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Highly Enantioselective Synthesis of 1,2,3-Substituted Cyclopropanes by Using α-Iodo- and α-Chloromethylzinc Carbenoids

Louis-Philippe B. Beaulieu,[a] Lucie E. Zimmer,[a] Alexandre Gagnon,[a, b] and André B. Charette*[a]

Abstract: Herein, we report the enantio- and diastereoselective formation of *trans*-iodo- and *trans*-chlorocyclopropanes from α-iodo- and α-chlorozinc carbenoids by using a dioxaborolane-derived chiral ligand. The synthetically useful iodocyclopropane building blocks were derivatized by an electrophilic trapping of the corresponding cyclopropyl lithium species or a Negishi coupling to give access to a variety of enantioenriched 1,2,3-substituted cyclopropanes. The synthetic utility of this method was demonstrated by the formal synthesis of an HIV-1 protease inhibitor. In addition, the related stereoselective bromocyclopropanation was also investigated. New insights about the relative electrophilicity of haloiodomethylzinc carbenoids are also presented.

Keywords: asymmetric synthesis · carbenoids · cyclopropanes · halogen scrambling · Simmons–Smith reactions · zinc

Introduction

The cyclopropane unit continues to generate interest due to its unique bonding properties, its rigidity, and its numerous applications in diverse chemical transformations.[1] This motif is present in several bioactive natural products as well as synthetic drugs, which has prompted the development of methodologies for their synthesis.[2] The Simmons–Smith cyclopropanation reaction[3] remains one of the most important methods for the formation of cyclopropane derivatives from alkenes.[1e,4] Following seminal reports[5] of a method that featured a zinc–copper couple and diiodomethane as reagents, many variations that increase the efficiency of the reaction, its reproducibility, and its solvent compatibility have been reported. For instance, Furukawa et al. reported[6] a major breakthrough when they substituted the zinc–copper couple with diethylzinc to form zinc carbenoids by an alkyl-exchange reaction with diiodomethane.[7] Subsequently, numerous substituted carbenoids were developed by using this strategy with other *gem*-diiodomethyl motifs ($RCHI_2$) and were employed for the formation of the corresponding cyclopropanes.[8] Along with these advances, several enantioselective cyclopropanation reactions of allylic alcohols were developed by using both unsubstituted[9,10] and substituted[11] iodoalkylzinc reagents. The high levels of enantio- and diastereoselectivity observed in the preparation of 1,2,3-substitued cyclopropanes by using alkyl-substituted zinc carbenoids and allylic alcohols in the presence of a dioxaborolane-derived chiral ligand clearly illustrate the potential of substituted zinc carbenoids in synthesis.[8d]

Despite its efficiency, the scope of this reaction is limited due to the instability of iodoalkylzinc carbenoids and the large number of molar equivalents of the 1,1-diiodoalkane precursors that are generally needed to achieve high conversions. A more divergent approach would be expected to rely on the use of an α-functionalized zinc carbenoid (RZnCHIX), in which the X substituent could be easily derivatized to obtain structurally diverse, enantioenriched 1,2,3-substituted cyclopropanes. Ideally, this species would be readily accessible from inexpensive reagents. In this context, the development of a halocyclopropanation methodology is quite appealing.

Since the pioneering efforts of Hashimoto and Miyano,[12] there has been very limited progress in the field of halocyclopropanation reactions that use α-iodomethylzinc carbenoids. A major drawback of these reactions is their poor diastereoselectivity, which typically ranges from 2:1 to 1:2 (Scheme 1). It appears that the two possible transition states involving the substituted carbenoid are too close in energy to provide synthetically useful diastereomeric ratios when unfunctionalized alkenes are used. Furthermore, the preparation of this reagent can be complicated by a second alkyl-exchange reaction between the α-iodozinc carbenoid **1** and an organozinc reagent (either **1**, EtZnI, or Et_2Zn), thus leading to a *gem*-dizinc carbenoid **2** (Scheme 2). This would lead to a lower yield of the desired iodo-substituted product.[13]

Although the first versatile and highly diastereoselective halocyclopropanation reaction of chiral allylic alcohols has

[a] L.-P. B. Beaulieu, Dr. L. E. Zimmer, Prof. A. Gagnon, Prof. A. B. Charette
Centre in Green Chemistry and Catalysis
Department of Chemistry, Université de Montréal
P.O. Box 6128, Station Downtown, Montréal, H3C 3J7 (Canada)
Fax: (+1) 514-343-7586
E-mail: andre.charette@umontreal.ca

[b] Prof. A. Gagnon
Department of Chemistry, Université du Québec à Montréal
P.O. Box 8888, Succ. Centre-Ville, Montréal, H3C 3P8 (Canada)

