DEDICATED TO DR. ALFRED BADER ON THE OCCASION OF HIS 85TH BIRTHDAY

Aldrichimica ACTA

VOL. 42, NO. 1 • 2009

ALDRICH Chemistry

The Super Silyl Group in Diastereoselective Aldol and Cascade Reactions

Iterative Cross-Coupling with MIDA Boronates: towards a General Strategy for Small-Molecule Synthesis

SIGMA-ALDRICH®

Editorial

"Please Call Me Alfred"

On April 28 of this year, Dr. Alfred Bader, undeniably the world's best-known Chemist Collector, celebrated his 85th birthday. Alfred's amazing life story has been covered extensively in books, magazines, and lectures, by Alfred himself and by others, and need not be repeated here. Furthermore, most of our readers are undoubtedly aware of Alfred's strong connections, past and present, not only to Sigma-Aldrich, but also to the *Aldrichimica Acta*, which he has showered with his attention for many years. Many of Alfred's paintings have graced the covers of the *Acta*, including this issue, which is featuring one of Alfred's favorite paintings.

We honor and thank Alfred for his outstanding contributions to Sigma-Aldrich and to the worlds of chemistry, business, and art. To what he calls the "ABC" (Art, Bible, Chemistry) of his life, one should add a "D" for Donating. Alfred's philanthropic activities are considerable and ongoing, and cover a wide range of causes that are near and dear to Alfred's heart.

The magnitude of Alfred's philanthropic efforts was made possible by the considerable financial rewards that he has reaped from two of his lifelong passions. The first is a spectacularly successful chemical business (Aldrich and Sigma-Aldrich) that he helped found and successfully managed for years. The second is his passion for collecting art works, particularly of Dutch and Flemish Masters, as well as rare stamps. His collection of about two hundred such paintings has been donated by Alfred to the Agnes Etherington Art Centre of Queen's University in Kingston, Ontario (Canada). This gift is one of several sizeable ones that he has made to Queen's in gratitude for the education he received there in the 1940s.

Photo Courtesy of Alfred Bader

Dr. Alfred Bader in 2005

Lesser known, but not less important to Alfred, is his Bible scholarship, particularly of Old Testament themes, which he has studied all his life and taught for a good many years. Another lesser known trait of Alfred is his modesty and unassuming lifestyle, which used to lead many a new employee of Aldrich, in the days when Alfred was company president, to think, when running into him for the first time, that he was just another employee. After meeting Alfred for the first time and calling him Dr. Bader, the editor of this publication was gently chided for calling him Dr. Bader, rather than Alfred, which is what he insists on being called even by people who don't know him that well.

On behalf of all Sigma-Aldrich employees, past and present, we wish Alfred a very happy 85th birthday and many more in years to come.

SAFC® Launches New Vendor Audit Services

On March 19, 2009, SAFC® announced details of its new Vendor Audit Services, designed to extend audit reach for customers that need to secure global supply chain integrity through enhanced traceability and quality confirmation for critical raw materials and key intermediates. SAFC's Vendor Audit Services are an extension of in-house auditing programs, and provide pharmaceutical and biotechnology firms with a team of highly trained auditors that have extensive regulatory compliance expertise and are on the ground in local regions, including China.

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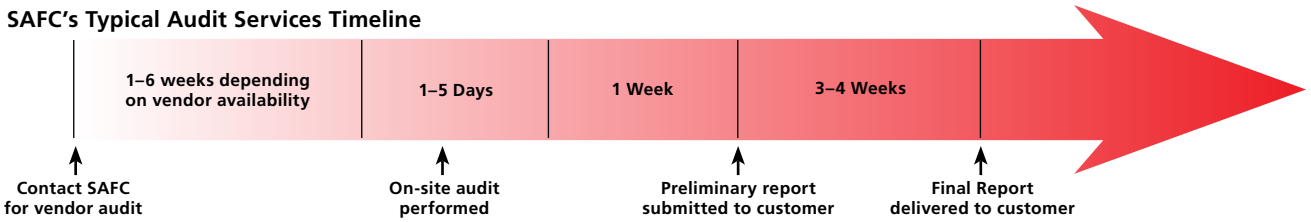

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Aldrichimica Acta

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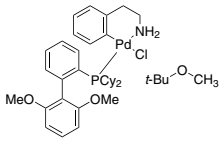
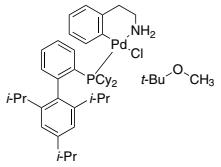
"PLEASE BOTHER US."

Joe Porwoll, President
Aldrich Chemical Co., Inc.

Professor Stephen Buchwald of the Massachusetts Institute of Technology kindly suggested that we make the single-component palladacycle precatalysts of SPhos and XPhos. These complexes simplify the use of these Buchwald ligands in a pre-defined metal-to-ligand ratio. The precatalysts are air- and moisture-stable, and can achieve high yields in C–N cross-coupling reactions using catalyst loadings as low as 0.1 mol % and 10-minute reaction times.



704946



704954

Biscoe, M. R. et al. *J. Am. Chem. Soc.* **2008**, *130*, 6686.

704946 SPhos-palladium(II)phenethylamine chloride (1:1 MTBE solvate)
250 mg
1 g

704954 XPhos-palladium(II)phenethylamine chloride (1:1 MTBE solvate)
250 mg
1 g

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

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

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ABOUT OUR COVER

Detail from ***Two Squirrels***. Photograph © Alfred Bader

Two Squirrels (oil on panel, 33.0 × 40.6 cm) was painted around 1616 and is attributed to the Flemish painter Jan Brueghel (or Bruegel) the Elder (1568–1625), also known as "Velvet" Brueghel and "Flower" Brueghel. He was the second son of Pieter Brueghel the Elder and trained with his older brother, Pieter Brueghel the Younger, in the family workshop in Antwerp.

The painting, which reflects the painter's focus later on in life on painting flowers and animals, depicts two sprightly squirrels clutching a gnarly, twisting branch set against an empty sky. This simple, engaging, and humorous depiction of a pair of lively small animals parallels the practice, at that time, of hanging portraits of husband and wife. Its high level of finish suggests that it probably was executed on commission or for sale in the market. The luminous effect created by the thin pigment layers and the fine detail are reminiscent of the style of the Brueghel family.

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

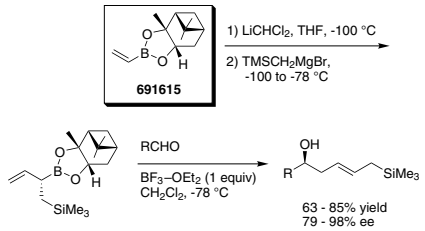
ALDRICH Chemistry

New Products from Aldrich R&D

Aldrich is Pleased to Offer Cutting-Edge Tools for Organic Synthesis

Double-Allylation Reagents

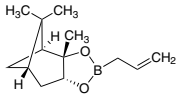
Reagents bearing multifunctional handles are of interest for the preparation of complex molecules. Professor Hall and coworkers developed a new multifunctional reagent that provides high diastereo- and enantiocontrol in a number of reactions, such as in the nucleophilic addition to aldehydes.



Peng, F.; Hall, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 3070.

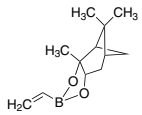
(+)-Allylboronic acid pinanediol ester, 97%

694584 1 g, 5 g
$C_{13}H_{21}BO_2$
FW: 220.12



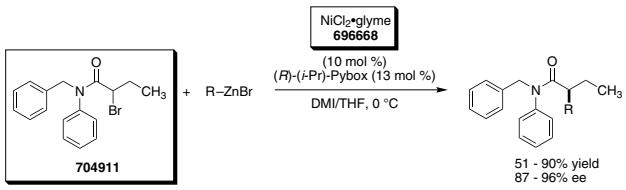
(+)-Vinylboronic acid pinanediol ester, 95%

691615 1 g, 5 g
$C_{12}H_{19}BO_2$
FW: 206.09



Substrate for Nickel-Catalyzed Negishi Coupling

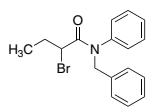
Chiral building blocks are of the utmost importance in the synthesis of more complex molecules. Professor Fu and coworkers devised the first catalytic enantioselective cross-coupling of secondary α-bromo amides with organozinc reagents. This new method proved to be highly selective for the coupling of unfunctionalized and functionalized organozincs with good yields.



Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594.

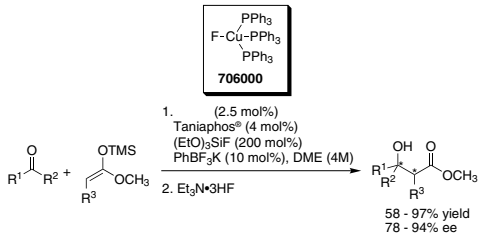
***N*-Benzyl-2-bromo-*N*-phenylbutanamide, 97%**

704911 5 g
[*851073-30-8*]
$C_{17}H_{18}BrNO$
FW: 332.23



Copper(I) Fluoride Complex for Aldol Reaction

Chiral tertiary alcohols are important building blocks for the synthesis of more complex molecules such as biologically active compounds or potential drugs. Shibasaki and coworkers developed a new copper fluoride catalyzed aldol reaction of ketones using ketene silyl acetals. Various aromatic ketones were screened and led to the desired aldol products in good yields and high selectivity.



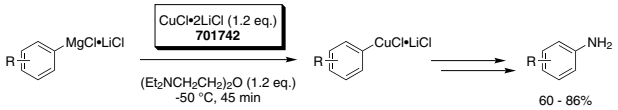
Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164. Taniaphos is a registered trademark of OMG AG and Co.

Fluorotris(triphenylphosphine)copper(I), 95% by HMR

706000 250 mg, 1 g
$C_{54}H_{45}CuFP_3$
FW: 869.40

Copper Chloride–Bis(lithium chloride) Solution for Transmetallation

Cross-coupling reactions are essential tools for chemists. In particular, the amination of aromatic halides has become a method highly relied upon to prepare aryl amines. Knochel and coworkers developed a new general amination procedure using amidocuprates. This method proved to be very versatile resulting in good yields of the amine products. This new method is a good complement to the Pd-catalyzed amination reactions.



Del Amo, V.; Dubbaka, S. R.; Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7838.

Copper(I) chloride–bis(lithium chloride) complex, 1 M in tetrahydrofuran

701742 50 mL
CuCl•2(LiCl)
FW: 183.79

The Super Silyl Group in Diastereoselective Aldol and Cascade Reactions

Dr. Matthew B. Boxer

Dr. Brian J. Albert

*Matthew B. Boxer, Brian J. Albert, and Hisashi Yamamoto**
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5735 S. Ellis Avenue
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Email: yamamoto@uchicago.edu

ACS Photo © Peter Cutts Photography, LLC.

Professor Hisashi Yamamoto (second from right) receiving the Sigma-Aldrich sponsored *2009 ACS Award for Creative Work in Synthetic Organic Chemistry*. Pictured with Professor Yamamoto are Dr. Thomas H. Lane (right), 2009 ACS President, and Dr. Joseph S. Francisco (left), 2009 ACS President-Elect. Presenting the award on behalf of Sigma-Aldrich is Dr. Mark Redlich (second from left), Product Line Manager, Chemical Synthesis.

Outline

1. Introduction

Silyl groups constitute a very important and distinct class of protective groups and serve as active participants in many thermal, and acid- and base-catalyzed reactions,[1] such as the Mukaiyama aldol, Mannich, Hosomi–Sakurai, and many cyclization reactions.[2] Their unique and important reactivity profile is manifested in several ways: (i) The silyl ethers, silyl enol ethers (SEEs), and allylsilanes of a large variety of substrates can be prepared under mild conditions.[1,3] (ii) A wide stability range exists for the many commercially available silyl-group-containing reagents.[1] Specifically, smaller silyl groups, such as TMS and TBS, can be cleaved under certain acidic or basic conditions, while larger silyl groups, like TIPS and TPS, are stable to those same conditions, This difference in reactivity allows for the development of selective protection–deprotection strategies. (iii) The particularly low electronegativity of silicon (1.8 vs 2.5 for carbon on the Pauling electronegativity scale) permits the stabilization of positive charges on silicon, while its large size (compared to carbon) stabilizes negative charges through polarization.[2,4] These properties, combined with their aforementioned thermal and chemical stabilities, have made silyl groups remarkably useful in many synthetic reactions. Lastly, one of the most distinct features of silyl groups is their facile and selective cleavage by the fluoride ion—conditions that generally do not affect the rest of the organic molecule.[1]

One silyl group that has been occasionally employed as a protective group, but rarely outside of radical reactions, is tris(trimethylsilyl)silyl {$[(CH_3)_3Si]_3Si$; TTMSS}, which is also known in the literature as the hypersilyl, sisyl, or super silyl group. In this review, we will use the term super silyl that was coined by Hans Bock in 1993.[5] Our group has found that the super silyl group exhibits peerless reactivity in a variety of diastereoselective C–C-bond-forming reactions,[6] which is the main topic of this article, as it has not been reviewed to date.

While many literature reports of the application of the super silyl group in chemistry have been published, the majority (61%) of these reports involve its use in radical reactions (**Figure 1**).[7] Tris(trimethylsilyl)silane (TTMSSH) won Fluka's Reagent of the Year Prize in 1990 for its use in radical reactions as an alternative to the toxic (n-Bu)$_3$SnH. By substituting the three alkyl groups of a silane with three TMS groups, a Si–H bond weakening of 11 kcal/mol is observed ($\Delta_f H^o$: TESH = 90 kcal/mol vs TTMSSH = 79 kcal/mol).[8] TTMSSH has been employed in hydrosilations of alkenes and alkynes,[9–11] radical cyclization reactions,[9] the reduction of acid chlorides,[9e] the hydrosilation of carbonyl groups,[9a,12] and the reduction of carbon–halogen bonds.[9b]

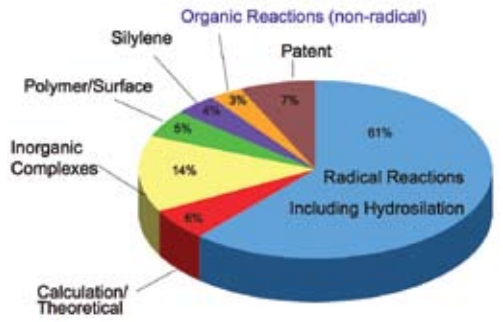
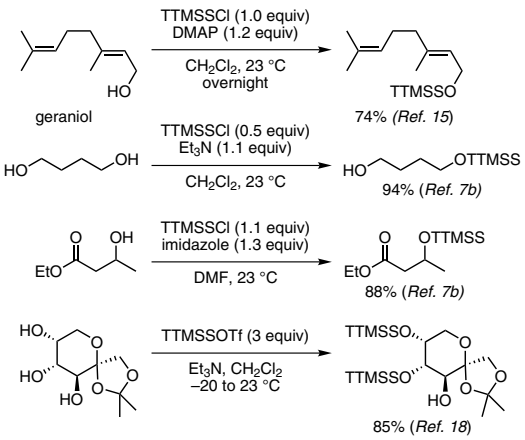
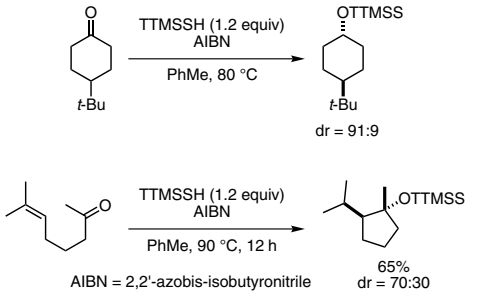


Figure 1. Pie Chart Showing the Breakdown by Application of Literature References Citing the Tris(trimethylsilyl)silyl (TTMSS) Group. *(Ref. 7)*



Scheme 1. Synthesis of Super Silyl Ethers under Standard Conditions.



Scheme 2. Radical Hydrosilylation Reactions. *(Ref. 12)*

The second most commonly reported application of the super silyl group deals with its complexation with transition metals and main group elements (14%).[13] Its extremely bulky size and electron-donating ability stabilize metals and main group elements in various oxidation states. In 2004, Kornev published a review on the tris(trimethylsilyl)silyl group, with emphasis on its complexation with transition metals and main group elements and on its application in radical reactions.[13c]

Surprisingly, the employment of the super silyl group in nonradical, standard acid–base, catalytic, and thermal reactions comprises only around 3% of the total literature.[13c,14,15] Much of this 3% is devoted to papers describing its photochemical and strong-acid- or strong-base-induced rearrangements, which are rarely accompanied by C–C-bond formation. A small portion of the 3% is devoted to its application as an alcohol protecting group.[15] Recently, the super silyl group has been incorporated into organic catalysts to increase their steric requirement and selectivity.[16]

The major structural difference between the super silyl group and the more typical silyl groups, which all contain only Si–C and Si–O bonds, is the presence of the Si–Si bonds. A number of experimental and theoretical calculations attribute many of the unique properties of this silyl group to its Si–Si bonds,[17] which render it UV active (allowing for straightforward TLC analysis) and impart other distinct electronic properties. These unique characteristics are demonstrated in the thoroughly studied polysilanes and oligosilanes, where the electrons are actually delocalized along the Si–Si σ bonds.[17] In these cases, photolysis reactions arise by promoting an electron from a σ orbital to the σ* orbital, which often takes place with remarkably low excitation energy (320 nm).

Recently, the unique reactivity of the super silyl group has led to its successful application in a variety of C–C-bond-forming reactions: [2 + 2] cyclizations, Mukaiyama aldol synthesis, and various sequential reactions.[6]

2. Installation of the Super Silyl Group

The protection of alcohols with the super silyl group can be easily achieved under standard conditions (**Scheme 1**).[7b,15,18] Brook and co-workers have demonstrated that protection of various primary and secondary alcohols can be accomplished using 1 equivalent of the alcohol, 1 equivalent of super silyl chloride, and 1.2 equivalents of DMAP.[15] We have found that unhindered primary alcohols can be efficiently protected by employing super silyl chloride and triethylamine in either THF or CH_2Cl_2.[7b] We have also been able to protect β-hydroxy esters using super silyl chloride and imidazole in DMF.[7b] Super silyl triflate has also been utilized in conjunction with triethylamine to selectively protect carbohydrates.[18]

Because of the ability of TTMSSH to participate in hydrosilation reactions, the radical reaction conditions shown in **Scheme 2** have been utilized to prepare super silyl ethers in one step from carbonyl compounds.[12]

The initial synthesis of the first super silyl enol ether (super SEE) utilized an n-BuLi induced THF fragmentation to generate the lithium enolate of acetaldehyde (**Scheme 3**).[19] The synthesis of super SEEs evolved over time to use a metal–halogen exchange of AgOTf and TTMSSCl to generate the silyl triflate, which was then employed under soft enolization conditions to form **1**. The synthesis of TTMSSOTf was further modified

and took advantage of a triflic acid–super silane reaction that liberated H_2 gas and generated the silyl triflate in situ, which was again utilized to prepare **1**.[6a-c]

3. [2 + 2] Cyclizations

The cyclobutane ring is found in various natural and unnatural bioactive molecules, and is commonly found in synthetic intermediates as well.[20] There is only a limited number of reports of efficient syntheses of this 4-membered ring by non-photochemical [2 + 2] cycloadditions,[20–22] in large part because one of the synthetic routes, the concerted cyclization, is disallowed by the Woodward–Hoffmann rules.[23] Thus, both thermal and ground-state catalytic reactions must proceed stepwise, which forms the basis for the proposed Michael aldol mechanism (**Scheme 4**).[6a,22a] This mechanism invokes a zwitterionic Michael addition intermediate, **A**, which may be present long enough to give rise to undesirable side-products. The use of aldehyde enol equivalents for this type of reaction had been previously unattainable, presumably due to this fact.

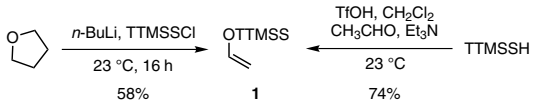
Takasu, Ihara, and co-workers have published numerous reports on formal [2 + 2] cyclizations of SEEs derived from ketones.[22] Their original report took advantage of in situ SEE formation with a TMSI–HMDS system and the use of a chiral auxilliary (8-phenylmenthyl ester).[22a] They later employed preformed TBS and TIPS enol ethers in cyclizations with hexafluoroisopropyl acrylate catalyzed by $EtAlCl_2$,[22c,d] which worked well for forming cyclobutane-containing products including 5,4-, 6,4-, 7,4-, and 8,4-fused bicyclic compounds. A few years later, they reported the use of a strong Brønsted acid, Tf_2NH, to effect the [2 + 2] cyclization of SEEs and methyl acrylate.[22e]

The same research group also investigated formal [2 + 2] cyclizations of α,β-unsaturated esters with acetaldehyde-derived SEEs, and reported that TBS[22d] and TIPS SEEs[22c] failed to give any desired products (**eq 1**). To prevent side reactions potentially stemming from high-energy intermediates such as **A**, it was envisaged that a bulky super silyl group, such as **1**, could stabilize and "shield" **A** from undesired reactions and decomposition. Fortunately, using **1**, hexafluoroisopropyl acrylate, and $EtAlCl_2$ as catalyst gave the desired cyclobutane in 45% yield with low diastereoselectivity.[6a] Interestingly, the use of the pentamethyldisilyl (PMDS) derived enol ether **2**, containing one Si–Si bond, also afforded the cyclobutane adduct, albeit in 7% yield. The effect of the R group of the ester was investigated next: aliphatic esters gave no product, whereas phenyl acrylate gave the best yield and diastereoselectivity.

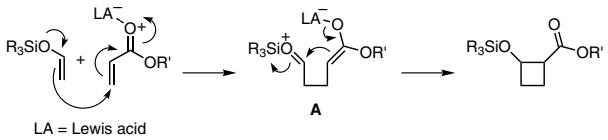
Various Lewis acids were screened, but only the $EtAlCl_2$-based catalyst gave acceptable results, while $TiCl_4$, $GaCl_3$, $SnCl_4$, $AgNTf_2$, TMSOTf, and $HNTf_2$ all gave <10% of the desired product. It has been observed that unwanted transfer of silyl groups during attempted asymmetric aldol synthesis could be prevented by using a bulky Lewis acid with the triflimide counteranion.[24] The use of bulky catalysts based on the methylaluminum bis(2,6-diphenylphenoxide) (MAPH)[25] scaffold were also investigated. The best result was obtained with bis(2,6-diphenylphenoxide) aluminum triflimide (BDAT).

Both aldehyde- and ketone-derived super SEEs were shown to succeed in this system. The reaction proceeded smoothly in all cases at –40 °C with a 3 mol % catalyst loading and gave high yields with high trans:cis ratios (**eq 2**).[6a] Acetaldehyde SEE afforded cyclobutane **4** with a >99:1:0:0 dr by use of the chiral *trans*-(1*R*,2*S*)-2-phenylcyclohexanol derived ester (entry 2). SEE **5** led to *gem*-dimethylcyclobutane **6**, with excellent stereoselectivity (entry 3), while super SEE **7** gave cyclobutane **8**, which contains a chiral quaternary carbon (entry 4). Interestingly, the highest yield (94%) and excellent selectivity were observed for cyclohexanecarboxaldehyde SEE **9** (entry 5). Three contiguous stereocenters were formed with excellent diastereoselectivity from the reaction of *E*-**11** with phenyl acrylate (entry 6).

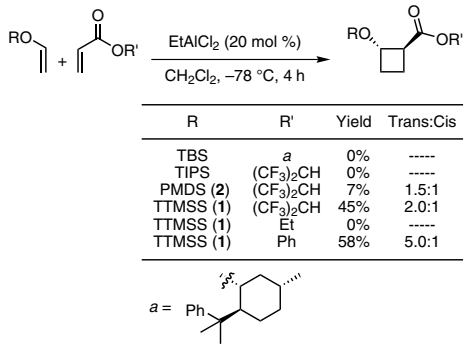
The significance of these super SEEs was clearly demonstrated by their success in the [2 + 2] cyclizations. That is, these examples represented the first formal [2 + 2] condensations between an acetaldehyde SEE and an acrylic



Scheme 3. Evolution of the Synthesis of Super Silyl Enol Ether **1**. *(Ref. 6a-c,19b)*

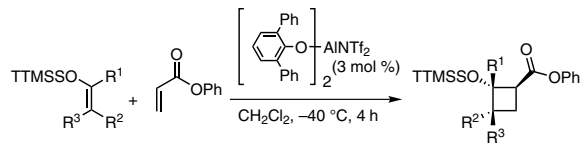


Scheme 4. Proposed Michael Aldol Mechanism for the Formal [2 + 2] Cyclization. *(Ref. 6a)*



R	R'	Yield	Trans:Cis
TBS	*a*	0%	-----
TIPS	$(CF_3)_2CH$	0%	-----
PMDS (**2**)	$(CF_3)_2CH$	7%	1.5:1
TTMSS (**1**)	$(CF_3)_2CH$	45%	2.0:1
TTMSS (**1**)	Et	0%	-----
TTMSS (**1**)	Ph	58%	5.0:1

eq 1 *(Ref. 6a,7b,22d)*



No	R^1	R^2,R^3	Yield	Trans:Cis
3	H	H,H	84%	10:1
4	H	H,H[a]	81%	>99:1:0:0
6	H	Me,Me	91%	>99:1
8	Me	H,H	81%	25:1
10	H	$(CH_2)_5$	94%	>99:1
12	H	Me,H[b]	93%	>99:1

[a] *trans*-(1*R*,2*S*)-2-Phenylcyclohexyl acrylate was used. [b] *E*:*Z* (of starting silyl enol ether **11**) = 92:8.

eq 2 *(Ref. 6a)*

ester. The necessity of the Si–Si bonds for these reactions was a first indication of the distinctiveness of the super silyl group in Lewis acid catalyzed reactions.

4. The Mukaiyama Aldol Reaction

The aldol reaction has emerged as a regular method for forming β-hydroxy carbonyl and/or 1,3-diol motifs typically seen in polyketides.[26] Of the various examples, a great deal utilize an ester, thioester, or ketone enolate (or enolate equivalent) as the nucleophile to circumvent problems associated with the aldehyde crossed aldol reaction. Frequently, the resulting products are reduced to the desired hydroxy-protected aldehydes through an additional one- or two-step procedure. Since Mukaiyama's seminal report on the titanium-catalyzed reaction of SEEs with aldehydes and ketones,[27] the Mukaiyama aldol reaction has developed into one of the most powerful and best-known synthetic reactions.[28] With a large number of reviews and books published in this area, this section will focus mainly on the aldehyde crossed aldol reaction.

4.1. α-Substituted Enol Ethers

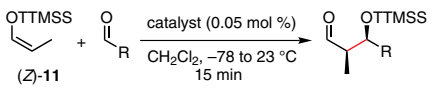
Although the Mukaiyama aldol synthesis is one of the most powerful variants of the aldol reaction, the aldehyde crossed aldol reaction has only been realized in a few cases, many of which are limited in scope.[29–31] In 1974, Mukaiyama followed his archetypal report with two examples of the isobutyraldehyde SEE crossed aldol reaction.[29b] This system took advantage of the fact that neopentyl aldehydes were formed after the first aldol reaction and, thus, further aldol reactions were retarded.

Later use of α-substituted aldehydes took advantage of in situ enolate formation. In 1980, Heathcock reported the use of the in situ formed lithium enolate of propanal, which gave low selectivity when reacted with benzaldehyde.[30a] In 1983, Kato and Mukaiyama reacted an in situ generated tin enolate of isobutyraldehyde with a variety of aryl and alkyl aldehydes.[29c] Mahrwald's[30b–d] and Oshima's[30e,f] groups utilized in situ formed titanium enolates for reaction with a variety of aldehydes.

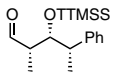
In 2001, Denmark reported that trichloro SEEs of propanal and heptanal successfully reacted with aromatic and aliphatic aldehydes in an enantioselective fashion catalyzed by a chiral phosphoramide base.[30g] The diastereoselectivity was controlled by the enol geometry, with the *Z* enols giving high syn selectivity and the *E* enols giving high anti selectivity.

After MacMillan's seminal report on the enantioselective proline-catalyzed aldehyde crossed aldol reaction,[31a] an explosion of variants of this reaction emerged. Publications from Jørgensen, Córdova, and Barbas all employed proline-based catalysts to effect the direct aldehyde crossed aldol reaction of α-alkyl-substituted aldehydes.[31]

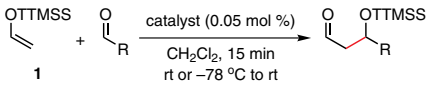
In 2006, our group published a diastereoselective reaction that worked very well with propionaldehyde-derived super SEE (*Z*)-**11**.[6b] High yields and good syn:anti ratios were obtained using $HNTf_2$ as the precatalyst. This Brønsted acid is termed the precatalyst due to the fact that the use of $(TTMSS)NTf_2$ (0.05 mol %) as the catalyst in all reactions shown in equations 3 and 4 led to results identical to those obtained using $HNTf_2$, implying that the silyl triflimide is likely the true catalyst (see Section 7 for the proposed protodesilylation mechanism). Aliphatic and branched aldehydes successfully underwent this reaction, generating aldolates in moderate-to-high diastereoselectivities (**eq 3**).[6b] The use of (*S*)-2-phenylpropanal exhibited high Felkin control in conjunction with syn selectivity, providing three adjacent stereocenters. Importantly, this provides a complementary method to the anti selectivity obtained by MacMillan.[31a]



R	Catalyst	Yield	Syn:Anti
n-Hep	$HNTf_2$	82%	80:20
n-Hep	$TTMSSNTf_2$	85%	79:21
Cy	$HNTf_2$	72%	85:15
Cy	$TTMSSNTf_2$	71%	82:18
t-Bu	$HNTf_2$	78%	95:5
t-Bu	$TTMSSNTf_2$	79%	95:5
(*S*)-PhCH(Me)	$HNTf_2$	84%	>95:5:0:0[a]
(*S*)-PhCH(Me)	$TTMSSNTf_2$	87%	>95:5:0:0[a]

[a] Ratio for 

eq 3 *(Ref. 6b)*



R	Catalyst	Yield	Syn:Anti
n-Hep	$HNTf_2$	87%	----
n-Hep	$TTMSSNTf_2$	85%	----
Cy	$HNTf_2$	89%	----
Cy	$TTMSSNTf_2$	86%	----
t-Bu	$HNTf_2$	90%	----
t-Bu	$TTMSSNTf_2$	91%	----
(*E*,*E*)-MeCH=CHCH=CH	$HNTf_2$	78%	----
(*E*,*E*)-MeCH=CHCH=CH	$TTMSSNTf_2$	75%	----
Ph	$HNTf_2$	83%	----
Ph	$TTMSSNTf_2$	87%	----
(*S*)-PhCH(Me)	$HNTf_2$	86%	>95:5
(*S*)-PhCH(Me)	$TTMSSNTf_2$	85%	>95:5
(2*R*)-EtCH(Me)	$HNTf_2$	93%	86:14
(2*R*)-EtCH(Me)	$TTMSSNTf_2$	90%	85:15
(2*S*)-MeCH(OTIPS)CH_2	$HNTf_2$	88%	85:15
(2*S*)-MeCH(OTIPS)CH_2	$TTMSSNTf_2$	89%	88:12

eq 4 *(Ref. 6b,7b)*

4.2. Acetaldehyde-Derived Enol Ethers

Interestingly, the direct installation of acetaldehyde had not been described in any *broad* sense before 2006. In 1958, Leech and co-workers reported the condensation of an alkyl vinyl ether with an aldehyde catalyzed by BF_3.[29a] Paterson et al. later utilized the TBS enol ether of acetaldehyde in a reaction with a highly electrophilic oxonium ion in the presence of super stoichiometric $Cl_2Ti(Oi\text{-}Pr)_2$.[32] There are a few reports on the use of the enzyme 2-deoxyribose-5-phosphate aldolase (DERA) for the aldol reaction of acetaldehyde with various aldehydes; however, the observed yields are rather low.[33]

Denmark and Bui have reported a chiral-phosphoramide-catalyzed enantioselective aldol reaction of the TMS-SEE of acetaldehyde with aldehydes.[30h] High enantioselectivities and good yields were obtained for a variety of aryl aldehydes, but the products were isolated as the dimethyl acetals after addition of MeOH followed by $NaHCO_3$ to the reaction mixture.

In 2006, our group reported a broad, highly diastereoselective, aldehyde crossed aldol reaction of acetaldehyde super SEEs (**eq 4**).[6b,7b] The use of $HNTf_2$ as the precatalyst gave consistently high yields of the aldol products with aliphatic, branched, aryl, and even α,β-γ,δ-unsaturated aldehydes. Moreover, (*S*)-2-phenylpropanal was tested and showed extremely high Felkin selectivity. Somewhat amazingly, good selectivity was

obtained in the reaction with 2-methylbutanal, demonstrating the ability of this reaction to differentiate between methyl and ethyl groups. Syn selectivity was observed for the reaction of **1** with a β-siloxy aldehyde, in contrast to previous studies by Evans and co-workers, wherein anti selectivity was observed for the open-transition-state Mukaiyama aldol additions to β-alkoxy aldehydes.[34] The syn selectivity observed in our system is proposed to arise from the size of the TIPS and super silyl groups, whereas the study reported by Evans dealt with much smaller β-alkoxy aldehydes. A more detailed discussion of these observations, including DFT calculations, is presented in Section 8.

Recently, acetaldehyde has been introduced through the Mannich reaction. A singular example was given in the $Yb(OTf)_3$ catalyzed reaction of vinyloxytrimethylsilane.[35] List later published a paper on the direct use of acetaldehyde under proline catalysis.[36] While yields were relatively low, enantiomer ratios were very high for a range of substrates.

4.3. Ketone-Derived Super Silyl Enol Ethers (SEEs)

Ketone-derived super SEEs were also examined in simple Mukaiyama aldol reactions.[6f] The acetone-derived super SEE gave exceedingly high Felkin selectivity with 2-methylbutanal and 2-phenylpropionaldehyde (**Scheme 5**). The reaction of cyclohexanone super SEE with isobutyraldehyde gave the aldol product in high yield and unprecedented high anti selectivity for this type of Mukaiyama aldol reaction. This is in stark contrast to the TBS and TMS SEEs of cyclohexanone, which have been reported to give little-to-no selectivity in aldol reactions with a variety of catalysts.[37]

5. Sequential Aldol–Aldol Reactions

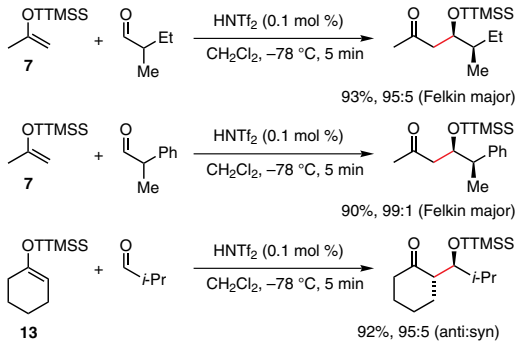
For many obvious and necessary reasons, there is considerable interest in economical and environmentally friendly reactions.[38,39] In this vein, one-pot, sequential and multicomponent reactions have emerged as an important means for accomplishing some of these goals. As Tietze and Beifuss wrote in a review on sequential reactions,[39] "if we compare our synthetic performance to date with that of Nature, then we must recognize that Nature is not just highly selective, but also very efficient, often employing sequential transformations. By this we understand a series of reactions steps in which several bonds are formed or broken, without the isolation of any intermediates". They later go on to say, "the quantity of solvents and eluents required in comparison with stepwise processes is considerably reduced. Sequential reactions should, therefore, be more frequently included in future synthetic planning". The use of sequential reactions not only saves bulk materials, but also time and labor.

Aldol–aldol reactions that incorporate more than three equivalents of starting aldehyde in the product have been described in discussions of aldolase-catalyzed reactions.[33,40] As previously mentioned, these systems suffer from low yields and limited applicability. MacMillan expanded his proline-catalyzed aldehyde crossed aldol reaction to include a two-step synthesis of enantiopure hexoses.[41,42] This elegantly designed system took advantage of the enantioselective aldol dimerization of α-siloxy- and α-benzyloxy aldehydes under proline catalysis. Various α-heteroatom-substituted TMS enol ethers were then added under $TiCl_4$ catalysis to give the cyclized hexoses in diastereo- and enantiomerically enriched forms, thereby providing an excellent means for protective-group control in ^{13}C-labelling experiments. Leighton and co-workers later used strained silacycles for a one-pot, ketone enol, aldol–aldol reaction, which provided hemiketal products containing two chiral quaternary carbon stereocenters.[43]

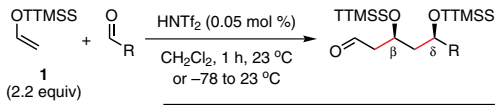
5.1. Cascade Reactions of Aldehyde-Derived SEEs

Our group described a cascade aldol reaction, later termed sequential aldol–aldol (SAA) reaction.[6b] Interestingly, this reaction stops at the 2:1 adduct (SEE:starting aldehyde) stage even when an excess of super SEE is employed. It is believed that after the first addition and silyl transfer, the steric encumbrance of the super silyl group kinetically slows down the addition of a second equivalent of SEE to a rate that does not compete with the rate of the first addition. When all of the aldehyde starting material has been consumed, a second addition occurs giving the 2:1 adducts with high diastereoselectivity. After the second aldol reaction, the substrate has two super siloxy groups (at the β and δ positions), and a third aldol reaction would require the coordination of a third super silyl group (as the catalyst), which should significantly slow the third aldol reaction due to steric hindrance.

The SAA reaction succeeded in generating a variety of protected β,δ-dihydroxy aldehydes in good yields and selectivities (**eq 5**).[6b] Pival- and cyclohexyl aldehydes showed comparable selectivities. Octyl aldehyde led to a slightly lower selectivity, while (*S*)-2-phenylpropanal resulted in high selectivity for the all-syn isomer. The β-TIPSoxy aldehyde afforded the all-syn protected β,δ,ζ-tris-siloxy aldehyde, and



Scheme 5. Mukaiyama Aldol Reactions of Ketone-Derived Super SEEs. *(Ref. 6f)*



R	Yield	Syn:Anti
t-Bu	75%	>99:1
Cy	72%	95:5
n-Hep	68%	90:10
(*S*)-PhCH(Me)[a]	74%	86:13:<1:<1
(*S*)-MeCH(OTIPS)CH_2	64%	----
rac-BnOCH(Me)	61%	----

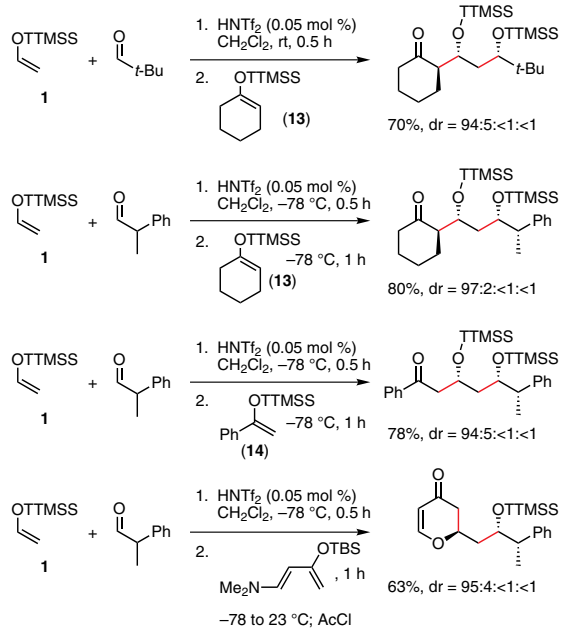
[a] Major product has the opposite configuration at the β and δ carbons.

eq 5 *(Ref. 6b)*

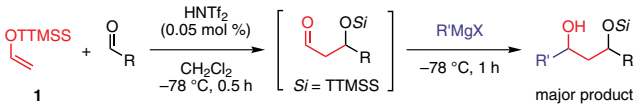
α-benzyloxypropanal formed a β,δ,ε-trihydroxy aldehyde adduct—consistent with a mechanism involving chelation-controlled first aldol addition followed by a syn-selective second aldol addition.

5.2. Cascade Reactions of Ketone- and Aldehyde-Derived SEEs

The SAA reaction was extended to ketone- and aldehyde-derived super SEEs (**Scheme 6**),[6d] which requires, in this case, the addition of first the aldehyde and then the ketone SEEs due to their competitive reactivity with the initial aldehyde. Following the standard aldol reaction of **1** with pivalaldehyde, addition of the super SEE of cyclohexanone (**13**) to the reaction mixture gave the SAA adduct in excellent diastereoselectivity. A similar reaction sequence employing 2-phenylpropionaldehyde in the first step generated a product with three new stereocenters highly stereoselectively. Substituting acetophenone super SEE (**14**) in the second step of the same reaction cascade similarly yielded the product with high diastereoselectivity. Using a hetero-Diels–Alder reaction with a siloxy-diene, developed by Kozmin and Rawal,[44] as the second step in the cascade formed a dihydropyranone with comparable diastereoselectivity.



Scheme 6. SAA and SA–Hetero-Diels–Alder Reactions of Super SEEs. *(Ref. 6d)*



R	R'MgX	Major Product	Yield	dr
	MgBr		84%	90:10[a]
Ph (±) Me	MgBr		83%	85:14:<1:<1
Ph Me (98.3% ee)	MgCl Me	(97% ee)	79%	86:13:<1:<1
OTBS	MgBr H		71%	75:13:10:<5
OTBS	MgBr		85%	74:18:<5:<5

[a] Reactions run at room temperature.

Scheme 7. Sequential Aldol–Grignard Addition with Super SEE **1**. *(Ref. 6d)*

6. Other Sequential Reactions of SEEs

The 1,3-diol substructure is very common in many important medicinal compounds.[28] The majority of syntheses of molecules containing this motif require a multistep protocol to access the stereodefined diol. Significant contributions by Leighton's group and ours have employed SEEs in tandem and sequential reactions to access the 1,3-diol motif in one step.[6b–f,43,45]

6.1. Silyl Dinucleophile Reagents

In 1999, Berrisford's group published a very interesting report of a silicon-tethered dinucleophile reagent that undergoes a sequential aldol–allylation reaction.[46] When this unique reagent was reacted with dimethyl acetals in the presence of BF_3•OEt_2, the aldol–allylation product was obtained in reasonable yield, but with rather low diastereoselectivity.

Leighton and co-workers later developed a number of strained silacycles that are very efficient at tandem aldol–allylation, aldol–crotylation, and aldol–aldol reactions.[43,45] These reagents rely on an increase in Lewis acidity of the silicon center that arises from the strained 5-membered ring, thus enabling the aldol–allylation and aldol–crotylation to proceed without the need for a catalyst. Moderate yields and reasonable selectivities were obtained for various combinations of enol and allyl or crotyl moieties. The strained silacycle approach was also extended to include the use of ketone enol equivalents for the synthesis of tertiary carbinols.[43] In this latter case, the sequential aldol–allylation, aldol–methallylation, aldol–crotylation, and aldol–aldol reactions proceeded in good yields and selectivities producing a variety of relatively complex polyketide-like products in one pot.

6.2. Sequential Aldol–Carbanion Addition Reactions

Due to the very low catalyst loading (0.05–0.10 mol % of $HNTf_2$) utilized in the aldol reactions and the high diastereoselectivity obtained in the SAA reactions, it was anticipated that the addition of Grignards would be tolerated and would proceed with high stereoselectivity in generating secondary and tertiary carbinols, which still remains a challenging task in organic chemistry.[47] Following the aldol reaction of pivalaldehyde and **1**, allylmagnesium bromide was added to give the aldol–allylation product in 90:10 syn:anti selectivity in one pot (**Scheme 7**).[6d] Chiral starting aldehydes 2-phenylpropionaldehyde and 3-TBSoxybutanal also led to good selectivities for the corresponding sequential SA–Grignard reaction product. The use of vinyl-, alkynyl-, and allylmagnesium halides generated synthetically useful allylic, propargylic, and homoallylic alcohols with high selectivity. Worthy of note is that enantioenriched (*S*)-2-phenylpropanal (98.3% ee) led to the major diastereomeric product in 97% ee, indicating no racemization during the acid-catalyzed aldol step.[6d]

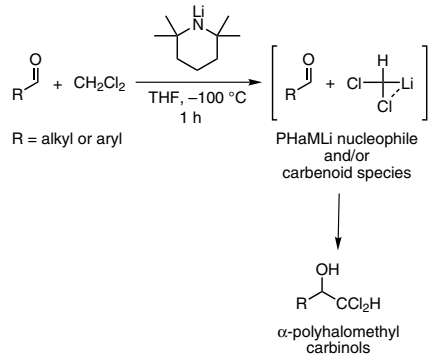
Polyhalomethanes (PHaMs) are small inexpensive molecules that are typically used as solvents (i.e., CH_2Cl_2 and $CHCl_3$). Halogens, of course, have a diverse reactivity profile and can render compounds electrophilic or nucleophilic.[48] Medicinal chemistry has revealed that fluorine- and chlorine-containing compounds have enhanced properties in biological settings as well as in crop management.[49] Despite considerable evidence of the importance of halogen-containing compounds, the stereocontrolled introduction of the polyhalomethyl group is not widely achievable.[50] To our knowledge, there exist only a few examples of the diastereoselective introduction of such groups.[50c,e,h]

One of the most straightforward pathways to these PHaMs is the nucleophilic addition of polyhalomethyllithiums (PHaMLi's) to aldehydes (**Scheme 8**).[6e] PHaMLi's are best generated by deprotonation of PHaMs with bulky lithium amides such as LiTMP (TMP = 2,2,6,6-tetramethylpiperidinyl). A potential difficulty with this approach is dealing with the instability of such carbenoid-type species even at low temperatures.[50,51] However, it has been shown that when a solution of an aldehyde or ketone, in the presence of excess PHaMs, is treated with a bulky lithium amide, the kinetically generated lithium carbenoid species reacts with the aldehyde or ketone before side reactions and decomposition occur.[50a]

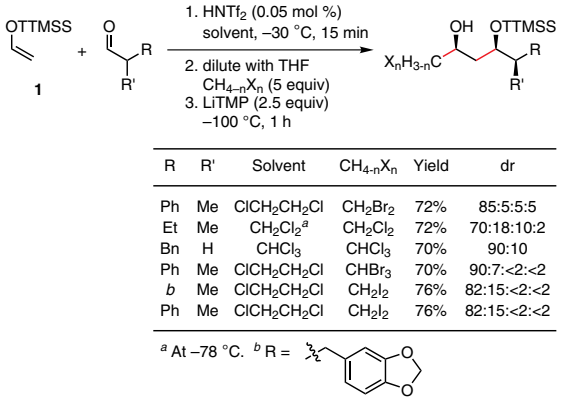
Thus, this reaction is a natural fit for our SA–nucleophile addition reaction sequence, since the requisite acid catalyst for the first step is present at only 0.05 mol % and the reaction proceeds in nonprotic solvents. Using our standard aldol reaction of **1** and 2-phenylpropionaldehyde, a variety of solvents and temperatures were screened for the diastereoselective sequential addition of dibromomethyllithium (**Scheme 9**).[6e] 1,2-Dichloroethane was utilized as solvent for the aldol reaction since CH_2Cl_2 is competitively deprotonated under the subsequent PHaMLi-generating reaction conditions. For PHaMLi generation and addition reactions, employing THF as solvent at –100 °C was optimal for producing the syn diols. The aldol solvent could also be utilized as the PHaMLi precursor. The highest selectivity was obtained with the largest such anion, tribromomethide, giving the product in high yield and high syn selectivity. Diiodomethane is also successfully deprotonated under these conditions and adds with high selectivity to give α-diiodomethylcarbinols in good yields.

