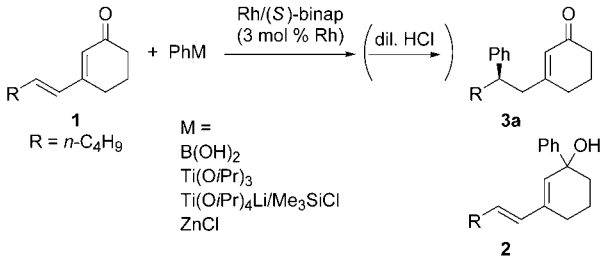
Asymmetric Catalysis

Rhodium-Catalyzed Asymmetric 1,6-Addition of Aryl Zinc Reagents to Dienones**

Tamio Hayashi, Shohei Yamamoto, and Norihito Tokunaga*

The catalytic asymmetric 1,4-addition of organometallic reagents to electron-deficient olefins is one of the most important methods of forming stereogenic centers in carbon–carbon bond-forming reactions.[1] In this field, attention has focused on asymmetric 1,4-additions catalyzed by copper,[2,3] rhodium,[4–8] palladium,[9] and nickel[10] complexes. On the other hand, asymmetric 1,6-addition to extended conjugate systems has developed less rapidly.[11] Although several reports have appeared on diastereoselective 1,6-additions,[12] the use of a chiral catalyst for this asymmetric transformation remains to be studied. Herein, we report the first example of a catalytic asymmetric 1,6-addition to 2,4-dien-1-ones, in which a stereogenic center at the C5 position is also formed; this reaction is realized by a rhodium-catalyzed addition of aryl zinc reagents to dienones in the presence of chlorotrimethylsilane.

To investigate conjugate addition to 3-((*E*)-hexenyl)-2-cyclohexenone (**1**), several phenyl organometallic reagents that had been successfully used in rhodium-catalyzed asymmetric 1,4-addition reactions to electron-deficient alkenes[4–7] were examined for their reactivity and selectivity (Scheme 1 and Table 1). When the reaction was carried out with phenylboronic acid under reaction conditions that have been shown to be very efficient for asymmetric 1,4-additions



Scheme 1. Rhodium-catalyzed addition of phenyl organometallic reagents (PhM) to dienone **1**.

[*] Prof. T. Hayashi, S. Yamamoto, N. Tokunaga
Department of Chemistry
Graduate School of Science, Kyoto University
Sakyo, Kyoto 606-8502 (Japan)
Fax: (+81) 75-753-3988
E-mail: thayashi@kuchem.kyoto-u.ac.jp

[**] This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (21 COE on Kyoto University Alliance for Chemistry). N.T. thanks the Japanese Society for the Promotion of Science for the award of a fellowship for graduate students.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/ange.200500678

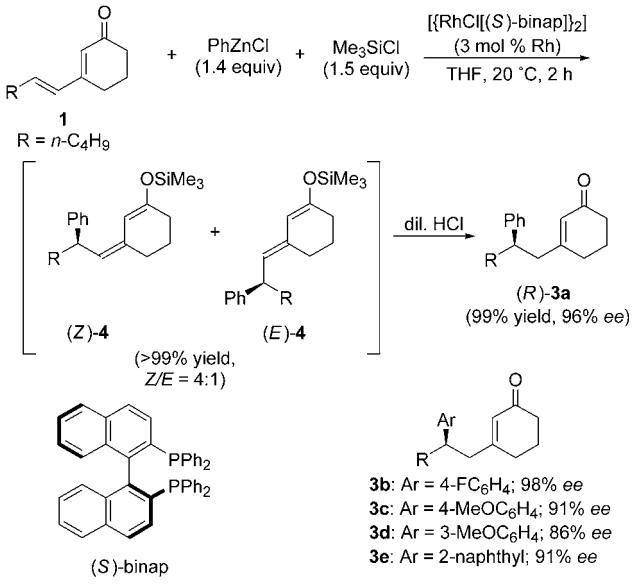
Table 1: Rhodium-catalyzed asymmetric 1,6-addition to **1** forming products **3a–e**.[a]

