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Stereodivergent Carbometalation Reactions of Cyclopropenylcarbinol Derivatives

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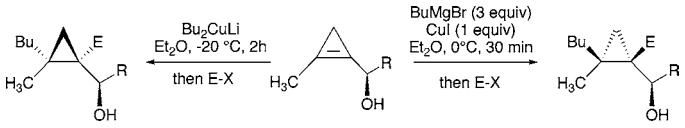
ABSTRACT



The diastereoselective formation of cyclopropylcarbinol from cyclopropenylcarbinol is very sensitive to the nature of the organometallic used for the carbometalation reaction. Both diastereoisomers can be obtained, at will, from the same precursor.

Progress in the area of diastereo- and enantioselective preparation of cyclopropanes has largely focused either on the modification of allylic alcohols[1] through the Simmons−Smith chemistry,[2] the rhodium carbenoid chemistry of terminal alkenes,[3] or the reactivity of lithiated aryloxiranes.[4] However, in the past few years, strain as a design principle for asymmetric transformations has found many interesting applications particularly in the chemistry of cyclopropenyl derivatives, and we have been witness to a complete renaissance of the field.[5] Indeed, upon breaking the π-bond, the trigonally coordinated ring carbons can pyramidalize, thus relieving the additional angle strain that results from the presence of the three-membered ring of carbons that are nominally sp^2, rather than sp^3, hybridized.[6] If such operations can now be performed on enantiomerically enriched cyclopropenes, they can provide a new entry to functionalized chiral cyclopropanes. Therefore, a large variety of diastereo- and enantiofacial additions of organometallic derivatives on the cyclopropenyl ring has recently appeared.[7] In this context, we have reported the preparation of enantiomerically pure cyclopropenylcarbinols via the kinetic resolution upon Sharpless epoxidation, in very high enantiomeric excesses and yields (Scheme 1).[8] Cyclopropenylcarbinols **1** were

(1) Charette, A. B.; Beauchemin, A. *Organic Reactions*; Wiley & Sons Inc.: Hobolen, NJ, 2001; Vol. 3.

(2) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

(3) Doyle, M. P. *J. Org. Chem.* **2006**, *71*, 9253.

(4) Capriati, V.; Florio, S.; Luisi, R.; Perna, F. M.; Barluenga, J. *J. Org. Chem.* **2005**, *70*, 5852.

(5) For recent reviews, see: (a) Samah, S.; Masarwa, A.; Marek, I. *Angew. Chem., Int. Ed.* **2007**, in press. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Synthesis* **2006**, 1221. (c) Fox, J. M.; Yan, N. *Curr. Org. Chem.* **2005**, *9*, 719. (d) Nakamura, M.; Isobe, H.; Nakamura, E. *Chem. Rev.* **2003**, *103*, 1295. (e) *Methods of Organic Chemistry* (*Houben-Weyl*); de Meijere, A., Ed.; Thieme: Stuttgart, Germany, 1996; Vol. E17.

(6) Bach, R. D.; Dmitrenko, O. *J. Am. Chem. Soc.* **2004**, *126*, 4444.

