Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 2106–2110
Tetrahedron Letters

A first high enantiocontrol of an asymmetric tertiary carbon center attached with a fluoroalkyl group via Rh(I)-catalyzed conjugate addition reaction

Tsutomu Konno *, Tomoo Tanaka, Tomotsugu Miyabe, Atsunori Morigaki, Takashi Ishihara

Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan

Received 14 January 2008; accepted 29 January 2008
Available online 1 February 2008

Abstract

Treatment of fluoroalkylated electron-deficient olefins with various boronic acids in the presence of a catalytic amount of Rh(I) coordinated with (*S*)-BINAP in toluene/H_2O at the reflux temperature for 3 h gave the corresponding conjugate addition products with high enantioselectivity in high yields.

Keywords: Fluorine-containing compounds; Asymmetric tertiary carbon; Enantioselective synthesis; Rhodium; Conjugate addition

Introduction of a fluoroalkyl group into an asymmetric carbon center constitutes a major interest in organofluorine chemistry owing to the recent outstanding applications of optically active fluoroalkylated compounds in the medicinal, pharmaceutical, and agricultural fields.[1] Out of such compounds, molecules having an asymmetric tertiary carbon center without any heteroatom substituent (**1**, Fig. 1) to date have been one of the most challenging synthetic targets due to their synthetic difficulty as well as their unique biological activities.[2]

There have been some reports on various *diastereoselective* synthetic methods for the preparation of optically active **1** thus far, for example, asymmetric Michael addition[3] or aldol reaction[4] by using chiral oxazolidinone derivatives, asymmetric 2,3-Wittig[5] or Ireland–Claisen[6] rearrangements, S_N2' reaction[7] by utilizing the chirality transfer system, the synthesis of **1** by using various sugars as a chiral template;[8] etc.[9] However, little attention has been paid to an *enantioselective* synthesis of **1** by using chiral transition-metal catalyst.[10] Herein, we wish to describe

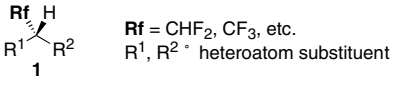
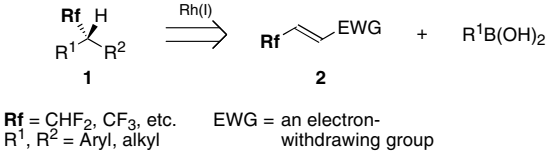


Fig. 1. Chiral fluoroalkylated compounds.

a first highly enantioselective synthetic approach to an asymmetric tertiary carbon framework **1** having a fluoroalkyl group via Rh(I)-catalyzed conjugate addition reaction of various fluoroalkylated electron-deficient olefins **2** with boronic acids (Scheme 1).

Our initial studies were performed using β-trifluoromethylated-α,β-unsaturated ketone **2a**, prepared readily according to the reported procedure,[11] and phenylboronic

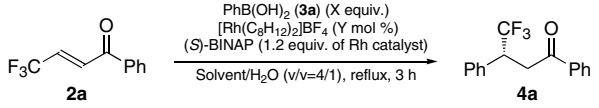


Scheme 1. The conjugate addition of fluoroalkylated electron-deficient olefins.

* Corresponding author. Tel.: +81 75 724 7517; fax: +81 75 724 7580.
E-mail address: konno@chem.kit.ac.jp (T. Konno).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.01.122

Table 1
Investigation of the reaction conditions



Entry	X (equiv)	Y (mol %)	Solvent	Yield[a] of **4a**/%	Enantiomeric excess[b] (% ee)
1	1.2	0.5	Toluene	60	55
2	2.4	0.5	Toluene	91	72
3	2.4	1.0	Toluene	95	74
4	2.4	5.0	Toluene	96	85
5	1.2	5.0	Toluene	96 (90)	90
6	1.2	5.0	Hexane	0	—
7	1.2	5.0	THF	23	34
8[c]	1.2	5.0	DMF	32	2
9	1.2	5.0	CH_3OH	9	4
10	1.2	5.0	1,4-Dioxane	78	23
11	1.2	5.0	CH_3NO_2	22	36

[a] Determined by ^{19}F NMR. Value in parentheses is of isolated yield.
[b] Determined by HPLC (Chiralpac AD).
[c] Carried out at 100 °C.

