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Diastereoselective Zinco-Cyclopropanation of Chiral Allylic Alcohols with *gem*-Dizinc Carbenoids

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1,2,3-Substituted cyclopropanes are important subunits in natural products and other biologically active molecules.[1] Our interest in developing stereoselective methods for their synthesis using zinc carbenoids[2] prompted us to look at novel organometallic species that would complement existing methods. Recently, an approach relying on the synthesis and reactivity of *gem*-dizinc carbenoids[3] prepared from Et_2Zn and iodoform was developed.[4] The reaction proceeds via a cyclopropylzinc intermediate **3**, which could then be further functionalized upon treatment with a suitable electrophile or undergo palladium-catalyzed cross-coupling reactions. The scope of the reaction could be significantly enhanced by using *gem*-dizinc carbenoid **2a** prepared from EtZnI and CHI_3. Herein, we report that the directed zinco-cyclopropanation of chiral acyclic allylic alcohols using *gem*-dizinc carbenoids (such as **2a)** is highly stereoselective, yielding either to *syn* or *anti* cyclopropanes, depending on the substitution pattern of the alkenes. This is quite remarkable given the overall instability of reagent **2a**.[4] The reaction provides an expedient route to chiral, nonracemic 1,2,3-substituted cyclopropanes.

It is well-established that proximal basic groups of chiral acyclic allylic alcohols, ethers, or zinc alkoxides can direct the cyclopropanation reaction of simple zinc and samarium carbenoids (MCH_2X), leading to one predominant diastereomer.[5] On the basis of this precedent, we were intrigued by the possibility of using *gem*-dizinc carbenoid reagents in a directed process. Since both iodozinc groups in **2a** are enantiotopic, complexation of this reagent to a zinc alkoxide derived from a chiral allylic alcohol can lead to many diastereomeric complexes since up to three additional stereocenters could be formed upon complexation (O, ZnI, and C1′ in Figure 1). Since the transition structure of the cyclopropanation reaction of zinc carbenoids is assumed to proceed in a well-defined manner via precomplexation of the basic group with the Lewis acidic reagent, good diastereocontrol for this reaction can only be achieved if the equilibrium between the diastereomeric complexes is faster than the zinco-cyclopropanation. Alternatively, it is also possible but highly unlikely that the various possible diastereomeric complexes could lead to a highly diastereoselective transfer. A simple model indicates that among the many possible diastereomeric complexes, two potential complexes **A** and **B** that minimize the A-1,3 strain could lead to two diastereomeric cyclopropylzinc derivatives.

The *Z*-alkene **5** was chosen as the test substrate since *Z*-substituted chiral allylic alcohols provide excellent diastereomeric ratios with samarium and zinc carbenoids. The optimization of the reaction conditions involved the deprotonation of alcohol **5** with 1.2 equiv of ethylzinc iodide. The zinc alkoxide was then added to 2.0 equiv of the *gem*-dizinc carbenoid prepared by mixing 2 equiv of iodoform with 4 equiv of ethylzinc iodide (leading theoretically to 2 equiv of the *gem*-dizinc carbenoid **2a**) at 0 °C. We were very pleased to observe that, under these conditions, **6a** could be isolated