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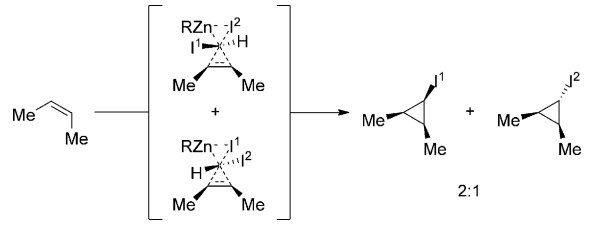
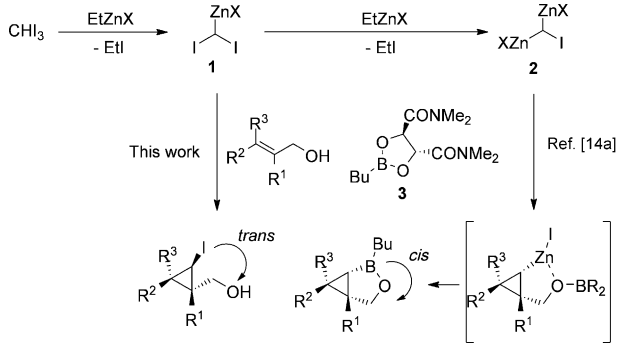


Scheme 1. Cyclopropanation of alkenes with α-diiodomethylzinc carbenoids.



Scheme 2. Stereodivergent methods for the preparation of 1,2,3-substituted cyclopropane derivatives.

recently been introduced by Walsh et al.,[8e] an enantioselective version of this transformation is desirable. We recently reported our preliminary results concerning two powerful and complementary methodologies that can provide access to stereoisomers of 1,2,3-substituted cyclopropane derivatives from stereodefined allylic alcohols by using α-functionalized zinc carbenoids (Scheme 2).[14]

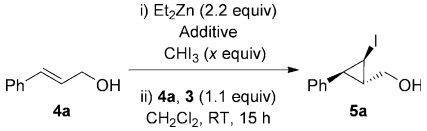
Both approaches rely on the use of substituted zinc carbenoid reagents, which are derived from iodoform and Et_2Zn, and dioxaborolane (**3**) for the enantio- and diastereoselective preparation of iodo- and zinc-substituted cyclopropanes. The complementarity of these reactions resides in the stereochemical outcome of the cyclopropanation. In the iodocyclopropanation reaction, the newly formed C–I bond is in a *trans* position to the hydroxymethyl group, whereas a *cis* relationship is observed between the C–Zn bond and the hydroxymethyl substituent in the reaction that involves the *gem*-dizinc carbenoid.

Herein, we describe an extended scope for the enantioselective iodocyclopropanation reaction. We also describe additional reactions of these products for derivatization into diverse 1,2,3-substituted cyclopropane motifs. The synthetic utility of this methodology is demonstrated by the formal synthesis of a biologically active peptidomimetic molecule. We have also developed an unprecedented, highly stereoselective chlorocyclopropanation reaction that starts from chlorodiiodomethane. Finally, new insights into the analogous stereoselective bromocyclopropanation reaction are also provided.

Results and Discussion

Iodocyclopropanation reaction: Our preliminary experiments related to the iodocyclopropanation reaction of allylic alcohols are summarized in Table 1. To maximize conversion to the iodocyclopropane and the diastereomeric ratio (d.r.) while minimizing the undesired zincocyclopropanation mediated by the *gem*-dizinc carbenoid **2**, we first studied the effect of the stoichiometry of CHI_3 relative to Et_2Zn. A low yield and modest diastereoselectivity were observed when cinnamyl alcohol was treated with CHI_3/Et_2Zn (2:1) under typical Furukawa–Miyano conditions (Table 1, entry 1). It appears that under these reaction conditions the zinc alkoxide promotes the rapid decomposition of the α-iodozinc carbenoid.[15] Surprisingly, the incorporation of dioxaborolane (**3**) led not only to an improved diastereoselectivity, but also to a much better yield of the desired *trans*-iodocyclopropane **5a** (Table 1, entry 2). A 1:1 ratio of CHI_3 relative to Et_2Zn did not ensure complete conversion (Table 1, entry 3). Other more-electrophilic carbenoids, such as $IZnCHI_2$ and $CF_3CH_2OZnCHI_2$[8e] (Table 1, entries 4 and 5, respectively), did not lead to any formation of the desired product.

Table 1. Optimization of the iodocyclopropanation with $RZnCHI_2$.[a]



	CHI_3 [equiv]	Additive[b]	SM [%][c]	Yield [%][d]	d.r.[e]
1[f]	4.4	–	≤2	16	5:1
2	4.4	–	≤2	76 (66)[g]	9:1
3	2.2	–	14	62	6:1
4	2.2	I_2	≥98	–	–
5	2.2	CF_3CH_2OH	≥98	–	–

[a] Unless otherwise noted, the zinc carbenoid was formed by adding neat Et_2Zn to a suspension of CHI_3 in CH_2Cl_2 at room temperature. [b] A solution of CHI_3 in CH_2Cl_2 was added to a preformed mixture of Et_2Zn and the additive (2.2 equiv) in CH_2Cl_2. [c] SM is the remaining starting material as determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [d] The yield of the *trans* diastereomer was determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [e] The diastereoselectivity was determined by ^1H NMR analysis of the crude reaction mixture. [f] The reaction was performed in the absence of **3**. [g] Yield of isolated product is given in brackets.