A mixed α-polyhalomethylcarbinol has also been synthesized by Kuroboshi's group using a slightly different protocol.[52] Following the standard aldol reaction, $CFBr_3$ was added, the solution diluted with 2:1 THF–Et_2O, cooled to –130 °C, and Br_2FCLi prepared in situ by lithium–bromine exchange with *n*-BuLi (**Scheme 10**).[6e] The α-dibromofluorocarbinol was produced in 55% yield with good selectivity, and was converted into the *Z* α-haloenol ester by treatment with acetic anhydride and then $CrCl_2$ in refluxing THF.[53] Moreover, a disubsituted *Z* fluoroalkene was prepared by an SA–Wittig-type olefination sequence.[6e] This sequential reaction succeeded when the aldol reaction was followed by addition of the in situ prepared $(n\text{-Bu})_3$P-CF-P$(n\text{-Bu})_3$Cl.[54] After stirring for 12 h, 10% NaOH was added and stirred for an additional 12 h, inducing hydrolysis of the vinylphosphonium salt, thereby generating the *Z* fluoroalkene, in moderate yield and high selectivity.

With a clear indication that ketone-derived super SEEs were satisfactory in the basic Mukaiyama aldol reaction, their use in SA–Grignard addition reactions was also demonstrated.[6f] While a plethora of literature reports have been published on the diastereoselectivity of additions to β-oxygenated aldehydes,[34,55] significantly fewer reports can be found for the corresponding simple β-oxygenated ketones (not including hydrogenation–reduction reactions).[47b,e,56] The majority of the reports that do exist, involve a β-hydroxy ketone and are proposed to undergo cyclic, 6-membered-ring transition states involving a Lewis acid catalyst or a metal from the organometallic species. While there is a report concerning syn selectivity for the methyl and butyl additions to β-TBSoxy-protected ketones,[47b] few examples of this type of diastereoselective reaction exist. This likely arises from



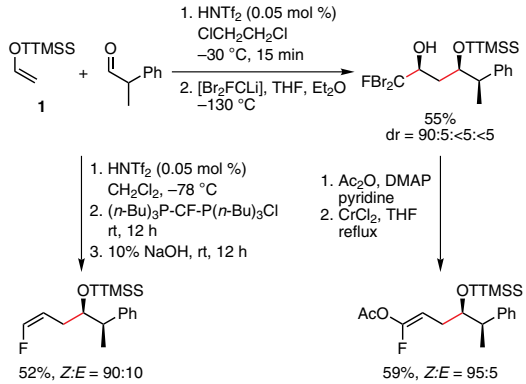
Scheme 8. PHaMLi Generation and in Situ Reaction with Aldehydes. *(Ref. 6e)*



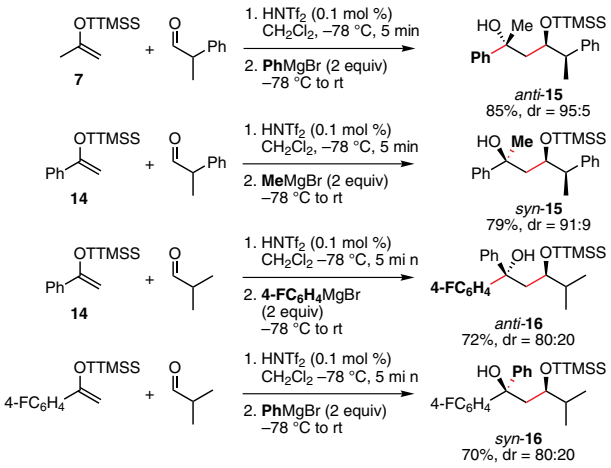
R	R'	Solvent	$CH_{4-n}X_n$	Yield	dr
Ph	Me	$ClCH_2CH_2Cl$	CH_2Br_2	72%	85:5:5:5
Et	Me	CH_2Cl_2[a]	CH_2Cl_2	72%	70:18:10:2
Bn	H	$CHCl_3$	$CHCl_3$	70%	90:10
Ph	Me	$ClCH_2CH_2Cl$	$CHBr_3$	70%	90:7:<2:<2
b	Me	$ClCH_2CH_2Cl$	CH_2I_2	76%	82:15:<2:<2
Ph	Me	$ClCH_2CH_2Cl$	CH_2I_2	76%	82:15:<2:<2

[a] At –78 °C. [b] R =

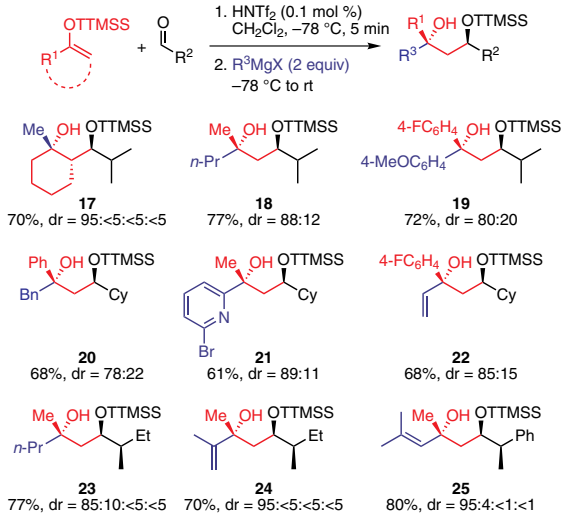
Scheme 9. Sequential Aldol–Polyhalomethyllithium Addition Reactions. *(Ref. 6e)*



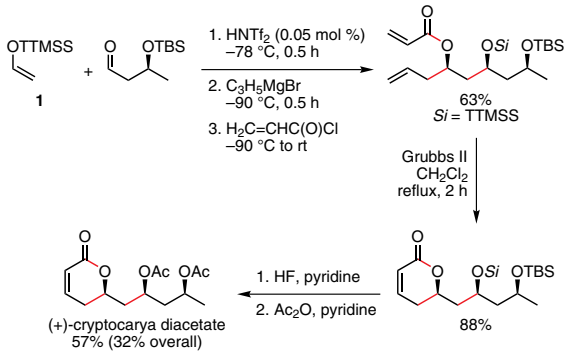
Scheme 10. Synthesis of Mixed α-Polyhalomethyl Carbinols and Fluoroalkenes. *(Ref. 6e)*



Scheme 11. Distinct Diastereomer Formation by Simple Substrate Choice. *(Ref. 6f)*



eq 6 *(Ref. 6f)*



Scheme 12. Total Synthesis of (+)-Cryptocarya Diacetate. *(Ref. 6d)*

two main factors: (i) ketones typically show lower selectivity and reactivity than aldehydes in many stereoselective reactions, and (ii) stereoselectivity induced by chirality at the β carbon is often lower than that induced by chirality at the α carbon.

Using the previously established, simple, one-pot SA–Grignard addition reaction protocol, acetone super SEE and 2-phenylpropionaldehyde underwent the aldol reaction initiated by 0.1 mol % of $HNTf_2$. PhMgBr was subsequently added leading to *anti*-**15** in good yield and excellent diastereoselectivity (**Scheme 11**).[6f] Interestingly, the anti product was the major diastereomer, and this sense of stereoinduction results from nucleophilic attack on the π face of the carbonyl *opposite* to that which is seen for SAA and SA–Grignard additions utilizing **1**. DFT calculations were carried out to investigate the nature of the transition state (TS) in these reactions; the results will be discussed in Section 8. Aware that the choice of substrate could lead to predictable, distinct diastereomer formation, *syn*-**15** was prepared with high selectivity by simply employing acetophenone super SEE in the first (SA) step, and adding MeMgBr in the second step. Extending this idea to generate a tertiary carbinol with similarly sized substituents, *anti*-**16** was obtained from acetophenone super SEE and *p*-fluorophenylmagnesium bromide in a similar reaction sequence. Next, using 4'-fluoroacetophenone super SEE and phenylmagnesium bromide sequentially led to the expected isomer *syn*-**16**. These examples clearly demonstrate the TS control exhibited by the super siloxy substituent in these open-chain β-super-siloxy ketone intermediates, as well as the ability to generate the desired diastereomers by the judicious choice of the SEE and the Grignard reagent.[6f]

The generality of this one-pot sequence was demonstrated by the success of a variety of ketone super SEEs, aldehydes, and Grignard reagents (**eq 6**).[6f] The reaction scope was quite broad, giving products such as **17**, which contains three contiguous stereocenters. The use of vinyl and alkyl Grignards worked quite well, giving products **18**–**25** with good selectivity. The formation of **24** and **23** again showcases the super silyl group's powerful control of diastereoselection by first differentiating methyl and ethyl groups to give a large excess of the Felkin isomer, and then by stereoselectively controlling the Grignard addition via its presence in the β position. Product **21**, containing the valuable pyridine moiety, was generated by the in situ preparation of the heteroaryl Grignard through Knochel's powerful *i*-PrMgCl–2,6-dibromopyridine exchange reaction.[57]

6.3. The Super Silyl Group in Four-Component Reactions

A four-component, one-pot reaction sequence was employed for the extremely concise synthesis of cryptocarya diacetate.[6d] This compound is isolated from the bark of the South African plant, *Cryptocarya latifolia*, which is used for medicinal purposes.[58,59] The synthesis was initiated with a one-pot, SA–Grignard addition–acylation sequence, which generated a diene in 63% yield along with a 24% yield of minor diastereomers (**Scheme 12**).[6d] The use of Grubbs's second-generation catalyst in the ring-closing metathesis step gave a dihydropyranone, which was treated with HF–pyridine and then excess Ac_2O–pyridine to furnish cryptocarya diacetate. This total synthesis was accomplished in only three laboratory steps and 32% overall yield.

The success achieved with SAA and SA–Grignard addition sequences, led our group to combine these methods in a four-component, SAA–Grignard addition protocol.[6f] The aldol reaction of **1** and cyclohexanecarboxaldehyde was followed by reaction

with a second ketone SEE and subsequent addition of MeMgCl, which gave the four-component product in moderate yield and high diastereoselectivity (**Scheme 13**).[6f] The same protocol was employed with **1**, isobutyraldehyde, 4'-fluoroacetophenone super SEE, and PhMgBr to give the product in moderate yield and selectivity. These four-component, one-pot reaction sequences truly showcase the power of this approach by producing relatively complex chiral architecture from simple starting materials.

7. Protodesilylation–Self-Repair Mechanism

Due to the prevalence of protodesilylation reactions of allyl silanes and SEEs under Brønsted acid conditions, we postulated that the reaction of super SEEs and aldehydes might be proceeding via this protodesilylation mechanism (**Scheme 14**).[6b,60] In this case, $HNTf_2$ would actually be the precatalyst and $(TTMSS)NTf_2$ the true catalyst. This was supported by the use of $(TTMSS)NTf_2$ (generated from the exchange reaction of TTMSS–Cl and $AgNTf_2$) as the catalyst, which led to essentially identical results to those obtained using triflimide (see eq 3 and 4). This fact, in combination with the tolerance of an extremely low catalyst loading (S:C = 2000:1), led us to propose a self-repairing catalyst system, wherein the silyltriflimide can be generated and regenerated even in the presence of water or other protic Lewis bases.[6b]

8. Transition-State Calculations

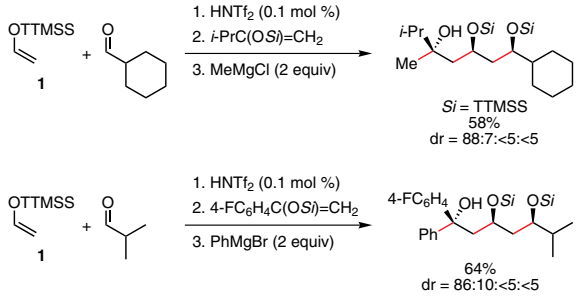
Much of the exceptional diastereoselectivity and control associated with the TTMSS group can likely be traced to its large steric size.[2,61] The super silyl group is extraordinarily bulky, and has been stated to shield molecular skeletons with a "H_3C-skin."[2] It has been reported that this group has a local steric influence comparable to that of the *t*-Bu group,[61a] and is among the strongest electron donors to π systems, lone-pair centers, and molecular cations.[61b] The important work done by Evans's group on the selectivity of additions to β-oxygenated aldehydes, led us to initially propose TS **B** as the reason for the syn selectivity. This TS does not suffer the unfavorable steric interaction that is present in conformation **C** between the Lewis acid coordinated oxygen and the R group (**Figure 2**).[6b,34]

This proposal was corroborated through DFT calculations at the B3LYP/6-31+G(d,p)//B3LYP/6-31G(d) level, which led to a TS structure particularly similar to **B**.[6f] Informative results were also gleaned regarding the reversal of selectivity observed for nucleophilic addition to β-super siloxy aldehydes versus that to β-super siloxy ketones. The calculations showed that the vinyl Grignard addition to the β-super siloxy aldehyde favored the syn pathway by 0.3 kcal/mol in the TS leading to the experimentally observed syn isomer. The calculations for the β-super siloxy methyl ketone gave a 2.6 kcal/mol preference in the TS for formation of the observed anti isomer. Significant steric repulsion between the methyl group of the ketone and the β-*iso*propyl group in the syn TS is a major reason for the divergence of TS energies. Akin to the work by Evans, the ketone and aldehyde transition states indicate a conformational preference that minimizes destabilizing electrostatic β-C–O and C=O dipole interactions.[34] In the case of the β-super siloxy aldehyde, the methyl group is replaced with a hydrogen, resulting in the oxygen being the larger atom (hydrogen vs oxygen in aldehyde and methyl vs oxygen in ketone). This leads to a preferable passing through the syn TS. A key feature that is revealed in these calculations is that the super silyl group creates a large "umbrella"-like structure under which the rest of the molecule aligns, and which restricts the conformational freedom of the remaining portion of the molecule.

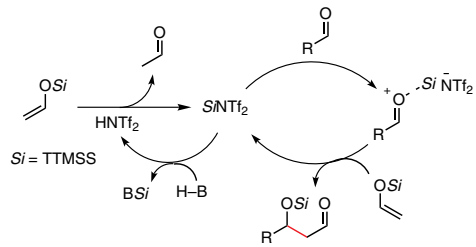
The stereochemical outcome is then largely determined by the interaction of the carbonyl and its substituent (Me for ketone and H for aldehyde) with the medium-sized β-group (*i*-Pr). This is in contrast to typical open-chain ketones and aldehydes, which have much more freedom of rotation due to the absence of the "umbrella" effect, which is why we believe we see such high selectivities for these β-super siloxy carbonyl addition reactions.

9. Stability and Cleavage of Super Silyl Ethers

As mentioned in the introduction, silyl groups occupy a distinct place in protective-group chemistry.[1] Their ease of preparation, combined with the range of stabilities associated with the various commercially available silyl-group-containing reagents, allow for tailor-made syntheses, in which a distinct deprotection step can be planned well in advance. Significant work by Brook's group has shown that the super silyl group is a unique, photolabile protecting group that is stable to a range of typical synthetic conditions, such as Grignards, Wittig reagents, and oxidation conditions (Jones reagent).[15] Through our research, we additionally found



Scheme 13. Four-Component SAA–Grignard Addition Reactions. *(Ref. 6f)*



Scheme 14. Proposed Protodesilylation–Self-Repair Mechanism. *(Ref. 6b)*

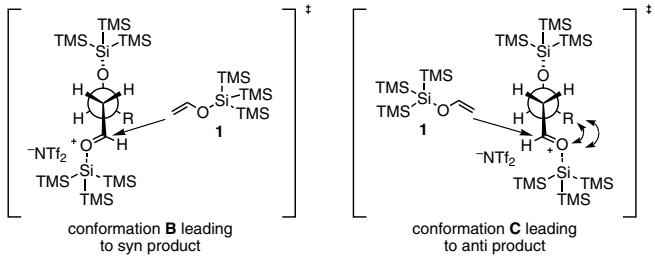


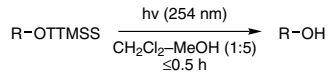
Figure 2. Original Transition-State Proposal for an Aldol Addition of **1** to a β-Super Siloxy Aldehyde. *(Ref. 6b)*

that super silyl ethers are stable to (i) reducing agents ($NaBH_4$, DIBAL-H, and L-Selectride®); (ii) oxidizing reagents (SO_3–pyridine–DMSO, OsO_4, and Dess–Martin periodinane); and (iii) the Tebbe reagent and organometallic reagents derived from Ce, Mn, and Cu. Interestingly, the super silyl group is also stable towards CsF and KF–18-crown-6, but is cleaved with $(n\text{-Bu})_4NF$ in under 1 min. Super silyl ethers show limited stability in the presence of *n*-BuLi or LAH for prolonged periods of time.

Perhaps the most appealing aspect of the reactivity of the super silyl group is its photochemical lability. In 1997, Brook reported that the super silyl group could be cleaved in methanolic dichloromethane upon irradiation with UV light (**eq 7**).[7b,15a] The absorption of super silane and the related super silyl ether derivatives at 254 nm was exploited to effect this deprotection. Moreover, the typical silyl group, TBS, wasn't deprotected under these conditions (254 nm irradiation in quartz cell). We decided to further explore this reactivity profile by irradiation of substrates containing both the super silyl group and other typical silyl groups.[7b] 1,4-Butanediol was used as the starting material for the preparation of various disilylated compounds. The experimental setup was designed to test an extremely simple and practical application of this selective photochemical deprotection. While the use of a quartz round-bottom flask was necessary, the deprotection was carried out by irradiation with a common UV lamp designed for analysis of typical fluoroescent TLC plates. All substrates tested gave high yields for the selective deprotection of the super silyl group.

10. Conclusions and Outlook

The super silyl group is superior in achieving many of the promises of one-pot sequential and multicomponent reactions. The reactivity profile of the super silyl group in a variety of C–C-bond-forming reactions is quite broad and useful. The super silyl group imposes significant steric bulk and possesses unique electronic properties that have enabled it to outperform commonly employed silyl groups in typical as well as atypical reactions. In particular, its use in sequential reactions has assigned the super silyl group a distinctive place in efficient one-pot transformations. Thus far, super SEEs have succeeded in [2 + 2] cyclization reactions, Mukaiyama aldehyde crossed aldol reactions, SAA reactions, SA–hetero-Diels–Alder reactions, SA–Grignard addition reactions, and SAA–Grignard addition reactions. While a number of SEEs have succeeded in these cases, we believe that an array of sequentially added acidic and/or basic reagents and substrates can be combined with the SA system to generate complex chiral architecture in simple and efficient one-pot protocols. We intend to include these sequential reactions in future synthetic planning whenever we encounter the 1,3-diol- and 1,3,5-triol motifs (**Figure 3**).



R	Yield
Cl_3CCH_2	89%
$Me(CH_2)_5CH(Me)$	95%
(*E*)-$Me_2C{=}CH(CH_2)_2C(Me){=}CHCH_2$	90%
$TESO(CH_2)_4$	90%
$TBSO(CH_2)_4$	88%
$TIPSO(CH_2)_4$	95%

eq 7 *(Ref. 7b,15a)*

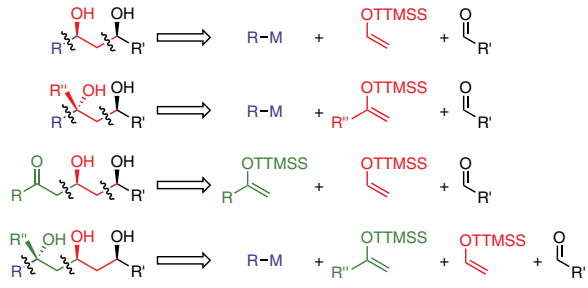


Figure 3. Anticipated Retrosynthetic Disconnections (All Would Be One-Pot Reactions).

11. Acknowledgements

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ALDRICH Chemistry

MIDA Boronates

For Suzuki–Miyaura Cross-Couplings

The Suzuki–Miyaura cross-coupling reaction is one of the most important and highly utilized reactions in organic chemistry, with applications in polymer science as well as in the fine chemicals and pharmaceutical industries. However, some classes of boronic acids are exceptionally unstable and susceptible to decomposition, which renders them inefficient in coupling reactions or makes long-term storage difficult. These limitations also make iterative cross-couplings challenging. Recently, Burke and coworkers have developed a method to allow such iterative couplings under mild conditions by attenuating the reactivity of boronic acids through complexation with *N*-methyliminodiacetic acid (**MIDA**). The MIDA ligand can be cleaved under mild conditions to liberate the corresponding boronic acid. MIDA boronates are easily handled, indefinitely bench-top stable under air, compatible with chromatography, unreactive under standard anhydrous cross-coupling conditions, even at temperatures up to 80 °C, and are stable to harsh reagents such as triflic acid and Jones reagent.

Palladium-catalyzed cross-coupling reactions are ideal methods for the synthesis of polyenes because of their stereospecificity and mildness. However, polyenylboronic acids are very unstable and therefore difficult to employ in the synthesis of polyenes by the Suzuki–Miyaura cross-coupling. In an exemplary demonstration of the stability and efficiency of MIDA boronates in iterative cross-couplings, Burke and coworkers utilized a common alkenyl, *trans*-2-bromovinylboronic acid MIDA ester (BB1, **703478**), to create a series of polyenyl building blocks. The MIDA boronate terminus is inert to Suzuki, Stille, and Heck couplings, yielding butadienyl MIDA boronates. Sonogashira and Negishi couplings, as well as Miyaura borylations also proved effective and yielded versatile bis-metallated lynchpin-type reagents.

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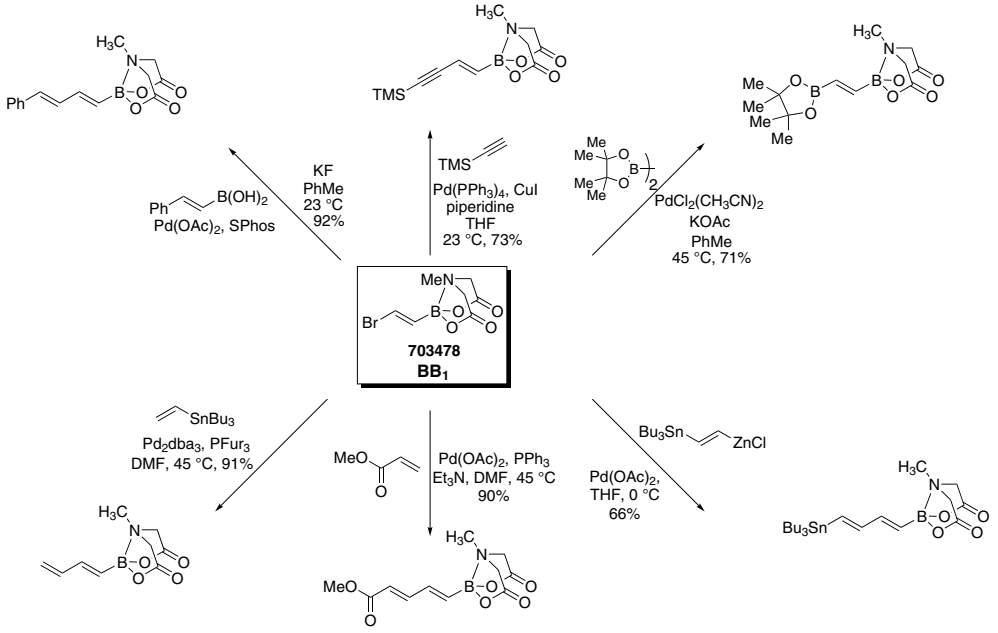

To view all the MIDA boronates offered by Sigma-Aldrich, see page 28 of this issue or visit ***sigma-aldrich.com/mida***.

Iterative Cross-Coupling with MIDA Boronates: towards a General Strategy for Small-Molecule Synthesis

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Outline

1. Introduction

Many organic molecules are inherently modular in their constitution. With respect to the molecules found in living systems, this modularity is a direct consequence of the fact that nearly all biosynthetic systems are based on the iterative coupling of bifunctional building blocks. For example, polypeptides are built from amino acids, oligonucleotides are derived from nucleotide monomers, and oligosaccharides are stitched together from individual sugar units. Interestingly, most *small-molecule* natural products are similarly constructed by the iterative coupling of bifunctional building blocks: e.g., polyketides from malonyl-CoA or methylmalonyl-CoA units, nonribosomal peptides from amino acids, polyterpenes from isopentenyl pyrophosphate or dimethylallyl pyrophosphate, and fatty acids from malonyl-CoA.[1] Similarly, many man-made pharmaceuticals are also highly modular because they are constructed by using different reactions to assemble collections of small building blocks, typically cyclic and heterocyclic fragments and their associated appendages. Thus, modularity is a remarkably general feature of many of the molecules that are targeted for synthesis in the laboratory.

Despite this common modularity, the strategies utilized for making polypeptides, oligonucleotides, and oligosaccharides are very different from those typically used to prepare small molecules. Specifically, all of the former classes of compounds are almost always constructed via iterative coupling of suitably protected forms of their constituent monomers.[2] Organic polymers can be similarly prepared.[3] Due to the powerfully simple nature of this iterative coupling approach, these processes are now increasingly performed in a fully automated fashion.[2,3] With peptides and oligonucleotides, the advanced development of such automation has made it possible for even nonchemists to routinely prepare these types of compound for a wide range of applications.

In stark contrast, it is typical for a synthetic chemist to develop a unique, customized strategy for each small molecule that is targeted for preparation in the laboratory. As a result, the synthesis of small molecules remains a relatively complex, unsystematized, and inflexible process that is practiced almost exclusively by highly trained specialists. Driven by the hypothesis that the inherent modularity in small molecules remains largely underutilized, we have established a research program that aims to develop a unified strategy for the construction of these compounds by the iterative coupling of bifunctional building blocks.[4–7] Specifically, we have targeted the development of building blocks representing substructures that appear frequently in natural products and man-made pharmaceuticals and the chemistry that will enable their precise union via iterative, metal-mediated, cross-coupling reactions. In the idealized form of this "Iterative Cross-Coupling" (ICC) approach, building blocks having all of the required functional groups preinstalled in the correct oxidation state and with the desired stereochemical relationships are iteratively united using only stereospecific cross-coupling reactions (**Figure 1**). In addition to being simple, efficient, and potentially amenable to automation, the modularity of this approach makes it inherently well-suited for generating diverse collections of compounds simply by substituting modified building blocks into the same synthesis pathway. It is anticipated that the advanced development of this ICC strategy will substantially enable the laboratory synthesis of a wide range of natural products, pharmaceuticals, and organic materials, and may even extend the power of small-molecule synthesis to the nonchemist.

As described in this review, *N*-methyliminodiacetic acid (MIDA) boronates[8,9] represent a highly promising platform for this type of synthesis strategy. These building blocks are remarkably convenient to prepare, analyze, purify, and store, and many are now commercially available. The MIDA boronate functional

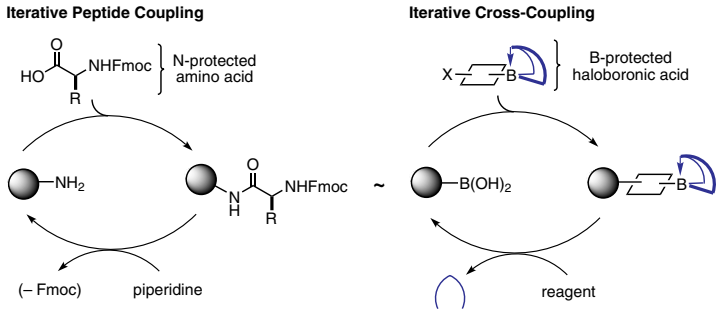
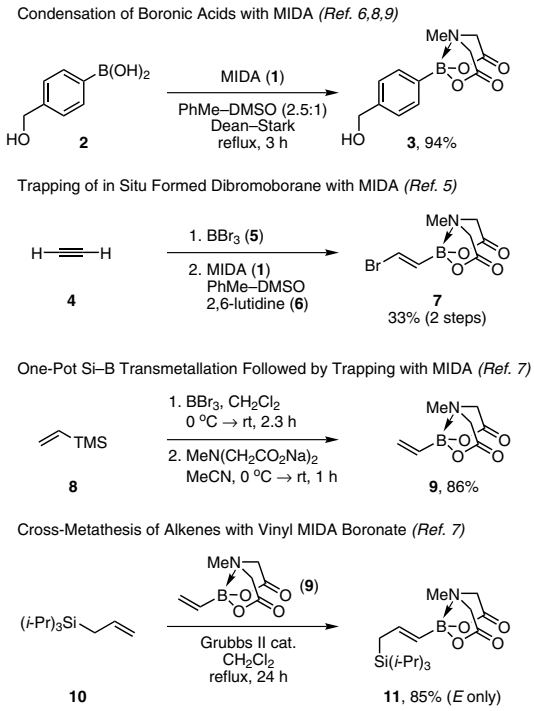


Figure 1. Analogous Strategies for the Synthesis of Peptides and Small Molecules.



Scheme 1. Examples of Known Methods for the Synthesis of MIDA Boronates.

group is also stable to anhydrous cross-coupling conditions, but is easily hydrolyzed with mild aqueous base, thereby enabling the controlled ICC of B-protected "haloboronic acids".[4–6] In addition, MIDA boronates are remarkably stable to a wide range of common reaction conditions and chromatography, which makes possible the facile preparation of complex borane building blocks from simple MIDA boronates via multistep synthesis.[6,7] This review aims to enable the effective utilization of this platform and the ICC strategy to promote the simple, efficient, and flexible construction of small molecules.

2. Synthesis of MIDA Boronates

N-Methyliminodiacetic acid, $MeN(CH_2CO_2H)_2$ (MIDA, **1**),[10] is nontoxic, biodegradable,[11] and commercially available. It can also be conveniently, efficiently, and inexpensively synthesized on a large scale[12] from the commodity chemical iminodiacetic acid.[13]

Presently, four different methods for the synthesis of MIDA boronates are known (**Scheme 1**).[4–9] Many boronic acids can be easily transformed into the corresponding MIDA boronates simply by condensation with MIDA under Dean–Stark conditions (Scheme 1, reaction 1).[4,6,8,9,12] The removal of water by a variety of alternative techniques (e.g., molecular sieves, azeotropic drying with CH_3CN, etc.) can also promote full conversion to the MIDA boronate product. Typically, this condensation process requires heating to at least 40 ºC, and the use of DMSO as a co-solvent is required to partially dissolve the MIDA ligand.

We have also developed several methods that enable the preparation of MIDA boronates without the intermediacy of a boronic acid. Alkenyl MIDA boronates can be synthesized via bromoboration of an alkyne to form the corresponding dibromoborane followed by trapping with MIDA in the presence of 2,6-lutidine (Scheme 1, reaction 2).[5] Alternatively, a one-pot procedure has been developed in which organotrimethylsilanes can be converted directly into MIDA boronates via transmetallation with BBr_3, followed by trapping with the disodium salt of MIDA (Na_2MIDA, Scheme 1, reaction 3).[7] This approach was employed in the efficient synthesis of vinyl MIDA boronate (**9**), for which condensation of MIDA with the related vinylboronic acid or vinylboronate species failed. Lastly, a variety of olefins can be transformed directly into alkenyl MIDA boronates via cross-metathesis with **9** (Scheme 1, reaction 4).[7] This approach is notable for its generality, efficiency, and mildness. Moreover, in contrast to previous reports involving the use of vinyl or propenyl pinacol boronic esters,[14,15] cross-metathesis with vinyl MIDA boronate yields only the *E* isomer, and the products are uniformly compatible with silica gel chromatography (vide infra).

3. Physical Properties of MIDA Boronates

MIDA boronates possess a number of highly enabling physical properties that make them useful as a platform for ICC and as convenient alternatives to boronic acids for a wide range of other applications. These properties are remarkably general, i.e., aryl, heteroaryl, alkenyl, and alkyl MIDA boronates all behave similarly. Specifically, MIDA boronates are monomeric, free-flowing, crystalline solids which are stable to storage on the bench top in closed containers under air. MIDA boronates are also universally compatible with silica gel chromatography, allowing convenient reaction monitoring by TLC and facile product isolation and purification.[4–7] If the goal is to separate different MIDA boronates of similar polarity, a ternary eluent of hexanes,

ethyl acetate, and up to 10% methanol is most effective. We have found that under these conditions even diastereomeric mixtures of MIDA boronates can be resolved. For the purification of nonpolar MIDA boronates, hexanes–ethyl acetate is an effective eluent. Additionally, acetic acid is generally compatible as a co-eluent in most solvent mixtures. Dichloromethane–methanol is a useful eluent for TLC analysis, but some decomposition of the MIDA boronates can occur if this eluent is used for preparative chromatography. Similarly, MIDA boronates should not be left to stand in solutions containing alcohols for more than an hour.

This compatibility with silica gel chromatography and the facility with which MIDA boronates can be formed from the corresponding boronic acids make it possible to utilize MIDA boronate formation and purification as a powerful tool to isolate high-purity boronic acids from crude mixtures that contain many nonboronic acid byproducts. Specifically, we have found that adding a small excess of MIDA to a crude mixture containing a boronic acid and performing a Dean–Stark complexation lead to the formation of the corresponding MIDA boronate while the other impurities remain largely unchanged. If the boronic acid is desired, a simple hydrolysis of the purified MIDA boronate with 1 M aqueous NaOH, followed by extraction of the boronic acid into an organic solvent, typically yields the pure boronic acid.

MIDA boronates are also easily purified by crystallization. A generally effective strategy is to dissolve the crude MIDA boronate in a minimum volume of acetone at 23 ºC and then slowly add Et_2O to promote crystallization. The crystallization is complete when the addition of Et_2O no longer clouds the solution. Alternative crystallization solvents include MeCN–Et_2O and EtOAc–Et_2O. X-ray quality crystals are conveniently prepared via vapor diffusion of petroleum ether into an acetone solution of the MIDA boronate: The acetone solution of the MIDA boronate is placed in a small vial (7 mL or 15 mL; the solution is 2–5 mm in height), and this vial is placed in a closed jar containing petroleum ether (about 1 cm in height). Crystals form upon standing at room temperature overnight.

Another important property of MIDA boronates is their solubility in many organic solvents. Reactions are typically performed using THF, dioxane, dichloromethane, DMF, toluene, DMSO, acetonitrile, acetone, or 1,2-dichloroethane. Prolonged exposure of MIDA boronates to aqueous conditions or alcoholic solvents leads eventually to hydrolysis of the MIDA ligand, and this effect is accelerated with heating or in the presence of base. However, water or alcoholic solvents have been successfully employed as co-solvents in some reactions with MIDA boronates.[6] Furthermore, MIDA boronates are generally compatible with aqueous extractions employing water, brine, aqueous acids (e.g., aq HCl or NH_4Cl), and even some oxidative or reductive aqueous solutions (e.g., aq H_2O_2 at pH < 6, or aq $Na_2S_2O_3$). Remarkably, even saturated aqueous $NaHCO_3$ is tolerated in the absence of alcoholic solvents. Aqueous extractions are typically performed using EtOAc or CH_2Cl_2 as the organic phase. For highly polar MIDA boronates, solvent mixtures of EtOAc–acetone (1:1) or THF–Et_2O (1:1) are convenient. As described below, despite this widespread stability, MIDA boronates are easily hydrolyzed to yield the corresponding boronic acids using very mild aqueous basic reagents at 23 ºC.

Interestingly, in contrast to MIDA boronates such as **3**, similarly pyramidalized *N*-methyldiethanolamine adducts such as **12 (Figure 2)** are not stable to silica gel. As described below, again in contrast to the MIDA boronates, *N*-methyldiethanolamine adducts are also reactive under cross-coupling and many other common reaction conditions.[4,6,16] The remarkable (and in many cases unique) stability of MIDA boronates to storage under air, chromatography, aqueous workups, as well as cross-coupling and many other reaction conditions is tentatively attributed to the unique conformational rigidity of the fused bicyclic [*N*-methyliminodiacetate-*O,O',N*] borane framework. Specifically, as shown in Figure 2, variable-temperature NMR experiments with a DMSO-d_6 solution of **3** reveal no coalescence of the diastereotopic methylene protons of the MIDA backbone, even at 150 ºC.[6,17] In contrast, the same experiment with **12** reveals coalescence of the diastereotopic methylene protons of the diethanolamine backbone over a temperature range of 23 to 60 ºC, suggesting that this complex is highly dynamic.[6,17] Although the fundamental underpinnings of these striking differences in conformational rigidity remain to be elucidated, these studies suggest that, uniquely in MIDA boronates, the potentially reactive boron p orbital and nitrogen lone pair are kinetically inaccessible, even at elevated temperatures. This kinetic stability may be responsible for many of the unique physical properties of MIDA boronates.

4. Iterative Cross-Coupling (ICC) with Halogenated MIDA Boronates

The now routinely automated process of iterative peptide coupling[2a] represents an inspiring benchmark for a potentially general strategy for making small molecules in the laboratory. It is interesting to note that peptides are quite complex in structure, having many different functional groups with varied oxidation states and a large number of stereogenic centers. However, the synthesis of many peptides is now very simple, involving the use of a single reaction to iteratively assemble a collection of amino acid building blocks having all of the required functional groups and stereochemistry preinstalled.

With the goal of developing an analogous process for the laboratory construction of small molecules, we decided to focus on the Suzuki–Miyaura reaction and the ICC of bifunctional "haloboronic acids" (see Figure 1).[6] To avoid random oligomerization of a haloboronic acid under cross-coupling

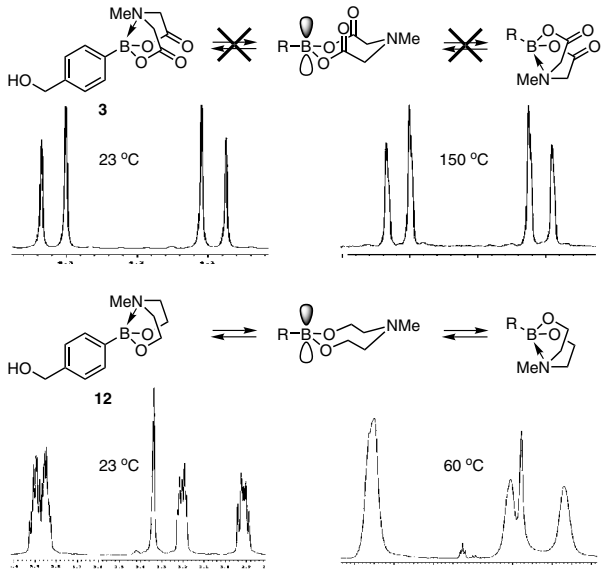


Figure 2. Variable-Temperature NMR Studies in DMSO-d_6 with MIDA Boronate and *N*-Methyldiethanolamine Adducts That Demonstrate the Unique and Remarkable Conformational Rigidity of the MIDA Boronate Framework. *(Ref. 6)*

conditions, it is necessary to reversibly attenuate the reactivity of one end of this type of bifunctional reagent, in analogy to the use of a protective group to control the reactivity of the amine terminus of an amino acid.[18] Toward this goal, we chose to focus on controlling the reactivity of the boronic acid functional group.

It is hypothesized that a vacant and Lewis acidic boron p orbital is required for transmetallation of a boronic acid under Suzuki–Miyaura cross-coupling conditions (**Figure 3a**).[19] Consistent with this, complexation with electron-donating, Lewis basic ligands is known to attenuate the reactivity of boronic acids towards cross-coupling (**Figure 3b**).[19a] For example, pinacol boronic esters can be less reactive towards cross-coupling than the corresponding boronic acids.[20] This reactivity attenuation can be attributed to the decreased Lewis acidity of the boron p orbital as a result of conjugation with the lone pairs of the ligand heteroatoms.[19a] This same approach has been utilized with a variety of other divalent heteroatomic ligands.[21] There is an inherent limitation, however, that precludes the general utilization of this approach for complex small-molecule synthesis. Specifically, conjugation between the heteroatom lone pairs and the boron p orbital produces relatively strong boron–heteroatom bonds, creating a high energy barrier for bond cleavage. Moreover, the equilibrium between the boronic acid and the corresponding boronic ester typically lies strongly towards the latter, thereby disfavoring hydrolysis. As a result, cleaving this type of ligand to regenerate the boronic acid typically requires harsh conditions[19–21] and/or additional reagents to destroy the divalent ligand after it has been cleaved.[22] These types of conditions can be problematic in the context of complex small-molecule synthesis.

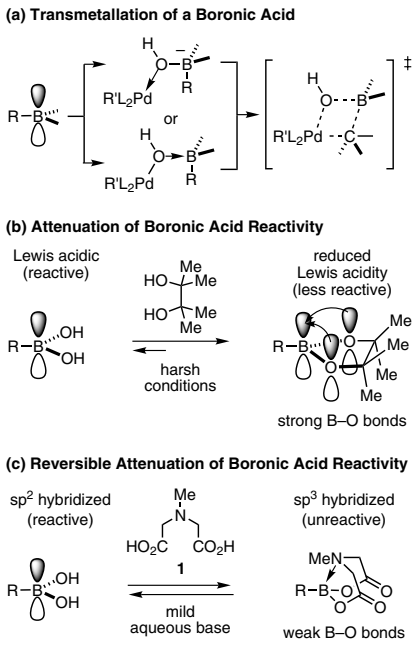
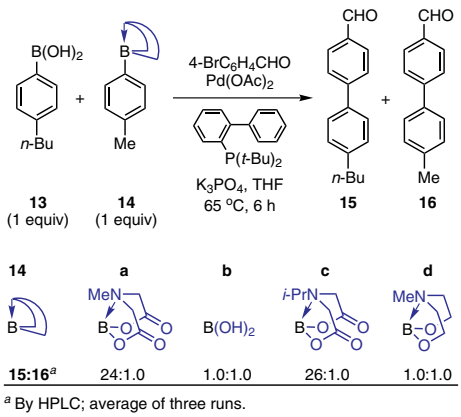


Figure 3. Under Suzuki–Miyaura Cross-Coupling Reaction Conditions: (a) Transmetallation Requires a Vacant and Lewis Acidic Boron p Orbital. (b) Strongly Electron-Donating Divalent Ligands Can Attenuate Boronic Acid Reactivity, but Typically Require Relatively Harsh Conditions for Cleavage. (c) The Reactivity of a Boronic Acid Can Be Reversibly Attenuated via Pyramidalization with a Trivalent Heteroatomic Ligand. *(Ref. 4)*



[a] By HPLC; average of three runs.

eq 1 *(Ref. 4)*

Recognizing the inherent limitations of this approach, we focused on an alternative strategy (**Figure 3c**).[4] Specifically, given that the boron p orbital is predicted to be critical for the transmetallation of a boronic acid, we hypothesized that removing this p orbital through rehybridization of the boron atom from sp^2 to sp^3 via complexation with a trivalent heteroatomic ligand would eliminate its reactivity towards cross-coupling. Further increasing our interest in this approach, it is known that boron–heteroatom bonds in tetrahedral adducts are weaker than those in their tricoordinate counterparts.[23] For example, the pyramidalization of trimethyl borate via complexation with ammonia weakens the boron–oxygen bonds by about 10–12 kcal/mol.[24] Thus, we felt that it might be possible to find relatively mild conditions that could hydrolyze this type of pyramidalized boronate and regenerate the reactive boronic acid. After surveying a series of trivalent heteroatomic ligands, we discovered that MIDA boronates embody all of these expectations and represent a powerful platform for ICC chemistry.

In a competition experiment between *p*-(*n*-butyl)phenylboronic acid (**13**) and *p*-tolyl MIDA boronate (**14a**) under Buchwald-type[25] anhydrous Suzuki–Miyaura cross-coupling conditions with *p*-bromoanisaldehyde, we observed a 24:1 ratio of products **15** and **16** (**eq 1**), consistent with a strong preference for cross-coupling of the sp^2-hybridized boronic acid.[4] Interestingly, a wide range of non-aryl substituents were tolerated on the nitrogen atom. The diethanolamine adduct, **14d**, lacking the carbonyl units of MIDA, was as reactive as boronic acid **13**. As described above, this difference in reactivity between **14a** and **14d** is attributed to differences in the conformational rigidity of these two complexes.

Encouraged by these results, we set out to prepare a series of bifunctional B-protected haloboronic acids and explore their capacity to undergo selective cross-coupling at the halide terminus. The efficient synthesis of aryl, heteroaryl, alkenyl, and alkyl derivatives was achieved via simple condensation of the corresponding boronic acids with MIDA under Dean–Stark conditions (**eq 2**).[4]

As shown in **Scheme 2**,[4] this B-protection strategy is remarkably general, with the same ligand similarly protecting aryl, heteroaryl, alkenyl, and alkyl haloboronic acids, thereby enabling the highly selective coupling of the halide terminus of building blocks **18a–f**. Moreover, consistent with our initial hypothesis, the MIDA boronate products **19a–f** can all be hydrolyzed under mild aqueous basic conditions (1 N NaOH(aq), THF, 23 ºC, 10 min) to generate the corresponding free boronic acids **20a–f**.

