ACCOUNTS
of chemical research

Efficient Approaches to the Stereoselective Synthesis of Cyclopropyl Alcohols

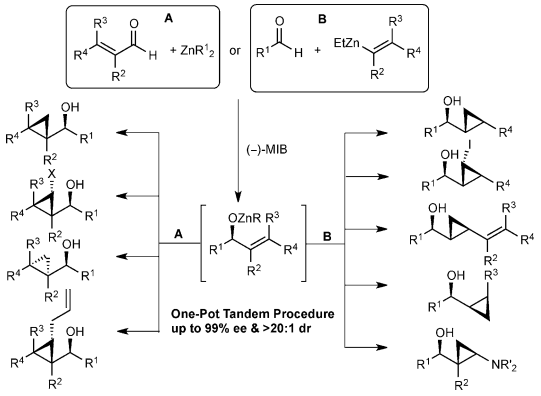
HUN YOUNG KIM[†] AND PATRICK J. WALSH[*,‡]

[†]*Department of Chemistry and Chemical Biology, Indiana University Purdue University Indianapolis, 402 North Blackford Street, Indianapolis, Indiana 46202, United States, and* [‡]*P. Roy and Diane T. Vagelos Laboratories, University of Pennsylvania, Department of Chemistry, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, United States*

RECEIVED ON FEBRUARY 14, 2012

CONSPECTUS

Cyclopropanes occur in a diverse array of natural products, including pheromones, steroids, terpenes, fatty acid metabolites, and amino acids, and compounds that contain cyclopropanes exhibit interesting and important pharmacological properties. These valuable synthetic intermediates can be functionalized, or their rings can be opened, and the synthetic utility and unique biological activity of cyclopropanes have inspired many investigations into their preparation. One of the most powerful methods to generate cyclopropanes is the Simmons–Smith cyclopropanation. Since the original studies in the late 1950s reported that $IZnCH_2I$ could transform alkenes into cyclopropanes, researchers have introduced various modifications of the original procedure. Significantly, Furukawa demonstrated that diethylzinc and CH_2I_2 react to generate carbenoids, and Shi described more reactive zinc carbenoids that contain electron-withdrawing groups on zinc ($XZnCHI_2$). Despite these advances, the development of catalytic asymmetric Simmons–Smith reactions remains challenging. Although researchers have achieved catalytic asymmetric cyclopropanation of allylic alcohols, these reactions have had limited success. One attractive approach to the synthesis of cyclopropanes involves tandem reactions, where researchers carry out sequential synthetic transformations without the isolation or purification of intermediates. Such a synthetic strategy minimizes difficulties in the handling and purification of reactive intermediates and maximizes yields and the generation of molecular complexity.



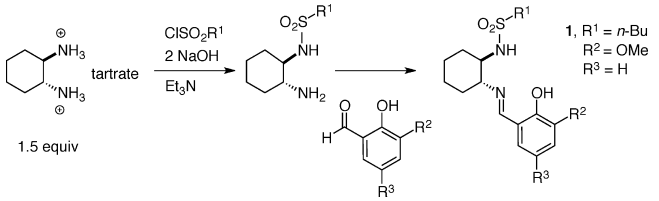
This Account summarizes our recent effort in the one-pot enantio- and diastereoselective synthesis of cyclopropyl alcohols. In one approach, an asymmetric alkyl addition to α,β-unsaturated aldehydes or asymmetric vinylation of aliphatic or aromatic aldehydes generates allylic zinc alkoxide intermediates. Directed *diastereoselective* cyclopropanation of the resulting alkoxide intermediates using *in situ* generated zinc carbenoids provides cyclopropyl or halocyclopropyl alcohols with high enantio-, diastereo-, and chemoselectivity. Other strategies employ bimetallic reagents such as 1-alkenyl-1,1-heterobimetallics or $CH_2(ZnI)_2$ and provide access to di- and trisubstituted cyclopropyl alcohols. These methods enable facile access to skeletally diverse chiral cyclopropyl alcohols in high yields and stereoselectivities without the isolation or purification of the intermediates.

1. Introduction

Cyclopropanes are encountered in diverse natural products, including pheromones, steroids, terpenes, fatty acid metabolites, and amino acids.[1,2] They exhibit a broad array of biological properties and are found in over 100 therapeutic agents.[1−4] Cyclopropanes are also useful building blocks in organic chemistry that undergo ring-opening reactions or can be elaborated to provide functionalized cyclopropanes.[1−6] Given the utility of these strained structural motifs, many syntheses have been reported.[2−7] One attractive approach to the synthesis of cyclopropanes involves tandem reactions, whereby sequential synthetic transformations are performed without isolation or purification of intermediates. Such a synthetic strategy minimizes difficulties handling and purifying reactive intermediates, and maximizes generation of molecular complexity and yields. This Account details novel

Published on the Web 06/22/2012 www.pubs.acs.org/accounts
10.1021/ar300052s

SCHEME 1. Synthesis of the Sulfonamide/Schiff Base Ligands



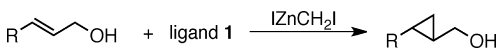
tandem approaches toward the synthesis of cyclopropyl alcohols and cyclopropanols with excellent control over enantio-, diastereo-, and chemoselectivity. In our tandem sequences, enantioenriched allylic alkoxide intermediates are generated via catalytic asymmetric additions to aldehydes. The *in situ* generated allylic alkoxides are subjected to the diastereoselective Simmons–Smith cyclopropanation to provide cyclopropyl alcohols with up to four stereogenic centers. By variation of the organozinc, aldehyde, and carbenoid, a wide variety of structurally diverse cyclopropanes can be accessed in good to excellent yields using these general methods.

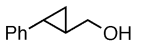
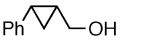
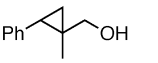
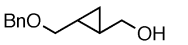
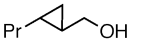
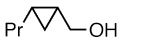
2. Tandem Routes to Cyclopropyl Alcohols

2.1. Catalytic Enantioselective Cyclopropanation of Allylic Alcohols. Our initial investigations in cyclopropanation chemistry in 1999 were focused on a long-standing problem: the catalytic asymmetric cyclopropanation of allylic alcohols. Enantioselective cyclopropanation of allylic alcohols using stoichiometric chiral additives[8−10] was known and had been used in natural product synthesis. The development of effective *catalytic asymmetric* cyclopropanations of allylic alcohols, however, remained a challenge. TADDOL and bis(sulfonamide)-based cyclopropanation catalysts, developed by Charette[11] and Kobayashi,[12] respectively, have been employed in this reaction with limited substrate scopes. To develop enantioselective Simmons–Smith cyclopropanations, we introduced easily prepared sulfonamide/Schiff base ligands (Scheme 1).[13] Our asymmetric cyclopropanation[14] employed Denmark's[15] two-flask method; allylic zinc alkoxide and the catalyst were formed in one flask, and the zinc carbenoid was generated in the other. The solutions were then combined. After screening our modular ligands, **1** was identified as the most enantioselective. Moderate enantioselectivities (up to 88%) were achieved with high catalyst loading (50 mol %) and limited substrate scope (Table 1).[14] The challenging nature of this project inspired us to rethink our approach to the synthesis of enantioenriched cyclopropyl alcohols.

2.2. Catalytic Asymmetric Alkyl Addition/Diastereoselective Cyclopropanation. Given the formidable challenge

TABLE 1. Asymmetric Cyclopropanation of Allylic Alcohols with Ligand **1**

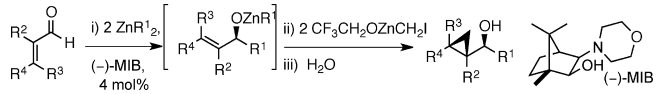


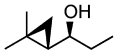
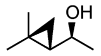
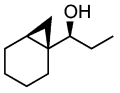
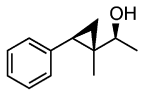
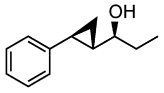
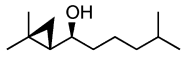
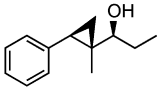
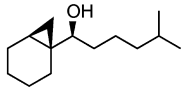
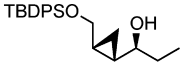
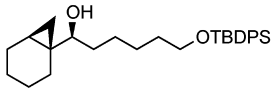
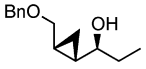
entry	product	20 mol% **1** % ee (% y)	50 mol% **1** % ee (% y)	config. (major enant.)
1		72 (98)	88 (98)	1*R*,2*R*
2		40 (96)	66 (96)	1*S*,2*R*
3		0 (90)	0 (96)	--
4		78 (96)	89 (98)	1*R*,2*R*
5		47 (95)	72 (92)	1*S*,2*R*
6		57 (92)	66 (91)	1*R*,2*R*
7		49 (90)	62 (93)	1*S*,2*R*

to develop catalytic enantioselective Simmons–Smith cyclopropanations, we considered alternative strategies. We envisioned a catalytic enantioselective carbonyl addition to generate an allylic zinc alkoxide intermediate followed by a diastereoselective cyclopropanation. Performing these reactions in tandem would generate three C–C bonds and three stereocenters in a one-pot procedure.