To gain further insight into the nature of the carbenoid involved in the iodocyclopropanation, we quenched the preformed zinc carbenoid with D_2O. A ratio of CHI_3 relative to $CHDI_2$ of 1 was observed upon forming the carbenoid at room temperature and with a 2:1 stoichiometric ratio of CHI_3 relative to Et_2Zn.This indicates that, under these conditions, diethylzinc undergoes a single alkyl exchange with iodoform to generate $EtZnCHI_2$ (Hashimoto's reagent).

The optimal reaction conditions (Table 1, entry 2) were selected to evaluate the scope of this reaction (Table 2).

Gratifyingly, the iodocyclopropanation reaction proved to be highly enantioselective and displayed good to excellent diastereoselectivities with most of the allylic alcohols tested. Synthetically useful yields of the isolated *trans* diastereomer were obtained from the reaction of a variety of allylic alcohols.[16] Both electron-rich and -poor (*E*)-3-aryl-2-propen-1-ols (Table 1, entries 1–9), some of which contain bulky aryl substituents (Table 1, entries 2 and 3), were well tolerated. Both primary and secondary (*E*)-3-alkyl-2-propen-1-ols (Table 1, entries 11–16) underwent the iodocyclopropanation reaction smoothly, although higher concentrations and longer reaction times were needed to ensure complete conversion. 2,2,3-Trisubstituted allylic alcohols (Table 1, entries 17 and 18) gave products in excellent diastereo- and enantioselectivities. The reaction proved to be chemoselective towards allylic alcohols (Table 1, entry 10) and was compatible with functionalities such as nitroarenes (Table 1, entry 5), chloroarenes (Table 1, entries 3 and 6), alkyl chlorides (Table 1, entry 13), and *tert*-butyldimethylsilyl ethers (Table 1, entry 12). The iodocyclopropanation of (*Z*)-2-hexen-1-ol illustrated the marked influence of **3**; a complete inversion of diastereoselectivity was observed when the reaction was performed in the absence of this ligand (Table 1, entry 15). In all instances, the diastereomers were readily separated by flash column chromatography, and the *cis* isomer was less polar than the *trans* in all cases. It is worth noting that the iodocyclopropanation of **4a** could be performed on a 10 mmol scale to provide **5a** in 64% yield with a d.r. of 9:1 and 96% *ee*.

The proposed transition-state model for the enantioselective iodocyclopropanation of cinnamyl alcohol in the presence of dioxaborolane **3** is depicted in Figure 1. The treatment of cinnamyl alcohol with diethylzinc results in the formation of a zinc alkoxide, which reacts with the dioxaborolane to produce an ate complex. We believe that the bulkier butyl substituent on the boron atom of this complex adopts the sterically less-congested pseudoequatorial position, whereas the allylic alkoxide assumes the electronically more favorable pseudoaxial position. The resulting ate complex is believed to coordinate to the zinc carbenoid in a bidentate fashion through the allylic alkoxide and one of the Lewis

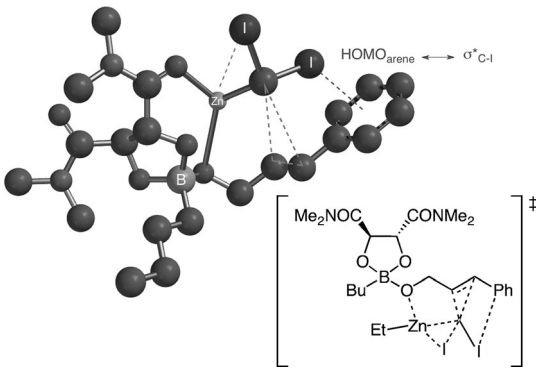
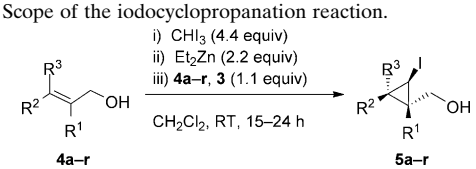
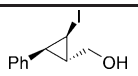
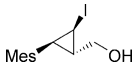
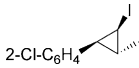
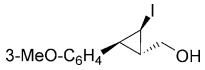
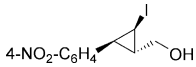
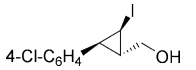
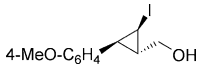
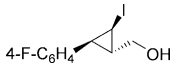
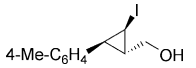
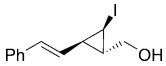
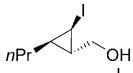
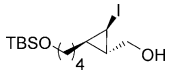
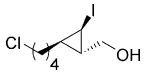
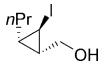
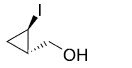
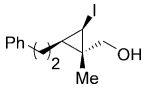
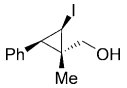


Figure 1. Representation of the proposed transition-state model for the enantioselective iodocyclopropanation reaction of cinnamyl alcohol.

