of an external nucleophile (**Scheme 9**).[51]

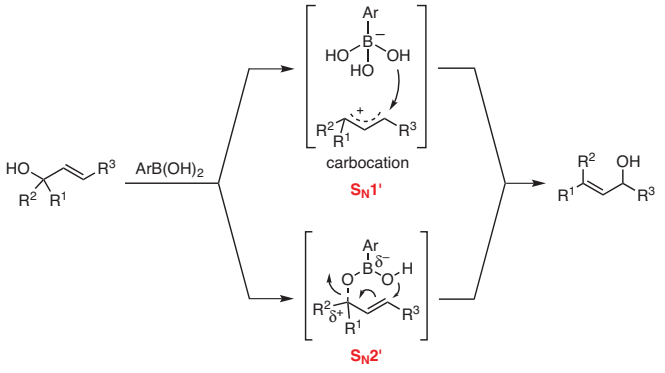
Reaction optimization, performed with 1-phenyl-2-propenol as a challenging model alcohol, revealed that highly electron-deficient polyfluorinated arylboronic acids are preferable.[51] Both 2,3,4,5-tetrafluorophenylboronic acid (**3**) and hexafluoronaphthylboronic acid (**14**) were significantly superior to pentafluorophenylboronic acid (**4**). Further optimization of solvent and catalyst loading confirmed that the use of 20 mol % of **3** or **14** in toluene provided the best reaction conditions. The use of molecular sieves was detrimental, while excess water suppressed the reaction. These observations suggest that a small quantity of water (formed by condensation between the boronic acid and the alcohol) is required for the catalytic turnover, but that a larger excess interferes with the formation of reactive intermediates. The substrate scope was explored using these optimal reactions conditions (**Scheme 10**).[51] Benzylic secondary and tertiary alcohols and tertiary non-benzylic alcohols were found to be suitable substrates. The transposition of allylic alcohols is potentially reversible, but it is driven forward in these examples by the formation of the thermodynamically favored alkene products incorporating a higher degree of substitution or extended conjugation. The less reactive allylic alcohols require catalyst **14** at elevated temperatures (50–80 °C). It is noteworthy that the *E/Z* selectivity of the boronic acid catalyzed reactions bettered that of the corresponding rhenium-catalyzed reactions (Scheme 10, Parts (b) and (c)).[52] For example, the isomerization of linalool into geraniol, an industrial process, proceeded with a selectivity superior to that of vanadium and rhenium oxo catalysts (Scheme 10, Part (c)).[52] Moreover, BAC succeeds where rhenium catalysis fails with functionalized substrates such as an Fmoc-protected piperidine (Scheme 10, Part (d)).[52] Substitution on the alkene unit was well tolerated except for strongly electron-withdrawing groups such as a carboxylic ester (examples not shown).

The corresponding transposition of propargylic alcohols, known as the Meyer–Schuster rearrangement, is a useful two-step alternative to phosphorus-based aldehyde olefination methods.[50] The facile addition of acetylide anions onto aldehydes and ketones provides the requisite propargylic alcohols, and BAC was very effective on those substrates too (Scheme 10, Parts (e) and (f)). Both terminal and disubstituted alkynes are suitable, including alkoxyacetylenes that afford the desired α,β-unsaturated esters in good yields and high *E/Z* selectivity (Scheme 10, Part (f)). If needed, thiophenol can be employed as an additive to promote in situ isomerization and afford higher *E/Z* selectivity. Unsaturated thioesters and amides were also prepared under similar conditions (not shown).[51] Phenylboronic acid can also be employed as a catalytic additive to help increase *E/Z* selectivity in the gold-catalyzed Meyer–Schuster reaction.[53]

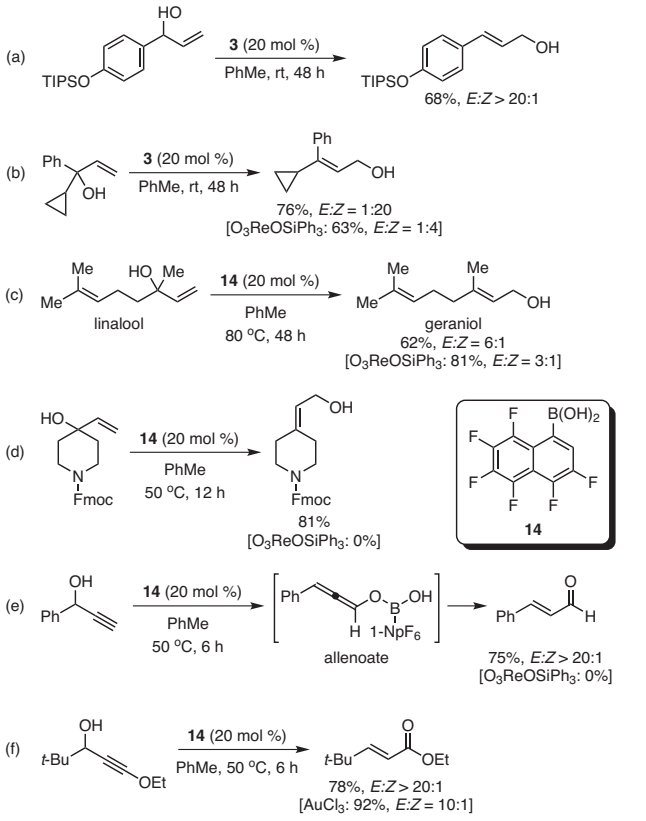
As demonstrated with this selection of substrates, it is worth noting that, in contrast to rhenium oxo and gold catalysis, BAC is effective




**eq 5** *(Ref. 48)*




**Scheme 9.** Two Possible Mechanisms for the 1,3-Transposition of Allylic Alcohols. *(Ref. 51)*




**Scheme 10.** 1,3-Transposition of Allylic and Propargylic Alcohols. *(Ref. 51–53)*

with both allylic and propargylic alcohols, and it tolerates both acid- and base-sensitive groups. The boronic acid catalyst is robust under the reaction conditions, and is still fully effective even after 24 hours in the reaction mixture.[51] The scope of substrates, reaction times, and product yields of these 1,3-transpositions are suggestive of a polar mechanism involving partial or full ionization into an allylic (or propargylic) carbocation. Using $O^{18}$-labeled alcohol substrates, the reaction of a model propargylic alcohol was shown to proceed through an $S_N1'$ mechanism (full ionization), whereas the reaction of a model allylic alcohol is likely to be more concerted ($S_N2'$-type) (see Scheme 9).[51]

### 5.5. Elimination and Cascade Reactions

In the course of our studies of the 1,3-transposition of allylic alcohols (see Section 5.4), our group demonstrated that the secondary aliphatic alcohol products from the 1,3-transposition of allylic alcohols can undergo a dehydrative elimination to give substituted butadienes when exposed to catalyst **3** (2,3,4,5-tetrafluorophenylboronic acid) for an extended period of time (**Scheme 11**).[51] This observation allowed the design of multicatalytic tandem reactions. For example, a substituted allylic alcohol can be subjected to a one-pot sequence of four reactions (1,3-transposition, elimination, [4 + 2] cycloaddition, and amidation) by employing three different boronic acid catalysts previously identified to be optimal for these respective reactions (see Scheme 11).[51]

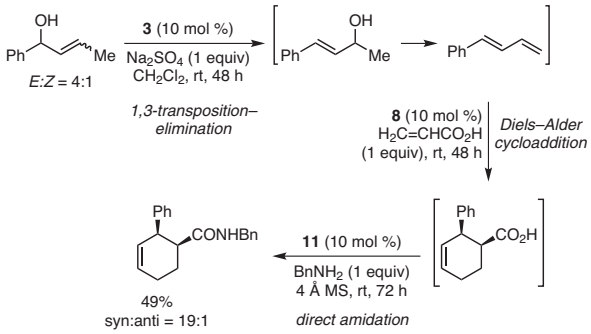
## 6. Activation of Carbonyl Groups

Because of their Lewis acidity, arylboronic acids can activate carbonyl compounds by increasing the electrophilicity of the carbonyl carbon or the nucleophilicity of the α carbon (i.e., via enolate formation) in a manner similar to that of other Lewis acids (**Figure 3**).[44] A number of interesting synthetic methodologies have been developed by employing this carbonyl activation concept.

In 2006, Debache and co-workers found that phenylboronic acid (**1**) can act as a catalyst to accelerate a one-pot, three-component (aromatic aldehydes, ethyl acetoacetate, and urea or thiourea) Biginelli reaction resulting in the synthesis of 3,4-dihydropyrimidinone derivatives (**Scheme 12**).[54] The authors proposed that the boronic acid was serving a dual function by increasing the nucleophilicity of ethyl acetoacetate through the formation of a boron enolate and enhancing the electrophilicity of the acylimine intermediate through boron–nitrogen coordination.[54] The same research group applied this concept to the preparation of 1,4-dihydropyridines and tetrahydrobenzo[*b*]pyrans.[55]

A number of similar methods for heterocycle synthesis catalyzed by phenylboronic acid (**1**) or 3-nitrophenyboronic acid (**9**) were reported by Bhusare and co-workers.[56] These authors proposed a mechanism involving the formation of a boron enolate; they also reported a related Mannich reaction that leads to β-amino carbonyl compounds.[57]

In 2008, Whiting and co-workers disclosed that *N*-butylbenzimidazole-2-phenylboronic acid sodium hydroxide complex (**15**) exhibits excellent catalytic activity for promoting the aldol addition and aldol condensation between hydroxyacetone or acetone and different aldehydes in water (**eq 6**).[58] Aldol addition products predominate with hydroxyacetone, whereas aldol condensation products are formed preferentially with acetone. The superior catalytic activity of **15** is believed to result from cooperative interactions from both the trihydroxyboronate unit and the imidazole function in the proposed transition state. When (*S*)-homoboroproline was employed as a chiral bifunctional catalyst in the aldol reaction between *para*-nitrobenzaldehyde and acetone, the *S* aldol product was obtained in 90% yield and 38% ee.[59] Interestingly, the tartrate boronic ester, formed in situ, provided an ee of 90%.




**Scheme 11.** Four-Reaction Synthetic Sequence Catalyzed by Three Different Boronic Acids. *(Ref. 51)*

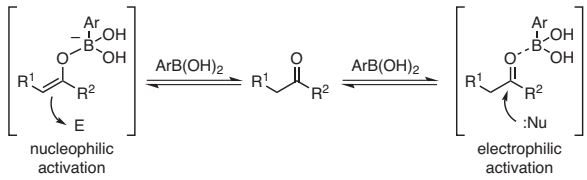
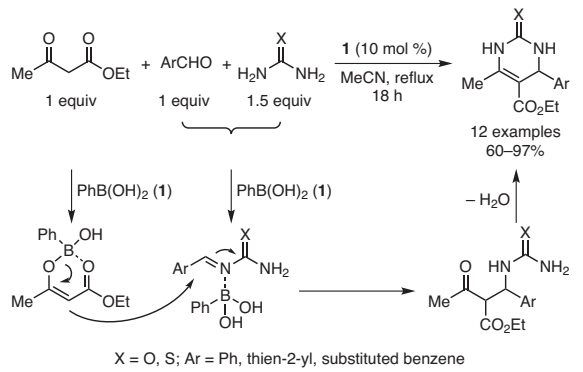
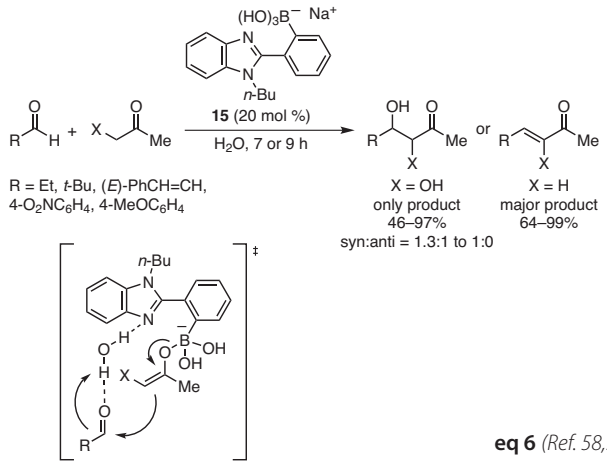



**Figure 3.** Activation of Carbonyl Groups with Arylboronic Acids. *(Ref. 44)*




**Scheme 12.** Biginelli Reaction Catalyzed by Phenylboronic Acid. *(Ref. 54)*




**eq 6** *(Ref. 58,59)*

More recently, Dixon and co-workers utilized 3-nitrophenylboronic acid (**9**) to catalyze the enolization of 1,3-dicarbonyl compounds.[60] In refluxing toluene, the generated enol subsequently underwent a concerted ene carbocyclization with a pendent alkyne substituent to afford carbocyclic products in good yields. The reaction is reported to be efficient, easy to perform, and applies to a wide range of ketoester substrates.[60]

## 7. Other Reactions

In 1991, Rao and Philipp reported that phenylboronic acid (**1**) accelerates the hydrolysis rate of salicylaldehyde imines through a phenol-directed effect.[61] Bhusare and co-workers employed 3-chlorophenylboronic acid to promote imine formation and activation in the 3-aminoalkylation of indoles[62] and the cyclodensation of *ortho*-phenylenediamines with ketones.[63] Recently, Beller and co-workers developed a boronic acid catalyzed hydrosilylation of amides, which, in contrast to conventional amide reduction methods, required very mild reaction conditions and exhibited remarkable functional group tolerance.[64] Although these particular transformations have not yet been adopted by others, 3,4,5-trifluorophenylboronic acid (**2**) was reported to catalyze the reduction of carboxylic acids to alcohols with sodium borohydride,[65] and the direct formation of acylazides.[66] The same group reported the transesterification of β-keto esters catalyzed by 3-nitrophenylboronic acid (**9**).[67]

## 8. Conclusions and Outlook

This review has covered many contributions on Boronic Acid Catalysis (BAC) from our laboratory and from others. This promising emerging area of organocatalysis offers an alternative strategy for activating hydroxyl-containing substrates such as carboxylic acids, alcohols, and other functionalities in a mild and selective manner. In the past five years alone, the list of reactions amenable to BAC—which had comprised the amidation and esterification of carboxylic acids—has increased significantly to include [4 + 2] and dipolar cycloadditions of unsaturated carboxylic acids; Friedel–Crafts-type alkylations with alcohols; transpositions and eliminations of allylic alcohols; and reactions of carbonyl compounds such as aldol condensations, ene reaction, cyclocondensations, and others. Based on the current rate of discovery, we anticipate that many more reactions catalyzed by boronic acids are likely to be identified. With the proper improvements, such as more potent catalysts with higher turnover numbers, one can expect that BAC will be adopted by more chemists in search of methods that provide enhanced atom- and step-economy.

