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Highly *anti*-Selective S_N2' Substitutions of Chiral Cyclic 2-Iodo-Allylic Alcohol Derivatives with Mixed Zinc–Copper Reagents

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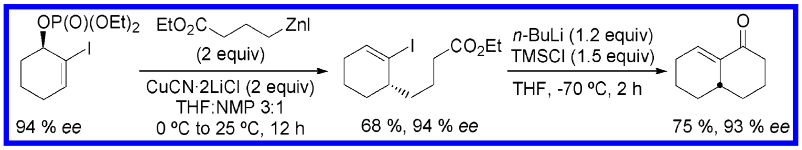
ABSTRACT



Functionalized allylic electrophilic reagents such as chiral 2-iodo-1-cyclohexenyl and -cyclopentenyl phosphates undergo highly stereoselective *anti*-S_N2'-allylic substitution reactions with a wide range of organozinc reagents (R_2Zn and RZnI) leading to chiral products with a transfer of the chiral information >95%. The use of functionalized organozinc iodides allows preparation of the bicyclic enones 8 and 9 in ≥93% ee.

Functionalized allylic electrophiles are useful multicoupling reagents[1] for the expedite formation of carbon−carbon bonds in a selective way. A variety of organometallic compounds undergo nucleophilic substitutions on allylic systems. Especially interesting are organocopper compounds[2] which are known to undergo S_N2' substitutions with various allylic electrophiles with high *anti*-selectivity.[3,4] Although catalytic allylic substitutions have also been reported,[5] the transfer of chirality with use of chiral allylic precursors has the advantage of being highly predictable. The required allylic alcohols are readily available by a range of asymmetric syntheses.[6,7] In the allylation reactions zinc-based organocoppers show high S_N2' selectivities.[8,9] Herein, we wish to report a highly *anti*-S_N2' substitution of chiral 2-iodo-

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(1) For the use of multicoupling reagents see: (a) Seebach, D.; Knochel, P. *Helv. Chim. Acta* **1984**, *67*, 261. (b) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 425. (c) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 1043. (d) Chen, H. G.; Gage, J. L.; Barret, S. D.; Knochel, P. *Tetrahedron Lett.* **1990**, *31*, 1829. (e) Rao, S. A.; Knochel, P. *J. Org. Chem.* **1991**, *56*, 4591. (f) Rottländer, M.; Palmer, N.; Knochel, P. *Synlett* **1996**, 573.

(2) (a) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (b) *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, Germany, 2002.

(3) (a) Goering, H. L.; Singleton, V. D., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 7854. (b) Goering, H. L.; Singleton, V. D., Jr. *J. Org. Chem.* **1983**, *48*, 1531. (c) Ibuka, T.; Nakao, T.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7420. (d) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864. (e) Karlström, A. S. E.; Bäckvall, J.-E. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, Germany, 2002; p 259. (f) Arai, M.; Kawasuji, T.; Nakamura, E. *J. Org. Chem.* **1993**, *58*, 5121. (g) Breit, B.; Demel, P. *Adv. Synth. Catal.* **2001**, *343*, 429.

(4) (a) Belelie, J. L.; Chong, J. M. *J. Org. Chem.* **2001**, *66*, 5552. (b) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370. (c) Marino, J. P.; Viso, A.; Lee, J.-D.; Fernandez de la Pradilla, R.; Fernandez, P.; Rubio, M. B. *J. Org. Chem.* **1997**, *62*, 645. (d) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **2000**, *65*, 1601. (e) Spino, C.; Beaulieu, C. *J. Am. Chem. Soc.* **1998**, *120*, 11832. (f) Spino, C.; Beaulieu, C. *Angew. Chem.* **2000**, *112*, 2006; *Angew. Chem., Int. Ed.* **2000**, *39*, 1930. (g) Spino, C.; Beaulieu, C.; Lafreniere, J. *J. Org. Chem.* **2000**, *65*, 7091. (h) Denmark, S. E.; Marble, L. K. *J. Org. Chem.* **1990**, *55*, 1984. (i) Fleming, I.; Winter, S. B. D. *Tetrahedron Lett.* **1995**, *36*, 1733.