In practice, the allylic zinc alkoxides were formed via a catalytic asymmetric alkyl addition to prochiral α,β-unsaturated aldehydes in the presence of 4 mol % of Nugent's (−)-MIB.[16,17] The resulting allylic alkoxide was then exposed to zinc carbenoids (Table 2)[18] prepared by the Furukawa method ($ZnEt_2 + CH_2I_2$).[19] To optimize the reaction conversion and diastereoselectivity, we screened various carbenoids. The optimal reagent, $CF_3CH_2OZnCH_2I$, originally introduced by Shi[20] was generated by mixing equimolar amounts of trifluoroethanol, diethylzinc, and diiodomethane followed by introduction of the allylic zinc alkoxide intermediate (Table 2). After completion of the reaction, workup, and purification, cyclopropyl alcohols were isolated with excellent enantio- and diastereoselectivities. This one-pot procedure was used to prepare cyclopropanes with a variety of substitution patterns (Table 2). To broaden the substrate scope, we also used Knochel's functionalized dialkylzinc reagents[21] in the asymmetric addition step (entries 9–11). Very high enantioselectivities (>96%) and single diastereomers were observed when 5 equiv of $CF_3CH_2OZnCH_2I$ was employed. The expected *syn* relationship between the hydroxyl and cyclopropane (entry 1) was confirmed by X-ray analysis. The reaction is believed to proceed via a

TABLE 2. Tandem Asymmetric Alkyl Addition/Diastereoselective Cyclopropanations



entry	product	% ee(% y)	dr	entry	product	% ee(% y)	dr
1		95 (78)	> 20:1	7		99 (76)	> 20:1
2		99 (90)	> 20:1	8		95 (85)	>20:1
3		89 (87)	> 20:1	9		96 (64)	> 20:1
4		96 (85)	> 20:1	10		97 (66)	>20:1
5		98 (80)	>20:1	11		98 (70)	>20:1
6		91 (91)	>20:1				

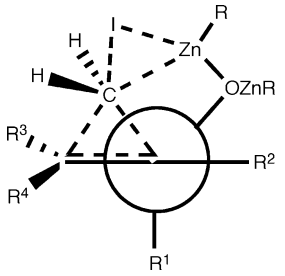
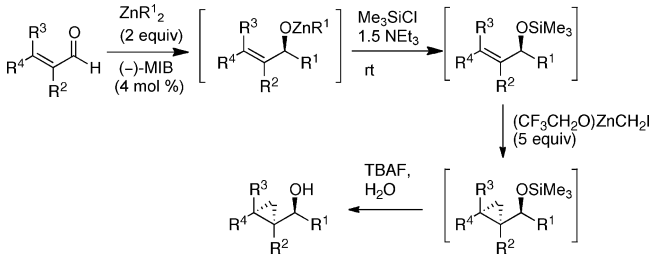


FIGURE 1. Butterfly-type transition state for the Simmons–Smith cyclopropanation.

SCHEME 2. Tandem Sequence to Afford *anti*-Cyclopropyl Alcohols with High Enantio- and Diastereoselectivity

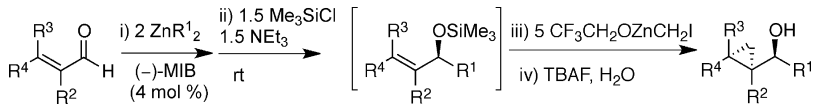


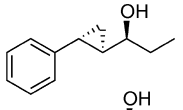
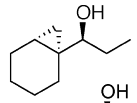
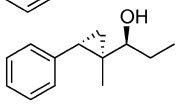
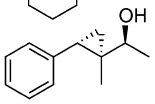
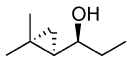
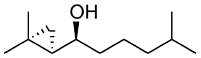
"butterfly-type" transition state (Figure 1).[6] Although diastereoselective cyclopropanations of chiral allylic alcohols had been previously reported, our work represented the most synthetically efficient synthesis of enantio- and diastereoenriched cyclopropyl alcohols from achiral precursors.

2.3. Tandem Asymmetric Synthesis of *anti*-Cyclopropyl Alcohols. The alkoxide-directed approaches described above are highly *syn* selective.[6] However, both *syn*- and *anti*-cyclopropanols are found in natural products, with the synthesis of *anti*-cyclopropyl carbinols being significantly more challenging. In 2002 Charette and Lacasse reported the synthesis of *anti*-cyclopropyl alcohols.[22] Their strategy involved use of bulky silyl-protected allylic alcohols to inhibit the coordination of zinc carbenoids to the allylic alkoxide, making the transition state for the *anti*-diastereomer lower in energy than that of the *syn*.[22]

2.3.1. Tandem Asymmetric Alkylation/Silyl Protection/*anti*-Cyclopropanation. Encouraged by the possibility of preventing zinc carbenoid coordination to the allylic oxygen, we incorporated Charette's *anti*-cyclopropanation protocol into our one-pot approach to the synthesis of cyclopropyl alcohols (Scheme 2). Our effort toward *anti*-cyclopropyl alcohols began with identification of conditions for the *in situ* silylation of the intermediate allylic zinc alkoxide that would be compatible with the diastereoselective cyclopropanation. For this study, the zinc allylic alkoxide intermediates, generated from the catalytic enantioselective alkylation of cinnamaldehyde, were treated with various silylating reagents (TIPS-Cl, TBS-Cl, and TES-Cl).

TABLE 3. One-Pot Tandem Asymmetric Synthesis of *anti*-Cyclopropyl Alcohols



entry	product	% ee (% y)	dr	entry	product	% ee (% y)	dr
1		89 (75)	> 20:1	4		99 (67)	> 20:1
2		96 (82)	> 20:1	5		95 (80)	> 20:1
3		95 (67)	> 20:1	6		97 (60)	~ 10:1

Despite significant effort, full conversion to the silyl ether proved difficult. Employing more reactive TIPS-OTf and TES-OTf provided silylated products with low yields due to a competitive elimination pathway. We hypothesized that the zinc alkoxides were unreactive because of aggregation. To break up zinc aggregates and increase the nucleophilicity of the zinc alkoxides, we added 1.5 equiv of triethylamine. In the presence of the amine, the silylation with 1.5 equiv of TMS-Cl the silylation proceeded readily. Due to the sensitivity of the O-Tms group, isolation of TMS-protected allylic ethers was not possible.

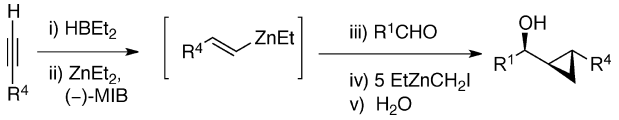
With the optimized *in situ* silylation in hand, compatible cyclopropanation conditions were investigated. The cyclopropanation of the allylic TMS ether was sluggish with excess $EtZnCH_2I$. The more reactive $CF_3CH_2OZnCH_2I$, however, resulted in full conversion to the cyclopropane within 24 h. Desilylative workup employing 2 equiv of TBAF provided *anti*-cyclopropyl alcohols with high diastereoselectivities (>10:1, Table 3).[18] Slightly lower dr was observed in entry 6, likely due to difficulty in generation of functionalized zinc reagents with high purity. Overall, this method is very efficient with four steps in one-pot (addition, silyl protection, cyclopropanation, and deprotection), and it complements our tandem *syn*-cyclopropanation.

3. Tandem Asymmetric Vinylation of Aldehydes/Diastereoselective Cyclopropanation

3.1. Asymmetric (*E*)-Vinyl Addition/Diastereoselective Cyclopropanation. To expand our one-pot method to synthesize *syn*-cyclopropyl alcohols, we envisioned a complementary C–C bond-formation entailing an enantioselective vinyl addition to a saturated aldehyde followed by cyclopropanation (Table 4). Vinylzinc reagents were generated following the Oppolzer/Srebnik hydroboration/boron to zinc transmetalation method.[23,24] In the presence of (–)-MIB, clean vinylation of aldehydes furnished allylic alkoxide intermediates with high ee. Direct cyclopropanation of these intermediates, however, was plagued by low yields and poor diastereoselectivities. We hypothesized that the triethylborane byproduct formed during the transmetalation step was interfering with the cyclopropanation. To circumvent this problem, after completion of the asymmetric addition, the volatile materials, including triethylborane, were removed under reduced pressure. Addition of diethylzinc and CH_2I_2 (5 equiv each) was then performed at 0 °C, leading to the cyclopropyl alcohols as a single diastereomer in 60–84% yield with >87% ee. A range of aliphatic aldehydes and alkynes were successfully used.[18] Aromatic aldehydes gave low yields under these conditions. By doubling the concentration in the cyclopropanation step, however, yields in the 70–80% range were observed (entries 9 and 10).[25]

3.2. Tandem Asymmetric Synthesis of *syn*-Vinyl Cyclopropyl Alcohols. The catalytic enantioselective vinylation was extended to the synthesis of vinyl cyclopropanes (VCPs). VCPs are found in biologically active compounds and are useful synthetic intermediates that readily undergo a variety of transformations.[26] Although the chemistry of vinyl cyclopropanes has been well studied, enantioenriched derivatives have rarely been employed due to difficulties in their preparation. The first general approach to enantioenriched VCPs was developed by Davies and co-workers with vinyldiazoacetates and dirhodium prolinate-based catalysts.[27,28] Charette reported the highly enantioselective cyclopropanation of dienyl alcohols using a boron tartrate-derived ligand and zinc carbenoid.[29] The reaction required the stoichiometric amount of ligand and also provided biscyclopropanation byproducts. Marek reported a novel