## 9. Acknowledgments

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## About the Authors

**Hongchao Zheng** was born in Heilongjiang, People's Republic of China. He received his B.S. degree in chemistry in 2001 and his M.Sc. degree in 2005 from Tsinghua University. After immigrating to Canada, Zheng earned a second M.Sc. degree in 2007 from McMaster University (Canada), where he worked under the guidance of Prof. Graham A. McGibbon. In the same year, he joined Professor Dennis Hall's group at the University of Alberta (Canada) to pursue his Ph.D. research in the field of boronic acid catalysis. He obtained his Ph.D. degree in 2012, and is currently conducting research in the field of gold catalysis as a postdoctoral associate in the laboratory of Professor Michel R. Gagné at the University of North Carolina at Chapel Hill (USA).

**Dennis Hall** obtained his Ph.D. degree in 1995 from Université de Sherbrooke, Canada, under the direction of Prof. Pierre Deslongchamps. He was then an NSERC Postdoctoral Fellow in the laboratory of Prof. Peter G. Schultz in the Department of Chemistry at UC Berkeley. He initiated his independent career in 1997 at the University of Alberta (Edmonton, Canada), where he is presently University Professor of Chemistry. The unifying theme of his research program is the development of new synthetic and biological applications of organoboronic acid derivatives. Hall served as Editor for the successful monograph *Boronic Acids* (Wiley-VCH), now in its 2nd edition. For his contribution of reference 27, he was awarded the *Journal of Organic Chemistry* 2013 Outstanding Author of the Year Award (ACS Organic Division).

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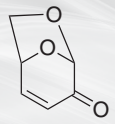

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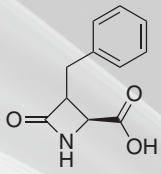

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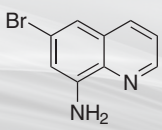

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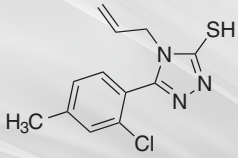

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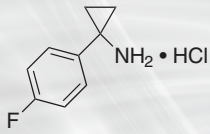

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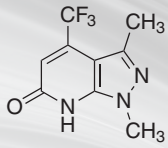

**TMT00542**
1,3-Dimethyl-4-(trifluoromethyl)-1*H*-pyrazolo[3,4-*b*]pyridin-6(7*H*)-one

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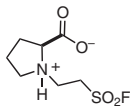


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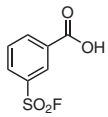


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## ABOUT OUR COVER

***Lady and Gentleman on Horseback*** (oil on canvas, 123 × 172 cm) was painted around 1655 and extensively reworked in 1660/1665 by Aelbert Jacobsz Cuyp (1620–1691), a painter from the Dutch Golden Age. Not much is known about Cuyp's education and artistic training, except that he apprenticed with his father, a well-known Dutch portraitist. He may have been influenced by the works of Jan van Goyen and Jan D. Both, two contemporary landscapists living in Cuyp's native Dordrecht and in Utrecht, respectively; and he was a strong influence on Abraham van Calraet. Cuyp had a relatively short painting career (ca. 1640–1660), and distinguished himself as a landscapist of the Dutch countryside, real or imagined, often rendered as charming and serene pastoral scenes.

Detail from ***Lady and Gentleman on Horseback***. Photo courtesy National Gallery of Art, Washington, DC.

This equestrian double portrait, uncommon in Dutch art of that period, is clearly intended to give center stage to the female rider, presumed to be the daughter of one of Cuyp's patrons. The elegantly attired couple is setting out for a hunt, assisted by the young man in the middle ground and the five hounds, one of which appears to draw the attention of the viewer to the leaves of the burdock plant, a recurring motif in Cuyp's work.* The scene has a dignified and warm feel to it, as conveyed by the elegant couple, the shades of brown, and the soft light. The attire of the female rider reflects the tastes of Dutch society at the time, shifting away from solemn black to the more cheerful and plush French clothing styles.

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

** The leaves of the burdock plant and a couple setting out for a hunt were symbols used by painters of that era. Can you guess what they are associated with? To find out, visit* ***Aldrich.com/acta473***

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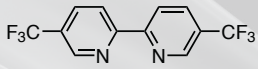

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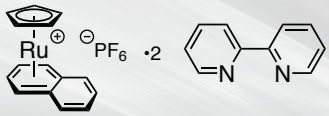

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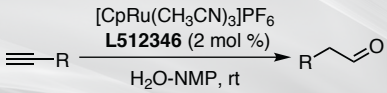


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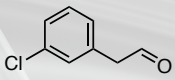

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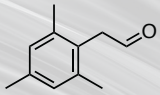

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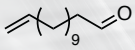

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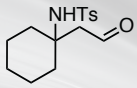

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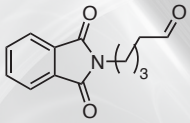

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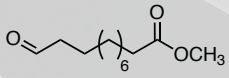

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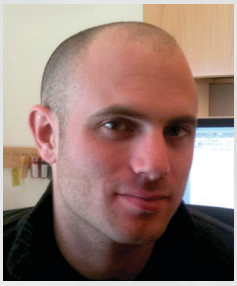

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(1) Li, L.; Herzon, S. B. *Nature Chem.* **2014**, *6*, 22.
(2) Li, L.; Zeng, M.; Herzon, S. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 7892.

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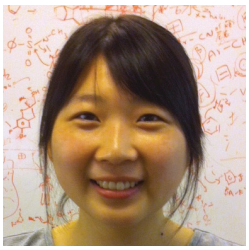
# Ruthenium-Catalyzed anti-Markovnikov Hydration and Reductive Hydration of Terminal Alkynes



Ms. M. Zeng

Prof. S. B. Herzon

**Mingshuo Zeng and Seth B. Herzon***

Department of Chemistry
Yale University
New Haven, CT 06520, USA
Email: seth.herzon@yale.edu

**Keywords.** catalysis; hydration; reductive hydration; alkyne; alcohol.

**Abstract.** Our laboratory has developed a family of highly practical catalysts that promote the transformation of terminal alkynes into aldehydes and linear alcohols by the anti-Markovnikov addition of water and dihydrogen. The scope, limitations, and mechanistic studies of these catalysts are presented. Our most active catalysts are air- and moisture-stable, and commercially available, which should promote application of this chemistry.

## Outline



## 1. Introduction

Terminal alkynes are advantageous starting materials for methods development. Thousands of terminal alkynes are commercially available, and they can be readily synthesized by carbonyl homologation,[1,2] metal-catalyzed cross-coupling,[3,4] or nucleophilic displacement reactions. Alkynes are inert to many oxidative, reductive, acidic, and basic reagents, yet they can be induced to react under mild conditions by metal-mediated, alkyne-specific mechanistic pathways, such as π-complexation or vinylidene formation (**Scheme 1**). This unique reactivity profile renders alkynes orthogonal to many heteroatom-based functional groups, and provides an opportunity for their selective transformation when found in complex multifunctional structures.

Much recent research has focused on the metal-catalyzed Markovnikov and anti-Markovnikov additions of heteroatom-based nucleophiles to alkynes.[5–8] Metal vinylidene intermediates can be formed from terminal alkynes using a wide array of transition-metal catalysts.[9–12] Subsequent nucleophilic addition, followed by cleavage of the metal–carbon bond, leads to linear (anti-Markovnikov) addition products. By comparison, π-complexation typically promotes addition to the internal position of the alkyne to generate branched (Markovnikov) addition products. The majority of existing processes focus on the addition of water to alkynes;[6,13–30] while hydroamination,[31–41] hydroamidation,[42,43] and hydroesterification[44–49] reactions have also been reported. Our laboratory recently introduced a family of practical, highly active catalysts for the anti-Markovnikov hydration[50] and reductive hydration (addition of water and dihydrogen)[51–53] of terminal alkynes to form aldehyde and linear alcohol products, respectively. Many of these catalysts are air-stable and display high activity across a broad range of substrates at ambient temperature. In addition, the catalysts are readily synthesized in one or two steps, and are commercially available.

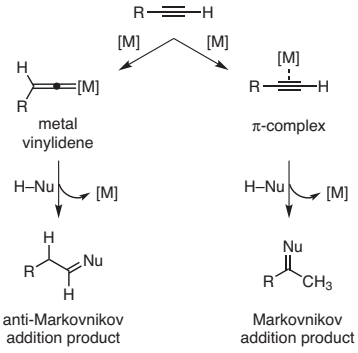
In this review, we summarize the development of the catalytic anti-Markovnikov hydration and reductive hydration of terminal alkynes, with an emphasis on the scope and applications of the catalysts. Much of our work has focused on synthesizing air-stable catalyst precursors for these transformations, which has been a challenge in the field of anti-Markovnikov hydration. While we have achieved this goal for both reaction types, the reactions must still be conducted under anaerobic conditions (e.g., in deoxygenated solvents)—a constraint that is likely unavoidable due to the nature of the intermediates in the catalytic cycles. Nonetheless, by using these catalysts, the reactions can be set up without recourse to a glovebox, and are no more challenging to implement than other common air-sensitive reactions, such as the Sonogashira coupling.

## 2. anti-Markovnikov Hydration

### *2.1. Background*

Classical methods for alkyne hydration employ catalysis by strong acids, mercury(II) salts, or other Lewis acidic transition-metal complexes. All of these conditions promote the Markovnikov addition of water, leading to the formation of methyl ketones.[8] Formal anti-Markovnikov hydration can be achieved indirectly by stoichiometric hydroboration[54] or hydrosilylation,[55] followed by oxidation.

Metal-catalyzed methods for the direct anti-Markovnikov addition of heteroatom-based nucleophiles to alkynes have been slower to develop. Tokunaga and Wakatsuki reported the first anti-Markovnikov hydration of terminal alkynes, which was catalyzed by an $\eta^6$-arene ruthenium complex.[15] Later, Wakatsuki's group reported that the $\eta^5$-cyclopentadienyl ruthenium complex **1** displayed higher activity and selectivity (**Figure 1**).[17] The $\eta^5$-cyclopentadienyl ruthenium fragment has emerged as a common substructure in the most active anti-Markovnikov hydration catalysts. Contemporaneously with the disclosure of **1**, Grotjahn and co-workers reported that the ruthenium complex **2**, which possesses a bifunctional imidazolylphosphine ligand, displayed high activity for the hydration.[16] A direct kinetic comparison (aqueous acetone, 70 °C) showed that catalyst **2** is 90 times more active than catalyst **1**.[21] Detailed mechanistic studies established that the pendant nitrogen functional group forms a hydrogen-bonding network with the alkynyl hydrogen atom and water, leading to an acceleration of vinylidene formation and nucleophilic addition (vide infra).[24,26,29] Further optimization of the ligand structure and counterion led to identification of the complex **3**; the activity of **3** surpasses that of **1** by a factor of 1000.[21] Breit and co-workers investigated the self-assembly of bidentate ligands through hydrogen-bonding association of monodentate subunits[56–60] to the $\eta^5$-cyclopentadienyl ruthenium fragment. The bis(phosphine) complex **4** displayed moderate activity in the hydration reaction.[22] Hintermann and co-workers showed that only one pyridylphosphine ligand in **3** is required for catalysis, and reported that the mixed phosphine complex **5** displays high activity in the hydration reaction.[23,30]




**Scheme 1**. Vinylidene Formation and π-Complexation Are Two Examples of the Reaction Pathways of Terminal Alkynes under Mild Conditions.

