ORGANIC LETTERS

2010
Vol. 12, No. 13
3054−3057

Development of Chiral Terminal-Alkene−Phosphine Hybrid Ligands for Palladium-Catalyzed Asymmetric Allylic Substitutions

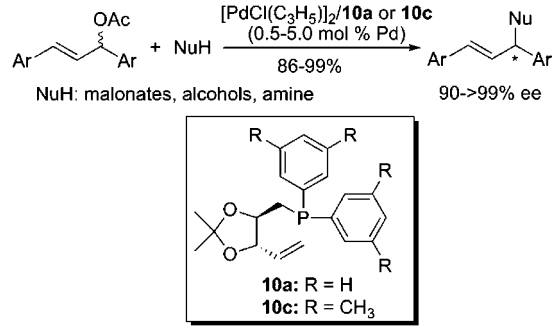
Zhaoqun Liu and Haifeng Du*

Beijing National Laboratory of Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

haifengdu@iccas.ac.cn

Received May 11, 2010

ABSTRACT



A variety of novel chiral terminal-alkene−phosphine hybrid ligands were successfully developed from diethyl L-tartrate for palladium-catalyzed asymmetric allylic alkylations, etherifications, and amination to give the desired products in excellent yields and ee's.

Chiral alkenes as one novel type of ligands have attracted intensive attention since Hayashi and Carreira reported the development of chiral bicyclic dienes as steering ligands independently in 2003 and 2004.[1,2] Generally, due to the relatively weak coordination ability of simple alkenes to transition metals, chelating alkene ligands are often necessary to ensure the generated catalysts maintain enough stability for asymmetric catalysis reactions.[3] The phosphorus atom usually displays higher coordination ability to transition metals; therefore, the combination of alkenes and phosphorus atoms allows the advantages of each class to be united which provides good opportunities to find highly efficient hybrid ligands.[1d,4] In 2004, Grützmacher reported enantiomerically pure ligand **1** (Figure 1) based on the 5-phosphanyl-5*H*-dibenzo[*a*,*d*]cycloheptene framework for iridium-catalyzed hydrogenation of an imine to achieve up to 86% ee.[5] Concurrently, Hayashi and co-workers reported chiral phosphine−alkene ligands **2** based on a norbornene frame-

(1) For reviews on chiral alkene ligands, see: (a) Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3364. (b) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840. (c) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482. (d) Shintani, R.; Hayashi, T. *Aldrichim. Acta* **2009**, *42*, 31.

(2) (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (b) Fisher, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628.

(3) For recent leading references on chiral diene ligands, see: (a) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336. (b) Gendrineau, T.; Chuzel, O.; Eijsberg, H.; Genet, J.-P.; Darses, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7669. (c) Mahoney, S. J.; Dumas, A. M.; Fillion, E. *Org. Lett.* **2009**, *11*, 5346. (d) Fournier, P.; Fiammengo, R.; Jäschke, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4426. (e) Brown, M. K.; Corey, E. J. *Org. Lett.* **2010**, *12*, 172. (f) Luo, Y.; Carnell, A. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 2750. (g) Shintani, R.; Isobe, S.; Takeda, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3795. (h) Shintani, R.; Takeda, M.; Nishimura, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3969.

(4) For leading references on amine−alkene hybrid ligands, see: (a) Marie, P.; Breher, F.; Schönberg, H.; Grützmacher, H. *Organometallics* **2005**, *24*, 3207. (b) Hahn, B. T.; Tewes, F.; Fröhlich, R.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1143.