(5) (a) van Klaveren, M.; Persson, E. S. M.; del Villar, A.; Grove, D. M.; Bäckvall, J.-E.; van Koten, G. *Tetrahedron Lett.* **1995**, *36*, 3059. (b) Karlström, A. S. E.; Huerta, F. F.; Meuzelaar, G. J.; Bäckvall, J.-E. *Synlett* **2001**, 923. (c) Meuzelaar, G. J.; Karlström, A. S. E.; van Klaveren, M.; Persson, E. S. M.; del Villar, A.; van Koten, G.; Bäckvall, J.-E. *Tetrahedron* **2000**, *56*, 2895. (d) Dübner, F.; Knochel, P. *Angew. Chem.* **1999**, *111*, 391; *Angew. Chem., Int. Ed.* **1999**, *38*, 379. (e) Dübner, F.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 9233. (f) Alexakis, A.; Malan, C.; Lea, L.; Benhaim, C.; Fournioux, X. *Synlett* **2001**, 927. (g) Alexakis, A.; Croset, K. *Org. Lett.* **2002**, *4*, 4147. (h) Malda, H.; van Zijl, A. W.; Arnold, L. A.; Feringa, B. L. *Org. Lett.* **2001**, *3*, 1169. (i) Luchaco-Cullis, C. A.; Mizutani, H.; Murphy, K. E.; Hoveyda, A. H. *Angew. Chem.* **2001**, *113*, 1504; *Angew. Chem., Int. Ed.* **2001**, *40*, 1456.

(6) For the asymmetric reduction with the CBS -method, see: (a) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986. (b) Wallbaum, S.; Martens, J. *Tetrahedron*: *Asymmetry* **1992**, *3*, 1475.

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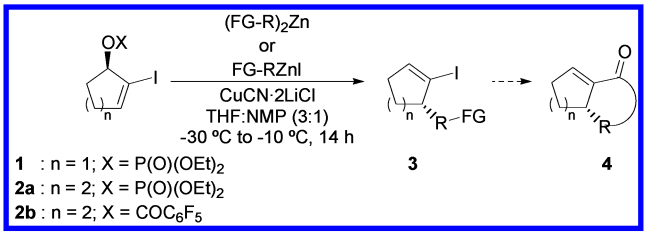
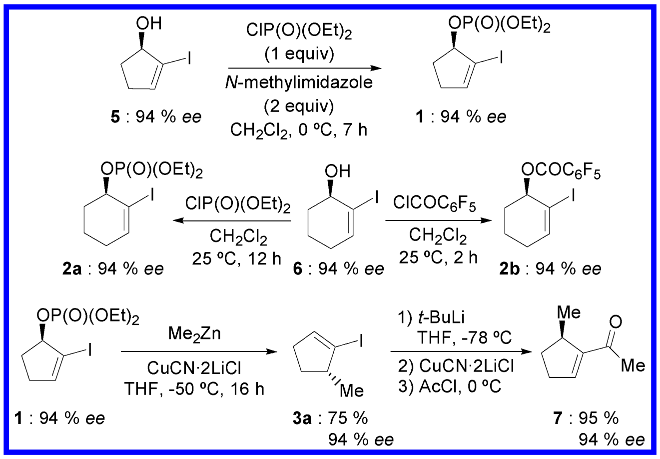
cycloallylic alcohol derivatives of type **1** or **2** (n = 1, 2) with various functionalized zinc reagents $(FG\text{-}R)_2Zn$ or FG-RZnI)[10] in the presence of $CuCN\cdot 2LiCl$[11] leading to products of type **3** which can be converted to chiral bicyclic products of type **4** with ≥93% ee, if the functional group FG is an ester or nitrile (Scheme 1).

Scheme 1



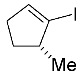
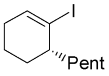
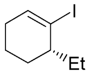
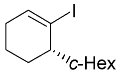
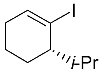
First, we have studied the substitution reaction using various unfunctionalized diorganozinc reagents (R_2Zn). Chiral (R)-2-iodocyclopentenol (**5**, 94% ee) and (R)-2-iodocyclohexenol (**6**, 94% ee) were converted into the corresponding phosphates **1** (76%) and **2a** (87%), which give S_N2' products when reacting with organocoppers.[12] The alcohol **6** was also converted into the pentafluorobenzoate **2b** in 93% yield (Scheme 2).

Scheme 2



Both the allylic phosphates and pentafluorobenzoates (**1**, **2**) reacted with diorganozincs in the presence of $CuCN\cdot 2LiCl$ (1.1 equiv) in a 3:1 mixture of THF:N-methylpyrrolidinone (NMP)[13] at −30 to −10 °C in 14 h furnishing the *anti*-S_N2' products **3a**−**e**. Primary as well as secondary diorganozincs undergo the substitution reaction in good yields (70−91%, Table 1).

