Directing Effect of a Neighboring Aromatic Group in the Cyclopropanation of Allylic Alcohols

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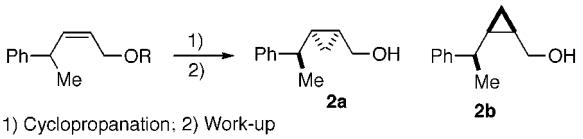
A significant number of synthetic operations involving organometallic species are depicted as heteroatom-directed reactions.[1] Their highly regio- and stereoselective character result from a strongly stabilizing coordinative interaction between the metal and the Lewis basic center. The basic π electrons of unsaturated functional groups should act in the same manner, as physical and experimental data have evidenced the occurrence of metal−π interactions.[2] However, their implications as key control elements in organic synthesis have been relatively limited.

The directing effect of a neighboring aromatic group has been illustrated in the regioselective formation and stereoselective alkylation of some β-aryl- and β-arylalkylcyclopentanone lithium enolates.[3] On the other hand, zinc−aryl, −alkenyl, and, −alkynyl interactions have been invoked to rationalize the stereochemical outcome of a 1,3-elimination reaction from a dimetallic species.[4] We report herein the occurrence of a metal−π interaction in the zinc-promoted cyclopropanation of a chiral racemic allylic alcohol bearing a phenyl group at the remote allylic position.

Treatment of the chiral racemic allylic alcohol **1**[5] with diethylzinc/chloroiodomethane (Et_2Zn/ICH_2Cl) in 1,2-dichloroethane (DCE) at −23 °C[6] afforded a mixture of two diastereoisomeric cyclopropanated products **2a** and **2b** in a 80/20 ratio (88% yield). These products were easily separated by flash chromatography, and the relative stereochemistry of the crystalline major diastereoisomer **2a** was unambiguously established by X-ray diffraction. The temperature has little influence on the diastereoisomeric ratio, but a slight improvement was observed by switching DCE to toluene. The use of more coordinating solvents such as diethyl ether was detrimental to the success of the cyclopropanation.[6] Furthermore, the same diastereoisomeric ratio was observed when the alcohol was protected as a TBS ether (compound **3**) or deprotonated with sodium hydride prior to the cyclopropanation, indicating that the coordination of zinc to the hydroxy group was not a key control element for the diastereoselectivity. We have to point out that the use of diiodomethane (CH_2I_2) instead of ICH_2Cl resulted in a nonstereoselective reaction (Table 1).

Table 1. Cyclopropanation of Allylic Alcohol 1 and Derivatives



1) Cyclopropanation; 2) Work-up

substrate	reagents	solvent	condns	diastereoisomeric ratio[a] **2a**/**2b**	yield[b] (%)
1 (R = H)	Et_2Zn, ICH_2Cl	DCE	−23 °C, 1 h	80/20	88
1	Et_2Zn, ICH_2Cl	DCE	−50 to −10 °C, 1 h	83/17	75
1	Et_2Zn, ICH_2Cl	toluene	−23 °C, 3 h	85/15	94
1	Et_2Zn, CH_2I_2	DCE	−23 °C, 4 h	50/50	49
R = Na[c]	Et_2Zn, ICH_2Cl	CH_2Cl_2	−23 to −10 °C, 3 h	80/20	*d*
3 (R = TBS)	Et_2Zn, ICH_2Cl	DCE	−23 °C, 2 h	80/20	45[e]
1	Sm(Hg), ICH_2Cl	THF	−50 to +20 °C, 1 h 20 °C, 1 h	30/70	74
1	Sm(Hg), CH_2I_2	THF	−50 to +20 °C, 1 h 20 °C, 2 h	20/80	40

[a] Ratio determined by ^1H NMR and GC−MS analysis of the crude reaction mixture. [b] Isolated yield of analytically pure products. [c] One equivalent of sodium hydride was added to the substrate prior to the cyclopropanation. [d] 100% conversion. Isolated yield was not determined. [e] Yield obtained after desilylation with *n*-Bu_4NF in THF.

A more striking result was observed when **1** was subjected to the samarium-promoted cyclopropanation reaction in THF.[7] A diastereoisomeric mixture of **2a** and **2b** was obtained in a 30/70 ratio (74% yield). Thus, Zn- and Sm-promoted cyclopropanations exhibit opposite stereoselectivities in the case of substrate **1**. To our knowledge, there is no precedent for such results in the field of cyclopropanations. Use of CH_2I_2 instead of ICH_2Cl in the Sm-promoted cyclopropanation resulted in an improved diastereoisomeric ratio at the expense of a poorer yield (Table 1).