10.1021/ol101069y
Published on Web 06/10/2010

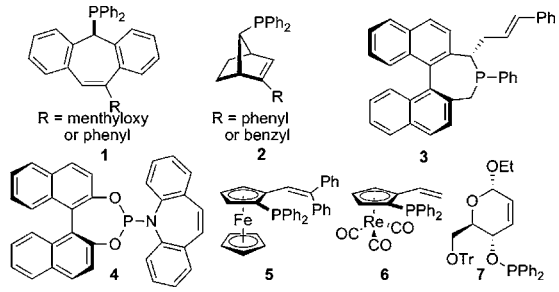


Figure 1. Representative phosphinoalkene hybrid ligands.

work.[6] Subsequently, Widhalm[7] and Carreira[8] developed binaphthyl-based phosphinoalkene ligands **3** and **4**. Štěka[9] and Bolm[10] reported planar chiral phosphine−alkene hybrid ligands **5** and **6**. Very recently, Boysen and co-workers reported an phosphinite−alkene hybrid ligand **7** derived from D-glucose.[11] Among them, ligands **2**,[6b] **5**,[9] and **7**[11] were employed in palladium-catalyzed asymmetric allylic alkylations,[12] and 96%, 43%, and 61% ee's were achieved, respectively.

We are interested in the development of chiral alkene ligands for asymmetric catalysis. We previously reported that flexible acyclic dienes **8** and **9** containing two terminal alkenes as coordinating moieties can be used as effective ligands for rhodium-catalyzed asymmetric 1,4-additions with promising activity and selectivity (Figure 2).[13] However, the enantioselectivity still cannot reach very high levels, which

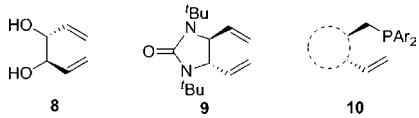
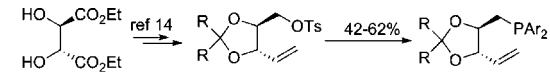


Figure 2. Chiral ligands containing terminal alkenes.

may be partially attributed to the weak coordination between flexible dienes and transition metals. We envisioned that installing the terminal alkene and phosphine moieties on suitable chiral backbones may provide a practical strategy for developing novel phosphine−alkene hybrid ligand **10** (Figure 2). Herein, we report our efforts on the development of highly efficient terminal-alkene−phosphine hybrid ligands derived from diethyl L-tartrate for palladium-catalyzed allylic alkylations, etherifications, and aminations as well.

At first, a variety of terminal-alkene-phosphine hybrid ligands **10a-f** were synthesized in reasonable yields from known compounds **11** which were obtained with diethyl L-tartrate as a starting material according to the reported procedures (Scheme 1).[14,15] With these ligands in hand, the initial studies were carried out with **10a** as ligand (5.0 mol

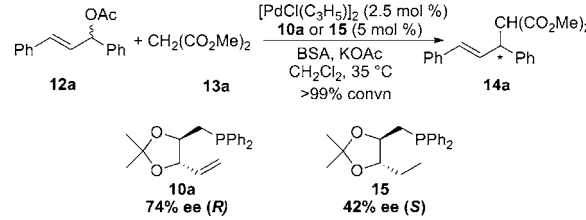
Scheme 1. Synthesis of Terminal-Alkene−Phosphine Ligands[10c]



10a: R = CH_3, Ar = Ph
10b: R = CH_3, Ar = 4-$MeOC_6H_4$
10c: R = CH_3, Ar = 3,5-$Me_2C_6H_3$
10d: R = CH_3, Ar = 2-Np
10e: R-R = $(CH_2)_5$, Ar = Ph
10f: R-R = $(CH_2)_5$, Ar = 4-$MeOC_6H_4$

%, 1:1 molar ratio to Pd(II)) for palladium-catalyzed allylic alkylation of racemic 1,3-diphenyl-2-propenyl acetate (**12a**) with dimethyl malonate (**13a**) at 35 °C in CH_2Cl_2, and the reaction proceeded smoothly to afford **14a** in quantitative conversion with 74% ee for the *R*-isomer (Scheme 2). We are curious for whether alkene moieties in ligand **10a** are

Scheme 2. Pd-Catalyzed Asymmetric Allylic Alkylation



involved in the coordination with palladium. Hence, monophosphine ligand **15** bearing ethyl instead of vinyl group was subjected to this reaction,[16] and it was interesting to find that 42% ee for the contrary configuration was obtained,

(5) (a) Deblon, S.; Grützmacher, H.; Schönberg, H. WO 03/048175 A1, 2003. (b) Marie, P.; Delbon, S.; Breher, F.; Geier, J.; Böhler, C.; Rüegger, H.; Schönberg, H.; Grützmacher, H. *Chem.—Eur. J.* **2004**, *10*, 4198. (c) Piras, E.; Läng, F.; Rüegger, H.; Stein, D.; Wörle, M.; Grützmacher, H. *Chem.—Eur. J.* **2006**, *12*, 15849.

