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ClickFerrophos: New Chiral Ferrocenyl Phosphine Ligands Synthesized by Click Chemistry and the Use of Their Metal Complexes as Catalysts for Asymmetric Hydrogenation and Allylic Substitution

Shin-ichi Fukuzawa,* Hiroshi Oki, Mitsuteru Hosaka, Jun Sugasawa, and Satoshi Kikuchi

Department of Applied Chemistry, Institute of Science and Engineering, Chuo University, 1-13-27 Kasuga, Bunkyo-ku, Tokyo 112-8551, Japan

fukuzawa@chem.chuo-u.ac.jp

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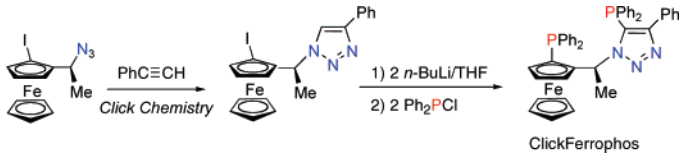
ABSTRACT



The new ferrocenyl *P,P*- and *P,N*-ligands 5 and 6 (collectively, "ClickFerrophos") were readily prepared in four steps using Click Chemistry methodology, starting from the commercially available aminoferrocene 1. Rhodium and ruthenium complexes of ClickFerrophos 5 were effective catalysts for the hydrogenation of alkenes and ketones, respectively, producing products with up to 99.7% ee. The analogous palladium complex with 6 worked well for asymmetric allylic alkylation.

Chiral ferrocenes have been of interest especially in asymmetric catalysis as chiral ligands. Ferrocenylphosphines are effective ligands in transition-metal complexes catalyzing asymmetric reactions, often with high enantioselectivity.[1] The unique structure of ferrocenes allows one to design a variety of chiral ferrocenyl phosphine ligands, which are useful tools in metal-catalyzed asymmetric reactions. Although some useful chiral ferrocenylphosphine ligands have already been reported, it is still an interesting challenge to create new ligands of this type in order to devise more effective metal complex catalysts and/or to be used in asymmetric reactions for which conventional ligands are not effective.

"Click Chemistry" has recently drawn considerable attention as a powerful and efficient way to synthesize desired compounds in high yields using a simple and benign procedure.[2] The Huisgen 1,3-dipolar cycloaddition of azide and alkynes is the most intensively studied click reaction, which yields 1,2,3-triazoles in high yields by just mixing the starting compounds with a Cu(I) catalyst in an aqueous solvent. The 1,2,3-triazole has recently generated interest as a ligand for metal-catalyzed organic reactions.[3] ClickPhos, triazole-based monophosphine ligands, have been prepared by Zhang et al. using Click Chemistry methodology, and their palladium complexes have been demonstrated to work effectively in Buchwald and Suzuki coupling reactions.[3a] We

(1) For reviews chiral ferrocenes in asymmetric synthesis, see: (a) Hayashi, T. Asymmetric Catalysis with Chiral Ferrocenylphosphine Ligands. In *Ferrocenes*; Togni, A., Hayashi, T., Eds.; Wiley-VCH: Weinheim, 1995; pp 105−142. (b) Togni, A. New Chiral Ferrocenyl Ligands for Asymmetric Catalysis. In *Metallocenes*; Togni, A., Halterman, R. L., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 2 pp 689−721. (c) Colacot, T. J. *Chem. Rev.* **2003**, *103*, 3101−3118. d) Sutcliffe, O. B.; Bryce, M. R. *Tetrahedron: Asymmetry* **2003**, *14*, 2297−2325. (e) Arrayás, R. G.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7674−7715.

(2) For reviews of Click Chemistry, see (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021. (b) Gil, M. V.; Arévalo, M. J.; López, Ó. *Synthesis* **2007**, 1589−1620.