Polyenes are especially challenging synthetic targets because of the sensitivity of this framework to light, oxygen, and acid. It is also critical to control the stereochemistry of each double bond. The ICC approach is particularly well-suited to preparing these types of compound due to the mild and stereospecific nature of the

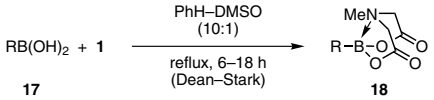
metal-mediated cross-couplings. Given the prevalence of alkenyl and polyenyl subunits in both natural products and pharmaceutical targets, we developed a collection of bifunctional building blocks specifically designed to enable polyene synthesis via ICC.[5]

As described in Scheme 1, *trans*-(2-bromovinyl) MIDA boronate (**7**) can be prepared via bromoboration of acetylene[26] followed by complexation with MIDA in the presence of 2,6-lutidine. An alternative and more convenient procedure involves transmetallation of 1-bromo-2-(trimethylsilyl)ethylene with BBr_3[27] followed by trapping with Na_2MIDA.[7] Bifunctional olefin **7** is a remarkably versatile cross-coupling partner (**Scheme 3**).[5] Specifically, Suzuki–Miyaura, Stille, and Heck couplings are all achieved at the bromide terminus without perturbing the MIDA boronate. A series of bismetallated lynchpin-type reagents are also created via Sonagashira coupling with trimethylsilylacetylene, Miyaura borylation with pinacolatodiborane (**25**), or a triply metal-selective (Zn vs Sn and B) Negishi coupling with bismetallated olefin **27**.

A generally useful strategy involves the boron-selective coupling of differentially ligated diboron reagents.[5,28] In the first example of such a reaction, **26** was selectively coupled with *trans*-1-chloro-2-iodoethylene at the sp^2-hybridized pinacol boronic ester terminus to generate chlorodienyl MIDA boronate **29** (**Scheme 4**).[5] A better-precedented Sn vs B coupling[29] between bismetallated diene **28** and *trans*-1-chloro-2-iodoethylene generated chlorotrienyl MIDA boronate **30**.[5]

The olefin cross-metathesis route to MIDA boronates is remarkably tolerant of a wide range of functional groups, including halogens. Thus, this method is also well-suited for preparing various haloalkenyl MIDA boronates, as shown for a series of bromostyrene derivatives (**eq 3**).[7]

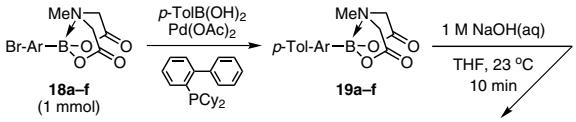
The capacity to prepare and selectively couple bifunctional halo MIDA boronates enables one to envision the synthesis of natural products or pharmaceuticals by using only a single reaction iteratively to bring together a collection of pre-assembled building blocks. This strategy was first realized with the total synthesis of ratanhine,[4] a complex neolignan isolated from the *Ratanhiae radix* by Arnone and co-workers in 1990.[30] This natural product was retrosynthetically fragmented using recursive Suzuki–Miyaura transforms to generate four simpler building blocks, **35**–**38** (**Figure 4**). There were several challenges associated with this plan that were expected to test the limits of the MIDA-based



18	R	Yield[a]
a	4-BrC_6H_4	98%
b	3-BrC_6H_4	93%
c	2-BrC_6H_4	97%
d	5-Br-thien-2-yl	99%
e	*trans*-3-Br-styryl	99%
f	2-(3-BrC_6H_4)-*c*-Pr	88%

[a] Yields refer to *analytically pure* materials obtained conveniently via silica gel chromatography.

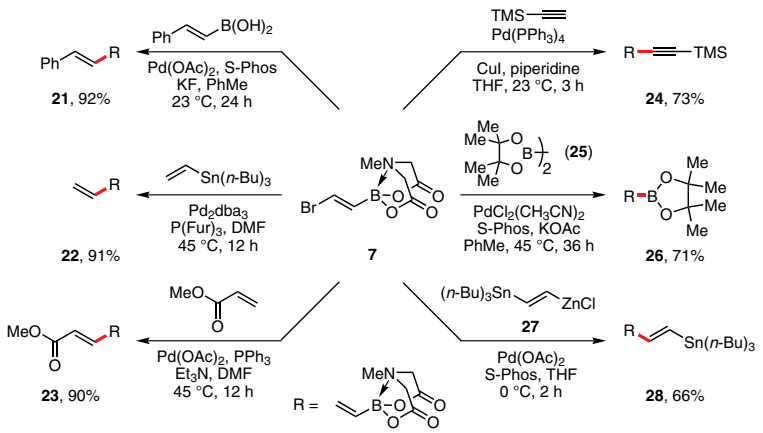
eq 2 *(Ref. 4)*



No.	*p*-TolAr	19	20
a	4-(*p*-Tol)C_6H_4	87%	86%
b	3-(*p*-Tol)C_6H_4	85%	92%
c	2-(*p*-Tol)C_6H_4	80%	97%[a]
d	5-(*p*-Tol)thien-2-yl	81%	88%[b]
e	*trans*-3-(*p*-Tol)styryl	82%	83%
f	2-[3-(*p*-Tol)C_6H_4]-*c*-Pr	94%	91%

[a] B-Deprotection was also achieved by treatment with saturated aq. $NaHCO_3$–MeOH, 23 °C, 6 h (85%). [b] X-Phos was used as the phosphine ligand.

Scheme 2. Selective Coupling and Mild Deprotection of Halogenated Aryl, Heteroaryl, Alkenyl, and Alkyl MIDA Boronates. *(Ref. 4)*

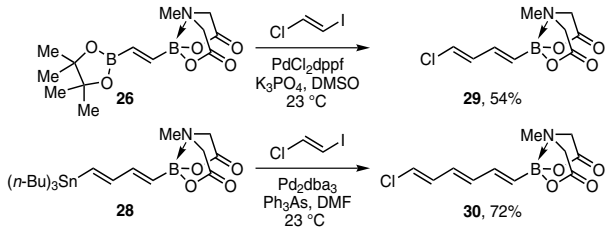


Scheme 3. Bifunctional Halogenated MIDA Boronate Building Blocks Such as **7** Can Be Rapidly and Selectively Elaborated at the Halogen Terminus. *(Ref. 5)*

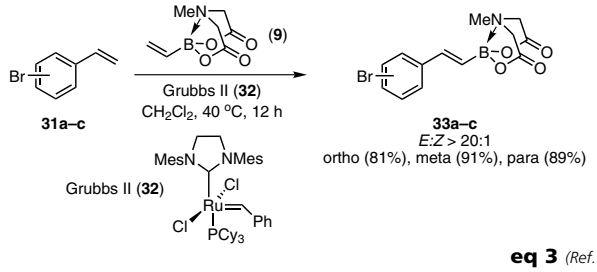
ICC methodology. First, couplings of alkenylboronic acids tend to be less efficient than those of their aryl counterparts, making the selective coupling between **35** and aryl MIDA boronate **36** unsecured. In addition, 2-substituted heterocyclic boronic acids such as **36** are notoriously unstable and difficult to purify, store, and cross-couple.[31] Finally, the coupling of highly deactivated bromoaryl MIDA boronate **37** was expected to demand more forcing reaction conditions that would test the limits of stability of the MIDA boronate functionality.

Despite these challenges, the total synthesis of ratanhine was achieved via ICC as shown in **Scheme 5**.[4] Specifically, selective coupling between propenylboronic acid (**35**) and 5-bromobenzofuran-2-yl MIDA boronate (**36**) proceeded smoothly to generate substituted benzofuranyl MIDA boronate **39**. Remarkably, while the corresponding benzofuranylboronic acid decomposed over the course of several days, MIDA boronate **39** was stored on the bench top under air without noticeable decomposition for more than 6 months. This MIDA boronate was hydrolyzed under mild conditions, and the resulting boronic acid was immediately utilized in a cross-coupling reaction with bromoaryl MIDA boronate **37**. As expected, this coupling required increased temperature (80 ºC in a sealed tube) and an extended reaction time (28 h). Remarkably, the MIDA boronate functional group was stable to these forcing conditions, yielding the highly conjugated MIDA boronate product **40**. A final sequence of boronic acid deprotection and coupling with alkenyl bromide **38** and MOM-ether deprotection completed the first total synthesis of ratanhine. More importantly, to the best of our knowledge, this represents the first total synthesis of any natural product in which a single reaction was utilized iteratively to assemble all of the required building blocks.

This ICC strategy is also highly effective in the synthesis of polyene natural products.[5] Specifically, *all-trans*-retinal[32] was prepared simply via ICC of boronic acid **42**, bromoalkenyl MIDA boronate **7**, and alkenyl bromide **44** (**Scheme 6**).[5] In a similar vein, β-parinaric acid[33] was prepared by ICC of butenylboronic acid (**46**), chlorodienyl MIDA boronate **29**, and alkenyl iodide **48** (**Scheme 7**).[5] Finally, despite the fact that



Scheme 4. The Preparation of Bifunctional Halogenated MIDA Boronates for Use in Polyene Synthesis. *(Ref. 5)*



eq 3 *(Ref. 7)*

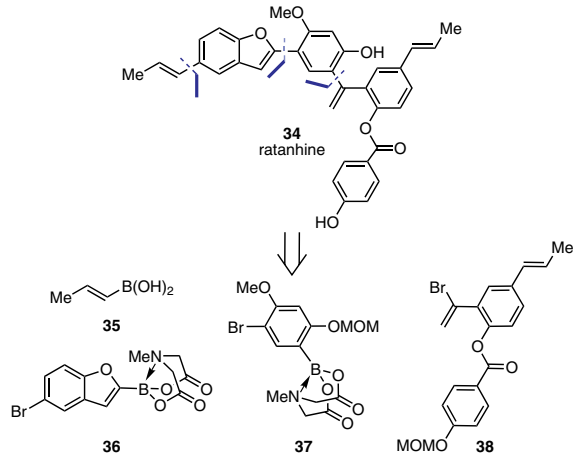
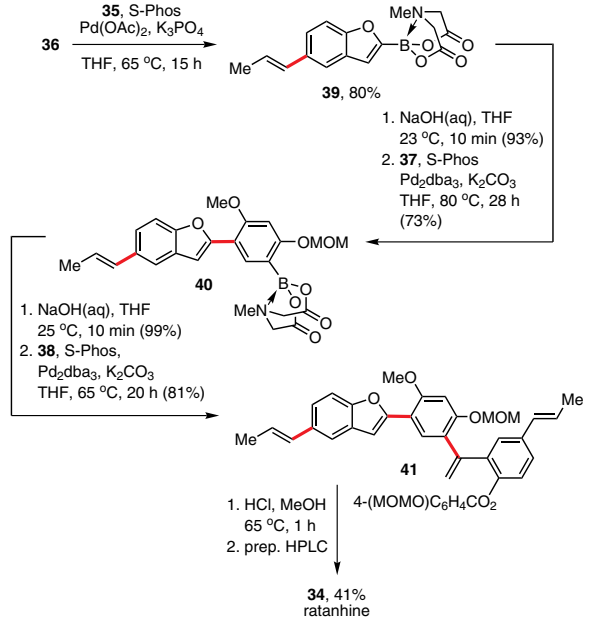
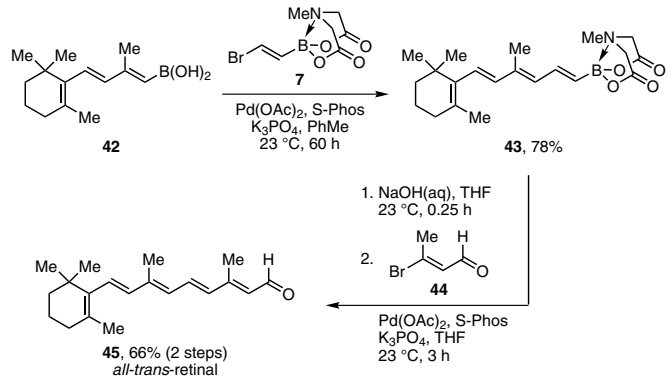


Figure 4. Retrosynthetic Analysis of the Natural Product Ratanhine Using ICC Identified Four Building Blocks, of Which **36** and **37** Are Bifunctional Halogenated MIDA Boronates. *(Ref. 4)*



Scheme 5. Application of ICC in the First Total Synthesis of Ratanhine. *(Ref. 4)*



Scheme 6. Application of ICC in the Synthesis of *All-trans*-Retinal. *(Ref. 5)*

polyenylboronic acids can be very unstable,[34] the notoriously challenging heptaene framework of the polyene natural product amphotericin B was prepared using only the Suzuki–Miyaura reaction to assemble a collection of bifunctional haloalkenyl MIDA boronates (**Scheme 8**).[5]

As demonstrated by these examples, the ICC approach has significant potential to enable the simple, efficient, and flexible construction of small molecules.

5. Multistep Synthesis of Complex Boronic Acids from Simple MIDA Boronates

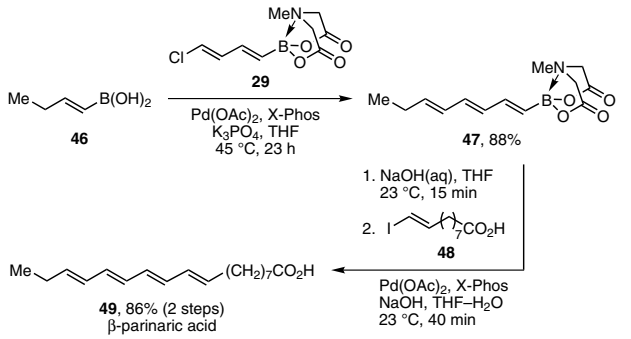
To avoid a general incompatibility with synthetic reagents, it is typically necessary to introduce the boronic acid functional group just prior to its utilization in a cross-coupling or other type of reaction. However, most of the methods that are available for achieving this have poor functional-group tolerance. Collectively, these limitations can render the synthesis of complex boronic acids very challenging. This can sometimes preclude the use of boronic acids in complex-molecule synthesis, and represents a potential bottleneck for the development of a truly general ICC-based approach.

Some sterically bulky boronic esters are known to be more tolerant of synthetic reagents;[35] however, removing these ligands to generate a targeted boronic acid usually requires harsh conditions that are generally incompatible with sensitive building blocks. Trifluoroborate salts represent very useful surrogates for boronic acids,[36] and Molander and co-workers have powerfully demonstrated that the trifluoroborate functional group is compatible with many synthetic reagents.[37] These features have provided novel access to many new organoborane building blocks. However, the incompatibility of trifluoroborate salts with chromatography can limit the utilization of these reagents in multistep synthesis, which is often necessary for accessing structurally and/or stereochemically complex building blocks.

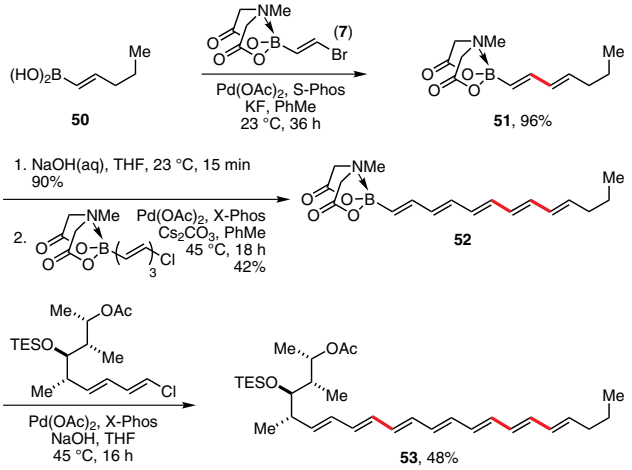
Overcoming these limitations, we have recently found that the MIDA boronate functional group is stable to a wide range of common synthetic reagents, presumably due to the lack of a reactive boron p orbital.[6] Combined with the general compatibility of MIDA boronates with chromatography and the capacity to release the corresponding boronic acids under very mild conditions, this stability enables the first reliable approach for the multistep synthesis of complex boronic acids from simple organoborane starting materials.

Specifically, *p*-(hydroxymethyl)phenyl MIDA boronate (**3**) can be smoothly oxidized under Swern conditions to generate the corresponding benzaldehyde (**Scheme 9**).[6] Remarkably, this MIDA boronate is also stable to the very strongly acidic and oxidizing Jones conditions (H_2SO_4–CrO_3). This latter stability is highly unique; i.e., under these same conditions, the corresponding boronic acid (**56a**), pinacolboronic ester (**56b**), 1,8-diaminonaphthalene adduct (**56c**), trifluoroborate salt (**56d**), and *N*-methyldiethanolamine boronate[16b,38] (**56e**) all decomposed. Similar to that which we observed under cross-coupling conditions, the remarkable difference in reactivity between the MIDA and diethanolamine boronates is likely related to the differences in conformational flexibility of the two complexes (see Figure 2).

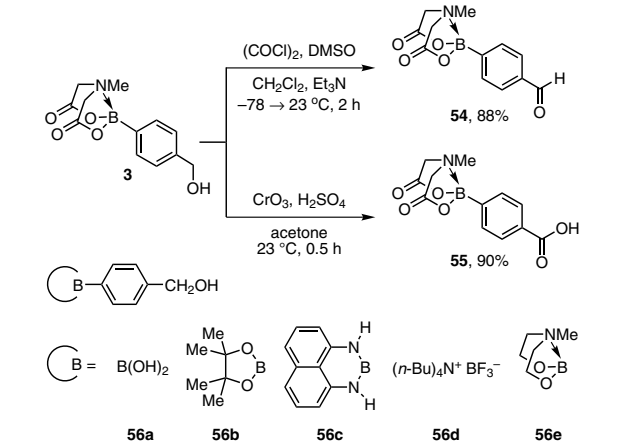
This unique compatibility with strong acid and oxidants suggested that MIDA boronates could be stable to a wide range of reaction conditions. In fact, even triflic acid (pK_a –14) was tolerated, enabling the *p*-methoxybenzylation of **3** and the reversal of this transformation with DDQ (**Scheme 10**).[6]



Scheme 7. Application of ICC in the Synthesis of β-Parinaric Acid. *(Ref. 5)*



Scheme 8. Application of ICC in the Synthesis of the Heptaene Framework of Amphotericin B. *(Ref. 5)*



Scheme 9. MIDA Boronates, Such as **3**, Are Uniquely Stable to the Strongly Acidic and Oxidizing Jones Conditions, Whereas Boronic Acids and Boronates, Such as **56a–e**, Are Not. *(Ref. 6)*

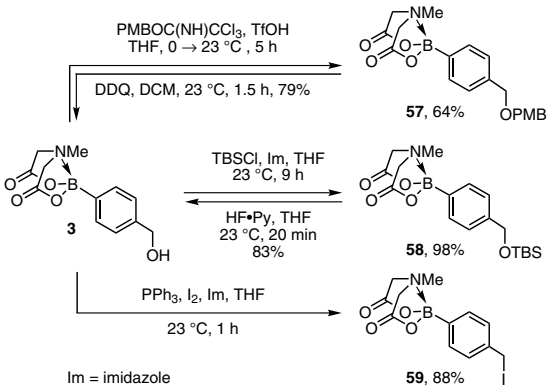
Similarly, silation and desilation were well-tolerated, as was the transformation into the corresponding benzyl iodide **59** with PPh_3–I_2.

This latter reaction suggested compatibility with soft nucleophiles. In this vein, benzaldehyde **54** was successfully utilized in a series of carbon–carbon-bond-forming reactions including the Evans aldol, Horner–Wadsworth–Emmons, and Takai olefination reactions. Reductive amination and aldehyde reduction were also well-tolerated (**Scheme 11**).[6]

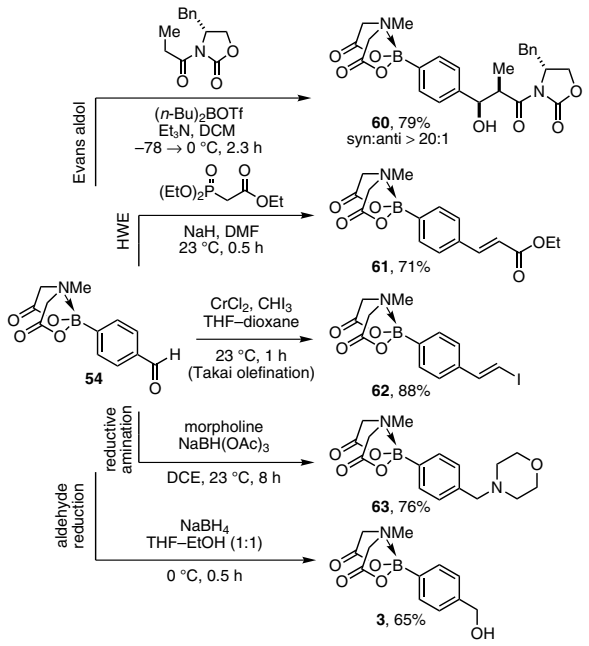
Whereas cyclopropanation of vinyl boranes[39,40] and epoxidation of 1,2-disubstituted alkenyltrifluoroborate salts[37b] are known, the versatility and broad compatibility of vinyl MIDA boronate (**9**) as a starting material has also been demonstrated (**Scheme 12**).[7] Specifically, cyclopropanation of **9** produced cyclopropyl MIDA boronate (**64**) in excellent yield. Remarkably, epoxidation of this olefin with *m*CPBA was also well-tolerated, and even this epoxide, **65**, was stable to column chromatography and bench top storage under air. Boronate **9** was successfully engaged in the Heck reaction[41] to yield styrenyl derivative **66**. Similarly, the White catalyst[42] promoted an efficient oxidative Heck-type[43] reaction[44] to yield **67**. As described previously (see eq 3), **9** is also an excellent substrate for olefin cross-metathesis[14,15] (analogous to *tert*-butylethylene), yielding (*E*)-octenyl MIDA boronate (**68**) as a chromatographically and air-stable crystalline solid and a single stereoisomer (see Scheme 12). Fortunately, this approach has proven to be quite general, and represents a very useful method for preparing a range of (*E*)-alkenyl MIDA boronates (**eq 4**).[7]

This broad compatibility of the MIDA boronate functional group with a wide range of reagents can enable the transformation of simple MIDA boronates into otherwise difficult-to-access complex boronic acids for use in a variety of synthesis applications. These include structurally complex B-protected haloboronic acids for use in ICC.

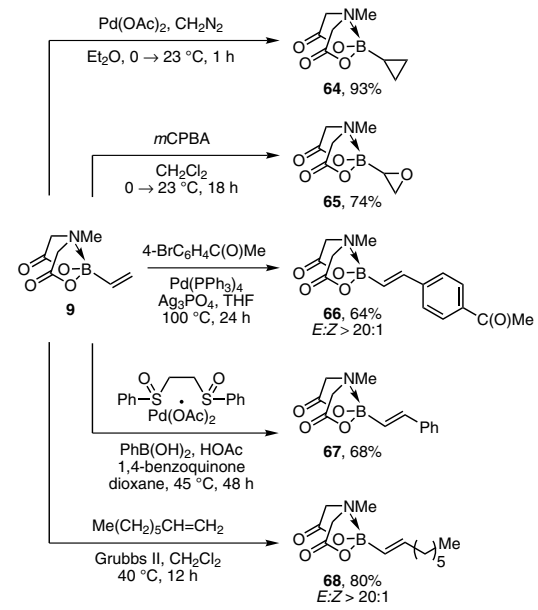
To explore the enabling potential of this approach, we targeted the total synthesis of the natural product crocacin C.[6,45] As shown in **Figure 5**, this molecule was retrosynthetically



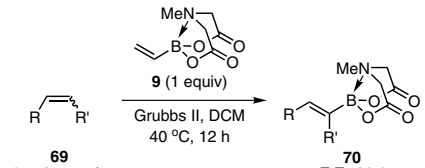
Scheme 10. MIDA Boronates Are Stable to a Number of Useful Reagents in Organic Synthesis. *(Ref. 6)*



Scheme 11. MIDA Boronate Building Blocks Can Be Elaborated Through a Number of Common Organic Reactions. *(Ref. 6)*



Scheme 12. Vinyl MIDA Boronate (**9**) Is an Exceptionally Versatile Building Block. *(Ref. 7)*



R	R'	Yield
$TIPSCH_2$	H	85%
$AcOCH_2$	$AcOCH_2$	84%
$BzOCH_2$	$BzOCH_2$	98%
Cy	H	96%
$Me_2C(OH)$	H	94%
Ph	H	93%

eq 4 *(Ref. 7)*

fragmented via recursive cross-coupling transforms into known building blocks **72** and **74** as well as the novel, complex iodoalkenyl MIDA boronate **73**. The preparation of the latter represented a significant challenge that we hypothesized could be overcome via multistep synthesis starting with simple MIDA boronate **75** (**Scheme 13**).[6]

In practice, a Paterson aldol reaction between **75** and **76** followed by diastereoselective reduction of the resulting β-hydroxy ketone yielded diol **77**. Importantly, the small amounts of diastereomeric byproducts that are typically generated in these types of transformations were readily removed by taking advantage of the compatibility of the MIDA boronate functional group with silica gel chromatography. A subsequent sequence of permethylation with Meerwein's salt, oxidative cleavage of the PMB ether, oxidation of the resulting primary alcohol, and Takai olefination yielded the targeted, complex halogenated MIDA boronate **73**. Importantly, **73**, **75**, and all intermediates were compatible with chromatography and storage on the bench top under air. With B-protected haloboronic acid **73** in hand, the synthesis of (+)-crocacin C was readily achieved via ICC.[6]

6. Conclusions and Prospects

As described herein, the inherent modularity found in many of the small molecules targeted for synthesis in the laboratory stands to be more effectively harnessed via the ICC approach. Analogous to the synthesis of peptides, oligonucleotides, and oligosaccharides, this strategy has the potential to enable the preparation of a wide range of small molecules by the simple, iterative union of pre-assembled, bifunctional building blocks. Due to their ease of synthesis, purification, characterization, and storage; their capacity for reversibly attenuated reactivity under cross-coupling conditions; and their compatibility with a wide range of common synthetic reagents; MIDA boronates represent a powerful platform for the development of this type of synthesis strategy. Moreover, it was recently discovered that, under novel "slow-release cross-coupling" conditions, MIDA boronates can serve as highly effective surrogates for even notoriously unstable boronic acids, such as 2-heterocyclic (including 2-pyridyl), vinyl, and cyclopropyl derivatives.[46] This remarkably general approach has transformed a wide range of unstable boronic acids into air-stable and highly effective cross-coupling partners.

Looking forward, the ever-expanding scope of the Suzuki–Miyaura coupling suggests that the potential generality of this ICC approach could be substantial. Particularly critical to realizing this potential will be finding a way to form Csp^3–Csp^2 and even Csp^3–Csp^3 bonds with the same efficiency that is now routinely achieved stereospecifically with Csp^2–Csp^2 linkages. The discovery of additional methods to prepare MIDA boronates that do not proceed through the intermediacy of a difficult-to-access and/or unstable boronic acid will also be vital. Moreover, to realize the ultimate goal of developing a machine with the capacity for fully automated ICC, it will be important to further develop cross-coupling conditions that are maximally general[25] (to avoid the requirement for ad hoc optimization of conditions for each combination of coupling partners) and amenable to translation into the solid phase or some other form of iterative-synthesis-enabling technology. While these challenges are admittedly considerable, we are convinced that they each can be solved. Achieving these goals could have a substantial impact on the synthesis of small molecules in the laboratory, and may ultimately even extend the power of this discovery engine to the nonchemist.

7. Acknowledgements

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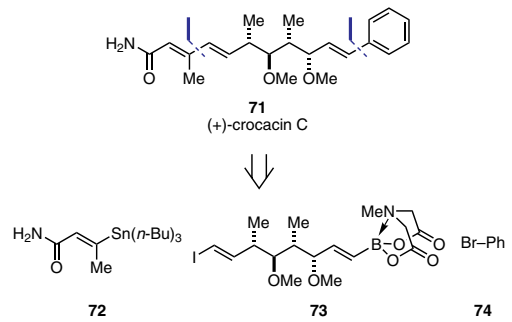
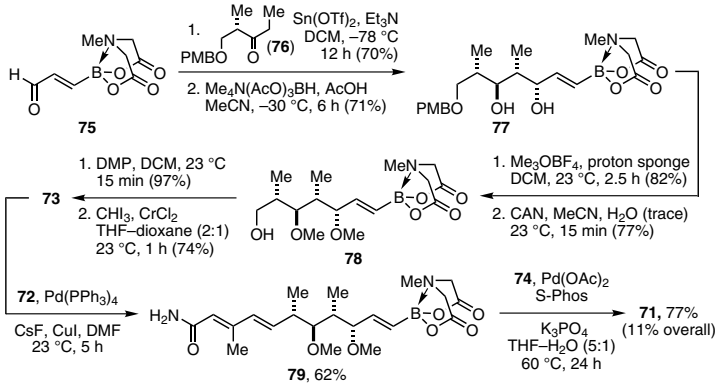


Figure 5. Retrosynthetic Analysis of the Natural Product (+)-Crocacin C Identified the Relatively Complex Halogenated MIDA Boronate Building Block **73**. *(Ref. 6)*



Scheme 13. The Broad Chemical Stability of the MIDA Boronate Functional Group Is Taken Advantage of in the Synthesis of (+)-Crocacin C. *(Ref. 6)*

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Keywords: MIDA boronate; iterative cross-coupling; automated synthesis; *N*-methyliminodiacetic acid; bifunctional molecules.

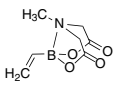
About the Authors

Eric Gillis grew up in Portland, ME, and received his undergraduate education at Grinnell College in Grinnell, IA. While at Grinnell, he worked with Professor T. Andrew Mobley on the synthesis and characterization of tungsten–tin complexes. In 2005, he began his doctoral studies under the direction of Professor Martin Burke at the University of Illinois at Urbana-Champaign. His current research focuses on the development of MIDA boronate esters as a platform to enable the automated synthesis of small molecules.

Marty Burke grew up in Manchester, MD, and graduated in 1998 with a B.A. degree in chemistry from Johns Hopkins University. He then moved to Harvard Medical School as a Ph.D. and M.D. student in the Health Sciences and Technology program. From 1999 to 2003, Marty completed his thesis research in organic synthesis under the direction of Professor Stuart Schreiber, and graduated from medical school in 2005. That same year, Marty began his independent career as an assistant professor in the Department of Chemistry at the University of Illinois at Urbana-Champaign. His research focuses on the synthesis and study of small molecules that perform protein-like functions. To enable these studies, Marty's group is pioneering a new synthesis strategy, dubbed *Iterative Cross-Coupling (ICC)*, that aims to make the process of complex-small-molecule synthesis as simple, efficient, and flexible as possible. The group is now harnessing the power of this new chemistry to systematically dissect the structure–function relationships that underlie the protein-like activities of a variety of prototypical small molecules, including the channel-forming polyene natural product amphotericin B.

ALDRICH Chemistry

MIDA Boronates from Sigma-Aldrich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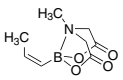
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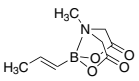
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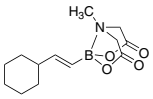
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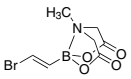
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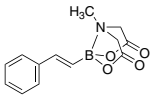
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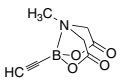
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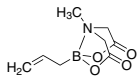
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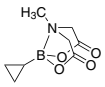
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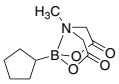
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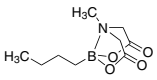
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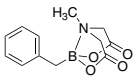
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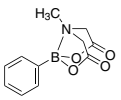
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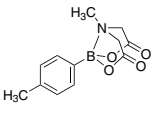
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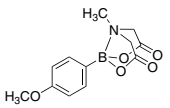
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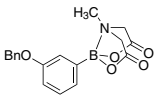
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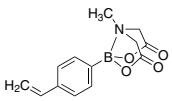
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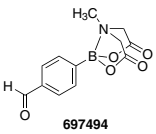
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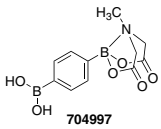
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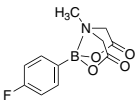
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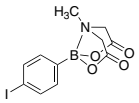
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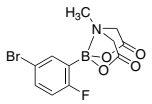
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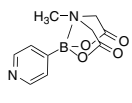
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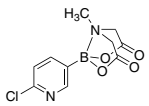
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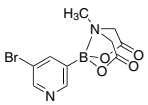
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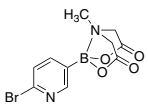
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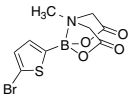
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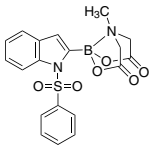
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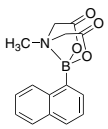
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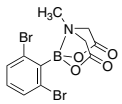
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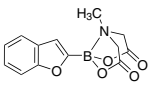
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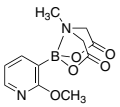
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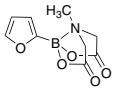
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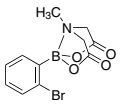
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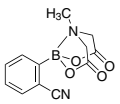
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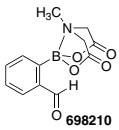
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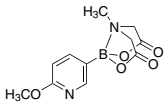
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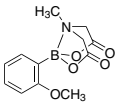
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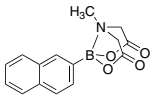
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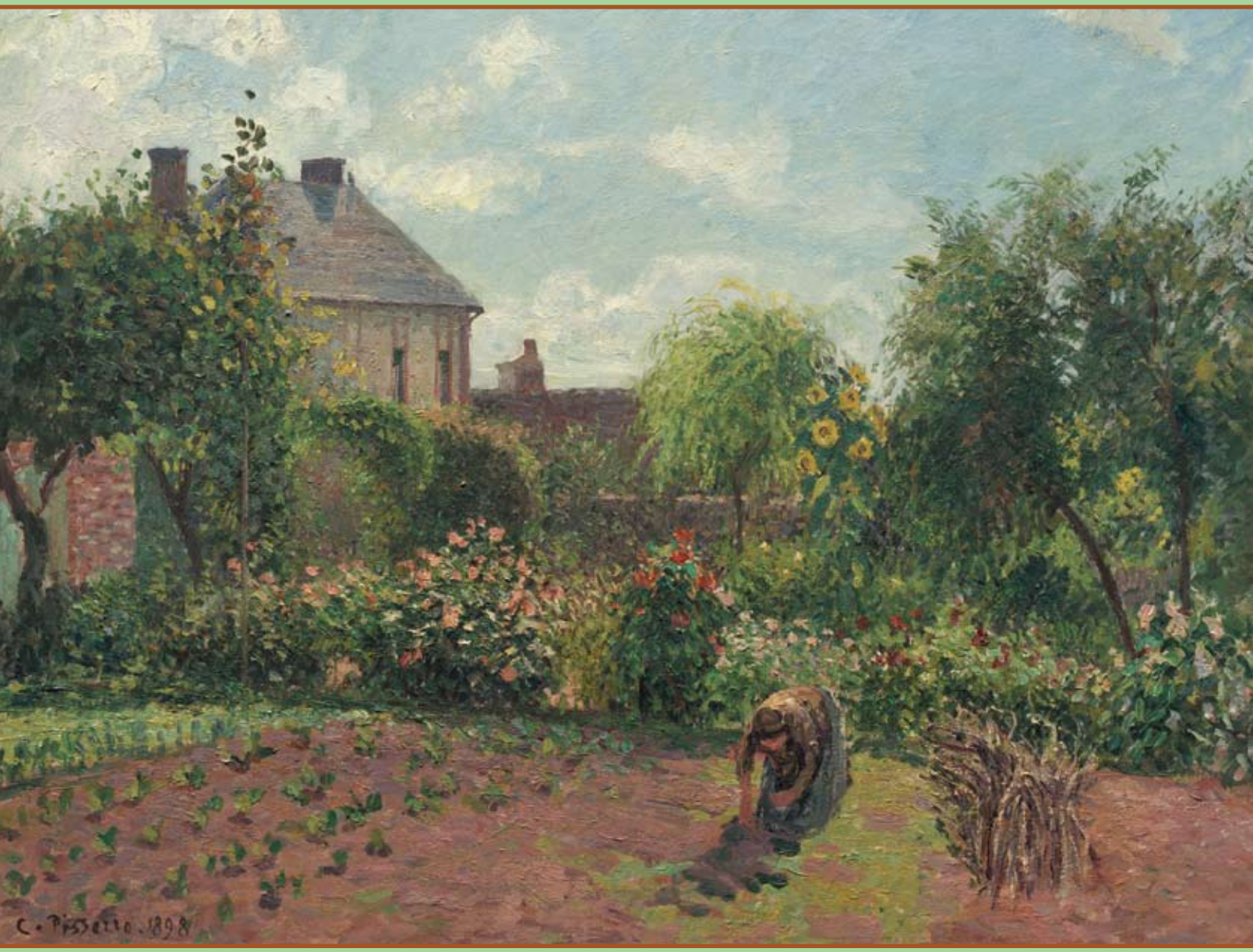

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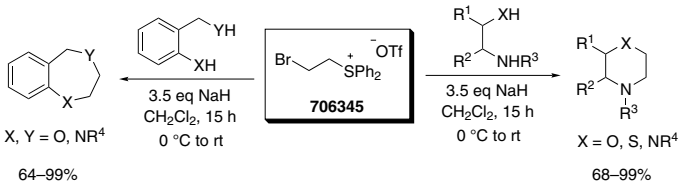
Annulation Agent for Heterocyclic Synthesis

Professor Varinder Aggarwal recently reported an efficient annulation reaction to prepare a variety of 1,4-heterocyclic products in good-to-excellent yields. The mild reaction employs a bromoethylsulfonium salt in the presence of 1,2- and 1,3-amino alcohols, amino thiols, or diamines to give access to pharmacologically important morpholines, piperazines, thiomorpholines, benzoxazepines, and benzodiazepines.



Yar, M. et al. *Org. Lett.* **2009**, *11*, 257.

(2-Bromoethyl)diphenylsulfonium trifluoromethanesulfonate

706345 1 g, 5 g
$C_{15}H_{14}BrF_3O_3S_2$
FW: 443.30

NEW Solutions of Common Reagents

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Di-*tert*-butyl dicarbonate, 1 M in THF

436267 100 mL, 800 mL
[*24424-99-5*]
$C_{10}H_{18}O_5$
FW: 218.25

Di-*tert*-butyl dicarbonate, 2 M in THF

703753 100 mL
[*24424-99-5*]
$C_{10}H_{18}O_5$
FW: 218.25

Di-*tert*-butyl dicarbonate, 2 M in dichloromethane

703737 100 mL
[*24424-99-5*]
$C_{10}H_{18}O_5$
FW: 218.25

Di-*tert*-butyl dicarbonate, 2 M in ethyl acetate

703745 100 mL
[*24424-99-5*]
$C_{10}H_{18}O_5$
FW: 218.25

(*S*)-(–)-α,α-Diphenyl-2-pyrrolidinemethanol trimethylsilyl ether, 0.05 M in toluene

706442 25 mL
[*848821-58-9*]
$C_{20}H_{27}NOSi$
FW: 325.52

(*R*)-(+)- α,α-Diphenyl-2-pyrrolidinemethanol trimethylsilyl ether, 0.05 M in toluene

706450 25 mL
$C_{20}H_{27}NOSi$
FW: 325.52

1,1′-Carbonyldiimidazole, 0.4 M in dichloromethane

705284 100 mL
[*530-62-1*]
$C_7H_6N_4O$
FW: 162.15

Triflic anhydride, 1 M in dichloromethane

704083 25 mL, 100 mL
[*358-23-6*]
$C_2F_6O_5S_2$
FW: 282.14

Tributyltin hydride 1 M in cyclohexane

704091 10 mL, 50 mL
[*688-73-3*]
$C_{12}H_{28}Sn$
FW: 291.06

Iodine monochloride, 1 M in dichloromethane

291048 100 mL, 800 mL
[*7790-99-0*]
ICl
FW: 162.36

Acetyl chloride, 1 M in dichloromethane

708496 100 mL, 500 mL
[*75-36-5*]
C_2H_3ClO
FW: 78.50

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"PLEASE BOTHER US."

Joe Porwoll

Joe Porwoll, President
Aldrich Chemical Co., Inc.

Mark Jensen of SCYNEXIS, Inc., kindly suggested that we make 5-chloro-1-aza-5-stannabicyclo[3.3.3]undecane. The derivatives formed from this stannatrane are typically air-stable and unusually reactive in various Stille couplings.[1–3] Furthermore, the byproduct of the coupling reaction can easily be recovered and recycled to afford the stannatrane in quantitative yield.[2]

707562

(1) Vedejs, E. et al. *J. Am. Chem. Soc.* **1992**, *114*, 6556. (2) Jensen, M. S. et al. *Org. Lett.* **2000**, *2*, 1081. (3) Sebahar, H. L. et al. *J. Org. Chem.* **2002**, *67*, 3788.

707562 5-Chloro-1-aza-5-stannabicyclo[3.3.3]undecane, 97%

500 mg
2 g

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ABOUT OUR COVER

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

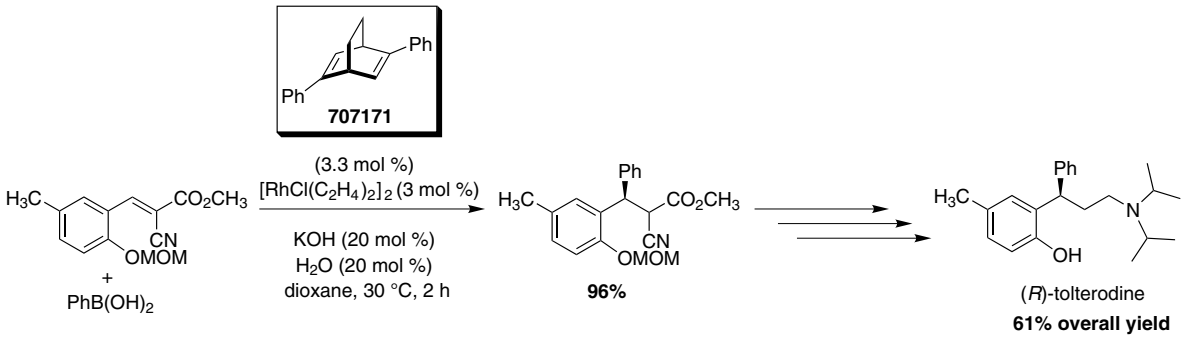
Camille Pissarro (1830–1903) painted ***The Artist's Garden at Éragny*** (oil on canvas, 73.4 × 92.1 cm) in 1898 in a small village (Éragny-sur-Oise) about 16 miles northwest of Paris. As seen in this painting and many of his other works, Pissarro was strongly attached to the land and to those who worked it. Critics complained about Pissarro's ability to find beauty in the rural way of life, but they never criticized the way he portrayed that beauty. As an originator of the movement, Pissarro remained committed to Impressionism's "fresh sensation" throughout most of his life. A bit older than the other impressionists and, by all accounts, a generous and sympathetic man, Pissarro was an important influence on many younger artists, including Cézanne and Van Gogh.

In the artist's garden, a woman is working amidst vegetables and blooming flowers of all kinds. A fresh breeze gently stirs the foliage and the puffy white clouds above. Nestled behind the garden wall is a charming chateau, no doubt where the vegetables being harvested will be made part of a sumptuous summer dinner later in the day.

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

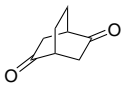
Chiral Diene Technology

In the past 5 years, a number of chiral diene ligands have emerged for a variety of asymmetric transformations. Hayashi[1] and Carreira[2] pioneered this field by synthesizing chiral diene ligands that formed stable complexes with metals and exerted high catalytic activities as well as high enantioselectivities. To demonstrate the potency of these new ligands, Hayashi and co-workers synthesized tolterodine, an antimuscarinic drug used to treat urinary incontinence, in a five-step sequence with an overall yield of 61%.[3] The first step of the sequence is an asymmetric 1,4 addition of phenylboronic acid, using a chiral diene ligand with a rhodium complex, to give the corresponding phenylated product in 96% yield.



References:

(1) Hayashi, T. et al. *J. Am. Chem. Soc.* **2003**, *125*, 11508.
(2) Fischer, C. et al. *J. Am. Chem. Soc.* **2004**, *126*, 1628.
(3) Sörgel, S. et al. *Org. Lett.* **2008**, *10*, 589.