acid (**3a**) as shown in Table 1. Thus, treatment of 1.0 equiv of **2a** with 1.2 equiv of **3a** in the presence of 0.5 mol % of $[Rh(C_8H_{12})_2]BF_4$ and 0.6 mol % of (*S*)-BINAP in toluene/H_2O (v/v = 4/1) at the reflux temperature for 3 h gave the corresponding conjugate addition product **4a** with 55% enantiomeric excess in 60% yield (entry 1). In this case, the product with *R* absolute configuration was afforded preferentially (vide infra). When 2.4 equiv of **3a** was used, the chemical yield and the enantiomeric excess were both increased (entry 2). Although the employment of 1 mol % of rhodium catalyst did not cause any influence of the reaction (entry 3), 5 mol % of the catalyst led to a significant improvement of the optical purity, the desired adduct with 85% enantiomeric excess being obtained in 96% yield (entry 4). Eventually, the best yield was obtained when the reaction was carried out by using 1.2 equiv of phenylboronic acid in the presence of 5 mol % of $[Rh(C_8H_{12})_2]BF_4$ and 6 mol % of (*S*)-BINAP (entry 5). In this case, the product with 90% enantiomeric excess was obtained in 96% yield.

As shown in entries 6–11, we also examined the solvent effect on the conjugate addition. As a result, hexane, THF, DMF, CH_3OH, and CH_3NO_2 were not the solvent of choice, the corresponding adducts being obtained in very low yields (0–32%). Quite interestingly, 1,4-dioxane, which is generally used in the Rh(I)-catalyzed conjugate addition of nonfluorinated electron-deficient olefins, resulted in the significant decrease of the optical purity of **4a** (23% ee), though the yield was high (entry 10).

With the optimum reaction conditions (Table 1, entry 5), we next investigated the conjugate addition of various boronic acids. The results are summarized in Table 2.

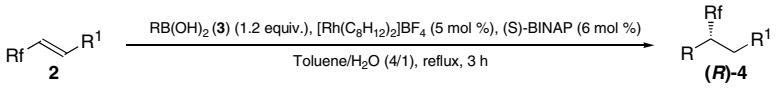
As shown in entries 2–4 and 7–9, various types of arylboronic acids **3b–d**, **3g–i** having an electron-donating (CH_3, CH_3O) or an electron-withdrawing group (Cl, F, CH_3CO, EtO_2C) on the benzene ring could participate nicely in the conjugate addition to give the corresponding adducts **4b–d**, **4g–i** in excellent yields (84–96% yield) with high enantioselectivity (90–94% ee). However, the use of *ortho*-substituted arylboronic acid, such as *o*-chlorophenyl- (**3f**) or 1-naphthylboronic acid (**3k**), resulted in a significant decrease of the reaction efficacy (3% or 51% yield in entry 6 or 11), while meta-substitution of the benzene ring of $RB(OH)_2$ did not influence on the reaction at all (entry 5). 2-Thienylboronic acid (**3j**) was also found to be a good Michael donor in the reaction (entry 10), though the yield decreased slightly. On the other hand, alkenylboronic acids **3l**, **3m** led to a significant decrease of the enantioselectivity or the chemical yield (entries 12 and 13).

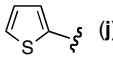
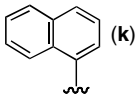
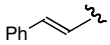
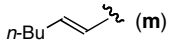
We also examined the conjugate addition reaction using various types of fluorine-containing electron-deficient olefins. As shown in entries 14–16, the reaction of various electron-deficient olefins, such as α,β-unsaturated ester **2b** or amide **2c**, nitroalkene **2d**, proceeded smoothly to give the corresponding adducts **4l–n** in good yields. Especially, the high enantioselectivity (92% ee) was observed in the case of the amide (entry 15). Unfortunately, the vinyl sulfone **2e** and the vinylphosphonate **2f** did not give the satisfactory results, the product being afforded in very low yields as well as in a very low enantioselective manner (entries 17 and 18). Changing the fluoroalkyl group from a CF_3 group to a CHF_2 group also caused a slight decrease of the enantiomeric excess. The use of (*Z*)-substrate **2h** afforded the Michael adduct **4a** with the same absolute configuration as in the reaction of (*E*)-substrate **2a** (entry 1 vs entry 20).