## 2.2. 2,2´-Bipyridyl Catalyst Development

Recently, our group discovered that catalysts derived from the cationic cyclopentadienyl ruthenium fragment and bidentate nitrogen ligands,[8] such as 2,2´-bipyridine, show high activity in the anti-Markovnikov alkyne hydration reaction.[50,52] These catalysts can be conveniently generated by heating for 3 h equimolar quantities of ($\eta^5$-cyclopentadienyl) ($\eta^6$-naphthalene)ruthenium hexafluorophosphate (**6**) and the bipyridine ligand at 60 °C, or immediately by mixing ($\eta^5$-cyclopentadienyl) tris(acetonitrile)ruthenium hexafluorophosphate (**7**) with the bipyridine ligand at ambient temperature (**Scheme 2**, Part (a)).[50,52] Although both **6** and **7** are commercially available, the naphthalene complex **6** is preferable from a preparative standpoint as it is stable to oxygen and moisture. We evaluated a wide array of catalysts formed in situ from **7** and various bidentate nitrogen ligands. Ultimately, we found that catalysts derived from 5,5´-bis(trifluoromethyl)-2,2´-bipyridine (**9**) displayed the highest activity, promoting the hydration reaction at ambient temperature with a range of alkyne substrates.[50]

With the goal of increasing the usefulness of this chemistry, we developed the single-component precatalyst **10** (Scheme 2, Part (b)).[50] This complex was targeted with the anticipation that the halogen ligand would impart air-stability.[61,62] Conveniently prepared in one step and 86% yield from **6**, **9**, and benzyltriethylammonium chloride, the structure of **10** was confirmed by X-ray analysis. In accord with our

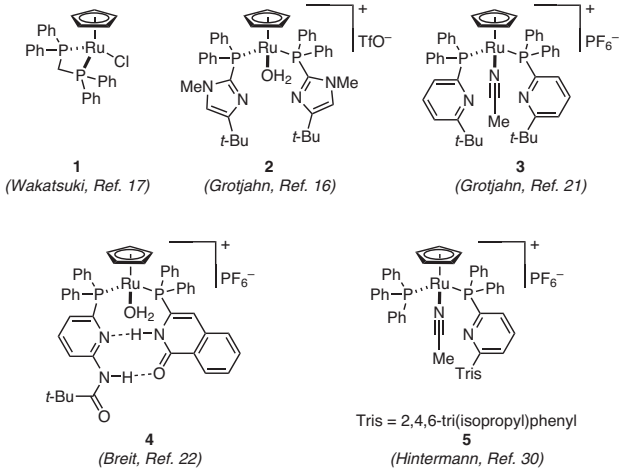
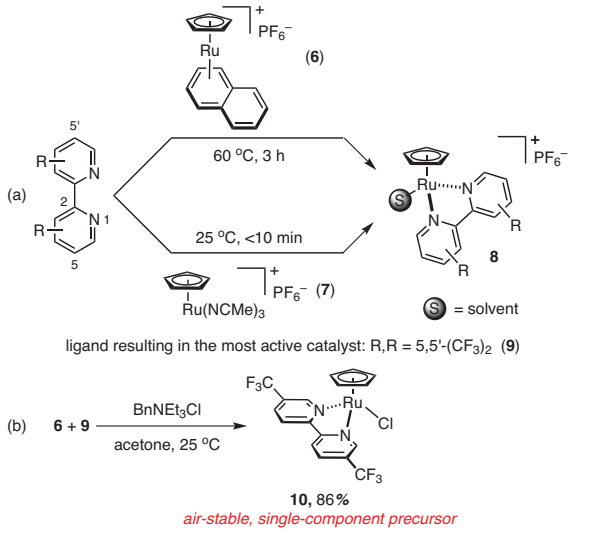



**Figure 1**. Earlier anti-Markovnikov Alkyne Hydration Catalysts.




**Scheme 2**. (a) Syntheses of 2,2'-Bipyridyl Alkyne-Hydration Catalysts. (b) Preparation of a Single-Component Precatalyst. *(Ref. 50,52)*

expectations, the complex is stable indefinitely on the benchtop under air. The activity of **10** is somewhat lower than the in situ generated catalysts described above, but is sufficient for most substrates. The use of precatalyst **10** obviates issues of metal–ligand stoichiometry, which should make it attractive for small-scale exploratory experiments.

### 2.3. Scope of Alkyne Hydration with 2,2´-Bipyridyl Catalysts

A wide array of arylalkynes undergo anti-Markovnikov hydration at ambient temperature within 8 hours by using 2 mol % of ruthenium complex **7** and bipyridine **9** in aqueous *N*-methyl-2-pyrrolidinone (NMP) (**Scheme 3**, Part (a)).[50] Sterically encumbered substrates, such as (2,4,6-trimethylphenyl)acetylene, require 24 h to reach completion.

Aliphatic alkynes can be converted into aldehydes within 24 h at ambient temperature using 2 or 4.5 mol % of **7** and **9** (Scheme 3, Part (b)).[50] A range of functional groups are compatible with this catalyst system, including chloro, amino, amido, imido, keto, hydroxy, carboxy, and carbomethoxy. *tert*-Butylacetylene, which is not efficiently hydrated by any other catalyst, is converted into 3,3-dimethylbutanal in 73% yield after 48 hours (90% after 72 hours) by using 2 mol % of **7** and **9**. In the case of the morpholinoalkyl-substituted acetylene, addition of 1 equiv of *para*-toluenesulfonic acid was found to increase the yield, presumably by preventing the amine from binding to the catalyst.

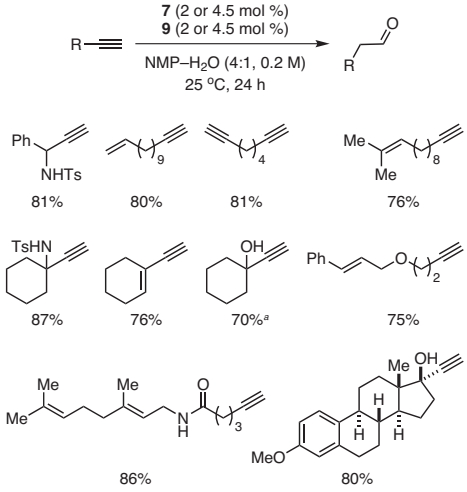
Aldehydes derived from enynes, including conjugated enynes, can also be efficiently prepared using **7** and **9** (**eq 1**).[50] In addition, diynes, such as 1,7-octadiyne can be hydrated at both alkyne functions in high yield. It is also noteworthy that the hydration of propargylic alcohols and amines proceeds in preparatively useful yields under the same conditions. Unsaturated aldehydes, which are the major side products formed in reactions employing **3** and **5**,[63] are produced in <15% when our catalytic system is employed.

### 2.4. Relative Efficiency of Hydration Catalysts

To rank-order the activity of our complexes, we monitored the hydration of (2-fluorophenyl)acetylene and 4-fluoro-1-decyne by $^{19}$F NMR, and compared the rates of hydration using our catalysts [(**7** + **9**) or **10**] to Grotjahn's catalyst (**3**) (**Scheme 4**).[50] For both alkynes, the rates of hydration using either our in situ generated catalyst (**7** + **9**) or the preformed catalyst **10** exceed that of Grotjahn's catalyst (**3**). These experiments also showed that the rate of hydration of aromatic alkynes is faster than that aliphatic alkynes when bipyridine catalysts are employed, while the opposite trend is observed when Grotjahn's catalyst (**3**) is utilized. Although the activity of **10** is somewhat lower than that of the in situ formed catalyst, it still displays useful reaction rates for the hydration of (2-fluorophenyl)acetylene. Moreover, the activity of **10** was unchanged after it had been exposed to air for one week, and its rate of hydration of aliphatic alkynes is comparable to that of **3**.

### 2.5. Mechanistic Studies of the anti-Markovnikov Hydration

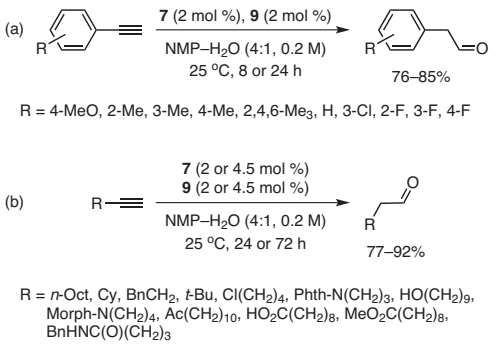
The anti-Markovnikov selectivity in the hydration reactions discussed above derives from the addition of water to a metal vinylidene intermediate. The formation of metal vinylidenes from terminal alkynes and transition-metal complexes is well-established.[9–11] Wakatsuki's and



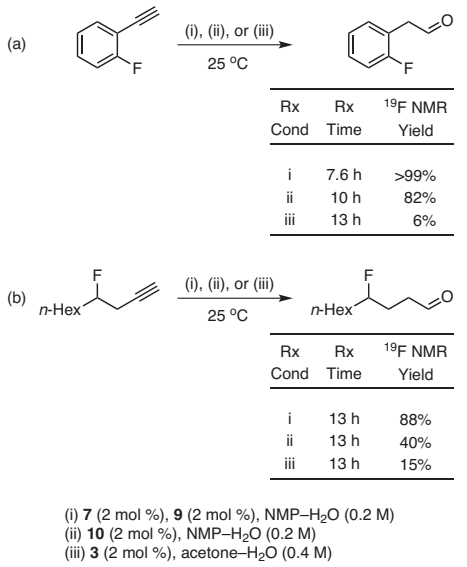

[a] 2,2'-BiPy was used as ligand

anti-Markovnikov hydration of enynes, diynes, propargylic amines, and propargylic alcohols.

**eq 1** *(Ref. 50)*



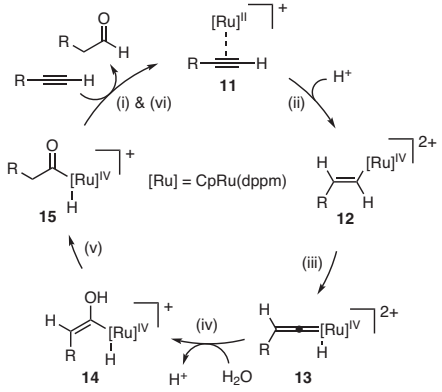

**Scheme 3**. anti-Markovnikov Hydration of (a) Aromatic and (b) Aliphatic Terminal Alkynes. *(Ref. 50)*




**Scheme 4**. Comparison of the Alkyne Hydration Reactivity of (**7** + **9**), **10**, and **3**. *(Ref. 50)*

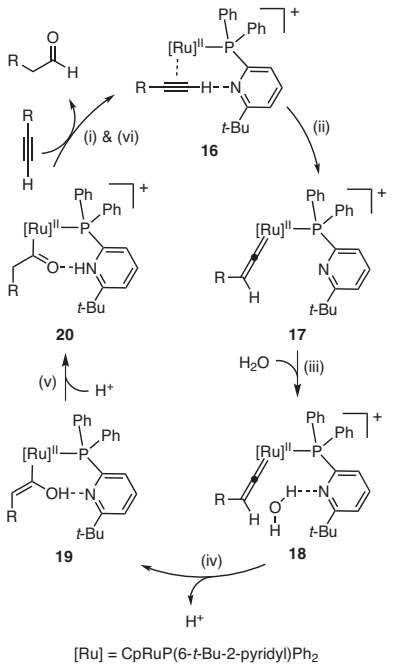
Grotjahn's groups have investigated in detail the mechanism of the anti-Markovnikov alkyne hydration that is catalyzed by their respective systems.

Deuterium-labeling experiments and Density Functional Theory (DFT) calculations led Wakatsuki and co-workers to postulate the formation of a metal vinylidene intermediate containing a Ru(IV) center (**Scheme 5**).[18,64] They proposed that the first step in the hydration cycle comprises coordination of the alkyne to form an $\eta^2$-alkyne intermediate (**11**). Protonation at the internal position generates the alkenylmetal intermediate **12**, which then undergoes isomerization to the Ru(IV) vinylidene hydride **13** via α-elimination. A mechanism involving a Ru(II)–vinylidene intermediate was excluded based on the observation that the Ru(II) complexes RuCp(C≡CPh)(dppm) and [RuCp(=C=CHPh)(dppm)][$PF_6$] were unreactive. Addition of water, followed by proton transfer, was proposed to provide the acyl ruthenium hydride **15**. Finally C–H reductive elimination and substrate coordination would regenerate the $\eta^2$-alkyne intermediate **11** and liberate the product.




(i) alkyne coordination; (ii) protonation; (iii) α-elimination and isomerization; (iv) addition of water; (v) tautomerization; (vi) C–H reductive elimination.

**Scheme 5**. anti-Markovnikov Alkyne Hydration Mechanism Proposed by Wakatsuki. *(Ref. 18,64)*




[Ru] = CpRuP(6-*t*-Bu-2-pyridyl)$Ph_2$

(i) formation of H-bonded $\eta^2$-alkyne; (ii) isomerization; (iii) H-bonding with water; (iv) water addition to the vinylidene; (v) isomerization; (vi) protonolysis to form the aldehyde product, and coordination of alkyne.

**Scheme 6**. anti-Markovnikov Alkyne Hydration Mechanism Proposed by Grotjahn. *(Ref. 29,66)*

An alternative model was developed by Grotjahn and co-workers in a series of careful mechanistic studies of their catalysts (**Scheme 6**).[26,29,65,66] A key element of their mechanism involves the generation of a hydrogen-bonding network between the aminophosphine ligand and the substrate or nucleophile, which accelerates the catalytic cycle. The formation of a C–H–N hydrogen-bonded $\eta^2$-alkyne intermediate, **16**, was proposed based on NMR studies.[65] This intermediate then undergoes isomerization to the vinylidene **17**. Association of water with the pyridine ligand (see **18**), followed by addition to the vinylidene (to form **19**), and isomerization, yields the ruthenium acyl intermediate **20**. Protonolysis of the acyl ligand and coordination of the alkyne substrate regenerates the $\eta^2$-alkyne intermediate **16** and liberates the product.

The hydrogen-bonding network elucidated by Grotjahn provides an explanation for the enhanced efficiency of catalysts derived from the aminophosphine ligands. We have not yet conducted detailed mechanistic studies of our bipyridine catalysts, but it is possible that the rate enhancements we observe derive from dissociation of one of the nitrogen atoms (to generate a $\kappa^1$-ligand) and formation of similar hydrogen-bonded intermediates. We plan to carry out studies that will focus on establishing the mechanistic basis for the rate enhancements displayed by our catalysts.

