Homogeneous Catalysis

DOI: 10.1002/ange.201008196

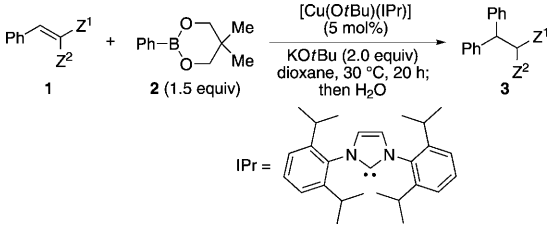
Copper-Catalyzed 1,4-Addition of Organoboronates to Alkylidene Cyanoacetates: Mechanistic Insight and Application to Asymmetric Catalysis**

Keishi Takatsu, Ryo Shintani, and Tamio Hayashi**

The copper-catalyzed 1,4-addition of organometallic reagents to α,β-unsaturated compounds is a powerful method for the efficient construction of carbon–carbon bonds.[1] Highly reactive nucleophiles such as Grignard reagents,[1a–c,2] diorganozinc compounds,[1d,e,3] and triorganoaluminum compounds[1d–f,4] are widely employed in these reactions, but the use of milder nucleophiles has been much less studied; in fact there has been only one such study reported, wherein Lee and Hoveyda used organo(trifluoro)silanes as nucleophiles in the presence of a fluoride additive.[5] In contrast, although the use of organoboronic acids and their derivatives would be highly attractive in view of their availability, stability, and ease of handling, there has been no such report to date as far as we are aware.[6–8] In this context, we herein describe a 1,4-addition of aryl boronic acid esters to alkylidene cyanoacetates catalyzed by a copper/N-heterocyclic carbene complex. We also describe the mechanistic details of the reaction and also demonstrate that the use of a chiral N-heterocyclic carbene ligand leads to an effective asymmetric variant of this process.[9]

In an initial investigation we attempted a reaction of *tert*-butyl cinnamate (**1a**) with phenylboronic acid neopentylglycol ester (**2**) in the presence of [Cu(O*t*Bu)(IPr)][10] (5 mol%) and KO*t*Bu (2.0 equiv) in dioxane at 30°C, but no 1,4-addition product was observed under these conditions (Table 1, entry 1). The use of cinnamonitrile (**1b**) was also unproductive (Table 1, entry 2), but more-electron-deficient substrates such as di-*tert*-butyl benzylidenemalonate (**1c**) and benzylidenemalononitrile (**1d**) led to the formation of 1,4-adducts in moderate yield (30% yield and 67% yield; Table 1, entries 3 and 4, respectively). We subsequently found that *tert*-butyl benzylidenecyanoacetate (**1e**) reacted more smoothly under the same conditions to give 1,4-adduct **3e** in 92% yield after aqueous workup (Table 1, entry 5). A similarly high yield was achieved for the reaction in THF (Table 1, entry 6), but the reaction became very sluggish in the absence of KO*t*Bu (Table 1, entry 7).

Table 1: Copper-catalyzed 1,4-addition of phenylboronate **2** to electron-deficient olefins **1**.



Entry	Substrate (Z^1, Z^2)	Product	Yield [%][a]
1	**1a** (CO_2tBu, H)	**3a**	0[b]
2	**1b** (CN, H)	**3b**	0[b]
3	**1c** (CO_2tBu, CO_2tBu)	**3c**	30[b]
4	**1d** (CN, CN)	**3d**	67
5	**1e** (CO_2tBu, CN)	**3e**	92
6[c]	**1e**	**3e**	89
7[d]	**1e**	**3e**	8[b]

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy with an internal standard ($MeNO_2$). [c] The reaction was conducted in THF. [d] The reaction was conducted in the absence of KO*t*Bu.

