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.

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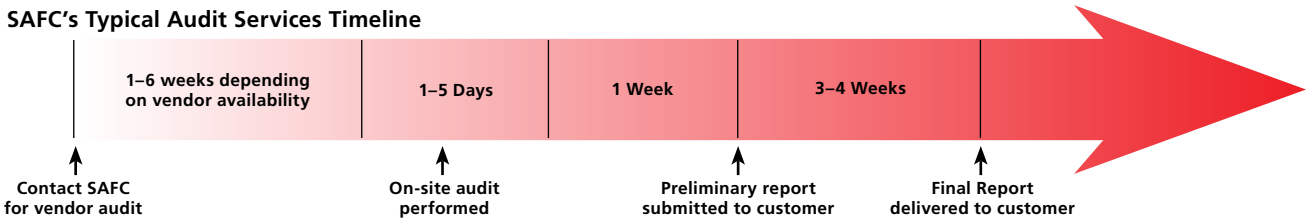

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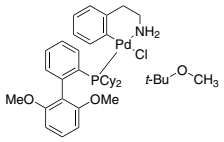
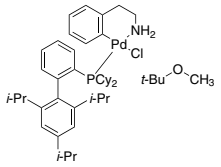
"PLEASE BOTHER US."

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.

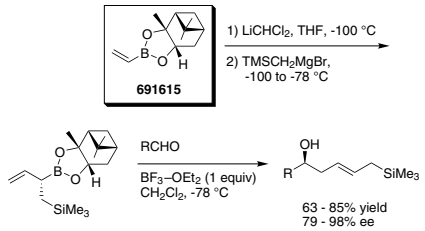
ALDRICH Chemistry

New Products from Aldrich R&D

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

Double-Allylation Reagents

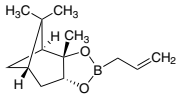
Reagents bearing multifunctional handles are of interest for the preparation of complex molecules. Professor Hall and coworkers developed a new multifunctional reagent that provides high diastereo- and enantiocontrol in a number of reactions, such as in the nucleophilic addition to aldehydes.



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

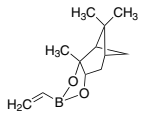
(+)-Allylboronic acid pinanediol ester, 97%

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



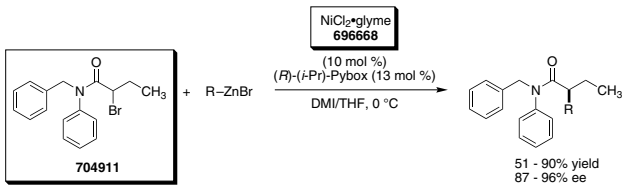
(+)-Vinylboronic acid pinanediol ester, 95%

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



Substrate for Nickel-Catalyzed Negishi Coupling

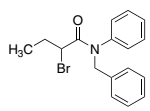
Chiral building blocks are of the utmost importance in the synthesis of more complex molecules. Professor Fu and coworkers devised the first catalytic enantioselective cross-coupling of secondary α-bromo amides with organozinc reagents. This new method proved to be highly selective for the coupling of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



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

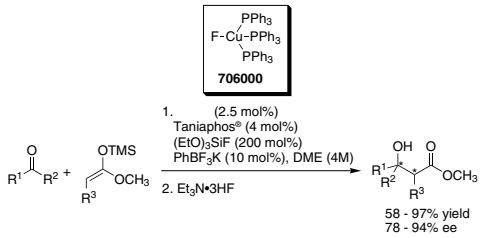
***N*-Benzyl-2-bromo-*N*-phenylbutanamide, 97%**

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.



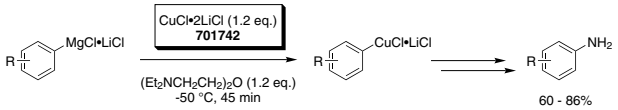
Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164. Taniaphos is a registered trademark of OMG AG and Co.

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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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]

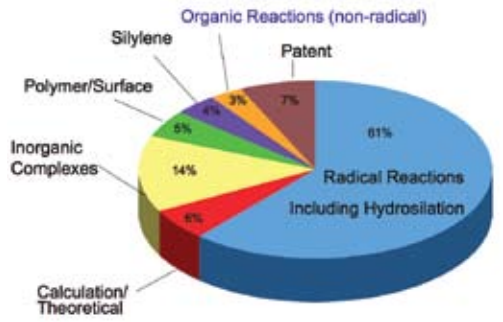
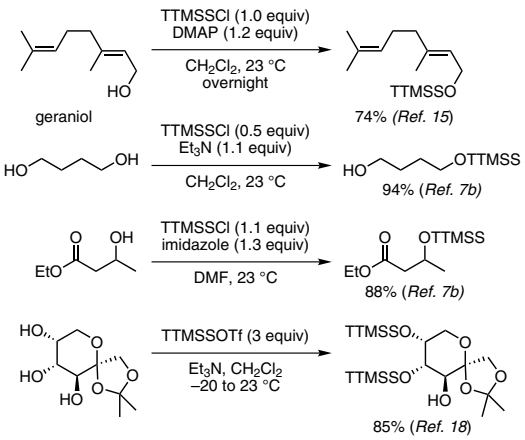
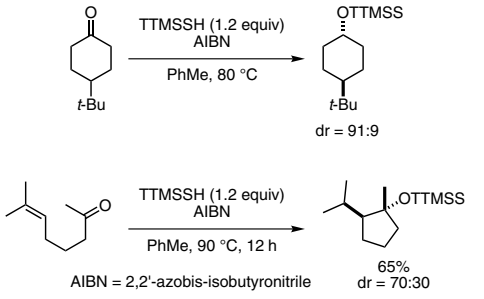


Figure 1. Pie Chart Showing the Breakdown by Application of Literature References Citing the Tris(trimethylsilyl)silyl (TTMSS) Group. *(Ref. 7)*



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.

