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Enantioselective Synthesis of 1,2,3-Trisubstituted Cyclopropanes Using *gem*-Dizinc Reagents

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The 1,2,3-trisubstituted cyclopropane subunit is present in numerous natural and synthetic products possessing important biological activities.[1] This densely functionalized unit also finds applications in drug discovery in the form of conformationally rigid peptide isosters.[2] 1,2,3-Trisubstituted cyclopropanes are generally synthesized by an addition/elimination sequence onto α,β unsaturated systems[3] or by the decomposition of diazo or iodonium ylides promoted by a transition-metal catalyst.[4] Although significant improvements in the stereocontrol of these reactions have been made recently, accessing interesting levels of enantio- and diastereoselectivity remains the underlying challenge in intermolecular versions of these transformations.[5] The Simmons−Smith cyclopropanation has been sporadically used to generate this class of compounds; however, the reaction typically displays a narrow scope.[6] We previously reported the use of an alkyl-substituted zinc carbenoid reagent **2** in conjunction with dioxaborolane **1** for the asymmetric cyclopropanation of allylic alcohols, leading to 1,2,3-trisubstituted cyclopropane derivatives (Scheme 1).[7] This method enabled the preparation of enantioenriched cyclopropanes in good yields with excellent diastereo- and enantiocontrol, where the substituent derived from the zinc carbenoid bears a trans relationship relative to the directing alcohol.

We recently disclosed the formation of *gem*-dizinc carbenoids **3** and their use in the diastereoselective cyclopropanation of allylic alcohols.[8,9] In the course of this reaction, chelation of the proximal basic group to one of the zinc atoms of the carbenoid results in its incorporation as a substituent on the cyclopropane ring with a cis relationship relative to the directing group. The ensuing cyclopropylzinc compounds can be further functionalized into 1,2,3-trisubstituted cyclopropanes with retention of stereochemistry.[10] Herein we report the first enantioselective cyclopropanation method involving *gem*-dizinc carbenoids.

The original method for preparing the *gem*-dizinc carbenoid was revisited (Table 1), since previous studies on substrates other than 1,4-butenediol derivatives indicated significant amounts of byproduct formation. Furthermore, these seminal conditions led to low enantioselectivities when applied to the enantioselective cyclopropanation of allylic alcohols. A major competing reaction in the zincocyclopropanation of alkenes bearing a single directing group was the formation of iodocyclopropanes from the α-iodozinc carbenoid (Scheme 1, $R^1 = I$) resulting from the incomplete formation of the *gem*-dizinc reagent (Table 1, entry 1). To address this problem, we decreased the CHI_3/Et_2Zn stoichiometric ratio in order to facilitate the formation of the *gem*-dizinc carbenoid. This markedly improved the cyclopropylzinc/iodocyclopropane ratio, albeit at the expense of conversion (entry 1 vs 2). Our reported modified protocol[10] utilizing the more Lewis acidic $(IZn)_2CHI\cdot 4Et_2O$ in presence of ZnI_2 yet again increased this ratio; however, the reaction suffered from considerably lower conversions. We then observed that the removal of the additive (ZnI_2) dramatically improved the conversion (entries 3 and 4). Additionally, performing the reaction at lower temperature and increasing the stoichiometric amount of the reagent inhibited the undesired reaction involving the α-iodozinc carbenoid (entries 5 and 6). Iodination experiments indicated that cyclopropylzinc **6** was produced as a single diastereomer.