(6) (a) Shintani, R.; Duan, W.-L.; Nagano, T.; Okada, A.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 4611. (b) Shintani, R.; Duan, W.-L.; Okamoto, K.; Hayashi, T. *Tetrahedron: Asymmetry* **2005**, *16*, 3400. (c) Duan, W.-L.; Iwamura, H.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 2130.

(7) Kasák, P.; Arion, V. B.; Widhalm, M. *Tetrahedron: Asymmetry* **2006**, *17*, 3084.

(8) (a) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139. (b) Mariz, R.; Briceño, A.; Dorta, R. *Organometallics* **2008**, *27*, 6605.

(9) (a) Štěpnička, P.; Císařová, I. *Inorg. Chem.* **2006**, *45*, 8758. (b) Štěpnička, P.; Lamač, M.; Císařova, I. *J. Organomet. Chem.* **2008**, *693*, 446.

(10) Stemmler, R. T.; Bolm, C. *Synlett* **2007**, *9*, 1365.

(11) Minuth, T.; Boysen, M. M. K. *Org. Lett.* **2009**, *11*, 4212.

(12) For leading reviews on asymmetric allylic alkylations, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(13) (a) Hu, X.; Zhuang, M.; Cao, Z.; Du, H. *Org. Lett.* **2009**, *11*, 4744. (b) Hu, X.; Cao, Z.; Liu, Z.; Wang, Y.; Du, H. *Adv. Synth. Catal.* **2010**, *342*, 651.

(14) (a) Wershofen, S.; Scharf, H.-G. *Synthesis* **1988**, 854. (b) Bell, T. W.; Ciaccio, J. A. *J. Org. Chem.* **1993**, *58*, 5153. (c) Mukai, C.; Kim, J. S.; Sonobe, H.; Hanaoka, M. *J. Org. Chem.* **1999**, *64*, 6822. (d) Pandey, G.; Kapur, M. *Org. Lett.* **2002**, *4*, 3883. (e) Pandey, G.; Kapur, M.; Khan, M. I.; Gaikwad, S. M. *Org. Biomol. Chem.* **2003**, *1*, 3321. (f) Horváth, A.; Benner, J.; Bäckvall, J.-E. *Eur. J. Org. Chem.* **2004**, 3240.

(15) Lee, S.-g.; Zhang, Y. J.; Song, C. E.; Lee, J. K.; Choi, J. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 847.

which suggests that the active catalyst species generated from palladium between ligands **10a** and **15** are completely different and vinyl group in ligand **10a** plays a very important role in the asymmetric induction.

Table 1. Evaluation of Ligands and Optimization of Reaction Conditions for Palladium-Catalyzed Alkylation of Allylic Acetate **12a** with **13a**[a]

entry	ligand	cat. (mol %)	temp (°C)	additive	convn[b] (%)	ee[c,d] (%)
1	**10a**	5.0	−40	KOAc	>99	83 (*R*)
2	**10b**	5.0	−40	KOAc	>99	85 (*R*)
3	**10c**	5.0	−40	KOAc	>99	90 (*R*)
4	**10d**	5.0	−40	KOAc	>99	86 (*R*)
5	**10e**	5.0	−40	KOAc	>99	85 (*R*)
6	**10f**	5.0	−40	KOAc	>99	83 (*R*)
7	**10c**	5.0	−20	LiOAc	>99	95 (*R*)
8	**10c**	**0.5**	**−20**	**LiOAc**	**>99**	**95 (*R*)**
9[e]	**10c**	0.1	−20	LiOAc	79	93 (*R*)
10[f]	**10c**	0.5	−20	LiOAc	57	80 (*R*)
11[g]	**10c**	0.5	−20	LiOAc	15	36 (*S*)
12	(−)-DIOP	0.5	−20	LiOAc	>99	19 (*S*)