(7) (a) Richey, H. G.; Bension, R. M. *J. Org. Chem.* **1980**, *45*, 5036. (b) Araki, S.; Nakano, H.; Subburaj, K.; Hirashita, T.; Shibutani, K.; Yamamura, H.; Kawai, M.; Butsugan, Y. *Tetrahedron Lett.* **1998**, *39*, 6327. (c) Araki, S.; Kenji, O.; Shiraki, F.; Hirashita, T. *Tetrahedron Lett.* **2002**, *43*, 8033. (d) Araki, S.; Shiraki, F.; Tanaka, T.; Nakano, H.; Subburaj, K.; Hirashita, T.; Yamamura, H.; Kawai, M. *Chem. Eur. J.* **2001**, *7*, 2784. (e) Isaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **1990**, *112*, 7428. (f) Liao, L.-a.; Fox, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 14322. (g) Liao, L.-a.; Zhang, F.; Yan, N.; Golen, J. A.; Fox, J. M. *Tetrahedron* **2004**, *60*, 1803. (h) Nakamura, E.; Kubota, K. *J. Org. Chem.* **1997**, *62*, 792. (i) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2002**, *124*, 11566. (j) Nakamura, M.; Arai, M.; Nakamura, E. *J. Am. Chem. Soc.* **1995**, *117*, 1179. (k) Nakamura, M.; Inoue, T.; Sato, A.; Nakamura, E. *Org. Lett.* **2000**, *2*, 2193. (l) Nakamura, M.; Inoue, T.; Nakamura, E. *J. Organomet. Chem.* **2001**, *624*, 300. (m) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978. (n) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198. (o) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2004**, *126*, 3688. (p) Liu, X.; Fox, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 5600. (q) Kawamura, N. Japanese Kokai Tokkyo Koho, JP 08073400, A2 19960319, 1996; *Chem. Abstr.* **1996**, 12557975. (r) Yang, Z.; Xie, X.; Fox, J. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3960.

(8) Simaan, S.; Masarwa, A.; Bertus, P.; Marek, I. *Angew. Chem., Int. Ed.* **2006**, *45*, 3963.

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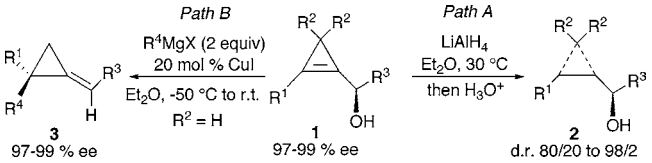
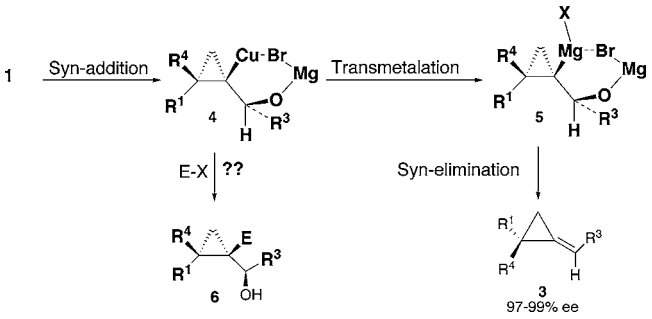
Scheme 1



diastereoselectively reduced with $LiAlH_4$ into *trans*-cyclopropylcarbinol **2** and the regioselectivity was established by deuterium labeling studies (Scheme 1, path A)[9] but they were also easily transformed into enantiomerically pure alkylidenecyclopropane derivatives **3** possessing a quaternary stereocenter (Scheme 1, path B).[8]

The absolute configuration of the enantiomerically enriched alkylidenecyclopropanes **3** was rationalized by a mechanism composed of (1) a *syn* copper-catalyzed carbomagnesiation reaction leading to the corresponding cyclopropylcopper **4** (this intermediate could be isolated in the range of 30−40% by hydrolysis of aliquots) followed by (2) a transmetalation reaction into the corresponding cyclopropylmagnesium **5** and then (3) a *syn*-elimination reaction (Scheme 2).[10] In such a process, we believe that the

Scheme 2

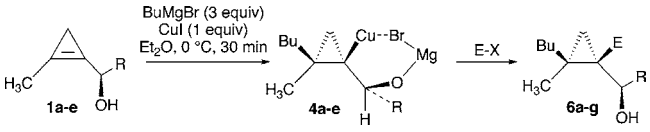


elimination proceeds only when the contrathermodynamic copper to magnesium transmetalation reaction occurs. Therefore, if such a transmetalation reaction could be avoided, then the carbometalated product **4** would be more stable toward β-elimination (the carbon−copper bond is usually less prone to β-eliminate than the carbon−magnesium bond),[11] and should react with different electrophiles to give functionalized cyclopropylcarbinol derivatives **6**. To achieve this goal, the carbometalation reaction should therefore be performed with a stoichiometric amount of copper salt.