Scheme 1. Stereoselective Synthesis of 1,2,3-Trisubstituted Cyclopropanes

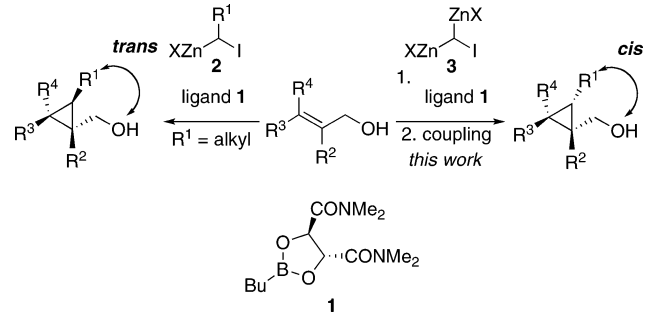
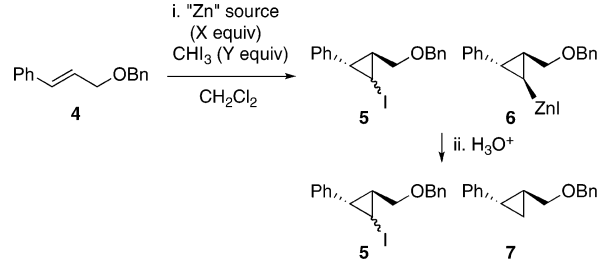


Table 1. Optimization of the Zincocyclopropanation



entry	"Zn" source	"Zn" (equiv)	CHI_3 (equiv)	*T* (°C)	**4/5/7** ratio[a]
1	Et_2Zn	2.1	2.1	0	<1/65/35
2	Et_2Zn	2.1	1.1	0	38/14/48
3[b]	$IZnEt\cdot 2Et_2O$	2.1	1.1	0	51/8/42
4	$IZnEt\cdot 2Et_2O$	2.1	1.1	0	18/7/75
5	$IZnEt\cdot 2Et_2O$	2.1	1.1	−40	11/<1/88
6	$IZnEt\cdot 2Et_2O$	4.2	2.1	−40	<1/<1/>98

[a] Ratio determined by ^1H NMR analysis. [b] With the addition of 1 equiv of ZnI_2.

Having achieved the efficient zincocyclopropanation of alkenes bearing a single directing group, we contemplated the possibility of developing an enantioselective version of this reaction. Many stoichiometric and catalytic chiral ligands have been developed for enantioselective Simmons−Smith cyclopropanations.[11] Of those tested with the *gem*-dizinc reagent,[12] only the dioxaborolane-based ligand[13,14] led to any promising results, although the original protocol needed to be significantly modified to this effect. The initial deprotonation of the alcohol with Et_2Zn (instead of the *gem*-dizinc reagent) was mandatory to prevent in situ formation of the

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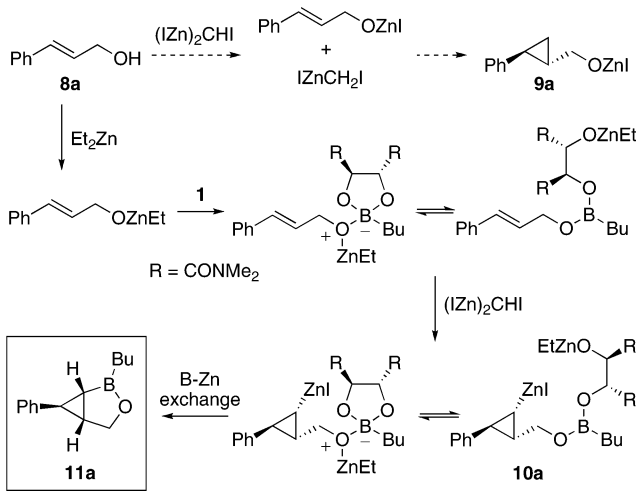
Scheme 2. In Situ Boron−Zinc Exchange



