ORGANIC LETTERS

2001
Vol. 3, No. 1
127−130

Stereoselective Synthesis of Secondary Organozinc Reagents and Their Reaction with Heteroatomic Electrophiles

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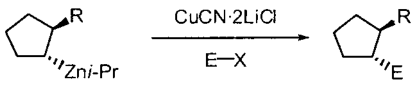
Received November 8, 2000

ABSTRACT

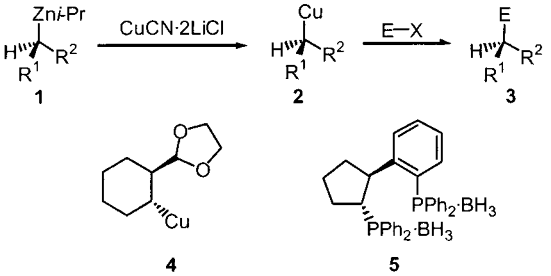


E = PPh_2, SnR_3, Br, SMe

Various trisubstituted olefins were converted to configurationally stable diorganozinc compounds with high diastereoselectivity. Their reaction with various electrophiles centered on tin, sulfur, bromine, and phosphorus provided the desired substitution products with retention of configuration. Novel, functionalized organocopper reagents such as 4 and chiral diphosphine 5 have been prepared.

The use of chiral organometallic reagents such as **1** in organic synthesis has been limited by the availability of configurationally stable organometallics.[1] Whereas unstabilized secondary alkyllithiums and -magnesiums[2] have moderate configurational stability,[3] secondary alkylzincs are configurationally stable at temperatures up to 25 °C in the absence of zinc halides.[4] After transmetalation to the corresponding copper reagent of type **2**, reactions with electrophiles such as allylic or propargylic bromides were found to proceed with high retention of configuration (up to 99%), leading to products of type **3**; Scheme 1.

Scheme 1



Herein, we wish to report a significant extension of the scope of this reaction. We have found that several heteroatomic electrophiles centered on tin, sulfur, bromine, and phosphorus react with high stereoselectivity with diastereomerically enriched cyclic and acyclic secondary organozinc

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[1] For the preparation of configurationally stable heteroatom-stabilized organolithiums, see: (a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (b) Chong, J. M.; Mar, E. K. *Tetrahedron* **1989**, *45*, 7709. (c) Matteson, D. S.; Tripathy, P. B.; Sarkar, A.; Sadhu, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 4399. (d) Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8546. (e) Reich, H. J.; Medina, M. A.; Bowe, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 11003. (f) Hoppe, D.; Zschage, O. *Angew. Chem., Int. Ed. Engl.* **1989**, *101*, 67. (g) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708. (h) Hoffmann, R. W.; Klute, W. *Chem. Eur. J.* **1996**, *2*, 694.

[2] (a) Whitesides, G. M.; Witanowski, M.; Roberts, J. D. *J. Am. Chem. Soc.* **1965**, *87*, 2854. (b) Witanowski, M.; Roberts, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 737. (c) Hoffmann, R. W.; Holzer, B.; Knopff, O.; Harms, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3072.

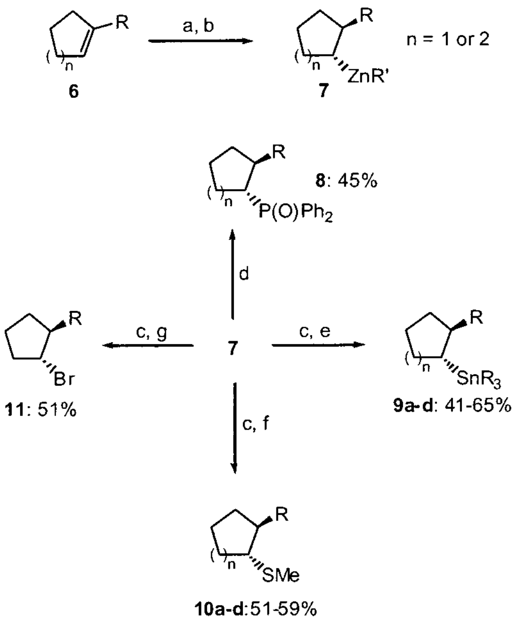
[3] (a) Duddu, R.; Eckhardt, M.; Furlong, M.; Knoess, H. P.; Berger, S.; Knochel, P. *Tetrahedron* **1994**, *50*, 2415. (b) Micouin, L.; Knochel, P. *Synlett* **1997**, 327. (c) Darcel, C.; Flachsmann, F.; Knochel, P. *J. Chem. Soc., Chem. Commun.* **1998**, 205. (d) Boudier, A.; Flachsmann, F.; Knochel, P. *Synlett* **1998**, 1438. (e) Boudier, A.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 687. (f) Boudier, A.; Darcel, C.; Flachsmann, F.; Micouin, L.; Oestreich, M.; Knochel, P. *Chem. Eur. J.* **2000**, *6*, 2748. (g) Boudier, A.; Hupe, E.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2294.

