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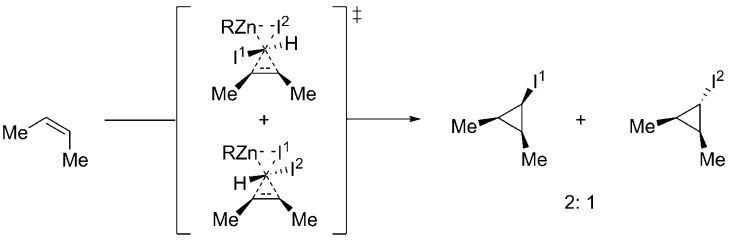
Enantio- and Diastereoselective Iodocyclopropanation of Allylic Alcohols by Using a Substituted Zinc Carbenoid

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

In addition to being present in several bioactive natural products,[1] 1,2,3-trisubstituted cyclopropanes embed significant structural complexity that has prompted their use as peptidomimetics,[2] and as substrates for various organic and organometallic reactions.[3] 2,3-Disubstituted iodocyclopropanes have been shown to be versatile precursors to access a multitude of highly functionalized cyclopropane units.[4] However, few methods for their asymmetric synthesis have been reported. Among them, Doyle and co-workers have performed the rhodium-catalyzed enantioselective intramolecular cyclopropanation of (*Z*)-3-iodo-2-propenyl diazoacetate.[5] The enantioselective, facially selective carbomagnesiation of cyclopropenes by using *N*-methylprolinol as a chiral ligand developed by Fox and Liu is an attractive route to 2,3-disubstituted iodocyclopropanes, albeit being restricted to the use of methyl Grignard reagents.[6] Walsh and co-workers have recently described a tandem enantioselective diorganozinc addition–diastereoselective Simmons–Smith iodocyclopropanation methodology towards the synthesis of 2,3-disubstituted iodocyclopropanes, whereby in most instances the iodine shows a *syn* relationship to the alkoxy group in the major diastereomer.[7]

We envisioned that a versatile enantioselective iodocyclopropanation reaction would be a valuable addition to the existing methodologies for the asymmetric synthesis of 2,3-disubstituted iodocyclopropanes. We previously reported the modified Simmons–Smith enantioselective cyclopropanation of allylic alcohols using alkyl-substituted zinc carbenoids and a stoichiometric dioxaborolane chiral ligand as a route towards 1,2,3-trisubstituted cyclopropanes.[8] Despite its high degree of stereoselectivity, this methodology suffered from limited compatibility with other *gem*-diiodoalkanes than 1,1-diiodoethane and from the required synthesis of these compounds. A more convergent approach would rely on the synthesis of 2,3-disubstituted iodocyclopropanes, which could then be further derivatized. Herein we report the first enantioselective Simmons–Smith iodocyclopropanation reaction, in which iodoform is used as the precursor to the substituted zinc carbenoid.

Since the pioneering efforts of Hashimoto and Miyano and the recent contributions by Walsh and co-workers, there has been very limited progress in the field of cyclopropanation using α-iodozinc carbenoids.[7,9] A challenging aspect of this reaction resides in its poor diastereoselectivity, which stems from the two possible reactive conformers of the zinc carbenoid (Scheme 1).



Scheme 1. Diastereoselectivity outcome dictated by the two reactive conformers of the zinc carbenoid.[9]

An additional complication lies in the development of conditions favoring the formation of the α-iodozinc carbenoid over the more reactive *gem*-dizinc carbenoid (Scheme 2).[10]

Bearing in mind that increasing the stoichiometric ratio of R_2Zn relative to CHI_3 results in an increased proportion of the *gem*-dizinc carbenoid relative to the α-iodozinc carbenoid,[11] we first examined the nature of the carbenoid by quenching the preformed zinc carbenoid with D_2O.[12] When a 2:1 stoichiometric ratio of CHI_3 relative to Et_2Zn was used, a ratio of CHI_3 relative to $CHDI_2$ of 1 was observed, thus demonstrating that diethylzinc undergoes a single alkyl

[a] L.-P. B. Beaulieu, L. E. Zimmer, Prof. A. B. Charette
Département de Chimie
Université de Montréal
P.O. Box 6128, Station Downtown, Montréal H3C 3J7 (Canada)
Fax: (+1) 714-343-5900
E-mail: andre.charette@umontreal.ca

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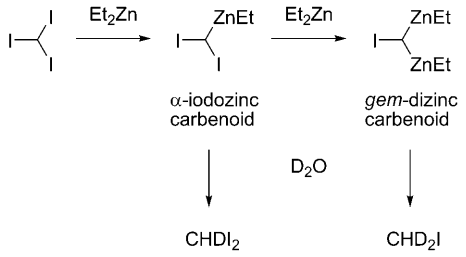
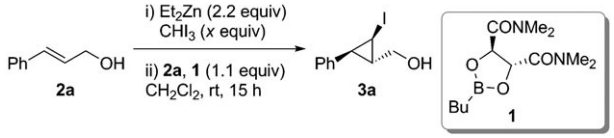


Scheme 2. Substituted zinc carbenoids formed by using iodoform as a precursor.

exchange with iodoform to generate $EtZnCHI_2$ (Hashimoto's reagent).[9] While virtually only $CHDI_2$ was observed using a 2:1 stoichiometric ratio of CHI_3 relative to Et_2Zn, up to 28% of the pool of deuterated iodomethane comprised CHD_2I when a 1:1 stoichiometric ratio of these reagents was employed.