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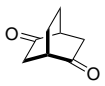

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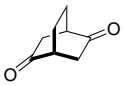

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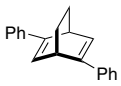

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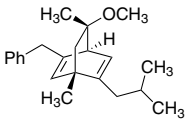

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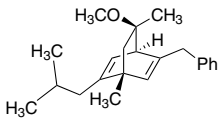

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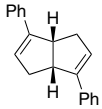

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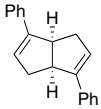

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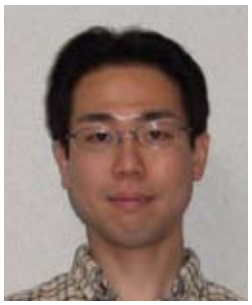
Chiral Diene Ligands for Asymmetric Catalysis



Professor Ryo Shintani

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Outline

1. Introduction

Asymmetric transformations that are catalyzed by transition metals coordinated to chiral ligands are powerful methods for efficiently constructing enantioenriched compounds from achiral substrates and reagents. Chiral ligands for late transition metals are typically based on phosphorus and/or nitrogen coordination, and several such ligands (e.g., BINAP[1] and bisoxazolines[2]) are highly effective for various asymmetric reactions.[3] In contrast, although dienes such as norbornadiene and 1,5-cyclooctadiene are also good ligands for various late transition metals—and natural and synthetic chiral olefins have been available for many decades—the development and application of chiral dienes as ligands for asymmetric catalysis have not been a focus of research investigations until recently. Early studies toward this goal by Suemune and co-workers were reported between 2000 and 2003, and involved the synthesis of several enantiopure chiral dienes and the preparation of their rhodium or iron complexes.[4] However, the successful application of these diene ligands in asymmetric catalysis was not disclosed in these reports. Subsequently, Hayashi's group reported in 2003 the first effective chiral diene ligand for asymmetric catalysis.[5] This article will review advances in the chemistry of chiral diene ligands starting with Hayashi's report up until the middle of 2008.[6]

2. Synthesis and Structure of Chiral Diene Ligands

2.1. Bicyclo[2.2.1]hepta-2,5-dienes

The first effective chiral diene ligand for asymmetric catalysis, (*R*,*R*)-Bn-nbd*, is based on a bicyclo[2.2.1]hepta-2,5-diene skeleton with benzyl groups at the 2 and 5 positions.[5] This compound can be prepared in an enantioselective manner from bicyclo[2.2.1]hepta-2,5-diene by using a Pd–(*R*)-MeO-MOP-catalyzed asymmetric hydrosilylation as the key step [(*R*)-MeO-MOP = (*R*)-2-diphenylphosphino-2'-methoxy-1,1'-binaphthyl] (**Scheme 1**).[7] 2,5-*exo*,*exo*-Bicyclo[2.2.1]heptane-2,5-diol, obtained in >99% ee after Tamao oxidation, is further oxidized to bicyclo[2.2.1]heptane-2,5-dione. This enantiopure diketone is converted into ditriflate (*R*,*R*)-**1**, which undergoes iron-catalyzed cross-coupling with benzylmagnesium chloride to give (*R*,*R*)-Bn-nbd*.[8] The diene ligand can also be isolated as a rhodium complex by treating the cross-coupling product with $[RhCl(C_2H_4)_2]_2$ in situ; this protocol is particularly effective for the volatile (*R*,*R*)-Me-nbd* and thermally unstable (*R*,*R*)-Ph-nbd* (**Scheme 2**).[8a]

2.2. Bicyclo[2.2.2]octa-2,5-dienes

Ligand **2**, based on a bicyclo[2.2.2]octa-2,5-diene skeleton, is readily prepared in enantiopure form in four steps from commercially available (*R*)-carvone (**Scheme 3**).[9] Installation of an isobutyl group into (*R*)-carvone in the first step of a multistep synthesis leads to pseudo-C_2-symmetric diene ligand **3**, in which the two newly introduced substituents occupy the 2 and 5 positions (**Scheme 4**).[10]

C_2-Symmetric, 2,5-disubstituted bicyclo[2.2.2]octa-2,5-dienes (bod*) can be synthesized from the known (±)-bicyclo[2.2.2]octane-2,5-dione[11] through ditriflate formation, palladium-catalyzed Grignard cross-coupling, and optical resolution (**Scheme 5**).[12] The most reliable method in this case is HPLC resolution using a chiral column, but optical resolution of (±)-bicyclo[2.2.2]octane-2,5-dione by forming diastereomeric hydrazones with (*R*)-5-(1-phenylethyl)semioxamazide, followed by fractional crystallization, is also possible.[12]

2.3. Other Bicyclic Chiral Dienes

C_2-Symmetric dienes having a 1,5-cyclooctadiene framework have also been reported. Thus, 2,6-diphenylbicyclo[3.3.1]nona-2,6-diene (Ph-bnd*) and 2,6-diphenylbicyclo[3.3.2]deca-2,6-diene (Ph-bdd*) can be prepared from the corresponding racemic diketones through phenylation, dehydration, and HPLC resolution of enantiomers (**Scheme 6**).[13]

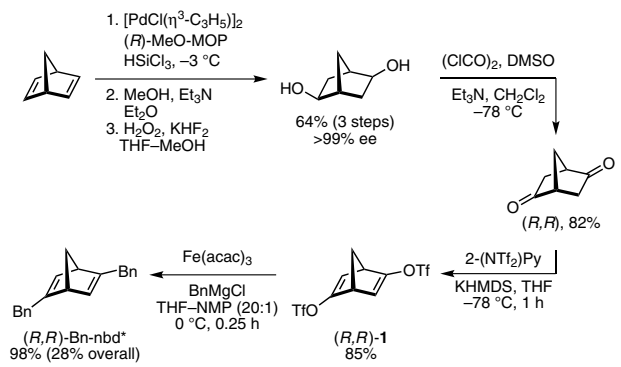
Ligand **6** with a bicyclo[3.3.0]octa-2,5-diene structure is synthesized from enantiopure diacetate **5**, which is obtained by enzymatic kinetic resolution of the corresponding diol, **4**.[14] Conversion of resolved **5** into the diketone, followed by ditriflation and Suzuki cross-coupling, provides ligand **6** in an enantiopure form (**Scheme 7**).[15]

2.4. Dienes Possessing Chirality Following Complexation with a Transition Metal

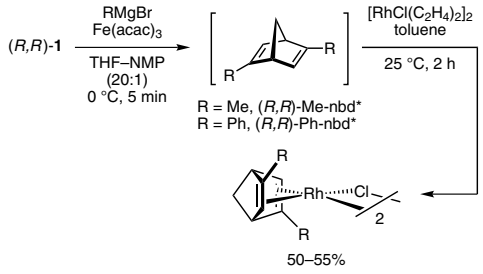
In addition to the above-mentioned dienes that possess an intrinsic stable chirality, some achiral dienes can exhibit chirality upon coordination to a transition metal. This concept was first established with ligand **7**, which is prepared from dibenzosuberenone in three steps (**Scheme 8**).[16] Complexation of **7** with $[RhCl(CO)_2]_2$ gives a racemic $[RhCl(\mathbf{7})]_2$, which can be resolved by forming a mixture of diastereomers with (*R*)-1,1'-binaphthyl-2,2'-diamine, followed by fractional recrystallization. The same method can also be applied to achiral 1,5-diphenyl-1,5-cyclooctadiene (Ph-cod), which is readily prepared from 1,5-dibromo-1,5-cyclooctadiene by a palladium-catalyzed Grignard cross-coupling reaction (**eq 1**).[17]

2.5. Structures of Rhodium–Chiral Diene Complexes

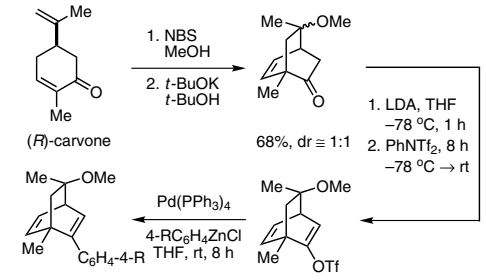
X-ray crystallographic analysis has been carried out for some of the chiral diene ligands coordinated to rhodium in the form of



Scheme 1. Preparation of (1*R*,4*R*)-2,5-Dibenzylbicyclo[2.2.1]hepta-2,5-diene ((*R*,*R*)-Bn-nbd*). *(Ref. 7,8)*

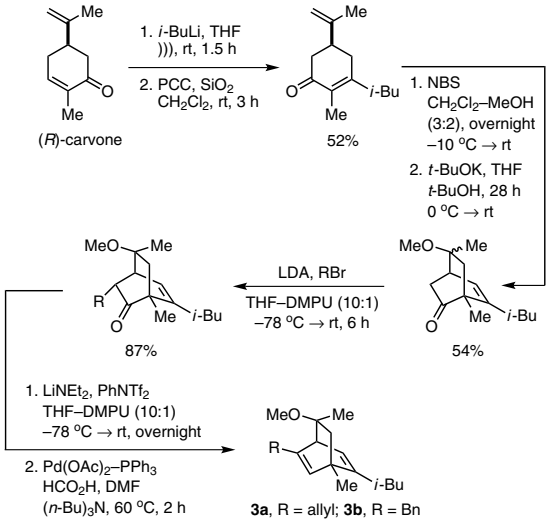


Scheme 2. Isolation of (1*R*,4*R*)-2,5-Dimethyl- and (1*R*,4*R*)-2,5-Diphenylbicyclo[2.2.1]hepta-2,5-dienes as Their Rhodium Complexes. *(Ref. 8a)*

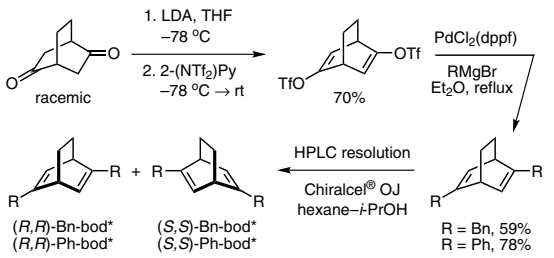


No	R	Yield
2a	H	62%
2b	Ph	53%
2c	PhO	53%
2d	*t*-Bu	53%

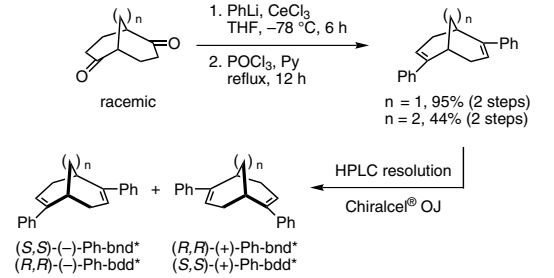
Scheme 3. Preparation of Chiral Diene **2** from (*R*)-Carvone. *(Ref. 9)*



Scheme 4. Preparation of Chiral Diene **3** from (*R*)-Carvone. *(Ref. 10)*



Scheme 5. Preparation of C_2-Symmetric 2,5-Disubstituted Bicyclo[2.2.2]octa-2,5-dienes (bod*). *(Ref. 12)*



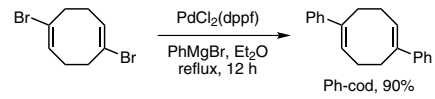
Scheme 6. Preparation of 2,6-Diphenylbicyclo[3.3.1]nona-2,6-diene (Ph-bnd*) and 2,6-Diphenylbicyclo[3.3.2]deca-2,6-diene (Ph-bdd*). *(Ref. 13)*

[RhCl(diene*)]$_2$. The structures of nbd*[8,18] and bod*[12b] are very similar, and the two double bonds in each are almost parallel with each other (torsion angle = 0–1°). In contrast, the two double bonds in (*R*,*R*)-Tol-bnd* are twisted by 23° and, as a result, the Rh–C$_\alpha$ bond length is much longer than the Rh–C$_\beta$ bond length; and the C$_\alpha$–Rh–C$_{\alpha'}$ bond angle is much smaller than the C$_\beta$–Rh–C$_{\beta'}$ bond angle.[13b] Although both (*R*,*R*)-Tol-bnd* and (*R*,*R*)-Ph-cod* have a 1,5-cyclooctadiene framework around rhodium, (*R*,*R*)-Ph-cod* is much less twisted (torsion angle = 9.4°) and shows a more symmetrical structure because of its monocyclic nature (**Figure 1**).[17]

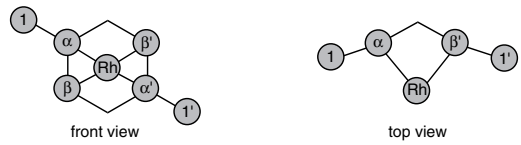
3. Application of Chiral Diene Ligands in Asymmetric Catalysis

3.1. 1,4 Addition of Organoboronic Acids to Electron-Deficient Olefins

The first effective chiral diene ligand, (1*R*,4*R*)-2,5-dibenzylbicyclo[2.2.1]hepta-2,5-diene ((*R*,*R*)-Bn-nbd*), has been utilized in the rhodium-catalyzed asymmetric 1,4 addition of aryl- and alkenylboronic acids to α,β-unsaturated ketones (**eq 2**).[5,19] The reaction proceeds smoothly under mild conditions, giving the 1,4 adducts of both cyclic and acyclic substrates in high yields and ee's. The absolute configuration of the 1,4 adducts under these conditions is *R*, and this outcome can be rationalized by an α*re*-face approach of enones to the Rh–(*R*,*R*)-nbd* complex, avoiding the steric repulsion between the benzyl group on the ligand and the carbonyl moiety of enones (**Scheme 9**).



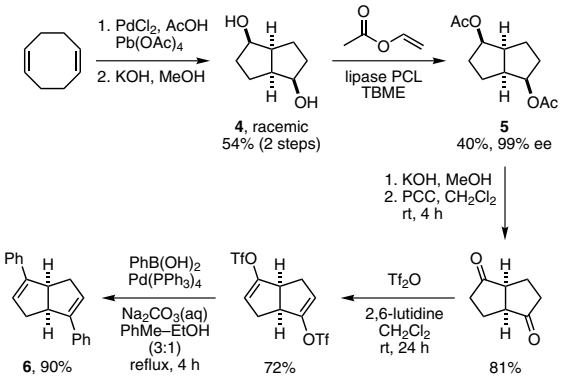
eq 1 *(Ref. 17)*



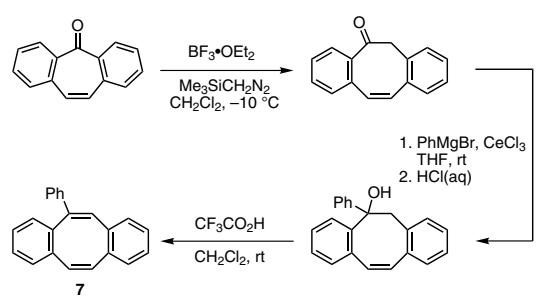
Diene*	Distance (Å)		
	Rh–Cα	Rh–Cβ	Rh–C1
(*R*,*R*)-Bn-nbd*	2.11	2.09	3.12
(*R*,*R*)-Ph-nbd*	2.11	2.10	3.01
(*S*,*S*)-Ph-bod*	2.12	2.10	3.05
(*R*,*R*)-Tol-bnd*	2.19	2.09	3.13
(*R*)-Ph-cod*	2.14	2.09	3.03

Diene*	Angle (°)			
	Cα–Rh–Cα'	Cβ–Rh–Cβ'	C1–Rh–C1'	(Cα–Cβ)/(Cα'–Cβ')
(*R*,*R*)-Bn-nbd*	82	81	131	0.1
(*R*,*R*)-Ph-nbd*	82	81	135	1.1
(*S*,*S*)-Ph-bod*	81	80	132	0.7
(*R*,*R*)-Tol-bnd*	87	103	137	23
(*R*)-Ph-cod*	93	93	149	9.4

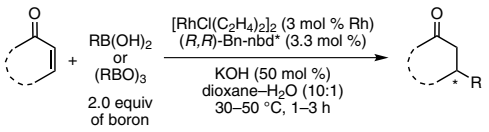
Figure 1. Structures of [RhCl(diene*)]$_2$ Complexes. *(Ref. 17)*



Scheme 7. Preparation of Ligand **6** from 1,5-Cyclooctadiene through Enzymatic Kinetic Resolution. *(Ref. 15b)*



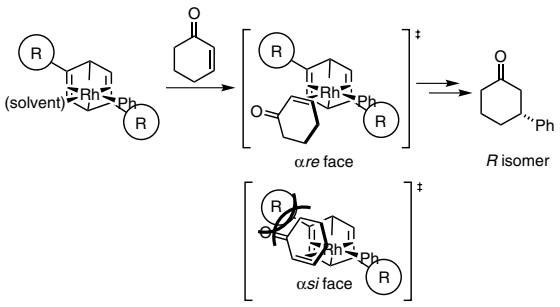
Scheme 8. Preparation of Ligand **7** from Dibenzosuberenone. *(Ref. 16)*



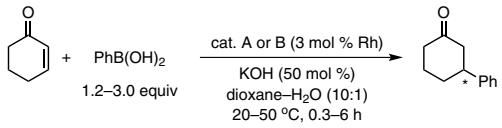
Enone	R	Yield	ee
2-cyclohexenone	Ph	94%	96%
2-cyclohexenone	4-MeOC$_6$H$_4$	89%	95%
2-cyclohexenone	4-F$_3$CC$_6$H$_4$	90%	99%
2-cyclohexenone	(*E*)-CH=CH(*n*-C$_5$H$_{11}$)	73%	88%
2-cyclopentenone	Ph	88%	88%
(*E*)-*i*-PrCH=CHC(O)Me	Ph	81%	97%

[a] In all of these cases, the product had the *R* configuration.

eq 2 *(Ref. 5)*



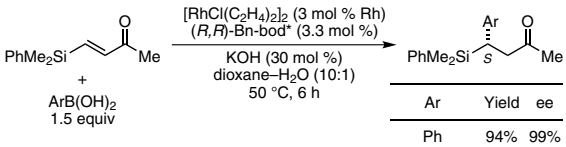
Scheme 9. Proposed Stereochemical Pathway for the Rh–(*R*,*R*)-nbd*-Catalyzed Asymmetric 1,4 Addition of Phenylboronic Acid to 2-Cyclohexenone. *(Ref. 5)*



Diene	Cat.[a]	Yield	ee[b]	*Ref.*
(*R,R*)-Bn-nbd*	A	94%	96%	*5*
(*R,R*)-Me-nbd*	B[c]	90%	95%	*8a*
(*R,R*)-Ph-nbd*	B[c]	89%	97%	*8a*
(*R,R*)-Bn-bod*	A	97%	95%	*12b*
(*R,R*)-Ph-bod*	A	97%	96%	*12b*
2d	A	52%	71%[d]	*10*
3a	A	87%	95%[e]	*10*
(*S,S*)-Ph-bnd*	B	93%	83%	*13b*
(*R,R*)-Ph-bdd*	B	98%	90%	*13b*
6	A[f]	96%	91%	*15b*
7	B[g]	92%	62%	*16*
Ph-cod	B	90%	43%	*17*
Ph-cod	B[h]	3%	91%	*17*

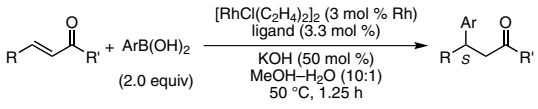
[a] Cat. A = $[RhCl(C_2H_4)_2]_2$–diene*; B = $[RhCl(diene^*)]_2$. [b] Except where noted, the configuration of the product is *R*. [c] $(PhBO)_3$ was used. [d] The product configuration was not determined. [e] The product has the *S* configuration. [f] Aqueous K_3PO_4 was used instead of aqueous KOH. [g] Catalyst loading was 1 mol %. [h] Reaction run for only 0.3 h.

eq 3



Ar	Yield	ee
Ph	94%	99%
4-$MeOC_6H_4$	95%	96%
4-$F_3CC_6H_4$	94%	95%

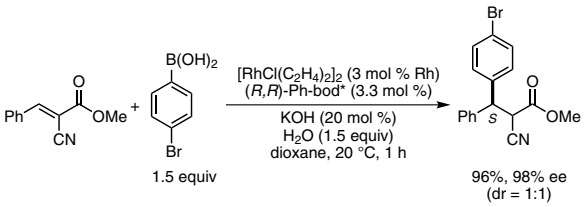
eq 4 *(Ref. 21)*



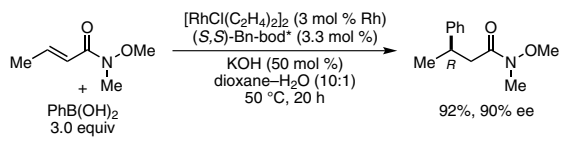
R	R'	Ar	Ligand	Yield	ee
Ph	H	4-$MeOC_6H_4$	**3b**	80%	92%
n-Bu	H	Ph[a]	(*R,R*)-Bn-bod*	88%	93%
Ph	O*t*-Bu	4-$MeOC_6H_4$	**3b**	85%	93%

[a] Reaction run at 10 °C for 6 h using 10 mol % KOH in MeOH–THF–H_2O (12:3:2).

Scheme 10. Asymmetric 1,4 Addition of Arylboronic Acids to α,β-Unsaturated Aldehydes and Esters. *(Ref. 22,24,25)*



eq 5 *(Ref. 26)*



eq 6 *(Ref. 27)*

Subsequently, a variety of chiral diene ligands were developed and tested in the rhodium-catalyzed 1,4 addition of phenylboronic acid to 2-cyclohexenone (**eq 3**). With regard to the catalytic activity of Rh–chiral diene complexes, a rhodium complex of (1*S*,4*S*)-2,5-dibenzylbicyclo[2.2.2]octa-2,5-diene ((*S,S*)-Bn-bod*) was examined in the 1,4 addition to 2-cyclohexenone: high yields and ee's were maintained even with as low as 0.005 mol % catalyst loading.[20]

The α,β-Unsaturated ketones that can be employed are not limited to simple ones. β-Silyl-α,β-enones are good substrates in the Rh–(*R,R*)-Bn-bod*-catalyzed 1,4 addition of arylboronic acids to give chiral organosilanes with high enantioselectivity (**eq 4**).[21] The products thus obtained can be readily converted into highly enantioenriched β-hydroxy ketones by Tamao oxidation. It is worth noting that the use of conventional chiral ligands such as (*R*)-BINAP in the reaction results in a lower enantioselectivity (e.g., 72% ee for Ar = Ph).

Rh–chiral diene complexes effectively catalyze the 1,4 addition of arylboronic acids, not only to α,β-unsaturated ketones, but also to other α,β-unsaturated compounds. For example, selective 1,4 addition of arylboronic acids to β-aryl α,β-unsaturated aldehydes is achieved by using ligand **3b**, giving β,β-diaryl aldehydes with high enantiomeric excess (**Scheme 10**).[22] These products can be readily converted into 1,1-diarylethanes, with retention of enantiopurity, through rhodium-catalyzed decarbonylation.[23] Asymmetric 1,4 addition to α,β-unsaturated aldehydes is also accomplished with similar efficiency by using (*R,R*)-Bn-bod* as ligand.[24]

Ligand **3b** is effective for the rhodium-catalyzed 1,4 addition of aryl boronic acids to β-aryl α,β-unsaturated esters to give β,β-diaryl esters (see Scheme 10).[25] A variety of substituents on the aromatic rings are tolerated under these conditions, and the use of bulky *tert*-butyl esters is essential for achieving high enantioselectivities.

The rhodium–chiral diene catalyzed asymmetric 1,4 addition of arylboronic acids to α-cyanocinnamates is also highly effective for the construction of a chiral center bearing two different aryl groups (**eq 5**).[26] (*R,R*)-Ph-bod* induces high enantioselectivity in these substrates (96–99% ee's); whereas other chiral diene ligands, such as (*R,R*)-Bn-bod* and **3b**, and chiral bisphosphine ligands, such as (*R*)-BINAP, give the products with lower enantioselectivity (46–81% ee's). This method has been successfully applied to the asymmetric synthesis of (*R*)-tolterodine with high enantiomeric excess as well.

α,β-Unsaturated Weinreb amides can also be employed as substrates for the rhodium–chiral diene catalyzed asymmetric 1,4 addition of arylboronic acids (**eq 6**).[27] (*S,S*)-Bn-bod* is particularly effective at inducing high enantioselectivity, and the products thus obtained are readily transformed into the corresponding ketones and aldehydes while maintaining the enantiomeric excess. These reaction conditions have also been used to achieve a highly enantioselective 1,4 addition to an α,β-unsaturated *N*-benzyl amide.

1,4 addition to fumaric and maleic acid derivatives efficiently provides chiral 1,4-dicarbonyl compounds. For example, the asymmetric 1,4 addition of arylboronic acids to di-*tert*-butyl fumarate is effectively catalyzed by Rh–(*R,R*)-Mm-nbd* (**eq 7**), and this complex also catalyzes the 1,4 addition to maleimides with relatively high enantioselectivity (**Scheme 11**).[18] It is noteworthy that a chiral ligand containing a carbon–carbon double bond and a phosphine group, **8**, is so far the best ligand for the rhodium-catalyzed asymmetric 1,4 addition of arylboronic acids to maleimides.[28]

Employment of *N*-(2-*tert*-butylphenyl)maleimide as a substrate for the 1,4 addition leads to simultaneous construction of a carbon stereocenter and a chiral C–N axis. The use of (*R*,*R*)-Ph-bod* controls both of these symmetry elements with high stereoselectivity (see Scheme 11).[29] The same mode of stereoinduction is observed in the 1,4 addition to ferrocobenzoquinone, controlling a carbon stereocenter and a planar chirality at the same time (**eq 8**).[29]

The use of 3-substituted maleimides raises the issue of regioselectivity in the 1,4 addition process. Chiral diene ligands such as (*R*,*R*)-Ph-bod* lead to 3,4-disubstituted succinimides with high regio- and enantioselectivity, whereas bisphosphine ligands such as (*R*)-BINAP selectively give 3,3-disubstituted succinimides (**eq 9**).[30]

In addition to the electron-deficient olefins described so far, *cis*-2-butene-1,4-diol can also be used as a substrate for the rhodium-catalyzed arylation with arylboroxines, giving formal S_N2'-type products. Relatively high enantioselectivity is achieved in this reaction by using ligand **3b** (**eq 10**).[31]

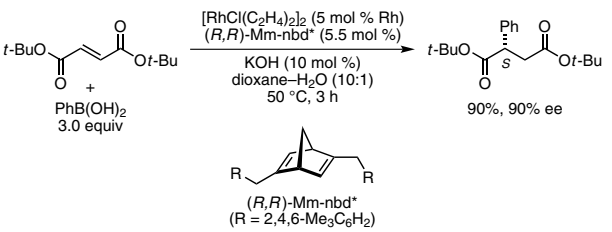
3.2. 1,4 Addition of Other Organometallic Reagents to Electron-Deficient Olefins

One of the advantages of using chiral diene ligands for rhodium-catalyzed 1,4-addition reactions is the fact that other organometallic reagents can also be employed with high catalytic activity. This is in contrast to the rhodium–bisphosphine catalysts, which sometimes exhibit significantly lower reactivity. For example, Rh–(*R*,*R*)-Bn-nbd* effectively catalyzes the 1,4 addition of phenyl(trimethyl)-stannane to give the corresponding 1,4 adduct in high yield and ee (**eq 11**).[5] In contrast, the use of BINAP as ligand results in less than 10% yield of the product.

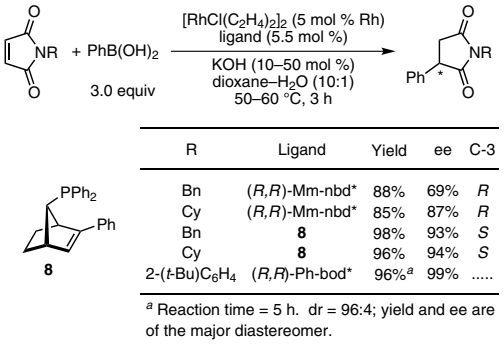
Organo[2-(hydroxymethyl)phenyl]dimethylsilanes[32] also function as good nucleophiles for the rhodium-catalyzed 1,4-addition reactions. Because the reactions are best catalyzed by a rhodium–1,5-cyclooctadiene complex, the asymmetric variant was developed by the use of chiral diene ligands such as (*R*,*R*)-Ph-bod* and (*R*,*R*)-Bn-bod* (**Scheme 12**).[33] Under mild conditions, both aryl and alkenyl groups can be added to cyclic and acyclic enones with high enantioselectivity.

Asymmetric 1,4 addition of alkenyl[2-(hydroxymethyl)-phenyl]dimethylsilanes to β-silyl α,β-unsaturated ketones leads to enantioenriched chiral allylsilanes. In the presence of (*S*,*S*)-Ph-bod* as ligand, various allylsilanes can be obtained with high enantioselectivity, although the use of linear 1-alkenylsilanes as nucleophiles results in moderate ee's (**eq 12**).[34]

In addition to organotin and organosilicon reagents, other organometallic reagents such as phenylzinc chloride (**eq 13**)[17] and diphenylindium hydroxide (**eq 14**)[35] have been employed as nucleophiles in the rhodium–chiral diene catalyzed asymmetric



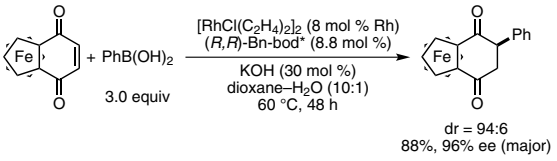
eq 7 *(Ref. 18)*



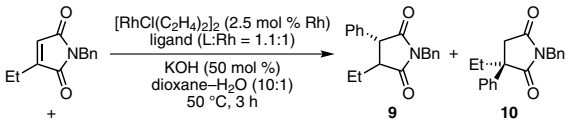
R	Ligand	Yield	ee	C-3
Bn	(*R*,*R*)-Mm-nbd*	88%	69%	*R*
Cy	(*R*,*R*)-Mm-nbd*	85%	87%	*R*
Bn	**8**	98%	93%	*S*
Cy	**8**	96%	94%	*S*
2-(*t*-Bu)C$_6$H$_4$	(*R*,*R*)-Ph-bod*	96%[a]	99%	.....

[a] Reaction time = 5 h. dr = 96:4; yield and ee are of the major diastereomer.

Scheme 11. Asymmetric 1,4 Addition of Phenylboronic Acid to Maleimides. *(Ref. 18,28,29)*

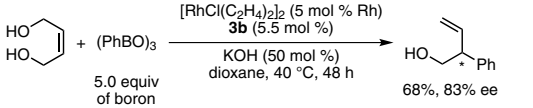


eq 8 *(Ref. 29)*

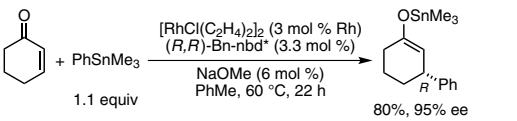


Ligand	**9**+**10**	**9**:**10**	*trans*-**9**	*cis*-**9**	**10**
(*R*,*R*)-Ph-bod*	94%	85:15	83% ee	>99% ee	97% ee
(*R*)-BINAP	99%	15:85	68% ee	96% ee	96% ee

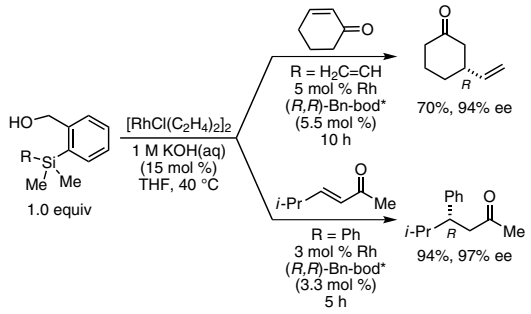
eq 9 *(Ref. 30)*



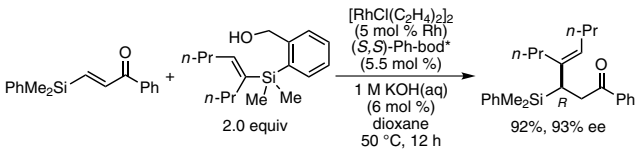
eq 10 *(Ref. 31)*



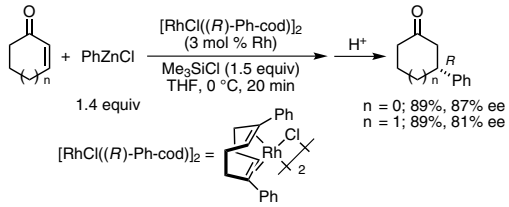
eq 11 *(Ref. 5)*



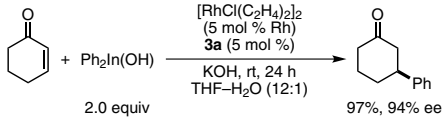
Scheme 12. Asymmetric 1,4 Addition of Organosilanes to α,β-Unsaturated Ketones Catalyzed by Rh–(*R,R*)-Bn-bod*. *(Ref. 33)*



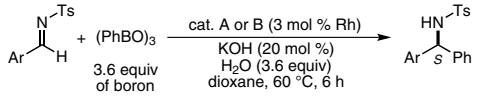
eq 12 *(Ref. 34)*



eq 13 *(Ref. 17)*



eq 14 *(Ref. 35)*



Ar	Ligand	Cat.[a]	Yield	ee	*Ref.*
4-ClC$_6$H$_4$	(*R,R*)-Ph-bod*	A	96%	98%	*12a*
4-MeOC$_6$H$_4$	(*R,R*)-Ph-bod*	A	96%	99%	*12a*
furan-2-yl	(*R,R*)-Ph-bod*	A	99%	99%	*12a*
4-ClC$_6$H$_4$	(*R,R*)-Bn-nbd*	A	98%	92%	*12a*
4-ClC$_6$H$_4$	(*R,R*)-Me-nbd*	B	96%	89%	*8a*
4-ClC$_6$H$_4$	(*R,R*)-Ph-nbd*	B	96%	99%	*8a*
4-ClC$_6$H$_4$	(*R,R*)-Bn-bod*	A	98%	94%	*12a*
4-ClC$_6$H$_4$	(*S,S*)-Ph-bnd*	B	95%	99%	*13b*
4-ClC$_6$H$_4$	(*R,R*)-Ph-bdd*	B	88%	94%	*13b*
4-ClC$_6$H$_4$	**6**[b]	A	81%	99%	*15a*

[a] Cat. A = [RhCl(C$_2$H$_4$)$_2$]$_2$–diene*; cat. B = [RhCl(diene*)]$_2$. [b] PhB(OH)$_2$ (4 equiv), Et$_3$N (2 equiv), toluene, 55 °C, 4–5 h.

eq 15

1,4 addition to enones to give the corresponding 1,4 adducts with high enantioselectivity.

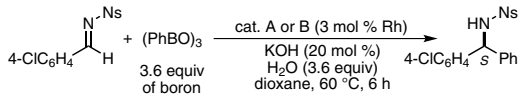
(*S,S*)-Bn-bod* functions well as an effective ligand in the rhodium-catalyzed asymmetric 1,4 arylation of enones with aryl methanols derived from 10-benzylacridin-9(10*H*)-one.[36] In addition, (*S,S*)-Ph-bod* can be employed as ligand in the rhodium-catalyzed asymmetric 1,3 rearrangement of alkynyl alkenyl carbinols to β-alkynyl ketones with high enantioselectivity. This reaction serves as a surrogate for the conjugate alkynylation of enones.[37]

3.3. 1,2 Addition to N-Sulfonyl Imines

Asymmetric 1,2 addition of arylboronic acids or arylboroxines to *N*-sulfonyl arylimines is an attractive method for the preparation of enantioenriched diarylmethylamines. Rh–(*R,R*)-Ph-bod* effectively catalyzes these reactions with excellent enantioselectivity when *N*-tosyl imines are employed. The efficiency of this ligand is much higher than those of conventional chiral phosphine ligands such as (*R*)-BINAP, which provides the 1,2 adducts in lower yields and ee's (e.g., 28% yield, 31% ee (*S*) for Ar = 4-ClC$_6$H$_4$). Subsequently, various other chiral diene ligands were utilized for this transformation (**eq 15**).[8a,12a,13b,15a]

N-Nosyl aldimines are also typically employed for the rhodium–chiral diene catalyzed asymmetric 1,2 addition of arylboronic acids or arylboroxines primarily due to the ease of removal of the nosyl group.[38] Several ligands such as (*R,R*)-Ph-nbd*, (*S,S*)-Ph-bnd*, and ligand **6** are particularly effective for inducing very high enantioselectivity (**eq 16**).[8a,13,15a]

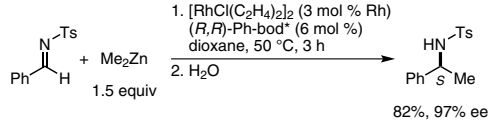
In addition to aromatic nucleophiles, methylation of *N*-tosyl aldimines is also catalyzed well by a rhodium complex containing (*R,R*)-Ph-bod*.[39] Thus, addition of dimethylzinc proceeds effectively with this catalyst system to give the corresponding adducts in high yields and excellent ee's (**eq 17**),



Ligand	Cat.[a]	Yield	ee	*Ref.*
(*R,R*)-Bn-nbd*	A	88%	81%	*13a*
(*R,R*)-Me-nbd*	B	93%	82%	*8a*
(*R,R*)-Ph-nbd*	B	92%	98%	*8a*
(*R,R*)-Bn-bod*	A	99%	70%	*13a*
(*R,R*)-Ph-bod*	A	96%	89%	*13a*
(*S,S*)-Ph-bnd*	B	96%	98%	*13a*
(*R,R*)-Ph-bdd*	B	99%	90%	*13b*
6[b]	A	35%	99%	*15a*

[a] Cat. A = [RhCl(C$_2$H$_4$)$_2$]$_2$–diene*; cat. B = [RhCl(diene*)]$_2$. [b] PhB(OH)$_2$ (4 equiv), Et$_3$N (2 equiv), toluene, 55 °C, 1 h.

eq 16



eq 17 *(Ref. 39)*

while the use of chiral phosphorus-based ligands typically results in low yields and ee's.

3.4. Arylative Cyclization with Arylboronic Acids

Rhodium(I) complexes are known to catalyze the addition of organoboronic acids to internal alkynes,[40] and employment of 5-alkynals leads to the formation of the corresponding cyclic allylic alcohols bearing a tetrasubstituted carbon–carbon double bond. This process is effectively catalyzed by a rhodium–diene complex having no phosphine ligands, and the use of (*S*,*S*)-Bn-bod* as ligand in this case provides the corresponding arylative cyclization products with high enantioselectivity (**Scheme 13**).[41]

A similar arylative cyclization takes place with alkyne-tethered electron-deficient olefins. Although both internal alkynes and electron-deficient olefins are reactive toward arylrhodium species, rhodium–diene complexes chemo- and regioselectively provide arylative cyclization products. Again, (*S*,*S*)-Bn-bod* induces excellent enantioselectivity in this transformation (see Scheme 13).[42]

The rhodium-catalyzed addition–cyclization of 2-formylphenylboronic acid with internal alkynes provides an efficient way of constructing indenols. The use of diene ligands is essential to promote the reaction, and (*S*,*S*)-Bn-bod* gives the products in an enantioselective manner (**eq 18**).[43] 2-Cyanophenylboronic acid reacts with norbornene derivatives in the presence of $[Rh(OH)(cod)]_2$ to give 1-indanones; in one case, ligand **3a** gave the product with relatively high enantioselectivity (80% ee).[44]

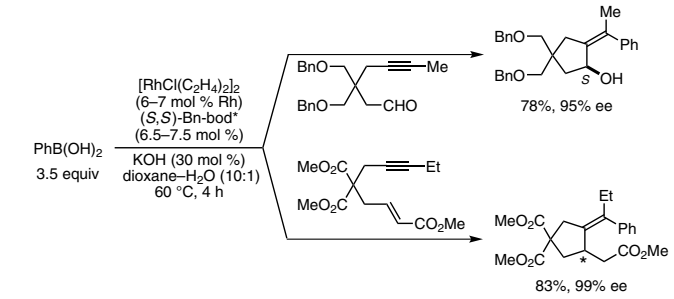
3.5. Other Reactions

All the reactions using chiral diene ligands described above are rhodium-catalyzed additions of carbon nucleophiles (mostly organometallic reagents such as organoboronic acids) to carbon–carbon or carbon–heteroatom unsaturated bonds. There are a few other asymmetric reactions that can be effectively catalyzed by a transition metal coordinated with a chiral diene ligand. For example, an iridium–**2d** complex catalyzes the kinetic resolution of racemic allylic carbonates to give the unreacted substrates in ~35% yield with high enantiomeric excess (e.g., **eq 19**).[9]

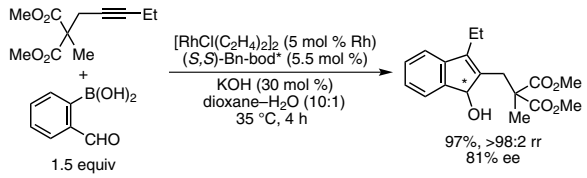
Rhodium–diene complexes show much higher catalytic activity than rhodium–bisphosphine complexes in the intramolecular [4 + 2] cycloaddition of alkyne-tethered 1,3-dienes. It is, therefore, desirable to use chiral diene ligands for the development of its asymmetric variant. By using (*S*,*S*)-Ph-bod* as ligand, high yields and ee's are achieved in this transformation (**eq 20**).[45] Due to the high catalytic activity of Rh–(*S*,*S*)-Ph-bod*, the reaction can also be efficiently conducted even with 0.5 mol % catalyst without noticeable reduction in stereoselectivity. Additionally, Rh–(*S*,*S*)-Ph-bod* can effectively catalyze intermolecular reactions between alkynes and 1,3-dienes.

4. Concluding Remarks

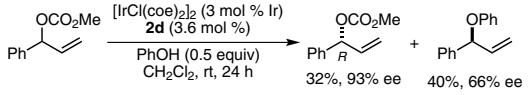
The recent successful development of chiral diene ligands is one of the most significant advances in asymmetric catalysis. Although this research area is still very new, there have already been many publications that point out the superiority of chiral dienes vis-à-vis other conventional chiral ligands in certain transformations. However, most of the successful examples are of the rhodium-catalyzed addition of organometallic reagents to carbon–carbon or carbon–heteroatom unsaturated bonds. Future studies should be directed more towards the application of chiral diene ligands in other metal-catalyzed asymmetric transformations.



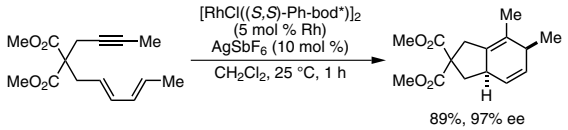
Scheme 13. Asymmetric Arylative Cyclizations of Acetylenic Aldehydes and Enoates Catalyzed by Rh–(*S*,*S*)-Bn-bod*. *(Ref. 41,42)*



eq 18 *(Ref. 43)*



eq 19 *(Ref. 9)*



eq 20 *(Ref. 45)*

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Keywords: chiral dienes; asymmetric synthesis; rhodium complexes; 1,2 addition; 1,4 addition.

About the Authors

Ryo Shintani was born in 1976 in Hiroshima, Japan. He received his bachelor's degree in 1999 from Kyoto University and his Ph.D. degree in 2003 from the Massachusetts Institute of Technology under the direction of Professor Gregory C. Fu. The title of his thesis is "Application of Planar-Chiral Phosphaferrocene-Oxazolines in Asymmetric Catalysis and Enantioselective Desymmetrization by Carbon Nucleophiles in the Presence of Chiral Ligands". He has been an assistant professor in the Graduate School of Science at Kyoto University since 2003. His research interest is in the development of new synthetic reactions that are catalyzed by transition-metal complexes, particularly ones that allow control of the absolute stereochemistry of the product. He received the Eisai Co. Award in Synthetic Organic Chemistry, Japan, in 2006 and the Mitsubishi Tanabe Pharma Corp. Award in Synthetic Organic Chemistry, Japan, in 2008.

Tamio Hayashi was born in 1948 in Gifu, Japan. He obtained his bachelor's degree in 1970 from Kyoto University and his Ph.D. degree in 1975 from Kyoto University under the direction of Professor Makoto Kumada. The title of his thesis is "Catalytic Asymmetric Hydrosilylation of Olefins and Ketones". From 1975 to 1989, he was a research associate in the Faculty of Engineering at Kyoto University, and from 1976 to 1977 a postdoctoral fellow at Colorado State University with Professor Louis S. Hegedus. In 1989, he was promoted to Full Professor in the Catalysis Research Center at Hokkaido University. Since 1994, he has been Full Professor in the Faculty of Science at Kyoto University. His research interests focus on the development of new selective organic transformations catalyzed by transition-metal complexes, especially catalytic asymmetric reactions. He has studied the mechanism of organometallic reactions including transition-metal-catalyzed organic reactions. His awards include the Award for Young Chemists of the Society of Synthetic Organic Chemistry of Japan (1983), the IBM (Japan) Prize (1991), The Chemical Society of Japan Award (2003), the Thomson Scientific Research Front Award (2004), the Molecular Chirality Award (2005), The Ryoji Noyori Prize (2008), and the Arthur C. Cope Scholar Award (2008).

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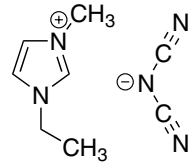

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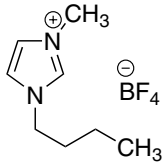

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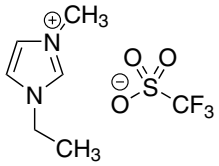

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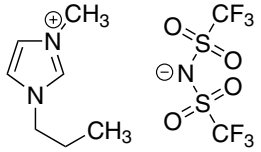

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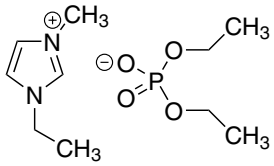

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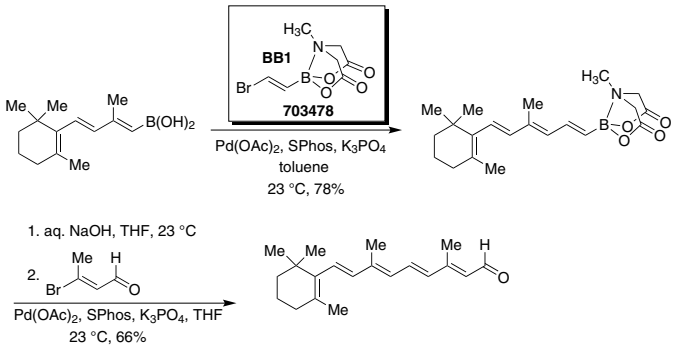

Reference:
Lee, S. J. et al. *J. Am. Chem. Soc.* **2008**, *130*, 466.

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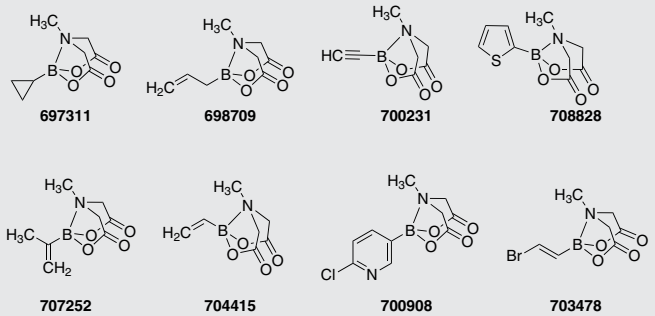

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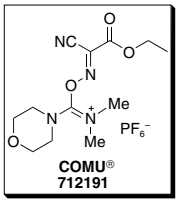
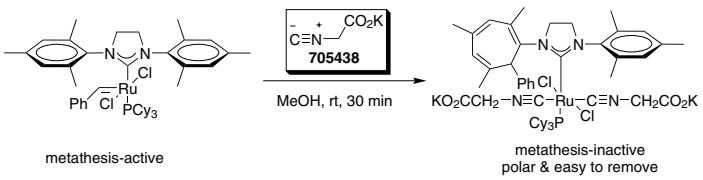


Dipeptide	Coupling Reagent	Base	Yield (%)	D, L (%)
Z-Phg-Pro-NH_2	HATU	DIEA	78.4	3.1
	HBTU	DIEA	80.2	8.2
	HOTU	DIEA	78.9	0.17
	COMU	DIEA	88.2	0.12
	HDMOPC	DIEA	86.0	13.6

Reference:
El-Faham, A. et al. *Chem.—Eur. J.* **2009**, Early View.