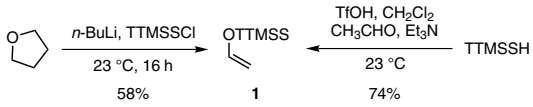
Takasu, Ihara, and co-workers have published numerous reports on formal [2 + 2] cyclizations of SEEs derived from ketones.[22] Their original report took advantage of in situ SEE formation with a TMSI–HMDS system and the use of a chiral auxilliary (8-phenylmenthyl ester).[22a] They later employed preformed 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.

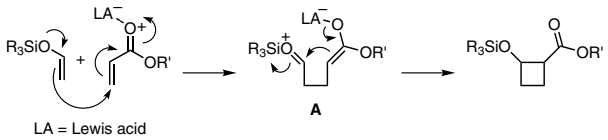
Various Lewis acids were screened, but only the $EtAlCl_2$-based catalyst gave acceptable results, while $TiCl_4$, $GaCl_3$, $SnCl_4$, $AgNTf_2$, TMSOTf, and $HNTf_2$ all gave <10% of the desired product. It has been observed that unwanted transfer of silyl groups during attempted asymmetric aldol synthesis 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).

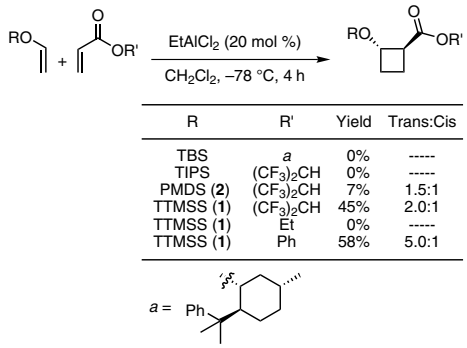
The significance of these super SEEs was clearly demonstrated by their success in the [2 + 2] cyclizations. That is, these examples represented the first formal [2 + 2] condensations between an acetaldehyde SEE and an acrylic



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

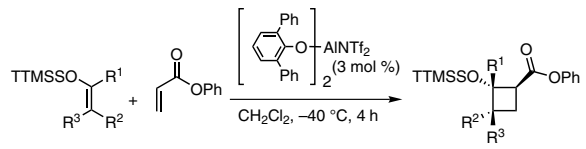


Scheme 4. Proposed Michael Aldol Mechanism for the Formal [2 + 2] Cyclization. *(Ref. 6a)*



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

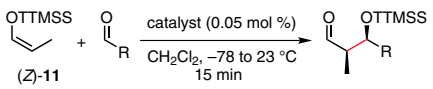
Although the Mukaiyama aldol synthesis is one of the most powerful variants of the aldol reaction, the aldehyde crossed aldol reaction has only been realized in a few cases, many of which are limited in scope.[29–31] In 1974, Mukaiyama followed his archetypal report with two examples of the isobutyraldehyde 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.

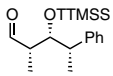
In 2001, Denmark reported that trichloro SEEs of propanal and heptanal successfully reacted with aromatic and aliphatic aldehydes in an enantioselective fashion catalyzed by a chiral phosphoramide base.[30g] The diastereoselectivity was controlled by the enol geometry, with the *Z* enols giving high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

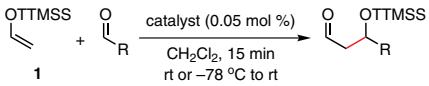
In 2006, our group published a diastereoselective reaction that worked very well with propionaldehyde-derived super SEE (*Z*)-**11**.[6b] High yields and good syn:anti ratios were obtained using $HNTf_2$ as the precatalyst. This Brønsted acid is termed the precatalyst due to the fact that the use of $(TTMSS)NTf_2$ (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

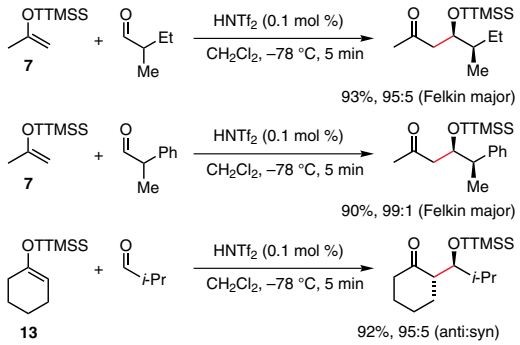
For many obvious and necessary reasons, there is considerable interest in economical and environmentally friendly reactions.[38,39] In this vein, one-pot, sequential and multicomponent reactions have emerged as an important means for accomplishing some of these goals. As Tietze and Beifuss wrote in a 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]

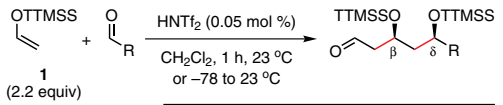
5.1. Cascade Reactions of Aldehyde-Derived SEEs

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%	----

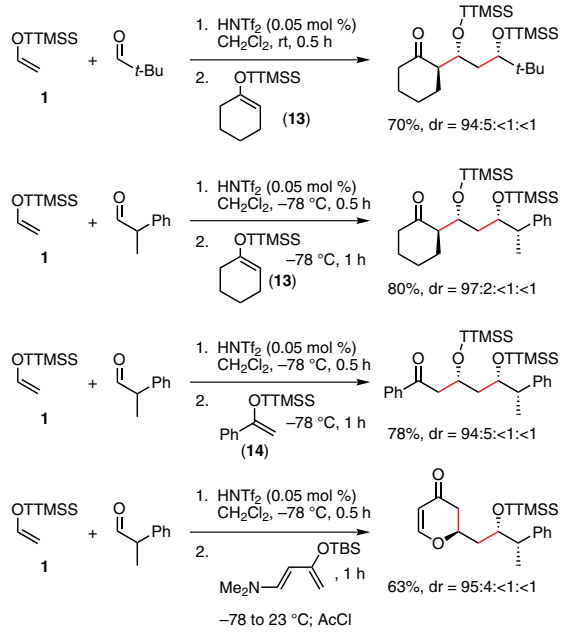
[a] Major product has the opposite configuration at the β and δ carbons.

eq 5 *(Ref. 6b)*

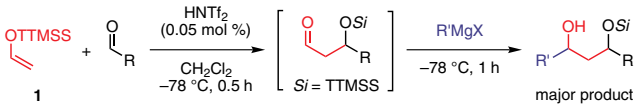
α-benzyloxypropanal formed a β,δ,ε-trihydroxy aldehyde adduct—consistent with a mechanism involving chelation-controlled first aldol addition followed by a syn-selective second aldol addition.

