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Asymmetric hydrogenation of quinolines activated by Brønsted acids

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ABSTRACT

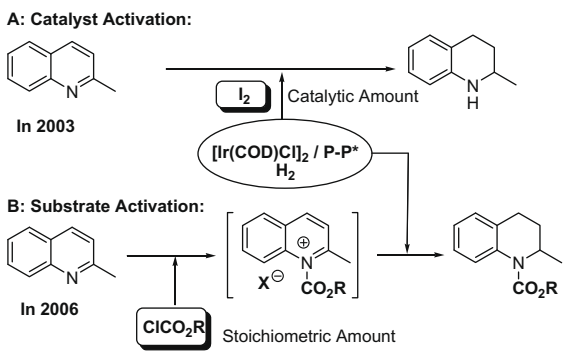
Enantioselective hydrogenation of quinolines and quinoxalines catalyzed by iridium/diphosphine complex with catalytic amount of Brønsted acid as activator was developed. In the presence of piperidine·TfOH as the activator, full conversions and up to 92% ee were obtained.

Catalytic asymmetric hydrogenation of prochiral unsaturated compounds, such as simple olefins, ketones, and imines, has been intensively studied which provides a straight and versatile access to the corresponding chiral compounds.[1] However, the asymmetric hydrogenation of heteroaromatic compounds such as quinolines is much less explored until very recently due to low activity of aromatic compounds.[2] Considering the importance of 1,2,3,4-tetrahydroquinolines, which are ubiquitous in natural alkaloids and have found broad application in pharmaceutical and agrochemical synthesis,[3] the asymmetric hydrogenation of quinolines to obtain these useful chemicals is urgently developed. In this context, two activation strategies have been developed by us successfully (Scheme 1).

In 2003, our group reported the first example of asymmetric hydrogenation of quinolines catalyzed by iridium/diphosphine complex with iodine as additive to activate the catalyst.[4,5] Thereafter, this field was flourishing with a number of effective ligands being introduced by other groups.[6,7] Substrate activation is the other choice for the asymmetric hydrogenation of heteroaromatic compounds. In 2006, we chose chloroformates as activator via forming quinolinium and isoquinolinium salts in situ, which were hydrogenated smoothly.[8] In this reaction, stoichiometric amounts of chloroformates were employed and the activation groups were attached covalently at the nitrogen atoms of the products, which needed additional steps for deprotection. Therefore, searching for a new catalytic amount of activator, which can be easily removed after the reaction, is a complement to the substrate activation and of significance.

In 2008, Feringa and co-workers reported the asymmetric hydrogenation of quinolines catalyzed by iridium complexes based on monodentate BINOL-derived phosphoramidites with 10 mol % of piperidine hydrochloride as additive.[9] Afterward, Fan and co-workers revealed the efficiency of the phosphine-free cationic Ru/Ts-DPEN and Ir/CF_3Ts-DPEN catalysts in the asymmetric hydrogenation of quinolines successively.[10,11] It was notable that, with these catalytic system, catalytic amount of Brønsted acid showed positive effect. Recently, Xiao group reported the Rh-catalyzed asymmetric transfer hydrogenation of quinolines in an aqueous formate solution with high enantioselectivities, the acidic buffer is crucial for the reactivity and enantioselectivity.[12] Zhang and co-workers developed the first asymmetric hydrogenation of the hydrochloride salt of unprotected N–H imines.[13]

For the above successful hydrogenation reactions, acid is very crucial for both the reactivity and enantioselectivity. Inspired by these examples, we envisioned that catalytic amount of Brønsted acid may play as activator in the asymmetric hydrogenation of quinolines. Since the basicity of the hydrogenated products and the quinolines is almost equivalent, the acid can recycle in the activation process (Scheme 2). During our investigation, Mashima and co-workers reported the asymmetric hydrogenation of quinoline hydrochloride salts by using Ir-complexes with Difluorphos.[14] This result encouraged us greatly and promoted us to stick to our initial hypothesis. Herein, we disclose an efficient Ir/diphosphine complex-catalyzed asymmetric hydrogenation of quinolines and



Scheme 1. Activation strategies for hydrogenation of quinolines.