In order to reveal why the same product, (*R*)-stereoisomer **4a**, was obtained preferentially in both (*E*)- and (*Z*)-substrates, we first treated (***Z***)-**2a** only with 5 mol % of $[Rh(C_8H_{12})_2]BF_4$ in the absence of arylboronic acid in toluene/H_2O (v/v = 4/1) at the reflux temperature for 3 h (Scheme 2). In this case, ca. 30% of (***E***)-**2a** was obtained together with ca. 70% of the starting material. On the other hand, treatment of (***Z***)-**2a** only with 6 mol % of (*S*)-BINAP gave (***E***)-**2a** in only ca. 3% yield. Very interestingly, the use of $[Rh(C_8H_{12})_2]BF_4$ and (*S*)-BINAP without arylboronic acid led to complete consumption of (***Z***)-**2a**, (***E***)-**2a** being obtained quantitatively. These experimental results indicate that rhodium catalyst coordinated with (*S*)-BINAP as a ligand catalyzes the isomerization much more rapidly than the conjugate addition reaction.

To evaluate the influence of a fluoroalkyl group upon the reaction, we also examined the reaction of nonfluorinated counterparts **2i–o** (Table 2, entries 21–27). As shown in entries 21–23, increasing the bulkiness of an Rf group caused a decrease of the yield as well as the enantiomeric excess. It should be emphasized that the substrate **2j** having an isopropyl group at β position, which is believed to be similar to a CF_3 group in bulkiness,[12] gave the Michael adduct **4r** with only 77% ee (entry 22). As shown in entries 24–27, introduction of an electron-withdrawing group on the benzene ring in Rf resulted in an increase of an

Table 2
Rhodium-catalyzed conjugate addition reactions of various arylboronic acids into various electron-deficient olefins



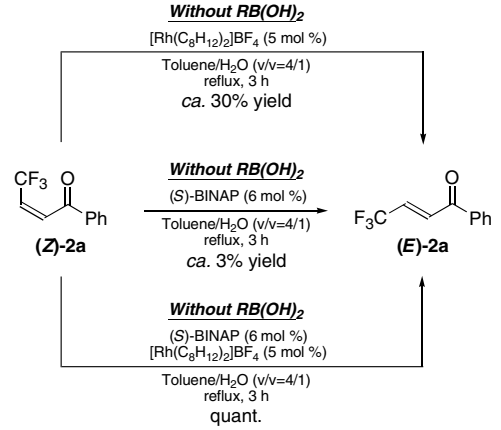
Entry	Rf	R^1	Product	R	Product	Yield[a]/% of **4**	Enantiomeric excess[b] (%)
1	CF_3	COPh	**2a**	Ph(**a**)	**4a**	96 (90)	90
2	CF_3	COPh	**2a**	*p*-$CH_3C_6H_4$ (**b**)	**4b**	95 (91)	92
3	CF_3	COPh	**2a**	*p*-$CH_3OC_6H_4$ (**c**)	**4c**	96 (89)	92
4	CF_3	COPh	**2a**	*p*-ClC_6H_4 (**d**)	**4d**	95 (94)	94
5	CF_3	COPh	**2a**	*m*-ClC_6H_4 (**e**)	**4e**	89 (81)	91
6	CF_3	COPh	**2a**	*o*-ClC_6H_4 (**f**)	—	3	N.D.[c]
7	CF_3	COPh	**2a**	*p*-FC_6H_4 (**g**)	**4f**	84 (80)	90
8	CF_3	COPh	**2a**	*p*-$CH_3(O)CC_6H_4$ (**h**)	**4g**	96 (95)	93
9	CF_3	COPh	**2a**	*p*-$EtO_2CC_6H_4$ (**i**)	**4h**	95 (80)	92
10	CF_3	COPh	**2a**	 (**j**)	**4i**	79 (64)	90
11	CF_3	COPh	**2a**	 (**k**)	**4j**	51	70
12	CF_3	COPh	**2a**	 (**l**)	**4k**	78 (70)	40
13	CF_3	COPh	**2a**	 (**m**)	—	11	N.D.[c]
14	CF_3	CO_2Et	**2b**	Ph(**a**)	**4l**	60	N.D.[c]
15	CF_3	$CONMe_2$	**2c**	Ph(**a**)	**4m**	53 (46)	92
16	CF_3	NO_2	**2d**	Ph(**a**)	**4n**	60	N.D.[c]
17	CF_3	SO_2Ph	**2e**	Ph(**a**)	**4o**	30 (27)	9
18	CF_3	$P(O)(OEt)_2$	**2f**	Ph(**a**)	—	13	N.D.[c]
19	CHF_2	COPh	**2g**	Ph(**a**)	**4p**	96 (92)	74
20[d]	CF_3	COPh	**2h**	Ph(**a**)	**4a**	91	90
21	CH_3	COPh	**2i**	Ph(**a**)	**4q**	75[e]	92
22	*i*-Pr	COPh	**2j**	Ph(**a**)	**4r**	57[e]	77
23	*t*-Bu	COPh	**2k**	Ph(**a**)	—	Trace	—
24	*p*-$CH_3C_6H_4$	COPh	**2l**	Ph(**a**)	**4s**	30[e]	67
25	*p*-$CH_3OC_6H_4$	COPh	**2m**	Ph(**a**)	**4t**	68[e]	65
26	*p*-$CF_3C_6H_4$	COPh	**2n**	Ph(**a**)	**4u**	84	75
27	*p*-NCC_6H_4	COPh	**2o**	Ph(**a**)	**4v**	40[e]	89