## 3. anti-Markovnikov Reductive Hydration

In the course of a synthetic project in our laboratory, we became interested in developing conditions to effect the addition of water and dihydrogen to alkynes to form linear alcohols, a reaction we call reductive hydration. The simplest way to envision this reaction proceeding is by an anti-Markovnikov hydration of the alkyne, to form an aldehyde intermediate, followed by in situ reduction. We have developed three catalytic protocols to effect this reaction. Following a brief description of the first- and second-generation systems, our most active third-generation catalyst is described in detail below.

### 3.1. First-Generation, Dual-Catalyst System

Using Grotjahn's catalyst (**3**)[21] and Shvo's hydrogenation catalyst (**21**),[67–69] we have developed a single-flask, tandem reductive hydration reaction to form primary alcohols from terminal alkynes (**eq 2**).[51] The reductive hydration employs isopropanol as reductant and, for most substrates, proceeds to completion with 4 mol % of **3** and 2 mol % of **21**. Reactions are typically conducted with heating to 70 °C for 48 h. By substituting Grotjahn's catalyst (**3**) with a cationic gold N-heterocyclic carbene complex,[25] branched alcohols are also accessible (not shown).

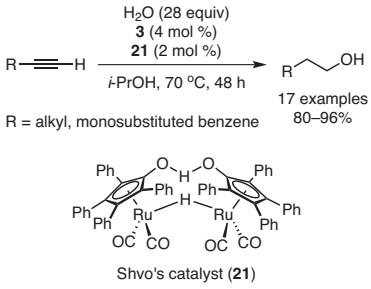
### 3.2. Second-Generation, Auto-Tandem Catalytic System

The structural similarities between Grotjahn's (**3**) and Shvo's (**21**) catalysts led us to ask whether a single catalyst architecture, that can support both the hydration and hydrogenation activities, could be identified. After some experimentation, we found that the ruthenium–2,2′-bipyridine complex **8a** (**8**, R = H), which can be formed in situ by heating ($\eta^5$-cyclopentadienyl) ($\eta^6$-naphthalene)ruthenium

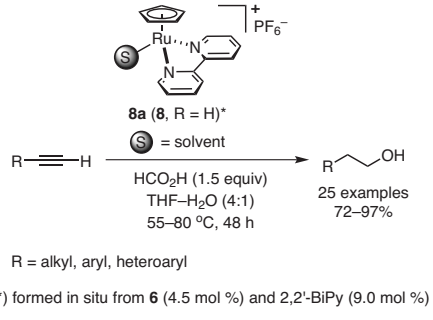
hexafluorophosphate (**6**) and 2,2′-bipyridine, is active for both the hydration and hydrogenation reactions (**eq 3**).[52] Interestingly, we observed that the hydration and hydrogenation activities of this catalyst were separated temporally: the aldehyde accumulated in solution and was not reduced until all of the alkyne starting material was consumed. We attributed this to the formation of stable $\eta^2$-alkyne intermediates, which sequesters the metal and blocks hydrogenation. The reactions required elevated temperatures (55–80 °C) and employed formic acid (rather than isopropanol, vide supra) as reductant. A wide range of aliphatic and aromatic alkynes were converted into the corresponding primary alcohols using this catalyst. The temporal separation phenomenon was exploited to effect the in situ functionalization of the aldehyde intermediate.

### 3.3. Third-Generation, Auto-Tandem Catalytic System

The catalyst systems described above possess several limitations. First, their hydrogenation activities are modest, and elevated temperatures are required to effect this step. These elevated temperatures can promote decomposition of the aldehyde intermediates (and in some cases the substrates), particularly for catalyst **8a**, wherein an excess of formic acid is employed. Second, Grotjahn's catalyst (**3**) and the bipyridine complex **8a** are both air-sensitive, necessitating recourse to a glovebox. Finally, the presence of two catalysts in the first-generation system complicates purification of the products. Thus, we sought to synthesize an air-stable catalyst that displayed higher hydrogenation activity. In addition, we focused on developing a single-component, preformed catalyst, as this was anticipated to increase the utility of this chemistry.




**eq 2** *(Ref. 51)*




**eq 3** *(Ref. 52)*

#### 3.3.1. Catalyst Synthesis

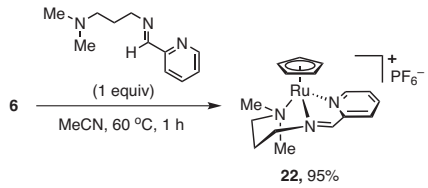
The details of our catalyst design strategy have been described.[53] After some experimentation, we identified the single-component complex **22** as a highly active and practical catalyst for the anti-Markovnikov reductive hydration (**eq 4**).[53] The hemilabile tertiary amine of the tridentate ligand serves to block formation of an open coordination site at the metal and prevent oxidative decomposition,[70–72] leading to high levels of air-stability. The tertiary amine also serves as a proton shuttle to facilitate activation of the reductant and the hydrogenation step.[73–75] Using catalyst **22**, the reductive hydration reaction could be conducted at ambient temperature for the first time.

Complex **22** is conveniently prepared in one step on a multigram scale by heating equimolar quantities of (*E*)-$N^1$,$N^1$-dimethyl-$N^3$-(pyridin-2-ylmethylene)propane-1,3-diamine (itself prepared in one step from commercial reagents) with ruthenium complex **6** in deoxygenated acetonitrile at 60 °C for one hour. The catalyst is isolated in 95% yield and >95% purity by extraction with hexanes (to remove naphthalene), followed by concentration of the acetonitrile layer. Notably, the workup is conducted in a separatory funnel open to air, using reagent grade (non-deoxygenated) solvents. The structure of **22** was established by multidimensional NMR analysis and X-ray crystallography.

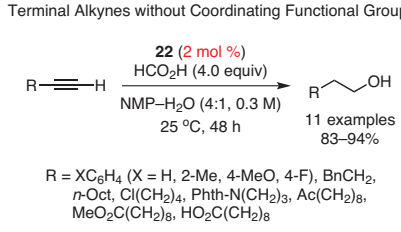
#### 3.3.2. Substrate Scope

Catalyst **22** displays broad substrate scope and functional group compatibility. Below, we categorize the substrates into three groups: (i) substrates without coordinating functional groups; (ii) substrates with coordinating functional groups; and (iii) sterically encumbered substrates and substrates containing monosubstituted olefins.

Simple aliphatic and aromatic alkynes—as well as alkynes containing noncoordinating functional groups such as primary alkyl chlorides, phthalimides, ketones, esters, and carboxylic acids—are efficiently converted into the corresponding linear alcohols with only 2 mol % **22** at ambient temperature (**eq 5**).[53] For substrates with functional groups that can coordinate to the catalyst—e.g., alcohols,

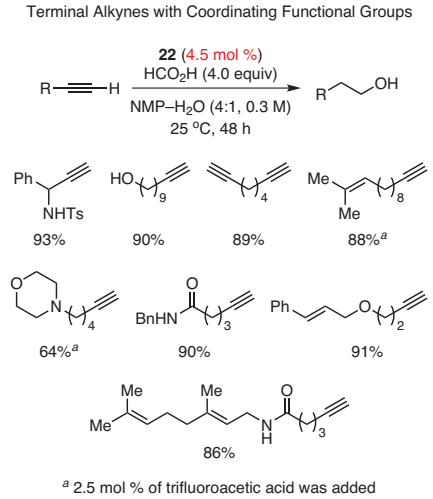



**eq 4** *(Ref. 53)*

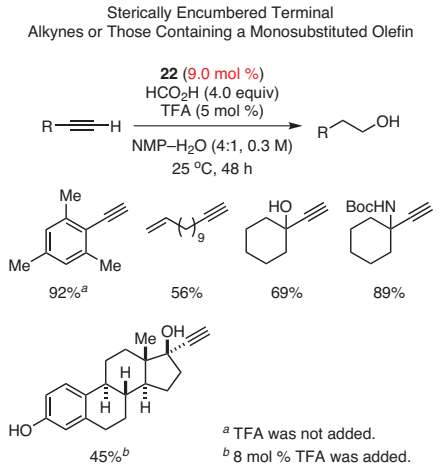



**eq 5** *(Ref. 53)*

di- or trisubstituted alkenes, amides, and tertiary amines—4.5 mol % of **22** is necessary (**eq 6**).[53] For some substrates, the yield was improved by conducting the reaction in the presence of 2.5 mol % trifluoroacetic acid (TFA). The trifluoroacetic acid may help to promote activation of the catalyst as the formic acid is consumed (vide infra).[53] Sterically encumbered substrates, and substrates containing monosubstituted olefins, require 9.0 mol % **22** to achieve high yields (**eq 7**).[53] For these reactions, the addition of 5 mol % TFA is required for all substrates examined except (2,4,6-trimethylphenyl)acetylene. The requirement for higher loadings of catalyst presumably derives from less efficient generation of catalyst–alkyne intermediates due to their increased steric encumbrance. In the case of (10-undecen)-1-ylacetylene, we presume that the olefin functionality deactivates the catalyst by formation of a $\eta^2$-alkene complex.




**eq 6** *(Ref. 53)*




**eq 7** *(Ref. 53)*

### 3.3.3. Mechanistic Studies of the anti-Markovnikov Reductive Hydration

We have elucidated the mechanism of the reaction mediated by **22** by stoichiometric experiments, deuterium-labeling studies, NMR analysis, and reaction progress kinetic analysis.[76,77] Collectively, these investigations led to the mechanistic model shown in **Scheme 7**. Our data indicate that three catalytic cycles are operating concurrently in reductive hydrations mediated by **22**. These include a hydration cycle, which converts the substrate into the aldehyde intermediate; a hydrogenation cycle, which reduces the aldehyde to the alcohol product; and a decarboxylation cycle, which converts formic acid into carbon dioxide and dihydrogen.

NMR studies indicate that the catalyst, **22**, exists exclusively in the $\kappa^3$-form (as shown in Scheme 7) in the absence of acid. The $\kappa^3$-state is a coordinatively saturated, 18-electron complex, and this architecture provides an explanation for the air-stability of the complex. Under the acidic conditions of the reductive hydration reaction, the tertiary amine is partially protonated to generate the ruthenium formate **23**. Solvolysis of **23** forms the cationic complex **24**. Displacement of the bound solvent molecule in **24** by the substrate generates the $\eta^2$-alkyne complex **25**. This complex has been observed by NMR analysis. The bound substrate in **25** is converted into the aldehyde. Although the elementary steps of this transformation were not elucidated, they are likely to parallel those established by Grotjahn and co-workers.

Alternatively, the formate complex **23** may undergo decarboxylation, to generate the ruthenium hydride **26**. The complex **26** may reduce the aldehyde intermediate (likely an outer-sphere process),[73] or undergo reductive elimination to regenerate **22** and produce dihydrogen. This latter pathway explains why an excess of formic acid is required, as it is consumed during the course of the reaction by this decarboxylation pathway. This leads to deactivation of the catalyst because less acid is now present to promote formation of **23** (and **24**). The addition of trifluoroacetic acid may help to promote formation of **25** when hindered (weakly coordinating) substrates are employed.

## 4. Concluding Remarks

We have described herein the development of air-stable catalysts for anti-Markovnikov hydration and reductive hydration of terminal alkynes. Our studies build on the earlier work of Grotjahn, Wakatsuki, and others, who established active catalysts for the anti-Markovnikov hydration. Our catalysts are commercially available or readily prepared in multigram quantities, and display broad substrate scope for both transformations at ambient temperature. The ability to convert a range of terminal alkynes into primary alcohols and aldehydes under mild conditions will find broad application in synthesis.

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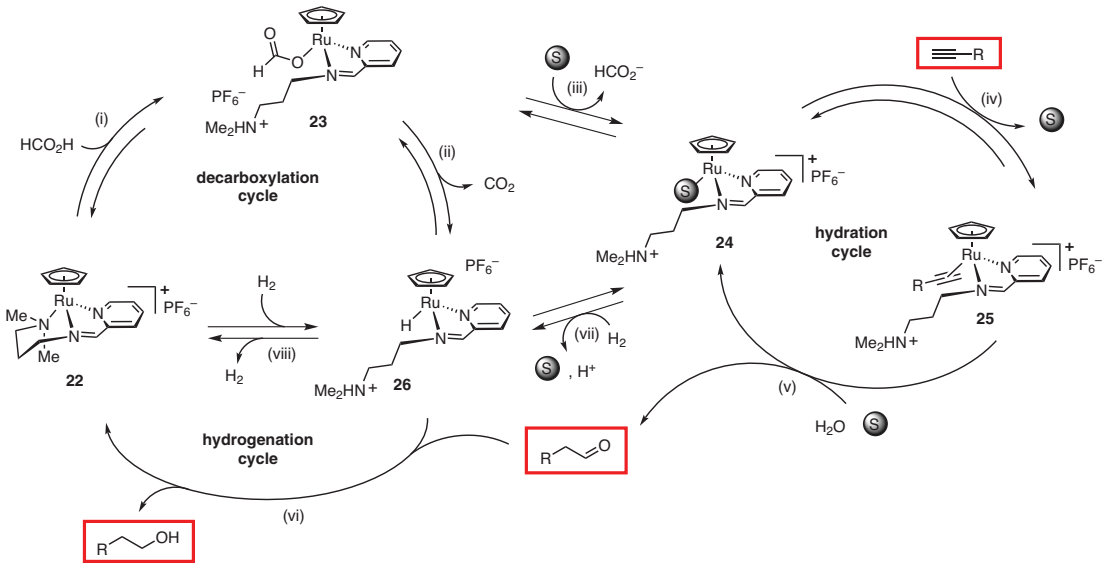


**Scheme 7**. Proposed Catalytic Cycles for Reductive Hydrations Mediated by **22**.

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## About the Authors

**Mingshuo Zeng** was born in 1989 in Jiangxi, China, and moved to Japan in 1994 with her family. In the spring of 2008, she graduated from Takamatsu High School in Kagawa, Japan. Soon after, she entered the University of Tokyo, where she received her B.A. degree in Pharmaceutical Science. While at the University of Tokyo, she conducted undergraduate research under the guidance of Professor Tohru Fukuyama, studying the synthesis and bioactivity of compounds related to neuroligin, a postsynaptic adhesion molecule. After her graduation in 2012, she joined Professor Herzon's group at Yale University, where she is pursuing her graduate-level studies with a focus on transition-metal chemistry.