10.1021/ol0068400 CCC: $20.00

reagents. Remarkably, all reactions occur with retention of configuration.[5] These results have been applied to the synthesis of new functionalized copper reagent **4** and the new chiral diphosphine **5**.

Thus, the hydroboration of trisubstituted cyclic olefins of type **6** with Et$_2$BH[6] (50 °C, 12−16 h) furnishes an intermediate organoborane which undergoes a smooth boron−zinc exchange upon reaction with Zn*i*-Pr$_2$ at room temperature. The resulting mixed diorganozinc species were further transmetalated to the corresponding copper reagents. These organometallics react with various heteroatomic electrophiles, leading to products **9**−**11** (Scheme 2). The reaction with ClPPh$_2$ followed by oxidation with H$_2$O$_2$ provides phosphine oxide **8** (entry 1 of Table 1) directly from the zinc reagent without the need of further transmetalation to copper. Although the reaction requires 4 d at 25 °C for completion, it affords **8** exclusively as the *trans* isomer (> 99%), showing that the reaction of the intermediate diorganozinc of type **7** proceeds with complete retention of configuration. The intermediate phosphine was oxidized directly with 30% aqueous H$_2$O$_2$ before workup (Scheme 2 and Table 1).

Scheme 2[a]

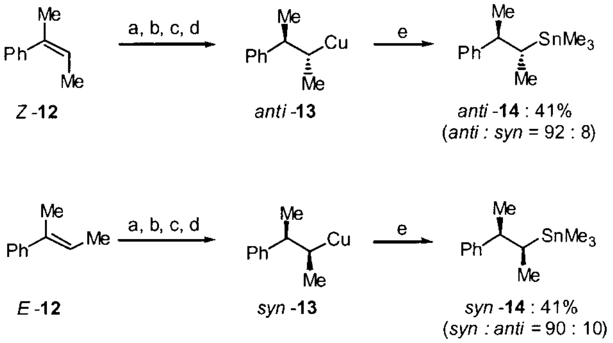


[a] (a) Et$_2$BH (3 equiv), 50 °C, 16 h; (b) Zn*i*-Pr$_2$ (3 equiv), 25 °C, 5 h; (c) CuCN·2LiCl (1 equiv), −78 °C, 0.5 h; (d) ClPPh$_2$ (4 equiv), 25 °C, 4 d, then 30% H$_2$O$_2$; (e) R$_3$SnCl (3 equiv), −40 °C, 16 h; (f) MeSSO$_2$Me (3 equiv), −40 °C, 16 h; (g) BrCl$_2$CCCl$_2$Br (3 equiv), −40 °C, 16 h.

Chlorotrialkylstannanes react more readily (−40 °C, 12 h), furnishing the expected stannanes (**9a**−**d**) with excellent *trans* selectivities (95−99% *trans*; see entries 2−5 of Table 1).

Interestingly, the alkenylsilane **6d** is hydroborated with excellent regioselectivity (only 1−2% of the other regioisomer was observed). After the usual transmetalation sequence (B−Zn−Cu), the resulting copper β-silyl bimetallic reagent reacts with Bu$_3$SnCl, providing the 1,2-bimetallic product **9c** (entry 4) in 50% yield (97% *trans*). Also, the fully diastereoselective hydroboration of the allylic ether **6e** (dr$_{(1,2)}$ = 99:1) affords, after stannylation with Me$_3$SnCl, the tin derivative **9d** (97% *trans*) in 58% overall yield (entry 5). A similar level of stereoselectivity has also been achieved in open-chain systems. Thus, the reaction of the *Z*- and *E*-styrenes *Z*-**12** and *E*-**12** furnishes, after the hydroboration−transmetalation sequence using (−)-IpcBH$_2$,[7] respectively, the *anti*-copper species *anti*-**13** and the *syn*-copper species *syn*-**13**. After reaction with Me$_3$SnCl, the diastereomeric stannane products *anti*-**14** (*anti*:*syn* ratio = 92:8) and *syn*-**14** (*syn*:*anti* ratio = 90:10) confirm the excellent stereoselectivity in the conversion of olefins to organostannanes: a process formally equivalent to a stereo- and regioselective alkene hydrostannation (Scheme 3). The enantioselectivity of the hydroboration of *Z*-**12** and *E*-**12** with (−)-IpcBH$_2$ lies between 46 and 74% ee.[3f]

Scheme 3[a]



[a] (a) (−)-IpcBH$_2$ (1 equiv), −35 °C, 48 h; (b) Et$_2$BH (5 equiv), 50 °C, 16 h; (c) Zn*i*-Pr$_2$ (5 equiv), 25 °C, 5 h; (d) CuCN·2LiCl (1 equiv), −78 °C, 0.5 h; (e) Me$_3$SnCl (5 equiv), −40 °C, 16 h.