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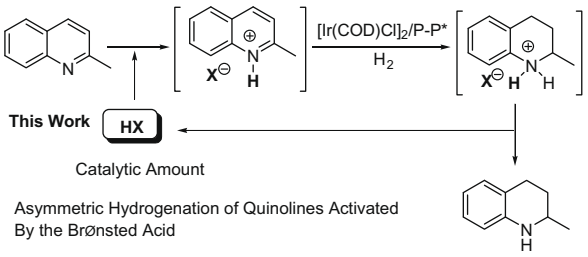


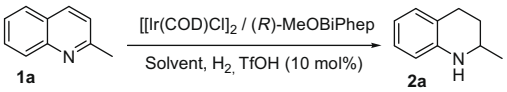
Scheme 2. Substrate activation with Brønsted acid.

quinoxalines with catalytic amount of Brønsted acid, piperidine·TfOH, as the activator with up to 92% ee.

Quinaldine **1a** was selected as the model substrate for the condition optimization. The initial reaction was carried out in toluene using $[Ir(COD)Cl]_2$/(*R*)-MeO–BiPhep and TfOH as the catalyst and activator, respectively. To our delight, both the reactivity and enantioselectivity were improved greatly in the presence of 10 mol % of TfOH (Table 1, entries 1 and 2, 48–76% conversion and 23–84% ee). This promising result encouraged us to screen the other reaction parameters. For the solvent effect, *i*-PrOH and CH_2Cl_2 resulted in lower conversions. Reversed enantioselectivity was observed for MeOH (51% ee (*S*)). Full conversions and high enantioselectivities were obtained with dioxane, THF and EtOAc (entries 6–8).

Considering the important impact of acid additives on activity and enantioselectivity, a number of acid additives were evaluated in THF (Table 2). Organic acids, such as TfOH, TFA, $TsOH·H_2O$, $PhCO_2H$ and salicylic acid, were tested. It was shown that stronger acids are more effective in terms of enantioselectivity, and TfOH gave the highest ee (entry 1, 79%). Inspired by Mashima's report,[14] 10 mol % of quinaldine·HCl was added as an additive, the reaction proceeded smoothly with full conversion and 70% ee (entry 6). Piperidine hydrochloride, which was effective in Ir-catalyzed asymmetric hydrogenation of quinolines with monodentate phosphoramidite ligand,[9] was also investigated in our catalytic system with 75% ee (entry 7). Finally, piperidine triflate was found to be the best activator with full conversion and 86% ee (entry 8). Question aroused as that whether the substrate was activated by acid or the triflate anion just as a counter anion of iridium complex? To confirm our hypothesis of acid activation, AgOTf was added instead of TfOH, poor conversion and enantioselectivity were obtained (entry 9). When AgOTf was cooperated with TfOH, low reactivity was observed (entry 10). The above experiments showed that it is not a counteranion exchange process.

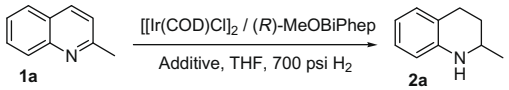
Table 1
Optimization of reaction conditions[a]



Entry	Solvent	Convn.[b] (%)	Ee[c] (%)
1[d]	Toluene	48	23 (*R*)
2	Toluene	76	84 (*R*)
3	*i*-PrOH	47	22 (*R*)
4	MeOH	28	51 (*S*)
5	CH_2Cl_2	23	29 (*R*)
6	Dioxane	>95	80 (*R*)
7	THF	>95	79 (*R*)
8	EtOAc	>95	79 (*R*)

[a] Conditions: 0.25 mmol of quinaldine, $[Ir(COD)Cl]_2$ (1 mol %), (R)-MeO–BiPhep (2.2 mol %), TfOH (10 mol %), 3 mL of solvent, rt, 16 h.
[b] Determined by ^1H NMR.
[c] Determined by HPLC.
[d] No acid was used.