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]

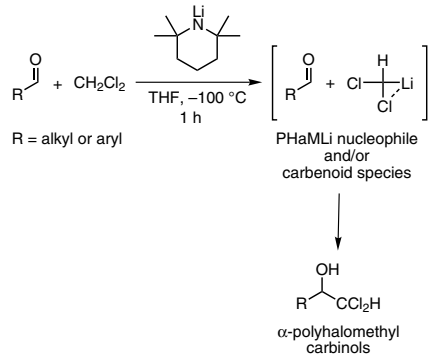
Polyhalomethanes (PHaMs) are small inexpensive molecules that are typically used as solvents (i.e., CH_2Cl_2 and $CHCl_3$). Halogens, of course, have a diverse reactivity profile and can render compounds electrophilic or nucleophilic.[48] Medicinal chemistry has revealed that fluorine- and chlorine-containing 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]

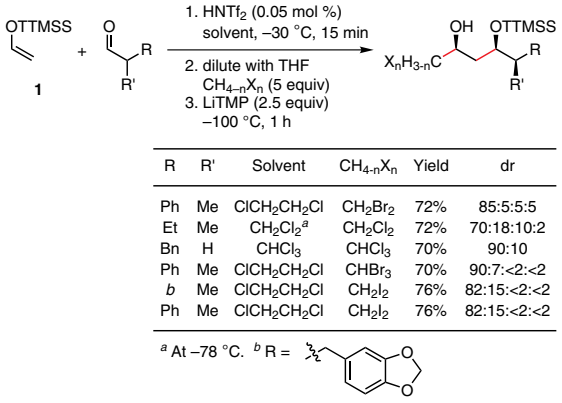
Thus, this reaction is a natural fit for our SA–nucleophile addition reaction sequence, since the requisite acid catalyst for the first step is present at only 0.05 mol % and the reaction proceeds in nonprotic solvents. Using our standard aldol reaction of **1** and 2-phenylpropionaldehyde, a variety 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



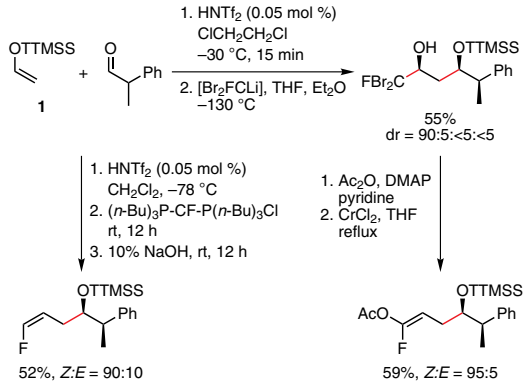
Scheme 8. PHaMLi Generation and in Situ Reaction with Aldehydes. *(Ref. 6e)*



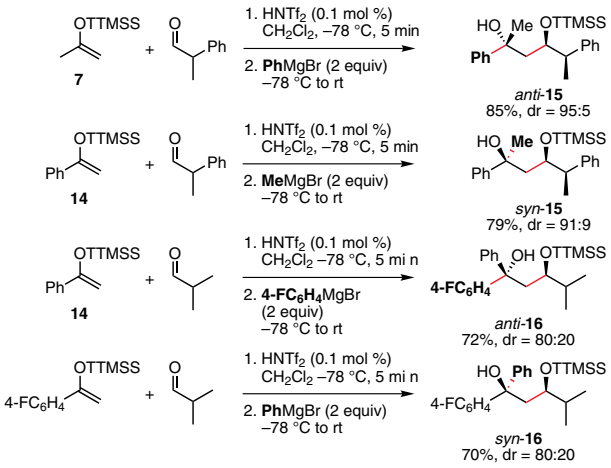
R	R'	Solvent	$CH_{4-n}X_n$	Yield	dr
Ph	Me	$ClCH_2CH_2Cl$	CH_2Br_2	72%	85:5:5:5
Et	Me	CH_2Cl_2[a]	CH_2Cl_2	72%	70:18:10:2
Bn	H	$CHCl_3$	$CHCl_3$	70%	90:10
Ph	Me	$ClCH_2CH_2Cl$	$CHBr_3$	70%	90:7:<2:<2
b	Me	$ClCH_2CH_2Cl$	CH_2I_2	76%	82:15:<2:<2
Ph	Me	$ClCH_2CH_2Cl$	CH_2I_2	76%	82:15:<2:<2

[a] At –78 °C. [b] R =

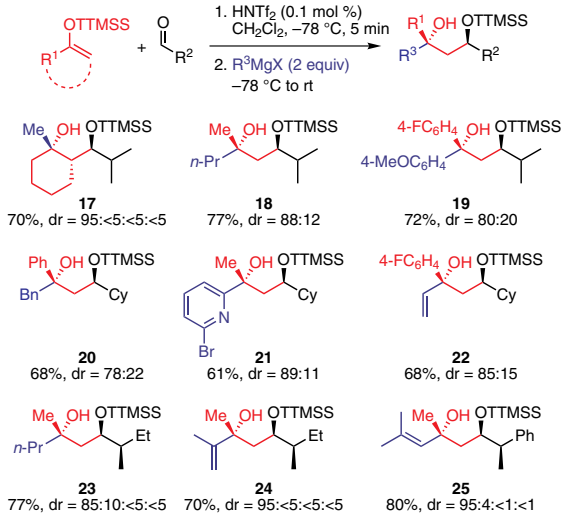
Scheme 9. Sequential Aldol–Polyhalomethyllithium Addition Reactions. *(Ref. 6e)*