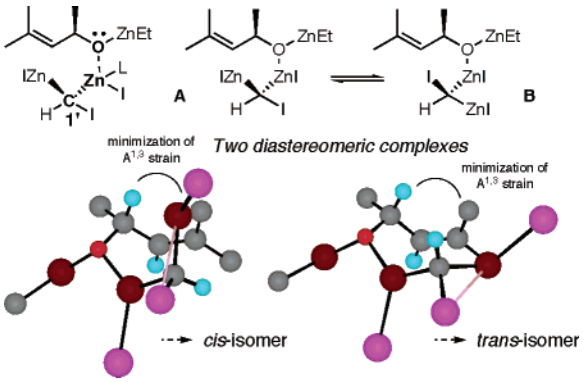
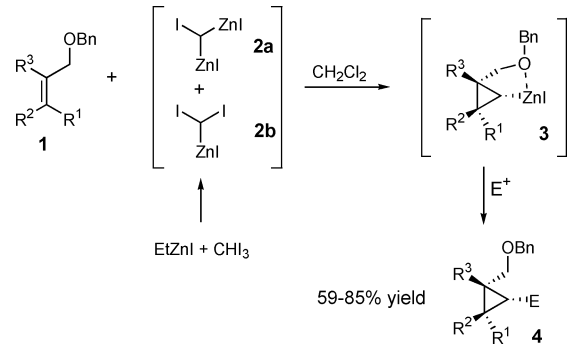
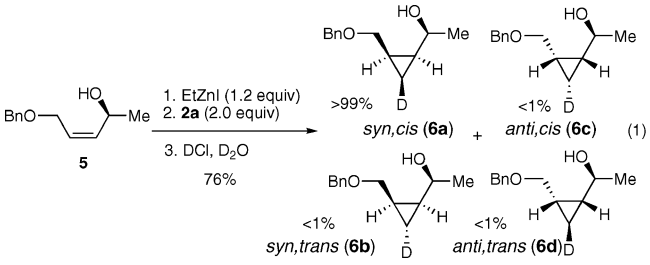


Figure 1. Two possible diastereomeric zinc complexes.

Scheme 1



in 76% yield and as a single diastereomer (out of four possible diastereomeric cyclopropanes) upon quenching with D_2O (eq 1).



The yield and the efficiency of the process could be improved if 0.5 equiv of ZnI_2 was added to the reaction mixture (Table 1, entry 1).[6] Under these conditions, the amount of **2a** could be decreased to 1.5 equiv and the reaction time to 20 min. Although the exact role of ZnI_2 is not known, it is believed to either stabilize **2a** (by avoiding its premature decomposition) or to lower the transition state energy of the zinco-cyclopropanation reaction. Equally high isolated yields were observed if the cyclopropylzinc intermediate was quenched with D_2O or with iodine.

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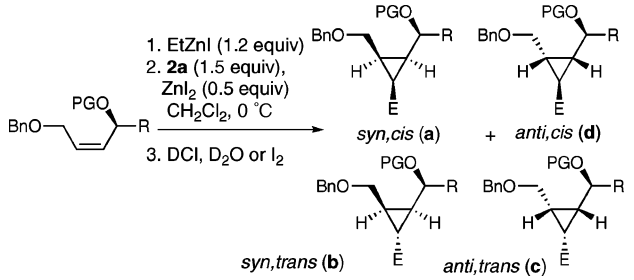
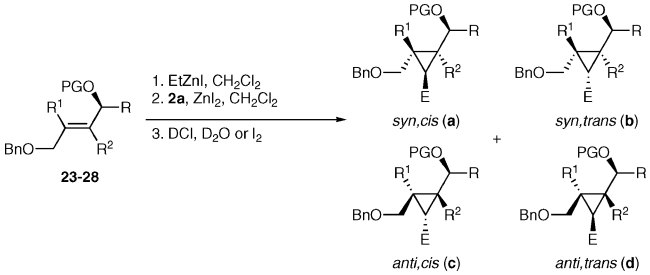
Table 1. Diastereoselective Zinco-Cyclopropanation of *cis*-Allylic Alcohols and Ethers



entry	R (PG)	dr (a:(b + c + d))	yield (%) (E = D)	yield (%) (E = I)
1	Me (H) (**5**)	>95:5	82 (**6**)	75 (**7**)
2	Et (H) (**8**)	>95:5	85 (**9**)	84 (**10**)
3	*i*-Pr (H) (**11**)	>95:5	86 (**12**)	87 (**13**)
4	*t*-Bu (H) (**14**)	>95:5	91 (**15**)	91 (**16**)
5	Ph (H) (**17**)	>95:5	62 (**18**)	58 (**19**)
6	Me (Bn) (**20**)	>95:5	86 (**21**)	77 (**22**)