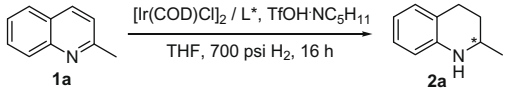
Table 2
The effect of the additives on the reactivity and stereoselectivity[a]



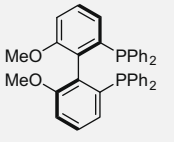
Entry	Additive	Convn.[b] (%)	Ee[c] (%)
1	TfOH	>95	79 (*R*)
2	TFA	>95	71 (*R*)
3	$TsOH·H_2O$	>95	74 (*R*)
4	$PhCO_2H$	>95	49 (*R*)
5	Salicylic acid	>95	53 (*R*)
6	HCl·quinaldine	>95	70 (*R*)
7	HCl·piperidine	>95	75 (*R*)
8	TfOH·piperidine	>95	**86** (***R***)
9	AgOTf	11	7 (*R*)
10	AgOTf + TfOH	13	29 (*S*)

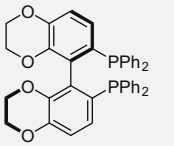
[a] Conditions: 0.25 mmol of quinaldine, $[Ir(COD)Cl]_2$ (1 mol %), (*R*)-MeO–BiPhep (2.2 mol %), additive (10 mol %), 3 mL of THF, rt, 16 h.
[b] Determined by ^1H NMR.
[c] Determined by HPLC.

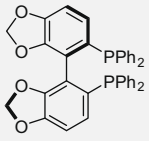
Table 3
The effect of ligands on the enantioselectivity[a]

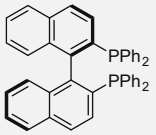


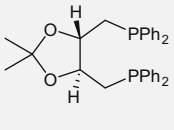
Entry	Ligand	Convn.[b] (%)	Ee[c] (%)
1	**L1**	>95	86 (*R*)
2	**L2**	61	88 (*R*)
3	**L3**	>95	89(*R*)
4	**L4**	>95	79 (*R*)
5	**L5**	>95	78 (*R*)
6	**L6**	>95	88 (*R*)
7[d]	**L3**	>95	91 (*R*)
8[e]	**L3**	<5	35 (*S*)
9[f]	**L3**	<5	N/A

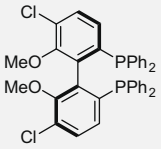

L1 (*R*)-MeO-BiPhep


L2 (*R*)-SynPhos


L3 (*R*)-SegPhos


L4 (*R*)-BINAP


L5 (*S,S*)-DIOP


L6 (*R*)-Cl-MeO-BiPhep

[a] Conditions: 0.25 mmol of quinaldine, $[Ir(COD)Cl]_2$ (1 mol %), Ligand (2.2 mol %), piperidine·TfOH (10 mol %), 3 mL of THF, rt, 16 h.
[b] Determined by ^1H NMR.
[c] Determined by HPLC.
[d] With 5 mol % of piperidine?TfOH.
[e] With $[Rh(COD)_2]BF_4$ as metal precursor.
[f] With $[RuCl_2(p\text{-cymene})]_2$ as metal precursor.

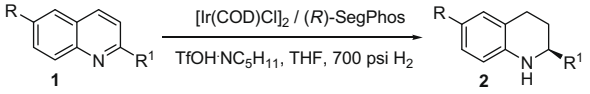
Next, some commercially available chiral diphosphine ligands were screened (Table 3). Enantioselectivities increased slightly when SynPhos, SegPhos, and Cl–MeO–BiPhep were employed instead of MeO–BiPhep (entries 2, 3, and 6). When BINAP and DIOP were used, the reaction proceeded with full conversion but with lower enantioselectivities (entries 4 and 5, 79% and 78% ee). Best enantioselectivity was obtained with SegPhos (89% ee). When piperidine·TfOH was reduced to 5 mol %, the enantioselectivity increased slightly (entry 7, 91% ee). The common metal precursors such as $[Rh(COD)_2]BF_4$ and $[RuCl_2(p\text{-cymene})]_2$ were also tested instead of $[Ir(COD)Cl]_2$ to ensure the scope of our strategy. Low conversions and poor enantioselectivities were obtained. Thus, the optimized conditions were $[Ir(COD)Cl]_2$/(*R*)-SegPhos/THF/ with 5 mol % of piperidine·TfOH as an additive.