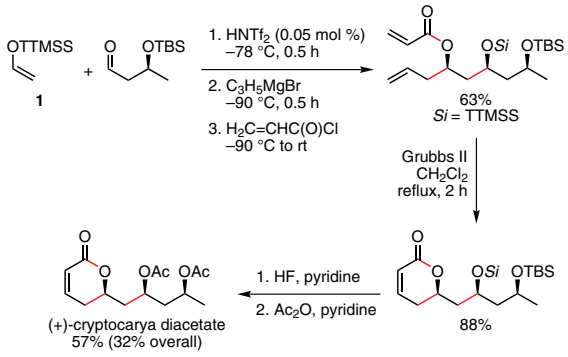
Scheme 10. Synthesis of Mixed α-Polyhalomethyl Carbinols and Fluoroalkenes. *(Ref. 6e)*



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

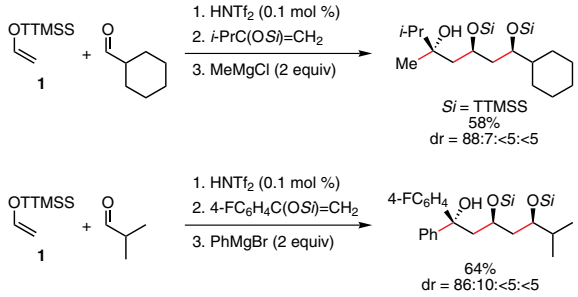
Much of the exceptional diastereoselectivity and control associated with the TTMSS group can likely be traced to its large steric size.[2,61] The super silyl group is extraordinarily bulky, and has been stated to shield molecular skeletons with a "H_3C-skin."[2] It has been reported that this group has 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.

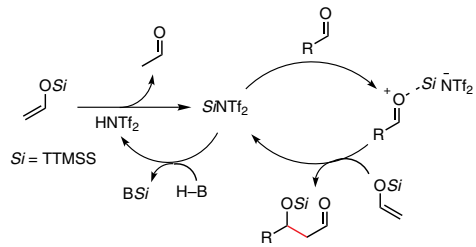
The stereochemical outcome is then largely determined by the interaction of the carbonyl and its substituent (Me for ketone and H for aldehyde) with the medium-sized β-group (*i*-Pr). This is in contrast to typical open-chain ketones and aldehydes, which have much more freedom of rotation due to the 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)*

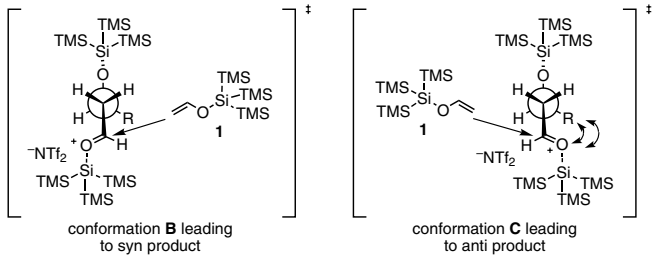


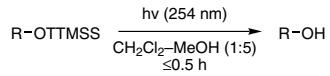
Figure 2. Original Transition-State Proposal for an Aldol Addition of **1** to a β-Super Siloxy Aldehyde. *(Ref. 6b)*

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)*

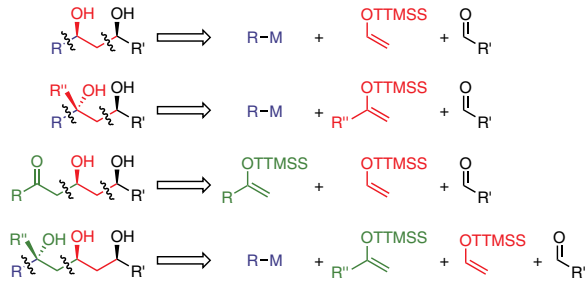


Figure 3. Anticipated Retrosynthetic Disconnections (All Would Be One-Pot Reactions).

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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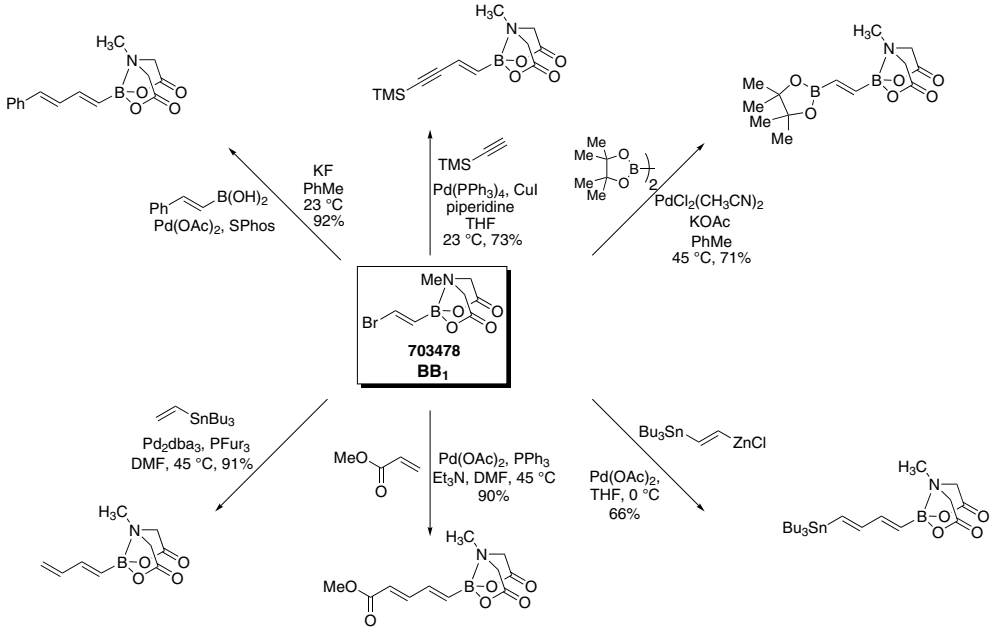

To view all the MIDA boronates offered by Sigma-Aldrich, see page 28 of this issue or visit ***sigma-aldrich.com/mida***.