TABLE 4. Tandem Asymmetric Vinyl Addition/Diastereoselective Cyclopropanation



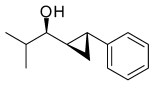
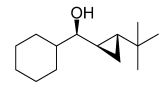
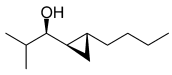
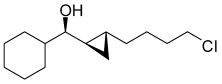
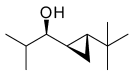
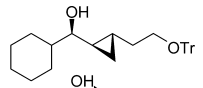
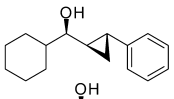
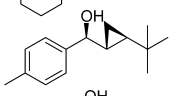
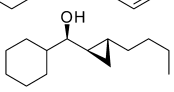
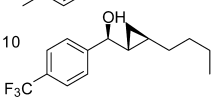
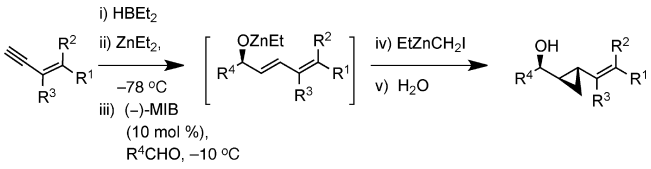
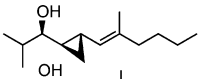
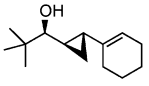
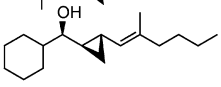
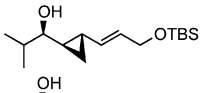
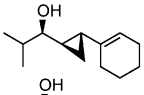
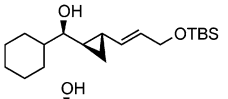
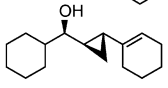
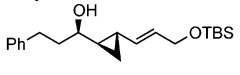
entry	product	% ee (% y)	dr	entry	product	% ee (% y)	dr
1		99 (75)	> 20:1	6		96 (74)	>20:1
2		92 (71)	> 20:1	7		94 (80)	>20:1
3		87 (78)	> 20:1	8		93 (73)	>20:1
4		99 (78)	> 20:1	9		95 (80)	>20:1
5		93 (84)	> 20:1	10		95 (71)	>20:1

TABLE 5. Tandem Asymmetric Dienylation/Diastereoselective Cyclopropanation



entry	product	% ee (% y)	dr	entry	product	% ee (% y)	dr
1		93 (75)	> 20:1	5		80 (65)	> 20:1
2		92 (80)	> 20:1	6		90 (71)	> 20:1
3		89 (80)	> 20:1	7		90 (79)	> 20:1
4		90 (85)	> 20:1	8		76 (85)	> 20:1

catalytic asymmetric cyclopropanation involving a (−)-sparteine-catalyzed organolithium carbolithiation/elimination of a dienol derivative (5−83% ee).[30] Other existing asymmetric approaches to VCPs required several steps. We envisioned the adaptation of our tandem vinylation/cyclopropanation sequence to the preparation of enantioenriched VCPs using enynes in place of terminal alkynes.

3.2.1. Asymmetric Dienylation/Chemo- and Diastereoselective Cyclopropanation. The first step in advancing the catalytic asymmetric synthesis of VCPs was to optimize asymmetric dienyl group addition to aldehydes (Table 5).[31] Enynes possessing terminal alkynes underwent hydroboration with diethylborane with high chemo- and regioselectivity to form the intermediate dienylboranes. Transmetalation with diethylzinc generated the dienylzinc intermediates, which were then added to aldehydes in the presence of catalytic amounts of (−)-MIB. The key proved to be use of 10 mol % (−)-MIB with slow addition of aldehyde, resulting in high enantioselectivities (>90% ee's) for most substrates.

SCHEME 3. Charette's Synthesis of Iodocyclopropanes

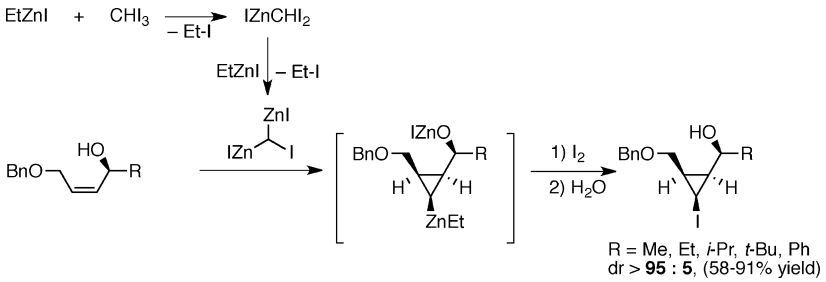
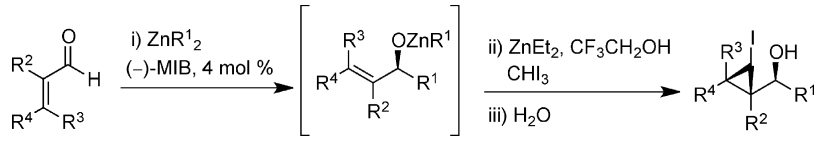
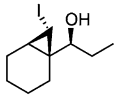
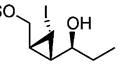
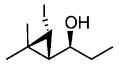
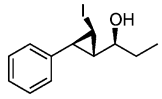
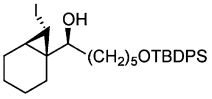
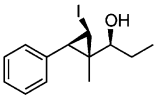
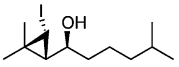


TABLE 6. Tandem Asymmetric Alkyl Addition/Diastereoselective Iodocyclopropanation



entry	product	% ee (% y)	dr	entry	product	% ee (% y)	dr
1		99 (66)	> 20:1	5		98 (74)	> 20:1
2		95 (62)	> 20:1	6		99 (78)	> 20:1
3		89 (79)	> 20:1	7		98 (70)	> 20:1
4		96 (56)	> 20:1	8		96 (60)	> 20:1

We next explored the tandem enantioselective dienylation/chemo- and diastereoselective cyclopropanation. It is known that alkoxide-directed cyclopropanation of allylic double bonds is faster than reaction of remote double bonds.[29] Employing $CF_3CH_2OZnCH_2I$, as outlined in previous sections, generated significant amounts of bis(cyclopropyl) alcohol with poor diastereoselectivity (1:1 dr), regardless of the amount of this zinc carbenoid. Other zinc carbenoids, such as $IZnCH_2I$ and $Zn(CH_2I)_2$, were also unsuccessful. Reactions of the milder $EtZnCH_2I$ (2 equiv) resulted in low conversion, while 5 equiv led to substantial bis(cyclopropyl) alcohol (1:1 dr). A solution to this problem was the portionwise addition of 4 equiv of $EtZnCH_2I$, which generated vinyl cyclopropyl alcohols with excellent diastereoselectivities (>20:1) and good yields (65–85%, Table 5).[31] Remote double bonds, including the electron rich trisubstituted olefins (entries 1–5), were significantly less reactive under these conditions. For reasons that are not clear, the reaction was unsuccessful with aromatic aldehydes.

4. Halocyclopropanation Reactions

4.1. Catalytic Asymmetric Alkyl Addition/Diastereoselective Halocyclopropanation. Given the success of the catalytic enantio- and diastereoselective tandem generation of cyclopropyl alcohols, we next targeted the challenging stereoselective synthesis of halo-substituted cyclopropyl alcohols. Halo cyclopropanation reactions with $XZnCHX_2$ derivatives tend to result in mixtures of diastereomers about the C–X bond[32–34] with few exceptions.[35,36]

4.1.1. Tandem Asymmetric Alkylation/Diastereoselective Iodocyclopropanation. An impressive iodocyclopropane synthesis that installs the iodide after cyclopropanation is complete is Charette's highly diastereoselective transfer of a zinc-bearing carbenoid to (*Z*)-allylic alcohols (Scheme 3).[37] After cyclopropanation with dizinc carbenoid $(IZn)_2CHI$, generated

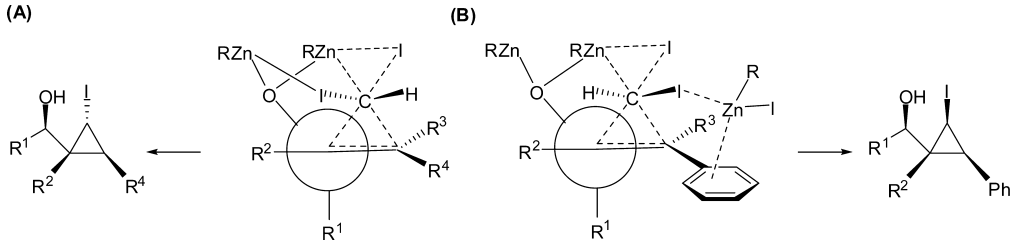
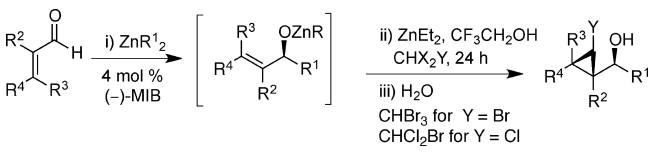


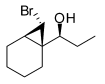
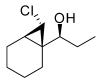
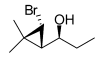
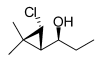
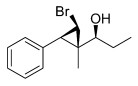
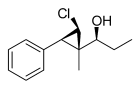
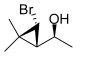
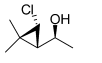
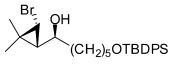
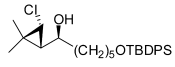
FIGURE 2. Proposed transition state for iodocyclopropanation leading to the *cis* (left) and *trans* (right) products.

from a 2:1 ratio of $ZnEt_2$ and CHI_3, quenching with iodine provides the iodocyclopropane with high dr.