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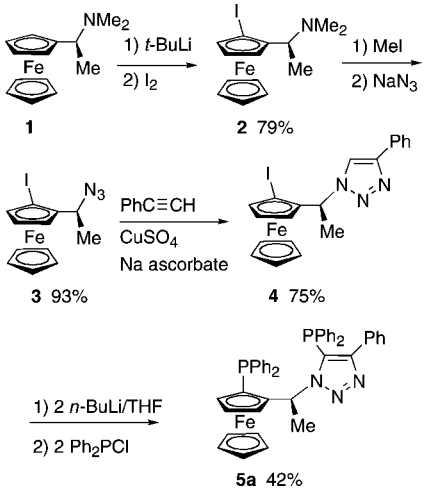
have succeeded in preparing the first new chiral 1,2,3-triazole ferrocenyl-based *P*,*P*- and *P*,*N*-ligands (ClickFerrophos) by this methodology and report their application in asymmetric hydrogenation and allylic alkylation reactions.[4]

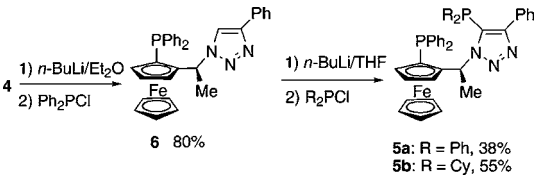
The chiral triazoleferrocenyl-1,5-phosphine **5a** was readily prepared starting from commercially available (*S*)-ferrocenyl amine (Ugi's amine)[5] **1** as illustrated in Scheme 1. The

Scheme 1. Preparation of ClickFerrophos **5a**



stereoselective ortho-lithiation of **1** followed by trapping with iodine gave the *o*-iodoferrocenyl amine **2**, whose amino group was replaced by the azide group with retention of configuration on treatment with methyl iodide and sodium azide.[6] The *o*-iodoferrocenyl azide **3** was subjected to Click Chemistry under Sharpless conditions (phenylacetylene, $CuSO_4$/sodium ascorbate in *t*-BuOH/H_2O)[7] to give the corresponding 1,4-disubstituted 1,2,3-triazole **4** in good yield. The treatment of **4** with 2 molar equiv of *n*-BuLi in THF at −78 °C followed by trapping with 2 molar equiv of Ph_2PCl gave the 1,5-diphosphine **5a** in moderate yield (Scheme 1). The lithiation of the triazole ring was critical and led to the successful preparation of the 1,5-diphosphine ligand (Taniaphos-type ligand).[8] The monophosphine **6** could be prepared by the reaction of **4** using 1 equiv of *n*- BuLi and Ph_2PCl in diethyl ether (Scheme 2) and led to the diphosphine **5a**,**b** by stepwise lithiation of the triazole ring in THF and trapping with R_2PCl (R = Ph, Cy). Thus, different phosphinyl groups could be introduced onto the cyclopentadienyl and the triazole ring with the (*S*,*Rp*) configuration. The structure of **5a** was confirmed by X-ray crystallography (Figure 1).

Scheme 2. Preparation of the *P*,*N*-Ligand **6** and *P*,*P*-Ligands **5a**,**b**



The 1,5-disubstituted 1,2,3-triazole **7** was prepared by the reaction of **3** with magnesium phenylacetylide.[9] The prepara-

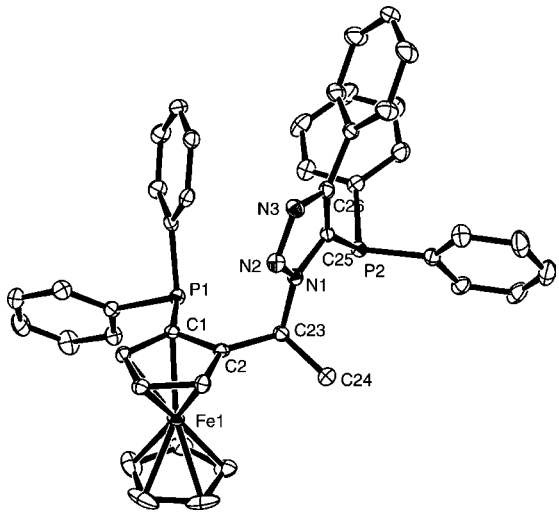
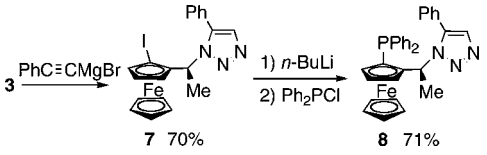


Figure 1. X-ray structure of ClickFerrophos **5a**.

tion of monophosphine **8** was achieved by the sequence of lithiation and trapping with Ph_2PCl. However, the 1,6-diphosphine could not be obtained from **7** or **8** (Scheme 3).