To elucidate the factors responsible for this selectivity reversal, the stereochemical outcome of the cyclopropanation of the chiral acyclic allylic alcohols **4**−**6**[5] bearing a stereogenic center at the remote allylic position was investigated (Table 2).

The Sm-promoted cyclopropanation of the (*E*)-isomer **4** proceeds without any stereoselectivity. On the contrary, the Zn-promoted cyclopropanation of **4** exhibits a diastereoisomeric ratio of **7a**/**7b** = 75/25, comparable to the one observed

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(3) Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934−946.

(4) Beruben, D.; Marek, I.; Normant, J.-F.; Platzer, N. *J. Org. Chem.* **1995**, *60*, 2488−2501.

(5) (a) The (*Z*)-allylic alcohols **1**, **5**, and **6** were prepared by a three-step homologation of the corresponding commercially available or known aldehydes: (i) PPh_3, CBr_4, CH_2Cl_2; (ii) *n*-BuLi (2 equiv), THF, then $(CH_2O)_n$; (iii) Zn(Cu), *i*-PrOH, THF reflux. (b) For the preparation of aldehydes involved in the synthesis of **5** and **6**, see: Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588−3597. (c) Smith, A. B., III; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011−12012. (d) For the preparation of **4**, see: Desert, S.; Metzner, P. *Tetrahedron* **1992**, *47*, 10327−10338.

(6) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974−6981.

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(8) The relative stereochemistry of **7a** and **7b** was assigned by comparison with authentic samples prepared from **2a** and **2b**, respectively, using the following sequence:

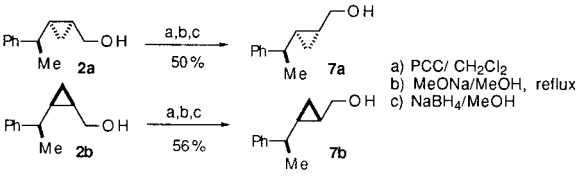

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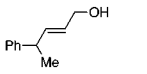
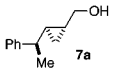
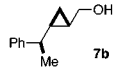
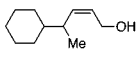
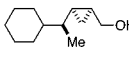
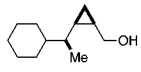
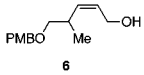
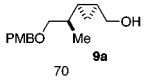
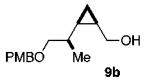
Table 2. Cyclopropanation of Allylic Alcohols Bearing a Remote Stereocenter

Substrate	Cyclopropanating conditions	Products (ratio)[a]		Combined yield[b]
 **4**	Et_2Zn, ICH_2Cl, DCE	 **7a** 75	 **7b** 25	94%
	Sm(Hg), ICH_2Cl, THF	50	50	95%
 **5**	Et_2Zn, ICH_2Cl, DCE	 **8a** 20	 **8b** 80	80%
	Sm(Hg), ICH_2Cl, THF	15	85	76%
 **6**	Et_2Zn, ICH_2Cl, DCE	 **9a** 70	 **9b** 30	81%[c]
	Sm(Hg), ICH_2Cl, THF	35	65	90%[c]

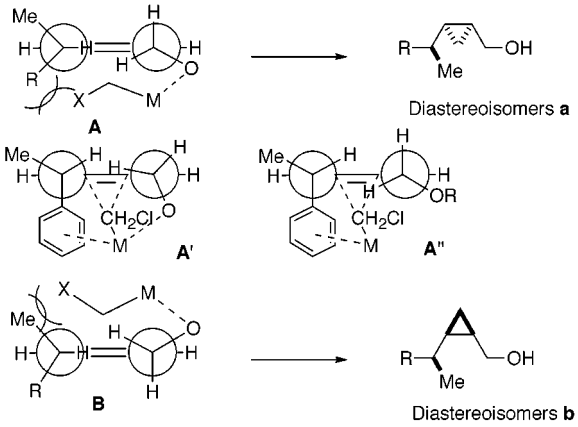
[a] Determined by ^1H NMR and GC−MS analysis of the crude reaction mixture. [b] Isolated yield of analytically pure material. [c] These two diastereoisomers can be easily separated by flash chromatography.