In this Letter, we report our preliminary results concerning remarkable stereodivergent carbometalation reactions of cyclopropenylcarbinols followed by reactions with electrophiles to lead to polysubstituted cyclopropylcarbinols.

When cyclopropenylcarbinols **1a**−**e** were treated with an excess of Grignard reagents (2 or 3 equiv) in the presence of 1 equiv of CuI in Et_2O at 0 °C, we were pleased to observe a fast carbometalation reaction led to the corresponding *trans*-cyclopropylcarbinol **6a**−**e** after hydrolysis (Table 1).

Table 1. Formation of *anti*-Cyclopropylcarbinol (CPC) by the Addition of Magnesium Organocopper Derivatives



entry	starting material	R	E-X	E	*anti*/*syn* ratio[a]	CPC	yield (%)[b]
1	**1a**	CH_2CH_2Ph	H_3O^+	H	75/25	**6a**	76
2	**1b**	*i*-Pr	H_3O^+	H	>95/5	**6b**	82
3	**1c**	$CH(Ph)_2$	H_3O^+	H	>95/5	**6c**	73
4	**1d**	*t*-Bu	H_3O^+	H	>95/5	**6d**	92
5	**1e**	Ph	H_3O^+	H	85/15	**6e**	70
6	**1c**	$CH(Ph)_2$	I_2	I	>95/5	**6f**	84
7	**1c**	$CH(Ph)_2$	AllylBr	C_3H_5	>95/5	**6g**	81

[a] Determined by ^1H NMR and GC on the crude reaction mixture. [b] Isolated after purification by column chromatography.

Under such conditions, alkylidenecyclopropanes **3** were not observed indicating that cyclopropylcopper derivatives **4a**−**e** are stable toward β-elimination reactions (Table 1). The formation of the *trans*-cyclopropylcarbinols can be rationalized by a *syn*-directed carbocupration reaction as indicated in Scheme 2. As summarized in Table 1, the carbometalation reaction has been successfully extended to a large variety of substrates (R = primary, secondary, tertiary alkyl and aromatic groups, see entries 1 to 5 respectively in Table 1). In general, these reactions exhibit excellent yields but the diastereomeric ratio is dependent on the steric hindrance of the R group at the carbinol center (compare Table 1, entries 1 and 5 with entries 2−4). The *anti*/*syn* ratio is higher than 95/5 with secondary and tertiary alkyl groups but only moderate with primary and aromatic groups. The reaction can also be performed with only 2 equiv of RMgBr instead of 3 equiv as quoted in Table 1 (1 equiv is necessary for the deprotonation reaction) with 1 equiv of CuI (i.e., **1a** leads to **6a** in identical diastereomeric ratio) but the reaction takes longer. The stereochemistry was deduced from comparison with authentic samples.[12] The presence of a discrete organometallic species was checked by iodinolysis or by reaction with allyl halide (Table 1, entries 5 and 6, respectively). Without copper salt, the reaction does not proceed.

Surprisingly, when the same reaction was performed with an organocuprate coming from *n*-BuLi (instead of *n*-BuMgBr) with the same copper salt, the observed diastereomeric ratio was 5/95 in favor of the *syn*-isomer in good isolated yield (Scheme 3)! A complete reversal of stereo-

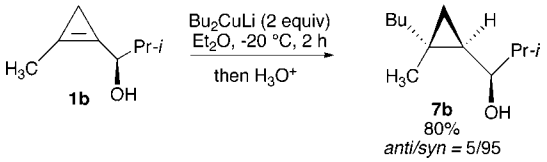
(9) Zohar, E.; Marek, I. *Org. Lett.* **2004**, *6*, 341.

(10) For references of *syn*-elimination of alkylmagnesium halide, see: Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *J. Am. Chem. Soc.* **1990**, *112*, 8042.

(11) (a) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron* **1991**, *47*, 1677. (b) Marek, I.; Alexakis, A.; Mangeney, P.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1992**, *129*, 171.