Scheme 3. Preparation of the *P*,*N*-Ligand **8**



Thus, new ferrocenyl phosphine ligands containing a triazole ring were prepared. Their ability to act as ligands in the asymmetric hydrogenation of alkenes was investigated.[10] Some rhodium complexes using **5a** as a ligand were first screened in the hydrogenation of methyl α-acetamidocinnamate (**11a**). The reaction was usually performed at room temperature for 2 h in MeOH/toluene or MeOH/CH_2Cl_2

(3) (a) Dai, Q.; Gao, W.; Liu, D.; Kapes, L. M.; Zhang, X. *J. Org. Chem.* **2006**, *71*, 3928−3934. (b) Dets, R. J.; Heras, S. A.; de Gelder, R.; van Leeuwen, P. W. N. M.; Hiemstra, H.; Reek, J. N. H.; van Maarseveen, J. H. *Org. Lett.* **2006**, *8*, 3227−3230.

(4) Examples of achiral ferrocenyl 1,2,3-triazoles: (a) Casas-Solvas, J. M.; Vergas-Berenguel, A.; Capitán-Valley, L. F.; Francisco, S.-G. *Org. Lett.* **2004**, *6*, 3687−3690. (b) Zhao, Y.-B.; Yan, Z.-Y.; Liang, Y.-M. *Tetrahedron Lett.* **2006**, *47*, 1545−1549.

(5) The ferrocenyl amine **1** can be prepared on a large scale (20g scale) by resolution of the racemate. Gokel, G. W.; Ugi, I. K. *J. Am. Chem. Soc.* **1972**, *49*, 294−296.

(6) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389−5393.

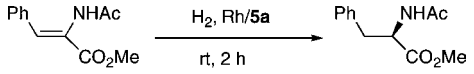
(7) Rostovsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.

(8) Uhlmann, P.; Felding, J.; Vesø, P.; Begtrup, M. *J. Org. Chem.* **1997**, *62*, 9177−9181.

(9) Krasinski, A.; Fokin, V. V.; Sharpless, K. B. *Org. Lett.* **2004**, *6*, 1237−1240.

under atmospheric pressure hydrogen using 1 mol % of rhodium complex and a ligand. The results are summarized in Table 1. Any typical cationic rhodium complex examined

Table 1. Asymmetric Hydrogenation of Methyl α-Acetamidocinnamate Catalyzed by Rhodium/**5a** Complexes[a]



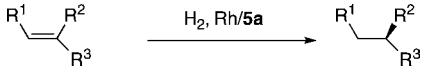
10a **11a**

entry	Rh complex	%, conv[b]	%, ee[c]
1	$[Rh(nbd)Cl]_2$	5	88
2	$[Rh(cod)_2]BF_4$	94	98
3	$[Rh(nbd)_2]PF_6$	>99	98
4	$[Rh(nbd)_2]BF_4$	>99	99
5[d]	$[Rh(nbd)_2]BF_4$	>99	97
6[e]	$[Rh(nbd)_2]BF_4$	>99	99
7[f]	$[Rh(nbd)_2]BF_4$	>99	99
8[g]	$[Rh(nbd)_2]BF_4$	>99	99
9[h]	$[Rh(nbd)_2]BF_4$	>99	67
10[i]	$[Rh(nbd)_2]BF_4$	0	

[a] **10a** (1 mmol), Rh (0.010 mol), **5a** (0.011 mol), MeOH/toluene (2/2 mL); rt, 2 h, H_2 (1 atm). [b] Determined by ^1H NMR from the crude reaction mixture. [c] Determined by HPLC (Chiralcel AD-H). [d] MeOH/toluene (1/5 mL). [e] MeOH/toluene (0.4/4 mL). [f] MeOH/CH_2Cl_2 (0.4/4 mL). [g] The enantiomer of **5a** (*R*,*Sp*) was used as a ligand, and the configuration of the product was *S*. [h] **5b** (0.011 mol) was used as a ligand. [i] **6** (0.011 mol) was used as a ligand.