Entry	PhM (equiv)	Conditions[b]	Yield [%][c]	*ee* [%][d]
1	$PhB(OH)_2$ (2.5)	A	0[e]	–
2	$PhTi(OiPr)_3$ (1.6)	B	0[f]	–
3	$PhTi(OiPr)_4Li/Me_3SiCl$ (1.5/2.0)	C	78 (**3a**)	88
4	PhZnCl[g] (1.4)	D	18 (**3a**)	96
5	$PhZnCl$[g]$/Me_3SiCl$ (1.4/1.5)	D	99 (**3a**)	96
6	$PhZnX$[h]$/Me_3SiCl$ (1.4/1.5)	D	94 (**3a**)	94
7	$4\text{-}FC_6H_4ZnX$[h]$/Me_3SiCl$ (1.4/1.5)	D	90 (**3b**)	98
8	$4\text{-}MeOC_6H_4ZnCl$[g]$/Me_3SiCl$ (1.4/1.5)	D	94 (**3c**)	91
9	$3\text{-}MeOC_6H_4ZnCl$[h]$/Me_3SiCl$ (1.4/1.5)	D	86 (**3d**)	86
10	2-naphthylZnCl[h]$/Me_3SiCl$ (1.4/1.5)	D	85 (**3e**)	91

[a] The reactions were carried out with 0.30 mmol of **1** in the presence of 3 mol% of the rhodium catalyst. [b] Conditions A: [{Rh(OH)[(*S*)-binap]}$_2$], dioxane/H_2O (10:1), 50°C, 3 h. Conditions B: [{Rh(OH)[(*S*)-binap]}$_2$], THF, 30°C, 1 h; hydrolysis with dilute HCl. Conditions C: [{RhCl[(*S*)-binap]}$_2$], THF, 20°C, 0.5 h; hydrolysis with dilute HCl. Conditions D: [{RhCl[(*S*)-binap]}$_2$], THF, 20°C, 2 h; hydrolysis with dilute HCl. [c] Yield of product isolated by column chromatography on silica gel (hexane/ethyl acetate, 4:1). [d] Determined by HPLC analysis with a chiral stationary-phase column (chiralpak OJ: hexane/2-propanol, 95:5); *ee* value for *R* enantiomer. [e] Dienone **1** was recovered. [f] A 1,2-addition product **2** was formed in 70% yield. [g] Generated from ArLi and $ZnCl_2$. [h] Generated from ArMgBr and $ZnCl_2$.

(3 mol% (Rh) of [{Rh(OH)[(*S*)-binap]}$_2$] (binap = 2,2′-bis-(diphenylphosphanyl)-1,1′-binaphthyl) as the catalyst in dioxane/H_2O (10:1) at 50°C for 3 h),[5b] the starting dienone **1** was recovered quantitatively (Table 1, entry 1). The use of the phenyltitanium reagent $PhTi(OiPr)_3$ in the presence of [{Rh(OH)[(*S*)-binap]}$_2$] in THF at 30°C, which gives titanium enolates as 1,4-addition products with high enantioselectivities from α,β-unsaturated ketones,[6a] does not react in the same way with the present substrate **1**. Instead, titanium reagent reacted to give the tertiary alcohol **2** (70% yield; Table 1, entry 2) by a noncatalyzed 1,2-addition. The lithium titanate reagent $PhTi(OiPr)_4Li$ (1.5 equiv), used in the presence of chlorotrimethylsilane (2.0 equiv) and [{RhCl[(*S*)-binap]}$_2$] (3 mol% Rh) in THF at 20°C, proved more promising.[6c] The 1,6-addition product (*R*)-3-(2-phenylhexyl)-2-cyclohexenone (**3a**) was afforded after acidic hydrolysis in 78% yield and with 88% *ee* (Table 1, entry 3). The zinc reagent PhZnCl (1.4 equiv), which has been recently found to be more efficient than boron or titanium reagents in rhodium-catalyzed asymmetric 1,4-addition reactions to enones,[7] gave the 1,6-addition product **3a** with higher enantioselectivity (96% *ee* (*R*)), although its yield was as low as 18% (Table 1, entry 4).