for the (*Z*)-isomer **1**.[8] In the case of compound **5** bearing a cyclohexyl group, it is noteworthy that both Zn- and Sm-promoted cyclopropanations exhibit comparable levels of stereoselectivity without any reversal of stereochemistry.[9] This result demonstrates the dramatic influence of the aromatic group in the Zn-promoted cyclopropanation of **1** or **4**. A reversal of selectivity between Zn- and Sm-promoted cyclopropanations was also observed for compound **6** bearing a *p*-methoxybenzyl group (CH_2OPMB), although the diastereoisomeric ratio was lower.[10]

The stereochemical outcome of the cyclopropanations of chiral allylic alcohols has been the subject of numerous investigations and is now well-established.[1,7,11] Whereas (*Z*)-substituted olefins give high *syn* selectivities, for the (*E*)-substituted ones the *syn* selectivities are usually modest. A staggered model has been proposed to account for the observed diastereoselectivities. In the case of substrates bearing a stereocenter at the remote allylic position, minimization of A-1,3 strain[12] led us to consider two possible transition states **A** and **B** for the cyclopropanation reactions (Scheme 1).

Sm-promoted cyclopropanation led to the major diastereoisomers **b** irrespective of the nature of the R group. Unless R contains an aromatic group, Zn-promoted cyclopropanations exhibit the same stereoselectivities. In these cases, the diastereoisomeric ratio probably reflects the preferential approach of the carbenoid from the less crowded face of the olefin in the transition state **B** and is related to the steric bulk of the R substituent compared to the methyl group, as it decreases ongoing from cyclohexyl, phenyl to CH_2OPMB. In the cyclopropanation of **1**, **4**, and **6** with Et_2Zn/ICH_2Cl, the approach of the carbenoid is probably directed by the aromatic group leading to a selectivity reversal. An aryl−metal interaction could be invoked to rationalize this sterochemical outcome. There should be enough leeway for the possible transition state **A** to reach conformation **A′** or **A″**, in which the aromatic group directly coordinates the Zn carbenoid leading to the major diastereoisomer **2a**. Coordination of the carbenoid to the hydroxy group is not necessarily required as shown in conformation **A″**, since TBS ether **3** gave a similar diastereoisomeric ratio compared to **1**. Finally, in the case of the (*E*)-allylic alcohol **4**, the lack of severe steric interactions in the different possible transition states leads to a stereorandom Sm-promoted cyclopropanation reaction, whereas the Zn-promoted one is apparently directed by the phenyl group.

Scheme 1. Possible Transition States



The Lewis acidic character of Zn is an essential parameter in these aryl-directed cyclopropanations. The use of CH_2I_2 instead of ICH_2Cl resulted in a stereorandom cyclopropanation in the case of **1** and might be due to the greater Lewis acidic character of the chloromethylzinc carbenoid.[12d,13] A similar interaction with Sm might have been possible, but since Sm-promoted cyclopropanation reactions are run in THF, this solvent destroys the acidic character of the metal, hence preventing such a kind of interaction. It can be anticipated that coordinating solvents such as THF would have the same effect in the Zn-promoted cyclopropanation reaction, but they interfere as well with the reaction itself.[6] Worthy of note is the fact that toluene as the solvent does not apparently compete with this intramolecular aryl−metal interaction.

In conclusion, we have shown that the cyclopropanation of chiral acyclic allylic alcohols bearing a stereocenter at the remote allylic position can proceed with synthetically useful levels of stereoselectivity. When an aryl group was present at this stereocenter, a reversal of selectivity has been observed between the Sm- and the Zn-promoted cyclopropanation reactions, which has been interpreted by a π−metal interaction resulting in a net directing effect of this substituent in the second case. We are currently performing synthetic transformations on the cyclopropanated products in order to exploit their potential in natural product synthesis.

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Supporting Information Available: Full experimental procedures and spectroscopic data are available for compounds **1**, **2a**,**b**, **3**, **5**, **6**−**12b**, and intermediates involved in the preparation of **1**, **5**, and **6**, an ORTEP drawing for **2a**, details of the data acquisition, and descriptions of the assignment of the stereochemistry of **8a** and **9a**,**b** (30 pages).

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(9) The relative stereochemistry of **8a** was assigned by comparison with an authentic sample prepared from **2a** (see the Supporting Information).

(10) The relative stereochemistry of **9a** and **9b** was assigned by converting them to the corresponding carboxylic acid and comparison with the acid obtained from **2a** by oxidation of the aromatic ring (see the Supporting Information).

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