Table 1. Products **3a**−**e** Obtained by the Reaction of Diorganozincs (R_2Zn) with the Chiral Allylic Derivatives **1** and **2a**,**b**

entry	starting reagent **1** or **2a-b**	R_2Zn (R)	product of type **3**	yield (%)[a]	*ee* (%)[b]
1	**1**	Me[c]	 **3a**	75	94
2	**2a**	Pent	 **3b**	90	94
3	**2b**	Pent	**3b**	91	93
4	**2b**	Et	 **3c**	85	93
5	**2b**	*c*-Hex	 **3d**	90	91
6	**2b**	*i*-Pr	 **3e**	70	93

[a] Yield of analytically pure product. [b] The enantiomeric excess was determined by capillary GC analysis on products **3** or derivatives of them (see Supporting Information). [c] The reaction was performed in THF at −50 °C for 16 h.

The enantiomeric excess (% ee) determined by capillary GC (see Supporting Information) was 91−94% ee, showing a high transfer of the stereochemical information.[14] The *anti*-selectivity was determined by converting vinylic iodide **3a** into ketone **7** of known configuration (Scheme 2).[15]

Thus, the reaction of **3a** with t-BuLi (2 equiv, THF, −78 °C, 20 min) followed by reaction with $CuCN\cdot 2LiCl$ (1.0 equiv, THF, 0 °C, 10 min) and CH_3COCl (2 equiv, 0 °C, 30 min) furnishes ketone **7** in 95% yield and 94% ee. Comparison with the optical rotation of **7** and the literature indicates that an *anti*-S_N2' substitution has taken place. The complete transfer of the stereochemical information from **1**

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(7) (a) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R., Ed.; Wiley: New York, 1994. (b) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (c) Carlier, P. R.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 2978.

(8) For an example of a mixed zinc−copper reagent derived from a diorganozinc reagent see: Reddy, C. K.; Knochel, P. *Angew. Chem., Int. Ed.* **1996**, *35*, 1700.

(9) For previous S_N2' selective allylic substitutions with organozinc reagents see: (a) Sekiya, K.; Nakamura, E. *Tetrahedron Lett.* **1988**, *29*, 5155. (b) Reference 3f. (c) Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3750. (d) Nakamura, E.; Sekiya, K.; Arai, M.; Aoki, S. *J. Am. Chem. Soc.* **1989**, *111*, 3091.

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(11) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(12) Yanagisawa, A.; Noritake, Y.; Nomura, N.; Yamamoto, H. *Synlett* **1991**, 251.

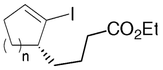
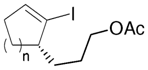
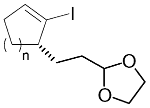
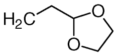
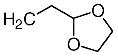
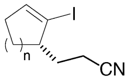
(13) We have observed that NMP strongly enhances the reactivity of these zinc−copper reagents, especially those of the copper species prepared from RZnI.

(14) (a) We have compared the reactivity of cuprates MeCu(CN)Li, $MeMgBr\cdot CuCN$, and Me_2CuLi with the one derived from Me_2Zn toward phosphate **1**. The first two organocoppers undergo also a highly stereoselective *anti*-S_N2' substitution to afford **3a** with 94% ee in good unoptimized yields (70 and 76%), whereas Me_2CuLi gives **3a** in only 18% ee and 74% yield. (b) The use of catalytic $CuCN\cdot 2LiCl$ for the preparation of mixed zinc−copper reagents lowers yields by ca. 20−30%.

(15) Graf, C.-D.; Knochel, P. *Tetrahedron* **1999**, *55*, 8801.

to **3a** shows also that neither a *syn*-S_N2' substitution nor an S_N2 substitution had occurred since these reaction pathways would lower the enantiomeric purity of **3a**. Remarkably, a range of functionalized zinc reagents undergo the S_N2' substitution with comparable selectivities and yields (Table 2).

Table 2. Products **3f**−**m** Obtained by Reaction of Functionalized Organozinc Halides with the Chiral Phosphates **1** and **2a**

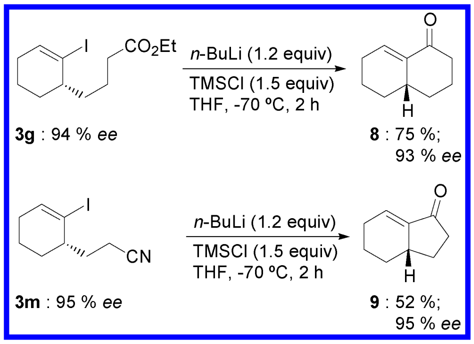
entry	allylic reagent **1** or **2a**	RZnI (R)	product of type **3**	yield (%)[a]	*ee* (%)[b]
					