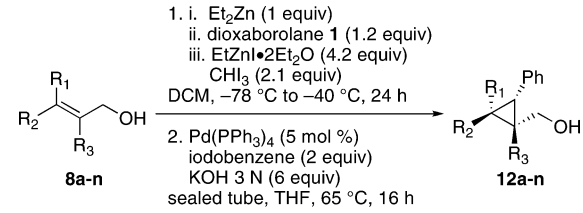
Simmons−Smith reagent $IZnCH_2I$ (Scheme 2), which would have led to a disubstituted cyclopropane (**9a**) rather than the desired cyclopropylzinc. The reaction of the zinc alkoxide with the chiral ligand presumably generates a tetracoordinated boron species that reacts with the *gem*-dizinc carbenoid to produce the cyclopropylzinc. These species were found to undergo a boron−zinc exchange to generate the corresponding cyclopropyl borinate **11a**.[15,16] *As such, the stoichiometric enantiopure ligand not only governs the enantioselectivity of the reaction but also serves as a stoichiometric boron source for the in situ generation of a very versatile Suzuki coupling partner.*[17] The ensuing cyclopropyl borinate is therefore much easier to handle than the corresponding cyclopropylzinc compound. As is the case with such intramolecular processes, the boron−zinc exchange proceeded in a stereoselective manner.

Although the cyclopropyl borinate could in principle be isolated, we elected to directly engage the crude reaction mixture in a Suzuki−Miyaura cross-coupling reaction.[18] This methodology enabled the preparation of 1,2,3-trisubstituted cyclopropanes in good yields over two steps with good to excellent enantioselectivities (Table 2).

The reaction is efficient with *trans*-alkenes bearing either an aryl (entries 1−5) or a primary or secondary alkyl group (entries 6, 9−11), leading to the corresponding 1,2,3-trisubstituted cyclopropanes in good yields over two steps with excellent diastereo- and enantioselectivities. As expected, the reaction is selective for the double bond bearing a directing group (entry 11). The reaction conditions tolerate the presence of functional groups such as aromatic or aliphatic chlorine atoms (entries 2, 3, and 14) as well as protected alcohols (entry 13).

The reaction of *cis*-alkyl-substituted allylic alcohols is more problematic, and a relatively low yield of the desired coupling product was observed (entry 12). In order to elucidate the reason for such an outcome, the reaction mixture was quenched with iodine prior to the cross-coupling step. Unexpectedly, we observed the formation of a significant amount of *trans*-iodocyclopropane **13j**, indicating that the diastereoselectivity of the zincocyclopropanation step was not high (Scheme 3). From this, we rationalized that since the boron−zinc exchange occurs exclusively intramolecularly in a stereospecific manner, as this exchange is not allowed because of steric constraints in the case of the trans diastereoisomer, the *trans*-cyclopropropylzinc is hydrolyzed during the reaction quench. Thus, the decrease in the overall yield can be attributed in part to the poorer diastereoselectivity of the zincocyclopropanation step.

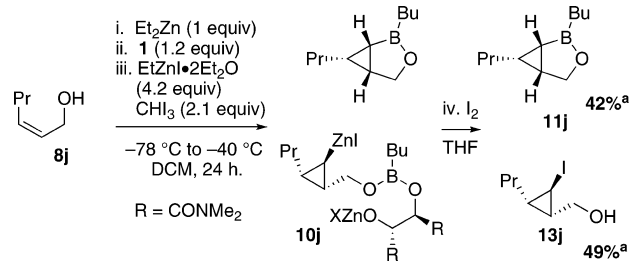
Table 2. Scope of the Reaction



entry	R_1	R_2	product[a]	yield (%)[b]	dr[c]	ee (%)[d]
1	H	Ph	**12a**	59	>20:1	92
2	H	*p*-ClPh	**12b**	58[e]	>20:1	94
3	H	*o*-ClPh	**12c**	59[e]	>20:1	91
4	H	*p*-MeOPh	**12d**	59[e]	>20:1	89
5	H	*m*-MeOPh	**12e**	49	>20:1	89
6	H	Pr	**12f**	51	>20:1	94
7[f]	H	Pr	**12f**	85[f]	>20:1	80[f]
8[g]	H	Pr	**12f**	62[g]	>20:1	96[g]
9	H	$PhCH_2CH_2$	**12g**	79[h]	>20:1	91
10	H	Cy	**12h**	71	>20:1	93
11	Me	$(CH_3)_2CCH(CH_2)_2$	**12i**	64[h]	>20:1	94
12	Pr	H	**12j**	26	>20:1	97
13	H	TIPSO-CH_2	**12k**	57	>20:1	97[i]
14	H	$Cl(CH_2)_4$	**12l**	61	>20:1	94