here worked well to give (*R*)-*N*-acetylphenylalanine methyl ester (**12a**) in excellent yield with high enantioselectivities (up to 99% ee) (entries 2−4). The ratio of MeOH/toluene (1/10−1/1) had little effect on yield and enantioselectivity, and the reaction in MeOH/CH_2Cl_2 (1/10) also gave satisfactory results (entries 5−7). The use of *ent*-**5a**[11] gave the *S*-isomer in the reaction with **11a** with 99% ee (entry 8). The use of **5b** resulted in lower selectivity that **5a** (entry 9). It must be noted that the reaction with Rh/monophosphine **6** complex did not proceed at all (entry 10), suggesting that the *P*,*P*-chelate complex was the active catalyst, not the *P*,*N*-chelate complex. The *P*,*P*-chelate complexation could be observed in the ^{31}P NMR spectrum; two signals of uncoordinated **5a** appearing at −35.1 (d, J = 32.4 Hz) and −23.8 (d, J = 32.4 Hz) ppm shifted +7.4 (dd, J = 27.8, 153.0 Hz) and + 15.0 (dd, J = 27.8, 162.3 Hz), respectively, upon coordination to rhodium.[12a] We chose $[Rh(nbd)_2]BF_4$ as a catalyst and MeOH/toluene (1/1) as a solvent in the asymmetric hydrogenation of alkenes, and the reaction was similarly performed at room temperature under atmospheric pressure hydrogen for various times. The results are shown in Table 2. The results of using a Knochel's Taniaphos **9**[12] (Figure 2) with (*R*,*Rp*) stereochemistry and which was structurally similar to **5a**, are also shown in Table 2 for

Table 2. Asymmetric Hydrogenation of Alkenes Catalyzed by $[Rh(nbd)_2]BF_4$/**5** Complexes[a]



entry	alkene	time (h)	conv[b] (%)	%, ee (config)[c]
1	**10a**	2	>99	99 (*R*)
2[d]	**10a**	3.5	100	86 (*R*)
3	**10b**	2	>99	98 (*R*)[e]
4	**12**	24	>99	84 (*R*)
5	**13a**	24	>99	99.3 (*R*)
6	**13b**	24	>99	98 (*R*)[e]
7	**14a**	12	>99	91 (*S*)
8[d]	**14a**	2.5	100	91 (*R*)
9	**14b**	12	>99	99.7 (*S*)[e]
10[f]	**15**	24	58	34 (*R*)[e]

[a] Alkene (1 mmol), $[Rh(nbd)_2]BF_4$ (0.010 mol), **5a** (0.011 mol), MeOH/toluene (2/2 mL); rt, H_2 (1 atm). [b] Determined by ^1H NMR from the crude reaction mixture. [c] Determined by HPLC (Chiralcel AD-H, OD) or GC (Chiraldex G-TA, CP-Chirasildex-CB). [d] Data from reference 12c using **9** as a ligand. [e] Conversion and % ee were determined after esterification with MeOH/$SOCl_2$. [f] The reaction was performed under 5 atm of hydrogen.

comparison (entries 2 and 8). The reaction with α-acetamidocinnamic acid (**10b**) proceeded smoothly to give the

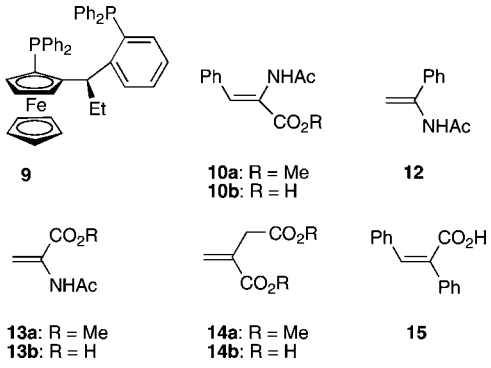


Figure 2. Taniaphos and examined alkenes.

product quantitatively with an excellent % ee value (entry 3) similar to its ester **10a**. The hydrogenation with other enamides such as **12** and **13a**,**b** proceeded but slowly to give the corresponding product in good to excellent enantioselectivities (up to 99.3% ee) (entries 4−6). This catalyst was also applied to the hydrogenation of itaconic acid and its methyl ester **14a**,**b**, giving high % ee values (up to 99.7% ee) (entries 7 and 9).