1	**1**	$(CH_2)_3CO_2Et$	**3f** : n = 1	81	93 (96)[c]
2	**2a**	$(CH_2)_3CO_2Et$	**3g** : n = 2	68	94 (94)[d]
					
3	**1**	$(CH_2)_3OAc$	**3h** : n = 1	91	94 (96)[c]
4	**2a**	$(CH_2)_3OAc$	**3i** : n = 2	84	97 (98)[d]
					
5	**1**		**3j** : n = 1	77	94 (94)[c]
6	**2a**		**3k** : n = 2	62	97 (98)[d]
					
7	**1**	$(CH_2)_2CN$	**3l** : n = 1	90	91 (96)[c]
8	**2a**	$(CH_2)_2CN$	**3m** : n = 2	84	95 (98)[d]

[a] Yield of analytically pure product. [b] The enantiomeric excess was determined by capillary GC analysis on **3** (see Supporting Information). [c] Enantiomeric excess of **1**. [d] Enantiomeric excess of **2a**.

Only zinc−copper reagents made from equimolecular amounts of zinc reagents and copper salts have been examined.[16]

Thus, the reaction of 3-carboethoxypropylzinc iodide (2 equiv) with **1** (or **2a**) in the presence of CuCN•2LiCl (2 equiv) proceeds in THF:NMP (3:1) at −30 to 25 °C within 12 h affording the functionalized substituted products **3f** and **3g** respectively in 81% and 68% yield and 93−94% ee (entries 1 and 2 of Table 2). Similarly the reaction of allylic phosphates **1** and **2a** with 3-acetoxypropylzinc iodide provides the products **3h** and **3i** respectively in 91% (94% ee) and 84% (97.8% ee) (entries 3 and 4). Organozincs bearing an acetal function (entries 5 and 6) or a nitrile (entries 7 and 8) react with high *anti*-S_N2' selectivity affording the products **3j**−**m** in 91−97% ee and 62−90% yield (entries 5−8). The functionalized cyclohexenyl iodides **3g** and **3m** can be converted into bicyclic ketones **8**[17] and **9**[18] respectively in 75 and 52% yield and 93−95% ee by reaction with *n*-BuLi (1.2 equiv) and TMSCl (1.5 equiv) in THF at −70 °C for 2 h (Scheme 3).

Scheme 3



In summary, we have described highly enantioselective *anti*-S_N2'-allylic substitutions of cyclic 2-iodoallylic alcohols with a wide range of zinc−copper reagents and have shown their utility for preparing chiral bicyclic ketones such as **8** and **9** in ≥93% ee. Applications to the preparation of natural products are currently underway.[19]

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Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For use of RLi/$ZnCl_2$/CuCN see: Yamamoto, Y.; Chounan, Y.; Tanaka, M.; Ibuka, T. *J. Org. Chem.* **1992**, *57*, 1024.

(17) (a) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 1104. (b) Agami, C.; Platzer, N.; Puchot, C.; Sevestre, H. *Tetrahedron* **1987**, *43*, 1091. (c) Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045. (d) Abbott, R. E.; Spencer, T. A. *J. Org. Chem.* **1980**, *45*, 5398.

(18) (a) Jones, T. K.; Denmark, S. E. *Helv. Chim. Acta* **1983**, *66*, 2377. (b) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *J. Org. Chem.* **1980**, *45*, 3017.

(19) **Typical Procedure: Preparation of 3j.** A flame-dried 25-mL flask equipped with a magnetic stirring bar, an argon inlet, and a septum was charged with a solution of CuCN•2LiCl (1 M solution in THF; 1.7 mL, 1.7 mmol, 2.0 equiv) and cooled to −30 °C. The freshly prepared alkylzinc halide reagent (1.5 M solution in THF, 1.2 mL, 1.7 mmol, 2.0 equiv) was added dropwise and the resulting mixture was stirred 0.5 h at −30 °C. Then (*R*)-2-iodo-2-cyclopenten-1-yl diethyl phosphate **1** (94% ee; 0.300 g, 0.87 mmol, 1.0 equiv) was added dropwise as a solution in NMP (sufficient to give an overall ratio of THF:NMP of 3:1) and the reaction mixture was allowed to stir for 16 h while warming up to 25 °C. Saturated aqueous NH_4Cl solution (20 mL) was added followed by 25% aqueous ammonia solution (1 mL), then the reaction mixture was stirred at 25 °C until the copper salts had dissolved. The mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine and dried over Na_2SO_4. Evaporation of the solvents and purification by column chromatography (SiO_2, pentane:Et_2O 9:1) afforded 198 mg (77% yield, 94% ee) of **3j** as a colorless oil.