Prior to our investigation, no precedent existed regarding the alkoxide-directed diastereoselective halocyclopropanation. To develop stereoselective iodocyclopropanations via our tandem enantioselective addition/cyclopropanation sequence, we explored the use of iodoform in place of diiodomethane (Table 6). Initially, the conversion and yield were low, but high diastereoselectivity was observed. To improve reaction efficiency, electron-withdrawing groups X on zinc carbenoids, $XZnCHI_2$, were investigated. We identified the new reagent $CF_3CH_2OZnCHI_2$ with activated 4 Å molecular sieves in DCM, which resulted in the formation of the desired iodocyclopropanes with good yields and excellent diastereoselectivities (Table 6).[13] It is noteworthy that up to four stereogenic centers are established with excellent diastereoselectivity from achiral precursors in this one-pot procedure. The stereochemistry of iodocyclopropanes was assigned by a combination of proton coupling constants and X-ray analysis. The results were very surprising. When R^4 = alkyl or H, the iodo was *cis* to the carbinol. In contrast, when R^4 = Ph, the stereochemistry about the C−I bond was opposite! To rationalize the disparate stereochemical outcomes, we proposed that the transition state for iodocyclopropanation involves a weak Zn···ICH interaction between the transferring iodocarbene and a zinc center, as illustrated in the modified "butterfly-type" transition state (Figure 2A). When the substrate possesses a phenyl group at R^4, we hypothesize that interaction of Zn(II) with a phenyl π system dominates, reversing the stereoselectivity (Figure 2B). Consistent with the proposal, use of 4-trifluoromethyl cinnamaldehyde resulted in a decrease in diastereoselectivity to 5:1 (compared to 20:1 with cinnamaldehyde). Some precedence for zinc π-interactions has been reported.[38,39] The most relevant is the formation of the toluene complex with (η^2-toluene)$Zn(C_6F_5)_2$ by Bochmann.[40] Shortly after our publication of our iodocyclopropanation, Charette published an elegant enantioselective iodocyclopropanation.[36]

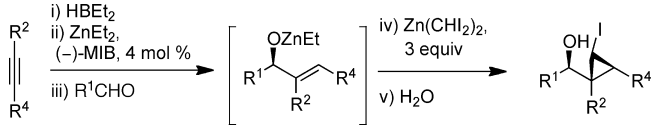
TABLE 7. Tandem Catalytic Enantioselective Alkyl Addition/Diastereoselective Bromo- and Chlorocyclopropanation

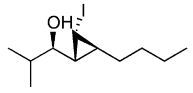
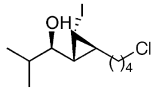
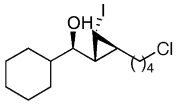
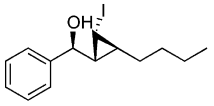
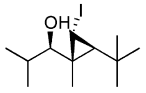
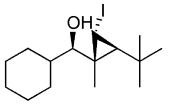
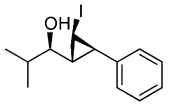


entry	product	% ee (% y)	dr	entry	product	% ee (% y)	dr
1		99 (70)	> 20:1	6		99 (65)	> 20:1
2		95 (75)	> 20:1	7		95 (70)	> 20:1
3		96 (80)	> 20:1	8		96 (70)	> 20:1
4		99 (70)	> 20:1	9		99 (59)	> 20:1
5		97 (77)	> 20:1	10		97 (70)	> 20:1

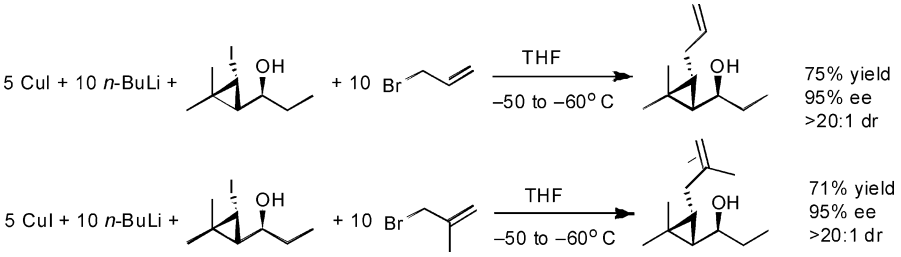
4.1.2. One-Pot Tandem Asymmetric Alkylation/Bromo- and Chlorocyclopropanation. Encouraged by the successful development of the one-pot tandem iodocyclopropanation, we envisioned the synthesis of other halocyclopropyl alcohols. We were concerned that changing the halide would impact the diastereoselectivity, especially if a zinc−halide interaction was responsible for the stereochemical outcome (Figure 2). Because alkyl exchange between dialkylzinc reagents and alkyl iodides was known to proceed rapidly,[41] the desired precursor for bromocyclopropanation was $CHBrI_2$. This reagent, however, is not readily available, so we focused on commercially available bromoform. To overcome the lower reactivity of bromoform relative to iodoform in the exchange reaction with diethylzinc, we employed an excess of carbenoid at higher concentrations (from 1.1 to 2.5 M) with CF_3CH_2OH as additive. Under these conditions, bromocyclopropyl alcohols were generated with dr's of >20:1 (Table 7).[42] For chlorocyclopropanation,

TABLE 8. Tandem Asymmetric Vinyl Addition/Diastereoselective Iodocyclopropanation



entry	product	% ee (% y)	dr	entry	product	% ee (% y)	dr
1		92 (64)	> 20:1	5		93 (80)	> 20:1
2		94 (78)	> 20:1	6		94 (52)	> 20:1
3		86 (67)	> 20:1				
4		87 (70)	> 20:1	7		99 (50)	> 20:1

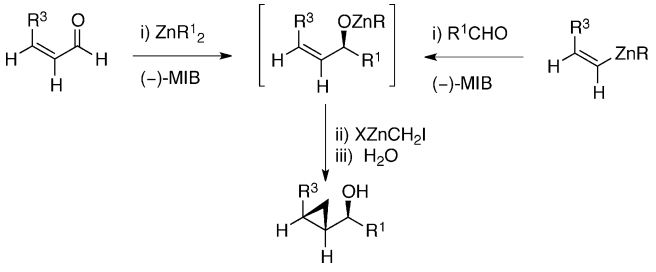
SCHEME 4. Allylation of Iodocyclopropyl Alcohols Using Organocuprate Chemistry



bromodichloromethane was used as the carbenoid precursor and the resulting chlorocyclopropyl alcohols were obtained as a single diastereomer with high enantioselectivities.[42] The stereochemistries of bromo- and chlorocyclopropyl alcohols were the same as those for the iodocyclopropanation: *cis* relationship between the halide and the carbinol when R^4 = alkyl or H and *trans* relationship when R^4 = phenyl. Access to fluorocyclopropyl alcohols remains elusive due, in part, to challenges obtaining fluorohalomethane precursors.

4.2. Asymmetric Vinyl Addition/Diastereoselective Halocyclopropanation. The iodocyclopropanation reaction was next combined with the aldehyde vinylation. Unfortunately, the iodocyclopropanation suffered from low conversion and poor diastereoselectivity. We hypothesized that interaction between $CF_3CH_2OZnCHI_2$ and excess vinylzinc reagent was problematic. We therefore conducted the asymmetric addition step using the vinylzinc as limiting reagent. We also examined other cyclopropanating

SCHEME 5. Two Possible Routes to *cis*-Disubstituted Cyclopropyl Alcohols

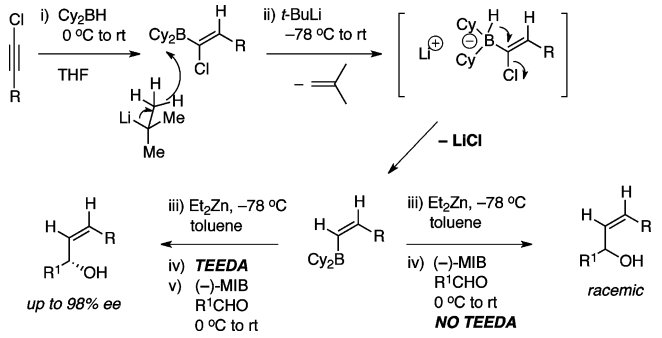


reagents. Finally, use of 3.0 equiv of $Zn(CHI_2)_2$ furnished the desired iodocyclopropyl alcohols as single diastereomers with good yields (Table 8).[42] Surprisingly, substrates bearing aromatic groups gave very low yields. Although the reasons for this behavior are puzzling, we found that increasing the zinc carbenoid from 0.24 to 0.42 M resulted in an increase in the yields to around 50% with excellent diastereoselectivities (entries 6–7). The stereochemistry

was assigned using a coupling constant and was consistent with those in section 4.1.

4.3. Functionalization of Iodocyclopropyl Alcohols. The stereoselective synthesis of functionalized cyclopropane derivatives often involves the generation and elaboration of metalated cyclopropanes. To explore functionalization of the halocyclopropyl alcohols, we prepared organocuprates by combining LiCu(*n*-Bu)$_2$ and iodocyclopropyl alcohols in dry THF at $-50\ ^{o}$C.[43,44] The addition of excess allyl or methallyl bromide at this temperature provided the desired 1,2,3-substituted cyclopropane derivatives in good yields as single diastereomers (Scheme 4).[42] The stereochemistry of the iodocyclopropane was maintained, as determined by analysis of ^{1}H NMR coupling constants.

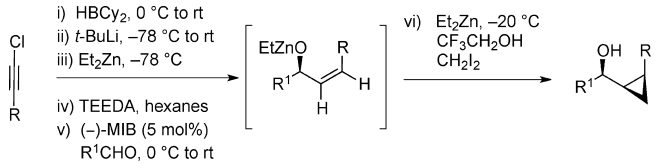
SCHEME 6. Enantioselective Synthesis of (*Z*)-Allylic Alcohols in the Presence of TEEDA

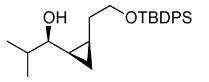
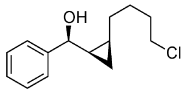
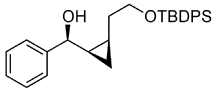
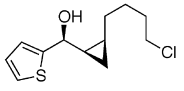
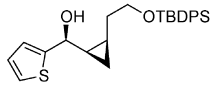
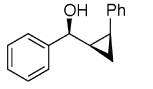
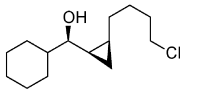
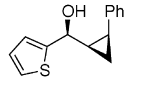


5. Further Application to a Variety of Cyclopropyl Alcohols

5.1. One-Pot Tandem Asymmetric Synthesis of *syn-cis*-Disubstituted Cyclopropyl Alcohols. The asymmetric (*E*)-vinylation method outlined in section 3.1 is not applicable to the synthesis of (*Z*)-disubstituted vinylzinc reagents or *cis*-cyclopropanes. Two routes to *cis*-disubstituted cyclopropyl alcohols are illustrated in Scheme 5. The first begins with alkyl addition to (*Z*)-enals followed by diastereoselective cyclopropanation, as exemplified in Table 2, entry 5. The second route is based on the asymmetric (*Z*)-vinylation to aldehydes/diastereoselective cyclopropanation. Although the synthesis of enantiopure (*Z*)-allylic alcohols using (*Z*)-vinyl organometallic reagents is challenging, the latter method is more versatile because (*Z*)-enals can be difficult