[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yields.
[b] Determined by HPLC (Chiralpac AD-H).
[c] Not determined.
[d] (*Z*)-Substrate was used instead of (*E*)-substrate.
[e] Determined by ^1H NMR.

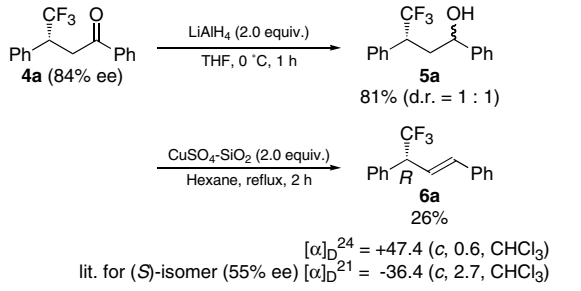
enantiomeric excess, while aromatic substituents having an electron-donating group on the benzene ring in Rf led to a decrease of an enantiomeric excess. These results indicate that high enantioselectivity in **2a**,**c** in spite of the bulkiness of a CF_3 group may be ascribed in part to a strongly electron-withdrawing effect of a CF_3 group.

The stereochemical assignment of **4** was made as follows (Scheme 3). Thus, treatment of **4a** with 2.0 equiv of $LiAlH_4$ in THF at 0 °C for 1 h gave a 1:1 diastereomeric mixture of the corresponding alcohol **5a** in 81% yield, which were subjected to 2.0 equiv of $CuSO_4$–SiO_2 in hexane at the reflux temperature for 2 h,[13] giving the known compound **6a**. The comparison of the observed optical rotation of **6a** with its literature value made it possible to determine the absolute configuration of **4a** as *R*.[9b] Additionally, the stereochemical determination of the major stereoisomer of **4a**, **b**, **h**, **u** was made on the basis of the single-crystal X-ray analysis, and it was found that all compounds had *R* absolute configuration.