Table 2. Scope of the iodocyclopropanation reaction.



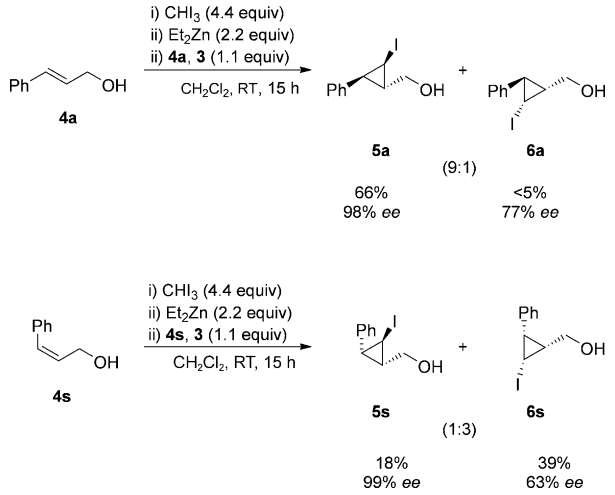
	Product		Method[a]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1		**5a**	A	66	9:1	98
2		**5b**	B	73	18:1	98
3		**5c**	A	81	12:1	98
4		**5d**	A	70	7:1	96
5[e]		**5e**	B	64	7:1	97
6		**5f**	A	69	9:1	98
7		**5g**	A	55	7:1	98
8		**5h**	A	70	11:1	98
9		**5i**	A	74	6:1	96
10		**5j**	B	53	5:1	98
11		**5k**	B	66	5:1	96
12		**5l**	B	63	5:1	96[f]
13		**5m**	B	59	6:1	95
14		**5n**	B	67	4:1	95
15[g]		**5o**	B	42	4:1	99
16		**5p**	B	46	8:1	90
17		**5q**	B	65	16:1	91
18		**5r**	A	68	≥20:1	93

[a] Method A: 0.1 M in CH_2Cl_2, RT, 15 h. Method B: 0.2 M in CH_2Cl_2, RT, 24 h. [b] Yield of isolated *trans* diastereomer. [c] Determined by ^{1}H NMR analysis of the crude reaction. [d] Determined by GC or SFC on a chiral stationary phase. [e] Yield after dihydroxylation of the remaining traces of the starting allylic alcohol. [f] Determined after removal of the protecting group. [g] The product where the C–I bond is in a *cis* relationship with the hydroxymethyl group was formed exclusively when the reaction was conducted in the absence of **3**. Mes = mesityl, TBS = *tert*-butyldimethylsilyl, Cy = cyclohexyl.

basic amide moieties. The most suitable conformation for CHI delivery is that in which the allylic chain is in its most stable conformation. It is generally accepted that over the course of the Simmons–Smith reaction the σ^*_{C-I} orbital must be synperiplanar to the π_{C-C} orbital.[17,18]

Of the two possible reactive conformers that meet this prerequisite, the conformer that contains an iodine atom *trans* to the sterically encumbered dioxaborolane–alkoxide complex leads to the major diastereomer. Recent density functional theory (DFT) studies of analogous cyclopropanation reactions conducted by Yu et al.[19] have corroborated this model by minimization of torsional strain, 1,3-allylic strain, and the ring strain that is generated in the intramolecular cyclopropanation transition state.

We observed one exception to the proposed model in the iodocyclopropanation of (*Z*)-3-phenylprop-2-en-1-ol (**4s**; Scheme 3).[20] In this particular case, the diastereoselectivity



Scheme 3. Contrasting diastereoselectivities in the enantioselective iodocyclopropanation of (*E*)- and (*Z*)-cinnamyl alcohol.

was reversed and the *cis* diastereomer was favored. This selectivity contrasts with that of the iodocyclopropanation of (*E*)-cinnamyl alcohol (**4a**) and, more strikingly, with that of (*Z*)-2-hexen-1-ol (**4o**), which both result in the preferential formation of the *trans* diastereomer. This observation led us to propose that the reversal of diastereoselectivity is due to a stabilizing halogen-bonding interaction between the HOMO of the aryl substituent (in **4a**–**j** and **4r**) and the α^* orbital of the carbon–iodine bond of the electrophilic zinc carbenoid (Figures 1 and 2).[21,22] This electrostatic stabilization could also account for the increase in diastereoselectivity when more electron-rich aryl substituents are present on the starting allylic alcohol. This interaction is important because a remarkably higher *trans* diastereoselectivity was observed in the cyclopropanation of the bulkier mesityl-substituted allylic alcohol (for example, see Table 2, entry 1 vs. 2). If the arene–halide interaction is the main stereodirecting effect for (*Z*)-cinnamyl alcohol, it is expected that the related chlorocyclopropanation would occur with a much lower

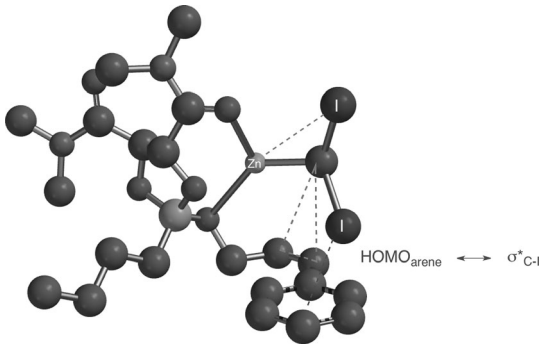


Figure 2. Representation of the proposed transition-state model for the enantioselective iodocyclopropanation reaction of (*Z*)-cinnamyl alcohol.