(12) Charette, A. B.; Lebel, H. *J. Org. Chem.* **1995**, *60*, 2966.

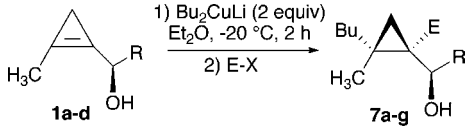
Scheme 3



selectivity was therefore observed when dialkyl cuprate was used (compare Scheme 3 and Table 1, entry 2).

Although it is still premature to propose a rational explanation for this stereodivergent carbocupration reaction, we have concentrated our initial efforts to improve the scope of this reaction in favor of the *syn*-isomer. The same *syn*/*anti* ratio can also be obtained when the carbocupration reaction is performed with only 1 equiv of lithium dialkyl cuprate on the prelithiated cyclopropenylcarbinol **1b**. Whatever the stoichiometry used in the preparation of the organocopper derivatives from alkyllithium species and CuI (1 to 4 equiv of Bu_2CuLi, Bu_2CuLi + *n*-BuLi, Bu_2CuLi + 2 *n*-BuLi, Bu_2CuLi + 2 CuI or $Bu_2CuCNLi_2$), the major isomer is always the *syn*-isomer, although this ratio depends on the experimental condition. Under our best conditions (see Table 2), the scope of the reaction is broad since it proceeds similarly on primary (Table 2, entry 1), secondary (Table 2, entries 2 and 3), tertiary (Table 2, entry 4), and even aromatic (Table 2, entries 5 and 6) cyclopropenylcarbinols. The presence of the organometallic species was checked by reaction with different electrophiles such as iodine (Table entry 7) and allylbromide (Table 2, entry 8) to lead to the preparation of functionalized cyclopropylcarbinols in good to excellent yields.

Table 2. Formation of *syn*-Cyclopropylcarbinol (CPC) by the Addition of Lithium Organocuprate Derivatives



entry	starting material	R	E-X	E	*anti*/*syn* ratio[a]	CPC	yield (%)[b]
1	**1a**	CH_2CH_2Ph	H_3O^+	H	5/95	**7a**	78
2	**1b**	*i*-Pr	H_3O^+	H	10/90	**7b**	87
3	**1c**	$CH(Ph)_2$	H_3O^+	H	6/94	**7c**	81
4	**1d**	*t*-Bu	H_3O^+	H	5/95	**7d**	83
5	**1e**	Ph	H_3O^+	H	10/90	**7e**	75
6	**1f**	mesityl	H_3O^+	H	1/99	**7h**	75
7	**1c**	$CH(Ph)_2$	I_2	I	6/94	**7f**	86
8	**1c**	$CH(Ph)_2$	AllylBr	C_3H_5	6/94	**7g**	77

[a] Determined by ^1H NMR and GC on the crude reaction mixture. [b] Isolated after purification by column chromatography.

Here again, alkylidenecyclopropanes **3** were not observed suggesting that the cyclopropylcopper derivatives formed after the carbocupration reaction are stable toward β-elimination reactions. The formation of each of the two possible diastereoisomers of polysubstituted cyclopropylcarbinols from cyclopropenylcarbinol derivatives, from a unique precursor just by variation of the nature of the organometallic species, is synthetically interesting.

In conclusion, cyclopropenylcarbinol derivatives **1** react diastereoselectively with organocopper derivatives and the stereochemical outcome of the reaction is dependent on the nature of the organocopper species (organocopper prepared from alkylmagnesium halide or from alkyllithium). As nonracemic cyclopropenylcarbinol is now easily accessible via kinetic resolution based upon Sharpless epoxidation, this reaction represents a new and versatile preparation of cyclopropyl derivatives that possesses two stereogenic quaternary stereocenters. Currently, it is unclear why alkylmagnesium halide versus alkyllithium leads to such a dramatic difference, and the goal of our ongoing studies is to rationalize this divergent reaction pathway.

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Supporting Information Available: Experimental procedures with a description of ^1H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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