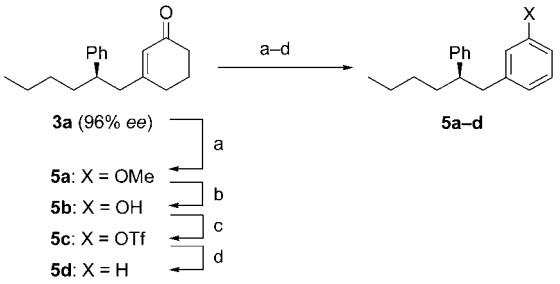
We have found, therefore, that chlorotrimethylsilane greatly accelerates[13] the rhodium-catalyzed 1,6-addition of aryl zinc reagents to dienone **1**. Thus, **1** was treated with PhZnCl (1.4 equiv; generated from PhLi and $ZnCl_2$ in THF) in the presence of chlorotrimethylsilane (1.5 equiv) and [{RhCl[(*S*)-binap]}$_2$] (3 mol% Rh) in THF at 20°C for 2 h, and the phenylation product (*R*)-**3a** was obtained in a quantitative yield with 96% *ee* after acidic hydrolysis (Scheme 2; Table 1, entry 5). The 1,6-addition product before hydrolysis was a 1,3-dienyl silyl ether **4** ($Z/E = 4:1$). The high yield of the addition product may be ascribed to the



Scheme 2. Rhodium-catalyzed asymmetric 1,6-addition of ArZnCl to dienone **1** in the presence of Me_3SiCl.

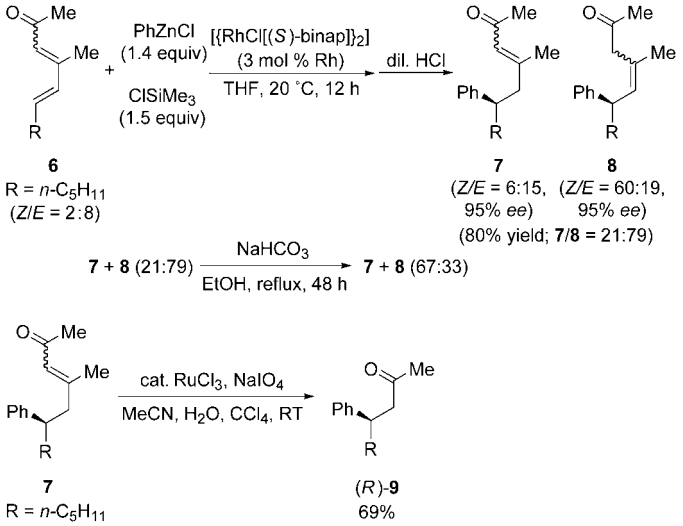
activation of **1** by the chlorosilane acting as a Lewis acid,[13] which accelerates the addition of **1** to a phenylrhodium species in the catalytic cycle (see below). The asymmetric addition of aryl zinc reagents generated from $4\text{-}FC_6H_4MgBr$, $4\text{-}MeOC_6H_4Li$, $3\text{-}MeOC_6H_4MgBr$, and 2-naphthylMgBr also gave the corresponding 1,6-addition products **3b–e**, respectively, in high yields and with high enantioselectivities (Table 1, entries 7–10). The formation of any 1,4- or 1,2-addition products was not detected in the reaction of **1** under the current conditions.

The absolute configuration of the 1,6-addition product **3a** was determined to be *R* after its conversion into (*R*)-1,2-diphenylhexane[14] (**5d**). The key step in the synthetic pathway to **5d** is the oxidation of the cyclohexenone moiety in **3a** into the methoxyphenyl group in **5a** (Scheme 3).[15]



Scheme 3. Determination of the absolute configuration of the 1,6-addition product **3a**. a) I_2, MeOH, reflux (99%); b) BBr_3, CH_2Cl_2, room temperature (90%); c) Tf_2O, pyridine, $ClCH_2CH_2Cl$, room temperature (99%); d) H_2, Pd/C, EtOH, $EtN(iPr)_2$, room temperature (86%). Tf = trifluoromethanesulfonyl.

The treatment of the linear dienone 4-methylundeca-3,5-dien-2-one (**6**) with PhZnCl and chlorotrimethylsilane in the presence of the Rh/(*S*)-binap (3 mol% Rh) catalytic system also proceeded with perfect 1,6-selectivity to give the phenylation product in high yield (Scheme 4). Hydrolysis with

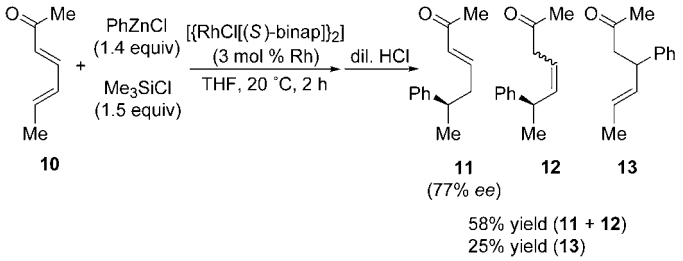


Scheme 4. Rhodium-catalyzed asymmetric 1,6-addition of PhZnCl to dienone **6** in the presence of Me_3SiCl.