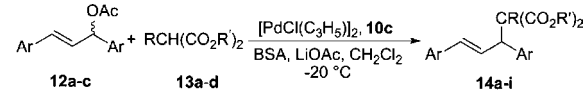
[a] All of the reactions were carried out with Pd/ligand = 1/1 (molar ratio) for 12 h unless otherwise stated. [b] The conversion was determined by crude ^{1}H NMR. [c] The ee was determined by chiral HPLC (Chiralpak AD-H column). [d] The absolute configuration was determined by comparing the optical rotation with the reported one. [e] The reaction time was 24 h. [f] Pd/**10c** = 1/2 (molar ratio). [g] Pd/**10c** = 1/3 (molar ratio).

Screening ligands and optimizing reaction conditions were subsequently carried out to search for more effective ligands. Some of the results are summarized in Table 1. When the temperature was decreased to −40 °C, under the catalysis of **10a**/Pd complex, the reaction of 1,3-diphenyl-2-propenyl acetate (**12a**) and dimethyl malonate (**13a**) still went efficiently to give the desired product **14a** in 83% ee (Table 1, entry 1). Under the same conditions, ligands **10b**−**f** were examined, and it was found that the substituents on phosphorus atoms have slightly impacts on the enantioselectivities (Table 1, entries 2−6). We were pleased to find that employing **10c** as ligand achieved up to 90% ee with quantitative conversion (Table 1, entry 3). Further studies on additives using **10c** as ligand showed that lithium acetate was a more effective additive for this reaction, and up to 95% ee with quantitative conversion was achieved at −20 °C with the catalyst loading as low as 0.5 mol % (Table 1, entry 8). Promising results were also obtained when the catalyst loading was reduced to 0.1 mol % (Table 1, entry 9), while the bisphosphine ligand (−)-DIOP[17] containing the same chiral framework only gave 19% ee for the *S*-isomer (Table 1, entry 12).

The excellent reactivity and enantioselectivity encouraged us to have better insight for the catalyst generated from $[PdCl(C_3H_5)]_2$ and phosphine−alkene hybrid ligand **10c**. NMR studies (see the Supporting Information) in CD_2Cl_2 were conducted, and it was observed that the complexes of Pd/**10c** can be formed efficiently and cleanly with $[PdCl(C_3H_5)]_2$ (0.5 equiv) and **10c** (1.0 equiv) (Pd/**10c** = 1:1), which can be kept at room temperature for at least 12 h without changes. The ^{31}P resonance for coordinated ligand **10c** was shifted obviously from −23.9 ppm to 17.4 ppm as a singlet. However, the signals for the protons on vinyl groups in the formed complexes had few changes compared to free ligand **10c**. Tuning the ratio of palladium and **10c** from 1:1 to 1:3 afforded messy spectra, which indicated that more than one species were formed. Subsequently, the impacts on the ratios of palladium and ligand **10c** were studied. It was found that only 57% conversion and 80% ee were obtained at the ratio of 1:2 (Table 1, entry 10). Alteration of the ratio to 1:3 led to a low conversion and 36% ee for the contrary configuration, which was consistent with the aforementioned results catalyzed by monophosphine ligand **15** (Table 1, entry 11 vs Scheme 2). According to these results, it was proposed that ligand **10c** acted as an alkene−phosphine hybrid ligand at a ratio of 1:1, and there may involve a very rapid coordination and dissociation process between alkene and palladium which accounted for the observed no changes for proton signals of vinyl group in ^{1}H NMR study. With the increasing amount of **10c**, some of them were supposed to act as monophosphine ligands to generate different active species with palladium giving the contrary configuration products which still awaits further studies.