A series of stoichiometric reactions were then conducted to gain some insight into the catalytic cycle for the reaction of substrate **1e** with phenylboronate **2** described above:[6d,k] The reaction of [Cu(O*t*Bu)(IPr)] with **2** proceeded smoothly in dioxane at 30°C to give [CuPh(IPr)] (**4**) in 64% yield after recrystallization [Eq. (1) and Figure 1a]. Complex **4** thus obtained underwent insertion of **1e** in [D_8]THF at 30°C to give copper enolate **5** almost quantitatively [Eq. (2) and Figure 1b]. The identity of **5** was confirmed by ^{1}H and ^{13}C NMR spectroscopy as well as by HRMS.[11] Protonolysis of **5** produced 1,4-adduct **3e** cleanly in 84% yield of the isolated product. To the best of our knowledge, this represents the first example of the direct observation of a copper enolate in the context of a 1,4-addition of an organocopper species to an electron-deficient olefin.[12] Treatment of compound **5** with 1.0 equivalent of KO*t*Bu in [D_8]THF at 30°C gave a clean ^{1}H NMR spectrum consisting of signals that correspond to [Cu(O*t*Bu)(IPr)] and potassium enolate **6** [Eq. (3) and Figure 1c]. The signals assigned to compound **6** matched with the ones that formed on treatment of the isolated compound **3e** with 1.0 equivalent of KO*t*Bu in [D_8]THF, thereby confirming its identity as a potassium enolate of the 1,4-adduct. In addition to these stoichiometric reactions, we also made the following observations: Copper enolate **5** remained intact and

[*] K. Takatsu, Dr. R. Shintani, Prof. Dr. T. Hayashi
Department of Chemistry
Graduate School of Science, Kyoto University
Sakyo, Kyoto 606-8502 (Japan)
Fax: (+81) 75-753-3988
E-mail: shintani@kuchem.kyoto-u.ac.jp
thayashi@kuchem.kyoto-u.ac.jp

[**] Support has been provided in part by a Grant-in-Aid for Young Scientists (B), the Ministry of Education, Culture, Sports, Science, and Technology (Japan), and in part by Mitsubishi Tanabe Pharma Corporation. K.T. thanks the JSPS for a fellowship.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201008196.

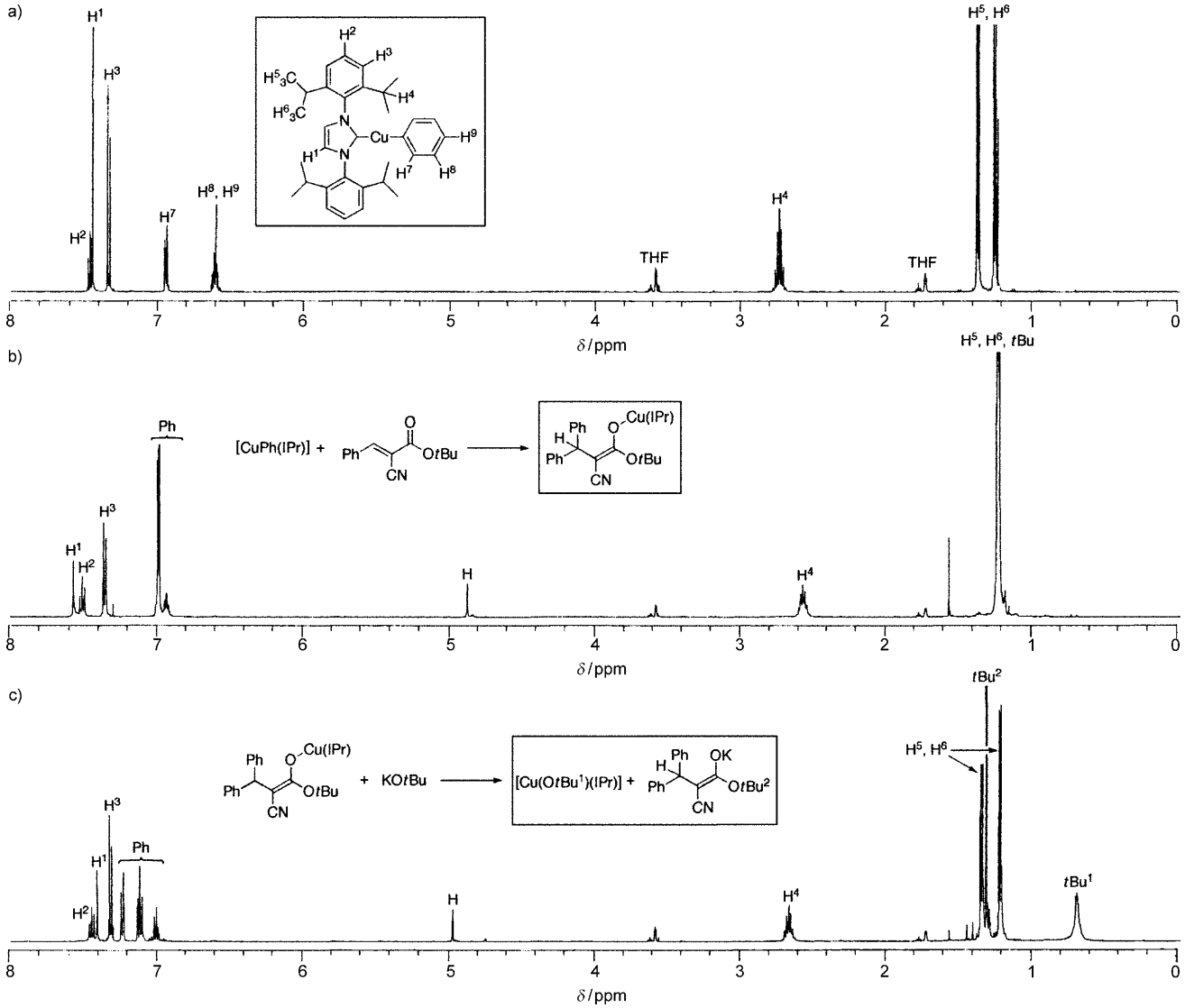
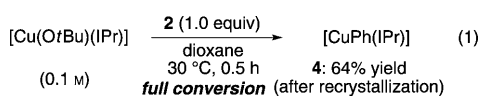
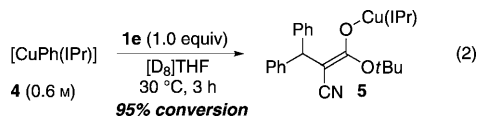
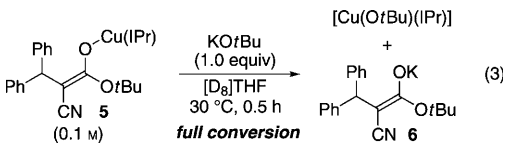