Under the optimal conditions, a variety of 2-substituted quinolines were hydrogenated smoothly to give the desired products in excellent yields and high enantioselectivities (Table 4, up to 92% ee). It was found that the length of the side chain influenced both the enantioselectivity and reactivity (entries 1–4). So iridium was increased to 2 mol % to guarantee full conversions for all substrates. It was noted that best result was obtained for quinoline with a free hydroxyl group on the side chain (entry 5, 92% ee). 2-Arenethyl-substituted quinolines were also hydrogenated with 88–89% ee (entries 6 and 7). Substitution at the 6-position had no obvious effect on either yield or enantioselectivity, slightly higher ee was obtained with more electron-donating group (entry 9, 91% ee). However, 2-phenylquinoline was hydrogenated with only moderate yield and enantioselectivity (entry 11, 78% ee).

In contrast to quinolines, the asymmetric hydrogenation of quinoxaline derivatives is much less studied. Very recently, it attracted much attention and achieved some progress.[15] Gratifying, the strategy developed here can also be extended to the asymmetric hydrogenation of quinoxaline derivatives. Under the above optimal conditions, both 2-ethyl- and 2-phenyl-substituted quinoxalines can be hydrogenated smoothly with 57% and 65% ee, respectively (Scheme 3).

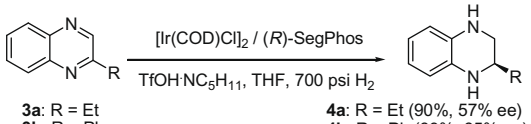
In conclusion, we have developed a new strategy for iridium-catalyzed asymmetric hydrogenation of quinolines and quinoxalines by Brønsted acid-mediated substrate activation. With catalytic amount of piperidine triflate (5 mol %), the reaction can proceed smoothly with up to 92% ee. This new method provides a supplement to the reported catalytic system with iridium-diphosphine complex. Its application in the asymmetric hydrogenation of other heteroaromatic compounds is under investigation.

Table 4
Asymmetric hydrogenation of quinolines[a]



Entry	R/R[1]	Yield[b] (%)	Ee[c] (%)
1	H/Me	95 (**2a**)	91 (*R*)
2	H/Et	99 (**2b**)	87 (*R*)
3	H/*n*-Pr	91 (**2c**)	89 (*R*)
4	H/*n*-Bu	98 (**2d**)	84 (*R*)
5	H/$Me_2CH(OH)CH_2$-	96 (**2e**)	92 (*S*)
6	H/Phenethyl	98 (**2f**)	88 (*R*)
7	H/3,4-$(MeO)_2C_6H_3(CH_2)_2$-	99 (**2g**)	89 (*R*)
8	Me/Me	88 (**2h**)	90 (*R*)
9	MeO/Me	95 (**2i**)	91 (*R*)
10	F/Me	88 (**2j**)	89 (*R*)
11	H/Ph	67 (**2k**)	78 (*S*)

[a] Conditions: 0.25 mmol of quinolines, $[Ir(COD)Cl]_2$ (2 mol %), (*R*)-SegPhos (4.4 mol %), piperidine·TfOH (5 mol %), 3 mL of THF, rt, 16 h.
[b] Isolated yields.
[c] Determined by HPLC.



Scheme 3. Asymmetric hydrogenation of quinoxalines.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.004.