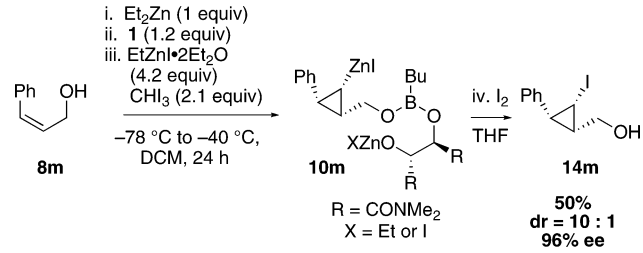
[a] Absolute and relative stereochemistries were assigned according to X-ray analysis of **12b**. [b] Yield over two steps. [c] Determined by ^1H NMR analysis. [d] Determined by SFC on a chiral stationary phase. [e] Yield after dihydroxylation of the remaining traces of the starting allylic alcohol. [f] Reaction was run on a 5 mmol scale. [g] Reaction was run on a 5 mmol scale using 0.7 equiv of Et_2Zn for the initial deprotonation and 1.6 equiv of carbenoid. [h] The product was contaminated with the corresponding disubstituted cyclopropane (∼10%). [i] Determined after removal of the protecting group.

Scheme 3. Cyclopropanation of *cis*-3-Hexen-1-ol



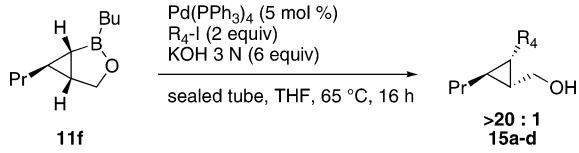
[a] ^1H NMR yield using 1,3,5-trimethoxybenzene as an internal standard

Scheme 4. Particularity of *cis*-Cinnamyl Alcohol



Interestingly, *cis*-cinnamyl alcohol smoothly underwent the zincocyclopropanation under the reaction conditions; however, the boron−zinc exchange did not proceed. Quenching the crude reaction mixture with iodine led to **14m** in good yield and stereoselectivity (Scheme 4). The surprisingly good diastereoselectivity of the zincocyclopropanation step compared with that in the reaction with **8j** can be explained by an interaction between the π system of the phenyl group and the zinc atom or the iodide bonded to it.[19] Since the boron−zinc exchange reaction is an equilibrium,[20] this coor-

Table 3. Other Electrophilic Partners[a]



11f **>20 : 1** **15a-d**

entry	R_4	yield (%)[b]
1	*p*-FPh (**15a**)	62
2	*p*-OMePh (**15b**)	75
3[c]	CH_2=CH (**15c**)	63
4	PhCH=CH (**15d**)	71

[a] Absolute and relative stereochemistry were confirmed by X-ray analysis of **12b**. [b] Yield from **8f**. [c] A solution of vinyl bromide in THF was used.

dination presumably favors the thermodynamically more stable cyclopropylzinc.

Besides phenyliodide, several coupling partners were submitted to the Suzuki−Miyaura reaction with **11f**. Iodoaryls bearing either electron-withdrawing or -donating groups as well as vinyl bromide and styryl iodide successfully reacted in the cross-coupling reaction (Table 3).

In conclusion, we have developed the first asymmetric zinco-cyclopropanation of allylic alcohols. The inexpensive stoichiometric chiral ligand incorporated in this methodology exercises the dual function of governing the enantioselectivity of the reaction and serving as an electrophilic boron source for the boron−zinc exchange leading to the Suzuki−Miyaura cross-coupling precursor. This reaction has enabled the stereoselective synthesis of highly functionalized 1,2,3-trisubstituted cyclopropanes that would be difficult to access otherwise. Further studies into the functionalization of the borinate synthetic intermediates are underway and will be reported in due course.

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Supporting Information Available: Experimental procedures for the preparation of the compounds, characterization data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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