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

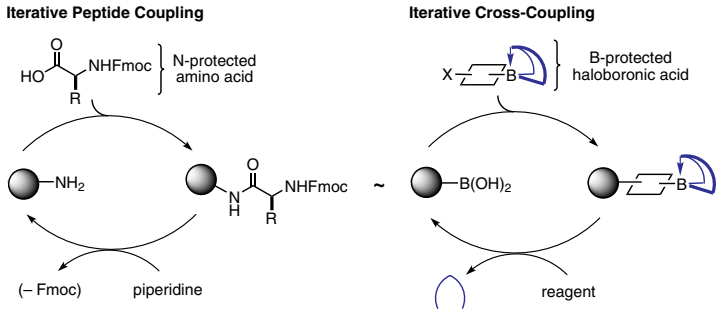
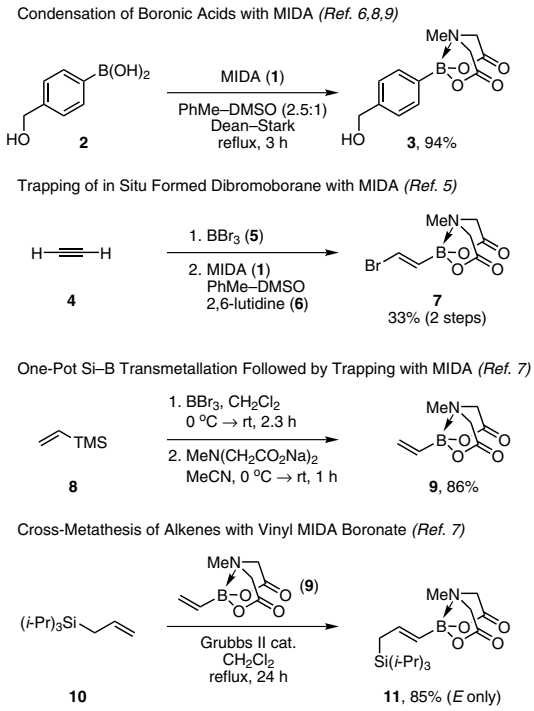


Figure 1. Analogous Strategies for the Synthesis of Peptides and Small Molecules.



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

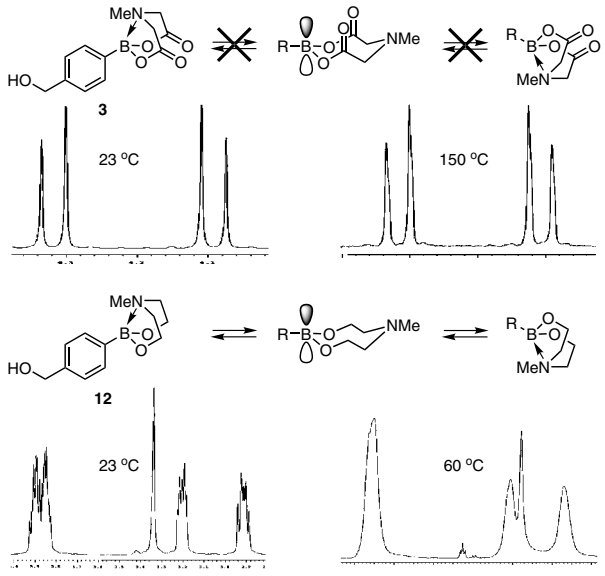


Figure 2. Variable-Temperature NMR Studies in DMSO-d_6 with MIDA Boronate and *N*-Methyldiethanolamine Adducts That Demonstrate the Unique and Remarkable Conformational Rigidity of the MIDA Boronate Framework. *(Ref. 6)*

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.

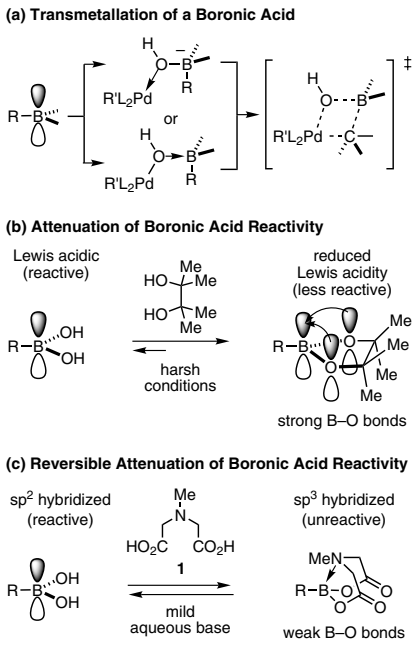
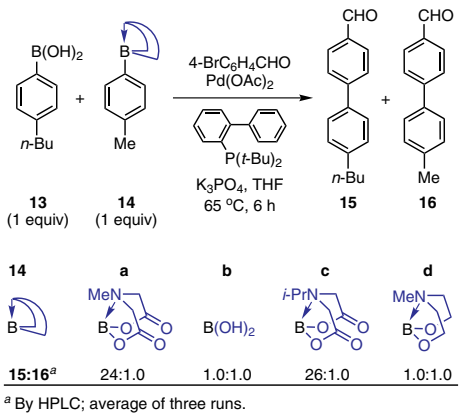


Figure 3. Under Suzuki–Miyaura Cross-Coupling Reaction Conditions: (a) Transmetallation Requires a Vacant and Lewis Acidic Boron p Orbital. (b) Strongly Electron-Donating Divalent Ligands Can Attenuate Boronic Acid Reactivity, but Typically Require Relatively Harsh Conditions for Cleavage. (c) The Reactivity 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

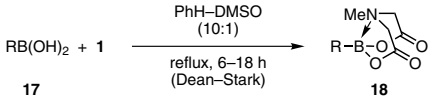
metal-mediated cross-couplings. Given the prevalence of alkenyl and polyenyl subunits in both natural products and pharmaceutical targets, we developed a collection of bifunctional building blocks specifically designed to enable polyene synthesis via ICC.[5]

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]

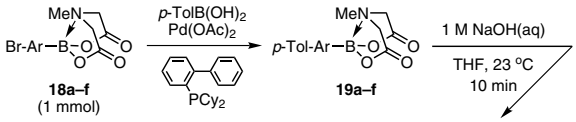
The capacity to prepare and selectively couple bifunctional halo MIDA boronates enables one to envision the synthesis of natural products or pharmaceuticals by using only a single reaction iteratively to bring together a collection of pre-assembled building blocks. This strategy was first realized with 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.