The conversion of the copper reagent derived from **7** to thioethers of type **10** can be achieved with MeSSO$_2$Me (−40 °C, 12 h); entries 6−9 of Table 1. The diastereoselectivities of the thioethers range from 94 to 99%. Furthermore, a diastereoselective bromination can be performed with 1,2-dibromotetrachlorethane (−40 °C, 12 h), leading to the *trans*-bromide **11** in 51% yield (95% *trans*) (Scheme 2; entry 10 of Table 1). This methodology can also be applied to functionalized olefins such as the unsaturated acetal **15**. For example, following the usual procedure, the functionalized

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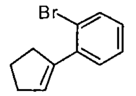
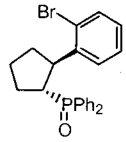
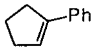
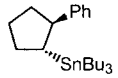
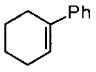
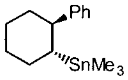
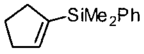
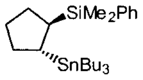
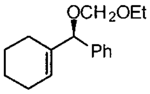
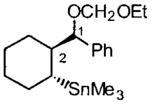
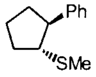
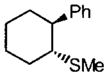
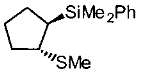
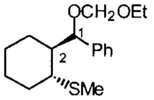
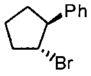
(4) (a) Klein, S.; Marek, I.; Normant, J.-F. *J. Org. Chem.* **1994**, *59*, 2925. (b) Houkawa, T.; Ueda, T.; Sakami, S.; Asaoka, M.; Takei, H. *Tetrahedron Lett.* **1996**, *37*, 1045. (d) Matsubara, S.; Toda, N.; Kobata, M.; Utimoto, K. *Synlett* **2000**, 987. (e) Matsubara, S.; Yamamoto, H.; Arioka, D.; Utimoto, K.; Oshima, K. *Synlett* **2000**, 1202.

(5) The relative configuration was determined by NOE experiments and by evaluation of the coupling constants in ^{1}H NMR experiments.

(6) Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229.

(7) Brown, H. C.; Mandal, A. K.; Yoon, N. M.; Singaram, B.; Schwier, J. R.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47*, 5069.

Table 1. Generation of Intermediate Chiral Zinc and Copper Reagents and Their Stereoselective Reaction with Heteroatomic Electrophiles Leading to Phosphine Oxide **8**, Stannanes **9a**–**d**, Thioethers **10a**–**d**, and Bromide **11**

entry	olefin of type 6	electrophile	product of type 8-11	*trans* : *cis* ratio	yield(%)[c]
1	 **6b**	$ClPPh_2$	 **8**	> 99 : < 1[a]	45
2	 **6a**	Bu_3SnCl	 **9a**	95 : 5	65
3	 **6c**	Me_3SnCl	 **9b**	> 99 : < 1	41
4	 **6d**	Bu_3SnCl	 **9c**	97 : 3	50
5	 **6e**	Me_3SnCl	 **9d**	97 : 3 (99 : 1)[b]	58
6	**6a**	$MeSO_2SMe$	 **10a**	94 : 6	59
7	**6c**	$MeSO_2SMe$	 **10b**	> 99 : < 1	51
8	**6d**	$MeSO_2SMe$	 **10c**	95 : 5	58
9	**6e**	$MeSO_2SMe$	 **10d**	96 : 4 (99 : 1)[b]	53
10	**6a**	$BrCl_2CCCl_2Br$	 **11**	95 : 5	51

[a] The crude phosphine was oxidized to the corresponding phosphine oxide by aqueous 30% H_2O_2. [b] Diastereomeric ratio between centers C(1) and C(2). [c] Overall yield of analytically pure product.

organocopper species **4** is formed. Its stannylation with Me_3SnCl gives the *trans*-tin derivative **16** (71%, 95% *trans*),[8] whereas its reaction with $MeSO_2SMe$ furnishes the thioether **17** (61%; 99% *trans*), Scheme 4.