Figure 1. ^{1}H NMR spectra in [D_8]THF of: a) [CuPh(IPr)] (**4**), b) copper enolate **5** obtained from the reaction of **4** with **1e**, and c) [Cu(O*t*Bu)(IPr)] and potassium enolate **6** obtained from the reaction of **5** with KO*t*Bu.

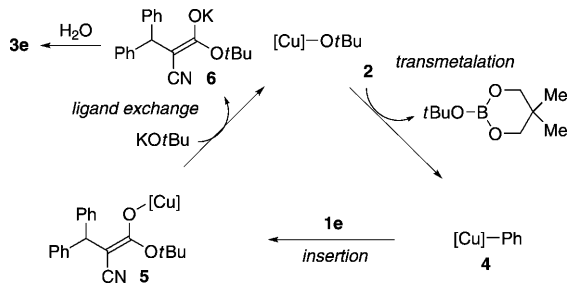
did not undergo direct transmetalation with phenylboronate **2** in [D_8]THF at 30 °C; phenylcopper complex **4** did not show any detectable interactions with KO*t*Bu or phenylboronate **2** in [D_8]THF at 30 °C; and the rate of reaction of **1e** with phenylcopper **4** was unaffected by the addition of KO*t*Bu and/or phenylboronate **2**.







On the basis of these results, a proposed catalytic cycle for the reaction depicted in Table 1, entry 5 is illustrated in Scheme 1.[6d,k] Thus, [Cu(O*t*Bu)(IPr)] undergoes transmetalation with phenylboronate **2** to give phenylcopper species **4**. Insertion of **1e** into **4** then gives copper enolate **5**, which reacts with KO*t*Bu to regenerate [Cu(O*t*Bu)(IPr)] along with potassium enolate **6**. The final product **3e** is obtained from **6** after aqueous workup. This proposed mechanism involving only copper(I) species throughout the cycle is in stark contrast to the reported reaction mechanisms for the copper-catalyzed 1,4-addition of organomagnesium or organozinc reagents to



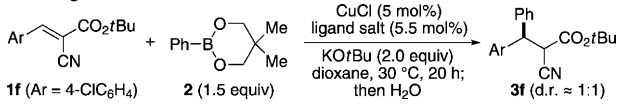
Scheme 1. Proposed catalytic cycle for the copper-catalyzed 1,4-addition of phenylboronate **2** to **1e** ([Cu] = Cu(IPr)).