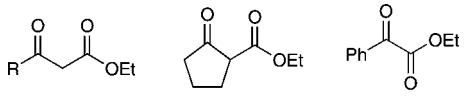
We next applied ClickFerrophos **5a** to the ruthenium complex-catalyzed asymmetric hydrogenation of ketones.[13]

(10) For reviews of Rh-catalyzed asymmetric hydrogenation, see: (a) Ohkuma, T.; Kitamura, M.; Noyori, R. Asymmetric Hydrogenation. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 1−110. (b) Chi, Y.; Tang, W.; Zhang, X. Rhodium-Catalyzed Asymmetric Hydrogenation. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; pp 1−31.

(11) The enantiomer of **5a** was prepared from enantiomer of **1** by the same procedure as shown in Scheme 1.

(12) (a) Ireland, T.; Grossheimann, G.; Wieser-Jeunesse, C.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 3212−3214. (b) Ireland, T.; Tappe, K.; Grossheimann, G.; Knochel, P. *Chem. Eur. J.* **2002**, *8*, 843−852. (c) Tappe, K.; Knochel, P. *Tetrahedron: Asymmetry* **2004**, *15*, 91−102. (d) Chen, W.; Roberts, S. M.; Whittall, J.; Steiner, A. *Chem. Comm.* **2006**, 2916−2918.

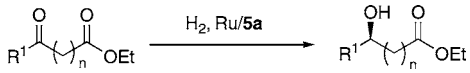
The hydrogenation was carried out using 0.5 mol % of [Ru(cod)(metallyl)$_2$]/HBr and ligand **5a** in EtOH under 10 atm of hydrogen at 50 °C. The results of the reaction with representative keto esters (**16**−**19**, Figure 3) and dibenzoylmethane (**20**) (a typical 1,3-diketone) are summarized in Table 3 including results using **9** for comparison (entries 2, 4, and 6). In the reaction with ethyl acetoacetate (**16**) and ethyl benzoylacetate (**17**), ruthenium complex with **5a** worked effectively to give high enantioselectivities (entries 1−4). The reaction with the ketoester **18** gave the product as almost a single diastereomer with high % ee (entry 5). The reaction with ethyl benzoylformate (**19**), a typical α-ketoester, resulted in poor enantioselectivity giving (*R*)-ethyl mandelate in 30% ee (entry 7). High diastereoselectivity (>99% de) and enantioselectivity (99% ee) were also observed in the reaction with the 1,3-diketone **20**, the corresponding diol **21** being obtained as almost a single diastereomer with 99% ee (Scheme 4). It was noteworthy that the stereochemical outcomes in the hydrogenations of **10a** and ketones **16**−**18** were the same as the results obtained with **9**, probably due to the structural similarity of these ligands (the reaction with **14a** gave the reverse stereochemistry).



16: R = Me
17: R = Ph
18
19

Figure 3. Examined keto esters.

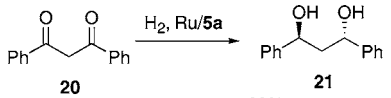
Table 3. Asymmetric Hydrogenation of Ketones Catalyzed by [Ru(cod)(metallyl)$_2$]/HBr/**5a** Complexes[a]



entry	ketone	time (h)	conv[b] (%)	ee (%) (config)[c]
1	**16**	8	>99	93 (*R*)
2[d]	**16**	13	100	80 (*R*)
3	**17**	12	>99	98 (*S*)
4[d]	**17**	14	100	88 (*S*)
5	**18**	24	>99	84 (*R,R*)[e]
6[d]	**18**	14	100	86 (*R,R*)
7	**19**	24	>99	30 (*R*)

[a] Ketone (2 mmol), [Ru(cod)(metallyl)$_2$]/HBr(0.010 mol), **5a** (0.011 mol), solvent (4 mL); 50 °C, H_2 (10 atm). [b] Determined by ^{1}H NMR from the crude reaction mixture. [c] Determined by HPLC (Chiralcel AD-H, OD-H) or GC (Chiraldex G-TA, CP-Chirasil dex-CB). [d] Data from ref 12c using **9** as a ligand. [e] Diastereomeric excess (>99%).