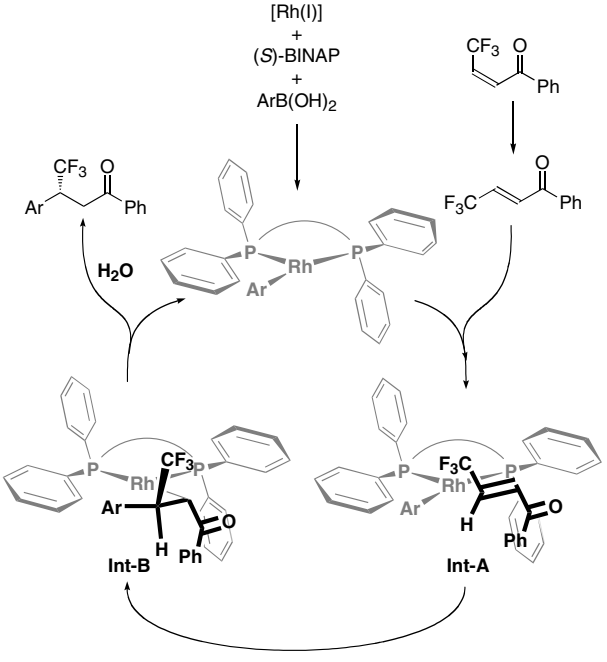
The proposed mechanism for the present reaction is outlined in Scheme 4.[14] Thus, (*E*)-substrate (or which produced via isomerization of *Z*-isomer) may come close to arylrhodium species coordinated with (*S*)-BINAP (**Int-A**), avoiding the phenyl group on phosphorus atom. Then, *si*



Scheme 2. The reaction of *Z*-isomer in the absence of arylboronic acid.



Scheme 3. Determination of the absolute configuration of **4a**.



Scheme 4. The reaction mechanism.

face of the alkene may coordinate with arylrhodium species, followed by the attack of the aryl group, affording the corresponding rhodium enolate (**Int-B**). Finally, the enolate may react with H_2O to give the corresponding Michael adduct, and the rhodium species coordinated with (*S*)-BINAP may be regenerated.

In summary, we have demonstrated the rhodium-catalyzed conjugate addition reaction of various arylboronic acids into various fluorine-containing electron-deficient olefins. As a result, the reaction of β-fluoroalkylated-α,β-unsaturated ketones and amide with various arylboronic acids led to a first example of the highly *enantioselective* construction of an asymmetric tertiary carbon center attached with a fluoroalkyl group. Further studies on the rhodium-catalyzed conjugate addition reactions are now under way in our laboratory.

Acknowledgement

We greatly acknowledge TOSOH F-TECH, INC. for supplying trifluoroacetaldehyde ethyl hemiacetal for the preparation of **2a** and ethyl 4,4,4-trifluorocrotonate.