α,β-unsaturated carbonyl compounds. In these latter cases, the active organocopper(I) species is tightly associated with magnesium or zinc salts to facilitate the oxidative addition of α,β-unsaturated compounds. The resulting copper(III) intermediate then undergoes reductive elimination with formation of a carbon–carbon bond.[13,14]

Having established the viability of the copper-catalyzed 1,4-addition of organoboronates to alkylidene cyanoacetates, we turned our attention to the development of its asymmetric variant by employing chiral N-heterocyclic carbene (NHC) ligands.[15,16] As a starting point, we carried out the reaction of *tert*-butyl 4-chlorobenzylidenecyanoacetate (**1f**) with phenylboronate **2** in the presence of CuCl (5 mol%) and the chiral NHC salt (*S*)-**7a**,[6k,17] which has a *tert*-leucinol-derived tether (5.5 mol%), in dioxane at 30°C. Under these conditions, 1,4-adduct **3f** was obtained in 85% yield, but the enantioselectivity was only moderate (47% *ee*; Table 2, entry 1). Changing the substitutent on the ligand tether from *tert*-butyl to isopropyl ((*S*)-**7b**, 62% *ee*; Table 2, entry 2) or phenyl ((*S*)-**7c**, 65% *ee*; Table 2, entry 3) gave somewhat higher enantioselectivity, and further improvement was observed by using a tether derived from 1-amino-2-indanols ((*S*,*R*)-**7d**, 68% *ee* and (*S*,*S*)-**7e**, 76% *ee*; Table 2, entries 4 and 5, respectively). We subsequently found that changing the 2,6-dimethylphenyl group on the other nitrogen atom of (*S*,*S*)-**7e** for a 9-anthryl group ((*S*,*S*)-**7f**) led to the formation of **3f** with 88% *ee* (Table 2, entry 6), and the use of CuBr instead of CuCl as a catalyst precursor turned out to be optimal (92% *ee*; Table 2, entry 7). The absolute configuration at the β position of **3f** thus obtained was determined to be *R* by X-ray crystallographic analysis after de-esterification.[18]

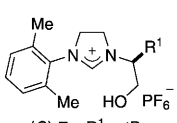
A combination of CuBr and (*S*,*S*)-**7f** resulted in the triethylmethyl ester **8a** giving a slightly higher enantioselectivity than *tert*-butyl ester **1f** (Table 3, entry 1 versus Table 2, entry 7).[19] Furthermore, not only **8a** but also several other aryl-, heteroaryl-, and alkenyl-substituted methylidenecyanoacetates (**8b–h**) can be used in the reaction with phenylboronate to give 1,4-adducts **9** with high enantioselectivity (57–93% yield, 87–94% *ee*; Table 3, entries 1–8). Various aryl groups can be incorporated effectively from the nucleophilic component into benzylidenecyanoacetate **8i** with a similarly high efficiency (81–95% yield, 88–94% *ee*; Table 3, entries 9–13). In addition to these aryl boronates, 1-cyclohexenyl- and methylboronates can also be used, although the *ee* values become somewhat lower (70 and 88% yield, 73 and 77% *ee*; Table 3, entries 14 and 15, respectively). Furthermore, 1,1-diaryl methylcyanoacetates having substituents on both of the

Table 2: Copper-catalyzed asymmetric 1,4-addition of phenylboronate **2** to **1f**: Ligand effect.

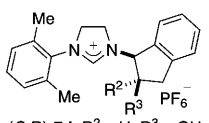


Entry	Ligand salt	Yield [%][a]	*ee* [%][b]
1	(*S*)-**7a**	85	47 (*R*)
2	(*S*)-**7b**	85	62 (*R*)
3	(*S*)-**7c**	84	65 (*R*)
4	(*S*,*R*)-**7d**	81	68 (*R*)
5	(*S*,*S*)-**7e**	86	76 (*R*)
6	(*S*,*S*)-**7f**	82	88 (*R*)
7[c]	(*S*,*S*)-**7f**	86	92 (*R*)

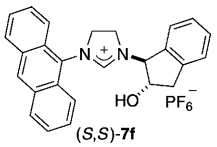
[a] Yield of isolated product. [b] Determined by HPLC on a chiral stationary phase (Chiralpak AD-H column) with hexane/2-propanol = 95:5 after de-esterification. [c] The reaction was conducted with CuBr instead of CuCl.