TABLE 9. Tandem Asymmetric Synthesis of *cis*-Disubstituted Cyclopropyl Alcohols



entry	product	% ee (% y)	dr	entry	product	% ee (% y)	dr
1		90 (65)	> 19:1	5		88 (69)	> 19:1
2		95 (62)	> 19:1	6		94 (62)	> 19:1
3		96 (52)	> 19:1	7		97 (65)	> 19:1
4		88 (55)	> 19:1	8		92 (42)	> 19:1

SCHEME 7. Asymmetric Generation of β-Hydroxy Enamines (R^1 = H, alkyl, Ar)

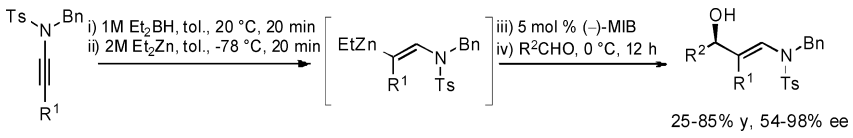
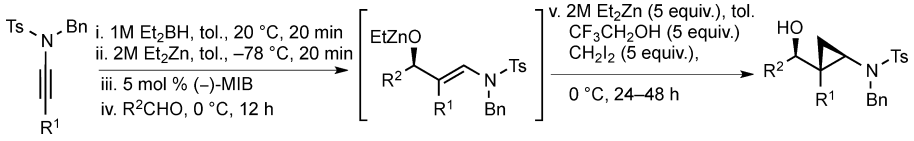
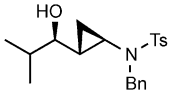
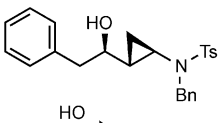
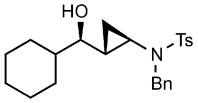
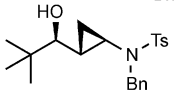
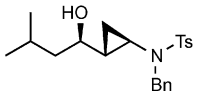
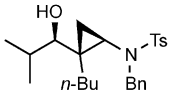
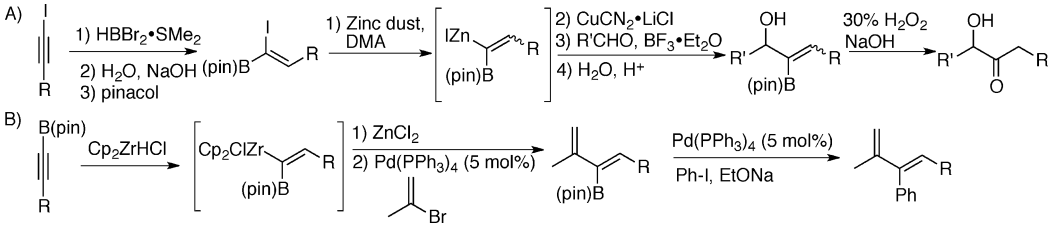


TABLE 10. Asymmetric One-Pot Tandem Synthesis of *syn*-Aminocyclopropyl Alcohols



entry	product	% ee (% y)	dr	entry	product	% ee(% y)	dr
1		93 (80)	>20:1	4		83 (78)	>20:1
2		94 (76)	>20:1	5		93 (72)	>20:1
3		76 (78)	>20:1	6		93 (28)	>20:1

SCHEME 8. Bimetallic Reagents by Knochel (A) and Srebnik (B)



to prepare with high stereopurity due to facile isomerization to the thermodynamically favored (*E*)-isomer.

We recently reported a one-pot tandem generation of enantioenriched (*Z*)-allylic alcohols with up to 98% enantioselectivity (Scheme 6).[45,46] In this reaction, (*Z*)-vinyl zinc reagents were generated *in situ* and stereospecifically from 1-chloro-1-alkynes via hydroboration, addition of *t*-BuLi as a hydride source,[46] and transmetalation to zinc. The key to this highly enantioselective process is the addition of TEEDA (*N*,*N*,*N*′,*N*′-tetraethylethylene diamine) to suppress the rapid nonenantioselective LiCl-promoted background reaction.[47,48] The generation and addition of (*Z*)-vinyl zinc reagents to aldehydes were then applied to the synthesis of *cis*-disubstituted cyclopropyl alcohols. Thus, the enantioenriched (*Z*)-allylic alkoxides were treated with 5 equiv of $CF_3CH_2OZnCH_2I$ (under conditions similar to those described above), generating highly enantio- and diastereoenriched *cis*-disubstituted cyclopropyl alcohols. A variety of 1-chloro-1-alkynes and aldehydes (saturated, aromatic, and heteroaromatic) were employed and furnished the products in good yields (Table 9).[31] This one-pot tandem method circumvents the synthesis of thermodynamically unstable (*Z*)-enals and isolation of (*Z*)-vinylzinc species.

5.2. One-Pot Tandem Synthesis of Enantioenriched Aminocyclopropyl Alcohols. Aminocyclopropanes have attracted considerable interest because of their abundance in biologically active natural products and medications. As a consequence, many synthetic approaches to these important compounds have been developed. However, there are relatively few direct syntheses of aminocyclopropane derivatives. Examples include cyclopropanation of enamines and enamide derivatives or transition metal mediated addition of diazo esters to alkenes followed by a Curtius or Schmidt reaction.[26,49] Our approach to aminocyclopropyl carbinols involves catalytic enantioselective synthesis of β-hydroxy enamines and subsequent cyclopropanation.

5.2.1. Asymmetric β-Aminovinylation/Diastereoselective Cyclopropanation. We found hydroboration of ynamides[50] generated β-amino vinyl boranes that underwent boron-to-zinc transmetalation followed by catalytic enantioselective carbonyl addition to aldehydes using

SCHEME 9. One-Pot Generation of B(pin)-Substituted Allylic Alcohols

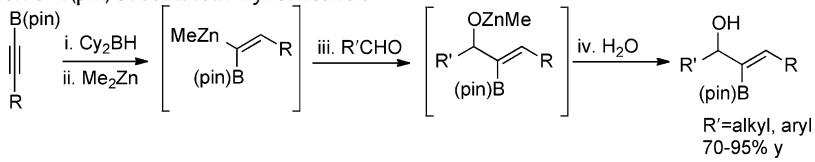
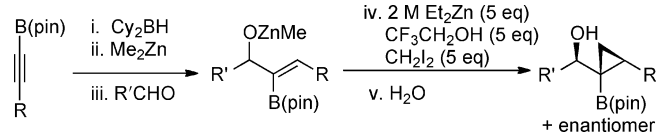


TABLE 11. Tandem Stereoselective Synthesis of Cyclopropyl Boronate Esters



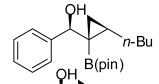
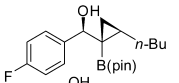
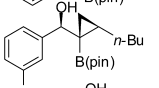
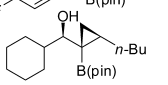
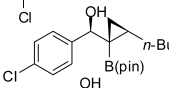
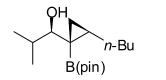
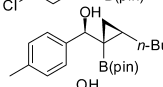
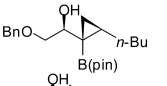
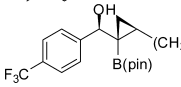
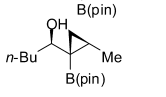
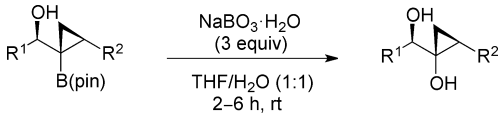
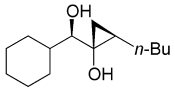
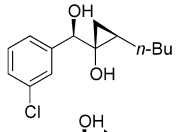
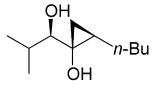
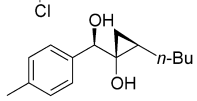
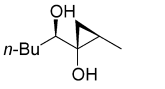
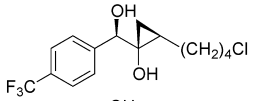
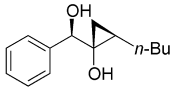
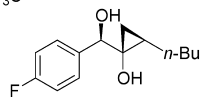
entry	cyclopropylboronate ester	dr	% y	entry	cyclopropylboronate ester	dr	% y
1		20:1	75	6		20:1	87
2		20:1	89	7		20:1	86
3		20:1	58	8		20:1	84
4		20:1	70	9		>15:1	58
5		20:1	71	10		20:1	86

TABLE 12. Stereoselective Synthesis of Trisubstituted α-Hydroxycyclopropyl Alcohols



entry	α-hydroxy cyclopropyl carbinol	% y	entry	α-hydroxy cyclopropyl carbinol	% y
1		89	5		86
2		93	6		88
3		91	7		75
4		90	8		80

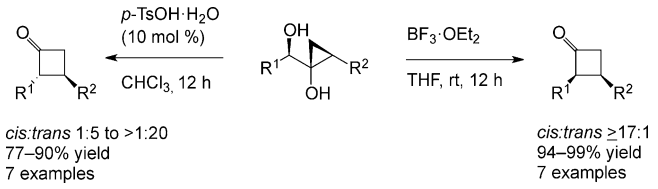
5 mol % (−)-MIB. The resulting β-alkoxy enamines were single double bond isomers formed with high enantioselectivities (Scheme 7).