References and notes

1. (a) Blaser, H.-U.; Pugin, B.; Spindler, F. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds., 2nd ed.; Wiley-VCH: Weinheim, 2000. Chapter 3.3.1; (b) Rylander, P. N. *Catalytic Hydrogenation in Organic Synthesis*; Academic Press: New York, 1979. p 175; (c)*The Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weiheim, 2007.
2. For recent reviews on hydrogenation of aromatic compounds, see: (a) Glorius, F. *Org. Biomol. Chem.* **2005**, *3*, 4171–4175; (b) Lu, S.-M.; Han, X.-W.; Zhou, Y.-G. *Chin. J. Org. Chem.* **2005**, *25*, 634–640; (c) Dyson, P. J. *Dalton Trans.* **2003**, 2964–2974; (d) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357–1366; (e) Kuwano, R. *Hetereocycles* **2008**, *76*, 909–922.
3. (a) Keay, J. G.. In *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 8. p 579; (b) Katrizky, A. R.; Rachwal, S.; Bachwal, B. *Tetrahedron* **1996**, *52*, 15031–15070; (c) Barton, D. H.; Nakanishi, K.; Meth-Cohn, O.. In *Comprehensive Natural Products Chemistry*; Elsevier: Oxford, 1999; Vol. 1–9.
4. Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536–10537.
5. For our group's work on asymmetric hydrogenation of quinolines, see: (a) Lu, S.-M.; Han, X.-W.; Zhou, Y.-G. *Adv. Synth. Catal.* **2004**, *346*, 909–912; (b) Yang, P.-Y.; Zhou, Y.-G. *Tetrahedron: Asymmetry* **2004**, *15*, 1145–1149; (c) Zhao, Y.-J.; Wang, Y.-Q.; Zhou, Y.-G. *Chin. J. Catal.* **2005**, *26*, 737–739; (d) Wang, D.-W.; Zeng, W.; Zhou, Y.-G. *Tetrahedron: Asymmetry* **2007**, *18*, 1103–1107; (e) Lu, S.-M.; Han, X.-W.; Zhou, Y.-G. *J. Organomet. Chem.* **2007**, *692*, 3065–3069; (f) Wang, X.-B.; Zhou, Y.-G. *J. Org. Chem.* **2008**, *73*, 5640–5642; (g) Wang, D.-W.; Wang, X.-B.; Wang, D.-S.; Lu, S.-M.; Zhou, Y.-G.; Li, Y.-X. *J. Org. Chem.* **2009**, *74*, 2780–2787; (h) Wang, D.-S.; Zhou, J.; Wang, D.-W.; Guo, Y.-L.; Zhou, Y.-G. *Tetrahedron Lett.* **2010**, *51*, 525–528; (i) Wang, D.-W.; Wang, D.-S.; Chen, Q.-A.; Zhou, Y.-G. *Chem. Eur. J.* **2010**, *16*, 1133–1136.
6. For other groups' work on iridium-catalyzed asymmetric hydrogenation of quinolines, see: (a) Xu, L. J.; Lam, K. H.; Ji, J. X.; Wu, J.; Fan, Q.-H.; Lo, W.-H.; Chan, A. S. C. *Chem. Commun.* **2005**, 1390–1392; (b) Lam, K. H.; Xu, L. J.; Feng, L. C.; Fan, Q.-H.; Lam, F. L.; Lo, W.-H.; Chan, A. S. C. *Adv. Synth. Catal.* **2005**, *347*, 1755–1758; (c) Wu, J.; Chan, A. S. C. *Acc. Chem. Res.* **2006**, *39*, 711–720; (d) Tang, W.-J.; Zhu, S.-F.; Xu, L.-J.; Zhou, Q.-L.; Fan, Q.-H.; Zhou, H.-F.; Lam, K.; Chan, A. S. C. *Chem. Commun.* **2007**, 613–615; (e) Wang, Z.-J.; Deng, G.-J.; Li, Y.; He, Y.-M.; Tang, W.-J.; Fan, Q.-H. *Org. Lett.* **2007**, *9*, 1243–1246; (f) Chan, S.-H.; Lam, K.-H.; Li, Y.-M.; Xu, L.-J.; Tang, W.-J.; Lam, F.-L.; Lo, W.-H.; Yu, W.-Y.; Fan, Q.-H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2007**, *18*, 2625–2631; (g) Reetz, M. T.; Li, X.-G. *Chem. Commun.* **2006**, 2159–2160; (h) Qiu, L.; Kwong, F. Y.; Wu, J.; Lam, W. H.; Chan, S.; Yu, W.-Y.; Li, Y.-M.; Guo, R.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2006**, *128*, 5955–5965; (i) Lu, S.-M.; Bolm, C. *Adv. Synth. Catal.* **2008**, *350*, 1101–1105; (j) Yamagata, T.; Tadaoka, H.; Nagata, M.; Hirao, T.; Kataoka, Y.; Ratovelomanana-Vidal, V.; Genet, J. P.; Mashima, K. *Organometallics* **2006**, *25*, 2505–2513; (k) Jahjah, M.; Alame, M.; Pellet-Rostaing, S.; Lemaire, M. *Tetrahedron: Asymmetry* **2007**, *18*, 2305–2312; (l) Deport, C.; Buchotte, M.; Abecassis, K.; Tadaoka, H.; Ayad, T.; Ohshima, T.; Genet, J.-P.; Mashima, K.; Ratovelomanana-Vidal, V. *Synlett* **2007**, 2743–2747; (m) Fache, F. *Synlett* **2004**, 2827–2829; (n) Fujita, K.-I.; Kitatsuji, C.; Furukawa, S.; Yamaguchi, R. *Tetrahedron Lett.* **2004**, *45*, 3215–3217; (o) Eggenstein, M.; Thomas, A.; Theuerkauf, J.; Franciò, G.; Leitner, W. *Adv. Synth. Catal.* **2009**, *351*, 725–732.
7. For the work on organocatalytic asymmetric transfer hydrogenation of quinolines, see: (a) Rueping, M.; Theissmann, T.; Antonchick, A. P. *Synlett* **2006**, 1071–1074; (b) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew.*