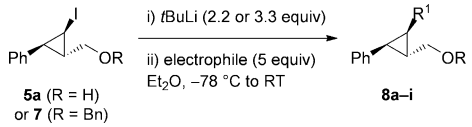
diastereoselectivity due to the weaker chloro–arene interaction than the corresponding iodo–arene interaction.[23] The chlorocyclopropanation of a (*Z*)-cinnamyl alcohol did indeed lead to a 1:1 diastereomeric ratio of products (see Table 6, entry 7 below).

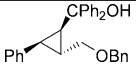
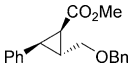
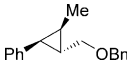
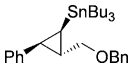
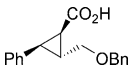
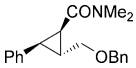
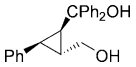
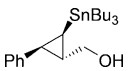
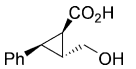
To illustrate the versatility with which 2,3-disubstituted iodocyclopropanes can be derivatized into several highly functionalized 1,2,3-substituted cyclopropanes, the unprotected or the *O*-benzyl-protected iodocyclopropanation products were submitted to a lithium–halogen exchange reaction followed by the addition of a variety of electrophiles (Table 3).[24] In all cases, the lithium–halogen exchange proceeded cleanly with complete retention of configuration when *t*BuLi was used. The electrophiles were also cleanly intercepted by the cyclopropyllithium reagents with complete retention of configuration (Table 3, entries 1–6). Interestingly, the reaction of an unprotected alcohol was successful when an additional equivalent of *t*BuLi was employed (Table 3, entries 7–9). A mixed cuprate could also be prepared from the iodocyclopropylmethanol **5a** and was subsequently treated with allyl bromide to provide the corresponding allylated derivative in good yield (Scheme 4).[8f]

The benzyl-protected iodocyclopropylmethanol **7** could be used in a Negishi cross-coupling reaction[25] with aryl iodides (Table 4).[26] An extensive screening of phosphine-based ligands indicated that several were effective in promoting the reaction.[27] Tris(*ortho*-tolyl)phosphine was chosen to elaborate the scope of the reaction. Electron-rich (Table 4, entry 5) and electron-deficient (Table 4, entries 1, 7, and 8) aryl iodides were well tolerated in this reaction. Sterically encumbered aryl iodides (Table 4, entries 4 and 6) also proved to be competent coupling partners.

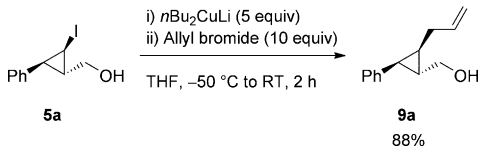
Having developed a powerful and versatile methodology for the synthesis of enantioenriched 2,3-disubstituted *trans*-iodocyclopropanes, we embarked on establishing its synthetic utility by using it to elaborate the cyclopropane subunit of the HIV-1 protease inhibitor **11**.[28] The inhibitor's cyclopropane core (**13**) was accessed very efficiently from (*E*)-crotyl alcohol by using our stereoselective iodocyclopropanation methodology (Scheme 5). Lithium–halogen exchange followed by quenching with carbon dioxide resulted in the formation of the corresponding carboxylic acid, which was pro-

Table 3. Functionalization of iodocyclopropanes by a sequential Li–I exchange and electrophilic quench.



	Product		Electrophile	Yield [%][a]
1		**8a**	PhC(O)Ph	90
2		**8b**	$ClCO_2Me$	70
3		**8c**	MeI	97
4		**8d**	Bu_3SnCl	85
5		**8e**	CO_2	75
6		**8f**	$ClC(O)NMe_2$	85
7		**8g**	PhC(O)Ph	65
8		**8h**	Bu_3SnCl	84
9		**8i**	CO_2	88

[a] Isolated yield of product as a single diastereomer. Bn = benzyl.