Encouraged by the results obtained with phosphine−alkene ligand **10c**, asymmetric alkylation of several allylic acetates **12** with different malonates **13** were subsequently investigated. As shown in Table 2, all the reactions can proceed efficiently to give the desired products in excellent yields and ee's. In particular, when malonates **13b** were employed as nucleophiles, >99% ee's were successfully achieved (Table 2, entries 2, 6, and 9).

Table 2. Asymmetric Alkylations Catalyzed by Pd/**10c**[a]



12a: Ar = Ph
12b: Ar = 4-ClC$_6$H$_4$
12c: Ar = 4-CH$_3$C$_6$H$_4$

13a: R = H, R' = Me
13b: R = Me, R' = Et
13c: R = Ph, R' = Et
13d: R = Bn, R' = Et

entry	Pd/**10c** (mol %)	**14**	Ar/R/R′	yield[b] (%)	ee[c] (%)
1	0.5	**14a**	Ph/H/Me	98	95 (*R*)[d]
2	3.0	**14b**	Ph/Me/Et	98	>99 (*S*)[d]
3	3.0	**14c**	Ph/Ph/Et	99	93
4	3.0	**14d**	Ph/Bn/Et	99	98
5	3.0	**14e**	4-ClC$_6$H$_4$/H/Me	93	91
6	1.0	**14f**	4-ClC$_6$H$_4$/Me/Et	88	>99
7	3.0	**14g**	4-ClC$_6$H$_4$/Bn/Et	95	98
8	3.0	**14h**	4-CH$_3$C$_6$H$_4$/H/Me	96	92
9	3.0	**14i**	4-CH$_3$C$_6$H$_4$/Me/Et	95	>99

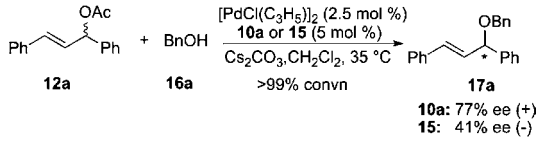
[a] All of the reactions were carried out with Pd/ligand =1/1 (molar ratio) for 12 h unless otherwise stated; for entry 1, the reaction time was 10 h. [b] Isolated yield. [c] The enantiomeric excess was determined by chiral HPLC (Chiralpak AD-H column). [d] The absolute configuration was determined by comparing the optical rotation with the reported one.

(16) Studies on **15**/Pd complexes at ratios of 1:1 and 2:1 for the asymmetric alkylation reactions afforded the same ee's and conversions.

(17) Kagan, H. B.; Dang, T.-P. *J. Am. Chem. Soc.* **1972**, *92*, 6429.

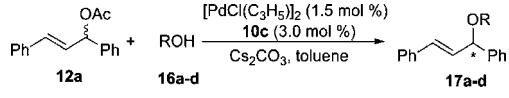
In contrast to the intensive studies on palladium-catalyzed allylic substitutions with carbon nucleophiles, only a few examples of palladium-catalyzed enantioselective allylic substitutions with relatively hard oxygen nucleophiles have been reported.[18] In particular, to the best of our knowledge, few chiral alkene ligands have ever been applied for this type of reactions.[2b] With terminal-alkene−phosphine ligands in hand, asymmetric allylic substitutions of 1,3-diphenyl-2-propenyl acetate **12a** with aliphatic alcohols were also studied. As shown in Scheme 3, the reaction of allylic acetate **12a** and benzyl alcohol (**16a**) using **10a** as ligand in the

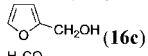
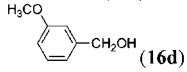
Scheme 3. Pd-Catalyzed Asymmetric Etherification of **12a**



presence of cesium carbonate as base gave the desired product in 77% ee for the (+)-isomer, while using monophosphine **15** as ligand afforded **17a** in the opposite configuration. It was found that the enantioselectivity can be improved to 91% when the temperature was decreased to −40 °C (Table 3, entry 1). Ligand **10c** and (−)-DIOP were also examined under the same conditions. It was found that ligand **10c** gave a slightly higher ee, while (−)-DIOP afforded almost racemic product (Table 3, entries 2 and 4). Alcohols **16b**−**d** as nucleophiles were subsequently investigated, and high yields (95−97%) and ee's (90−93%) have been achieved (Table 3, entries 5−7). Terminal-alkene−phosphine hybrid ligand **10a** was also effective for Pd-catalyzed allylic substitution with morpholine as a nucleophile to give the desired product in high yield and ee (Scheme 4).[19]