We then attempted the iodocyclopropanation reaction of cinnamyl alcohol in the presence of the dioxaborolane **1** under various reaction conditions (Table 1). While a 1:1 stoi-

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



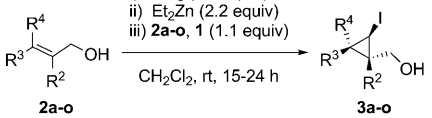
Entry	CHI_3 (x equiv)	Additive[b]	Conv. [%][c]	Yield [%][d]	d.r.[e]
1	2.2	–	86	62	6:1
2	4.4	–	≥98	76	9:1
3[f]	4.4	–	≥98	16	5:1
4	2.2	I_2	≤5	–	–
5	2.2	CF_3CH_2OH	≤5	–	–

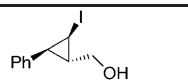
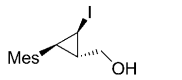
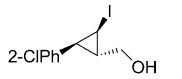
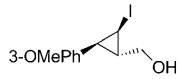
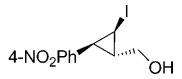
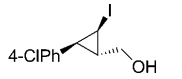
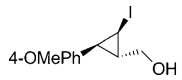
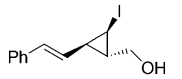
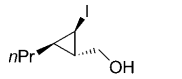
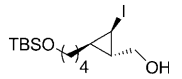
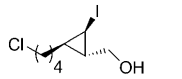
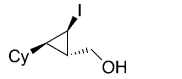
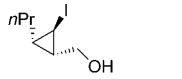
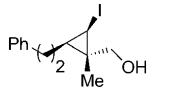
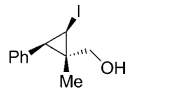
[a] Unless otherwise noted, the zinc carbenoid was formed by adding neat Et_2Zn to a suspension of CHI_3 in CH_2Cl_2 at room temperature. [b] A solution of CHI_3 in CH_2Cl_2 was added to a preformed mixture of Et_2Zn and the additive (2.2 equiv) in CH_2Cl_2. [c] Determined by ^1H NMR spectroscopy based on unreacted starting material. [d] ^1H NMR yield of the *anti* diastereomer using 1,3,5-trimethoxybenzene as an internal standard. [e] Determined by ^1H NMR spectroscopy from the crude reaction. [f] The reaction was performed in the absence of **1**.

chiometric ratio of CHI_3 relative to Et_2Zn did not ensure complete conversion (Table 1, entry 1),[13] we were pleased to observe complete conversion using a 2:1 stoichiometric ratio of these reagents (Table 1, entry 2). High levels of diastereoselectivity favoring the *anti* diastereomer were obtained. Interestingly, a much lower yield and lower diastereoselectivity were observed if the reaction was performed in the absence of **1** (Table 1, entry 3). Furthermore, other more electrophilic carbenoids such as $IZnCHI_2$ (Table 1, entry 4) and $CF_3CH_2OZnCHI_2$ (Table 1, entry 5) were not compatible with this methodology.

The optimal reaction conditions (Table 1, entry 2) were selected to elaborate the scope of this reaction (Table 2). Gratifyingly, the iodocyclopropanation reaction proved to

Table 2. Scope of the reaction.



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

[a] Procedure A: 0.1 M relative to the allylic alcohol in CH_2Cl_2, room temperature, 15 h. Procedure B: 0.2 M in CH_2Cl_2, room temperature, 24 h. [b] Isolated yield of the *anti* diastereomer. [c] Determined by ^1H NMR spectroscopy from the crude reaction. [d] Determined either by GC or SFC on chiral stationary phase. [e] Yield after dihydroxylation of the remaining traces of the starting allylic alcohol. [f] Determined after removal of the protecting group.

be highly enantioselective and displayed moderate to excellent diasterometric ratio (d.r.), with modest to good isolated yields of the *anti* diastereomer obtained over a range of substrates.[14] Both electron- rich and poor (*E*)-3-aryl-2-propen-