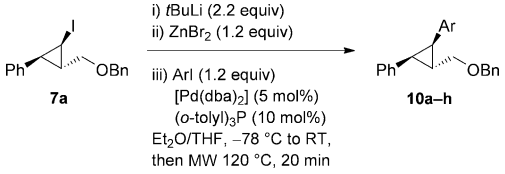


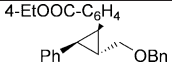
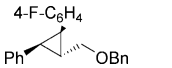
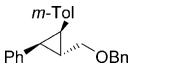
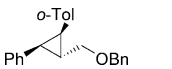
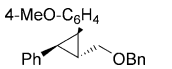
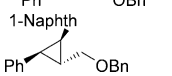
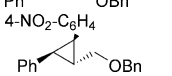
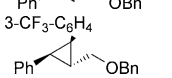
Scheme 4. Allylation through the cyclopropylcuprate.

tected as the methyl ester. Oxidation of the primary alcohol to the carboxylic acid, followed by peptide coupling with benzylamine and saponification of the methyl ester, led to the isolation of an advanced intermediate (**18**) towards the HIV-1 protease inhibitor in 33% overall yield over six steps, which compares favorably to the reported eight-step route developed by Martin and collaborators, which has an overall yield of 11%.[28a]

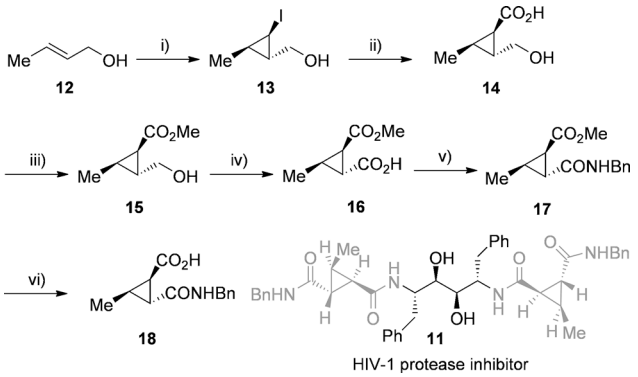
Chloro- and bromocyclopropanation reactions: To increase the scope of the enantioselective cyclopropanation reaction, we were interested in investigating the analogous stereoselective chloro- and bromocyclopropanation reactions, which have very few literature precedents.[8f] This reaction would also provide further evidence to support the models presented in Figures 1 and 2 because the halogen-bonding interactions may not be as strong with these two halides. The α-chloro and α-bromozinc carbenoids could be generated from the readily accessed haloforms $ClCHI_2$ and $BrCHI_2$, respectively.[29] The chlorocyclopropanation performed by

Table 4. Negishi cross-coupling of iodocyclopropane derivatives.



	Product		Yield [%][a]
1		**10a**	65
2		**10b**	80
3		**10c**	85
4		**10d**	84
5		**10e**	73
6		**10f**	59
7		**10g**	62
8		**10h**	51

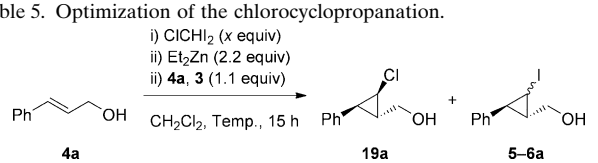
[a] Yield of isolated product as a single diastereomer. dba = dibenzylideneacetone, Tol = tolyl, Naphth = naphthyl.



Scheme 5. Formal synthesis of a peptidomimetic HIV-1 protease inhibitor. a) $EtZnCHI_2$, **3**, CH_2Cl_2, RT, 63%, d.r. 5:1, 94% *ee*; b) i) *t*BuLi; ii) CO_2, Et_2O, −78 °C to RT, 65%; c) $SOCl_2$, MeOH, 0 °C to RT, 89%; d) $RuCl_3{\cdot}xH_2O$, $NaIO_4$, $CCl_4/H_2O/MeCN$, 93%; e) EDC·HCl, $BnNH_2$, DMAP, CH_2Cl_2, RT, quant.; f) $LiOH{\cdot}H_2O$, THF, MeOH, RT, 96%.

using 4.4 equivalents of $ClCHI_2$ at room temperature led to an unsatisfactory mixture of chlorocyclopropane and iodocyclopropane products and a low conversion (Table 5, entry 1). These observations suggested that the zinc carbenoid may be unstable under these reaction conditions. Lowering the reaction temperature led to interesting ratios of **19a**/**5**–**6a** and complete conversion (Table 5, entries 2–4). Under the optimal conditions, chlorocyclopropane **19a** was isolated in good yield and with a high *ee* (Table 5, entry 4). Decreasing

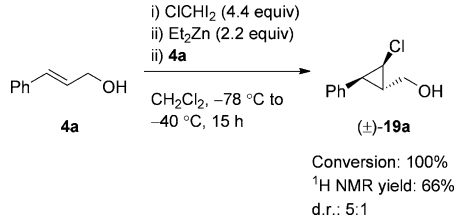
Table 5. Optimization of the chlorocyclopropanation.