(*S*)-**7a**: R^1 = *t*Bu
(*S*)-**7b**: R^1 = *i*Pr
(*S*)-**7c**: R^1 = Ph

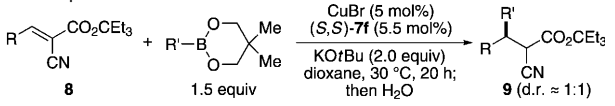


(*S*,*R*)-**7d**: R^2 = H, R^3 = OH
(*S*,*S*)-**7e**: R^2 = OH, R^3 = H



(*S*,*S*)-**7f**

Table 3: Copper-catalyzed asymmetric 1,4-addition of organoboronates to **8**: Scope.



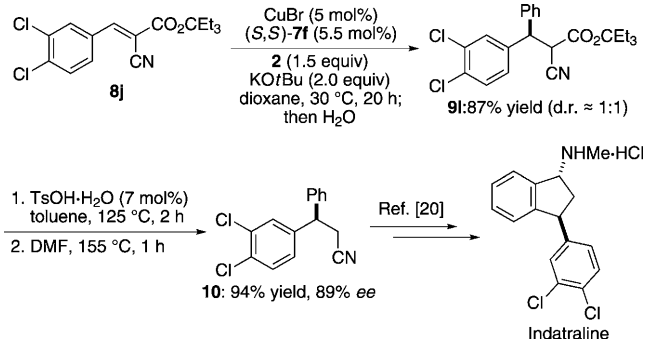
8a: R = 4-ClC$_6$H$_4$
8b: R = 4-NCC$_6$H$_4$
8c: R = 4-MeC$_6$H$_4$
8d: R = 4-MeOC$_6$H$_4$
8e: R = 3-MeC$_6$H$_4$
8f: R = 2-MeC$_6$H$_4$
8g: R = 3-thienyl
8h: R = 1-cyclohexenyl
8i: R = Ph

Entry	**8**	R′	Product	Yield [%][a]	*ee* [%][b]
1	**8a**	Ph	(*R*)-**9a**	93	94
2	**8b**	Ph	(*R*)-**9b**	92	87
3	**8c**	Ph	(*R*)-**9c**	88	91
4	**8d**	Ph	(*R*)-**9d**	82	92
5	**8e**	Ph	(*R*)-**9e**	87	88
6	**8f**	Ph	(*R*)-**9f**	79	91
7	**8g**	Ph	(*R*)-**9g**	78	94
8[c]	**8h**	Ph	(*S*)-**9h**	57	90
9	**8i**	4-ClC$_6$H$_4$	(*S*)-**9a**	84	88
10	**8i**	4-MeC$_6$H$_4$	(*S*)-**9c**	87	94
11	**8i**	4-MeOC$_6$H$_4$	(*S*)-**9d**	81	92
12	**8i**	3-MeC$_6$H$_4$	(*S*)-**9e**	87	91
13	**8i**	2-naphthyl	(*S*)-**9i**	95	89
14	**8i**	1-cyclohexenyl	(*R*)-**9h**	88	73
15[c]	**8i**	Me	(*S*)-**9j**	70[d]	77
16	**8a**	4-MeC$_6$H$_4$	(*R*)-**9k**	91	95

[a] Yield of isolated product. [b] Determined by HPLC on a chiral stationary phase with hexane/2-propanol after de-esterification. [c] The reaction was conducted with 3.0 equiv of the organoboronate and 3.0 equiv of KO*t*Bu in the presence of 10 mol% catalyst. [d] Determined by ^{1}H NMR spectroscopy after chromatographic purification on silica gel.

aryl groups can be prepared in a highly enantioselective fashion (91% yield, 95% *ee*; Table 3, entry 16).