Table 2. Diastereoselective Zinco-Cyclopropanation of Trisubstituted Allylic Alcohols[a]



entry	PG	R	R^1	R^2	dr (*syn:anti*)	dr (*cis:trans*)	yield (%)
1	H	Me	H	H (**23**)	60:40		85 (**29**)[b]
2	H	*t*-Bu	H	H (**24**)	94:6	28:72	73 (**30**)[b]
3	TIPS	*t*-Bu	H	H (**25**)	>95:5	75:25	64 (**31**)[b]
4	H	Me	H	TMS (**26**)	<5:95	>95:5	68 (**32c**)
5	H	*t*-Bu	H	TMS (**27**)	<5:95	>95:5	77 (**33c**)
6	H	*t*-Bu	TMS	H (**28**)	>95:5	<5:95	84 (**34b**)
7	H	*t*-Bu	TMS	H (**28**)	>95:5	<5:95	81 (**35b**)

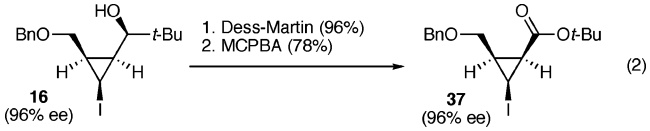
[a] In entries 2−6, cyclopropylzinc was quenched with D_2O (E = D). I_2 was used in entries 2 and 7 (E = I). H_2O was used in entry 1. [b] Combined yield of the diastereomers.

These conditions were then applied to the zinco-cyclopropanation of several *cis*-disubstituted allylic alcohols bearing various sterically demanding substituents at the allylic position (Table 1). High diastereomeric ratios were observed with a wide range of substituents (entries 2−5). The facial selectivity for the attack of the *gem*-zinc carbenoid on the alkene was excellent and is consistent with an alkoxy-directed reaction involving the $A^{1,3}$ minimized conformer. In all the cases, the resulting cyclopropylzinc had a *cis*-relationship with the other substituents on the ring as determined by trapping with a suitable electrophile. High diastereoselectivity leading to the *cis*,*syn*-isomer was also observed using a protected allylic alcohol (entry 6). It is also possible to trap the intermediate cyclopropylzinc in a copper-mediated allylation reaction.[7,8]

The zinco-cyclopropanation of the corresponding *trans*-isomer leads to a mixture of stereoisomers (Table 2, entry 1). This is not surprising since the cyclopropanation of this substrate with unsubstituted zinc carbenoids proceeds with poor diastereocontrol. Treatment of **23a** with 5 equiv of Et_2Zn and 5 equiv of CH_2I_2 led to a 57:43 *syn:anti* ratio.[9] As expected, increasing the size of the R group in the zinco-cyclopropanation led to an improvement in the *syn:anti* ratio; however, the *trans*-cyclopropylzinc was now the major product, indicating that the benzyl ether became a better directing group than the more sterically hindered zinc alkoxide (entry 2).[10] A *cis*-selective reaction could be achieved by replacing the benzyl protecting group by a triisopropylsilyl (entry 3).

This level of diastereocontrol could be increased by using a TMS-substituted allylic alcohol.[11,12] Introducing a TMS substituent at either the R^1 or the R^2 position led to the exclusive formation of the *anti,cis* or of the *syn,trans* diastereomer.[13]

Access to enantiomerically pure orthogonally protected 1,2,3-*cis*-substituted cyclopropane is easily accomplished starting from enantioenriched **14**, which is readily available using Carreira's catalytic asymmetric alkynylation of aldehydes, and when followed by reduction led to **16**.[14,15] Treatment of alcohol **16** with Dess−Martin periodinane afforded ketone **36** that underwent Baeyer−Villiger oxidation to afford **37** (overall, five steps from pivaldehyde).



(2)

In conclusion, the directed zinco-cyclopropanation reaction of *gem*-dizinc carbenoid of chiral allylic alcohols provides an expedient entry into the 1,2,3-substituted cyclopropane motif.[16] Further studies are in progress to extend the scope of the reaction and for its application in natural product synthesis.

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Supporting Information Available: Experimental procedures for the preparation of all the compounds and characterization data for each reaction and detailed structural assignment. This material is available free of charge via the Internet at http://pubs.acs.org.

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