Finally, the hydroboration of olefin **6b**, using (−)-$IpcBH_2$ as the hydroborating agent, allows the preparation of

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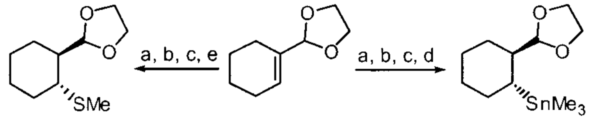
[8] **Typical procedure: preparation of 16.** A flame-dried 25 mL flask equipped with a magnetic stirring bar, an argon inlet, and a septum was charged with alkene **15** (154 mg, 1 mmol). Et_2BH (0.4 mL, 7.3 M in Me_2S, 3 equiv) was added, and the resulting mixture was stirred for 16 h at 50 °C. After pumping off the volatiles (0.1 mmHg, 25 °C, 2 h), Zn*i*-Pr_2 (0.6 mL, 5 M in Et_2O, 3 equiv) was added and the mixture was stirred for 5 h at 25 °C. The boron–zinc exchange was ca. 85% as monitored by GC analysis of oxidized aliquots (aqueous 3 M NaOH/aqueous 30% H_2O_2). The volatiles were pumped off (0.1 mmHg, 25 °C, 0.5 h), and the gray-black residue was diluted with THF (2 mL) and cooled to −78 °C. A freshly prepared solution of CuCN·2LiCl (1 mL, 1 M in THF, 1 equiv) was added over 30 min and the mixture was stirred for 30 min at −78 °C. Then, Me_3SnCl (3 mL, 1 M in THF, 3 mmol, 3 equiv) was slowly added (30 min). After stirring for 30 min at −78 °C, the mixture was allowed to warm to −40 °C and stirred at this temperature for 16 h. The reaction mixture was then poured into an aqueous saturated KF solution (100 mL). After extraction with Et_2O and normal workup, column chromatography (SiO_2, hexanes: Et_2O = 24:1) afforded 227 mg (71%) of **16** as a colorless oil.

Scheme 4[a]



17 : 61%
trans : *cis* = 99 : 1

15

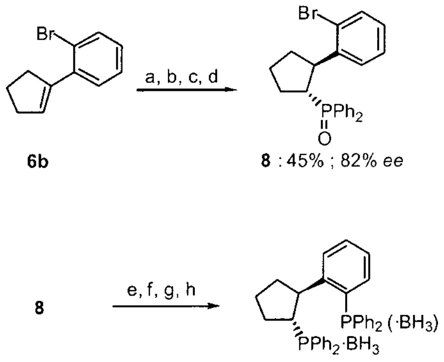
16 : 71%
trans : *cis* = 95 : 5

[a] (a) Et_2BH (3 equiv), 50 °C, 16 h; (b) Zn*i*-Pr_2 (3 equiv), 25 °C, 5 h; (c) CuCN•2LiCl (1 equiv), −78 °C, 0.5 h; (d) Me_3SnCl (3 equiv), −40 °C, 16 h; (e) $MeSSO_2Me$ (3 equiv), −40 °C, 16 h.

chiral phosphine oxide **8** in 45% yield, 82% ee, and > 99% *trans* selectivity. Compound **8** has been converted to the borane-protected diphosphine **5** as indicated in Scheme 5.[9]

In summary, we have prepared a range of new diastereomerically well-defined zinc−copper secondary alkyl organometallics and have demonstrated that they react with retention of configuration with various heteroatomic electrophiles. The new chiral diphosphine **5** has been prepared by this method. Further applications of secondary chiral alkylzinc reagents in asymmetric catalysis and natural product synthesis are currently underway.

Scheme 5[a]



6b

8 : 45% ; 82% *ee*

8

5a, (**b**) : 76%

[a] (a) (−)-IpcBH_2 (1 equiv), −35 °C, 48 h; (b) Et_2BH (5 equiv), 50 °C, 16 h; (c) Zn*i*-Pr_2 (5 equiv), 25 °C, 5 h; (d) $ClPPh_2$ (5 equiv), 25 °C, 4 d, then 30% H_2O_2; (e) Cl_3SiH (5 equiv), 120 °C, 12 h; (f) *n*-BuLi, (1.2 equiv), −78 °C, 2 h; (g) PPh_2Cl (1.2 equiv), −78 °C to 25 °C, 7 h; (h) BH_3•DMS (5 equiv), 25 °C, 12 h.

Acknowledgment. We thank the DFG (Leibniz program) and the Fonds der Chemischen Industrie (Kekulé scholarship for E.H.) for generous support. We thank Dr. Yasunari Monguchi for the preparation of some starting materials. We thank also the BASF AG (Ludwigshafen), Chemetall GmbH (Frankfurt), Aventis (Frankfurt), and DEGUSSA-HÜLS AG (Hanau) for the generous gift of chemicals.

Supporting Information Available: All analytical data for compounds of Table 1 and Schemes 3, 4, and 5 and procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] Hupe, E.; Knochel, P. Patent application with Aventis Research & Technologies GmbH & Co KG.