**Seth B. Herzon** obtained his undergraduate degree from Temple University in 2002. He was a graduate student at Harvard University in the laboratory of Professor Andrew G. Myers, and conducted postdoctoral studies with Professor John F. Hartwig at the University of Illinois, Urbana-Champaign. He joined the Yale faculty in 2008 as Assistant Professor of Chemistry. In 2012, he was appointed Associate Professor of Chemistry and, in 2013, was appointed Professor of Chemistry. His research program is focused on organic synthesis, organometallic chemistry, and chemical biology.

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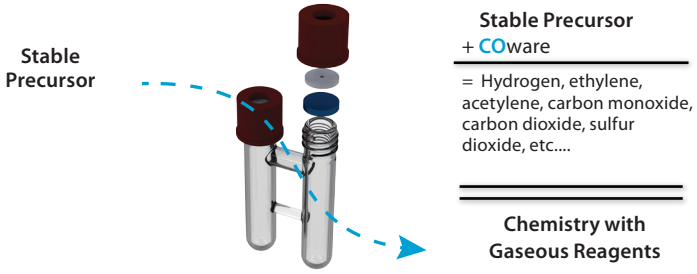



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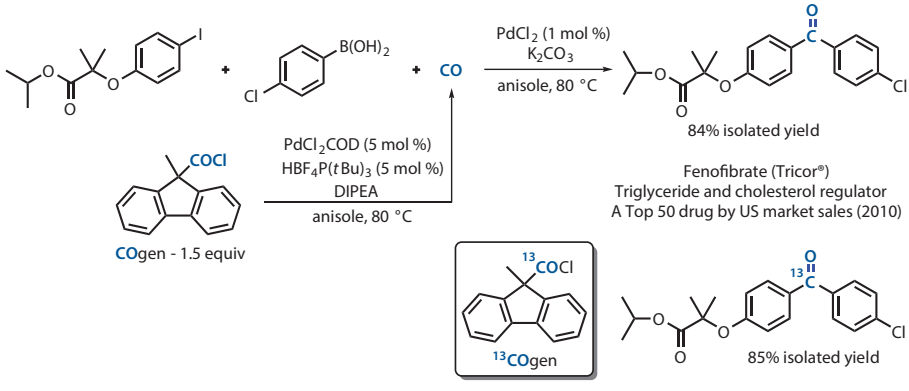


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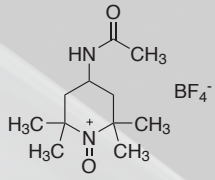

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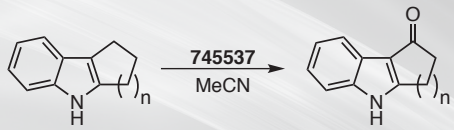


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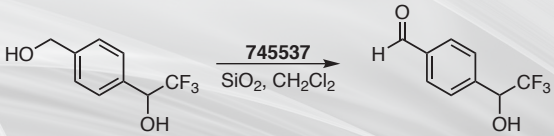
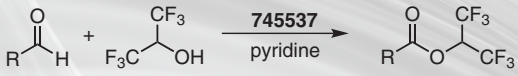



### Oxidative Esterification

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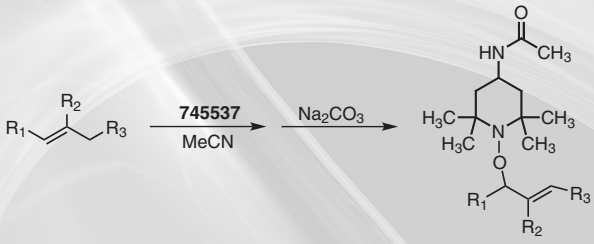


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# TEMPO-Derived Oxoammonium Salts as Versatile Oxidizing Agents

Prof. N. E. Leadbeater

Prof. Emeritus J. M. Bobbitt

**Nicholas E. Leadbeater* and James M. Bobbitt**

Department of Chemistry
University of Connecticut
55 North Eagleville Road
Storrs, CT 06269-3060, USA
Email: nicholas.leadbeater@uconn.edu

**Keywords.** oxidation; green chemistry; C–H bond activation; esterification; alcohols.

**Abstract.** The diverse synthetic applications of 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (**4**) as a versatile, user-friendly reagent are surveyed. In addition to alcohol oxidation, its use in a variety of other functional-group transformations, such as C–H bond activation and oxidative esterification, are also highlighted.

## Outline

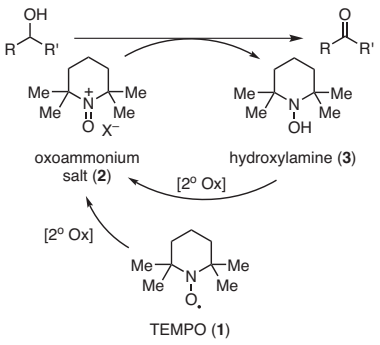


## 1. Introduction

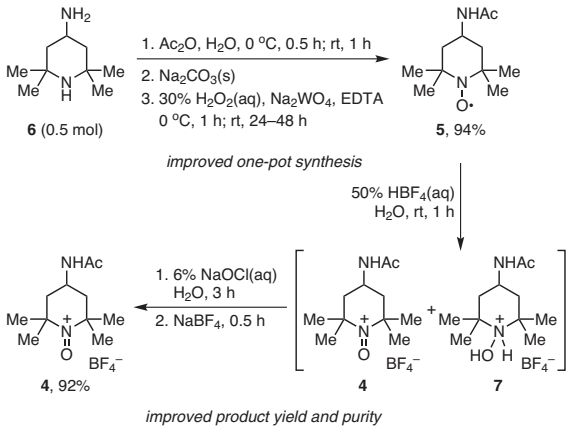
Oxidation reactions play a key role in organic chemistry.[1] They allow for functional group interconversion, activation, and even atom removal. The increasing demand for selective, mild, and rapid oxidation methods has led to many developments over the last few decades.[2] Oxoammonium salts and their nitroxide cousins have been found to be highly attractive oxidants because they are stable, metal-free, environmentally benign, very user-friendly, and can accomplish oxidations under mild conditions. In the field of catalytic chemistry, the best known example is TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl, **1**), which is presently used on an industrial scale.[3] By employing a secondary oxidant such as sodium hypochlorite (bleach), TEMPO can be utilized for a wide array of oxidation reactions.[4] While often more complex,[5] experimental data are consistent with a mechanism whereby the secondary oxidant transforms **1** into the corresponding oxoammonium salt, **2**, which functions as the primary oxidant. This results in the formation of a hydroxylamine, **3**, that is oxidized back to **2** by the secondary oxidant, thus completing the catalytic cycle (**Scheme 1**).[5] More recently, transition-metal catalyst systems have been developed for the TEMPO-mediated oxidation of alcohols under an oxygen atmosphere.[6,7]

The use of oxoammonium salts as stoichiometric oxidants does have some noteworthy advantages, particularly when working on a smaller scale. When the appropriate solvent is utilized, the spent oxidant precipitates out of solution, along with unused oxoammonium salt, and is separated from the product by a simple filtration. In addition, the reactions are colorimetric, so progress can be monitored visually. The spent oxidant can be easily regenerated, thus making it recyclable. The reaction can also be performed under anhydrous conditions, which is valuable in cases where the reaction products are prone to hydrolysis. The stoichiometric use of oxoammonium salts is not limited to simple oxidation reactions. They are versatile reagents for a variety of other functional-group transformations such as C–H bond activation, debenzylation, and oxidative esterification. Starting with a discussion of its preparation and use in alcohol oxidation, this review will then transition to some of the newer applications of 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (**4**, **Scheme 2**).[8–10] Relevant examples that employ the tetrafluoroborate salt of TEMPO will also be discussed.

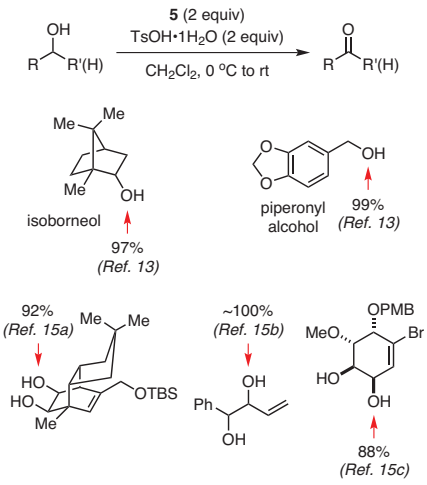
Oxoammonium salts are prepared by the oxidation of nitroxides such as TEMPO (**1**). Derivatives functionalized in the 4 position such as 4-hydroxy-TEMPO or 4-acetamido-TEMPO (**5**) are most commonly used since they can be obtained from the inexpensive precursor triacetoneamine, a readily available material manufactured on a large scale as a stabilizer for plastics. While oxoammonium salt **4**, bearing the tetrafluoroborate counterion, has been employed extensively over recent years, it was the perchlorate analogue that was first utilized as a stoichiometric oxidant.[8] However the perchlorate was later reported on one occasion to detonate upon drying. Given the parity in charge and size, the tetrafluoroborate salt proves just as active a reagent as the perchlorate, but without the safety concerns. The original[8,9] and improved[10] syntheses of **4** both start from 4-amino-2,2,6,6-tetramethylpiperidine (**6**). Because the first step (acetylation of




**Scheme 1**. Mechanism of the TEMPO-Catalyzed Oxidation of Alcohols. *(Ref. 5)*




**Scheme 2**. Improved Synthesis of Oxoammonium Salt **4**. *(Ref. 10)*




**eq 1**

**6**) in the original synthesis is carried out in anhydrous diethyl ether, it makes the original synthesis of **4** costly. We have recently introduced a modification that permits the synthesis of **4** from **6** in 90% yield in one pot by using water as solvent (Scheme 2).[10] Addition of sodium tetrafluoroborate in the final step results in common-ion assisted (improved) precipitation of **4**, enhancing both yield and product purity.

## 2. Oxoammonium Salts as Stoichiometric Reagents for Alcohol Oxidation

First observed in 1965 by Golubev, Rozantsev, and Neiman,[11] and later extensively developed by Bobbitt and co-workers,[12] alcohol oxidation with oxoammonium salts such as **4** can be performed under neutral or slightly acidic conditions, or in the presence of bases. Another variant of the reaction involves using *two equivalents* of nitroxide **5** and two equivalents of *para*-toluenesulfonic acid (**eq 1**).[13,14] The nitroxide disproportionates to produce one equivalent of the hydroxylamine tosylate and one equivalent of the oxoammonium tosylate, the latter oxidizing the substrate and getting converted into a second equivalent of the hydroxylamine. The spent oxidant can be easily removed by filtration and recycled. This approach has seen significant application in natural product synthesis.[15]

### 2.1. Alcohol Oxidation under Neutral or Slightly Acidic Conditions

Primary and secondary alcohols can be oxidized to the corresponding aldehydes and ketones using a slight stoichiometric excess (1.05 equiv) of oxoammonium **4**, which is soluble enough in dichloromethane for the reaction to take place.[8,16] On the other hand, the reduced oxidant, **7**, is essentially insoluble in dichloromethane. This means that separation of the desired product from the spent oxidant at the end of the reaction requires just a filtration. The rate of reaction is relatively slow and highly dependent on the nature of the alcohol starting material: benzyl or allyl > secondary aliphatic and acetylenic > primary aliphatic. Addition of silica gel to the reaction mixture accelerates the reaction significantly, with the oxidation of allyl alcohols taking place within minutes, benzyl alcohols within 1–3 hours, and aliphatic alcohols taking a day or two to reach completion. From a practical standpoint, the reaction is performed at room temperature using approximately the same weight of silica gel as that of the oxidant employed. The role of the silica gel is not fully understood, but the phenomenon is not limited to this reaction. A number of synthetic transformations have been accelerated using silica.[17] It can serve as a slightly acidic medium and also can putatively lead to localized aggregation of polar species. Both of these processes could feasibly facilitate the reaction of alcohols with **4**. The reaction mixture goes from a bright yellow color to white, allowing progress to be monitored easily. A disadvantage of the methodology is that alcohols bearing an oxygen atom β to the site of oxidation react so slowly as to be unreactive. In addition, if the substrate bears a free amine functionality, the reaction with **4** leads to a variety of byproducts, so as to make alcohol oxidation impractical. While generally used for oxidation to aldehydes and ketones, oxoammonium salts can convert diols to lactones, especially when a five- or six-membered ring can be formed (**Scheme 3**).[8,18–21]