Reagent for Quenching Metathesis Reactions

Diver and co-workers recently described an efficient metathesis cleanup procedure using potassium 2-isocyanoacetate, which addresses the challenges associated with removal of the ruthenium at the end of the reaction. Upon quenching with the polar isocyanide, a benzylidene insertion into the mesityl group occurs, thus destroying the catalyst and imparting increased polarity for easy removal. Potassium 2-isocyanoacetate was successfully used to quench a range of metathesis reactions and the authors demonstrated it can be employed with various highly utilized Grubbs complexes.



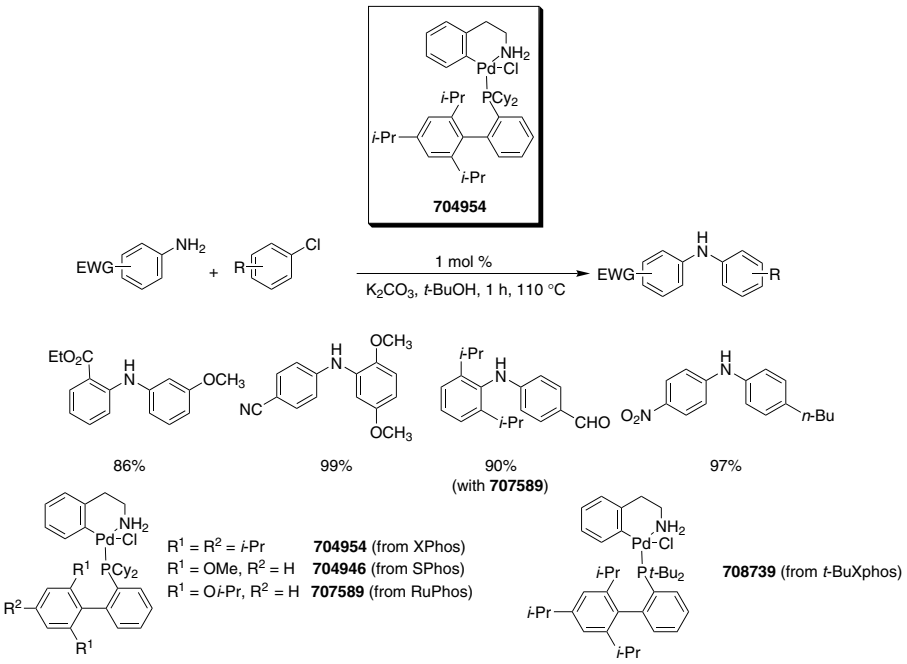
Reference:
Galan, B. R. et al. *Org. Lett.* **2007**, *9*, 1203.

Air-Stable Palladacycles for Amination

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

Reference:

Biscoe, M. R. et al. *J. Am. Chem. Soc.* **2008**, *130*, 6686.

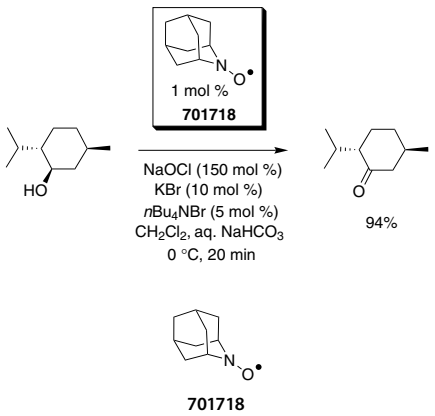


Organocatalyst for Oxidation of Hindered Alcohols

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

Reference:

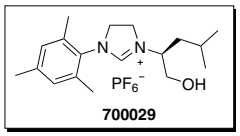
Nissan Chemical Industries, Ltd., Tokyo, Jpn. Unpublished results, 2008.
See also Shibuya, M. et al. *J. Am. Chem. Soc.* **2006**, *128*, 8412.

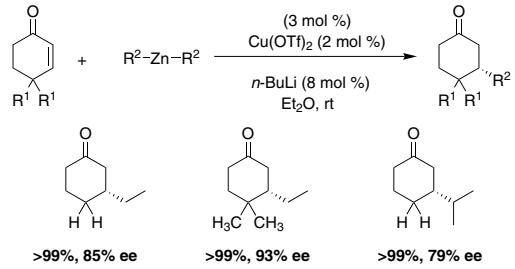


Explore the Copper-Catalyzed Asymmetric Conjugate Addition

Chiral NHC Ligand

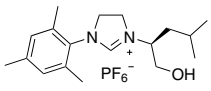
The asymmetric conjugate addition reaction has been extensively studied for the past decade. This effort stems from the importance of this method for the formation of C–C bonds concomitant with the introduction of a chiral center. Mauduit and co-workers developed new chiral N-heterocyclic carbene ligands for this transformation. One of the examples highlighted in the review is the copper-catalyzed asymmetric conjugate addition of dialkyzincs to cyclic enones. Good yields and selectivities were reported.





Reference:

Clavier, H. et al. *Tetrahedron: Asymmetry* **2005**, *16*, 921.



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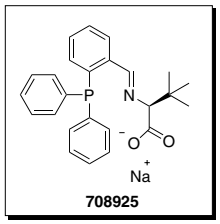
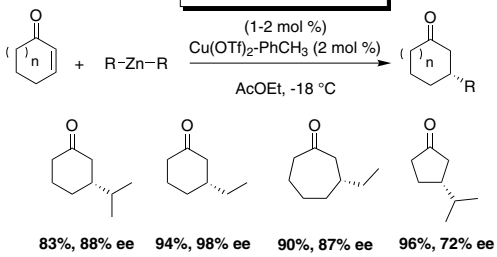
Chiral Phosphinoazomethinylate Salts as Ligands

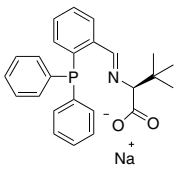
In 2008, Mauduit and co-workers reported the copper-catalyzed asymmetric conjugate addition using a phosphine-based ligand. Starting from the work of Hoveyda and co-workers who used small peptide-type ligands, Wencel et al. described the use of a chiral phosphinoazomethinylate sodium salt with copper for the addition of various dialkylzincs to cyclic enones.





Reference:

Wencel, J. et al. *Tetrahedron: Asymmetry* **2008**, *19*, 1804.



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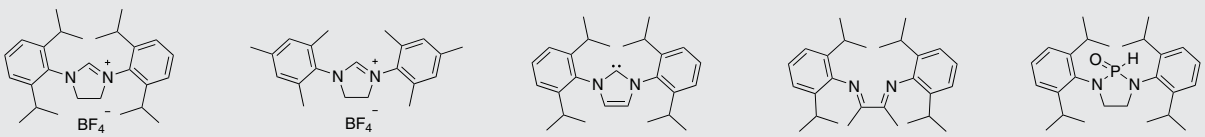
New N-Heterocyclic-Carbene-Type Ligands and Precursors from Sigma-Aldrich



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Chiral, Chelating, Hydroxyalkyl and Hydroxyaryl N-Heterocyclic Carbenes: Design, Synthesis, and Application in Copper-Catalyzed Asymmetric Conjugate Addition (Cu-ACA)


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Outline

1. Introduction

Since their discovery in 1968 by Öfele[1] and Wanzlick,[2] and their first isolation in the free state by Arduengo[3] in the early 1990s, N-heterocyclic carbene (NHC) ligands have received a growing attention from the scientific community, notably in organometallic chemistry.[4] These ligands are likely to surpass in popularity well-known phosphorus-based ligands because of their remarkable ability to establish strong bonds with the metal center and their capacity to permit significant doping of catalyst activity in a wide range of chemical transformations[4] such as olefin metathesis, carbon–carbon and carbon–nitrogen cross-coupling reactions, hydrogenation, and hydrosilylation. Not surprisingly, these promising ligands have been intensely explored in asymmetric catalysis.[5] This notwithstanding, and among the growing number of chiral NHC ligands possessing a wide variety of structures, a new, especially promising class has recently emerged: the chelating hydroxyalkyl- and hydroxyaryl-imidazolium carbenes **1–4**, which have been successfully applied in enantioselective catalysis (**Figure 1**).[6–8] We intend to highlight in this review their design, synthesis strategy, and their fruitful application in the copper-catalyzed Asymmetric Conjugate Addition (Cu-ACA),[9] leading to the efficient formation of chiral building blocks of interest.

2. Efficient Ligand Design Strategies Leading to Chiral Chelating NHCs

The tremendous impact of NHC ligands in asymmetric catalysis is not only due to their high efficiencies in terms of activity and enantioselectivity, but also due to their ready availability and diverse three-dimensional structures. In the context of a push for economically and environmentally friendly modern chemical processes, the importance of designing low-cost chiral

ligands by such processes cannot be underestimated. The area of asymmetric catalysis has evolved into a complex science, wherein the development of new chiral ligands now focuses on the most straightforward and atom-economical approaches that involve the minimum number of reaction steps. Moreover, in spite of the major discoveries made in this area during the past two decades, further efforts need to be made in order to extend the scope of asymmetric catalysis. Some of the impediments to achieving this goal have been: (i) high loadings of the chiral catalysts owing to their low stability in the reaction media, and (ii) some catalyst systems that are too expensive for industrial applications because of the significant synthetic effort required to construct the three-dimensional structure of the ligand. This makes obvious the need to design stable, inexpensive, and efficient chiral catalytic systems. Chiral NHCs are attractive target ligands, since they are readily accessible, easily tunable, and form highly stable and efficient NHC–metal catalysts. Another significant advantage of NHCs is the good chemical stability of their precursors (i.e., the azolium salts), which permits their multigram synthesis and easier storage.

Although the electronic donor properties of NHCs are quite similar to those of their phosphine counterparts, their topological features are quite different. Phosphines possess a conical environment, whereas NHCs have a planar chelation site. Consequently, the design strategy of replacing only phosphine units with NHC moieties in well-known efficient phosphorus ligands is often unfruitful in terms of enhancing the resulting enantioselectivity.[10] A serious design effort of ligand architecture would thus be required for each targeted organometallic transformation, and the quest for new and efficient chiral NHC frameworks could become laborious. Fortunately, in light of their wide synthetic tunability, a rapid elaboration of NHC ligand libraries based on the same scaffold can be envisaged and would enhance the chances of discovering an ideal enantiodiscriminating candidate for a given metal-catalyzed asymmetric transformation.

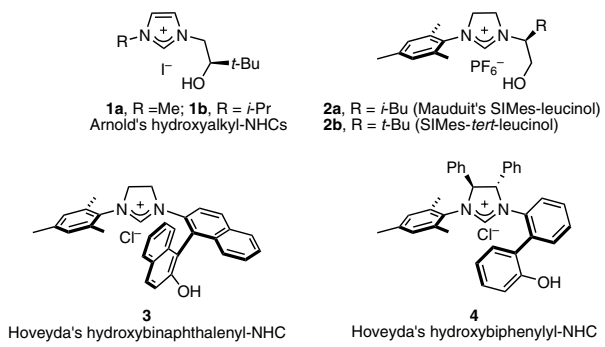
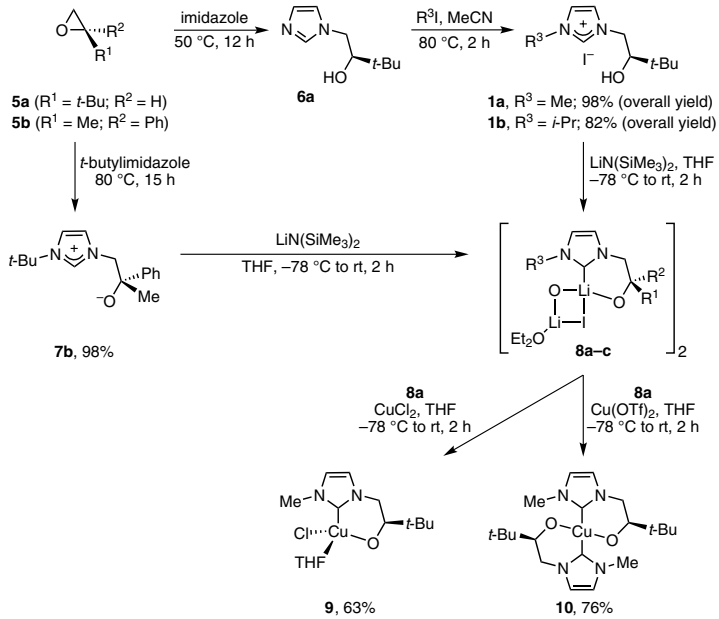


Figure 1. Representative Chiral, Chelating, Hydroxyalkyl- and Hydroxyaryl-NHC Precursors Designed for Cu-ACA. *(Ref. 6–8)*

2.1. Design of Chiral Hydroxyalkyl-NHC Precursors

Enantiopure, chelating hydroxyalkylimidazolinium carbenes were first reported in 2004 by Arnold and co-workers, who described an efficient, one-pot synthesis of a wide range of hydroxyalkylimidazolium salts, **1** (**Scheme 1**).[8] These salts led to new lithium hydroxyalkyl-NHCs and their copper(II)–carbene counterparts. Arnold's synthetic approach is based on the ring opening of enantiopure alkyl-substituted epoxides. Thus, the reaction of imidazole with 2-*tert*-butyloxirane (**5a**), followed by quaternarization with alkyl iodides, yielded imidazolium salts **1a** and **1b** in 98% and 82% yields, respectively. Interestingly, when the ring opening involved epoxide **5b**, zwiterionic salt **7b** was directly formed also in 98% yield. Deprotonation of these salts by LiHMDS afforded the first isolated enantiopure lithium hydroxyalkylimidazolinium carbenes **8a–c** in excellent yields. The structure of NHC–Li complex **8a** was confirmed by X-ray



Scheme 1. Arnold's Synthesis of Hydroxyalkyl-NHC Precursors and the Derived NHC-Lithium and Copper(II) Complexes. *(Ref. 8)*

analysis. Finally, reaction of **8a** with copper(II) chloride afforded the expected mono-substituted hydroxyalkyl-NHC–Cu(II) complex **9** in 63% yield, whereas its treatment with copper(II) triflate provided the bis(NHC)–copper complex **10** in 76% yield.

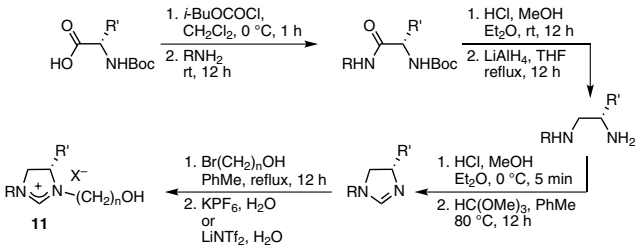
The following year, Mauduit's group reported two other classes of chiral hydroxyalkyl-NHCs derived from hydroxyalkylimidazolinium salts **11** and **2,** which differ from Arnold's ligands by the position of the stereogenic center (within the N-heterocycle in **11**, or in the β position with respect to the hydroxyl group in **2**).[11] The first generation of azolium salts, **11**, were synthesized by a straightforward six-step process (**Scheme 2**).[11b,c] The mixed-anhydride-mediated coupling between commercially available Boc-protected amino acids and substituted anilines led to the formation of the corresponding amides. After removal of the carbamate, the amide function was reduced affording the acyclic diamines. At this point, the diamine hydrochloride was condensed with trimethyl orthoformate yielding enantiopure imidazolines. Alkylation with 2-bromoethanol, followed by anion exchange with KPF_6 or $LiNTf_2$, afforded the expected hydroxyalkylimidazolinium salts **11** in moderate-to-good overall yields over 6 steps. Using this pathway, a small library of optically pure hydroxyalkylimidazolinium salts, **11a**–**h**, were isolated (see Scheme 2).[11b,c]

A more tunable and less expensive synthetic route has been elaborated for the second generation of hydroxyalkylimidazolinium salts **2** (**Scheme 3**).[11] Mesitylamine was condensed with commercially available ethyl oxalyl chloride to give the corresponding oxalinic diethyl ester. Reaction with enantiopure β-amino alcohols in refluxing dichloromethane afforded the oxalamides, which were reduced to the acyclic diamines. The corresponding hydrochlorides were reacted with trimethyl orthoformate in refluxing toluene to provide the desired imidazolinium chloride salts. Finally, anionic metathesis with KPF_6 afforded the pure hydroxyalkylimidazolinium hexafluorophosphate salts **2** in good overall yields over five steps. The structure of **2a** was confirmed by X-ray analysis. Following this modular pathway that does not require any purification step, a library of 25 azolium salts **2** was generated from various commercially available substituted anilines, alkylamines, or α-alkyl-arylamines and diversely 1,2-substituted chiral β-amino alcohols (see Scheme 3).[11]

2.2. Design of Chiral, Hydroxyaryl-NHC Precursors

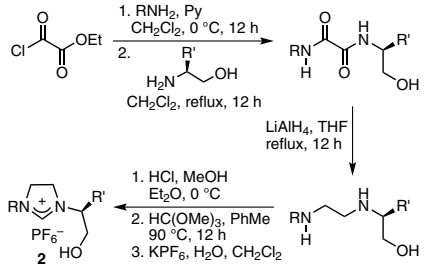
The class of enantiopure chelating hydroxyaryl-NHCs used in ACA, as typified by imidazolinium salt **3**, was first reported in 2002 by Hoveyda and co-workers.[6] Initially designed for Ru-catalyzed asymmetric olefin metathesis, the strategy to build the three-dimensional framework of these chelating NHCs takes advantage of the axial chirality of the 1,1'-binaphthyl unit. The key synthetic step is reductive amination of aniline-based aldehyde **12** with optically pure aminobinaphthol **13** (**Scheme 4**).[6a,12] The resulting secondary aminobinaphthol is converted into the desired binaphtholimidazolinium chloride salt **3** in 56% overall yield after treatment with anhydrous hydrogen chloride followed by cyclization in neat triethyl orthoformate. The dimeric NHC–Ag complex **15** can be isolated in excellent yield by simple treatment of **3** with silver oxide. Treatment of **15** with copper(II) chloride dihydrate provides the corresponding dimeric complex, **16**, of hydroxyaryl-NHC and copper(II) in 95% yield.[12] Both **15** and **16** have been fully characterized, and their X-ray structures determined. Several other binaphthol-imidazolinium salts similar to **3** have been synthesized by varying the aminonaphthol and the arylamine (or alkylamine) used.[12]

A year later, Hoveyda and co-workers reported a shorter synthesis of analogues of **3**.[13] In this approach, the expensive, optically pure aminobinaphthol unit was replaced by the commercially available chiral diamine **17** (**Scheme 5**). In this case, the chirality of the stereogenic centers in the diamine backbone is transferred to the achiral chelating biphenyl moiety, enabling the formation of a single atropoisomer after coordination with the metal center. The key synthetic steps involve a one-pot double arylamination first with aryl iodide **18** and then mesityl bromide.



11	R	R'	n	X	Yield
a	Mes	*i*-Pr	2	PF_6	52%
b	Mes	*t*-Bu	2	PF_6	14%
c	Mes	Me	2	PF_6	39%
d	Mes	Ph	2	PF_6	32%
e	Ph	*i*-Pr	2	Tf_2N	42%
f	2-PhBn	*i*-Bu	2	PF_6	47%
g	2-*t*-BuC_6H_4	*i*-Pr	2	Tf_2N	34%
h	2-*t*-BuC_6H_4	*i*-Pr	3	PF_6	....

Scheme 2. Mauduit's Synthesis of a Small Library of First-Generation Optically Pure Hydroxyalkyl-NHC Precursors **11.** *(Ref. 11c)*



2	R	R'	Yield[a]	2	R	R'	Yield[a]
a	Mes	*i*-Bu	76%	**n**	2-MeSC_6H_4	*i*-Pr	33%
b	Mes	*t*-Bu	66%	**o**	2,6-(*i*-Pr)$_2C_6H_3$	*i*-Pr	59%
c	Mes	*i*-Pr	73%	**p**	2,6-(*i*-Pr)$_2C_6H_3$	*i*-Bu	----
d	Mes	Me	71%	**q**	(*R*)-Ph(Me)CH	*i*-Pr	83%
e	Mes	Bn	76%	**r**	$MesCH_2$	*i*-Bu	34%
f	Mes	Ph	74%	**s**	1-NpCH_2	*i*-Bu	53%
g	Mes	Ph[b]	43%	**t**	(*R*)-1-Np(Me)CH	*t*-Bu	42%
h	Mes	Me[c]	52%	**u**	(*R*)-1-Np(Me)CH	*i*-Bu	59%
i	Mes	*d*	----	**v**	(*S*)-1-Np(Me)CH	*i*-Bu	50%
j	Mes	*e*	51%	**w**	(*R*)-1-indanyl	*i*-Bu	62%
k	Ph	*i*-Pr	67%	**x**	*n*-Bu	*i*-Pr	72%
l	2-*t*-BuC_6H_4	*i*-Pr	54%	**y**	*t*-Bu	*i*-Pr	53%
m	2-PhBn	*i*-Bu	47%				

[a] Overall yield for six steps. [b] (1*R*,2*S*)-2-Amino-1,2-diphenylethanol was used. [c] (1*S*,2*R*)-2-Amino-2-methyl-1-phenylethanol was utilized. [d] (1*S*,2*R*)-1-Amino-2-indanol was employed. [e] (1*R*,2*S*,3*R*,4*S*)-2-Aminoisoborneol was used.

Scheme 3. Mauduit's Synthesis of a Small Library of Second-Generation Optically Pure Hydroxyalkyl-NHC Precursors **2.** *(Ref. 11b,c)*

The resulting secondary diamine is converted into the desired hydroxybiphenylylimidazolinium salt **4** following cleavage of the methyl ether. As mentioned above, chelating NHC ligand **4** can be easily converted into the corresponding enantiomerically and diastereomerically pure silver complex **19** and the derived copper(II) complex **20** in excellent yields.[13]

3. Application in Copper-Catalyzed Asymmetric Conjugate Addition (Cu-ACA)

The copper-catalyzed Asymmetric Conjugate Addition (Cu-ACA) of hard, unstabilized nucleophiles to unsaturated carbonyls is a powerful and versatile synthetic tool that affords enantiomerically enriched building blocks that can be used in the total synthesis of natural products.[9] Since the original reports in the early 1990s,[14] a wide range of successful chiral ligands, notably phosphorus-based ones, have emerged, leading to excellent selectivities with various Michael acceptors such as cyclic and acyclic enones, lactones and lactams, nitroalkenes, amides, and malonates.[9] Not surprisingly, chiral NHC ligands have been extensively studied since the pioneering work of Fraser and Woodward, reported in 2001, on the beneficial effect of Arduengo-type carbenes in enhancing the reactivity of the copper-catalyzed addition.[15] Initial attempts at using chiral NHCs in Cu-ACA were carried out jointly by Alexakis and Roland, and involved monodentate chiral NHCs. This led to enantioselectivities ranging from 42% to 93% ee in the addition of dialkylzincs to cyclic and acyclic Michael acceptors.[16]

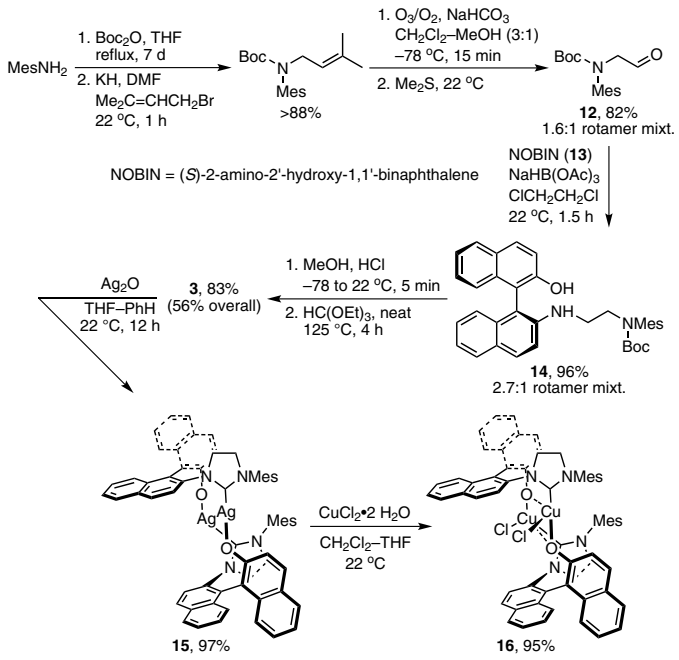
3.1. Cu-ACA with Diorganozinc Reagents

3.1.1. Addition to Disubstituted Enones

The first attempt at using a chelating hydroxyalkyl-NHC in the addition of diethylzinc to cyclohexenone was carried out by Arnold and co-workers, who employed the copper complex, **9**, of ligand **1a** (**eq 1**).[8] Although a quantitative conversion was reached, a maximum of only 51% ee was observed.

By screening the library of first-generation hydroxyalkyl-NHC precursors, **11**, bearing a stereogenic center within the N-heterocycle, our group slightly improved the selectivity up to 60% ee (**eq 2**).[11b,c] In situ formation of the hydroxyalkyl-NHC–copper(II) complex was achieved by double deprotonation of the hydroxyalkylimidazolinium salt in the presence of copper(II) triflate. The highest selectivity was observed with the NHC bearing the sterically demanding *tert*-butyl group. Another important piece of information about the behavior of the three-dimensional NHC scaffold was gained through variation of the nonchelating moiety. It was found that the mesityl group, which hinders one side and thereby disfavors approach of the substrate from this direction, is necessary for this C_1-symmetrical ligand to work.

A significant jump in enantioselectivity was achieved with the second generation of hydroxyalkyl-NHCs, **2**, in which the stereogenic center is located in the hydroxyalkyl side chain, near the NHC backbone (**eq 3**).[11a,b] When members of the readily available library (see Scheme 3) of hydroxyalkyl-NHCs were screened for the addition of diethylzinc to 2-cyclohexenone, several efficient candidates, such as **2a,b** and **2u**, were identified. Optimum ee's ranging from 83% to 90% were observed at ambient temperature with full conversion within only 30 minutes. Interestingly, the catalyst loading could be decreased down to 0.1 mol % without any significant impact on enantiocontrol, attesting to the efficiency of these NHCs and their suitability as environmentally benign reagents. Moreover, greener molecular (organic) solvents such as ethyl acetate were also suitable for this transformation, resulting in similar enantioselectivities, but requiring the use of an organic base to generate the alkoxylate carbene ligand. The most recent tuning of these NHCs concerned the nonchelating moiety, wherein the mesityl group was replaced with a chiral α-methylnaphthyl substituent (**2u**). The observed enantioselectivity was 90%,



Scheme 4. Hoveyda's Synthesis of Hydroxybinaphthalenyl-NHC Precursor **3** and the Derived Ag and Cu(II) Complexes, **15** and **16.** *(Ref. 6a,12)*

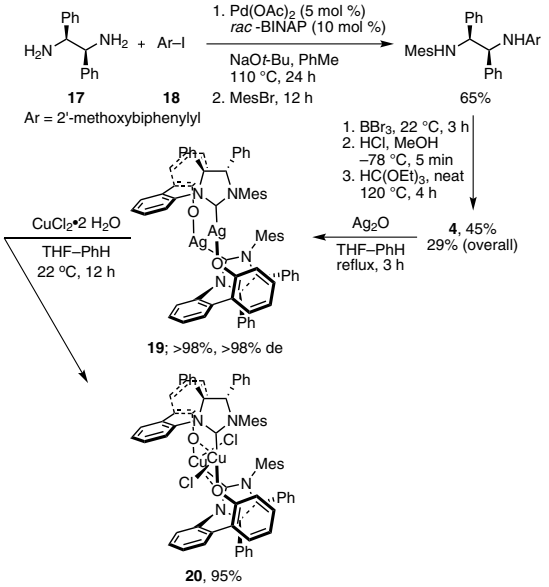
the highest ee reported so far with NHCs for the addition of diethylzinc to cyclohexenone.[11c]

Nevertheless, this beneficial effect of the chiral α-methylnaphthyl group was not observed with other Michael acceptors[11c] relative to the enantioselectivities observed with the mesityl-substituted homologue **2a** (**eq 4**).[11a,b] A survey of the reaction scope involving several cyclic enones and dialkylzincs was reported with SIMes-leucinol **2a** (see eq 4). Remarkably, alkylation involving *dimethyl*zinc (Me_2Zn), which proved to be a challenging nucleophile in light of its poor reactivity and selectivity in the conjugate addition, led to a quantitative yield within 3 h and a good selectivity of 88% ee. Similar good yields and selectivities (up to 94% ee) were observed when both bulkier dialkylzincs and sterically hindered cyclic enones were involved. Finally, limitations in the reaction scope were identified when either cyclopentenones or acyclic Michael acceptors including nitroalkenes were employed. Despite excellent reactivities in these latter cases, enantioselectivities remained significantly lower, with no value over 53% ee observed for the formation of chiral tertiary centers. These limitations point to the need for new three-dimensional scaffolds, since no chiral NHCs have yet been reported as efficient ligands for these classes of Michael acceptors. As enantioselectivities of over 95% have been obtained with the most efficient Cu–phosphine-based systems,[17] the development of new and more efficient chiral chelating NHCs for acyclic substrates continues to be a challenge.

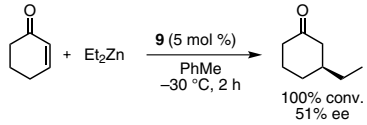
3.1.2. Addition to Trisubstituted Enones: Formation of All-Carbon Chiral Quaternary Centers

The formation of all-carbon quaternary centers by conjugate addition to polysubstituted enones is a synthetic challenge.[18] It is well known that classical Gilman cuprates can undergo such achiral additions.[19] However, diorganozinc reagents are not reactive enough with the usual chiral-phosphine-based ligands, whatever the copper salt catalyst.[9] Fortunately, tetrahydroimidazole carbene ligands can provide a stronger acceleration than phosphorus ligands to this copper-catalyzed reaction. Among the various carbenes, hydroxyarylimidazolinium carbenes derived from **3** and **4** appeared to be promising candidates for this difficult reaction.[20] A rapid screening of readily available such NHC–silver and NHC–copper complexes in the addition of diethylzinc to 3-methyl-2-cyclohexenone showed that NHC–silver complex **19** was the most efficient, promoting the formation of the quaternary center in 92% isolated yield and up to 93% ee (**eq 5**).[20] Curiously, significantly lower reactivities and enantioselectivities were observed when preformed NHC–copper complexes **16** and **20** (see Schemes 4 and 5) were employed.

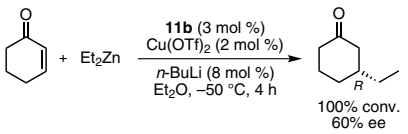
This transformation, catalyzed by NHC–Ag complex **19**, exhibited an impressive scope involving a wide range of cyclohexenones and cycloheptenones and various dialkyl- or diarylzincs (**eq 6**).[20] In most cases, good-to-excellent isolated yields and moderate-to-high enantioselectivities were observed.



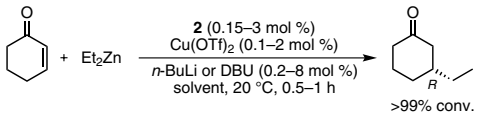
Scheme 5. Hoveyda's Shortened Synthesis of Hydroxybiphenylyl-NHC Precursor **4** and the Corresponding Ag and Cu(II) Complexes, **19** and **20.** *(Ref. 13)*



eq 1 *(Ref. 8)*

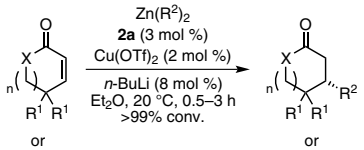


eq 2 *(Ref. 11c)*



2	Cu(II)	Solv.	ee
a	2 mol %	Et_2O	86%
a	0.1 mol %	Et_2O	83%
a	2 mol %	EtOAc	85%
b	2 mol %	Et_2O	87%
u	2 mol %	Et_2O	90%

eq 3 *(Ref. 11)*

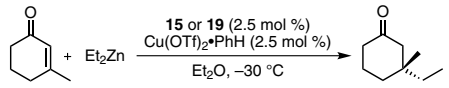


X	n	R^1	R^2	ee
CH_2	1	H	Me	88%
CH_2	2	H	Et	90%
CH_2	1	H	*i*-Pr	79%
O	1	H	Et	72%
CH_2	1	Me	Et[a]	94%
CH_2	0	H	*i*-Pr	53%

[a] Salt **2e** was used.

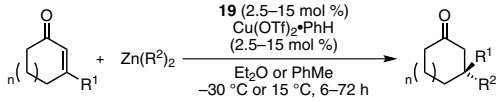
R^3	EWG	R^2	ee
Ph	Ac	Et	34%
n-Pent	Ac	Et	11%
Ph	NO_2	Et	37%

eq 4 *(Ref. 11b)*



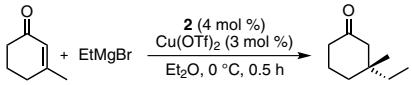
Cat.	Time	Conv.	ee
15	48 h	85%	96%
19	6 h	94%	93%

eq 5 *(Ref. 20)*



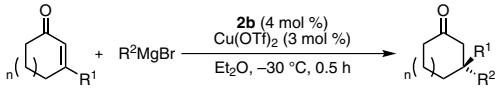
n	R^1	R^2	Yield	ee
1	Me	*n*-Bu	83%	86%
1	4-penten-1-yl	Et	92%	84%
1	PhC≡C	Et	78%	74%
2	Me	Et	83%	85%
2	Me	*n*-Bu	67%	77%
2	*n*-Bu	Et	81%	76%
3	Me	Et	34%	54%
1	Ph	Et	89%	94%
1	4-MeOC$_6$H$_4$	Me	89%	90%
2	Ph	Me	88%	96%

eq 6 *(Ref. 20)*



2	Conv.	ee
a	85%	81%
b	99%	80%
r	90%	90%

eq 7 *(Ref. 25)*



n	R^1	R^2	Yield	ee
1	Me	*n*-Bu	*a*	77%
1	Me	3-buten-1-yl	80%	90%
1	Me	*i*-Bu	72%	96%
1	Me	*i*-Pr	77%	77%
1	Me	*c*-Pent	80%	85%
1	Me	Cy	79%	74%
1	Me	Ph	61%	66%
2	Me	Et	*a*	82%
0	Me	Et	90%	46%
1	Et	Me	67%	68%
1	3-buten-1-yl	Et	84%	69%
1	*i*-Bu	Et	69%	81%
1	Ph	Et	87%	72%
1	Me[b]	Et	85%	82%

[a] 99% conversion in each case. [b] 3,5,5-Trimethyl-2-cyclohexenone was used.

eq 8 *(Ref. 25)*

The main limitations of this catalytic process are the high loading (up to 15 mol %) required for higher-membered-ring analogues (cycloheptenones and cyclooctenones) and the fact that the unreactive Me_2Zn could not be used. Finally, it should be recalled that triorganoaluminum reagents afford equally good results with phosphoramidites[21] or the more recently developed chelating arylsulfonyloxy carbenes.[22]

3.2. Cu-ACA with Grignard Reagents: A Practical Process for Generating All-Carbon Chiral Quaternary Centers

The Cu-catalyzed conjugate addition of Grignard reagents has been fully studied with a variety of phosphorus-based ligands.[14a,b,23] Two of the interesting economical aspects of these nucleophiles, as compared to their zinc or aluminum counterparts, are: (i) They exhibit good reactivity with only a slight excess needed to complete the addition (without any loss of organic material), and (ii) they are readily accessible and highly tunable (commercially or not). Their use in combination with hydroxyalkylimidazolinium carbenes derived from **2** has recently been studied by our groups. In the case of simple enones, such as 2-cyclohexenone, hydroxyalkylimidazolinium salts **2** afforded moderate results (50–70% ee's).[24] However, with 3-substituted cyclic enones the results were excellent.[25] This is quite remarkable, since the resulting adduct in each case possesses an all-carbon chiral quaternary center.[26] Among the available library of carbene precursors **2** (see Scheme 3), hydroxyalkylimidazolinium salts **2a,b** and **2r** were best for the addition of EtMgBr to 3-methyl-2-cyclohexenone (**eq 7**).[25] From a practical point of view, it is interesting to note that imidazolinium salt **2** is directly deprotonated to the carbene, with the Grignard reagent itself acting as the base.

Although similar results can be obtained with triorganoaluminum reagents,[21,22] the higher structural tunability of Grignard reagents makes this approach particularly attractive as illustrated in **eq 8**.[25] The best enantioselectivities were observed for primary and secondary alkyl Grignards and six-membered- or higher-ring enones (ee's ranged from 68% to 96%). Interestingly, PhMgBr also underwent conjugate addition, albeit with moderate ee (66%). The limitation of this catalytic system is related to the lower selectivity observed for cyclopentenone and the lack of reactivity of bulkier Grignard reagents such as *tert*-butylMgBr. It should be noted that the Rh-catalyzed addition of $PhB(OH)_2$ does not work with these types of enones.[27]

In the course of these studies, we made the observation that dienones could undergo a 1,4 or 1,6 conjugate addition, depending on the type of organometallic reagent and copper catalyst used (**Scheme 6**).[28] With classical phosphoramidite ligands, only the 1,6 adduct is obtained in moderate-to-good enantioselectivity, both with diorganozinc and triorganoaluminum reagents.[28] This is the expected way of addition, in view of previous achiral reports on polyenones.[29] However, with carbene **2b'** (the chloride analogue of **2b**), the 1,4 adduct is predominant, or almost exclusive, if the reaction is run in CH_2Cl_2.[28] This 1,4 selectivity is unusual, and results in the formation of an all-carbon quaternary center, despite the fact that position 6 is less sterically crowded.

In view of this particular regioselectivity, various dienones and Grignard reagents were screened (**Scheme 7**).[28] In all cases, the enantioselectivities observed were very high, ranging from 92% to >99%. Of note, the steric factor predominated in the case of MeMgBr, leading to only the 1,6 adduct. Nevertheless, the 1,4 adduct could be obtained de novo with high regioselectivity by increasing the steric bias at position 6.

The resulting adducts could be used in further synthetic steps by taking advantage of the exocyclic unsaturation in each. As examples, some interesting enantioenriched building blocks have been elaborated (**Scheme 8**),[28] showing the versatility of this highly stereoselective synthetic approach that can be a promising synthetic tool in the total synthesis of natural products.[30]

4. Summary and Outlook

Chelating hydroxyalkyl and hydroxyaryl N-heterocyclic carbenes (NHCs) appear to be among the most efficient ligands in copper-catalyzed asymmetric conjugate additions. Not only do they have a strong accelerating effect on the reaction rate, but they also provide very high levels of enantioselection. In addition, they operate on various types of primary organometallics (e.g., Zn and Mg reagents), and offer an efficient and straightforward way for the construction of challenging, chiral, all-carbon quaternary centers. Most of these remarkable results are due to the high synthetic tunability and synthetic efficiency of NHCs. We can imagine that focusing efforts in the next decade on producing new and more powerful chelating NHCs could lead to promising breakthroughs for solving major hurdles in asymmetric catalysis.

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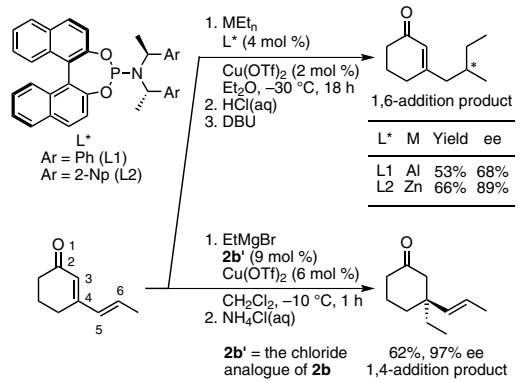
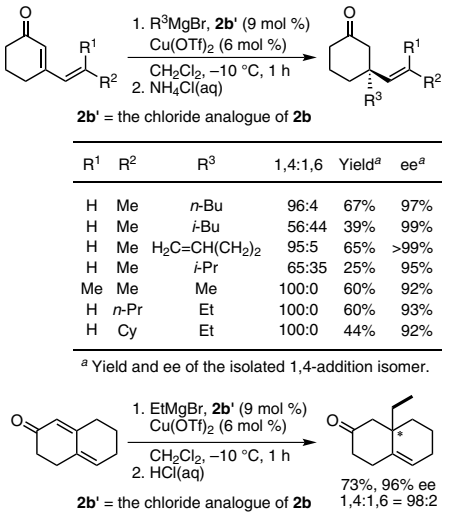
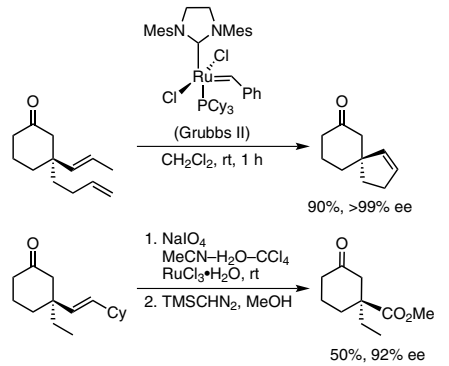


Scheme 6. 1,4- vs 1,6-Conjugate Addition of Organometallics to Dienones. *(Ref. 28)*



Scheme 7. Scope and Regioselectivity of the Conjugate Addition of Grignard Reagents to Dienones. *(Ref. 28)*



Scheme 8. Applications of the 1,4-Conjugate Addition of Grignard Reagents to Dienones in the Synthesis of Optically Enriched Building Blocks. *(Ref. 28)*

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Keywords: N-heterocyclic carbenes; asymmetric conjugate addition; copper catalysis; chiral quaternary centers; organometallic reagents.

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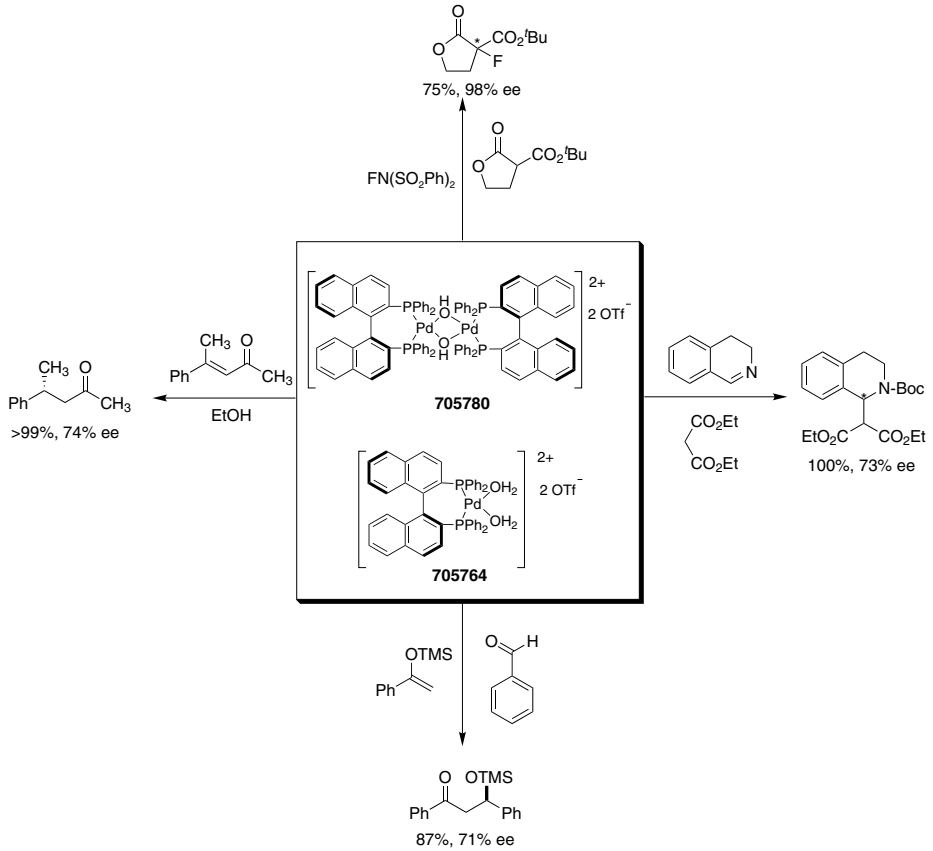

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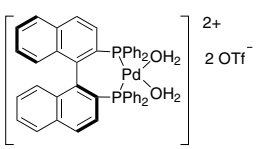

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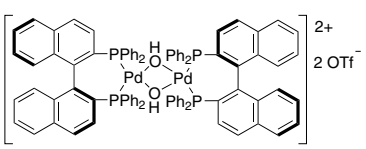

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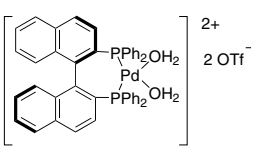

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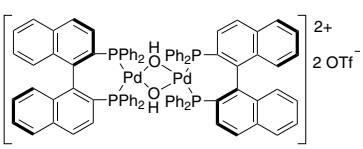

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OPENING NEW FRONTIERS IN SYNTHESIS AND CATALYSIS

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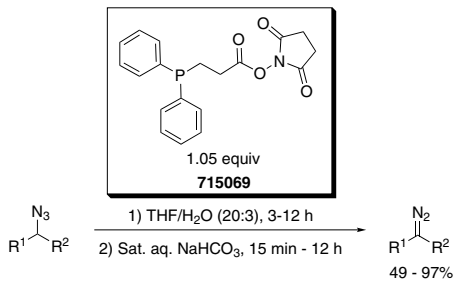
Phosphine for the Conversion of Azides into Diazo Compounds

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

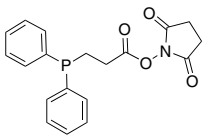


Myers, E. L; Raines, R. T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2359.

_N_-Succinimidyl 3-(diphenylphosphino)propionate, 95%

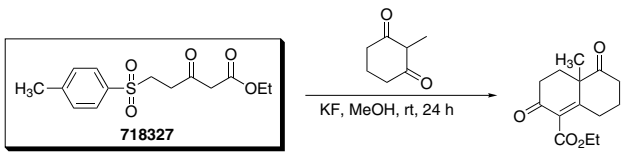
715069 1 g, 5 g

[*170278-50-9*]
$C_{19}H_{18}NO_4P$
FW: 355.32



Stable Precursor for Nazarov's Reagent

Nazarov's reagent is a commonly used annulating agent, but its synthesis is often fraught with poor yields or difficulties isolating the material. De Risi and coworkers recently reported a bench-stable powder that can be demasked under various conditions to generate Nazarov's reagent in situ.