hydrochloric acid afforded α,β-unsaturated ketone **7** and β,γ-unsaturated ketone **8** as a mixture of olefinic isomers in a ratio of 21:79. Treatment of the mixture with sodium bicarbonate in ethanol at reflux for 48 h shifted the ratio of **7**/**8** to 67:33. Both **7** and **8** were found to be *R* enantiomers in 95% *ee*. The configuration was determined by correlation with (*R*)-3-phenylnonen-2-one[5a] ((*R*)-**9**), which was obtained by oxidative cleavage of the double bond in **7**.

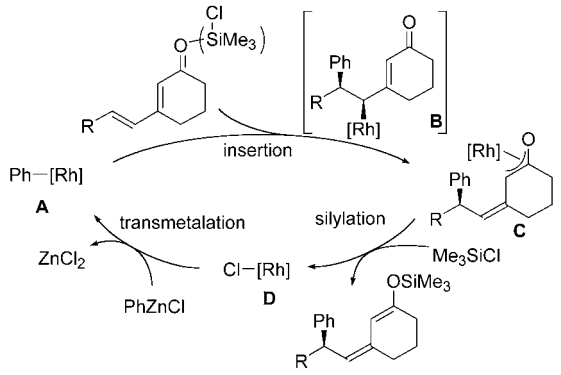
The selectivity of the 1,6-addition was not as high in the reaction of hepta-3,5-dien-2-one (**10**); the 1,4-addition product was formed as a by-product because **10** lacks a substituent at the β position. Thus, the addition of PhZnCl to **10** in the presence of chlorotrimethylsilane under similar conditions gave the 1,6-addition products **11** (77% *ee*) and **12** in a combined yield of 58% together with the 1,4-addition product **13** in 25% yield (Scheme 5).

The catalytic cycle proposed for the rhodium-catalyzed 1,4-addition of aryl titanates in the presence of chlorotrimethylsilane[6c] can be applied to the 1,6-addition of aryl zinc



Scheme 5. Rhodium-catalyzed asymmetric addition of PhZnCl to dienone **10** in the presence of Me_3SiCl.

reagents (Scheme 6), as this mechanism involves the reaction of an oxo-π-allyl rhodium intermediate with chlorosilane to afford a chlororhodium complex and a silyl enolate as the product. With a dienone as the substrate, insertion of its γ,δ-double bond into the phenyl–rhodium bond in **A** is slow

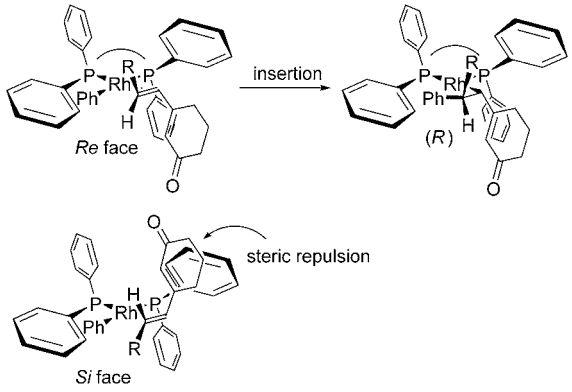


Scheme 6. The catalytic cycle for the rhodium-catalyzed 1,6-addition reaction. [Rh] = [Rh{(*S*)-binap}].

compared with the insertion of the α,β-double bond of an α,β-unsaturated ketone; therefore, insertion of the dienone γ,δ-double bond takes place more smoothly with the assistance of a chlorosilane as a Lewis acid. An alkyl rhodium intermediate **B** is formed by the insertion reaction and undergoes isomerization to a thermodynamically stable oxo-π-allyl rhodium complex **C**. A silylation reaction of **C** with chlorotrimethylsilane yields a chlororhodium species **D** and a silyl dienyl ether as the 1,6-addition product. Transmetalation between **D** and PhZnCl regenerates the phenylrhodium species **A**.

The absolute configuration *R* of the 1,6-addition product **3**, obtained with (*S*)-binap as a chiral ligand, was rationalized by using the stereochemical pathway shown in Scheme 7. At the insertion step, coordination of the γ,δ-double bond at the *Re* face is more favorable than coordination at the *Si* face because of the steric repulsions between one of the phenyl rings of the binap ligand and the cyclohexene moiety.