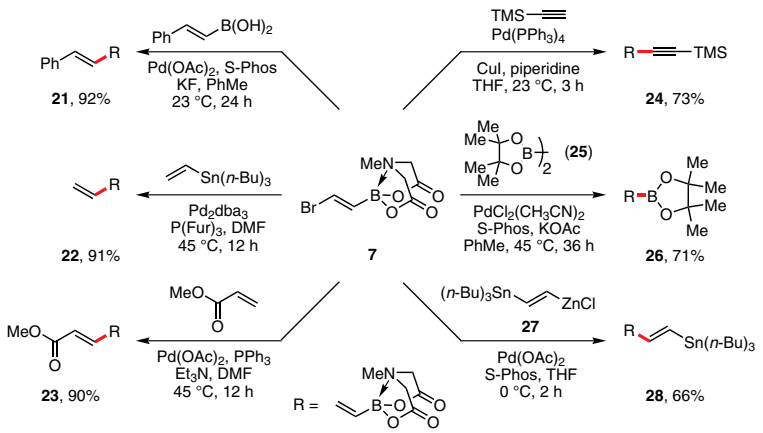
eq 2 *(Ref. 4)*



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)*

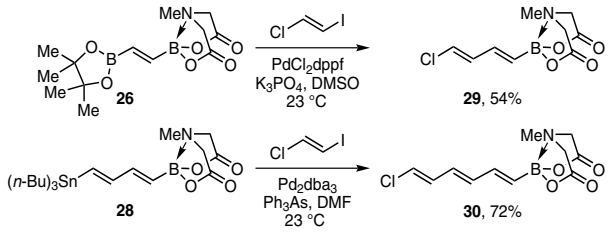


Scheme 3. Bifunctional Halogenated MIDA Boronate Building Blocks Such as **7** Can Be Rapidly and Selectively Elaborated at the Halogen Terminus. *(Ref. 5)*

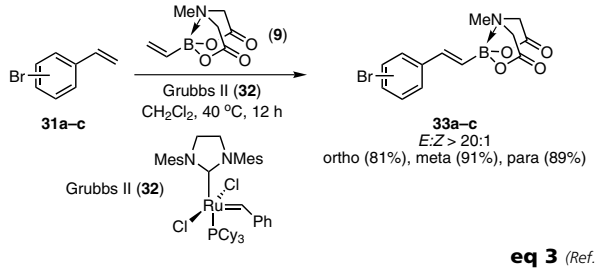
ICC methodology. First, couplings of alkenylboronic acids tend to be less efficient than those of their aryl counterparts, making the selective coupling between **35** and aryl MIDA boronate **36** unsecured. In addition, 2-substituted heterocyclic boronic acids such as **36** are notoriously unstable 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)*

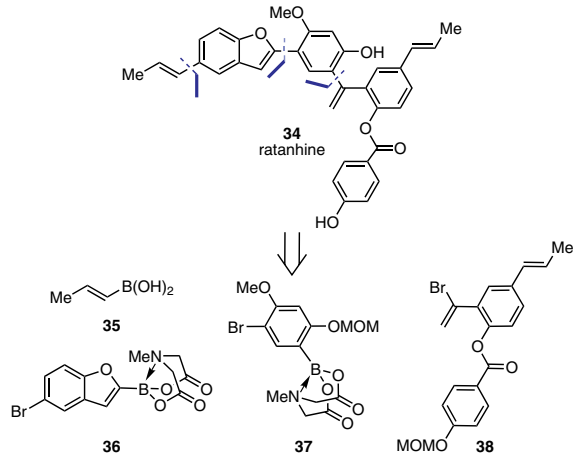
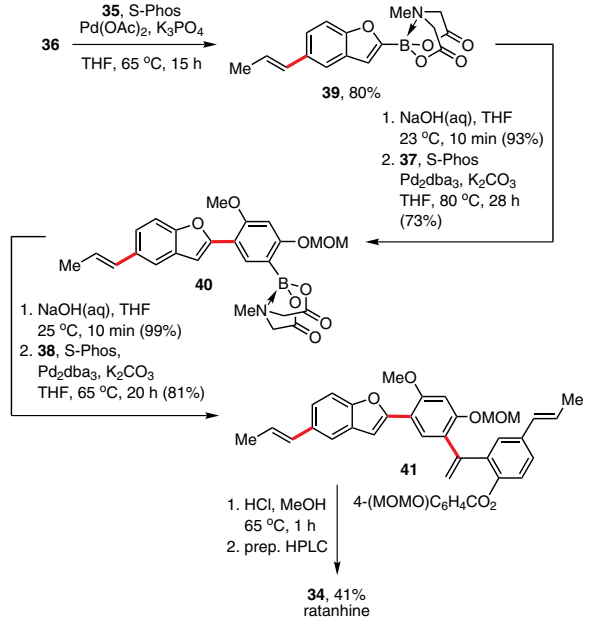
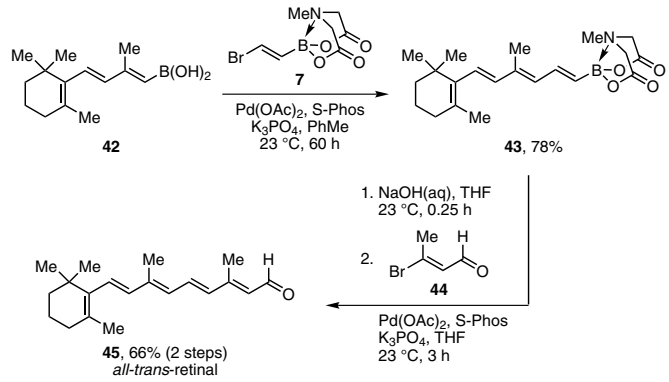