The utility of the present asymmetric catalysis is highlighted in the stereoselective and straightforward synthesis of enantioenriched 3-(3,4-dichlorophenyl)-3-phenylpropionitrile (**10**; Scheme 2), which is a key intermediate in the synthesis of the potent psychoactive (+)-indatraline.[20,21]



Scheme 2. Asymmetric synthesis of compound **10**, an intermediate for (+)-indatraline. Ts = toluene-4-sulfonyl.

In summary, we have developed a 1,4-addition of organoboronates to alkylidene cyanoacetates catalyzed by a copper/N-heterocyclic carbene under mild conditions. The catalytic cycle consisting of transmetalation/insertion/ligand exchange has been proposed on the basis of a series of stoichiometric reactions. Furthermore, an effective asymmetric variant has also been achieved through the use of a newly synthesized chiral N-heterocyclic carbene ligand.

Received: December 27, 2010
Revised: March 29, 2011
Published online: April 28, 2011

Keywords: 1,4-addition · asymmetric catalysis · copper · N-heterocyclic carbenes · organoboronates

[1] For reviews, see a) S.-Y. Wang, T.-P. Loh, *Chem. Commun.* **2010**, *46*, 8694; b) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev.* **2008**, *108*, 2824; c) F. López, A. J. Minnaard, B. L. Feringa, *Acc. Chem. Res.* **2007**, *40*, 179; d) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796; e) J. Christoffers, G. Koripelly, A. Rösiak, M. Rossle, *Synthesis* **2007**, 1279; f) P. von Zezschwitz, *Synthesis* **2008**, 1809.

[2] For recent examples, see a) P. H. Bos, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2008**, *10*, 4219; b) T. den Hartog, A. Rudolph, B. Maciá, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2010**, *132*, 14349; c) J. C. H. Lee, D. G. Hall, *J. Am. Chem. Soc.* **2010**, *132*, 5544.

[3] For recent examples, see a) A. Wilsily, T. Lou, E. Fillion, *Synthesis* **2009**, 2066; b) P. H. Bos, B. Maciá, M. Á. Fernández-Ibáñez, A. J. Minnaard, B. L. Feringa, *Org. Biomol. Chem.* **2010**, *8*, 47; c) L. Palais, L. Babel, A. Quintard, S. Belot, A. Alexakis, *Org. Lett.* **2010**, *12*, 1988; d) K. Endo, M. Ogawa, T. Shibata, *Angew. Chem.* **2010**, *122*, 2460; *Angew. Chem. Int. Ed.* **2010**, *49*, 2410.

[4] For recent examples, see a) X. Tang, A. J. Blake, W. Lewis, S. Woodward, *Tetrahedron: Asymmetry* **2009**, *20*, 1881; b) D. Müller, C. Hawner, M. Tissot, L. Palais, A. Alexakis, *Synlett* **2010**, 1694; c) M. Tissot, D. Müller, S. Belot, A. Alexakis, *Org. Lett.* **2010**, *12*, 2770.

[5] K. Lee, A. H. Hoveyda, *J. Org. Chem.* **2009**, *74*, 4455.

[6] For examples of copper-catalyzed carbon–carbon bond-forming reactions with organoboronic acid derivatives, see a) R. Wada, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 8910; b) R. Wada, T. Shibuguchi, S. Makino, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 7687; c) D. Tomita, M. Kanai, M. Shibasaki, *Chem. Asian J.* **2006**, *1*, 161; d) T. Ohishi, M. Nishiura, Z. Hou, *Angew. Chem.* **2008**, *120*, 5876; *Angew. Chem. Int. Ed.* **2008**, *47*, 5792; e) J. Takaya, S. Tadami, K. Ukai, N. Iwasawa, *Org. Lett.* **2008**, *10*, 2697; f) Y. Yamamoto, N. Kirai, Y. Harada, *Chem. Commun.* **2008**, 2010; g) Y. Yamamoto, N. Kirai, *Org. Lett.* **2008**, *10*, 5513; h) H. Zheng, Q. Zhang, J. Chen, M. Liu, S. Cheng, J. Ding, H. Wu, W. Su, *J. Org. Chem.* **2009**, *74*, 943; i) H. Ohmiya, U. Yokobori, Y. Makida, M. Sawamura, *J. Am. Chem. Soc.* **2010**, *132*, 2895; j) A. M. Whittaker, R. P. Rucker, G. Lalic, *Org. Lett.* **2010**, *12*, 3216; k) R. Shintani, K. Takatsu, T. Hayashi, *Chem. Commun.* **2010**, *46*, 6822.