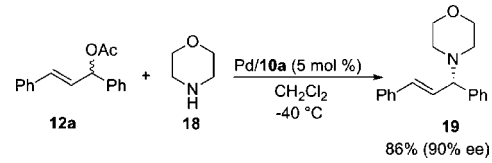
Table 3. Asymmetric Etherifications Catalyzed by Pd/**10c**[a]



entry	alcohol	ligand	product	yield (%)[b]	ee (%)[c]
1	BnOH (**16a**)	**10a**	**17a**	97	91
2	BnOH (**16a**)	**10c**	**17a**	97	93
3	BnOH (**16a**)	**10c**	**17a**	96	88
4	BnOH (**16a**)	(-)-DIOP	**17a**	94	5
5	^{n}BuOH (**16b**)	**10c**	**17b**	96	93
6	 (**16c**)	**10c**	**17c**	95	92
7	 (**16d**)	**10c**	**17d**	97	90

[a] All of the reactions were carried out with 1,3-diphenyl-2-propenyl acetate (**12a**) (0.33 mmol), alcohol (1.0 mmol), $[PdCl(C_3H_5)]_2$ (0.005 mmol), ligand (0.010 mmol), and cesium carbonate (1.0 mmol) in toluene (1.0 mL) for 12 h; for entries 1 and 2, the reaction temperature was −40 °C; for entries 3−7, the reaction temperature was −20 °C. [b] Isolated yield. [c] The ee was determined by chiral HPLC (Chiralcel OJ-H column).

Scheme 4. Pd/**10a**-Catalyzed Asymmetric Amination



In summary, a variety of terminal-alkene−phosphine hybrid ligands have been successfully developed for palladium-catalyzed enantioselective allylic alkylations, etherifications with aliphatic alcohols, and amination as well, giving the desired products in good yields with high enantioselectivities. Interestingly, these ligands are also possible to partially act as monophosphine ligands in some cases to give the contrary configuration products which still awaits further study in detail. Further searching for more effective terminal-alkene−phosphine hybrid ligands as well as expansion of their applications in asymmetric catalysis are currently underway.

Acknowledgment. We are grateful for the generous financial support from the National Science Foundation of China (20802079), the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry, Ministry of Science and Technology (2009ZX09501-018), and the National Basic Research Program of China (973 Program, 2010CB833300).

Supporting Information Available: Procedures for the synthesis of ligands, allylic substitutions, characterization, and data for the determination of ee's along with NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101069Y

(18) (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815. (b) Haight, A. R.; Stoner, E. J.; Peterson, M. J.; Grover, V. K. *J. Org. Chem.* **2003**, *68*, 8092. (c) Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P. *J. Am. Chem. Soc.* **2003**, *125*, 9276. (d) Tietze, L. F.; Lohmann, J. K.; Stadler, C. *Synlett* **2004**, *6*, 1113. (e) Uozumi, Y.; Kimura, M. *Tetrahedron: Asymmetry* **2006**, *17*, 161. (f) Lam, F. L.; Au-Yeung, T. T.-L.; Kwong, F. Y.; Zhou, Z.; Wong, K. Y.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 1280. (g) Kato, M.; Nakamura, T.; Ogata, K.; Fukuzawa, S.-i *Eur. J. Org. Chem.* **2009**, 5232. (h) Caldentey, X.; Pericàs, M. A. *J. Org. Chem.* **2010**, *75*, 2628.

(19) When benzylamine was used as a nucleophile for this reaction at 35 °C, a lower ee (55%) was obtained which may be partially due to its relatively strong coordination ability with palladium.