References and notes

1. (a) Young, S. D.; Britcher, S. F.; Tran, L. O.; Linda, L. S.; Lumma, W. C.; Lyle, T. A.; Hyff, J. R.; Anderson, P. S.; Olsen, D. B.; Carrol, S. S.; Pettibone, Z. D.; Obrien, J. A.; Ball, R. G.; Balani, S. K.; Lin, J. H.; Chen, I. W.; Schleif, W. A.; Sardana, V. V.; Long, W. J.; Brynes, V. W.; Emini, E. A. *Antimicrob. Agents Chemother.* **1995**, *39*, 2602–2605; (b) Pierce, M. E.; Parsons, R. L., Jr.; Radesca, L. A.; Lo, Y. S.; Silverman, S.; Moore, J. R.; Islam, Q.; Choudhury, A.; Fortunak, J. M. D.; Nguyen, D.; Luo, C.; Mogan, S. J.; Davis, W. P.; Confalone, P. N.; Chen, C.; Tillyer, R. D.; Frey, L.; Tan, L.; Xu, F.; Zhao, D.; Thompson, A. S.; Corley, E. G.; Grabowski, E. J. J.; Reamer, R.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 8536–8543; (c) Sculptoreanu, A.; Yoshimura, N.; de Grout, W. C. *J. Pharmacol. Exp. Ther.* **2004**, *310*, 159–168.
2. (a) Richardson, T. I.; Dodge, J. A.; Durst, G. L.; Pfeifer, L. A.; Shah, J.; Wang, Y.; Durbin, J. D.; Krishnan, V.; Norman, B. H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4824–4828; (b) Peleg, S.; Petersen, K. S.; Suh, B. C.; Dolan, P.; Agoston, E. S.; Kensler, T. W.; Posner, G. H. *J. Med. Chem.* **2006**, *49*, 7513–7517; (c) Jeannot, F.; Gosselin, G.; Standring, D.; Bryant, M.; Sommadossi, J.-P.; Loi, A. G.; Colla, P. L.; Mathé, C. *Bioorg. Med. Chem.* **2002**, *10*, 3153–3161; (d) Pu, Y. M.; Torok, D. S.; Ziffer, H.; Pan, X.-Q.; Meshnick, S. R. *J. Med. Chem.* **1995**, *38*, 4120–4124.
3. (a) Yamazaki, T.; Ishikawa, N.; Iwatsubo, H.; Kitazume, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1340–1342; (b) Yamazaki, T.; Haga, J.; Kitazume, T. *Chem. Lett.* **1991**, 2175–2178; (c) Shinohara, N.; Haga, J.; Yamazaki, T.; Kitazume, T.; Nakamura, S. *J. Org. Chem.* **1995**, *60*, 4363–4374; (d) Konno, T.; Yamazaki, T.; Kitazume, T. *Tetrahedron* **1996**, *52*, 199–208.
4. (a) Shimada, T.; Yoshioka, M.; Konno, T.; Ishihara, T. *Org. Lett.* **2006**, *8*, 1129–1131; (b) Shimada, T.; Yoshioka, M.; Konno, T.; Ishihara, T. *Chem. Commun.* **2006**, 3628–3630.
5. (a) Konno, T.; Umetani, H.; Kitazume, T. *J. Org. Chem.* **1997**, *62*, 137–150; (b) Konno, T. *J. Synth. Org. Chem. Jpn.* **2005**, *63*, 26–39.
6. (a) Konno, T.; Daitoh, T.; Ishihara, T.; Yamanaka, H. *Tetrahedron: Asymmetry* **2001**, *12*, 2743–2748; (b) Konno, T.; Ishihara, T.; Yamanaka, H. *Tetrahedron Lett.* **2000**, *41*, 8472–8476; (c) Konno, T.; Nakano, H.; Kitazume, T. *J. Fluorine Chem.* **1997**, *86*, 81–87; (d) Konno, T.; Kitazume, T. *Tetrahedron: Asymmetry* **1997**, *8*, 223–230; (e) Konno, T.; Kitazume, T. *Chem. Commun.* **1996**, 2227–2228.
7. (a) Yamazaki, T.; Umetani, H.; Kitazume, T. *Tetrahedron Lett.* **1997**, *38*, 6705–6708; (b) Yamazaki, T.; Umetani, H.; Kitazume, T. *Isr. J. Chem.* **1999**, *39*, 193–205; (c) Kimura, M.; Yamazaki, T.; Kitazume, T.; Kubota, T. *Org. Lett.* **2004**, *6*, 4651–4654.

8. (a) Hiraoka, S.; Yamazaki, T.; Kitazume, T. *Chem. Commun.* **1997**, 1497–1498; (b) Hiraoka, S.; Yamazaki, T.; Kitazume, T. *Synlett* **1997**, 669–670; (c) Yamazaki, T.; Hiraoka, S.; Kitazume, T. *Tetrahedron: Asymmetry* **1997**, 1157–1160; (d) Hiraoka, S.; Yamazaki, T.; Kitazume, T. *Heterocycles* **1998**, *47*, 129–132.
9. (a) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 961–974; (b) Konno, T.; Takehana, T.; Mishima, M.; Ishihara, T. *J. Org. Chem.* **2006**, *71*, 3545–3550.
10. Only one example of the enantioselective synthesis of **1** by using chiral transition metal catalyst has been reported, but the enantioselectivity was not so high and depends significantly on the structure of the substrates. See: Iseki, K.; Kuroki, Y.; Nagai, T.; Kobayashi, Y. *J. Fluorine Chem.* **1994**, *69*, 5–6.
11. Funabiki, K.; Matsunaga, K.; Nojiri, M.; Hashimoto, W.; Yamamoto, H.; Shibata, K.; Matsui, M. *J. Org. Chem.* **2003**, *68*, 2853–2860.
12. Bott, G.; Field, F. G.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618–5626.
13. (a) Nishiguchi, T.; Machida, N.; Yamamoto, E. *Tetrahedron Lett.* **1987**, *28*, 4565–4568; (b) Nishiguchi, T.; Kamio, C. *J. Chem. Soc., Perkin Trans. 1* **1989**, 707–710.
14. The similar mechanism has been proposed. See: (a) Takaya, Y.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **1998**, *120*, 5579–5580; (b) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951–5955; (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844; (d) Hayashi, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13–21.