More recently, water and aqueous acetonitrile have both been employed as solvents for the oxidation of alcohols with **4**. In the case of the former, a range of alcohols can be oxidized to aldehydes and ketones in 6–36 h at reflux.[22] While this offers the operational advantage that silica gel is not needed, product isolation requires extraction with diethyl ether, and recovering the spent oxidant from the aqueous phase is not trivial, thus impeding its recycling. Using acetonitrile–water (90:10) as

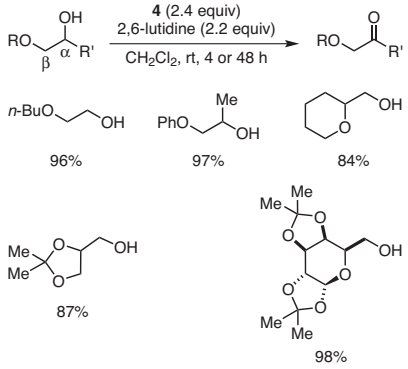
the solvent, primary alcohols can be converted into the corresponding carboxylic acids by employing two equivalents of **4**.[23] This reaction is surprisingly selective to aliphatic alcohol substrates; for example the benzylic alcohol functionality in 4-(3-hydroxypropyl)benzyl alcohol gets oxidized to the aldehyde, while, at the same time, the aliphatic alcohol is fully oxidized to the carboxylic acid in the presence of three equivalents of **4**.[23]

### 2.2. Alcohol Oxidation under Basic Conditions

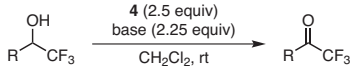
By using 2,6-dimethylpyridine (2,6-lutidine) as a base, the substrate scope in the oxidation of alcohols by **4** can be expanded to those bearing a β-oxygen functionality (**eq 2**).[24] The reactions, performed in dichloromethane using 2.2 equivalents of 2,6-lutidine and 2.4 equivalents of **4**, are complete in around 1 h and are colorimetric, turning from yellow to red. They are allowed to continue for an additional 3 h to aid in product isolation. Indeed, while product isolation is trivial when performing the reaction under neutral conditions, it is somewhat more complex in the 2,6-lutidine-mediated oxidation. The spent oxidant, **5**, and lutidinium tetrafluoroborate have to be removed by partial evaporation of the dichloromethane solvent and precipitation with anhydrous diethyl ether. The ether solution is then filtered through silica gel to remove any remaining byproducts. A superstoichiometric quantity (and thus a sacrificial equivalent) of **4** is required for complete oxidation of the alcohol, because, in the presence of base, the hydroxylamine byproduct (**7**) initially formed undergoes a comproportionation reaction with a further equivalent of **4** to generate two equivalents of nitroxide **5**.

This base-mediated methodology has also been employed recently for the preparation of trifluoromethyl ketones from the corresponding α-trifluoromethyl alcohols.[25] This reaction is often challenging with other oxidants.[26] For example, the most successful oxidant of perfluoro alcohols is the Dess–Martin periodinane (DMP), but a 3.5- or 4-fold excess is sometimes required to ensure complete reaction.[27] By using **4**, a range of aryl, alkenyl, and alkynyl α-trifluoromethyl alcohols can be oxidized to the corresponding ketones in good-to-excellent yields (**eq 3**).[25] Alkyl trifluoromethyl alcohols do not react in the presence of 2,6-lutidine, but are rapidly oxidized when 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) is used instead, albeit at the expense of more extensive purification and, hence, somewhat diminished yields.

The chemoselectivity of **4** in alcohol oxidation has been highlighted using a substrate containing both an α-trifluoromethyl alcohol and a benzyl alcohol functionality (**Scheme 4**).[25] The benzyl alcohol was readily oxidized in excellent yield under neutral conditions, leaving the




**eq 2** *(Ref. 24)*

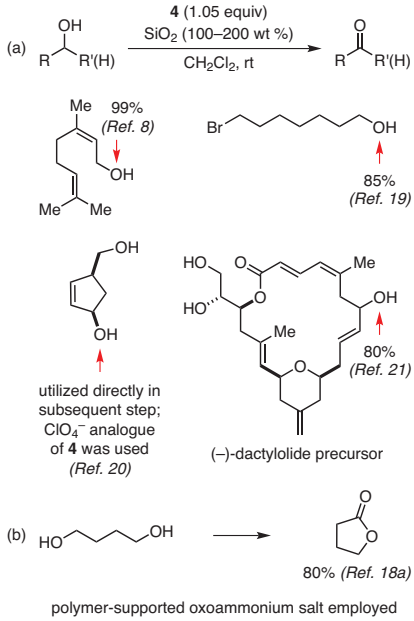



R = $XC_6H_4$, $XYC_6H_3$; base = 2,6-lutidine; yield = 71–99%

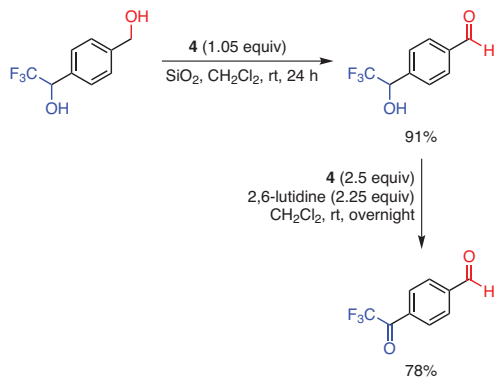
R = 2-Py, alkenyl, alkynyl; base = 2,6-lutidine; yield = 72–99%

R = alkyl; base = DBN (2.5 equiv); **4** (3.0 equiv); yield = 49–60%

**eq 3** *(Ref. 25)*




**Scheme 3**. Oxidation of Alcohols with **4** in the Presence of Silica Gel.



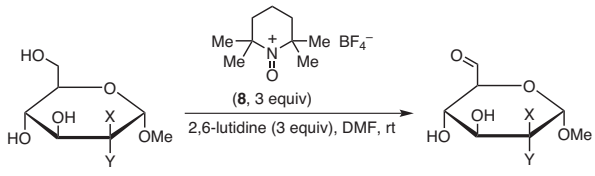

**Scheme 4**. Chemoselective Oxidation of Alcohols with **4**. *(Ref. 25)*

α-trifluoromethyl alcohol group untouched. The latter could then be readily oxidized using the standard basic conditions in similarly good yield. In the case of most other oxidants, selective oxidation is unlikely, and hence a protecting group strategy would need to be employed. It is worth noting that the base-mediated methodology can selectively oxidize the primary alcohol of methylated carbohydrates, such as methyl-α-D-mannopyranoside and methyl-α-D-glucopyranoside, to the corresponding aldehyde by using the tetrafluoroborate salt of TEMPO (**8**) ( **eq 4**).[28]

### 2.3. Mechanistic Insights

There have been a number of attempts to rationalize the reactivity of oxoammonium salts with alcohols under neutral conditions and in the presence of nitrogen bases (**Scheme 5**).[12,24,29,30] In the case of the former, the mechanism is thought to involve a hydride transfer; the carbon–oxygen double bond being formed by electron flow from the hydrogen–oxygen bond of the hydroxyl group of the alcohol substrate (Scheme 5, Part (a)). Given the steric bulk around the nitrogen center of the oxoammonium cation, it is the oxygen atom that is involved in the initial interaction with the alcohol. Thus, the cation can be considered to behave as if it is bearing an electrophilic oxygen atom, a rare situation in organic chemistry.[24] The hydride transfer mechanism explains the observed trend in reactivity of the alcohols. In alcohols bearing an electron-withdrawing group close to the carbinol carbon—such as substrates containing a β-oxygen or an α-trifluoromethyl substituent—electron density at the reaction center is reduced, as is the reactivity. In the case of the base-mediated reaction, the mechanism is not as clear-cut, and two plausible pathways have been proposed.[24] The mechanisms start with the pyridine base either polarizing the alcohol (Scheme 5, Part (b)) or activating the electrophilic oxygen of the oxoammonium cation (Scheme 5, Part (c)).

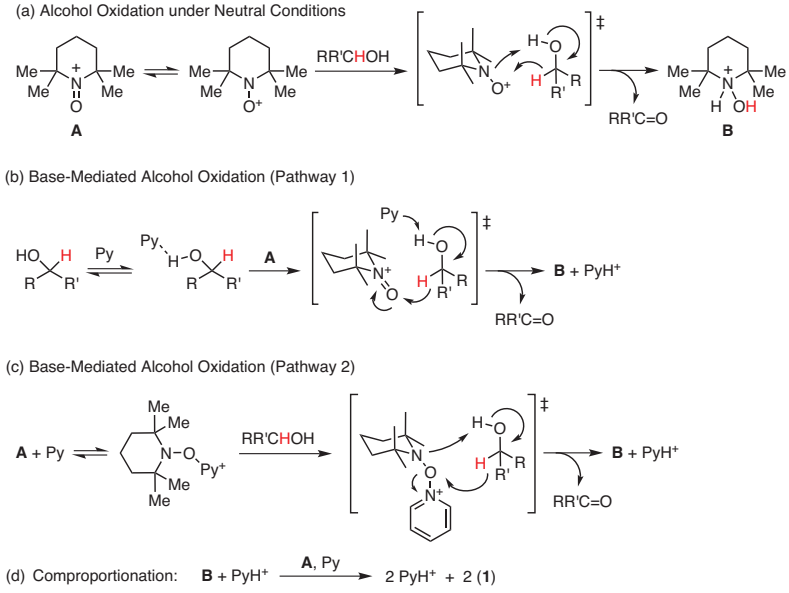
Quantum mechanical calculations have been used to probe in more detail the mechanisms depicted in Parts (a) and (b) of Scheme 5, assuming hydrogen-bonding interactions occur in the transition states formed.[24] The calculations showed a much higher activation energy for the oxidation under neutral conditions than that required for the base-mediated counterpart. This is borne out experimentally: reaction times for the oxidation under neutral conditions are significantly longer (12–48 h) than those for the base-mediated reaction (1–4 h). The transition state energy also decreases as base strength increases; this again is corroborated experimentally in the case of trifluoromethyl ketone synthesis.[25]




**eq 4** *(Ref. 28)*

## 3. Oxidative Esterification Reactions

Performing the reaction of **4** with primary alcohols bearing a β-oxygen functionality using pyridine in place of 2,6-lutidine does not result in the expected aldehyde products. Instead, an *oxidative* condensation occurs to yield an ester (**Scheme 6**).[31] The reaction conditions used are key to the success of the methodology. It is necessary to use 2.5 equiv of **4** and 2.3 equiv of pyridine, and to perform the reaction in




**Scheme 5**. Proposed Mechanisms for the Oxidation of Alcohols with Oxoammonium Salts. *(Ref. 24)*

dichloromethane at a substrate concentration of approximately 1 M. Activated molecular sieves are sometimes utilized to remove traces of water and thus inhibit the formation of the carboxylic acid byproduct formed by further oxidation of the aldehyde intermediate. At the end of the reaction, a small volume of methanol is added to consume any remaining oxidant. Using these optimized conditions, not only is the product formed in good-to-excellent conversion, but product isolation is also facilitated.

Mechanistically, the first step of the reaction is oxidation of the alcohol to the aldehyde, which then reacts with pyridine to form betaine intermediate **A**.[24] Of note is that **A** does not form readily with 2,6-lutidine due to the steric bulk of the methyl groups flanking the pyridine nitrogen atom. Betaine **A** is then rapidly and irreversibly oxidized by a second equivalent of **4**, forming an *N*-acylpyridinium species (**B**).[32] Reaction of the highly reactive acylating agent **B** with a second molecule of the alcohol starting material results in the ester product.

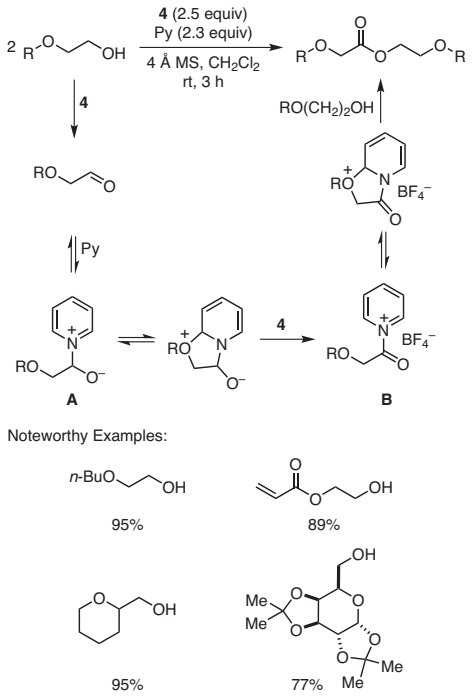
Building on this work, a range of hexafluoroisopropyl (HFIP) esters have been prepared by reaction of aldehydes with hexafluoroisopropanol in the presence of **4** (**eq 5**).[33] The transformation is performed under highly concentrated conditions using pyridine (~12 equiv) as solvent and 3 equivalents of hexafluoroisopropanol, and is complete within one hour at room temperature. Electron-rich and electron-poor derivatives of benzaldehyde all undergo rapid oxidation and give excellent yields of their corresponding HFIP esters, as do furyl- and pyridyl-substituted aldehydes. The reactivity of aliphatic substrates is somewhat dependent on the substitution around the aldehyde group. Those substituted at the α position react slower than their straight-chain analogues and require additional **4** and HFIP–OH to achieve complete conversion. This retardation in rate is likely due to the steric encumbrance caused by the α-substituent. By moving the substituent to the β position, the reaction proceeds readily, giving good-to-excellent yields of the desired esters. Mixed success is achieved when α,β-unsaturated and propargylic substrates are employed, with polymerization being an issue.