The asymmetric aminovinylation of aldehydes was then adapted to the asymmetric synthesis of *syn*-aminocyclopropyl alcohols. Very few examples of cyclopropanation of enamines have been reported[51,52] and it was not clear how the enamine nitrogen would impact the double bond reactivity. Nonetheless, we performed the asymmetric aminovinylation addition to aldehydes and subjected the resulting alkoxide intermediates to cyclopropanation using Shi's carbenoid, $CF_3CH_2OZnCH_2I$. Although the cyclopropanation proceeded in low yield, the desired cyclopropyl amines were formed as single diastereomers (Table 10). Optimization to increase yields focused on removal of byproducts formed during transmetalation from boron to zinc. The best results were obtained with addition of hexanes to the β-amino alkoxide reaction mixture followed by removal of volatile materials under reduced pressure. To ensure removal of all the boron-containing byproducts, this procedure was repeated three times. The resulting enantioenriched β-amino alkoxides (76−94% ee) underwent cyclopropanation with excellent diastereoselectivities (>20:1) in 72−82% yield (Table 10).[53] Although terminal ynamides were good substrates, internal ynamides were not (maximum 28% yield). Additionally, conditions for the cyclopropanation of β-alkoxy enamines generated from aromatic aldehydes or aryl-substituted ynamides remain undeveloped.

6. Stereoselective Syntheses of Cyclopropylboronate Esters and Cyclopropanols Using Bimetallic Reagents

6.1. Tandem Stereoselective Syntheses of Cyclopropyl Boronate Esters from *in Situ* Generated 1-Alkenyl-1,1-heterometallics. Bimetallic reagents are potentially useful in synthesis, especially if each M−C bond can be selectively functionalized.[54,55] The application of alkenylbimetallic reagents in stereoselective transformation, however, is often hampered by difficulties controlling double bond geometry,[56] multistep preparations, or limited functional group tolerance.[57] Pioneering work by Knochel and coworkers employed boron and zinc or copper 1,1-bimetallic

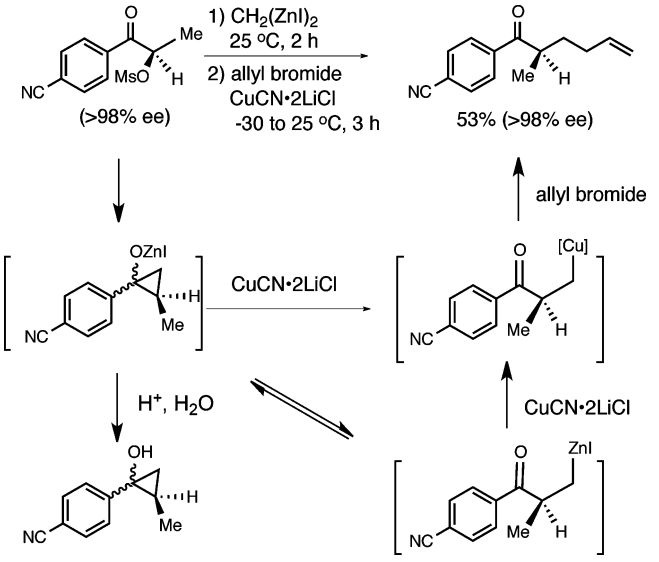
SCHEME 10. Synthesis of *cis*- and *trans*-2,3-Disubstituted Cyclobutanones



reagents to synthesize α-hydroxy ketones, although loss of double bond geometry during the formation of the bimetallic reagents has limited their full synthetic potential (Scheme 8A).[56] Srebnik and co-workers circumvented the loss of double bond geometry by generation of boron−zirconium bimetallics via hydrozirconation of B(pin) alkynes with Schwartz's reagent (Cp_2ZrHCl, Scheme 8B).[58] From the practical point of view, Schwartz's reagent is prohibitively expensive for large-scale applications. To exploit the potential of 1-alkenyl-1,1-heterobimetallic reagents, practical and straightforward methods for their generation were necessary. We investigated the stereoselective formation of 1-alkenyl-1,1-heterobimetallic reagents based on boron and zinc (Scheme 9). Beginning with readily available air-stable 1-alkynyl-1-boronate esters, hydroboration with dicyclohexylborane generates 1-alkenyl-1,1-diboro species. Neither B−C bond is very nucleophilic; however, we knew that the Cy_2B−C bonds underwent transmetalation at −78 °C. In contrast, the (pin)B−C transmetalates significantly above room temperature due to resonance donation from the pin oxygens to boron. *In situ* transmetalation of the Cy_2B−C with dialkylzinc reagents furnished 1-alkenyl-1,1-heterobimetallic intermediates, which were treated with aldehydes to generate B(pin)-substituted allylic alcohols in 70−95% yield (Scheme 9).[59] The straightforward one-pot generation of B(pin)-substituted allylic alkoxides facilitated development of tandem reactions with these intermediates.

The synthesis of B(pin)-substituted cyclopropanes began with regioselective hydroboration of B(pin) alkynes, chemoselective transmetalation, and addition to aldehydes. As outlined previously, the volatile materials were removed to circumvent problems caused by the borane byproduct. The resulting B(pin)-substituted allylic alkoxide was treated with a toluene solution of 5 equiv of $CF_3CH_2OZnCH_2I$ to afford the *syn*-cyclopropyl boronate esters. Cyclopropyl boronate esters were generated with a series of aromatic and aliphatic aldehydes in good yields (58−89%) and excellent diastereoselectivities (>15:1, Table 11).[48] The asymmetric addition of

SCHEME 11. Matsubara's Generation of Cyclopropanes



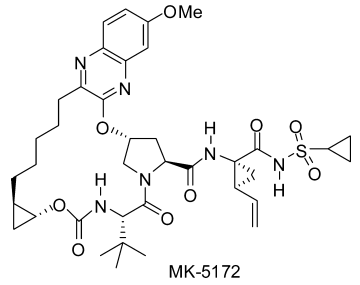


FIGURE 3. Merck's HCV protease inhibitor with potent activity against resistance mutations in vitro.

the 1-alkenyl-1,1-heterobimetallic reagents to aldehydes has proven very challenging and is under investigation.

6.3. Stereoselective Syntheses of Trisubstituted Cyclopropane Diols. Substituted cyclopropanols are valuable building blocks in synthetic transformations, including ring cleavage/expansion reactions. An interesting approach to trisubstituted cyclopropanols was developed by Kulinkovich and co-workers, but it suffers from low diastereoselectivities.[60] We turned our attention to cyclopropyl boronate esters for the stereoselective preparation of cyclopropanols (Table 12). Several reagents were examined to oxidize the B−C bond of cyclopropyl boronate esters; $NaOH/H_2O_2$ gave poor yields of cyclopropanols along with ring-cleaved carbonyl compounds. Sodium perborate in a 1:1 THF/H_2O provided the desired cyclopropane diols as single diastereomers in excellent yields. As shown in Table 12, a variety of aliphatic and aromatic cyclopropyl boronate esters were smoothly oxidized to the corresponding α-hydroxy cyclopropyl carbinols.[61] As anticipated, the oxygen insertion into the B−C bond proceeded with the retention of stereochemistry.

SCHEME 12. Proposed Mechanism of Equilibration of *cis*- and *trans*-Cyclopropoxides

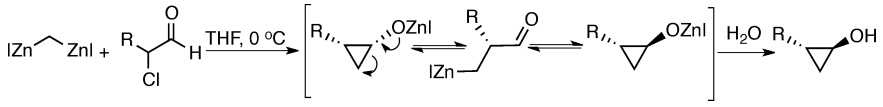
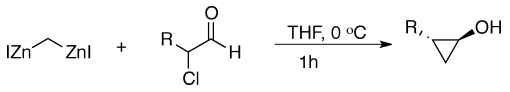
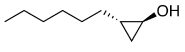
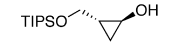
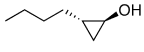
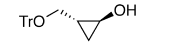
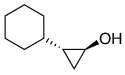
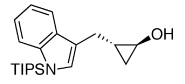
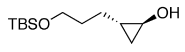


TABLE 13. Diastereoselective Synthesis of *trans*-Cyclopropanol Using $CH_2(ZnI)_2$



entry	product	dr	% y	entry	product	dr	% y
1		18:1	88	7		12:1	71
2		11:1	87	8		11:1	89
3		13:1	65	9		13:1	86
4		12:1	73	10		19:1	61
5		16:1	64	11		11:1	66
6		10:1	83				

It is noteworthy that the diols in Table 12 are excellent precursors for the synthesis of both the *cis*- and *trans*-2,3-disubstituted cyclobutanones with high diastereoselectivity (Scheme 10).[61]

6.4. Diastereoselective Syntheses of *trans*-2-Substituted Cyclopropanols. Our interest in bimetallic reagents inspired us to consider other types of dianion synthons for the synthesis of cyclopropanes. Bimetallic $CH_2(ZnI)_2$ has been employed in tandem C−C bonds forming reactions to generate cyclopropanols. Matsubara and co-workers reported the reaction of $CH_2(ZnI)_2$ with α-diketones and α-ketoimines to form *cis*-cyclopropan-1,2-diols and *cis*-2-aminocyclopropanols, respectively.[62] They also examined reactions of $CH_2(ZnI)_2$ with enantioenriched α-sulfonyloxy ketones to generate cyclopropoxides (Scheme 11). It is known that cyclopropoxides are in equilibrium with homoenolates,[63] as shown on the bottom of Scheme 11. In Matsubara's case, the *cis*- and *trans*-cyclopropoxides are similar in energy and the cyclopropanols formed on workup were isolated with low dr. The addition of CuCN·2LiCl followed by allyl bromide allowed trapping of the homoenolate. Interestingly, the ee of sulfonyloxy ketones was conserved in the final product.