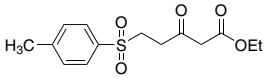


Benetti, S. et al. *Synlett* **2008**, 2609.

Ethyl 5-[(4-methylphenyl)sulfonyl]-3-oxopentanoate, 95%

718327 1 g

$C_{14}H_{18}O_5S$
FW: 298.35



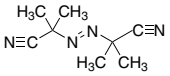
More NEW Solutions of Common Reagents

Every researcher has experienced the frustration of using on a regular basis some lab reagent that is annoying to handle: It might be difficult to weigh out, extremely volatile, prone to static, or noxious. Sigma-Aldrich has designed a series of solutions intended to make many of these common reagents easier to measure, handle, and dispense.

2,2′-Azobis(2-methylpropionitrile) solution, 0.2 M in toluene

714887 100 mL

[*78-67-1*]
$C_8H_{12}N_4$
FW: 164.21



Iodine monochloride, 1 M in acetic acid

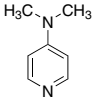
714836 100 mL

[*7790-99-0*]
ICl
FW: 162.36

4-(Dimethylamino)pyridine solution, 0.5 M in ethyl acetate

714720 100 mL

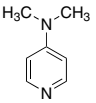
[*1122-58-3*]
$C_7H_{10}N_2$
FW: 122.17



4-(Dimethylamino)pyridine solution, 0.5 M in THF

714844 100 mL

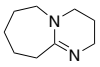
[*1122-58-3*]
$C_7H_{10}N_2$
FW: 122.17



1,8-Diazabicyclo[5.4.0]undec-7-ene solution, 1 M in ethyl acetate

714860 100 mL

[*6674-22-2*]
$C_9H_{16}N_2$
FW: 152.24



1,8-Diazabicyclo[5.4.0]undec-7-ene solution, 1 M in THF

714852 100 mL

[*6674-22-2*]
$C_9H_{16}N_2$
FW: 152.24

Acetaldehyde solution, 5 M in THF

719099 50 mL

[*75-07-0*]
C_2H_4O
FW: 44.05

Carbon disulfide, 5 M in THF

721476 50 mL

[*75-15-0*]
CS_2
FW: 76.14

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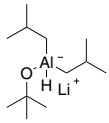
"PLEASE BOTHER US."

Joe Porwoll, President
Aldrich Chemical Co., Inc.

Dr. Biagetti Matteo from GlaxoSmithKline kindly suggested that we make lithium diisobutyl-*t*-butoxyaluminum hydride (LDBBA). LDBBA is an effective reducing agent for the conversion of esters into aldehydes without the problematic over-reduction or the inconvenience of requiring lower temperatures.

Kim, M. S.; Choi, Y. M.; An, D. K. *Tetrahedron Lett.* **2007**, *48*, 5061.



718386

718386 **Lithium diisobutyl-*t*-butoxyaluminum hydride (LDBBA), 0.5 M in THF-hexanes** 25 mL, 100 mL

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

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

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ABOUT OUR COVER

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

Paul Cézanne (1839–1906), who painted ***Landscape near Paris*** (oil on canvas, 50.2 × 60 cm) around 1876, was born in Aix-en-Provence in 1839. His father, a prosperous businessman, decided that his only son should become a lawyer. Cézanne attended the Aix law school, but preferred classes at the Musée d'Aix (now the Musée Granet) and decided on a life as an artist instead.

In 1861, Cézanne, encouraged by his boyhood friend, the novelist Émile Zola, traveled to Paris. There, he frequented the Salon, studied the old masters, and copied Delacroix at the Louvre. He also forged friendships with many important artists, one of whom, Camille Pissarro, became a pivotal, lifelong influence on Cézanne.

Cézanne exhibited with the impressionists in 1874 and 1877. Our cover possibly painted in the company of Pissarro in Auvers-sur-Oise, a northwestern suburb of Paris, was completed sometime between the two exhibitions. The work clearly denotes Cézanne's departure from his early romantic and realist influences, and displays his enduring interest in *plein-air* painting. In this work, Cézanne placed an emphasis on the observation of nature and the rendering of light and atmospheric effects. He achieved structure by applying paint directly to the canvas, recording his response to the sensation of color.

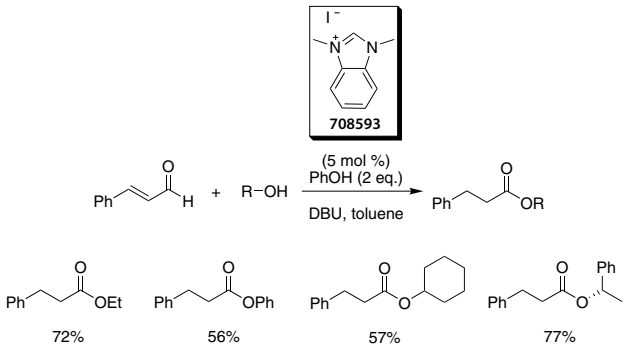
This painting is part of the Chester Dale Collection at the National Gallery of Art, Washington, DC.

N-Heterocyclic Carbene Organocatalysts

Organocatalysis has been an active field of research with over 2,000 publications in the past 10 years. Interest in this relatively new field derives from the many advantages of organocatalysis such as easy experimental procedures, reduction of chemical waste, avoidance of metal contamination in the product, and cost saving from not using expensive metals for the catalysis.

Scheidt and coworkers have developed a series of N-heterocyclic carbene organocatalysts for various reactions. These catalysts are efficient, and the chiral ones have given rise to good enantioselectivities.

In 2005, Audrey Chan and Karl A. Scheidt reported the transformation of unsaturated aldehydes into saturated esters in good yields by using as low as 5 mol % of an N-heterocyclic carbene catalyst.



Reference:
Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905.

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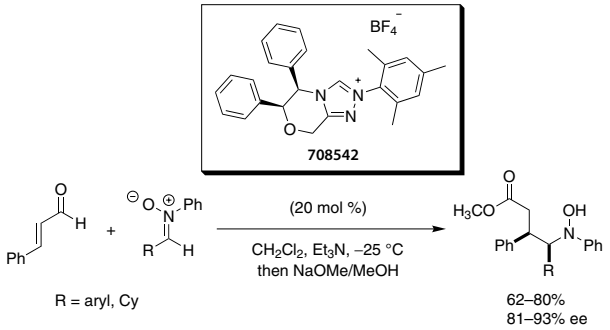
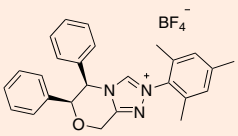
Recently, Phillips et al. reported the utilization of a chiral triazole for the enantioselective addition of homoenolates to nitrones affording γ-amino esters. This reaction is very versatile and tolerates electron-rich and electron-poor groups on the aldehyde. Using 20 mol % of the chiral triazole at –25 °C affords the desired products in good yields and selectivities.



Reference:
Phillips, E. M. et al. *J. Am. Chem. Soc.* **2008**, *130*, 2416.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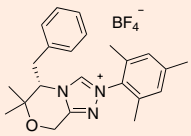
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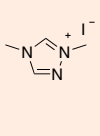
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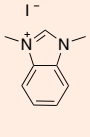
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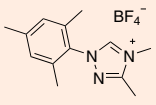
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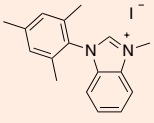
708585

Discovering New Reactions with N-Heterocyclic Carbene Catalysis


Mr. Eric M. Phillips


Dr. Audrey Chan


Professor Karl A. Scheidt

*Eric M. Phillips, Audrey Chan, and Karl A. Scheidt**
Department of Chemistry
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Outline

1. Introduction

Inspired by advances in our understanding of biological processes, new reactions employing organic molecules as catalysts have grown significantly over the last two decades.[1] In the broadest of terms, the most successful of these catalysts can be classified either as Brønsted acids,[2,3] hydrogen-bond donors,[4–7] or Lewis bases.[8–11] Each of these catalytic manifolds activates substrates in biological settings and provides an inspiring blueprint to create smaller, synthetic versions of these impressive biocatalysts. Lewis base catalysis is presently an exciting area of research and encompasses a wide variety of strategies to initiate both established and new chemical processes.[12,13] An elegant and key biological transformation utilizes the cofactor thiamine, a coenzyme of vitamin B_1, to transform α-keto acids into acetyl CoA, a major building block for polyketide synthesis. In this process, a normally electron-deficient molecule (e.g., pyruvic acid) is converted into an intermediate that possesses electron density on the carbon atom that was initially part of the carbonyl system. These carbonyl or acyl anions are unusual since they have "umpolung" (reversed polarity) when compared to the initial keto acids. In 1954, Mizuhara and Handler proposed that the active catalytic species of thiamine-dependent enzymatic reactions is a highly unusual divalent carbon-containing species,[14] later on referred to as an N-heterocyclic carbene (NHC). An alternative description of the active thiamine cofactor employs the term zwitterion, which can be viewed as a resonance form of the carbene description. This unique cofactor accomplishes fascinating Lewis base catalyzed transformations by utilizing the lone pair of electrons at C-2.

In the early 1960s, Wanzlick and co-workers realized that the stability of carbenes could be dramatically enhanced by the presence of amino substituents, and they attempted to prepare a carbene center at C-2 of the imidazole ring.[15,16] However, only the dimeric electron-rich olefin was isolated. Later on, Wanzlick's group demonstrated that potassium *tert*-butoxide can deprotonate imidazolium salts to afford imidazol-2-ylidenes, which can be trapped with phenyl isothiocyanate and mercury salts.[17–19] However, Wanzlick's group never reported the isolation of the free carbene. Following these results, Arduengo et al. isolated in 1991 a stable crystalline N-heterocyclic carbene by the deprotonation of 1,3-di(1-adamantyl)imidazolium chloride with sodium or potassium hydride in the presence of a catalytic amount of either potassium *tert*-butoxide or dimethyl sulfoxide.[20] The structure was unequivocally established by single-crystal X-ray analysis, and the carbene was found to be thermally stable, which stimulated extensive research in this field.

The nature of the stabilization is ascribed to the steric and electronic effects of the substituents: The two adamantyl substituents hinder reactions of the carbene center with external reagents as well as prevent dimerization. In 1992, Arduengo et al. expanded this carbene class by successfully isolating the carbene from 1,3,4,5-tetramethylimidazolium chloride by treating the latter with sodium hydride and catalytic amounts of potassium *tert*-butoxide in tetrahydrofuran.[21] The successful isolation of carbenes with less bulky substituents demonstrates that electronic factors may have greater impact on the stability of the carbene than steric ones. Such electronic factors operate in both the π and σ frameworks, resulting in a "push-pull" synergistic effect to stabilize the carbene. π donation into the carbene from the out-of-the-plane π orbital of the heteroatoms adjacent to C-2 stabilizes the typical electrophilic reactivity of carbenes. The electronegative heteroatoms adjacent to C-2 provide additional stability through the framework of σ bonds, resulting in a moderation of the nucleophilic reactivity of the carbene (**Figure 1**).[22] The combination of these two effects serves to increase the singlet–triplet gap and stabilize the singlet-state carbene over the more reactive triplet-state one.

The electronic properties of NHCs are a key determinant of the unique reactivity of these catalysts. Lewis bases are normally considered as single electron-pair donors. However, the singlet

carbenes of NHCs are distinct Lewis bases that have both σ basicity and π acidity characteristics. These attributes allow for the generation of a second nucleophile in the flask. Nucleophilic addition of the carbene to an aldehyde results in the formation of a new nucleophile. The "doubly" nucleophilic aspect is unique to the carbenes. The combination of these characteristics allows NHCs to react as powerful nucleophiles, which has driven the development of a distinct class of catalytic processes during the last decade. This review highlights our work in this young and promising field.

2. Acyl Anions

The earliest application of these unique Lewis bases was the development of the benzoin reaction.[23] This umpolung process utilizes a thiamine-related NHC as a nucleophilic catalyst. In 1943, Ugai and co-workers reported that thiazolium salts can catalyze the self-condensation of benzaldehyde to produce benzoin.[23] This process is clearly related to the earliest reports of laboratory organocatalysis from Wöhler and Liebig in 1832 detailing the cyanide-catalyzed benzoin reaction.[24] Based on Ugai's report, Breslow proposed the mechanism in which the active catalytic species is a nucleophilic carbene derived from a thiazolium salt to generate the carbanion known as the Breslow intermediate.[1b] In 1966, Sheehan and Hunneman reported the first investigations into an asymmetric variant of the benzoin condensation employing a chiral thiazolium salt as precatalyst.[25a] Most recently, Enders and Kallfass accomplished the first high-yield and highly enantioselective intermolecular benzoin condensation (**Scheme 1**).[25b] This seminal work by Enders on carbene catalysis using *triazolium* salts focused the interest of the community on these unique structures and moved interest away from thiazolium catalysts.

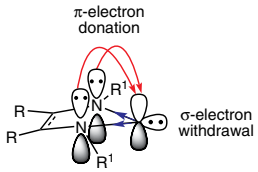
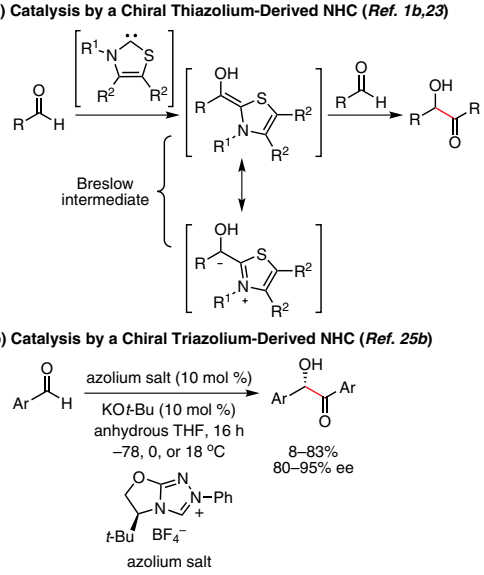
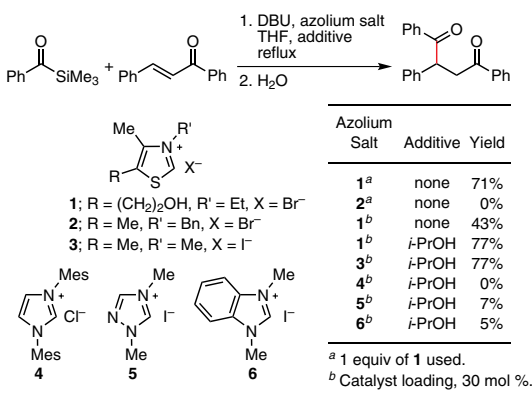


Figure 1. Proposed Stabilization of N-Heterocyclic Carbenes through σ and π Electronic Effects. *(Ref. 22)*



Scheme 1. Asymmetric Benzoin Condensation.



Azolium Salt	Additive	Yield
1[a]	none	71%
2[a]	none	0%
1[b]	none	43%
1[b]	*i*-PrOH	77%
3[b]	*i*-PrOH	77%
4[b]	*i*-PrOH	0%
5[b]	*i*-PrOH	7%
6[b]	*i*-PrOH	5%

[a] 1 equiv of **1** used.
[b] Catalyst loading, 30 mol %.

eq 1 *(Ref. 36–38)*

2.1. Stetter Reactions

In the 1970s, Stetter demonstrated that catalysis with thiazolium species can be employed to accomplish the addition of acyl anions to 1,4-conjugate acceptors.[26] This transformation is a useful carbon–carbon-bond-forming strategy that has attracted the attention of researchers interested in producing 1,4-dicarbonyl species. Like the benzoin reaction, the addition of an NHC to an aldehyde generates the acyl anion equivalent, and this initial step is typically facile due to the highly electrophilic nature of the aldehyde. However, this electrophilicity is also detrimental to processes other than dimerization in that multiple side-products are formed, *because the aldehyde is at least as reactive as the secondary electrophile needed for a benzoin or Stetter reaction*. A possible approach to circumvent this problem is to utilize acylsilanes.[27–29] Disclosures by Heathcock's[30] and then Degl'Innocenti's[31] groups have shown that, upon exposure of acylsilanes to charged nucleophilic species (e.g., fluoride, cyanide), the carbonyl carbon can participate in alkylation reactions or conjugate additions. Acylsilanes have become a useful alternative to aldehydes in the generation of acyl anions, because the sterically congested nature of the silyl group precludes problematic dimerization reactions (e.g., benzoin reaction).[32,33]

Inspired by this early acylsilane work of Heathcock and Degl'Innocenti, we began a research program in 2002 directed toward the investigation of catalytic carbonyl addition reactions. Well-established routes to acyl anion equivalents from the combination of aldehydes and NHCs have been heavily investigated,[33,34] and we hypothesized that a complementary approach utilizing acylsilanes would enhance known reactions (e.g., Stetter reaction) and provide a platform for the discovery of new reverse polarity. In this process, nucleophilic addition of an NHC to an acylsilane would facilitate a Brook 1,2 rearrangement[35] with concomitant formation of the acyl anion equivalent or Breslow intermediate. However, at the onset of our investigations, it was unknown if a nucleophile larger than fluoride or cyanide would add to the sterically congested carbonyl carbon of the acylsilane, let alone facilitate the requisite 1,2 migration of the silyl group from the carbon to the oxygen.

We first explored the NHC-catalyzed 1,4 addition of acylsilanes to chalcone. The use of stoichiometric amounts of thiazolium salt **1** and DBU led to the formation of the desired 1,4-diketone in 71% yield from benzoyltrimethylsilane and chalcone (**eq 1**).[36–38] While this result was reassuring, rendering

this reaction catalytic in azolium salt was not straightforward. When the amount of **1** was reduced to 30 mol %, the isolated yield became only 43%. Interestingly, no product was observed when one equivalent of thiazolium **2** was employed. This lack of catalytic activity led us to believe that the alcohol moiety in **1** played a pivotal role in the reaction. Indeed, upon addition of four equivalents of 2-propanol to an acylsilane reaction containing 30 mol % **1**, the isolated yield improved to 77%. A similar yield was obtained with thiazolium **3** and four equivalents of 2-propanol, further supporting our contention. Attempts to incorporate other azolium salt derivatives such as imidazolium, benzimidazolium, and triazolium salts proved to be unsuccessful and highlighted the importance of the catalyst structure for this sila-Stetter process. This divergent reactivity among different azolium salts provided a strong impetus to explore varying catalyst structures in several different reaction pathways.

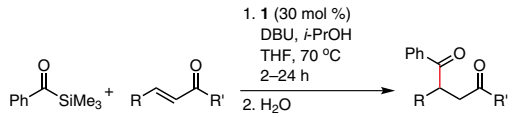
As illustrated, this catalytic acyl anion addition is compatible with a wide range of α,β-unsaturated ketones (**eq 2**).[36] Both electron-withdrawing and electron-donating substituents are accommodated on either aryl ring of the chalcone core and give rise to good yields. Other classes of α,β-unsaturated carbonyl electrophiles emphasized the utility of this sila-Stetter reaction. Acylsilanes reacted with diethyl fumarate and dimethyl maleate to furnish the corresponding conjugate addition products in good yields. Unsubstituted α,β-unsaturated compounds such as methyl vinyl ketone and ethyl acrylate were also competent coupling partners in this process. The compatibility of a wide range of highly reactive unsaturated carbonyl components is an impressive feature of this reaction. These compounds are notorious for being susceptible to polymerization reactions and are exposed to multiple nucleophilic species in solution. In spite of this precarious situation, the acyl anion addition products are isolated in good yields.

The reaction was then examined with respect to the acylsilane component (**eq 3**).[36] Aromatic acylsilanes with methyl or chloro substitution are competent reaction partners, producing the desired product in 70% and 82% yield, respectively. Interestingly, para-chloro substitution renders the acylsilane most reactive, most likely due to the increased stabilization of the anion generated in the reaction. Acylsilanes containing enolizable protons are successful substrates for this reaction as well. Several 1,4-dicarbonyl compounds can be synthesized with varying substitution patterns under extremely mild conditions. The combination of an NHC and acylsilane bypasses the need for toxic cyanide catalysis and provides a highly practical and safe method for the construction of 1,4-dicarbonyl products, which can be further telescoped to provide useful furans and pyrroles (**Scheme 2**).[37,38]

2.2. Imine Additions

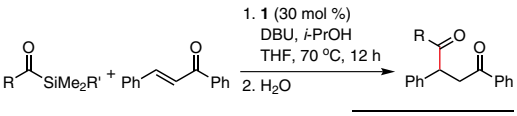
We succeeded in enhancing the utility of the Stetter reaction with acylsilanes in our first carbene-catalyzed reaction. These initial studies were a pivotal step for our catalysis program and demonstrated the ability to access Breslow-type intermediates *without aldehydes*. Our early successful 1,4 additions allowed us to explore 1,2 additions as a means to fully realize the potential of the NHC-catalyzed generation of acyl anions from acylsilanes. Since we could access competent acyl anions without reactive carbonyl groups present, there was a strong chance that new electrophile classes could be employed to engage these useful nucleophilic intermediates formed in situ. An appropriate manifold for the investigation of 1,2 additions would be the reaction of acylsilanes with activated imines. In addition to expanding the breadth of possible reaction platforms, a successful application would produce valuable α-amino ketones directly in a particular oxidation state.[39–41]

The choice of imine protecting group proved pivotal to the success of the reaction. Attempts to incorporate *N*-Bz, *N*-sulfinyl, and *N*-sulfonyl imines were fruitless, whereas *N*-phosphinoyl imines provided the right balance of activation to be successful substrates as reported by Weinreb and Orr.[42] This stark contrast in reactivity demonstrates a crucial consideration of any reaction utilizing carbenes as Lewis base catalysts, namely selective reaction of the NHC with one of two electrophiles present. During these carbene processes, there is the primary electrophile (e.g., the aldehyde) and a secondary electrophile, in this case the imine. Importantly, an irreversible reaction with the imine would preclude the desired productive carbene addition to the acylsilane. This intrinsic reaction characteristic makes the development of new carbene-catalyzed processes a significant challenge. In contrast, when a Lewis acid fails to promote a reaction, a stronger Lewis acid can be employed to further activate the electrophile. However, the failure of an NHC to catalyze a reaction cannot



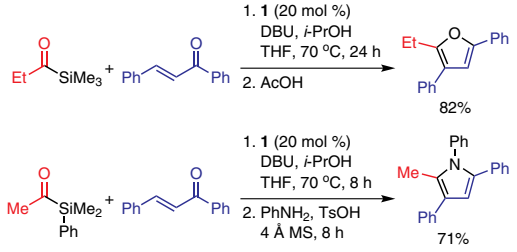
R	R'	Yield
Ph	Ph	77%
Ph	4-MeOC$_6$H$_4$	80%
Ph	4-ClC$_6$H$_4$	82%
4-MeC$_6$H$_4$	Ph	84%
4-ClC$_6$H$_4$	Ph	74%
H	Me	75%
H	EtO	72%
(*E*)-EtO$_2$C	EtO	65%
(*Z*)-MeO$_2$C	MeO	72%

eq 2 *(Ref. 36)*



R	R'	Yield
Ph	Me	77%
4-ClC$_6$H$_4$	Me	82%
4-MeC$_6$H$_4$	Me	70%
Ph	Ph	61%
Me	Ph	70%
Cy	Ph	63%

eq 3 *(Ref. 36)*

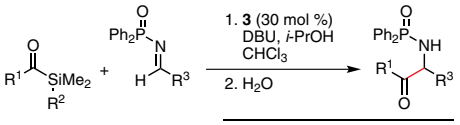


Scheme 2. Single-Flask Furan and Pyrrole Synthesis by the Conjugate Addition of Acylsilanes to α,β-Unsaturated Ketones. *(Ref. 37,38)*

be solved by simply increasing the nucleophilicity of the catalyst or the electrophilicity of the reaction partner, as there are too many facets of the reaction that have to be considered, such as primary and secondary electrophiles as well as key proton-transfer events.

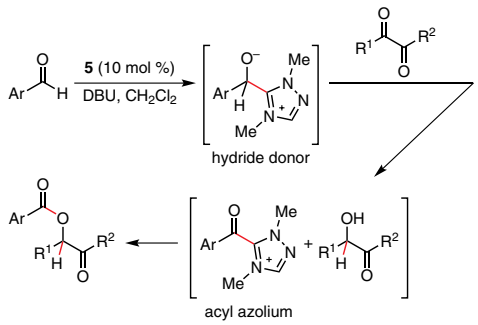
The optimal reaction conditions turned out to be similar to those of the 1,4-addition reaction. A wide variety of substitution was accommodated on the acylsilane (**eq 4**).[43] Both alkyl and aryl acylsilanes provided the desired α-amino ketones in good yields. Several phosphinoyl imines with various substitution patterns, including both electron-withdrawing and electron-donating groups, were suitable substrates for this transformation. In addition, aromatic heterocycles such as thiophene provided the desired products in high yields. Unfortunately, *N*-phosphinoyl imines derived from aliphatic aldehydes do not furnish the desired products. This limitation is attributed to the ability of the imine to readily undergo conversion into the more stable enamide, rendering it unsusceptible to nucleophilic addition.

The strategy of employing acylsilanes with NHCs as acyl anion precursors has allowed for the successful addition of acyl anion equivalents to conjugate acceptors and activated imines. This catalytic process generates 1,4-diketones and α-amino ketones in good-to-excellent yields. This initial discovery by our group propelled us to investigate new NHC-catalyzed reactions and polarity reversal (umpolung) strategies.



R^1	R^3	Yield
Ph	Ph	93%
Ph	4-MeC_6H_4	94%
Ph	4-$MeOC_6H_4$	86%
Ph	2-ClC_6H_4	77%
Ph	4-ClC_6H_4	85%
Ph	thien-2-yl	80%
4-MeC_6H_4	Ph	81%
4-ClC_6H_4	Ph	90%
Me	Ph	87%
$BnO(CH_2)_3$	Ph	63%

eq 4 *(Ref. 43)*



Ar	R^1	R^2	Yield
Ph	Ph	MeO	78%
furan-2-yl	Ph	MeO	73%
4-FC_6H_4	Ph	MeO	71%
4-$MeOC_6H_4$	thien-2-yl	EtO	73%
4-$MeOC_6H_4$	4-ClC_6H_4	EtO	81%
Ph	Ph	Ph	83%

Scheme 3. Hydroacylation of α-Keto Esters and 1,2-Diketones. *(Ref. 44)*

3. Oxidation Reactions

The combination of NHCs and aldehydes has led to useful new chemistry in our laboratory beyond the area of umpolung catalysis. While a plethora of the existing carbene catalysis is focused on polarity reversal chemistry, alternative modes of reactivity are possible, and have indeed been explored. One different avenue is oxidation of the initial tetrahedral intermediate formed from the addition of an NHC to an aldehyde. Collapse of this intermediate would generate an acyl azolium species with concomitant formation of a hydride equivalent.

In 2006, we disclosed the application of this route in the context of an NHC-catalyzed hydroacylation (**Scheme 3**).[44] In this Tishchenko-like process, an aromatic aldehyde–NHC adduct generates a hydride equivalent in the presence of an organic oxidant, an α-keto ester. The initial collapse of the tetrahedral intermediate to produce an activated ester is unprecedented, and adds an interesting facet to the potential avenues of NHC-catalyzed reactions. Once the ketone undergoes reduction, the resulting alkoxide regenerates the catalyst through addition to the acyl azolium intermediate. In aprotic solvents, such as CH_2Cl_2, the hydroacylation products are isolated in good yields when triazolium precatalyst **5** is used. Additionally, when the reaction is conducted in MeOH, the α-hydroxy ester can be isolated as the sole product due to catalyst regeneration by the solvent. One limitation of this methodology is the requirement that the aldehyde starting material possess a nonenolizable α-carbon atom.

In order to further explore this reaction pathway, a crossover experiment was performed with an α-keto ester and 0.5 equiv each of deuterated benzaldehyde and *p*-tolualdehyde.[44] In this reaction, all four potential products were observed, supporting our contention that reduction and acylation are separate steps in the reaction pathway. Additionally, when benzoin is exposed to the reaction conditions, the hydroacylation product is isolated suggesting that the benzoin reaction is reversible and may be operating under the reaction conditions. In this new reaction, the carbene catalyst is responsible for two distinct processes: oxidation and acylation. The novelty of this reaction is further illustrated through the combination of two components (aldehyde and ketone) participating in a disproportionation reaction.

Following this initial report, we focused on the use of more conventional oxidants to facilitate the formation of acyl azoliums. An interesting, but underutilized, approach to unsaturated esters has been the Corey–Gilman oxidation. In this process, an allylic alcohol is oxidized in the presence of 10 to 20 equivalents of cyanide and MnO_2, first to the corresponding aldehyde and then to the ester. This streamlined process to convert alcohols into esters would be incredibly useful if the reaction avoided the use of superstoichiometric amounts of cyanide. Our previous success of replacing cyanide with NHCs in the context of the Stetter reaction encouraged us to pursue a similar strategy with regard to this oxidation. Importantly, MnO_2 was chosen in order to allow the presence of the inactivated nucleophilic alcohol required for catalyst regeneration.[45]

We chose to evaluate this process to demonstrate the use of carbenes as oxidation co-catalysts and to develop a practical

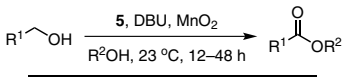
oxidation procedure. When butanol is used as solvent, several allylic and benzylic alcohols are successfully oxidized to the corresponding unsaturated butyl esters with 10 mol % precatalyst **5** (**eq 5**).[45] In many cases, the nucleophilic alcohol may be too costly to use as solvent. In this circumstance, slight modifications to the reaction conditions allow the alcohol to be used as a reagent as opposed to solvent. In toluene, just 5 equivalents of the nucleophilic alcohol are required to facilitate ester formation.

During these initial carbene-catalyzed oxidation investigations, we recognized that the addition of an NHC to any aldehyde (activated or inactivated) should generate a transient benzylic-type alcohol! The catalyst itself is aromatic and should induce mild oxidations of the resulting intermediate. Indeed, the addition of azolium salt **5** to a variety of saturated aldehydes in the presence of MnO_2 and a nucleophilic alcohol enables oxidation of the aldehydes to their respective esters (**Scheme 4**).[46] It is noteworthy that aldehydes with electron-rich aromatic rings are accommodated under these reaction conditions, whereas typical Pinnick oxidation conditions result in significant chlorination of the aromatic ring. For example, when 3-(2,4,6-trimethoxyphenyl)propanal is oxidized using Pinnick conditions a substantial amount of monochlorination of the aromatic trimethoxyphenyl ring occurs, whereas under NHC-catalyzed conditions only the desired ester is produced.[47,48]

Interestingly, the use of a chiral NHC in this reaction offers the opportunity to desymmetrize meso diols through the in situ formation of chiral activated ester equivalents. In a proof of concept experiment, in the presence of triazolium salt **7** with the combination of K_2CO_3 and a proton sponge as a base, a meso diol is acylated with modest enantioselectivity (**eq 6**).[45] Problems with base-catalyzed intramolecular acyl-transfer reactions presumably inhibit higher selectivities for this process, but these initial results pave the way for carbene-catalyzed stereoselective acylation reactions using simple aldehydes.

4. Homoenolates

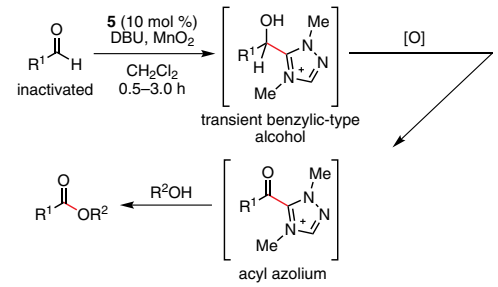
From 2003 onward, our substantial interest in accessing Breslow intermediates with acylsilanes and understanding the mechanistic aspects of this process stimulated our thinking about new potential applications of related structures. An intriguing possibility was the "extension" of the nucleophilic character at C-1 of the aldehyde to the distal site C-3 through a C–C multiple bond. In this approach, the addition of carbenes to aldehydes containing an additional unsaturation unit could relocate the electron density in the Breslow intermediate to the β carbon of the aldehyde (**Scheme 5**).[49] This transient nucleophile is a "vinylogous" carbonyl anion or a homoenolate.



R^1	R^2	Yield[a]
(*E*)-PhCH=CH	Me	95%
(*E*)-PhCH=CH	*i*-Pr	89%
(*E*)-PhCH=CH	$MeO(CH_2)_2$	82%
(*E*)-PhCH=CH	$TMS(CH_2)_2$	74%
(*E*)-PhCH=CH	$Cl_3C(CH_2)_2$	82%
(*E*)-PhCH=CH	*n*-Bu	93%
(*E*)-PhCH=CMe	*n*-Bu	91%
Ph	*n*-Bu	88%
2-Np	*n*-Bu	91%
furan-2-yl	*n*-Bu	73%
(*E*)-EtCH=CH	*n*-Bu	87%
(*E*)-EtO_2CCH=CH	*n*-Bu	65%
PhC≡C	*n*-Bu	85%

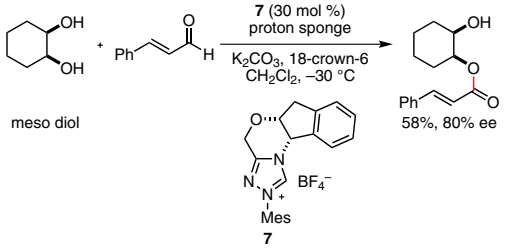
[a] Entries 1–5: **5** (15 mol %), R^2OH (5 equiv) in toluene as solvent; entries 6–13: **5** (10 mol %) in *n*-BuOH as solvent.

eq 5 *(Ref. 45)*

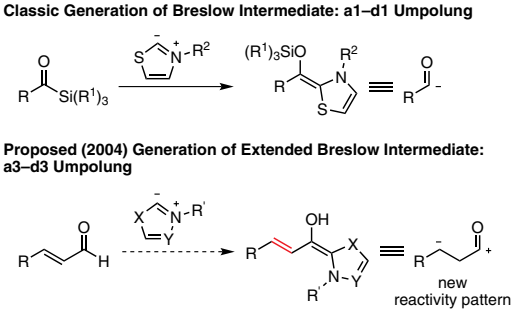


R^1	R^2	Yield
$BnCH_2$	Me	98%
$BnCH_2$	*n*-Pr	82%
$BnCH_2$	Cy	88%
$BnCH_2$	$TMSCH_2CH_2$	85%
$BnCH_2$	(*S*)-MeO_2CCHMe	74%
2-$PyCH_2CH_2$	Me	88%
2,4,6-$(MeO)_3C_6H_2CH_2CH_2$	Me	99%
1-methylinden-3-ylCH_2CH_2	Me	90%
n-Pent	Me	91%
$TBSOCH_2CH_2$	Me	94%
(*S*)-$TBSOCH_2CHMe$	Me	91%

Scheme 4. Oxidation of Inactivated Aldehydes to the Corresponding Esters via a Benzylic-Type Alcohol Intermediate. *(Ref. 46)*



eq 6 *(Ref. 45)*

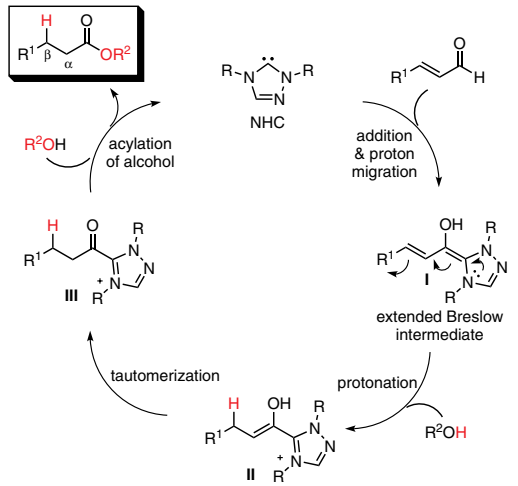


Scheme 5. Envisaged Generation of Vinylogous Carbonyl Anions (Homoenolates). *(Ref. 49)*

This type of reactivity has been exploited by our group[49] and others,[50,51] which has led to the disclosure of an extensive number of NHC-catalyzed homoenolate reactions over the last four years.

4.1. β Protonation

Our group began investigating this electronic reorganization with the goal of intercepting this possible homoenolate intermediate with a suitable electrophile for β functionalization and a suitable nucleophile for subsequent acylation.[49,52] We initially chose to explore this reaction with a simple electrophile: a proton. The proposed pathway for this process begins with the initial 1,2 addition of the NHC to the α,β-unsaturated aldehyde (**Scheme 6**).[49,52] Following proton migration, the electron density that would be typically located at the carbonyl carbon is extended to the β position with formation of the extended Breslow intermediate (**I**). Addition of a proton generates enol **II**, which tautomerizes to activated acylating agent **III**. In the presence of a nucleophile, the NHC catalyst is regenerated and the catalytic cycle is restarted. The obvious choice for a proton source is an alcohol that also serves as a nucleophile in the last step to promote catalyst turnover.

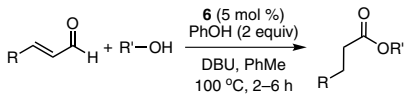


Scheme 6. Proposed Pathway for β Protonation. *(Ref. 49,52)*

Initial probing of this reaction was moderately successful. Exposure of cinnamaldehyde to 30 mol % **6**, DBU, and phenol in toluene led to a 55% isolated yield of the desired saturated ester. A serendipitous discovery was made when the reaction was run in $CHCl_3$, which had been passed through basic Al_2O_3 but not distilled. With phenol being used as the proton source, a large amount of the saturated ethyl ester was isolated. In hindsight, it became clear that the source of the ethanol was the chloroform, which uses ethanol as a stabilizer. With the knowledge that two alcohols can be used simultaneously (one as a proton source and one as the nucleophile), we quickly discovered that high yields could be obtained for this process when phenol is employed as a proton source and a second alcohol is used as a nucleophile.

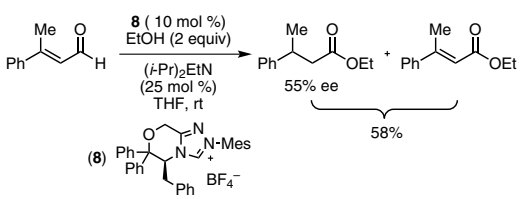
Under these new reaction conditions, which employ 5 mol % of azolium salt **6**, 2 equiv of phenol, and 4 equiv of the nucleophilic alcohol, a variety of saturated esters can be synthesized (**Scheme 7**).[49,52] Both secondary and primary alcohols are accommodated under the reaction conditions. Optically active alcohols retain their integrity in this process to generate enantioenriched esters. Not surprisingly, *tert*-butyl alcohol was unreactive. Additionally, the reaction tolerates a variety of α,β-unsaturated aldehydes with both alkyl and aryl substitution. Aldehydes with additional substitution at the α position, as well as substrates with β,β-diaryl substitution, afford the corresponding products in good yields. Our group has also explored asymmetric variants of this process.

This initial report demonstrated that homoenolate activity could be generated and utilized in a productive fashion. The formation of simple saturated esters provided a platform for the investigation of homoenolates and introduced our group to a new and exciting area of chemistry. Following the success of this reaction, we actively pursued new applications with these atypical nucleophiles. The most significant challenge encountered with these reactions is the vinylogous benzoin reaction. Homoenolate addition to an equivalent of unsaturated aldehyde starting material must be avoided in these reactions if a secondary electrophile is incorporated into a new reaction sequence. The most reasonable approach to this problem would be to increase the electrophilicity of this secondary electrophile. This adjustment, however, can make the addition of the NHC to the secondary electrophile more likely, thus inhibiting the reaction. These complications highlight the impressive nature of all homoenolate reactions reported to date and demonstrate the balance of electronic and steric effects that are required for future reaction development.



R	R'	Yield	R	R'	Yield
Ph	Et	72%	4-MeOC$_6$H$_4$	Bn	76%
Ph	Ph	56%	4-ClC$_6$H$_4$	Bn	71%
Ph	Bn	82%	*n*-Pr	Bn	90%
Ph	Cy	57%	(*E*)-MeCH=CH	Bn	70%
Ph	*a,b*	77%	*c*	Bn	82%
			d	Bn	82%

[a] (*S*)-1-Phenylethanol (99% ee) used.
[b] Ester product obtained with 99% ee.
[c] (*E*)-4-ClC$_6$H$_4$C(Ph)=CHCH=O utilized.
[d] (*E*)-PhCH=C(Me)CH=O employed.



Scheme 7. NHC-Catalyzed β Protonation. *(Ref. 49,52)*

4.2. Formal [3 + n] Cycloadditions

A carbene-catalyzed homoenolate addition that forms new carbon–carbon bonds would clearly be a valuable reaction and enhance the applicability of this process. An appropriate strategy would be to utilize an electrophile, which, upon homoenolate addition, generates a transient nucleophile to aid in catalyst regeneration (**Scheme 8**). In this vein, ylides contain the appropriate functionality, and the ability of these dipolar species to undergo cycloadditions is well-precedented.[53–56]

3-Oxopyrazolidin-1-ium-2-ides are stable compounds that can be prepared in gram quantities, and can thus be practical coupling partners[57–60] for the investigation of this reaction.[61] To our gratification, a variety of azolium salts catalyzed the reaction

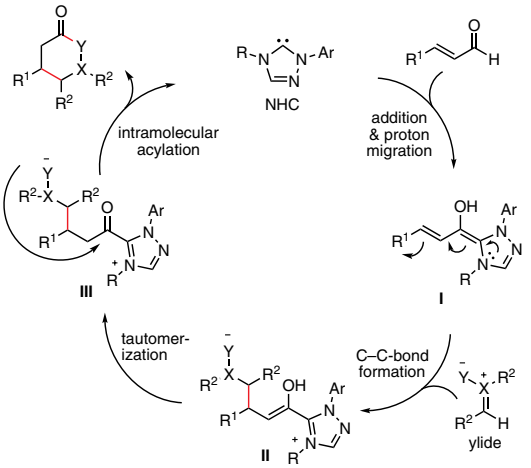
between cinnamaldehyde and the diphenyl-substituted azomethine imine in the presence of DBU with excellent diastereoselectivity albeit in low yields. The optimal reaction conditions were obtained using 20 mol % of azolium salt **9** and DBU in CH_2Cl_2 while heating the reaction at 40 °C (**eq 7**).[62] A survey of α,β-unsaturated aldehydes revealed that a variety of electron-rich aromatic rings are accommodated in the reaction. Unfortunately, electron-deficient unsaturated aldehydes are not compatible. β-Alkyl substitution and extended dienylic substitution are also tolerated. Investigation of the reaction with respect to the azomethine imine component demonstrated that several substitution patterns are allowed. However, azomethine imines derived from aldehydes with enolizable protons do not afford any tetrahydropyridazinone product. Successful azomethine imine substrates in this reaction typically possess phenyl substitution in the 5 position, primarily due to the insolubility of the unsubstituted analogues.

We investigated this reaction platform further with the incorporation of a second 1,3-dipole: nitrones. In addition to being well-known partners for cycloadditions,[63–66] successful homoenolate addition to these ylides would potentially produce γ-amino acid[67–69] derivatives as well as γ-lactams. While we were pleased to discover that the homoenolate addition does occur, the initial 6-membered-ring heterocyclic product was unstable toward chromatography. Addition of NaOMe to the reaction mixture upon consumption of starting material helped bypass this problem and afforded γ-hydroxy amino ester products (**Scheme 9**).[70] The products can be manipulated further with $Pd(OH)_2/C$ and H_2 to provide γ-amino esters. An impressive aspect of this reaction is the synthesis of optically active products with chiral azolium **10**. The high degree of asymmetric induction is surprising considering the distance between the reactive carbon atom and the stereogenic centers of the homoenolate intermediate.

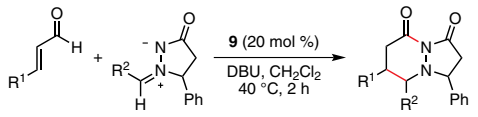
We then wondered whether this methodology could be extended to heteroatom electrophiles such as in a homoenolate-based amination reaction, which would constitute a reverse-polarity approach to creating β-amino carbonyl compounds. These carbonyl compounds are commonly synthesized through conjugate additions of nitrogen nucleophiles.[71–74] When we employed diazenes (RN=NR') as electrophilic amination partners, significant complications were encountered due to the reactive nature of the diazene functional group. A notable side product in these reactions was 1-benzoyl-2-phenylhydrazine [PhC(O)NHNHPh]. Based on the previously discussed hydroacylation and oxidation reactions, we posit that the initial tetrahedral aldehyde–carbene adduct can behave as a hydride source and perform conjugate reductions on the diazene. The damage to the outcome of the reaction is heightened by not only sacrificing the diazene, but an equivalent of the aldehyde as well. Fortunately, employing precatalyst **11** and lowering the temperature of the reaction circumvented these problems (**eq 8**).[75]

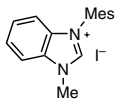
5. Enolate Chemistry

Our success with generating homoenolate reactivity using NHCs led us to believe that enolate generation and utilization were possible. The current mechanistic understanding of the homoenolate process includes the possible generation of a short-lived enol (**Scheme 10**, structure **II**).[76,77] The tautomerization of this enol followed by nucleophilic attack on the transient acyl azolium intermediate drives catalyst regeneration. This observation provides an opportunity to tap into the powerful ability of the carbene to functionalize the α, β, and carbonyl carbons of an α,β-unsaturated aldehyde in a single flask! Our



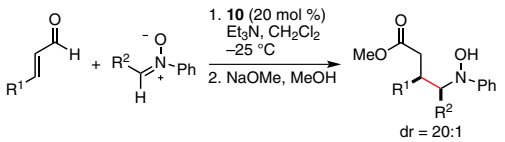
Scheme 8. Formal [3 + 3] Cycloadditions with Homoenolates.