## 4. Oxidative Cleavage of Ethers

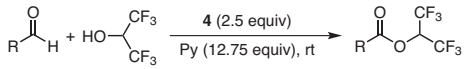
The benzyl ether functionality is one of the most common protecting groups for an alcohol.[34] Benzylic ethers can be cleaved using either oxidative or reductive methods and, in the case of the former, **4** can be employed as a reagent (**eq 6**).[35,36] Using a 0.7 M solution of the ether and **4** in aqueous acetonitrile, the reactions are complete after 8 h at room temperature.[35] The products obtained depend on the substrate: the corresponding aromatic aldehyde and alcohol are initially formed, but primary and secondary alcohol products are further oxidized to yield carboxylic acids and ketones, respectively. As a result, one molar equivalent of **4** is needed to cleave ethers derived from tertiary alcohols, two equivalents are required for oxidative cleavage of substrates derived from secondary alcohols, and three equivalents are necessary when the ether is derived from a primary alcohol.

## 5. Oxidative Rearrangement Reactions

The oxidative rearrangement of tertiary allylic alcohols to β-substituted α,β-unsaturated carbonyl compounds can be effected using oxoammonium salts, including **4**.[37,38] This offers a cleaner, greener alternative to the traditional routes employing stoichiometric quantities of highly toxic metal oxidants such as Cr(VI) salts. In the presence of 1.5 equivalents of **4** and acetonitrile, a range of alkyl- and aryl-functionalized alcohols undergo the rearrangement at room temperature

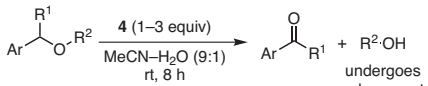



**Scheme 6**. Oxidative Esterification of Alcohols. *(Ref. 24,31)*




| R | Yield | R | Yield |
|---|---|---|---|
| 4-(*t*-Bu)$C_6H_4$ | 96% | 2-BrFur | 91% |
| 4-Me$C_6H_4$ | 94% | 2-Py | 88% |
| 4-$O_2$N$C_6H_4$ | 89% | 3-Py | 95% |
| 4-MeO$C_6H_4$ | 95% | $CH_3(CH_2)_{10}$ | 79% |
| 3-Cl$C_6H_4$ | 94% | Cy | 75% |
| 3-MeO$C_6H_4$ | 79% | $BnCH_2$ | 87% |
| 2-$O_2$N$C_6H_4$ | 94% | $Ph_2CHCH_2$ | 87% |
| 1-Np | 86% | PhCH=CH | 78% |

**eq 5** *(Ref. 33)*



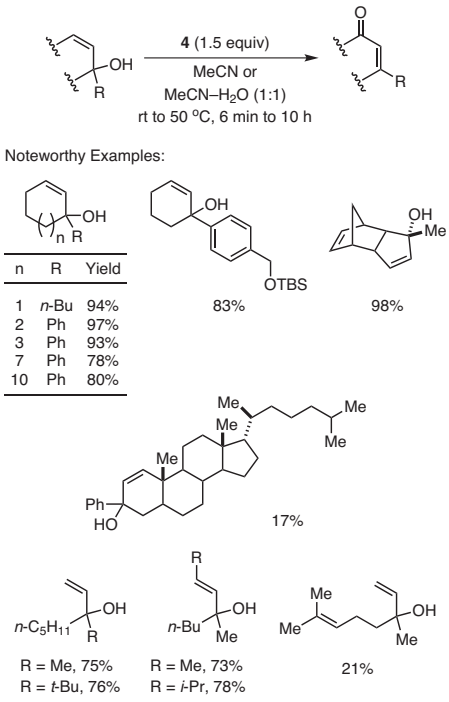

| Ar | $R^1$ | $R^2$ | Product | Yield |
|---|---|---|---|---|
| Ph | H | Bn | PhCH=O | 86% |
| Ph | H | *n*-Oct | PhCH=O | 90% |
| 2-Np | H | *t*-Bu | 2-NpCH=O | 93% |
| 2-Fur | H | Et | 2-FurCH=O | 90% |
| Ph | H | isobornyl | camphor | 92% |
| Ph | H | 1-Ad | 1-AdOH | 93% |
| Ph | Me | *n*-Oct | PhMeC=O | 89% |
| Ph | *t*-Bu | *n*-Oct | no reaction | ---- |

**eq 6** *(Ref. 35)*

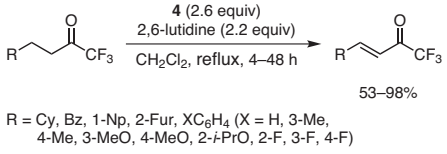
in between 6 min and 6 h (**eq 7**).[37] Both cyclic and acyclic substrates can be employed, although medium- and large-ring alcohols suffer from significant byproduct formation. In these cases, high yields of the desired product can be obtained by performing the reaction in a 1:1 mixture of acetonitrile and water. In one of the very few examples of such a study, the role of the counterion in the oxoammonium salt was also probed.[36] While the tetrafluoroborate and hexafluoroantimonate salts were highly active, the chloride and tribromide analogues were unreactive. Mechanistic pathways for the rearrangement reaction and the archetypal alcohol oxidation reaction of benzyl alcohol have been proposed based on these observations. In the case of the latter, they involve the counterion either abstracting a proton from the benzylic position or deprotonation of the benzyl alcohol. In light of the more recent mechanistic studies,[24] these earlier postulates seem unlikely; but the role of the counterion in oxoammonium salt mediated transformations must not be dismissed.

## 6. Dehydrogenation Reactions

A novel oxidative dehydrogenation reaction employing **4** and 2,6-lutidine converts a range of perfluoroalkyl ketones into the corresponding α,β-unsaturated products (**eq 8**).[39] While reaction times are quite long (heating at reflux for 4–48 h), hydrocinnamyl substrates have proven particularly amenable to this methodology, with the driving force for dehydrogenation in this case being extended conjugation (and an activated benzyl methylene functionality). With aliphatic substrates, substantially diminished product yields are obtained, and far longer reaction times are required. The reaction is likely a two-step process with the first step involving a precedented α-alkylation of the intermediate enolate (or enol) whose formation is likely facilitated by lutidine.[40] This is followed by an E2-like elimination. As with other reactions employing pyridine bases, a second equivalent of **4** is required.




**eq 7** *(Ref. 37)*



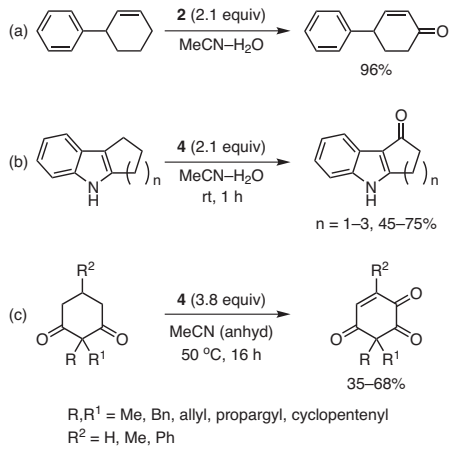

**eq 8** *(Ref. 39)*

## 7. C–H Bond Activation

The selective functionalization of unactivated carbon–hydrogen bonds is one of the most challenging transformations for synthetic chemists to accomplish.[41] Methods to do so must be effective, but at the same time highly selective. Oxoammonium salts have found a role in this endeavor, primarily for C–O and C–C bond-forming reactions at $sp^3$-hybridized centers.

### 7.1. C–O Bond-Forming Reactions

Oxoammonium salts can effect the allylic oxidation of conjugated alkenes and indoles in the presence of water to generate the corresponding α,β-unsaturated ketones (**Scheme 7**, Parts (a) and (b)).[42,43] The reactions are thought to involve hydride abstraction from the allylic position and subsequent trapping of the cation with water to form an intermediate allylic alcohol, which in turn is oxidized to the ketone. In a similar vein, 1,3-diketones can be converted into 1,2,3-triketones.[40] The fact that this reaction occurs without carbon–carbon bond cleavage is particularly interesting. By blocking the 2 position of 1,3-diketones, 5-ene-1,2,4-triones are obtained in moderate-to-good (35–68%) yields (Scheme 7, Part (c)).[44] The purity of **4** plays a considerable role in the outcome of the reaction, with residual water diminishing the yield significantly. For this application, **4** has to be




**Scheme 7**. C–O Bond-Forming Reactions Mediated by Oxoammonium Salts. *(Ref. 42–44)*

recrystallized and rigorously dried prior to use. This is in contrast to its use in alcohol oxidation, where it can essentially be utilized without any further purification.

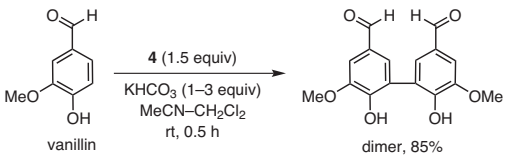
In many regards, the oxidative cleavage of benzyl ethers discussed earlier (see Section 4) could also be classed as a C–H bond activation process.[35] The key step in the process is thought to involve a formal hydride transfer from the benzylic carbon of the ether to the oxygen of the oxoammonium salt. The preparation of lactones from isochroman (90%) and phthalan (94%)—by employing **4** (2 equiv) in MeCN–$H_2O$ (9:1) at rt for 8 h—is particularly interesting.[35]

### 7.2. C–C Bond-Forming Reactions

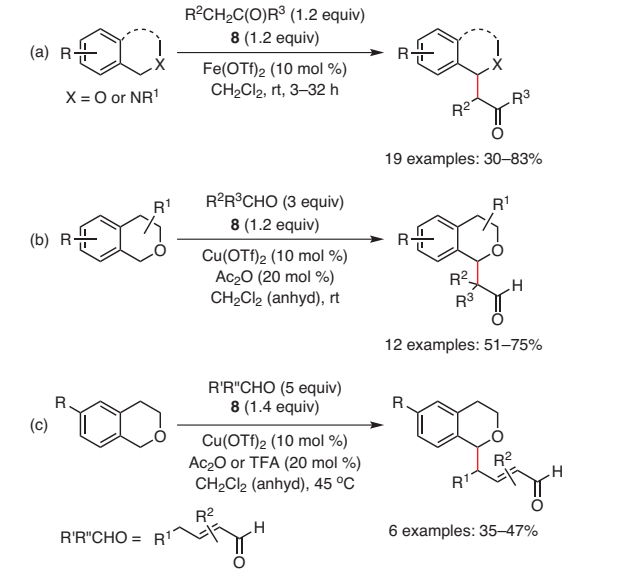
Oxidative coupling reactions are becoming a powerful tool for carbon–carbon bond formation, either directly from C–H bonds[45,46] or by using organometallic reagents.[47] Focusing on the former, many of the published methods rely on the use of (super)stoichiometric quantities of either metal oxidants or else hypervalent iodine compounds, organic peroxides, or quinones. Oxoammonium salts clearly offer a cleaner, greener, safer alternative,[48] as, for example, in the oxidative coupling of phenols.[49] In the case of 2,6-disubstituted phenols, coupling occurs at the 4 position, whereas if the ortho position is unsubstituted, as for example in vanillin, dimerization occurs at that site (**eq 9**).[49] Quinones can also be prepared by this methodology.[50,51] The reactions likely occur by electron transfer from the phenol to the oxoammonium cation, with subsequent deprotonation leading to the formation of a phenoxyl radical, which then dimerizes. The single-electron-transfer mechanism is further supported by the fact that the byproduct of the reaction is nitroxide **5**.