Figure 4. Retrosynthetic Analysis of the Natural Product Ratanhine Using ICC Identified Four Building Blocks, of Which **36** and **37** Are Bifunctional Halogenated MIDA Boronates. *(Ref. 4)*



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

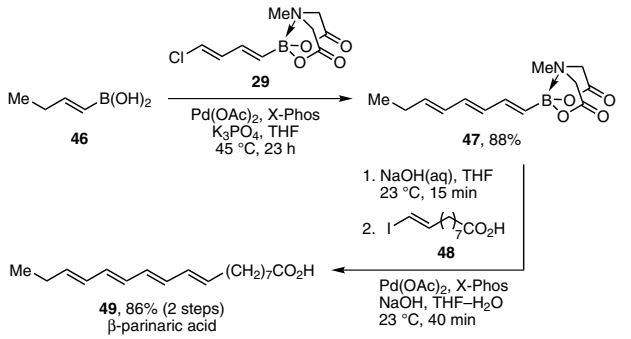
To avoid a general incompatibility with synthetic reagents, it is typically necessary to introduce the boronic acid functional group just prior to its utilization in a cross-coupling or other type of reaction. However, most of the methods that are available for achieving this have poor functional-group 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.

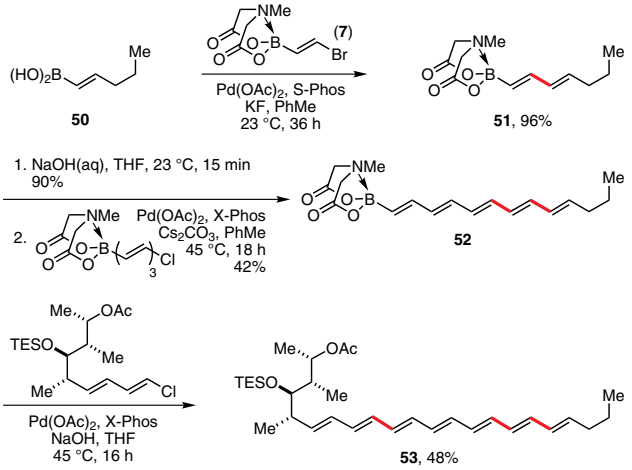
Overcoming these limitations, we have recently found that the MIDA boronate functional group is stable to a wide range of common synthetic reagents, presumably due to the lack of a reactive boron p orbital.[6] Combined with the general compatibility of MIDA boronates with chromatography and the capacity 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).

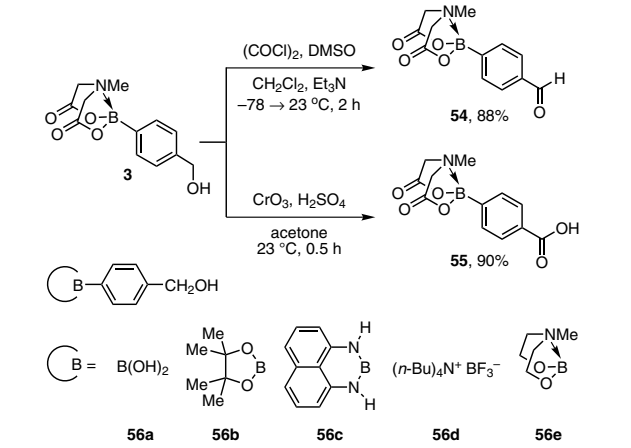
This unique compatibility with strong acid and oxidants suggested that MIDA boronates could be stable to a wide range of reaction conditions. In fact, even triflic acid (pK_a –14) was tolerated, enabling the *p*-methoxybenzylation of **3** and the reversal of this transformation with DDQ (**Scheme 10**).[6]



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)*

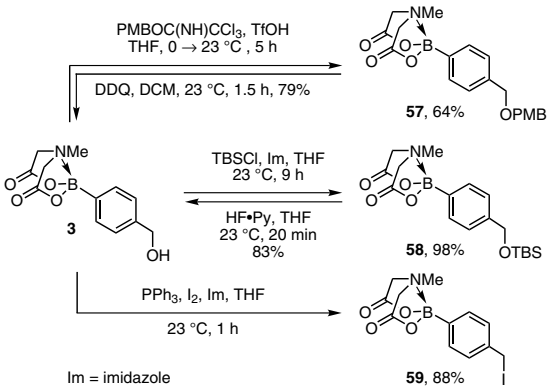
Similarly, silation and desilation were well-tolerated, as was the transformation into the corresponding benzyl iodide **59** with PPh_3–I_2.

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]

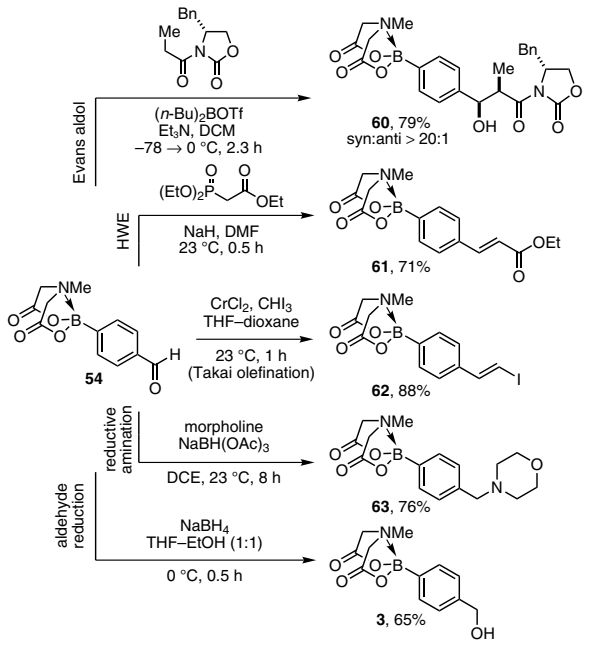
Whereas cyclopropanation of vinyl boranes[39,40] and epoxidation of 1,2-disubstituted alkenyltrifluoroborate salts[37b] are known, the versatility and broad compatibility of vinyl MIDA boronate (**9**) as a starting material has also been demonstrated (**Scheme 12**).[7] Specifically, cyclopropanation 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.