In summary, catalytic asymmetric 1,6-additions to 2,4-dien-1-ones has been realized with up to 98% *ee* using a chiral



Scheme 7. The stereochemical pathway in the rhodium-catalyzed asymmetric 1,6-addition reaction.

bisphosphine/rhodium catalyst, aryl zinc reagents, and a chlorosilane. Further studies on the scope and limitations of this new catalytic asymmetric carbon–carbon bond-forming reaction are underway.

Received: February 23, 2005
Published online: June 1, 2005

Keywords: 1,6-addition · asymmetric catalysis · organometallic reagents · rhodium · zinc

[1] For recent reviews on catalytic asymmetric 1,4-addition reactions, see: a) N. Krause, A. Hoffmann-Roder, *Synthesis* **2001**, 171; b) M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033; c) K. Tomioka, Y. Nagaoka in *Comprehensive Asymmetric Catalysis, Vol. 3* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, chap. 31.1; d) M. Kanai, M. Shibasaki in *Catalytic Asymmetric Synthesis, 2nd ed.* (Ed.: I. Ojima), Wiley, New York, **2000**, p. 569.

[2] For selected reviews on enantioselective copper-catalyzed conjugate addition, see: a) A. Alexakis, C. Benhaim, *Eur. J. Org. Chem.* **2002**, 3221; b) B. L. Feringa, R. Naasz, R. Imbos, L. A. Arnold, *Modern Organocopper Chemistry* (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**, p. 224; c) B. L. Feringa, *Acc. Chem. Res.* **2000**, *33*, 346.

[3] For recent examples, see: a) L. A. Arnold, R. Naasz, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2001**, *123*, 5841; b) C. A. Luchaco-Cullis, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 8192; c) S. J. Degrado, H. Mizutani, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 13362; d) A. Duursma, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2003**, *125*, 3700; e) A. W. Hird, A. H. Hoveyda, *Angew. Chem.* **2003**, *115*, 1314; *Angew. Chem. Int. Ed.* **2003**, *42*, 1276; f) K. Agapiou, D. F. Cauble, M. J. Krische, *J. Am. Chem. Soc.* **2004**, *126*, 4528.

[4] For reviews, see: a) T. Hayashi, *Synlett* **2001**, 879; b) K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169; c) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829; d) T. Hayashi, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13.

[5] For organoboron reagents, see: a) Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579; b) T. Hayashi, M. Takahashi, Y. Takaya, M. Ogasawara, *J. Am. Chem. Soc.* **2002**, *124*, 5052; c) T. Hayashi, K. Ueyama, N. Tokunaga, K. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 11508; d) R. Shintani, K. Ueyama, I. Yamada, T. Hayashi, *Org. Lett.* **2004**, *6*, 3425; e) S. Sakuma, M. Sakai, R. Itooka, N. Miyaura, *J. Org. Chem.* **2000**, *65*, 5951; f) S. Sakuma, N. Miyaura, *J. Org. Chem.* **2001**, *66*, 8944; g) M. Kuriyama, K. Tomioka, *Tetrahedron Lett.* **2001**, *42*, 921; h) M. Kuriyama, K. Nagai, K.-i. Yamada, Y. Miwa, T. Taga, K. Tomioka, *J. Am. Chem. Soc.* **2002**, *124*, 8932; i) M. T. Reetz, D. Moulin, A. Gosberg, *Org. Lett.* **2001**, *3*, 4083; j) R. Amengual, V. Michelet, J.-P. Genêt, *Synlett* **2002**, 1791; k) M. Pucheault, S. Darses, J.-P. Genêt, *Tetrahedron Lett.* **2002**, *43*, 6155; l) M. Pucheault, S. Darses, J.-P. Genêt, *Eur. J. Org. Chem.* **2002**, 3552; m) R. Itooka, Y. Iguchi, N. Miyaura, *J. Org. Chem.* **2003**, *68*, 6000; n) J.-G. Boiteau, R. Imbos, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2003**, *5*, 681; J.-G. Boiteau, R. Imbos, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2003**, *5*, 1385; o) Q. , Shi, L. Xu, X. Li, X. Jia, R. Wang, T. T.-L. Au-Yeung, A. S. C. Chan, T. Hayashi, R. Cao, M. Hong, *Tetrahedron Lett.* **2003**, *44*, 6505; p) Y. Iguchi, R. Itooka, N. Miyaura, *Synlett* **2003**, 1040; q) J.-G. Boiteau, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2003**, *68*, 9481; r) Y. Ma, C. Song, C. Ma, Z. Sun, Q. Chai, M. B. Andrus, *Angew. Chem.* **2003**, *115*, 6051; *Angew. Chem. Int. Ed.* **2003**, *42*, 5871; s) C. Defieber, J.-F. Paquin, S. Serna, E. M. Carreira, *Org. Lett.* **2004**, *6*, 3873; t) L. Navarre, S. Darses, J.-P. Genêt, *Angew. Chem.* **2004**, *116*, 737; *Angew. Chem. Int. Ed.* **2004**, *43*, 719; u) M. Pucheault, V. Michaut, S. Darses, J.-P. Genêt, *Tetrahedron Lett.* **2004**, *45*, 4729; v) A. Duursma, J.-G. Boiteau, L. Lefort, J. A. F. Boogers, A. H. M. De Vries, J. G. De Vries, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2004**, *69*, 8045; w) K. M. Belyk, C. D. Beguin, M. Palucki, N. Grinberg, J. DaSilva, D. Askin, N. Yasuda, *Tetrahedron Lett.* **2004**, *45*, 3265; x) P. Mauleon, J. C. Carretero, *Org. Lett.* **2004**, *6*, 3195; y) R. J. Moss, K. J. Wadsworth, C. J. Chapman, C. G. Frost, *Chem. Commun.* **2004**, 1984; z) B. M. Bocknack, L.-C. Wang, M. J. Krische, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5421.