Oxidative functionalization of $Csp^3$–H bonds α to a heteroatom can be performed by treatment of benzylic ethers or amines with activated pronucleophiles in the presence of TEMPO tetrafluoroborate (**8**) and a Lewis acid catalyst.[52] The methodology offers a valuable route to the synthesis of α-functionalized ethers and amines, such as isochroman and tetrahydroisoquinoline derivatives. As before, the oxoammonium salt is thought to abstract a hydride from the α carbon of the substrate to yield an oxonium or iminium intermediate that then reacts with the enolate-type nucleophile generated by Lewis acid activation of the pronucleophile. Optimized conditions involve the use of 1.2 equivalents of **8**, 10 mol % $Fe(OTf)_2$, and running the reaction at room temperature for 3–32 h in dichloromethane (**Scheme 8**, Part (a)).[52] The scope of the reaction can be increased by employing $Cu(OTf)_2$ as the Lewis acid catalyst and adding catalytic quantities of either trifluoroacetic acid or acetic anhydride. Benzyl ethers can be coupled with aliphatic and α,β-unsaturated aldehydes using this approach (Scheme 8, Parts (b) and (c)).[53]

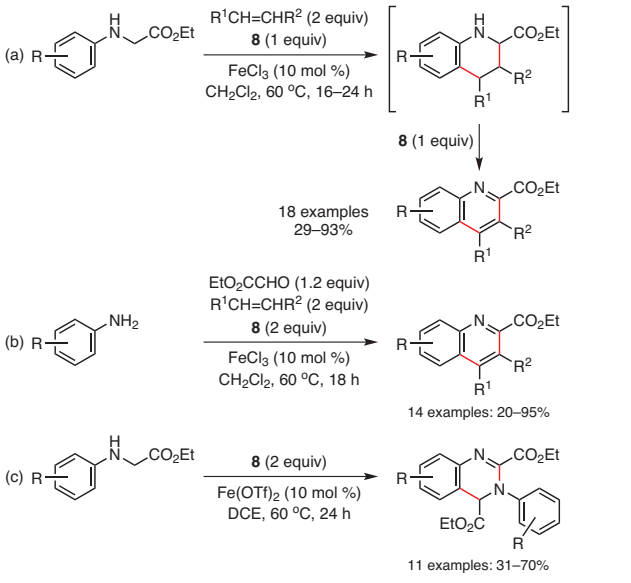
Polysubstituted quinolines can be prepared from *N*-alkylanilines and alkenes in the presence of **8** and an iron Lewis acid catalyst (**Scheme 9**, Part (a)).[54,55] The oxoammonium salt plays a dual role: First, it oxidizes the aniline starting material to give a reactive iminium ion that undergoes a Povarov-type reaction with the alkene to generate a tetrahydroquinoline intermediate. Next, a second equivalent of **8** is involved in the dehydrogenation of the tetrahydroquinoline intermediate to form the corresponding aromatic quinoline product. Although the formal abstraction of five hydrogen atoms is required overall, only two equivalents of **8** are needed, with the complete




**eq 9** *(Ref. 49)*




**Scheme 8**. Oxidative Functionalization of $Csp^3$–H Bonds α to a Heteroatom. *(Ref. 52,53)*

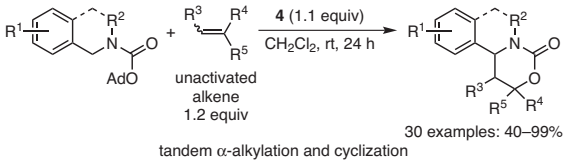



**Scheme 9**. Oxidative Functionalization of $Csp^3$–H Bonds α to a Heteroatom Leading to Polysubstituted Quinolines and Dihydroquinazolines. *(Ref. 54,55)*

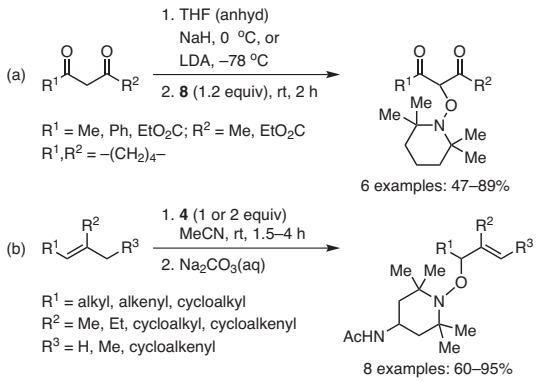
reduction of the oxoammonium salt occurring and leading to the formation of 2,2,6,6-tetramethylpiperidine as a byproduct. In another variant, quinolines can be prepared in a three-component reaction of anilines, ethyl glyoxylate, and alkenes (Scheme 9, Part (b)).[55] This multicomponent approach opens the avenue for generating products of broad structural diversity. In the absence of the alkene coupling partner, dihydroquinazolines can be prepared by oxidative dimerization of *N*-alkylanilines (Scheme 9, Part (c)).[55] This formally involves a C–N coupling–cyclization–oxidation tandem reaction.

The exact role of the iron catalyst is not completely clear in these transformations. Since the formation of oxonium or iminium intermediates is achieved using oxoammonium salts in the absence of metal complexes (vide supra), it is more likely that the iron salt behaves as a Lewis acid in the cyclization and/or C–N bond formation rather than as a co-oxidant in the oxidative step.[54] Of note is that the metal salt is essential for the formation of the dihydroquinazolines, but not for the preparation of the quinolines. That said, in the case of the latter, the iron catalyst does both increase the reaction rate and allow for complete conversion of the starting material.

Oxazinones can be prepared by a metal-free coupling reaction between benzylic carbamates and alkenes in the presence of **4** (**eq10**).[56] Specifically, *N*-benzyl-*O*-adamantyl carbamates undergo a tandem oxidation–cyclization with mono-, di-, and trisubstituted alkenes at room temperature in the presence of 1.1 equivalents of **4**. Although




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




**Scheme 10**. Synthesis of Allylic Alkoxyamines from Oxoammonium Salt **4**. *(Ref. 59,60)*

**8** is also effective as the oxidizing agent, just as with simple alcohol oxidation reactions, the fact that the hydroxylamine byproduct of **4** is significantly less soluble in dichloromethane than that of **8** means that product isolation is facilitated when the 4-acetylamido derivative is employed.

## 8. Other Reactions

In the reactions presented in the preceding sections, **4** and **8** served as reagents, but no part of them was incorporated into the reaction product. Oxoammonium salts can be employed as precursors to alkoxyamines,[57] which are of interest as initiators of living free-radical reactions in polymer chemistry.[58] Enolates of 1,3-dicarbonyl compounds react readily with **8** to yield the corresponding alkoxyamine product (**Scheme 10**, Part (a)).[59] The oxoammonium cation of **4** adds rapidly at room temperature in an ene-like fashion to trisubstituted alkenes to afford an allylic alkoxyamine salt that is readily converted into the free base upon treatment with aqueous sodium carbonate (Scheme 10, Part (b)).[60] Of note is the selectivity of this transformation: terminal, di-, and tetra-substituted alkenes proving either unreactive or, in the case of the last type, reacting very slowly. This trend in reactivity can be leveraged for the chemoselective addition to dienes containing a terminal and a trisubstituted double bond. The addition is also highly regioselective, the reaction occurring at the less substituted carbon of the double bond to give the secondary allylic alkoxyamine product.

## 9. Conclusions

Oxoammonium salts have been established as very valuable reagents for an array of synthetic transformations, ranging from the traditional alcohol oxidation to the state-of-the-art $Csp^3$–H bond activation. In particular, **4** has been proven easy to use, safe, often recyclable, and effective in cases where other oxidants fail. Rarely, if ever, are isomerizations observed, chiral centers racemized, or carbon–carbon bonds cleaved. Oxoammonium salt **4** should prove extremely valuable at the research and development stage, even if not on an industrial scale. A case in point is the synthesis of trifluoromethyl ketones, which are highly prone to hydration, impeding product isolation and hence yield: Traditional oxidants (e.g., catalytic TEMPO conditions with a biphasic aqueous–organic mixture and a secondary oxidant) proved ill-suited to the reaction with α-trifluoromethyl alcohols, but the reaction can be performed easily with **4** and the products readily isolated.[25]

C–H bond activation is presently a very active area of research, and 4-acetamido- (**4**) and 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (**8**) are beginning to be used in these studies. It is interesting, however, that much of the chemistry of today has its roots in the 1960s and 1970s. For example, the observation in 1972 by Golubev and Miklyush that methylene moieties can be selectively activated and converted into carbonyl groups by oxoammonium salts[40] has proven to be the starting point for a plethora of subsequent transformations.

Not only are oxoammonium salts holding their own in synthetic chemistry, but the products of their reactions are finding synthetic applications too. The preparation of ene triketones by oxidation of 1,3-dicarbonyl compounds is a case in point.[44] The triketones are reactive dienophiles in Diels–Alder reactions, leading to very densely functionalized products that are of interest in medicinal chemistry. Likewise, in the reaction of enolates and alkenes, the alkoxyamine products, formed when **4** reacts with alkenes,[60] can be employed in polymer chemistry.

We believe that oxoammonium salts will have a very interesting future, and we look forward to continuing to play our part in exploring and shaping it.

## 10. Acknowledgments

The study at the University of Connecticut of the synthetic utility of oxoammonium salts started with the work of Zhenkun Ma and Cecile Guttermuth in Professor Bobbitt's research group, and a number of graduate students have since investigated the use of **4** for alcohol oxidation. More recently, in one of a number of fruitful collaborations with Professor W. F. Bailey, graduate student Priya Pradhan has expanded the repertoire of reactions in which **4** can be employed. Collaboration with Professor C. Brückner and his graduate student Nabil Merbouh opened up avenues for the oxidation of sugars and for oxidative esterification. In 2012, Leadbeater and co-workers became involved in the field, and have utilized **4** extensively in their development of new synthetic methods. In these studies, graduate students Trevor Hamlin, Christopher Kelly, and Michael Mercadante; as well as undergraduates Rebecca Wiles, Robin Cywar, and John Ovian have played, and continue to play, key roles. Funding from the University of Connecticut and the National Science Foundation (CAREER award CHE-0847262 to NL) has allowed them to carry out the chemistry discussed here.

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## About the Authors

**Nicholas E. Leadbeater** is currently Associate Professor at the University of Connecticut. A native of the United Kingdom, he received his Ph.D. degree from the University of Cambridge in 1996 under the supervision of Professor Lord Jack Lewis and Dr. Paul Raithby. After a further three years in Cambridge as a College Research Fellow, he moved to King's College London where he was a Lecturer (U.K. equivalent of an assistant professor) from 1999 until his move to Connecticut in 2004. The overarching theme of his research group is the development of new methods for preparative organic chemistry. The group's current hot topics are clean, green oxidation methods using oxoammonium salts, the selective incorporation of fluorine into organic molecules, and the application of microwave heating and continuous-flow processing in synthetic chemistry. Allied to the preparative chemistry being explored, in situ reaction monitoring and computational chemistry are also employed to investigate the mechanisms by which chemical reactions take place. The group is a strong advocate for the incorporation of new technology into the undergraduate teaching laboratory, and has developed laboratory manuals focused on the use of microwave heating and flow chemistry.

**James McCue Bobbitt** studied at West Virginia University, receiving his B.S. degree in chemistry in 1951. He then attended The Ohio State University, obtaining his Ph.D. degree in 1955 under the supervision of Professor M. L. Wolfrom. After a year of postdoctoral work at Wayne University with Professor Carl Djerassi, he moved to the University of Connecticut in 1956, reaching the rank of Professor in 1967. James spent 1959–1960 at the University of Zürich in the laboratory of Professor Hans Schmid as an NSF Postdoctoral Fellow and, in 1964–1965, he was a guest professor at East Anglia University in England with Professor Alan Katritzky. He was a guest professor at La Trobe University in Australia in 1971–1972 and at the University of Adelaide in 1986. From 1973 until 1993, he collaborated with Professors Tetsuji Kametani and Tetsuo Osa at the Pharmaceutical Institute of Tohoku University in Sendai, Japan. In 1991, he received the University of Connecticut Alumni award for teaching and retired in 1992, but has remained active at the University of Connecticut since that time. His research has ranged from natural product chemistry (the iridoid glycosides), chromatography, heterocyclic chemistry (isoquinoline synthesis), and electro-organic oxidations of heterocycles. For the last 30 years, he has focused his efforts on oxoammonium salt mediated oxidations of alcohols and other compound classes.

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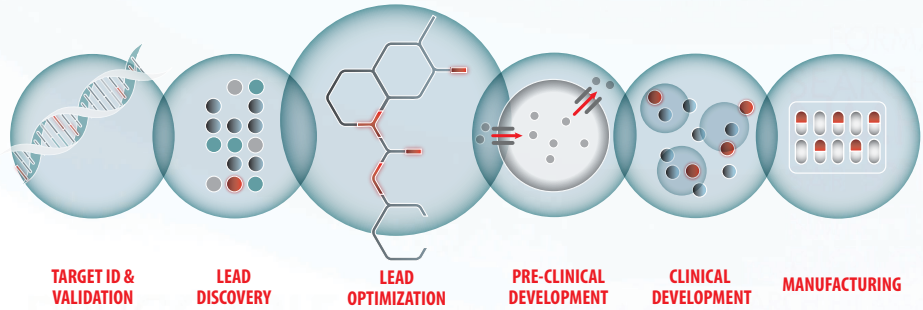


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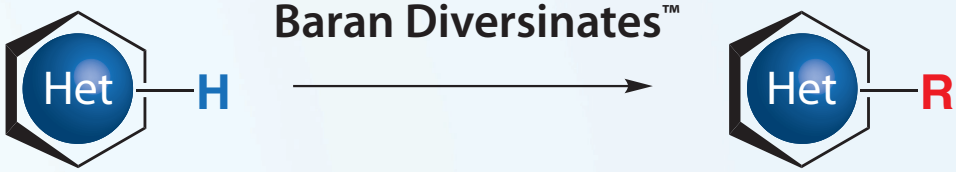


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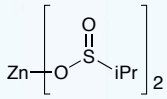
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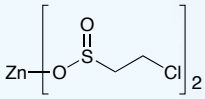
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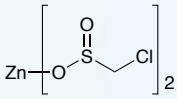
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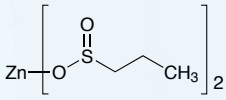
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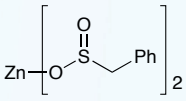
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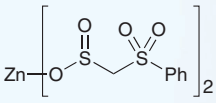
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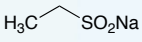
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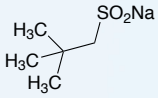
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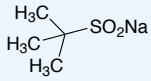
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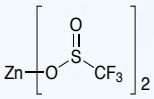
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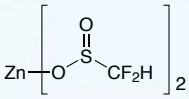
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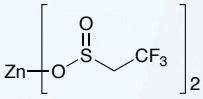
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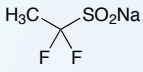
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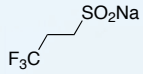
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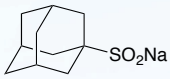
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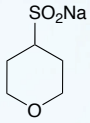
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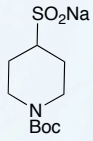
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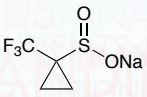
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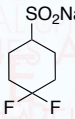
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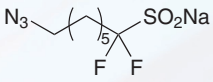
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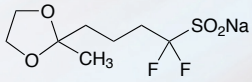
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