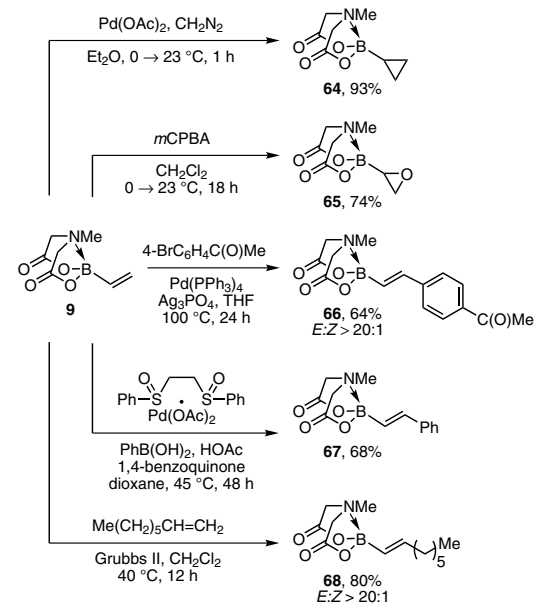
To explore the enabling potential of this approach, we targeted the total synthesis of the natural product crocacin C.[6,45] As shown in **Figure 5**, this molecule was retrosynthetically



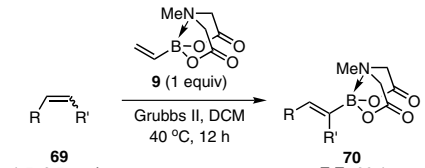
Scheme 10. MIDA Boronates Are Stable to a Number of Useful Reagents in Organic Synthesis. *(Ref. 6)*



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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8. References and Notes

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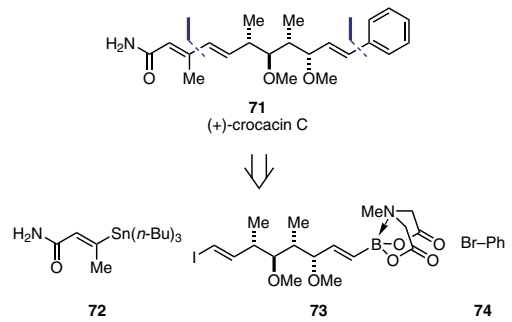
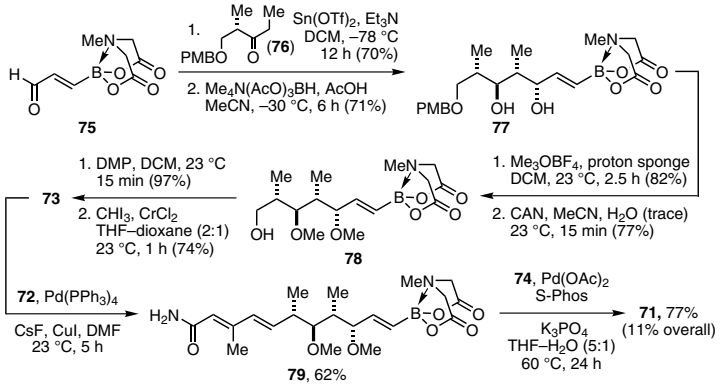


Figure 5. Retrosynthetic Analysis of the Natural Product (+)-Crocacin C Identified the Relatively Complex Halogenated MIDA Boronate Building Block **73**. *(Ref. 6)*



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.

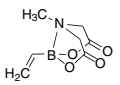
About the Authors

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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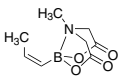
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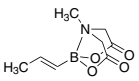
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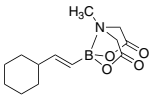
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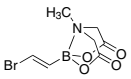
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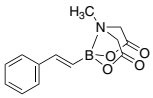
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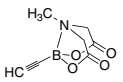
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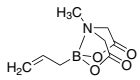
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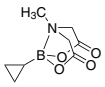
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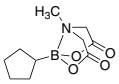
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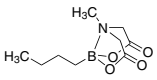
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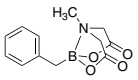
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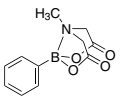
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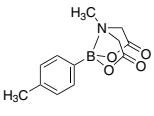
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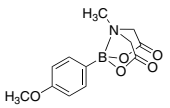
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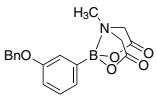
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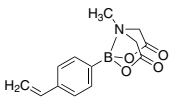
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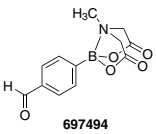
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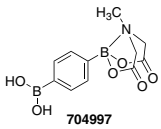
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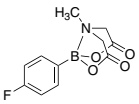
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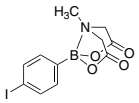
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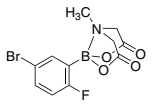
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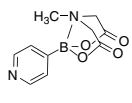
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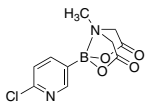
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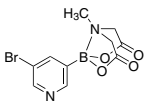
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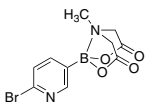
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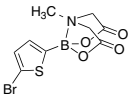
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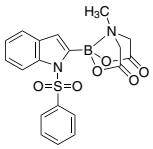
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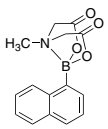
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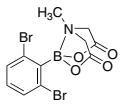
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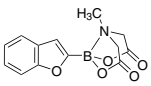
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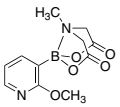
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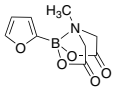
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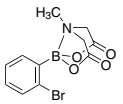
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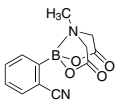
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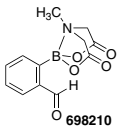
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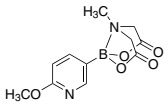
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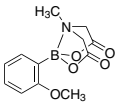
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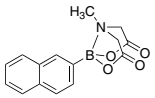
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