[7] For examples of copper-catalyzed 1,4-addition of diboron compounds, see a) H. Ito, H. Yamanaka, J. Tateiwa, A. Hosomi, *Tetrahedron Lett.* **2000**, *41*, 6821; b) K. Takahashi, T. Ishiyama, N. Miyaura, *Chem. Lett.* **2000**, *29*, 982; c) K. Takahashi, T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2001**, *625*, 47; d) S. Mun, J.-E. Lee, J. Yun, *Org. Lett.* **2006**, *8*, 4887; e) J.-E. Lee, J. Yun, *Angew. Chem.* **2008**, *120*, 151; *Angew. Chem. Int. Ed.* **2008**, *47*, 145; f) X. Feng, J. Yun, *Chem. Commun.* **2009**, 6577; g) I.-H. Chen, L. Yin, W. Itano, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 11664; h) J. M. O'Brien, K. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 10630.

[8] For examples of copper-catalyzed 1,4-addition of silylboronates, see K. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 2898.

[9] Rhodium-catalyzed asymmetric 1,4-addition of aryl boronic acids to alkylidene cyanoacetates with up to 99% *ee* has been reported: S. Sörgel, N. Tokunaga, K. Sasaki, K. Okamoto, T. Hayashi, *Org. Lett.* **2008**, *10*, 589.

[10] N. P. Mankad, D. S. Laitar, J. P. Sadighi, *Organometallics* **2004**, *23*, 3369.

[11] Analytical data for **5**: ^{1}H NMR ([D$_8$]THF): $\delta = 7.57$ (s, 2H), 7.52 (t, $J = 7.8$ Hz, 2H), 7.36 (d, $J = 7.8$ Hz, 4H), 7.01–6.96 (m, 8H), 6.96–6.91 (m, 2H), 4.87 (s, 1H), 2.57 (sept, $J = 6.8$ Hz, 4H), 1.26–1.19 ppm (m, 33H); ^{13}C NMR ([D$_8$]THF): $\delta = 171.6$, 148.0, 146.5, 135.6, 131.3, 129.4, 129.0, 128.0, 125.3, 125.2, 125.0, 75.2, 51.3, 47.8, 29.6, 29.3, 25.2, 24.0 ppm; HRMS (ESI-TOF) calcd for $C_{47}H_{57}CuN_3O_2$ ($M + H^+$): 758.3741, found: 758.3739.

[12] For examples of NMR spectroscopic studies on 1,4-addition of organocuprates, see a) B. Christenson, T. Olsson, C. Ullenius, *Tetrahedron* **1989**, *45*, 523; b) S. H. Bertz, R. A. Smith, *J. Am. Chem. Soc.* **1989**, *111*, 8276; c) S. H. Bertz, M. K. Carlin, D. A. Deadwyler, M. Murphy, C. A. Ogle, P. H. A. Seagle, *J. Am. Chem. Soc.* **2002**, *124*, 13650; see also: d) K. Nilsson, C. Ullenius, N. Krause, *J. Am. Chem. Soc.* **1996**, *118*, 4194.

[13] a) S. R. Harutyunyan, F. Lopéz, W. R. Browne, A. Correa, D. Peña, R. Badorrey, A. Meetsma, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2006**, *128*, 9103; b) A. Alexakis, C. Benhaim, S. Rosset, M. Humam, *J. Am. Chem. Soc.* **2002**, *124*, 5262; see also: c) K. Nakano, Y. Bessho, M. Kitamura, *Chem. Lett.* **2003**, *32*, 224.

[14] For relevant theoretical studies, see a) E. Nakamura, S. Mori, K. Morokuma, *J. Am. Chem. Soc.* **1997**, *119*, 4900; b) E. Nakamura, M. Yamanaka, S. Mori, *J. Am. Chem. Soc.* **2000**, *122*, 1826; c) M. Yamanaka, E. Nakamura, *Organometallics* **2001**, *20*, 5675; d) M. Yamanaka, E. Nakamura, *J. Am. Chem. Soc.* **2005**, *127*, 4697.