1-ols (Table 2, entries 1–7), some of which contained greater steric bulk (Table 2, entries 2 and 3), were well tolerated. (*E*)-3-Alkyl-2-propen-1-ols (either primary or secondary, Table 2, entries 9–12) underwent the iodocyclopropanation reaction smoothly, although more forcing conditions were needed to ensure complete conversion. Trisubstituted allylic alcohols (Table 2, entries 14 and 15) gave excellent d.r. and very good *ee*. In addition to being chemoselective towards allylic alcohols (Table 2, entry 8), the reaction was compatible with functionalities such as a nitro group (Table 2, entry 5), aromatic or aliphatic chlorine atoms (Table 2, entries 3, 6, 11) and a protected alcohol (Table 2, entry 10). (*Z*)-2-Hexen-1-ol illustrated the profound impact of **1** on the diastereoselectivity of the reaction, as none of the desired *anti* diastereomer was obtained in its absence (Table 2, entry 13). Although the diastereoselectivity of the reaction was modest in some cases, it is worth noting that both diastereomers were easily separated by flash chromatography.[15]

The proposed transition state for the enantioselective iodocyclopropanation of cinnamyl alcohol in the presence of dioxaborolane **1** is illustrated in Figure 1. The zinc alkoxide

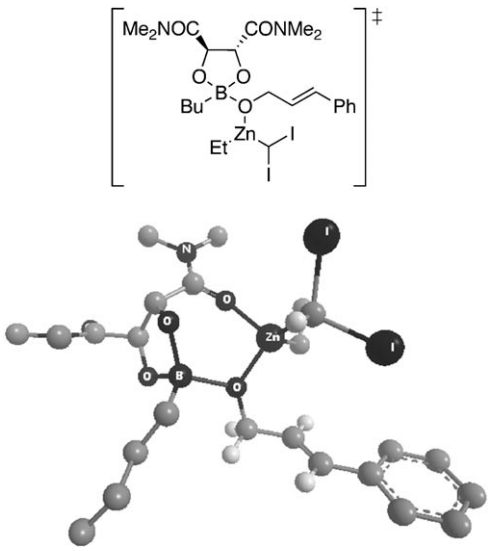
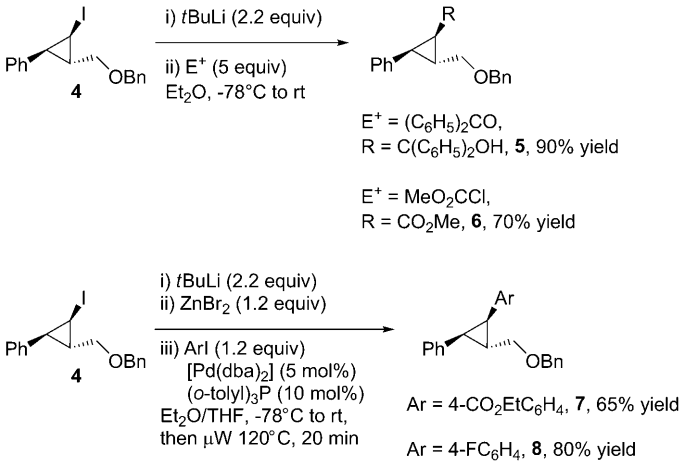


Figure 1. Chem 3D representation of the proposed transition state for the enantioselective iodocyclopropanation reaction of allylic alcohols.

formed upon treatment of cinnamyl alcohol with diethylzinc presumably reacts with the dioxaborolane to produce an ate complex. It is postulated that the bulkier butyl substituent on the dioxaborolane adopts the less sterically congested pseudoequatorial position and the allylic alkoxide the more favorable pseudoaxial position. The resulting ate complex is believed to act as a bidentate ligand for the zinc carbenoid involving the allylic alkoxide and the carbonyl 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 the σ^*_{C-I} must be synperiplanar to the π_{C-C} in the course of the Simmons–Smith cyclopropanation.[16] Of the two possible conformers that could meet such a prerequisite, the conformer bearing an iodine atom *anti* to the sterically encumbered dioxaborolane–alkoxide complex would lead to the major diastereomer.

To illustrate the versatility with which 2,3-disubstituted iodocyclopropanes may be converted into several highly functionalized 1,2,3-trisubstituted cyclopropanes, the iodocyclopropanes were submitted to a lithium–halogen exchange reaction followed by treatment with an electrophile (Scheme 3).[4] Additionally, the cyclopropyllithium was



Scheme 3. Functionalization of the iodocyclopropanes.

transmetallated to zinc and employed in a Negishi Coupling.[17] In all cases, the desired compounds were isolated as single diastereomers with the overall retention of configuration relative to the starting iodocyclopropane starting material.

In conclusion, we have developed the first enantioselective Simmons–Smith iodocyclopropanation reaction. The use of the 1,2,3-disubstituted iodocyclopropanes as versatile enantioenriched building blocks has been demonstrated.

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Keywords: asymmetric synthesis · carbenoids · iodine · iodocyclopropanation · zinc

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[12] The full experimental details are disclosed in the Supporting Information.
[13] Incomplete conversion could originate from the consumption of diethylzinc during its reaction with the α-iodozinc carbenoid to form the *gem*-dizinc carbenoid.
[14] The absolute configuration of **3e** was determined by X-ray crystallography; see the Supporting Information. CCDC-744857 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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