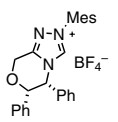




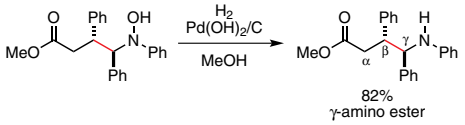
R^1	R^2	Yield
Ph	3-$MeOC_6H_4$	67%
Ph	4-FC_6H_4	82%
Ph	3-BrC_6H_4	78%
Ph	Ph	79%
4-$MeOC_6H_4$	Ph	76%
2-Np	Ph	77%
(*E*)-MeCH=CH	Ph	51%
n-Pr	Ph	67%

eq 7 *(Ref. 62)*





R^1	R^2	Yield	ee
Ph	Ph	70%	93%
Me	Ph	73%	94%
4-ClC_6H_4	Ph	78%	90%
4-$MeOC_6H_4$	Ph	72%	89%
Ph	4-MeC_6H_4	71%	90%
Ph	4-BrC_6H_4	68%	84%



Scheme 9. Homoenolate Additions to Nitrones and Elaboration of the Resulting Products into γ-Amino Esters. *(Ref. 70)*

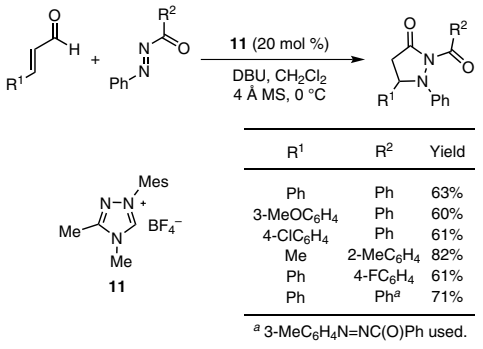
goal was to intercept this nucleophile (**II**) with a competent electrophile and thus expand the number of NHC-catalyzed reactions.

Toward this end, we synthesized substrates that would not only maximize the potential success of the reaction but also provide interesting structural motifs (**eq 9**).[77] This three-atom functionalization proceeded as envisaged in Scheme 10. While the β-protonation step is not well-understood, it has been observed that weaker bases, such as $(i\text{-Pr})_2$EtN, and their conjugate acids, are more accommodating in this process. An intramolecular Michael addition follows the β-protonation step and results in the construction of a five-membered ring. Under these conditions, catalyst regeneration is afforded by the O-acylation of the newly formed (second) enol. However, the addition of methanol is required to avoid hydrolysis of the initial labile lactone products and to facilitate purification. Importantly, when aminoindanol-derived precatalyst **7** is used in combination with $(i\text{-Pr})_2$EtN, excellent diastereo- and enantioselectivities are achieved for a wide range of substrates.

The success achieved with this highly diastereo- and enantioselective intramolecular NHC-catalyzed Michael addition led our group to investigate an intramolecular aldol reaction.[78,79] Readily prepared symmetrical 1,3-diketones undergo intramolecular aldol reactions to afford optically active cyclopentene rings. In this reaction, the enol generated from the addition of chiral, optically active NHC **10** to the aldehyde performs a desymmetrization of the 1,3-diketone. Acylation of the resulting alkoxide is coupled with a decarboxylation step to afford the cyclopentene adducts with excellent enantiocontrol (**eq 10**).[78,79] Importantly, degassing of the solvent leads to a dramatic increase in yield. In some cases, unsaturated acids are observed, and they are thought to originate from the oxidation of the homoenolate intermediate.

The high selectivity achieved with this system is believed to arise from a 6-membered hydrogen-bonded feature in the Breslow-type intermediate. The enol proton behaves as a bridge between the enol oxygen and the ketone oxygen, which predisposes the complex to undergo the aldol reaction and minimizes the nonbonding interactions between the catalyst and the keto group not undergoing attack. The regeneration of the catalyst is also a result of the hydrogen bonding in the adduct since an anti disposition of the alkoxide and acyl azolium groups in the adduct would inhibit subsequent intramolecular acylation.

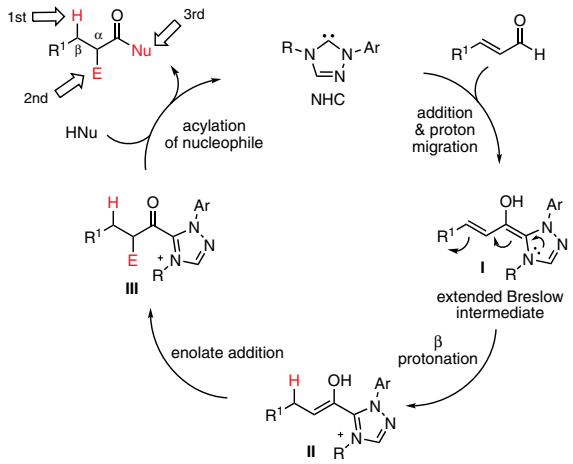
In order to demonstrate the intrinsic value of this desymmetrization process, we adapted this methodology to the synthesis of the bakkenolide family of natural products.[80,81] The bakkanes are comprised of a cis-fused 6,5-cyclic system with two quaternary stereogenic centers, one of which contains an angular methyl group. This key structural element provided an excellent opportunity to apply our methodology and provide a modern demonstration of the power of carbene catalysis in total synthesis.[82–84] The crucial NHC-catalyzed bond-forming



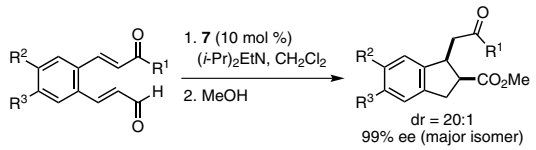
R^1	R^2	Yield
Ph	Ph	63%
3-MeOC$_6$H$_4$	Ph	60%
4-ClC$_6$H$_4$	Ph	61%
Me	2-MeC$_6$H$_4$	82%
Ph	4-FC$_6$H$_4$	61%
Ph	Ph[a]	71%

[a] 3-MeC$_6$H$_4$N=NC(O)Ph used.

eq 8 *(Ref. 75)*



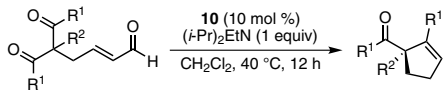
Scheme 10. Proposed Pathway for Enolate Formation and Three-Atom Functionalization. *(Ref. 77)*



R^1	R^2	R^3	Yield
Ph	H	H	69%
4-BrC$_6$H$_4$	H	H	62%
Ph	MeO	MeO	73%
Ph	F	H	68%
4-MeC$_6$H$_4$	H	H	80%
H	H	H	68%
Me	H	H	59%
Me	*a*	*a*	66%

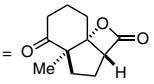
[a] Using (*E*,*E*)-MeC(O)CH=CH(CH$_2$)$_2$CH=CHC(O)H.

eq 9 *(Ref. 77)*



R^1	R^2	Yield	ee
Ph	Me	80%	93%
Ph	H_2C=CHCH$_2$	70%	83%
Ph	H_2C=C(Me)CH$_2$	69%	83%
Ph	(*E*)-PhCH=CHCH$_2$	64%	82%
4-ClC$_6$H$_4$	Me	76%	94%
a	*a*	51%	96%

[a] dr = 20:1; major product =



eq 10 *(Ref. 78,79)*

event occurs early in the synthesis and furnishes appropriate functionality to complete the synthesis of bakkenolides I, J, and S (**Scheme 11**).[79b]

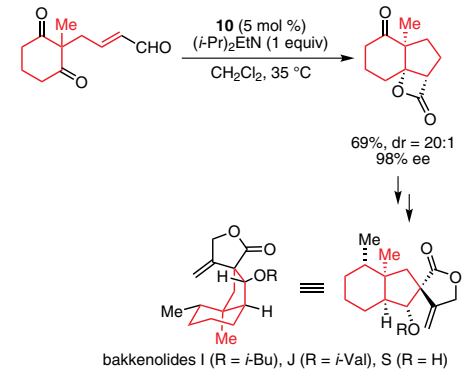
6. Elimination Reactions

The formation of reactive enols through carbene catalysis is an exciting area. The use of α,β-unsaturated aldehydes in this process requires extensive atom and electronic reorganization. In addition to our continued studies along these lines, we are also investigating new approaches using carbenes to generate enols or enolates. Specifically, we hypothesized that carbon–carbon-bond-forming reactions were possible with acetate-type enols derived from the addition of NHCs to α-aryloxyacetaldehydes. The aryloxy (ArO) group would not only facilitate enol formation through an elimination event, but would also assist in catalyst regeneration by adding to the acyl azolium. While this new concept to generate acetate enolates has been successful (vide infra), the initial approach requiring a functional group to behave as both a good leaving group and a competent nucleophile was challenging. A good leaving group may initiate the formation of the enol faster, but would not be effective at catalyst regeneration.[85] Thus, the optimal ArO group must strike a balance between good-leaving-group ability and sufficient nucleophilicity.

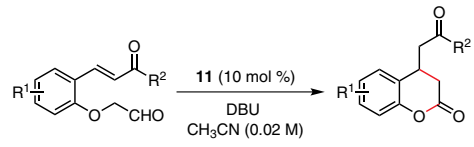
In order to explore the potential of this process, we chose to incorporate enones with tethered aldehydes. The strategy of tethering the conjugate acceptor to the potential nucleophile not only increases the chance of a productive bond formation, but also forms privileged 3,4-dihydrocoumarin structures. Indeed, exposure of these enones to 10 mol % **11** in MeCN affords 3,4-dihydrocoumarins with varying substitution patterns (**eq 11**).[86a]

The fragmentation required for this reaction to occur was a strong impetus for investigating the reaction pathway. First, the possibility of the alkoxide undergoing acylation and then performing a Michael addition was a plausible route. To discount this option, the potential intermediate was synthesized and exposed to the reaction conditions. No reaction was observed, thus refuting the presence of the acylated phenoxide in the catalytic cycle. A crossover experiment was also performed to determine if fragmentation was occurring. When two α-aryloxy aldehydes were exposed to the reaction conditions in a single flask, a randomized mixture of 3,4-dihydrocoumarin products was obtained, supporting the contention that the starting material fractures during the reaction.[86]

These interesting enolate precursors were further applied in Mannich-type reactions. In this case, we sought to synthesize an enolate precursor that would allow for facile elimination and subsequent enol formation, but yet retain enough nucleophilicity to assist in catalyst regeneration (**Scheme 12**).[86b] After much optimization, we discovered that a 4-nitrophenoxide anion was the most suitable leaving group. In contrast to the previous studies of acyl anion additions to imines with *N*-phosphoryl protecting groups, *N*-tosylimines proved to be the most compatible. Additionally, as opposed to the previously described NHC-catalyzed reactions, which use a consortium of amine bases to deprotonate the azolium precatalyst, the most successful base in this process is sodium 4-nitrophenoxide. One drawback of this process is that the initial aryl β-amino ester products are unstable toward column chromatography. However, addition of benzylamine upon consumption of the starting material circumvents this problem and affords a wide variety of β-amino amides (**eq 12**).[86b] Interestingly, these acetate-type enols add to imines with

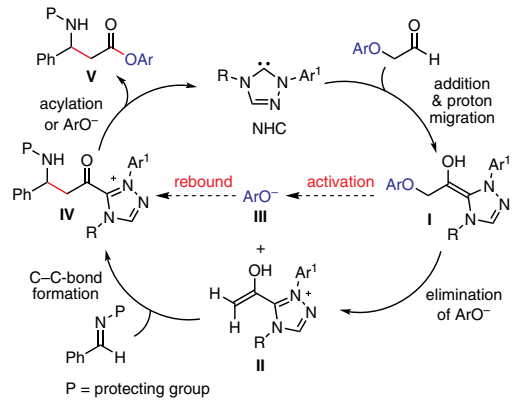


Scheme 11. Application of the NHC-Catalyzed Desymmetrization to the Synthesis of Bakkenolides I, J, and S. *(Ref. 79b)*

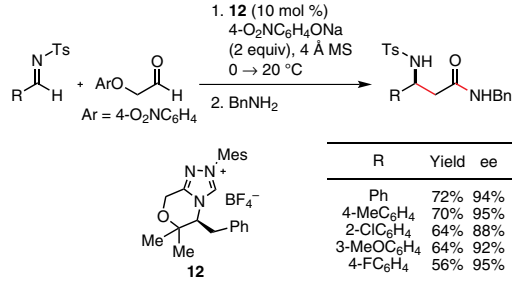


R^1	R^2	Yield
H	Ph	83
H	4-$MeOC_6H_4$	80
H	4-BrC_6H_4	77
7-Me	Ph	66
6-F	Ph	91
8-Me	Ph	66

eq 11 *(Ref. 86a)*



Scheme 12. Proposed Pathway for the NHC-Catalyzed Mannich Reaction of α-Aryloxy Aldehydes. *(86b)*



R	Yield	ee
Ph	72%	94%
4-MeC_6H_4	70%	95%
2-ClC_6H_4	64%	88%
3-$MeOC_6H_4$	64%	92%
4-FC_6H_4	56%	95%

eq 12 *(Ref. 86b)*

excellent levels of stereoselectivity despite the problems typically associated with 1,2 additions of acetate enolates.

The highly selective Mannich-type reaction of α-aryloxy aldehydes provides an opportunity to synthesize products that are valuable to the chemical and biological communities. In addition to α-unbranched β-amino amides, synthesis of the corresponding β-amino acids is also possible with exposure to NaOH (**Scheme 13**).[86b] Formation of 1,3-amino alcohols is accomplished with $LiBH_4$, and the synthesis of more stable esters is demonstrated by the addition of sodium methoxide. Lastly, β-peptide formation is possible by in situ interception with benzyl-protected (*S*)-alanine.[86b] These two reaction manifolds, the Michael and Mannich reactions, demonstrate the viability of this type of "rebound" catalysis, and will surely open doors to new reactions.

7. Theoretical Calculations

As discussed above, the combination of NHCs with α,β-unsaturated aldehydes can result in two divergent pathways: (i) oxidation of the aldehyde or (ii) internal redox reactions through addition of the homoenolate to an electrophile followed by oxidation of the aldehyde carbon. In many cases, both pathways operate under the same reaction conditions.[49,87] Even though NHC-promoted reactions have garnered significant attention in recent years, the discovery of the conditions required for new reactions has remained empirical. Methods to predict and control which pathway is likely to be operating are imperative to the development of new reactions.

One course of action following the addition of the NHC to the aldehyde is the formation of the homoenolate. As previously stated, this option requires a formal 1,2-proton shift to succeed the formation of the tetrahedral intermediate. The second possible pathway includes a collapse of the tetrahedral intermediate, generating an acyl azolium intermediate and a formal reducing equivalent. Our goal, in collaboration with Cramer's group at the University of Minnesota, was to apply computational models toward this complex problem in order to better understand the potential reaction pathways and factors that control the reaction preference for one pathway or the other.[88]

Using crotonaldehyde as a model system for α,β-unsaturated aldehydes, enthalpies of the proposed intermediates were obtained using Density Functional Theory (DFT) calculations with solvation models providing a correction for the solution environment.[89]

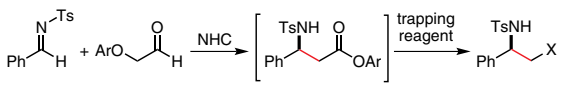
The results of these calculations are in agreement with the experimental findings: the homoenolate pathway is more dependent on the choice of catalyst, while the choice of solvent is less influential. In the corresponding experimental studies, a 10:1 mixture of solvent to methanol was employed to assist in catalyst turnover. Four different, but relatively simple, azolium salts were surveyed as precatalysts over a narrow range of solvents. While the GC yields of these reactions were low, the ratio of oxidation product to homoenolate product was the important statistic. The results indicated that polar protic solvents such as methanol favor the oxidation pathway; but as solvent polarity decreases, the homoenolate pathway becomes more favored.[88] While catalysts **5** and **9** showed that catalyst structure could be used to favor the oxidation pathway, the choice of solvent also played a key role in the distribution of products in the case of 1,3-dimethylimidazolium chloride and 1,3-dimethylbenzimidazolium iodide.

These initial results suggest that a desired pathway can be favored with a specific choice of catalyst and solvent, a choice that is informed by a rational theoretical exploration of the reaction parameters. This first computational exploration of these Lewis base reactions will hopefully lead to a more systematic approach toward the development of NHC-catalyzed reactions.

8. Conclusions and Outlook

We have constructed a large stable of azolium precatalysts, the divergent reactivity of which makes it possible to carry out several types of reaction (**Figures 2** and **3**).

Our laboratory has been inspired by nature and by the pioneering work of Ugai and Breslow to develop whole new families of acyl anion, homoenolate, enolate, and redox processes. The structural diversity of these intriguing azolium catalysts allows them to effect several transformations and leads to the conclusion that their potential has not been realized. A high degree of stereocontrol is possible through the use of chiral, optically active N-heterocyclic carbenes. The integration of experimental data with computational analysis has provided the first study suggesting that the further



Trapping Reagent	X	Yield	ee
NaOH	CO_2H	71%	92%
NaOMe	CO_2Me	61%	94%
$LiBH_4$	CH_2OH	70%	98%
HOBt, *a*	*b*	61%	94%

[a] (*S*)-Alanine benzyl ester used.
[b] X = (*S*)-HNCHMeCO_2Bn

Scheme 13. Investigation of Trapping Reagents for the Mannich-Type Reaction of α-Aryloxy Aldehydes. *(Ref. 86b)*

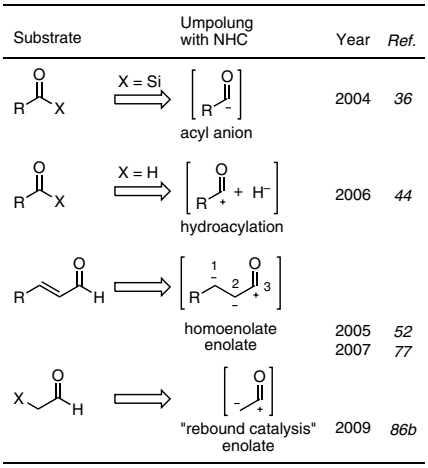


Figure 2. New Concepts in Carbene Catalysis.

Precatalyst	Year First Introduced	Reactions It Catalyzes: Homoenolate	Enolate	Oxidation	Ref.
6	2005	√			*52*
5	2006			√	*44*
9	2007	√			*62*
10	2008	√	√		*70*
12	2008		√		*70*
11	2008	√	√	√	*75*

Figure 3. Milestones in the Growth of This Area of Organocatalysis over the Past Five Years.

development and/or optimization of carbene-catalyzed reactions need not be based solely on empirical approaches. With continued mechanistic investigation, additional insight into these powerful reactions will drive further development of the carbene catalysis field. In the future, new discoveries that allow for lower catalyst loadings may enable the incorporation of these catalysts into synthetic plans for the construction of complex molecules. Ultimately, the continued exploration of carbene catalysis will undoubtedly produce new reactions and strategies, and we look forward to participating in these discoveries.

9. Acknowledgements

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Keywords: catalysis; N-heterocyclic carbenes; umpolung; acyl anions; homoenolates.

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Eric Phillips was born in 1983 in Grand Rapids, MI. He received his B.S. degree in chemistry from Western Michigan University. In 2005, he joined the laboratory of Professor Karl A. Scheidt at Northwestern University, where he is currently a fifth-year graduate student. The majority of his graduate work has focused on the development of reactions catalyzed by N-heterocyclic carbenes, and has received an ACS Division of Organic Chemistry Graduate Fellowship sponsored by *Organic Reactions*. Upon completion of his Ph.D. requirements, he will join the laboratory of Professor Jon A. Ellman at the University of California, Berkeley, as a postdoctoral fellow.

Audrey Chan was born in São Paulo, Brazil, and immigrated to Brooklyn, New York, at the age of six. She received her B.S. degree in chemistry in 2002 from Cornell University. After working at Merck Research Laboratories as a medicinal chemist, she joined the group of Professor Karl A. Scheidt at Northwestern University in 2003. As a Dow Chemical Company Predoctoral Fellow, she studied N-heterocyclic carbene catalyzed homoenolate and hydroacylation reactions. Upon completion of her Ph.D. requirements in 2008, she joined Cubist Pharmaceuticals in Lexington, Massachusetts, where her research focuses on drug development for anti-infectious diseases.

Karl Scheidt became interested early in science because of his father, W. Robert Scheidt, a prominant inorganic chemistry professor at the University of Notre Dame. He received his Bachelor of Science degree from Notre Dame in 1994 while working in the laboratory of Professor Marvin J. Miller. Under the direction of Professor William R. Roush, Karl earned his Ph.D. degree from Indiana University, and was a National Institutes of Health Postdoctoral Fellow with Professor David Evans at Harvard University. Since joining Northwestern University in 2002, Karl's research has focused on the development of new catalytic reactions and the total synthesis of molecules with important biological and structural attributes. He currently holds the Irving M. Klotz Research Chair in Chemistry and is the Alumnae of Northwestern Teaching Professor. He is a fellow of the Alfred P. Sloan Foundation, an American Cancer Society Research Scholar, and the recipient of a National Science Foundation CAREER Award. His recent honors include: The GlaxoSmithKline Scholar Award (2008), AstraZeneca Excellence in Chemistry Award (2007), Novartis Chemistry Lecture Award (2007), Amgen Young Investigator Award (2006), Boehringer Ingelheim New Investigator Award in Organic Chemistry (2005), Northwestern University Distinguished Teaching Award (2005), 3M Nontenured Faculty Award (2005), Abbott Laboratories New Faculty Award (2005), and the Amgen New Faculty Award (2004).

***Correction** (June 11, 2010). The two sentences that start on line 20 and end on line 26 of page 55, column 1, paragraph 1 should be amended to read:*

In 1954, Mizuhara and Handler proposed that the active catalytic species of thiamine-dependent enzymatic reactions is a "pseudobase" that acts through the lone pair of electrons on the tertiary thiazole nitrogen.[14] However, in 1958, Breslow offered an alternative mechanism whereby the active catalytic species of thiamine-dependent enzymatic reactions is a highly unusual divalent carbon-containing species,[1b] later on referred to as an N-heterocyclic carbene (NHC).

The authors of the review regret the confusion the original text may have caused.

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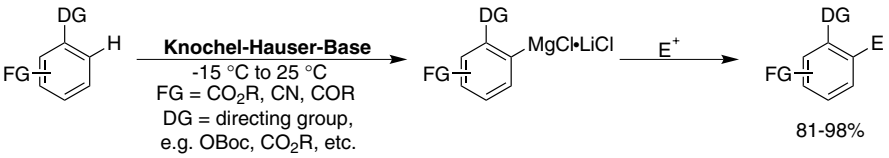
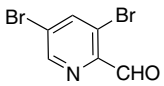
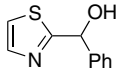
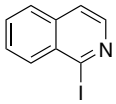




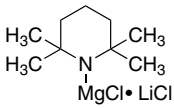
85% (E^+ = DMF)



94% (E^+ = PhCHO)



92% (E^+ = I_2)



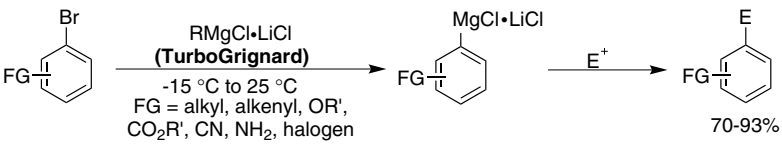
703540
(1.0 M in THF–PhMe)

- Improved reactivity and basicity
- Increased functional group compatibility
- Mild reaction conditions
- Side reactions inhibited
- Excellent solubility in THF

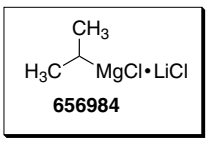
Reference:

Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958.

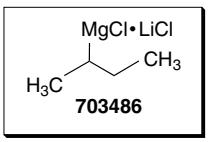
TurboGrignards for Halogen–Magnesium Exchange in Aryl and Heteroaryl Compounds



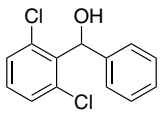
RMgCl•LiCl =
TurboGrignards

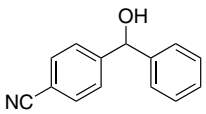


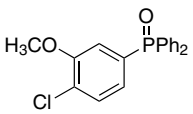
656984

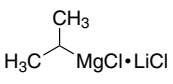


703486

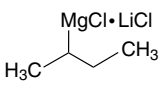








656984
(1.3 M in THF)



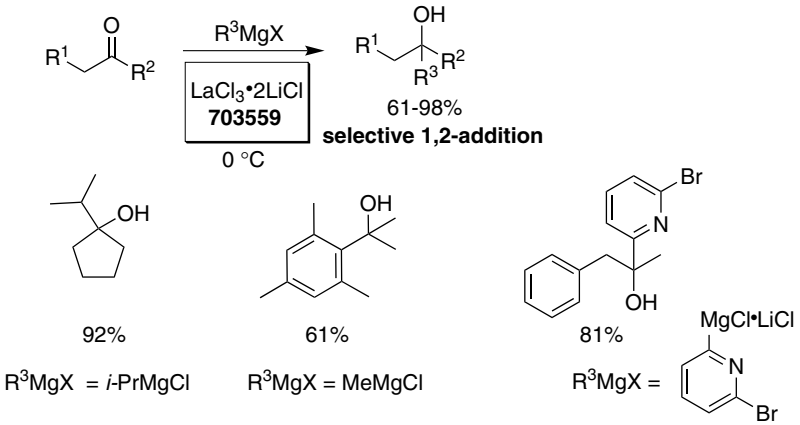
703486
(1.2 M in THF)

- Increased functional group compatibility
- Mild reaction conditions
- Side reactions inhibited

Reference:

(1) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.
(2) Knochel P. Eur. Patent 1582 524 A1.

Selective 1,2-Additions of Ketones, Michael Acceptors, and Imines



$LaCl_3$/LiCl
703559
(0.6 M in THF)

- Enolizable and sterically hindered ketones
- Low H_2O content and THF-soluble
- Decrease in side products

Reference:
(1) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 497.
(2) Knochel P. Eur. Patent 050 19 026.3.

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Ethylmagnesium bromide solution, 3.4 M in 2-methyltetrahydrofuran	703591
Methylmagnesium bromide solution, 3.2 M in 2-methyltetrahydrofuran	703583
Phenylmagnesium bromide solution, 2.9 M in 2-methyltetrahydrofuran	703575
Isopropylmagnesium bromide solution, 2.9 M in 2-methyltetrahydrofuran	703567
Zinc chloride solution, 1.9 M in 2-methyltetrahydrofuran	703516
Lithium aluminum hydride solution, 2.2 M in 2-methyltetrahydrofuran	703508

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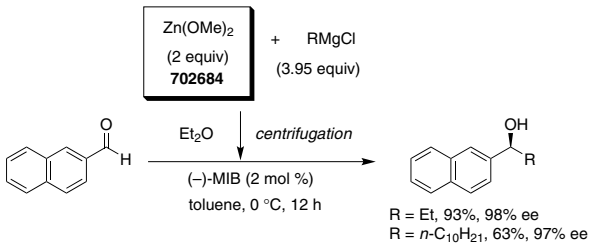


Reference:
Côté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 2771.

Diorganozincs from Sigma-Aldrich

Dimethylzinc solution, 1.0 M in heptane

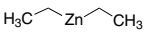
417246 — 50 mL

[*544-97-8*]
C_2H_6Zn
FW: 95.46

Diethylzinc solution, 1.0 M in hexanes

296112 — 100 mL, 800 mL

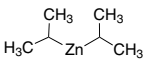
[*557-20-0*]
$C_4H_{10}Zn$
FW: 123.51



Diisopropylzinc solution, 1.0 M in toluene

568112 — 5 mL, 25 mL

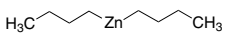
[*625-81-0*]
$C_6H_{14}Zn$
FW: 151.57



Dibutylzinc solution, 1.0 M in heptane (Aldrich Brand)

34905 — 100 mL

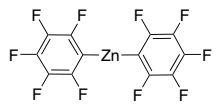
[*1119-90-0*]
$C_8H_{18}Zn$
FW: 179.62



Bis(pentafluorophenyl)zinc, 97%

566748 — 1 g

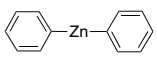
[*1799-90-2*]]
$C_{12}F_{10}Zn$
FW: 399.50



Diphenylzinc, 92%

481076 — 1 g, 5 g

[*1078-58-6*]
$C_{12}H_{10}Zn$
FW: 219.60



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Synthesis and Applications of Diorganozinc Reagents: Beyond Diethylzinc

Dr. Alexandre Lemire

Dr. Alexandre Côté

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Outline

1. Introduction

Diorganozinc reagents are unique nucleophiles because of the right balance between their nucleophilicity and basicity and because of the low reactivity of the byproducts of their reactions. These reagents possess very high functional-group tolerance and react sluggishly in the absence of a catalyst or the appropriate reaction conditions (**Figure 1**). For all these reasons, diorganozinc reagents can be viewed as privileged reagents in enantioselective catalysis.[1]

Our research group has been interested in diorganozinc compounds for the past 20 years, and has developed a number of enantioselective reactions using diorganozinc reagents. Like others, we have developed several asymmetric reactions using diethylzinc as the standard reagent in part because of its good reactivity, relatively low cost and wide availability. One impediment to the widespread use of diorganozinc chemistry in novel catalytic asymmetric processes has been the lack of commercial availability of most diorganozinc reagents, especially when compared to other common organometallic reagents, such as RZnX, RMgX, and RLi.

It is thus not surprising to see that diethylzinc (the cheapest diorganozinc reagent) accounts for 60% of all the references found in Scifinder Scholar® on diorganozinc reagents! Dimethylzinc accounts for 21%, dibutylzinc for 4%, diisopropylzinc for 4%, diphenylzinc for 5%, and all the others for the remaining 6%.

Obviously, new methodologies employing only diethylzinc as the reagent would only fully blossom if they could be shown to be more general and applicable to other diorganozinc reagents. For example, we reported in 2003 the copper-catalyzed asymmetric addition of diorganozinc reagents to *N*-diphenylphosphinoylimines in the presence of (*R,R*)-BozPhos (**1**), in which diethyl-, dimethyl-, dibutyl-, and diisopropylzincs were successfully employed (**eq 1**).[2] The only functionalized dialkylzinc successfully utilized in this reaction was di[6-*tert*-butyldimethylsilyloxy)hexyl]zinc (52%, 90% ee).

A fundamental problem associated with the preparation of diorganozinc reagents is the removal of the reaction byproducts. Even if numerous methods exist to synthesize diorganozinc reagents,[3] the chemist who needs a noncommercial diorganozinc reagent faces a dilemma: either the diorganozinc is easily prepared in solution from simple reagents and used without purification (but two equivalents of a lithium or a magnesium halide byproducts are formed), or he/she embarks on a time-consuming purification of the diorganozinc. Most purification methods are either difficult to realize in a normal

laboratory environment, or they require the manipulation of pyrophoric reagents.

In numerous cases, the byproducts can be very detrimental to subsequent catalytic asymmetric transformations, since they often interfere with the catalytic cycle. For example, the addition of in situ prepared dipropylzinc to *N*-diphenylphosphinoylbenzaldimine gives the product with only a 27% ee (compared to 96% ee for addition of dibutylzinc as depicted in equation 1). The presence of even a very small amount of a magnesium or lithium salt affords N-protected secondary amines with significantly reduced enantiomeric excesses and variable yields.[4,5]

Pure diorganozinc reagents are typically obtained by distillation or sublimation (vide infra), and the great majority have to be kept under an inert atmosphere as they react with water or oxygen. When diorganozinc reagents are nonvolatile or thermally unstable, a preparation method is chosen to ensure that the reaction byproducts are volatile and distilled off the reaction mixture along with excess reagents and solvents (if any). This approach implies that distillation of pyrophoric diethylzinc, triethylborane, or diisopropylzinc is sometimes required. Therefore, considerable effort has been expended on the development of methods in which the metal halide byproducts are removed from the reaction mixture by simple filtration. Most of these preparation methods, as well as our findings in this area, will be discussed in Section 2, whereas applications of diorganozinc reagents in synthesis will be covered in Section 3.

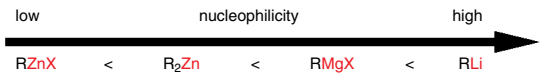
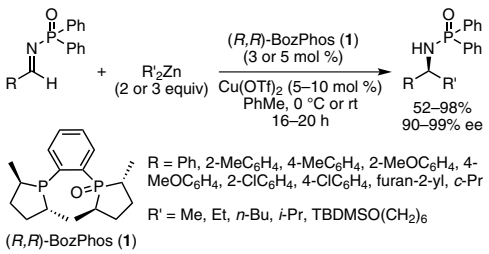
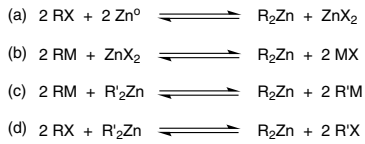


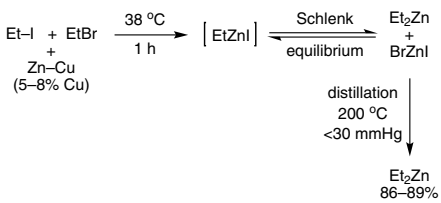
Figure 1. Reactivity of Diorganozinc Reagents Relative to Those of Other Organometals.



eq 1 *(Ref. 2a)*



Scheme 1. Four General Approaches to Diorganozinc reagents. *(Ref. 1,3,6)*



eq 2 *(Ref. 8a,b)*

2. General Syntheses of Diorganozinc Reagents

The different methods for preparing diorganozinc compounds can be grouped into four general approaches (**Scheme 1**):[1,3] (a) the oxidative addition between zinc metal and an alkyl halide followed by Schlenk equilibration, (b) the transmetallation of a zinc halide with an organometallic reagent, (c) the transmetallation of a diorganozinc starting material with an organometallic reagent, and (d) the zinc–halogen exchange between an alkyl halide and a diorganozinc.

2.1. Metallic Zinc Insertion and Schlenk Equilibration

Von Frankland prepared diethylzinc from iodoethane and zinc metal.[6] Oxidative insertion of zinc into the carbon–iodine bond led to ethylzinc iodide, which generated diethylzinc upon distillation.[7] Removal of the product diethylzinc by distillation shifted the Schlenk equilibrium towards the diorganozinc.

Since this initial work, many improvements have been made to the process, and most of these improvements concern the zinc activation protocol. A zinc–copper couple has traditionally been used to synthesize low-boiling and thermally stable diorganozinc reagents, either from alkyl iodides or mixtures of alkyl iodides and alkyl bromides (**eq 2**).[8]

2.2. Transmetallation of an Organometallic Reagent with a Zinc Salt

The second general approach consists of reacting a zinc salt with an organolithium or a Grignard reagent, which may bear various functional groups (see Scheme 1, Part (b)).[9] While this reaction is typically run in ethereal solvents, it produces lithium or magnesium halides as byproducts. In most cases, these byproducts need to be removed if the diorganozinc reagent is to be subsequently used as a nucleophile in catalytic enantioselective processes. The detrimental effect of the salts resides in the fact that they can either catalyze a background racemic reaction, or inhibit the activity of a chiral Lewis acid through complexation with the halide anion of the salt.[4] One common procedure to remove the salt byproducts is by distilling off the diorganozinc reagent; but, this can sometimes lead to low yields. For instance, after solvent removal, diisopropylzinc tolerates distillation from magnesium salts under reduced pressure (60% yield). However, distillation from magnesium salts is less satisfactory for dicyclobutylzinc (28%), dicyclopentylzinc (19%), and dicyclohexylzinc (21%).[10]

In 1929, Schlenk showed that 1,4-dioxane forms insoluble complexes with magnesium halides, thus allowing the preparation of diorganomagnesium reagents from Grignard reagents by displacement of the Schlenk equilibrium upon precipitation of the magnesium halide–dioxane complex.[7,11] Seebach used this finding to develop a synthesis of diorganozinc reagents from Grignard reagents.[12] Diorganozincs were thus prepared as a solution in 1,4-dioxane and diethyl ether. This approach allowed the synthesis of enantioenriched secondary alcohols from diorganozinc reagents that were not commercially available (vide infra).

More recently, Walsh and co-workers reported an alternative procedure to sequester the lithium halide byproduct formed during the preparation of diarylzinc and aryl(alkyl)zinc reagents. They achieved this by using low-polarity solvents in

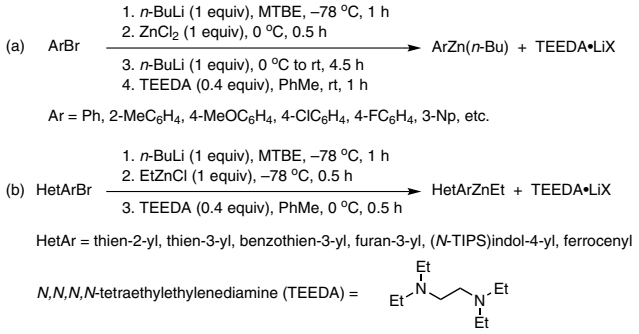
the reaction to minimize the solubility of lithium halides and by adding *N,N,N,N*-tetraethylethylenediamine (TEEDA) to scavenge the remaining salts in solution (**Scheme 2,** Part (a)).[5d] This procedure allowed for the in situ formation of aryl(alkyl)-zinc reagents that were compatible with the catalytic asymmetric preparation of enantioenriched diarylmethanols (vide infra). This approach was later extended to the synthesis of heteroaryl- and diheteroarylmethanols using ethylzinc chloride instead of zinc chloride to generate the heteroaryl(alkyl)zinc reagent (Scheme 2, Part (b)).[5e] Low-temperature transmetallation was essential as heteroaryllithiums decompose upon warming, which necessitated the use of ethylzinc chloride as this reagent is soluble at low temperatures in low-polarity solvents.

Our research group recently disclosed a practical synthesis of dialkylzinc reagents from alkylmagnesium chlorides and zinc methoxide (**Scheme 3**).[4,13] The byproduct from this reaction, methoxymagnesium chloride (MeOMgCl), precipitates from the reaction mixture as it is formed. After centrifugation or filtration, the diorganozinc is obtained as an ether solution (ca. 0.5 M). The absence of deleterious impurities was ascertained using the afforded diorganozinc reagent solutions in numerous enantioselective reactions (see Sections 3.1.1–3.1.3). The synthesis of diorganozinc reagents from alkyl- and arylmagnesium bromides is also possible by using a modified procedure that is needed to remove the slightly soluble methoxymagnesium bromide (MeOMgBr) and formally convert it into an insoluble mixture of magnesium methoxide and sodium bromide.

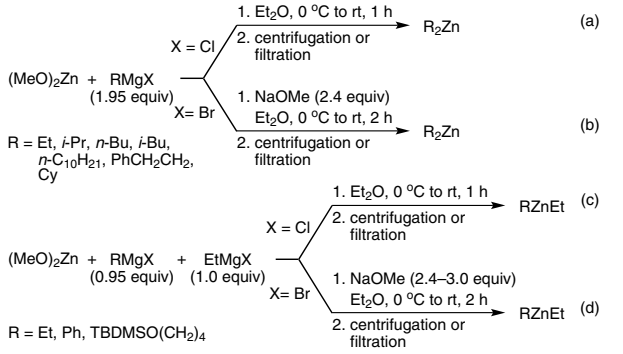
2.3. Transmetallation of an Organometallic Reagent with a Diorganozinc

Transmetallation of organoboron, organonickel, and organozirconium compounds with dimethyl-, diethyl-, or diisopropylzinc are valuable methods for the synthesis of functionalized diorganozinc reagents. The use of organomercury[14] and organoaluminum[15] reagents will not be detailed here.

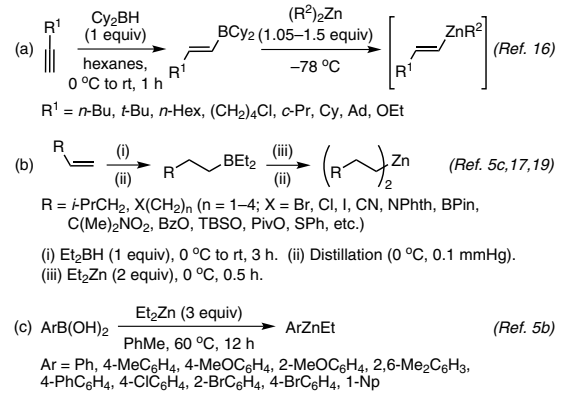
Boron-to-zinc transmetallation was popularized by Oppolzer and others for alkenyl transfer,[16] by Knochel for alkyl transfer,[17] and by Bolm for aryl transfer.[5b] Hydroboration of alkynes and alkenes readily affords triorganoboron compounds, which can also be accessed from the reaction of boron halides with Grignard reagents.[18] Transmetallation of alkenylborons to alkenyl(alkyl) zincs is a rapid process and needs only a small excess of diethyl- or dimethylzinc (**Scheme 4**, Part (a)).[16e] In situ reactions, without the need for removing triethyl- or trimethylborane byproducts before addition of the amino alcohol chiral ligand (vide infra) and aldehyde, provide very convenient processes for the enantioselective synthesis of secondary allylic alcohols. Internal alkynes have also been used in this reaction, but unsymmetrical ones can lead to more than one regioisomer being observed.[16b] Transmetallation of trialkylboranes with diethylzinc (2 equiv) at 0 °C proceeds well in hexane, ether, or in the absence of a solvent. It is complete within 0.5 h with all primary diethyl(alkyl)boranes, but requires longer reaction times with secondary diethyl(alkyl)-boranes. The byproduct, triethylborane, is distilled off to drive the equilibrium towards the desired dialkylzincs (see Scheme 4, Part (b)).[17] Under these reaction conditions, the boron–zinc exchange occurs with loss of stereochemistry. Numerous research groups have successfully used this procedure to generate functionalized diorganozincs.[5c,19] The boron–zinc exchange is dramatically accelerated when $(i\text{-Pr})_2Zn$ is used instead of Et_2Zn. This allows for the synthesis of chiral secondary dialkylzincs with complete retention of configuration at the carbon bearing the boron atom.[20] Secondary dialkylzincs can also be prepared from the corresponding boranes and diethylzinc, albeit with loss of stereochemistry at the carbon attached to the boron.[17] Transmetallations are quite slower with secondary alkylboranes (i.e., 3–40 h at rt), varying with the steric hindrance of the secondary alkylborane (up to 6 equiv of Et_2Zn needed for bulkier secondary alkylboranes). Arylboronic acids and esters, as well as triarylboroxines, can be transmetallated with diethylzinc to afford aryl(ethyl)zinc species (see Scheme 4, Part (c)),[5b] which can be utilized in situ in the enantioselective arylation of aldehydes.



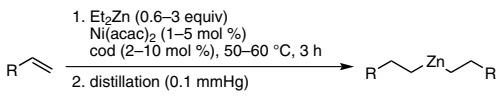
Scheme 2. Walsh's Synthesis of Mixed Aryl(butyl)zincs and Heteroaryl(ethyl)zincs *(Ref. 5d,e)*



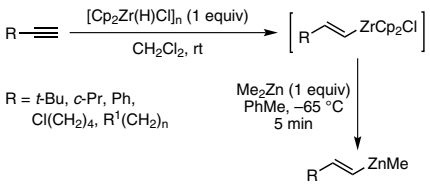
Scheme 3. Charette's Synthesis of Diorganozinc Reagents Using $(MeO)_2Zn$. *(Ref. 4,13)*



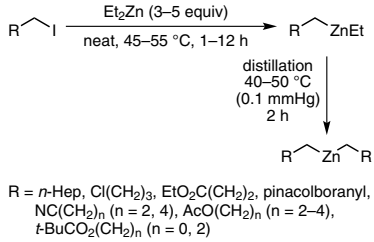
Scheme 4. Functionalized Diorganozincs Prepared by the Transmetallation of Organoboron Reagents with Diethylzinc.



eq 3 *(Ref. 21a)*



Scheme 5. Alkenyl(alkyl)zinc Reagents by the Zirconium–Zinc Transmetallation. *(Ref. 22)*



Scheme 6. Synthesis of Diorganozincs by Iodine–Zinc Exchange. *(Ref. 23a)*

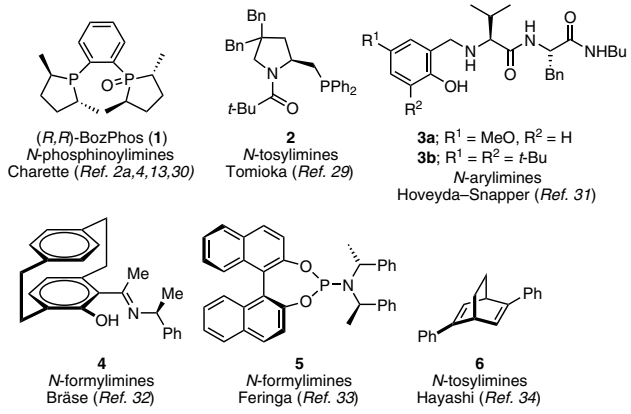
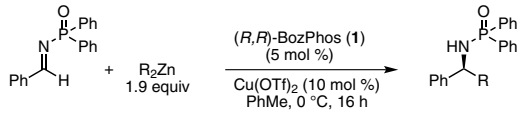


Figure 2. Chiral Ligands Employed in Efficient, Catalytic, and Asymmetric Additions of Diorganozincs to Imines.



[a] R_2Zn was generated in situ from RMgCl (3.9 equiv) and $Zn(OMe)_2$ (2 equiv), as described in the top equation in Scheme 3. [b] $Zn(OMe)_2$ was formed in situ from $ZnCl_2$ (2 equiv) and NaOMe (4.2 equiv). [c] $Zn(OMe)_2$ was obtained in situ from $ZnBr_2$ (2 equiv) and NaOMe (4.2 equiv). [d] Commercial, neat Et_2Zn was dissolved in Et_2O. [e] **1** (10 mol %), $Cu(OTf)_2$ (20 mol %), and styrene (1 equiv) as additive (see reference 35). [f] Reaction was run for 48 h.

R	Yield	ee
Et[a]	95%	98%
Et[b]	90%	98%
Et[c]	94%	94%
Et[d]	96%	98%
n-Bu[a]	96%	96%
i-Pr[a,e]	57%	95%
n-decyl[a,f]	73%	97%

eq 4 *(Ref. 4,13,30)*

The catalytic hydronickellation of alkenes followed by transmetallation with diethylzinc is an alternative approach to hydroboration (**eq 3**).[21] The nickel hydride species is formed in situ upon reacting diethylzinc with nickel(II) to generate an ethylnickel species that undergoes β-hydride elimination. This process releases ethylene gas as a byproduct, and the excess diethylzinc and unreacted olefin are distilled off leaving behind the newly formed diorganozinc reagent, which can be used directly in subsequent catalytic asymmetric additions to aldehydes.