[6] For organotitanium reagents, see: a) T. Hayashi, N. Tokunaga, K. Yoshida, J. W. Han, *J. Am. Chem. Soc.* **2002**, *124*, 12102; b) K. Yoshida, T. Hayashi, *J. Am. Chem. Soc.* **2003**, *125*, 2872; c) N. Tokunaga, K. Yoshida, T. Hayashi, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5445.

[7] For organozinc reagents, see: R. Shintani, N. Tokunaga, H. Doi, T. Hayashi, *J. Am. Chem. Soc.* **2004**, *126*, 6240.

[8] Other organometallic reagents: for silicon, see: a) S. Oi, A. Taira, Y. Honma, Y. Inoue, *Org. Lett.* **2003**, *5*, 97; b) Y. Otomaru, T. Hayashi, *Tetrahedron: Asymmetry* **2004**, *15*, 2647; for zirconium, see: c) S. Oi, T. Sato, Y. Inoue, *Tetrahedron Lett.* **2004**, *45*, 5051.

[9] T. Nishikata, Y. Yamamoto, N. Miyaura, *Chem. Commun.* **2004**, 1822.

[10] For a recent example, see: Y.-S. Kwak, E. J. Corey, *Org. Lett.* **2004**, *6*, 3385.

[11] A rhodium-catalyzed asymmetric 1,6-addition to 3-alkynyl-2-en-1-ones that affords axially chiral allenes has been reported: T. Hayashi, N. Tokunaga, K. Inoue, *Org. Lett.* **2004**, *6*, 305.

[12] For organocopper reagents, see: a) J. A. Marshall, H. Roebke, *J. Org. Chem.* **1966**, *31*, 3109; b) J. A. Marshall, R. A. Ruden, L. K. Hirsch, M. Phillippe, *Tetrahedron Lett.* **1971**, *12*, 3795; c) N. Krause, *J. Org. Chem.* **1992**, *57*, 3509; d) N. Krause, S. Thorand, *Inorg. Chim. Acta* **1999**, *296*, 1; e) M. Uerdingen, N. Krause, *Tetrahedron* **2000**, *56*, 2799; for an iron-catalyzed reaction, see: f) K. Fukuhara, H. Urabe, *Tetrahedron Lett.* **2005**, *46*, 603.

[13] For the acceleration of a 1,4-addition reaction of organocuprates by chlorotrimethylsilane, see: a) E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1985**, *26*, 6015; b) E. J. Corey, N. W. Boaz, *Tetrahedron Lett.* **1985**, *26*, 6019.

[14] S. Norsikian, I. Marek, S. Klein, J. F. Poisson, J. F. Normant, *Chem. Eur. J.* **1999**, *5*, 2055; $[\alpha]_D^{20} = -70$ ($c = 1.1$, Et_2O).

[15] A. S. Kotnis, *Tetrahedron Lett.* **1990**, *31*, 481.