Scheme 4. Asymmetric Reduction of β-Diketone **21**

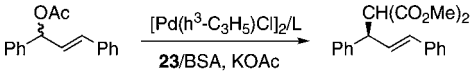


20 **21**

>99% conv.
(*R,Sp*)-**5a**; 99% ee (*S,S*)
(*S,Rp*)-**5a**; 99% ee (*R,R*)

Last, the palladium-catalyzed asymmetric allylic alkylation of (±)-(*E*)-1,3-diphenyl-2-propenyl acetate **22** with dimethyl malonate **23** was examined[14] using *P,N*- ligand **6** and **8**.[15] The reaction was carried out at room temperature for 18 h in CH_2Cl_2 using 5 mol % of [Pd(η^3-C_3H_5)Cl]$_2$ and a ligand (**6**, **8**) in the presence of *N,O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of potassium acetate as bases. The complex with **6** quantitatively yielded the product **24** with 79% ee, while **8** was not effective for the reaction, giving the product with poor % ee (Scheme 5).

Scheme 5. Asymmetric Allylic Alkylation Catalyzed by Pd/**6** and **8** Complexes



22 **24**

L = **6**; 99% yield, 79% ee (*S*)
L = **8**, 99% yield,10% ee (*S*)

In conclusion, ClickFerrophos **5** was successfully used as a ligand in the rhodium and ruthenium complex-catalyzed hydrogenation of alkenes and ketones, respectively, producing products with up to 99.7% ee.[16] The ligand can be prepared by simple procedure of Click Chemistry which allows an efficient fine-tuning of the ligand. The variation of chiral ferrocenyl ligands which have a triazole backbone would have an potential in asymmetric synthesis.

Acknowledgment. This study was financially supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS) (No. 16550044).

Supporting Information Available: Full experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for new chiral ferrocenyl compounds **2**−**8**; crystallographic datafor **5a**, **6**, and **8** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL702519F

(13) For reviews of Ru-catalyzed asymmetric hydrogenation, see: (a) Ohkuma, T.; Noyori, R. Hydrogenation of Carbonyl Groups. In *Comprehensive Asymmetric Synthesis*; Jacobsen, E. N., Pfalz, A., Yamamoto, H., Eds.; Springer: Berlin, 2000; Vol. 1, pp 199−246. (b) Kitamura, M.; Noyori, R. Hydrogenation and Transfer Hydrogenation. In *Rhuthenium in Organic Synthesis;* Murahashi, S.-i., Ed.; Wiley-VCH: Weinheim, 2004; pp 3−52.

(14) For reviews of asymmetric allylic substitution, see: (a) Pfalz, A.; Lautens, M. *Allylic Substitution Reactions*; Springer: Berlin, 2000. (b) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497−537.

(15) The chiral pyrazole ferrocenylphosphine ligands, which are similar to **6** and **8**, have been applied to the asymmetric allylic substitutions. (a) Togni, A.; Burckhart, Urs.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Am. Chem. Soc.* **1996**, *118*, 1031−1047. (b) Burckhart, Urs.; Baumann, M.; Trabesinger, G.; Gramlich, V.; Togni, A. *Organometallics* **1997**, *16*, 5252−5259.

(16) For recent examples of efficient chiral ferrocenylphosphine ligands in asymmetric hydrogenations, see: (a) Boaz, N. W.; Mackenzie, E. B.; Debenham, S. D.; Large, S. E.; Ponasik, J.; James, A. *J. Org. Chem.* **2005**, *70*, 1872−1880. (b) Li, X.; Jia, X.; Xu, L.; Kok, S. H. L.; Yip, C. W.; Chan, A. S. C. *Adv. Synth. Catal.* **2005**, *347*, 1904−1908. (c) Hu, X.-P.; Zheng, Z. *Org. Lett.* **2004**, *6*, 3585−3588. (d) Liu, D.; Li, W.; Zhang, X. *Org. Lett.* **2002**, *4*, 4471−4474.