Zirconium–zinc transmetallation has also been employed in the alkenylzinc addition to electrophiles.[22] Wipf found that alkenylzirconocenes, preformed by hydrozirconation of alkynes with $Cp_2Zr(H)Cl$ (Schwartz's reagent), readily form alkenyl(methyl) zinc reagents upon reaction with dimethylzinc (**Scheme 5**).[22a] While this transformation is conceptually identical to the hydroboration–zinc transmetallation sequence (see Scheme 4, Part (a)), it has also proven useful in the enantioselective addition of alkenylzinc reagents to ketones.[22d] Internal symmetrical alkynes were also successfully employed in the synthesis of an enantioenriched trisubstituted *E* allylic alcohol.[22b]

2.4. Halogen–Zinc Exchange

Iodine–zinc exchange allows for the conversion of functionalized iodoalkanes into diorganozincs using diethylzinc or diisopropylzinc (**Scheme 6**).[23] Diethylzinc was used at first for the synthesis of primary diorganozinc reagents. Later, Knochel found that addition of cuprous iodide accelerates the reaction,[23b] while our research group reported that UV light also facilitates the exchange.[24] However, as with the synthesis of dialkylzincs via alkylboron reagents, the removal of excess diethylzinc and iodoethane by distillation is necessary to drive the equilibrium towards the products. Several research groups have since employed this procedure to prepare functionalized diorganozincs.[5c,19] Use of diisopropylzinc allows for the synthesis of secondary dialkylzincs[25] as well as diarylzincs, by using Li(acac) as catalyst.[26]

3. Synthetic Applications of Diorganozincs

3.1. Enantioselective Additions

3.1.1. Addition to Imines Leading to Chiral Amines

The asymmetric synthesis of α-branched chiral amines is a very important process, and the addition of nucleophiles to imines is a versatile approach for accessing these compounds in enantiomerically enriched form.[27,28] Diorganozinc reagents are widely utilized in catalytic enantioselective additions to imines as pioneered by Tomioka.[29] A number of such methodologies, employing a diverse set of chiral ligands (**Figure 2**), have been reported by our research group (**1** with $Cu(OTf)_2$, see eq 1 and **eq 4**),[2,4,13] Tomioka (**2** with $Cu(OTf)_2$),[29] Hoveyda–Snapper (**3** with $Zr(O\ i\text{-}Pr)_4$),[31] Bräse (**4**),[32] Feringa (**5** with $Cu(OTf)_2$),[33] and Hayashi (**6** with $[RhCl(C_2H_4)_2]$]),[34] Unfortunately, it is only in a few instances that a wide array of different diorganozinc reagents were tested in these reactions.

The use of zinc methoxide and alkylmagnesium chlorides allows the in situ preparation of the corresponding diorganozinc reagents (see Scheme 3, Part (a)) that add to imines with moderate-to-excellent yields and excellent enantioselectivities in the presence of copper(II) and (*R,R*)-BozPhos (**1**) (see eq 4).[4,13] In one case, styrene was employed by Li and Alexakis as an additive to enhance the enantioselectivity of the reaction.[35]

A mixed diorganozinc reagent[36] was also prepared from zinc methoxide and was added to the imine under similar conditions, affording the protected secondary amine with moderate yield but very good enantioselectivity (**Scheme 7**).[4,36] Methyl,[22] ethyl,[5a,e,16a,e] neopentyl,[37] and neophyl[37] groups are other typically used

nontransferable alkyl groups. This strategy minimizes the potential waste of a precious functionalized alkyl group, while providing higher yields and enantioselectivities in some reactions.

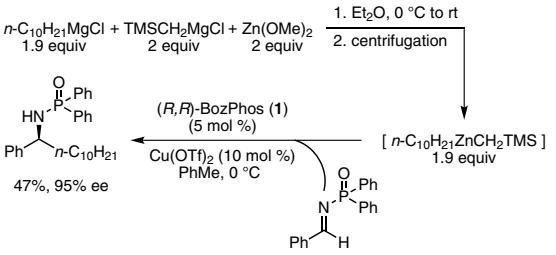
The asymmetric synthesis of α-branched dialkylamines was accomplished by employing a similar catalytic system, but the unstable enolizable imines were generated in situ from the corresponding sulfinic acid adducts (**eq 5**).[38] A one-pot synthesis of enantioenriched, unprotected secondary amines from aldehydes was also reported using a modification of this procedure.[39] Similar reaction conditions enabled the enantioselective addition of dimethylzinc and diethylzinc to trifluoromethyl ketimines generated in situ from the corresponding ethanol adducts (i.e., OEt instead of Ts on the imine precursor).[40]

Fu, Snapper, and Hoveyda have reported a catalytic asymmetric addition of dialkylzinc reagents to aryl-, alkyl-, and trifluoroalkyl-substituted activated *N*-(2-methoxyphenyl)ketimines.[41,42] They utilized protected dipeptide **3a** as a chiral promoter, in conjunction with zirconium tetraisopropoxide, for the enantioselective addition of dimethylzinc to aryl- and heteroaryl-substituted ketimines (**eq 6**).[41] When R = Ph in the ketimine, lowering the catalyst loading to 1 mol % had little impact on enantioselectivity and yield (92%, 93% ee). Dipeptide catalyst **3b** gave the best enantioselectivities in the addition of dimethylzinc to alkyl-substituted α-ketimine esters (see eq 6), as well as to aryl-substituted trifluoromethyl ketimines (not shown, 66–96%, 96–98% ee's, 5 examples).

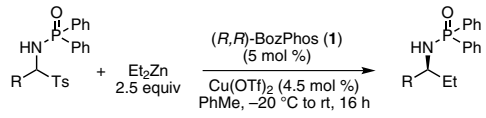
3.1.2. Addition to Aldehydes and Ketones Leading to Chiral Alcohols

The catalytic enantioselective alkylation of aldehydes to afford enantioenriched secondary alcohols was extensively studied in the 1980s. Diorganozinc reagents were the most widely used nucleophiles in this reaction, due to their low propensity to add to carbonyl derivatives without the presence of a suitable catalyst. In 1986, Noyori reported that catalytic quantities of 3-*exo*-dimethylaminoisoborneol (DAIB, **7**, **Figure 3**), an amino alcohol derived ligand, triggered the ethyl-transfer reaction from diethylzinc to an aldehyde to provide secondary alcohols in high enantiomeric excesses.[43] A few years later, Yoshioka,[44] Ohno,[45] and Kobayashi[46] reported a titanium(IV)-based enantioselective addition of diethylzinc (and of di-*n*-butyl-, and di-*n*-pentylzinc) to aldehydes, using a catalytic amount (as low as 0.05 mol %) of a chiral bis(sulfonamide), **8**. Knochel also showed the potential of this methodology by using funtionalized dialkylzincs as nucleophiles, which were prepared either from a boron–zinc (see Scheme 4, Part (b))[17] or an iodine–zinc exchange (see Scheme 6).[23] Seebach employed titanium tetraisopropoxide as a Lewis acid in the asymmetric addition of diethylzinc to aldehydes promoted by a catalytic amount (10 mol %) of TADDOL (**9**).[47] The scope of this reaction was greatly enhanced by the development of an in situ protocol for the generation of dialkylzinc derivatives from Grignard reagents.[12] In 1999, Nugent reported an improved amino alcohol ligand, 3-*exo*-morpholinoisoborneol (MIB, **10**), which proved to be as good as DAIB in the addition of diethylzinc to aldehydes.[48] MIB also displayed a large positive nonlinear effect similar to DAIB.[49] The main advantage of MIB consists in its ease of preparation and its extended bench stability.[50]

Following Nugent's report on MIB, Walsh greatly expanded its scope by applying it in the addition of alkenyl(alkyl)zincs (prepared as in Scheme 4, Part (a)) to aldehydes.[16,51] Access to enantiomerically enriched *Z*-disubstituted allylic alcohols from 1-chloroalkynes was later reported by the same group (**Scheme 8**).[52] *tert*-Butyllithium added onto the boron center to generate an ate complex that underwent a 1,2-hydride shift to the vinylic carbon, followed by halide elimination, to generate the *Z*-alkenylboron

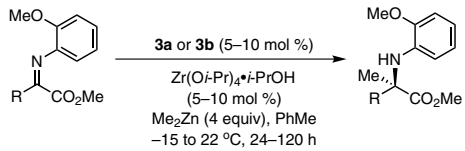


Scheme 7. Synthesis of a Mixed Diorganozinc and Its Addition to *N*-Diphenylphosphinoylbenzaldimine. *(Ref. 4)*



R	Yield	ee
Me	97%	90%
i-Pr	86%	96%
i-Bu	97%	96%
n-Hex	98%	95%
c-Pent	92%	95%
Cy	89%	96%
$Ph(CH_2)_2$	98%	96%
Ph	87%	97%

eq 5 *(Ref. 38a)*



3a; R = aryl, heteroaryl; 91–98%, 88–97% ee
3b; R = alkyl; 38–85%, 82–93% ee

eq 6 *(Ref. 41)*

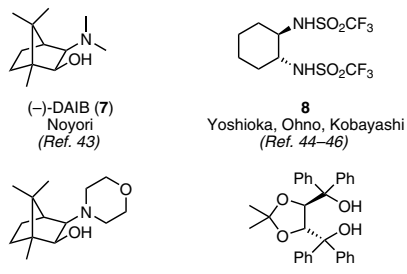
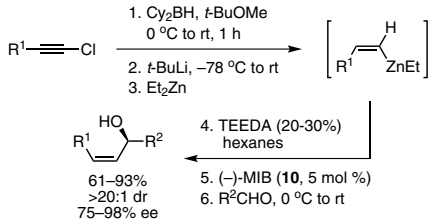
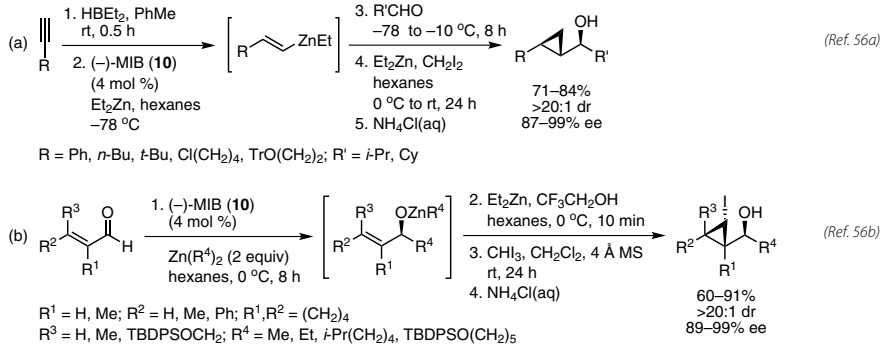


Figure 3. Chiral Ligands for the Enantioselective Addition of Diorganozincs to Aldehydes.

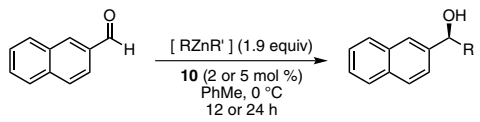


R^1 = TBDPSO$(CH_2)_2$, *n*-Hex, Cl$(CH_2)_4$, Ph
R^2 = alkyl, cycloalkyl, aryl, heteroaryl

Scheme 8. Synthesis of Enantioenriched *Z*-Disubstituted Allylic Alcohols. *(Ref. 52)*



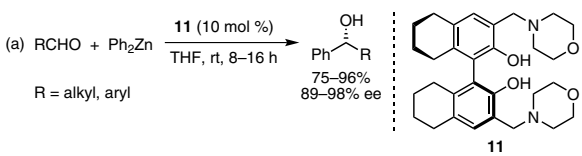
Scheme 9. Enantioselective Alkylation and Vinylation of Aldehydes and in Situ Cyclopropanation.



R	R'	RZnR' Source[a]	Yield	ee
Et	Et	**A**	93%	98%
Et[b]	Et	**A**	95%	98%
Et	Et	**B**	96%	97%
n-decyl[c]	*n*-decyl	**A**	63%	97%
Ph	Et	**C**	90%	98%
Ph	Et	**D**	98%	98%
Ph	Et	**E**	63%	93%
Et	Et	**C**	96%	98%
$TBDMSO(CH_2)_4$	Et	**C**	70%	98%

[a] **Method A**: (i) RMgCl (3.9 equiv), $Zn(OMe)_2$ (2 equiv), Et_2O, 0 °C to rt; (ii) centrifugation. **Method B**: Commercial, neat Et_2Zn was dissolved in Et_2O. **Method C**: (i) RMgBr (1.9 equiv), R'MgBr (2 equiv), $Zn(OMe)_2$ (2 equiv), NaOMe (4.8 or 6.0 equiv), Et_2O, 0 °C to rt; (ii) centrifugation. **Method D**: PhZnEt was prepared by mixing commercially available, neat Et_2Zn (0.75 equiv) with Ph_2Zn (0.75 equiv). **Method E**: (i) EtMgBr (1.5 equiv), PhMgBr (1.45 equiv), and $ZnCl_2$ (1.5 equiv) in Et_2O; (ii) 1,4-dioxane (14 equiv). [b] $Zn(OMe)_2$ formed in situ from $ZnCl_2$ (2 equiv) and NaOMe (4.2 equiv). [c] Lower yield due to reduction of the aldehyde.

eq 7 *(Ref. 13)*



X	**11**	Yield	ee
3-CN	40 mol %	74–87%	79 to >98%
4-CO_2Me	20 mol %	52–97%	87–96%
3-MeO	10 mol %	85–95%	83 to >99%

Scheme 10. Enantioselective Addition of Diarylzincs to Aldehydes. *(Ref. 57,58)*

intermediate ($KHB(O\textit{i}\text{-}Pr)_3$ was also shown to be a suitable hydride donor). Subsequent boron–zinc exchange with Et_2Zn generated the *Z*-alkenylzinc species. Addition of TEEDA as a lithium salt scavenger (see Scheme 2) was needed to afford high enantioselectivity in the alkenylzinc addition to aldehydes. The synthesis of *Z*-trisubstituted allylic alcohols from 1-bromoalkynes was also reported.[53,54]

The enantioselective addition of diorganozinc reagents to aldehydes was also used in tandem one-pot vinylation–epoxidation reactions,[55] as well as in tandem one-pot alkylation– and vinylation–cyclopropanation reactions (**Scheme 9**).[56] The bromo- and chlorocyclopropanation could also be achieved using this methodology, while the opposite halide epimer was obtained when R^2 was a phenyl group. Alkynes (terminal and internal) were also transformed into iodocyclopropanes.

Walsh reported a general method for preparing enantioenriched diarylmethanols in 55–96% yields and 78–99% ee's by the catalytic arylation of aldehydes with mixed aryl(alkyl)zincs obtained from aryl bromides (see Scheme 2).[5d,e,28]

Likewise, we have tested the dialkylzinc reagents prepared from alkylmagnesium chlorides and zinc methoxide (see Scheme 3, Part (a)), in Nugent's MIB-catalyzed addition to 2-naphthaldehyde (**eq 7**).[13] Very good yields and enantioselectivities are obtained with diethylzinc using either preformed or in situ generated zinc methoxide. Didecylzinc also displays a very good enantioselectivity, although the isolated yield is lower due to reduction of the aldehyde.

Diorganozinc reagents prepared from organomagnesium bromides have also been utilized in the (–)-MIB-catalyzed arylation and alkylation of 2-naphthaldehyde (see eq 7). The results for the addition of the phenyl group, generated as in Scheme 3, Part (d), are comparable to results obtained with PhZnEt generated by mixing commercially available neat diphenylzinc and diethylzinc (eq 7, Method D). In comparison, freshly prepared PhZnEt, in which the magnesium salts are removed by precipitation with 1,4-dioxane, results in only a slight reduction of enantioselectivity, but a lower yield. Diethylzinc prepared from ethylmagnesium bromide and zinc methoxide with sodium methoxide (as in Scheme 3, Part (b)) also results in only a comparable result to that from a solution of commercial reagent. Transfer of a functionalized alkyl group on a mixed diorganozinc (prepared according to Scheme 3, Part (d)) generates the secondary alcohol in good yield and enantioselectivity.

The enantioselective addition of diphenylzinc to aldehydes has received considerable attention in the last decade.[28] Recently, Qin and Pu designed an H_8-binol-based catalyst, **11**, that is highly enantioselective in this arylation reaction (**Scheme 10**, Part (a)).[57] Catalyst **11** is easily prepared in one step from commercially

available materials and is effective for aromatic and aliphatic aldehydes. Pu's group also succeeded in using **11** with functionalized diarylzincs[58] that were prepared according to Knochel's procedure (Scheme 10, Part (b)).[26a]

The enantioselective arylation that utilizes arylboron species as the arylzinc precursors is an alternative strategy, which takes advantage of the wide availability of arylboronic acids. Using a boron–zinc transmetallation (see Scheme 4, Part (c)) developed by Bolm,[5b] even triarylboroxines can be transformed into aryl(ethyl)-zinc reagents upon heating with diethylzinc in toluene.[59] This methodology has recently been applied to the enantioselective arylation of an aldehyde on a 17.6-kilogram scale, en route to a mGlu2 receptor potentiator (**Scheme 11**).[60]

The enantioselective synthesis of tertiary alcohols is also an important research topic in contemporary organic chemistry.[42] In 1998, Dosa and Fu reported the first catalytic asymmetric addition of an organometallic reagent to ketones using DAIB (**7**) as catalyst and diphenylzinc as nucleophile.[61] The same year, Ramón and Yus reported the first enantioselective addition of diethyl- and dimethylzinc to ketones using a sulfonamide-based catalyst.[62,63] Walsh has also been quite active in this area using bis(sulfonamide) **12**[64] to catalyze the addition of a variety of alkyl- and alkenylzinc nucleophiles, as well as diphenylzinc, to ketones (**eq 8**).[22d,65] This topic has recently been reviewed quite thoroughly.[66]

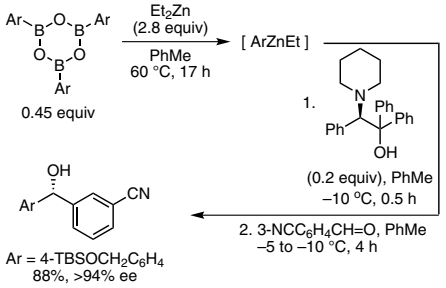
3.1.3. Conjugate Addition Giving Rise to β-Substituted Ketones, Nitroalkanes, and Sulfones

Diorganozinc reagents are widely employed in asymmetric catalytic additions of nucleophiles to enones.[67,68] We tested a wide array of diorganozinc reagents (see Scheme 3, Part (a)) in the copper-catalyzed enantioselective 1,4 addition to cyclohexenone using Feringa's conditions.[69,70] Commercially available diethylzinc or in situ prepared reagent from zinc methoxide and ethylmagnesium chloride gave similar yields and enantioselectivities (**eq 9**).[4,13] The addition of long alkyl chains was also possible using the boron–zinc protocol (see Scheme 4, Part (b)). Secondary dialkylzincs reacted with very good enantioselectivities upon addition of styrene as a radical inhibitor,[35] while di-(*t*-butyl)zinc could not be added with good selectivity.

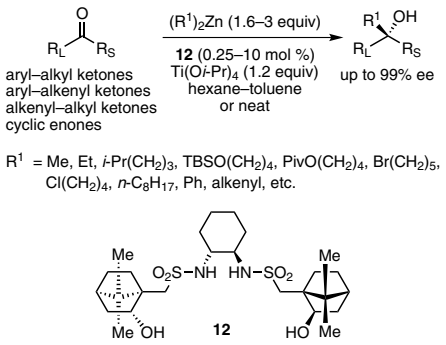
The synthesis of all-carbon stereogenic centers has been achieved with an NHC–Cu complex by the highly enantioselective addition of dialkyl- and diarylzincs to 3-substituted enones (**eq 10**).[71,72] The NHC–Cu complex is formed in situ from the corresponding NHC–Ag complex, **13**, and a copper(I) salt. The reaction gives the antipode of the product when *diaryl*zincs are added to enones. Hoveyda later reported another NHC–Cu complex that gives higher selectivities with cyclic γ-keto esters (R = CO_2Me or CO_2*t*-Bu).[73]

Nitroalkanes are very useful intermediates in organic chemistry owing to the synthetic versatility of the nitro group.[74] Our research group recently reported that these substrates could be readily prepared with ((*R,R*)-BozPhos)$_2$•CuOTf catalyzed diorganozinc addition to β-nitroalkenes (**eq 11**).[75,76] Good-to-excellent yields of highly enantioenriched nitroalkanes were observed when commercial diethylzinc was added to either aryl- or alkyl-substituted β-nitroalkenes. High yields and enantioselectivities required an additional amount of (*R,R*)-BozPhos (**1**) (2.5 mol %), which could be replaced by pivalamide (20 mol %) to favor a less aggregated ethylcopper species (3 examples, 69–91%, 93–96% ee's). Using diethylzinc prepared from zinc methoxide and ethylmagnesium chloride led to results almost identical to those obtained with neat Et_2Zn (92%, 94% ee).[13]

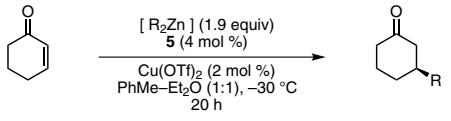
Sulfones possessing a stereocenter at the β carbon are powerful chiral synthons for preparing complex natural and biologically active molecules. These sulfones can be derivatized into a variety of products, including carbonyl derivatives, alkynes, alkenes, alkanes, and haloalkanes.[77] The catalytic enantioselective



Scheme 11. Triarylboroxine Transmetallation with Diethylzinc and Enantioselective Arylation of 3-Cyanobenzaldehyde on a Large Scale. *(Ref. 60)*



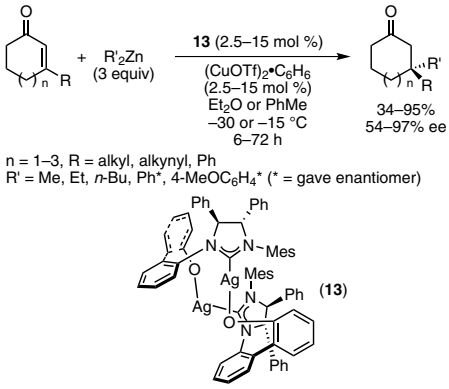
eq 8 *(Ref. 65)*



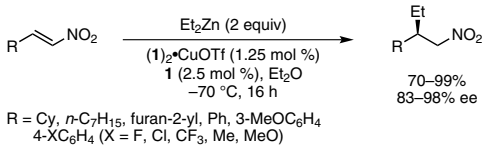
[a] **A**: (i) RMgCl (3.9 equiv), $Zn(OMe)_2$ (2.0 equiv), Et_2O, 0 °C to rt; (ii) centrifugation. **B**: Commercial, neat Et_2Zn was diluted in Et_2O. [b] $Zn(OMe)_2$ was prepared in situ from $ZnCl_2$ (2 equiv) and NaOMe (4.2 equiv). [c] Feringa's group (*Ref. 69*) reported 94% (>98% ee). [d] Feringa's group (*Ref. 69,70*) reported 92–95% (72-83% ee) for reaction run at –80 °C. [e] Styrene (1 equiv) was added as a radical inhibitor (see *Ref. 35*). [f] Feringa's group (*Ref. 69,70*) reported 95% (94% ee) for reaction run at –80 °C in the presence of styrene. [g] Feringa's group (*Ref. 69,70*) reported 95% (95% ee) for the addition of di(*n*-heptyl)zinc.

R_2Zn R	Source[a]	Yield	ee
Et	**A**	89%	>98%
Et[b]	**A**	88%	>98%
Et[c]	**B**	86%	>98%
n-Bu	**A**	94%	>95%
i-Bu	**A**	95%	97%
i-Pr[d]	**A**	92%	85%
i-Pr[e,f]	**A**	93%	94%
Cy	**A**	90%	80%
Cy[e]	**A**	94%	94%
$Ph(CH_2)_2$	**A**	97%	>98%
n-decyl[g]	**A**	97%	>98%
t-Bu	**A**	84%	6%
t-Bu[e]	**A**	19%	27%

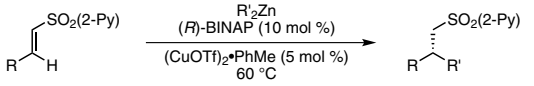
eq 9 *(Ref. 4,13)*



eq 10 *(Ref. 71)*



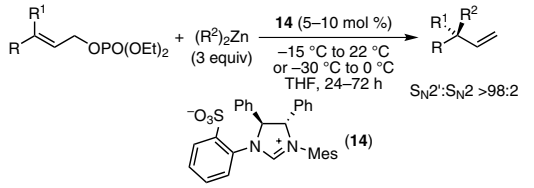
eq 11 *(Ref. 75)*



R	R'	R'2ZN Source	Yield	ee
Me	Et	**A**	93%	88%
i-Pr	Et	**A**	55%	96%
2-Np	Et	**A**	63%	97%
4-MeOC$_6$H$_4$	Et	**A**	61%	98%
4-F$_3$CC$_6$H$_4$	Et	**A**	57%	94%
Ph	Et	**A**	72%	98%
Ph[b,c]	Me	**B**	81%	98%
Ph[b]	*n*-Pr	**C**	52%	89%
Ph[b]	*n*-Bu	**C**	53%	90%
Ph[b,c]	Ph(CH$_2$)$_2$	**C**	72%	90%
Ph[b]	Cy	**C**	14%	17%

[a] **A**: Et$_2$Zn (3 equiv) in THF. **B**: Commerical, neat Me$_2$Zn was employed. **C**: (i) R'MgCl (5.85 equiv), Zn(OMe)$_2$ (3 equiv), Et$_2$O, 0 °C to rt; (ii) centrifugation. [b] Benzene was substituted for THF. [c] 6 equivalents of R'$_2$Zn used.

eq 12 *(Ref. 78)*



R	R^1	R^2	Yield	ee	R	R^1	R^2	Yield	ee
Ph	H	*i*-Pr	60%	81%	Ph	Me	Et	91%	91%
2-MeC$_6$H$_4$	H	Et	62%	83%	Ph	Me	*n*-Bu	71%	91%
Cy	H	Me	54%	79%	Ph	Me	*i*-Pr	52%	91%
Cy	H	Et	79%	85%	4-F$_3$CC$_6$H$_4$	Me	Et	68%	89%
Cy	H	*i*-Pr	64%	92%	4-O$_2$NC$_6$H$_4$	Me	Et	82%	89%
PhMe$_2$Si	H	Et	59%	90%	Cy	Me	Et	58%	94%
PhMe$_2$Si	H	*n*-Bu	59%	86%	*t*-BuO$_2$C	Me	*n*-Bu	85%	88%

eq 13 *(Ref. 82)*

addition of diorganozincs to vinyl sulfones is easily accomplished with copper(I) triflate and (*R*)-BINAP (**eq 12**).[78] The use of the 2-pyridyl group on the sulfone is mandatory for high reactivity and enantioselectivity. Fortunately, 2-pyridyl sulfones had been previously identified as the optimal coupling partner in the Julia–Kocienski olefination to generate *E,Z* dienes.[79]

It is also possible to use diorganozinc reagents prepared from alkylmagnesium chlorides and zinc methoxide to introduce an alkyl group at the β position of the sulfone. Good yields and enantioselectivities are obtained, except when dicyclohexylzinc is used.

3.2. Asymmetric Allylic and Propargylic Substitution Reactions

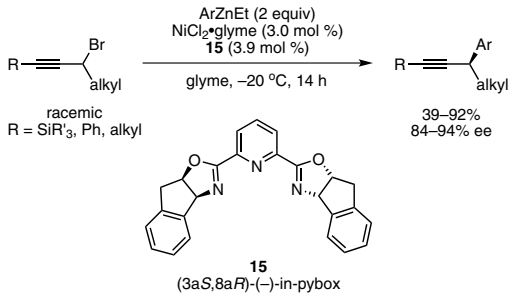
While enantioselective allylic substitution reactions with soft nucleophiles (as enolate derivatives) typically use palladium-, molybdenum-, or iridium-based catalysts,[80] the reaction with hard nucleophiles (dialkylzincs and Grignard reagents) is generally catalyzed by copper salts.[68,81] It was recently reported that chiral N-heterocyclic carbene complexes such as **14** (**eq 13**) are efficient catalysts in the Cu-free enantioselective allylic alkylation using diorganozinc reagents and allylic phosphates.[82] Generation of enantioenriched all-carbon quaternary stereogenic centers is also possible starting with trisubstituted olefins.

Smith and Fu succeeded in generating enantioenriched alkynes by employing a nickel(II) salt and a pybox ligand.[83] They first utilized diphenylzinc as the nucleophilic partner, and later adapted Bolm's method[5b] to generate phenyl(ethyl)zinc via a boron–zinc exchange in glyme as the reaction solvent. A wide array of aryl(ethyl)zinc reagents were cross-coupled with either TMS-protected propargylic bromides or nonterminal propargylic bromides (**eq 14**).[83] Similar enantioselective nickel-catalyzed cross-coupling reactions, utilizing secondary α-bromoamides,[84] secondary allylic chlorides,[85] or benzylic halides,[86] have also been developed by Fu's group. However, they are typically achieved with the more readily available alkylzinc halides as coupling partners.

The S$_N$2' reaction of organozincs with propargyl mesylates leading to trisubstituted allenes was dramatically improved by using DMSO as solvent (**Scheme 12**, Part (a)).[87] The stereoselective conversion of a chiral propargyl mesylate into a trisubstituted allene was successfully achieved using LiCl-free dibutylzinc[13] (Scheme 12, Part (b)).[87]

3.3. C–H Bond Arylation of Heteroaromatic Compounds

Diphenylzinc was recently employed in the nickel-catalyzed C–H bond arylation of electron-deficient heteroaromatic compounds



eq 14 *(Ref. 83)*

(**eq 15**).[88] Quinoline was also arylated with aryl(ethyl)zinc reagents that were formed by zinc–boron exchange. On the basis of preliminary experiments, the authors reported that the diphenylzinc transmetallates with the nickel catalyst to form a phenylnickelate complex, which is nucleophilic enough to add to the most electrophilic carbon of the N-heterocycles.

3.4. Electrophilic Amination of Organozinc Nucleophiles

The copper-catalyzed electrophilic amination of diorganozincs with *O*-benzoyl hydroxylamines is an alternative to the Buchwald–Hartwig cross-coupling. The electrophilic amination reagents are prepared from primary or secondary amines and benzoyl peroxide (**Scheme 13**). Good-to-excellent yields of di- or trisubstituted amines are obtained from dialkyl- or diarylzinc reagents.[89] Electrophilic amination of diorganozinc reagents by oxaziridines is also possible.[90] Very recently, another copper(I)-catalyzed amination reagent, $Me_2C{=}NOSO_2Mes$, was reported to generate aniline derivatives from aryl(ethyl)zincs in 34–66% yields.[91]

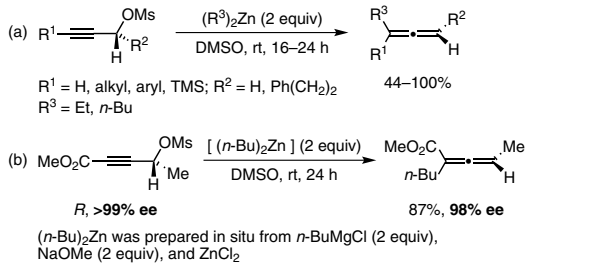
3.5. Carbozincation Reactions

The Rhodium-catalyzed carbozincation[92] of ynamides was very recently reported as an expedient protocol for generating di- and trisubstituted enamides in 49–91% yields and with good-to-excellent regioselectivities (rr > 4:1).[93] Addition of dibenzylzinc, diarylzincs, and dialkenylzincs to the ynamide was possible using in situ generated diorganozinc reagents. The synthesis of trisubstituted enamides was possible by functionalizing the dialkenylzinc intermediate obtained after the carbozincation reaction (**Scheme 14**).

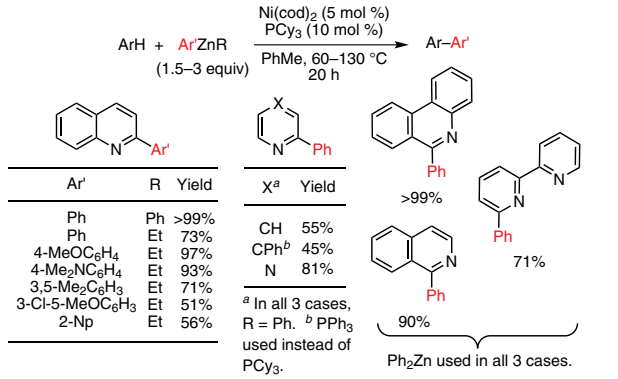
The diastereoselective Cu-catalyzed addition of diorganozincs to cyclopropenes was reported very recently.[94] Ester and oxazoline groups on the cyclopropene directed the addition of a variety of diorganozincs with excellent facial selectivity. The regioselectivity was high for carbozincation reactions of the carboxylate esters of 2-alkyl-substituted 2-cyclopropene (**Scheme 15**, Part (a)). The resulting cyclopropylzinc intermediates were captured via a stereoselective reaction with electrophiles. The commercially unavailable diorganozinc reagents utilized in the carbozincation reaction were prepared in situ using Seebach's protocol.[12]A chiral oxazolidinone auxiliary was effective in controlling the diastereoselectivity of the carbometallation reaction (Scheme 15, Part (b)).

3.6. Catalytic Enantioselective Addition of Dialkylzincs to N-Acylpyridinium Salts

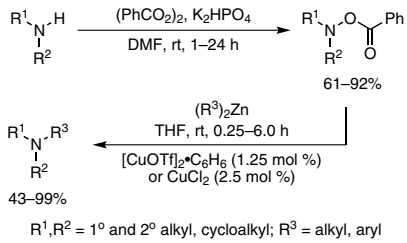
Substituted piperidinones are key structural units in medicinal chemistry and highly versatile intermediates in organic synthesis. A number of synthetic methodologies have been developed to access these useful heterocyclic compounds. Feringa and co-workers have very recently disclosed the first highly enantioselective addition of dialkylzincs to *N*-acylpyridinium salts using copper–phosphoramidite catalysts (**Scheme 16**).[95] The noncommercial dialkylzincs were prepared by using the new methodology introduced by Côté and Charette.[13] The addition of diethyl-, dipropyl-, dibutyl-, and diphenethylzincs gave the corresponding 2,3-dihydro-4-pyridinones with good yields and excellent enantioselectivities. In the case of diisopropylzinc, the enantioselectivity was lower, while the less reactive Me_2Zn did not provide the desired product at –78 °C or –55 °C (the starting material was recovered).



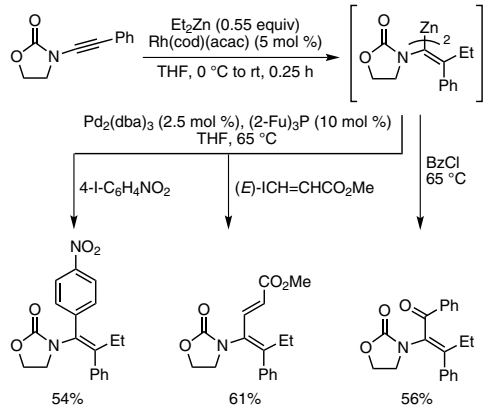
Scheme 12. Stereoselective Synthesis of Trisubstituted Allenes. *(Ref. 87)*



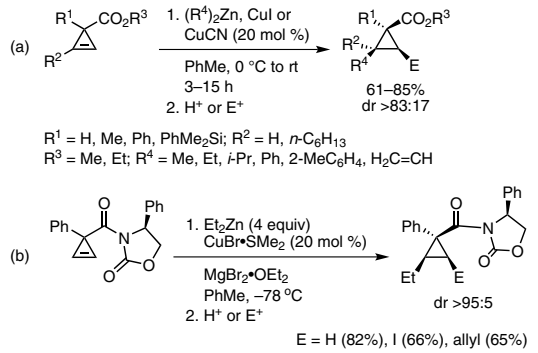
eq 15 *(Ref. 88)*



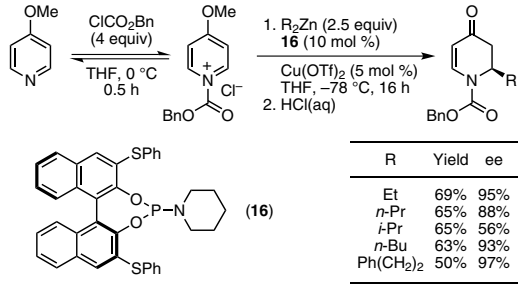
Scheme 13. Preparation of *O*-Benzoyl Hydroxylamines and Their Copper-Catalyzed Amination with Diorganozinc Reagents. *(Ref. 89)*



Scheme 14. Synthesis of Trisubstituted Enamides by the Rhodium-Catalyzed Carbozincation of Ynamides with Diorganozinc Reagents. *(Ref. 93)*



Scheme 15. Copper-Catalyzed, Directed Carbozincation of Cyclopropene Derivatives with Diorganozinc Reagents. *(Ref. 94)*



R	Yield	ee
Et	69%	95%
n-Pr	65%	88%
i-Pr	65%	56%
n-Bu	63%	93%
$Ph(CH_2)_2$	50%	97%

Scheme 16. Addition of Dialkylzinc Reagents to *N*-Acylpyridinium Salts. *(Ref. 95)*

4. Conclusions and Outlook

Diorganozinc reagents are versatile nucleophiles that accommodate either Lewis base or metal catalysis in enantioselective additions to electrophiles. They also display a very high functional-group tolerance. While a large number of diorganozinc reagents are now readily available via simple procedures, and despite tremendous improvements in accessing functionalized diorganozincs, as pioneered by Knochel, Seebach, Bolm, and others, there is still a strong need to increase their availability, which should significantly enhance their usefulness in synthesis.

It is worth mentioning that diorganozinc reagents have several other applications in organic synthesis, which have not been covered in this review. These include the Negishi coupling,[96] oxidation to alcohols,[97] addition to anhydrides[98] or acylation,[99] cyclopropanation or epoxide formation (with carbenoids),[100] and the allylzincation of alkenylmetals.[101]

5. Acknowledgements

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6. References and Notes

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Alexandre Lemire received his B.Sc. degree in chemistry in 2000 from the Université de Sherbrooke, QC, Canada. He then joined the research group of Professor André Charette at the Université de Montréal to work towards a Ph.D. degree in chemistry. His graduate studies focused on the stereoselective synthesis of piperidines. In 2006, he joined Professor K. C. Nicolaou's group at The Scripps Research Institute as an NSERC postdoctoral fellow. He conducted initial studies

towards the total synthesis of BE-43472B, a bisanthraquinone antibiotic. He subsequently moved back to Montreal and worked in the Chemical Development department at Wyeth Research. He is currently in Professor Charette's laboratory working on the process development of new diorganozinc reagents, with financial support from Soluphase Inc.

Alexandre Côté received his B.Sc. degree in chemistry in 1999 from the Université Laval (Quebec City). From 2000 to 2002, he was a medicinal chemist at Pharmacor in Laval (near Montreal), where he worked on HIV protease and integrase inhibitors. In 2002, he entered graduate school at the Université de Montréal, where he earned his M.Sc. (2004) and Ph.D. degrees (2007) under the supervision of Professor André Charette. His dissertation research focused on the development of new catalytic methods for the preparation of chiral amines and nitroalkanes using diphosphine monoxide ligands. He also worked on the synthesis of salt-free diorganozinc reagents and their applications in asymmetric catalysis. In January 2008, he joined Professor Erik Sorensen's group at Princeton University as an NSERC postdoctoral fellow. His current research is centered on the total synthesis of complex natural molecules.

Marc K. Janes was born in 1974 in Montréal, Canada. After receiving his B.Sc. degree in chemistry in 1999 from the Université de Montréal, he worked as a researcher in medicinal chemistry at the Merck Frosst Center for Therapeutic Research. He then went on to pursue graduate studies, and earned his M.Sc. and Ph.D. degrees in organic chemistry under the supervision of Professor André B. Charette, and co-directed by Professor Hélène Lebel. Based on these studies, he published articles on enantioselective cyclopropanation, soluble supports for organic synthesis, and abnormal NHC palladium catalysts (co-authored by Professor Steven P. Nolan). Presentation of this work earned him the Shire Pharmaceuticals Best Presentation Award (QOMSBOC, 2003) and the Outstanding Presentation Award (CSC Conference, 2004). In 2005, he became a consultant advising on the potential of transferring enabling technologies in the chemical industry. Since 2007, he has been co-founder and Vice President at Soluphase, Inc., a Canadian company that aims to commercialize technologies that accelerate drug discovery or make chemical processes easier, greener, and more cost-effective.

André B. Charette was born in 1961 in Montréal, QC. Shortly after obtaining his B.Sc. degree in 1983 from the Université de Montréal, he moved to the University of Rochester, NY, to pursue graduate studies. He earned his M.Sc. (1985) and Ph.D. (1987) degrees in organic chemistry under the supervision of Professor Robert Boeckman, Jr. He began his academic career in 1989 at the Université Laval (Québec City) following a two-year NSERC postdoctoral fellowship with Professor David A. Evans at Harvard University. In 1992, he joined the Université de Montréal, where he quickly rose through the ranks to become full professor in 1998. He is presently the holder of the NSERC/Merck Frosst/Boehringer Ingelheim Industrial Chair on Stereoselective Drug Synthesis and of a Canada Research Chair on the Stereoselective Synthesis of Bioactive Molecules. His research focuses primarily on the development of new methods for the stereoselective synthesis of organic compounds and natural products. Among his recent honors are the Urgel Archambault Award (2006), the ACS Cope Scholar Award (2007), the Prix Marie-Victorin (2008), and the CSC Alfred Bader Award (2009).

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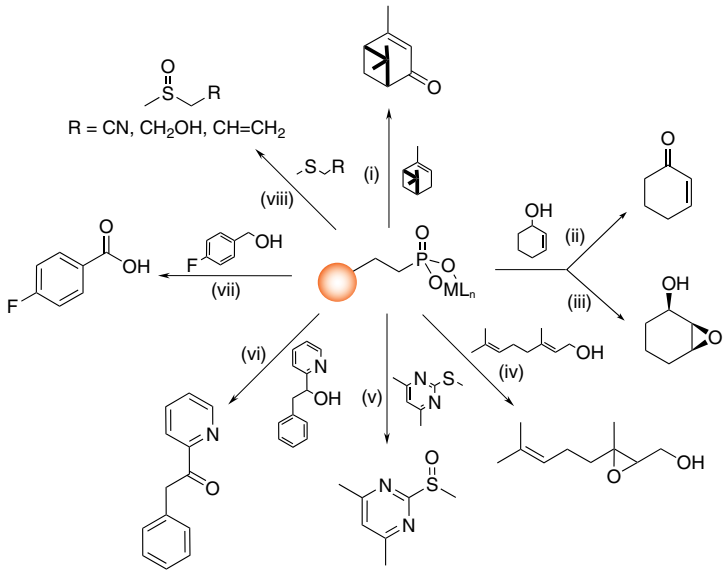
References:

(1) Al-Haq, N. et al. *Tetrahedron Lett.* **2003**, *44*, 769.
(2) Jurado-Gonzalez, M. et al. *Tetrahedron Lett.* **2003**, *44*, 4283.
(3) Jurado-Gonzalez, M. et al. *Tetrahedron Lett.* **2004**, *45*, 4465.
(4) Al-Hashimi, M. et al. *Tetrahedron Lett.* **2005**, *46*, 4365.



(i) & (ii) ML_n = Co(II) (*POCo*); (iii) & (iv) ML_n = VO(II) (*POVO*); (v)–(viii) ML_n = Ce(IV) (*POCe*)

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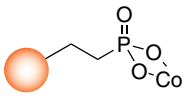
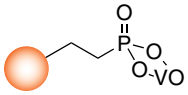
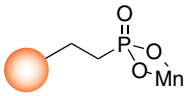
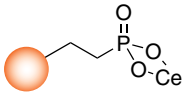
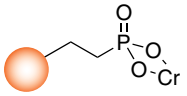
Oxidation Catalyst	Substrate	Product	Re-Oxidant
	Allylic/Benzylic CH_2 Allylic alcohols	Ketones Enones	*t*-BuOOH
	Allylic alcohols Sulfides	Epoxides Sulfoxides	*t*-BuOOH or $NaBrO_3$ or H_2O_2
	Allylic CH_2 or Benzylic CH_2	Ketones	*t*-BuOOH
	1° alcohols 2° alcohols Sulfides	Acids Ketones Sulfoxides	$NaBrO_3$ or *t*-BuOOH
	Sulfides	Sulfoxides	$NaBrO_3$ or *t*-BuOOH

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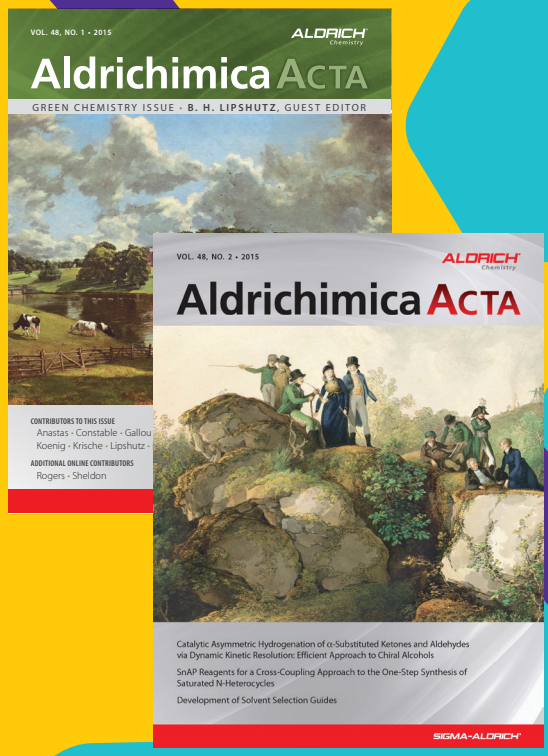

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