Chem., Int. Ed. **2006**, *45*, 3683–3686; (c) Rueping, M.; Theissmann, T.; Raja, S.; Bats, J. W. P. *Adv. Synth. Catal.* **2008**, *350*, 1001–1006; (d) Guo, Q.-S.; Du, D.-M.; Xu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 759–762; (e) You, S.-L. *Chem. Asian J.* **2007**, *2*, 820–827.
8. Lu, S.-M.; Wang, Y.-Q.; Han, X.-W.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2260–2263.
9. Mršić, N.; Lefort, L.; Boogers, J. A. F.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Adv. Synth. Catal.* **2008**, *350*, 1081–1089.
10. (a) Zhou, H.-F.; Li, Z.-W.; Wang, Z.-J.; Wang, T.-L.; Xu, L.-J.; He, Y.-M.; Fan, Q.-H.; Pan, J.; Gu, L.-Q.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2008**, *47*, 8464–8467; (b) Wang, Z.-J.; Zhou, H.-F.; Wang, T.-L.; He, Y.-M.; Fan, Q.-H. *Green Chem.* **2009**, *11*, 767–769.
11. Li, Z.-W.; Wang, T.-L.; He, Y.-M.; Wang, Z.-J.; Fan, Q.-H.; Pan, J.; Xu, L.-J. *Org. Lett.* **2008**, *10*, 5265–5268.
12. Wang, C.; Li, C. Q.; Wu, X. F.; Pettman, A.; Xiao, J. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 6524–6528.
13. Hou, G. H.; Gosselin, F.; Li, W.; McWilliams, J. C.; Sun, Y. K.; Weisel, M.; O'Shea, P. D.; Chen, C. Y.; Davies, I. W.; Zhang, X. M. *J. Am. Chem. Soc.* **2009**, *131*, 9882–9883.
14. Tadaoka, H.; Cartigny, D.; Nagano, T.; Gosavi, T.; Ayad, T.; Genet, J.-P.; Ohshima, T.; Ratovelomanana-Vidal, V.; Mashima, K. *Chem. Eur. J.* **2009**, *15*, 9990–9994.
15. (a) Bianchini, C.; Barbaro, P.; Scapacci, G.; Farnetti, E.; Graziani, M. *Organometallics* **1998**, *17*, 3308–3310; (b) Henschke, J. P.; Burk, M. J.; Malan, C. G.; Herzberg, D.; Peterson, J. A.; Wildsmith, A. J.; Cobley, C. J.; Casy, G. *Adv. Synth. Catal.* **2003**, *345*, 300–307; (c) Mršić, N.; Jerphagnon, T.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Adv. Synth. Catal.* **2009**, *351*, 2549–2552; (d) Tang, W.-J.; Xu, L.-J.; Fan, Q.-H.; Wang, J.; Fan, B.-M.; Zhou, Z.-Y.; Lam, K.-H.; Chan, A. S. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 9135–9138; (e) Rueping, M.; Tato, F.; Schoepke, F. R. *Chem. Eur. J.* **2010**, *16*, 2688–2691.