	4a [equiv]	*T* [°C]	Ratio **19/5–6a**[a]	SM [%][b]
1	4.4	25	3:1	60
2	4.4	−20	12:1	53
3	4.4	−40	≥20:1	10
4	4.4	−78 to −40	≥20:1[c,d]	≤2
5	3.3	−78 to −40	≥20:1	19
6	2.2	−78 to −40	–	≥95

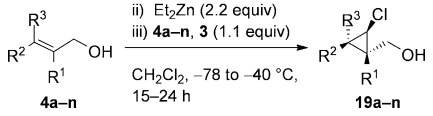
[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. The d.r. for the formation of **19a** was ≥20:1. [b] SM is the remaining starting material as determined by ^{1}H NMR analysis by integrating the signals from the chlorocyclopropane and cinnamyl alcohol. [c] Diastereomerically pure **19a** was isolated in 78% yield. [d] A 93% *ee* was determined by SFC on chiral stationary phase.

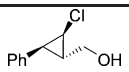
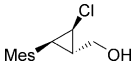
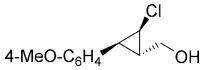
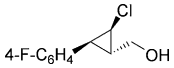
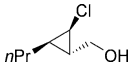
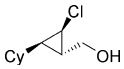
the amount of $ClCHI_2$ relative to diethylzinc resulted in lower conversions (Table 5, entries 5 and 6). Interestingly, conducting the reaction in the absence of the dioxaborolane **3** (Scheme 6) led to a much lower diastereoselectivity, a result which highlights the role of the dioxaborolane ligand for both the enantio- and diastereoselectivity of the reaction.



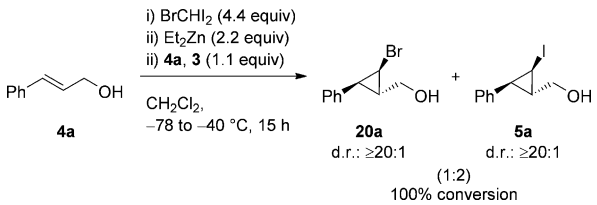
Scheme 6. Decreased diastereoselectivity observed for the chlorocyclopropanation of **4a** in the absence of **3**.

Table 6. Scope of the chlorocyclopropanation.



	Product		Method,[a] Yield [%][b]	d.r.[c]	*ee* [%][d]
1		**19a**	A, 78	≥20:1	93
2		**19h**	B, 73	≥20:1	97
3		**19g**	B, 73	10:1	85
4		**19b**	B, 55	≥20:1	95
5		**19k**	B, 73	≥20:1	90[e]
6		**19n**	B, 55	≥20:1	92[e]
7		**19s**	A, 46	1:1	98[f]

[a] Method A: 0.1 M in CH_2Cl_2, −78 to −40 °C, 15 h. Method B: 0.2 M in CH_2Cl_2, −78 to −40 °C, 24 h. [b] Isolated yield of diastereomerically pure **19**. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by SFC on a chiral stationary phase. [e] Determined by SFC analysis of the benzoylated product on a chiral stationary phase. [f] Determined by ^{19}F NMR analysis of the corresponding Mosher's ester.



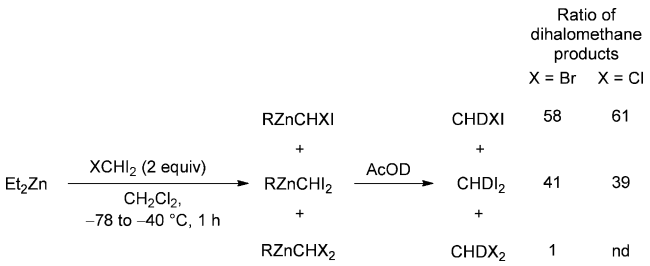
Scheme 7. Attempted bromocyclopropanation reaction.

The enantioselective chlorocyclopropanation reaction is compatible with cinnamyl alcohol derivatives that contain electronically different substituents (Table 6, entries 1–4). Steric hindrance on the aromatic ring was also tolerated (Table 6, entry 2). Finally, the reaction proceeded smoothly with allylic alcohols containing a primary or secondary (Table 6, entries 5 and 6, respectively) alkyl substituent. In all cases, reasonable yields and excellent diastereoselectivities and enantioselectivities were observed.[30] To the best of our knowledge, this is the first reported enantioselective chlorocyclopropanation reaction.

Upon attempting the analogous bromocyclopropanation under the optimal reaction conditions, we observed complete conversion to a mixture of iodo- and bromocyclopropanes. Surprisingly, the iodocyclopropane was the major component of the mixture (Scheme 7).

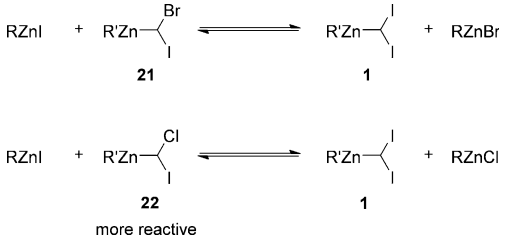
At this point, we wanted to shed some light on the mechanism of iodocyclopropane formation so we performed deuterium carbenoid-quenching experiments with $BrCHI_2$ as the carbenoid precursor (Scheme 8). Upon the addition of one equivalent of diethylzinc to two equivalents of $BrCHI_2$ and subsequently quenching with deuterated acetic acid, we observed all possible combinations of deuterated dihalomethanes by GC/MS, with complete consumption of the $BrCHI_2$ starting material. This observation is indicative of a halogen scrambling that takes place on the zinc carbenoid. We observed the formation of the same byproducts when the stoichiometric ratio of $BrCHI_2$ to diethylzinc was brought to 1:1, which suggested that this exchange could also be intermolecular in nature and mediated by the presence of zinc halides. Similar results were obtained upon quenching the carbenoids generated from diethylzinc and chlorodiiodomethane.