We were interested in the synthesis of *trans*-cyclopropanols, such as the one found in Merck's MK5172, a promising new hepatitis C candidate (Figure 3). On the basis of the reversible formation of homoenolates from cyclopropyl alkoxide derivatives, we devised a simple and highly diastereoselective route to *trans*-cyclopropanols using $CH_2(ZnI)_2$ and α-haloaldehydes. The key to successful optimization of the diastereoselectivity was to conduct the reaction at 0 °C, where equilibration between the *cis*- and *trans*-cyclopropoxides and homoenolates led to high diastereoselectivity (Scheme 12). In contrast, lower temperatures resulted in low diastereoselectivity that reflected the diastereoselectivity of the carbonyl addition step. The α-bromo- and α-chloroaldehyde analogues gave comparable results with $CH_2(ZnI)_2$ under the same conditions. Excellent diastereoselectivities were observed in a variety of α-chloroaldehydes (Table 13).[64]

In our proposed mechanism, carbonyl addition occurs with low diastereoselectivity and, therefore, the S_N2 displacement of the halide provides a mixture of *cis*- and *trans*-cyclopropoxides. Ring-opening generates transient homoenolates and allows the equilibration of diastereomers, which favors the *trans* geometry to minimize steric interaction (Scheme 12). In support of this proposal, when a mixture of *cis*- and *trans*-cyclopropanols (*cis*/*trans* = 3:1) was treated with $CH_2(ZnI)_2$ at 0 °C, equilibration occurred to provide, after workup, cyclopropanol with a *cis*/*trans* ratio of 1:16 (69% cyclopropanol recovery). Also of significance, use of enantioenriched α-chloroaldehyde resulted in generation of *trans*-cyclopropanols without loss of ee.[64]

7. Outlook

Due to the importance of cyclopropanes in naturally occurring and synthetic compounds with biological activity, the synthesis of cyclopropanes has attracted significant attention. In this Account we summarize methods that we developed to prepare a variety of cyclopropyl-containing compounds. In most cases, the cyclopropyl alcohols outlined can be prepared from achiral starting materials in efficient, one-pot procedures with high enantio- and diastereoselectivity.

We thank the NSF (CHE-0848467 and -1152488) for support of this work. We are grateful to the students who have participated in these studies both experimentally and intellectually.

BIOGRAPHICAL INFORMATION

Hun Young Kim graduated from the Ewha Women's University, South Korea, in 1997 with a B.S. degree in Chemistry. Remaining at the same institution, she obtained her M.S. degree in 1999. Upon her graduation, she joined Samsung R & D center in Suwon, Korea, as a research chemist, and moved to Philadelphia in 2003 to undertake her Ph.D. at the University of Pennsylvania. While at Penn, she developed stereoselective syntheses of cyclopropyl derivatives under the guidance of Professor Patrick J. Walsh. In late 2008, she became a research scientist in the Department of Chemistry & Chemical Biology at the Indiana University Purdue University Indianapolis (IUPUI). Her current research interest lies in the field of divergent asymmetric catalysis.

Patrick J. Walsh received his B.A. from UC San Diego and his Ph.D. at UC Berkeley with Prof. Robert G. Bergman (Ph.D., 1991). He was an NSF postdoctoral fellow with Prof. K. B. Sharpless at the Scripps Research Institute. Moving across town, from 1994 to 1999 he was an assistant professor at San Diego State University and also professor at Centro de Graduados e Investigación, Instituto Tecnológico de Tijuana, Mexico (1996−1999). In 1999 he moved to the University of Pennsylvania, where he is the Alan G. MacDiarmid Professor of Chemistry. With Prof. Marisa Kozlowski, Walsh coauthored *Fundamentals of Asymmetric Catalysis* (University Science Books).

FOOTNOTES

*E-mail: pwalsh@sas.upenn.edu.
The authors declare no competing financial interest.

REFERENCES

1 Salaun, J. Cyclopropane Derivatives and their Diverse Biological Activities. *Top. Curr. Chem.* **2000**, *207*, 1–67.

2 Pellissier, H. Recent Developments in Asymmetric Cyclopropanation. *Tetrahedron* **2008**, *64*, 7041–7095.

3 Pietruszka, J. Synthesis and Properties of Oligocyclopropyl-Containing Natural Products and Model Compounds. *Chem. Rev.* **2003**, *103*, 1051–1070.

4 Wessjohann, L. A.; Brandt, W.; Thiemann, T. Biosynthesis and Metabolism of Cyclopropane Rings in Natural Compounds. *Chem. Rev.* **2003**, *103*, 1625–1648.

5 Reissig, H.-U.; Zimmer, R. Donor-Acceptor-Substituted Cyclopropane Derivatives and Their Application in Organic Synthesis. *Chem. Rev.* **2003**, *103*, 1151–1196.

6 Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. Stereoselective Cyclopropanation Reactions. *Chem. Rev.* **2003**, *103*, 977–1050.

7 Rubin, M.; Rubina, M.; Gevorgyan, V. Transition Metal Chemistry of Cyclopropenes and Cyclopropanes. *Chem. Rev.* **2007**, *107*, 3117–3179.

8 Ukaji, Y.; Nishimura, M.; Fujisawa, T. Enantioselective Construction of Cyclopropane Rings via Asymetric Simmons-Smith Reaction of Allylic Alcohols. *Chem. Lett.* **1992**, 61–64.

9 Charette, A. B.; Prescott, S.; Brochu, C. Improved Procedure for the Synthesis of Enantiomerically Enriched Cyclopropylmethanol Derivatives. *J. Org. Chem.* **1995**, *60*, 1081–1083.

10 Charette, A. B.; Lemay, J. Diastereo- and Enantioselective Synthesis of 1,2,3-Substituted Cyclopropanes with Zinc Carbenoids. *Angew. Chem., Int. Ed.* **1997**, *36*, 1090–1092.

11 Charette, A. B.; Molinaro, C.; Brochu, C. Catalytic Asymmetric Cyclopropanation of Allylic Alcohols with Titanium-TADDOLate: Scope of the Cyclopropanation Reaction. *J. Am. Chem. Soc.* **2001**, *123*, 12168–12175.

12 Takahashi, H.; Yoshioka, M.; Shibasaki, M.; Ohno, M.; Imai, N.; Kobayashi, S. A Chiral Enantioselective Reaction Using a C_2-Symmetric Disulfonamide as a Chiral Ligand: Simmons-Smith Cyclopropanation of Allylic Alcohols by the Et_2Zn-CH_2I_2-Disulfonamide System. *Tetrahedron* **1995**, *51*, 12013–12026.

13 Balsells, J.; Mejorado, L.; Phillips, M.; Ortega, F.; Aguirre, G.; Somanathan, R.; Walsh, P. J. Synthesis of Chiral Sulfonamide/Schiff Base Ligands. *Tetrahedron: Asymmetry* **1998**, *9*, 4135–4142.

14 Balsells, J.; Walsh, P. J. Asymmetric Cyclopropanation of Allylic Alcohols Employing Sulfonamide/Schiff Base Ligands. *J. Org. Chem.* **2000**, *65*, 5005–5008.

15 Denmark, S. E.; O'Connor, S. P. Catalytic, Enantioselective Cyclopropanation of Allylic Alcohols. Substrate Generality. *J. Org. Chem.* **1997**, *62*, 584–594.

16 Nugent, W. A. MIB: An Advantageous Alternative to DAIB for the Addition of Organozinc Reagents. *J. Chem. Soc., Chem. Commun.* **1999**, 1369–1370.

17 Chen, Y. K.; Jeon, S. J.; Walsh, P. J.; Nugent, W. A. Synthesis of (2S)-(−)-3-exo-Morpholinoisoborneol. *Org. Synth.* **2005**, *82*, 87–92.

18 Kim, H. Y.; Lurain, A. E.; García-García, P.; Carroll, P. J.; Walsh, P. J. Highly Enantio- and Diastereoselective Tandem Generation of Cyclopropyl Alcohols with up to Four Contiguous Stereocenters. *J. Am. Chem. Soc.* **2005**, *127*, 13138–13139.

19 Furukawa, J.; Kawabata, K.; Nishimura, J. A Novel Route to Cyclopropanes from Olefins. *Tetrahedron Lett.* **1966**, *28*, 3353–3354.

20 Lorenz, J. C.; Long, J.; Yang, Z.; Xue, S.; Xie, Y.; Shi, Y. A Novel Class of Tunable Zinc Reagents (RXZnCH2Y) for Efficient Cyclopropanation of Olefins. *J. Org. Chem.* **2004**, *69*, 327–334.

21 Knochel, P.; Vettel, S.; Eisenberg, C. Catalytic Asymmetric Synthesis of Chiral Secondary Polyfunctional Alcohols Using Diorganozincs. *Appl. Organomet. Chem.* **1995**, *9*, 175–188.

22 Charette, A. B.; Lacasse, M.-C. Cyclopropanation of Protected Chiral, Acyclic Allylic Alcohols: Expedient Access to the anti-Cyclopropylcarbinol Derivatives. *Org. Lett.* **2002**, *4*, 3351–3354.

23 Oppolzer, W.; Radinov, R. N. Catalytic Asymmetric Synthesis of Secondary (E)-Allyl Alcohols from Acetylenes and Aldehydes via (1-Alkenyl)zinc Intermediates. *Helv. Chim. Acta* **1992**, *75*, 170–173.

24 Srebnik, M. Stereospecific Preparation of Trisubstituted Allylic Alcohols by Alkene Transfer from Boron to Zinc. *Tetrahedron Lett.* **1991**, *32*, 2449–2452.

25 Kim, H. Y.; Walsh, P. J. Tandem Catalytic Enantio- and Diastereoselective Synthesis of Cyclopropyl Alcohols using Aryl Aldehydes. *J. Phys. Org. Chem.* **2012**, *in press*.

26 Baldwin, J. E. Thermal Rearrangements of Vinylcyclopropanes to Cyclopentenes. *Chem. Rev.* **2003**, *103*, 1197–1212.

27 Davies, H. M. L.; Bruzinski, P. R.; Lake, D.; Kong, N.; Fall, M. Asymmetric Cyclopropanations by Rhodium(II) N-(Arylsulfonyl)prolinate Catalyzed Decomposition of Vinyldiazomethanes in the Presence of Alkenes. Practical Enantioselective Synthesis of the Four Stereoisomers of 2-Phenylcyclopropan-1-amino Acid. *J. Am. Chem. Soc.* **1996**, *118*, 6897–6907.