[15] For reviews, see a) J. Wencel, M. Mauduit, H. Hénon, S. Kehrli, A. Alexakis, *Aldrichimica Acta* **2009**, *42*, 43; b) L. H. Gade, S. Bellemin-Laponnaz, *Coord. Chem. Rev.* **2007**, *251*, 718; c) V. César, S. Bellemin-Laponnaz, L. H. Gade, *Chem. Soc. Rev.* **2004**, *33*, 619; d) M. Perry, K. Burgess, *Tetrahedron: Asymmetry* **2003**, *14*, 951.

[16] For recent progress, see a) R. E. Giudici, A. H. Hoveyda, *J. Am. Chem. Soc.* **2007**, *129*, 3824; b) T. L. May, M. K. Brown, A. H. Hoveyda, *Angew. Chem.* **2008**, *120*, 7468; *Angew. Chem. Int. Ed.* **2008**, *47*, 7358; c) Y. Lee, H. Jang, A. H. Hoveyda, *J. Am. Chem. Soc.* **2009**, *131*, 18234; d) K. Akiyama, F. Gao, A. H. Hoveyda, *Angew. Chem.* **2010**, *122*, 429; *Angew. Chem. Int. Ed.* **2010**, *49*, 419; e) M. R. Chaulagain, G. J. Sormunen, J. Montgomery, *J. Am. Chem. Soc.* **2007**, *129*, 9568; f) Y.-X. Jia, J. M. Hillgren, E. L. Watson, S. P. Marsden, E. P. Kündig, *Chem. Commun.* **2008**, 4040; g) H. Hénon, M. Mauduit, A. Alexakis, *Angew. Chem.* **2008**, *120*, 9262; *Angew. Chem. Int. Ed.* **2008**, *47*, 9122; h) T. Uchida, T. Katsuki, *Tetrahedron Lett.* **2009**, *50*, 4741; i) K. B. Selim, Y. Matsumoto, K. Yamada, K. Tomioka, *Angew. Chem.* **2009**, *121*, 8889; *Angew. Chem. Int. Ed.* **2009**, *48*, 8733; j) N. Shibata, M. Okamoto, Y. Yamamoto, S. Sakaguchi, *J. Org. Chem.* **2010**, *75*, 5707.

[17] For precedents of this family of chiral NHCs, see a) H. Clavier, L. Coutable, J.-C. Guillemin, M. Mauduit, *Tetrahedron: Asymmetry* **2005**, *16*, 921; b) H. Clavier, L. Coutable, L. Toupet, J.-C. Guillemin, M. Mauduit, *J. Organomet. Chem.* **2005**, *690*, 5237; c) D. Martin, S. Kehrli, M. d'Augustin, H. Clavier, M. Mauduit, A. Alexakis, *J. Am. Chem. Soc.* **2006**, *128*, 8416; d) S. Kehrli, D. Martin, D. Rix, M. Mauduit, A. Alexakis, *Chem. Eur. J.* **2010**, *16*, 9890; See also: e) P. L. Arnold, M. Rodden, K. M. Davis, A. C. Scarisbrick, A. J. Blake, C. Wilson, *Chem. Commun.* **2004**, 1612.

[18] CCDC 804933 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] a) The use of a substrate having a smaller ester group such as a methyl ester gives the product with lower enantioselectivity (e.g., 78% yield, 76% *ee* for the reaction of the methyl ester variant of **8a** with phenylboronate **2**); b) the use of organoboronic acid pinacol esters instead of neopentylglycol esters results in lower enantioselectivity by ca. 10%; c) essentially the same result is obtained by conducting the reaction in the presence of *t*BuOH (1.0 equiv) or by using NaO*t*Bu as the base; d) significantly lower reactivity is observed by using KOMe as the base (e.g., 45% yield, 92% *ee* for the reaction of **8a** with phenylboronate **2**), presumably because of the poor solubility of KOMe in dioxane.

[20] H. M. Davies, T. M. Gregg, *Tetrahedron Lett.* **2002**, *43*, 4951.

[21] a) K. P. Bogeso, A. V. Christensen, J. Hyttel, T. Liljefors, *J. Med. Chem.* **1985**, *28*, 1817; b) J. Hyttel, J. J. Larsen, *J. Neurochem.* **1985**, *44*, 1615.