These observations indicate that several reagents are simultaneously present in these reactions. The formation of a single, major, chloro-substituted cyclopropane product from



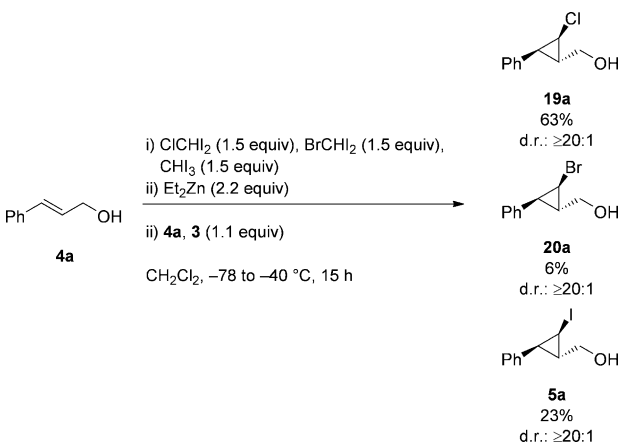
Scheme 8. Deuterium quenching experiments of the zinc carbenoids generated from $XCHI_2$ (X = Br and Cl).[31] nd = not determined.

chlorodiiodomethane suggests that the chloroiodomethylzinc carbenoid **22** is more reactive than the corresponding diiodomethylzinc species **1**. Conversely, the bromoiodomethylzinc species **21** and the analogous diiodomethylzinc **1** seem to have comparable reactivities (Scheme 9).



Scheme 9. α-Dihalomethylzinc carbenoid equilibration.

This was confirmed by conducting a competition experiment in which all three reagents were present (Scheme 10). When **4a** was treated with the reagents derived from diethylzinc and equimolar amounts of all three halodiiodomethanes, the chlorocyclopropane **19a** was the major product. This result unambiguously confirms that the chloroiodomethylzinc carbenoid that contains the more electronegative chloro substituent is more reactive than the other two reagents, probably due to an increased electrophilicity.



Scheme 10. Competition experiment with a mixture of reagents.

Conclusion

We have developed conditions for the enantioselective iodocyclopropanation of allylic alcohols from commercially available reagents. The versatile *trans*-iodocyclopropylmethanols have been functionalized to gain access to a variety of highly enantioenriched 1,2,3-trisubstituted cyclopropanes, which would be difficult to access otherwise. The synthetic utility of the stereoselective iodocyclopropanation reaction was demonstrated by the formal synthesis of a biologically active peptidomimetic molecule. In addition, we have investigated the analogous stereoselective bromo- and chlorocyclopropanation reactions. Although the bromocyclopropanation was inefficient due to the competing iodocyclopropanation reaction that stemmed from a halogen scrambling on the zinc carbenoid, the enantioselective chlorocyclopropanation proceeded in good yield and with excellent stereoselectivity. We demonstrated that the chloro-substituted zinc carbenoid is more reactive than the corresponding iodo- and bromo-substituted zinc carbenoids. To the best of our knowledge, these are the first accounts of enantioselective chloro- and iodocyclopropanation reactions. These methodologies provide an efficient route to numerous, synthetically versatile, enantioenriched 1,2,3-trisubstituted cyclopropanes.

Acknowledgements

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[31] It was not possible to unambiguously quantify nor identify $CHDCl_2$ since the reaction was run in CH_2Cl_2.

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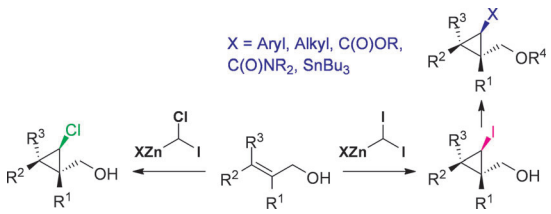

Propping up the enantioselectivity: The enantio- and diastereoselective formation of *trans*-iodo- and *trans*-chlorocyclopropanes from α-iodo- and α-chlorozinc carbenoids by using a dioxaborolane-derived chiral ligand is reported. The iodocyclopropanes were derivatized into a variety of 1,2,3-substituted cyclopropanes and new insights into the relative electrophilicity of α-haloiodomethylzinc carbenoids are presented (see scheme).

Asymmetric Synthesis

*L.-P. B. Beaulieu, L. E. Zimmer, A. Gagnon, A. B. Charette** ▮▮▮▮–▮▮▮▮

Highly Enantioselective Synthesis of 1,2,3-Substituted Cyclopropanes by Using α-Iodo- and α-Chloromethylzinc Carbenoids