28 Davies, H. M. L.; Panaro, S. A. Novel Dirhodium Tetraprolinate Catalysts Containing Bridging Prolinate Ligands for Asymmetric Carbenoid Reactions. *Tetrahedron Lett.* **1999**, *40*, 5287–5290.

29 Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. Enantioselective Cyclopropanation of Allylic Alcoholc with Dioxaborolane Ligands: Scope and Synthetic Applications. *J. Am. Chem. Soc.* **1998**, *120*, 11943–11952.

30 Majumdar, S.; de Meijere, A.; Marek, I. Catalytic Asymmetric and Stereoselective Synthesis of Vinylcyclopropanes. *Synlett* **2002**, *2002*, 0423–0426.

31 Kim, H. Y.; Salvi, L.; Carroll, P. J.; Walsh, P. J. One-Pot Catalytic Enantio- and Diastereoselective Syntheses of anti-, syn-cis-Disubstituted, and syn-Vinyl Cyclopropyl Alcohols. *J. Am. Chem. Soc.* **2010**, *132*, 402–412.

32 Miyano, S.; Matsumoto, Y.; Hashimoto, H. Synthesis of Monobromocyclopropanes from Olefins using a Bromocarbenoid of Zinc. *J. Chem. Soc., Chem. Commun.* **1975**, 364–365.

33 Sugimura, T.; Katagiri, T.; Tai, A. Methyl Carbenoid Addition to Enol Ethers Carrying a Chiral Auxiliary. Stereocontrol of Three Chiral Centers on Cyclopropyl Ether. *Tetrahedron Lett.* **1992**, *33*, 367–368.

34 Fletcher, R. J.; Motherwell, W. B.; Popkin, M. E. The Generation and Trapping of Organozinc Carbenoids from Orthoformates: a Novel Alkoxycyclopropanation Reaction. *Chem. Commun.* **1998**, 2191–2192.

35 Takai, K.; Toshikawa, S.; Inoue, A.; Kokumai, R. Stereoselective Iodocyclopropanation of Terminal Alkenes with Iodoform, Chromium(II) Chloride, and N,N,N′,N′-Tetraethylethylenediamine. *J. Am. Chem. Soc.* **2003**, *125*, 12990–12991.

36 Beaulieu, L.-P. B.; Zimmer, L. E.; Charette, A. B. Enantio- and Diastereoselective Iodocyclopropanation of Allylic Alcohols by Using a Substituted Zinc Carbenoid. *Chem.—Eur. J.* **2009**, *15*, 11829–11832.

37 Fournier, J.-F.; Mathieu, S.; Charette, A. B. Diastereoselective Zinco-Cyclopropanation of Chiral Allylic Alcohols with gem-Dizinc Carbenoids. *J. Am. Chem. Soc.* **2005**, *127*, 13140–13141.

38 Marek, I.; Beruben, D.; Normant, J.-F. Metal-Alkene pi-Chelation: A Stereodirecting Effect in Allylzincation Reactions and in Zinc Mediated Cyclopropanations. *Tetrahedron Lett.* **1995**, *36*, 3695–3698.

39 Beruben, D.; Marek, I.; Normant, J. F.; Platzer, N. Stereodefined Substituted Cyclopropyl Zinc Reagents from Gem-Bismetallics. *J. Org. Chem.* **1995**, *60*, 2488–2501.

40 Guerrero, A.; Martin, E.; Hughes, D. L.; Kaltsoyannis, N.; Bochmann, M. Zinc(II) η1- and η2-Toluene Complexes: Structure and Bonding in $Zn(C_6F_5)_2\cdot$(toluene) and $Zn(C_6F_4$-2-$C_6F_5)_2\cdot$(toluene). *Organometallics* **2006**, *25*, 3311–3313.

41 Knochel, P.; Singer, R. D. Preparation and Reactions of Polyfunctional Organozinc Reagents in Organic Synthesis. *Chem. Rev.* **1993**, *93*, 2117–2188.

42 Kim, H. Y.; Salvi, L.; Carroll, P. J.; Walsh, P. J. Highly Enantio- and Diastereoselective One-Pot Methods for the Synthesis of Halocyclopropyl Alcohols. *J. Am. Chem. Soc.* **2009**, *131*, 954–962.

43 House, H. O.; Fischer, W. F. J. Chemistry of Carbanions. XVII. Addition of Methyl Organometallic Reagents to Cyclohexenone Derivatives. *J. Org. Chem.* **1968**, *33*, 949–951.

44 Hiyama, H.; Yamamoto, H.; Nishio, K.; Kitatani, K.; Nozaki, H. Alkylation of Bromocyclopropanes and Bromoarenes by Means of Dibutylcopperlithium and Alkyl Halides. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3632–3637.

45 Jeon, S.-J.; Fisher, E. L.; Carroll, P. J.; Walsh, P. J. Direct, Stereospecific Generation of (Z)-Disubstituted Allylic Alcohols. *J. Am. Chem. Soc.* **2006**, *128*, 9618–9619.

46 Campbell, J. B. J.; Molander, G. A. Improved Synthesis of cis-Alkenylboranes. *J. Organomet. Chem.* **1978**, *156*, 71–79.

47 Salvi, L.; Jeon, S.-J.; Fisher, E. L.; Carroll, P. J.; Walsh, P. J. Catalytic Asymmetric Generation of (Z)-Disubstituted Allylic Alcohols. *J. Am. Chem. Soc.* **2007**, *129*, 16119–16125.

48 Salvi, L.; Kim, J. G.; Walsh, P. J. Practical Catalytic Asymmetric Synthesis of Diaryl-, Heteroaryl- and Diheteroarylmethanols. *J. Am. Chem. Soc.* **2009**, *131*, 12483–12493.

49 Davies, H. M. L.; Cantrell, W. R., Jr. α-Hydroxy Esters as Inexpensive Chiral Auxiliaries in Rhodium (II)-Catalyzed Cyclopropanation with Vinyldiazomethanes. *Tetrahedron Lett.* **1991**, *32*, 6509–6512.

50 Hamada, T.; Ye, X.; Stahl, S. S. Copper-Catalyzed Aerobic Oxidative Amidation of Terminal Alkynes: Efficient Synthesis of Ynamides. *J. Am. Chem. Soc.* **2008**, *130*, 833–835.

51 Tsai, C.-C.; Hsieh, I. L.; Cheng, T.-T.; Tsai, P.-K.; Lin, K.-W.; Yan, T.-H. New, General, and Practical Enamine Cyclopropanation Using Dichloromethane. *Org. Lett.* **2006**, *8*, 2261–2263.

52 Song, Z.; Lu, T.; Hsung, R. P.; Al-Rashid, Z. F.; Ko, C.; Tang, Y. Stereoselective Simmons-Smith Cyclopropanation of Chiral Enamides. *Angew. Chem., Int. Ed.* **2007**, *46*, 4069–4072.

53 Valenta, P.; Carroll, P. J.; Walsh, P. J. Stereoselective Synthesis of β-Hydroxy Enamines, Aminocyclopropanes, and 1,3-Amino Alcohols via Asymmetric Catalysis. *J. Am. Chem. Soc.* **2010**, *132*, 14179–14190.

54 Marek, I.; Normant, J.-F. Synthesis and Reactivity of sp^3-Geminated Organodimetallics. *Chem. Rev.* **1996**, *96*, 3241–3268.

55 Marek, I. Synthesis and Reactivity of sp^2 Geminated Organobismetallic Derivatives. *Chem. Rev.* **2000**, *100*, 2887–2900.

56 Waas, J. R.; Sidduri, A.; Knochel, P. Preparation and Reactions of 1,1-Zinc, Boron and 1,1-Copper, Boron Alkenyl Bimetallics. *Tetrahedron Lett.* **1992**, *33*, 3717–3720.

57 Shimizu, M.; Kurahashi, T.; Kitagawa, H.; Hiyama, T. gem-Silylborylation of an sp Carbon: Novel Synthesis of 1-Boryl-1-silylallenes. *Org. Lett.* **2003**, *5*, 225–227.

58 Deloux, L.; Srebnik, M.; Sabat, M. Stereospecific Synthesis of Temarotene, Its Structural Isomers, and Mixed Triaryl Alkenes from gem-Borazirconocene Alkenes. *J. Org. Chem.* **1995**, *60*, 3276–3277.

59 Li, H.; Carroll, P. J.; Walsh, P. J. Generation and Tandem Reactions of 1-Alkenyl-1,1-Heterobimetallics: Practical and Versatile Reagents for Organic Synthesis. *J. Am. Chem. Soc.* **2008**, *130*, 3521–3531.

60 Kulinkovich, O. G. The Chemistry of Cyclopropanols. *Chem. Rev.* **2003**, *103*, 2597–2632.

61 Hussain, M. M.; Li, H.; Hussain, N.; Ureña, M.; Carroll, P. J.; Walsh, P. J. Applications of 1-Alkenyl-1,1-Heterobimetallics in the Stereoselective Synthesis of Cyclopropylboronate Esters, Trisubstituted Cyclopropanols and 2,3-Disubstituted Cyclobutanones. *J. Am. Chem. Soc.* **2009**, *131*, 6516–6524.

62 Ukai, K.; Oshima, K.; Matsubara, S. Preparation of cyclopropanediol: Novel [2 + 1] cycloaddition reaction of bis(iodozincio)methane with 1,2-diketones. *J. Am. Chem. Soc.* 2000, 122, 12047−12048.

63 Nomura, K.; Matsubara, S. Preparation of Zinc-Homoenolate from alpha-Sulfonyloxy Ketone and Bis(iodozincio)methane. *Chem. Lett.* **2007**, *36*, 164–165.

64 Cheng, K.; Carroll, P. J.; Walsh, P. J. Diasteroselective Preparation of Cyclopropanols Using Methylene Bis(iodozinc). *Org. Lett.* **2011**, *13*, 2346–2349.