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Iridium-Catalyzed Asymmetric Hydrogenation of Quinoline Derivatives with C_3*-TunePhos

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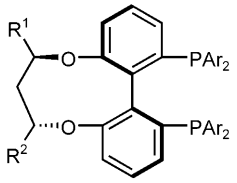
Abstract: A series of C_3*-TunePhos chiral diphosphine ligands has been successfully applied in the iridium-catalyzed enantioselective hydrogenation of quinolines, and this methodology provided an efficient access to a variety of optically active tetrahydroquinolines with up to 93% *ee*. Furthermore, attempts on the asymmetric hydrogenation of quinoline *N*-oxide are also discussed.

Keywords: asymmetric catalysis; enantioselectivity; hydrogenation; iridium; quinolines



(*S*),(*S*,*S*)-**1a:** Ar = C_6H_5; $R^1 = R^2 = H$;
(*S*),(*S*,*S*)-**1b:** Ar = C_6H_5; $R^1 = R^2 = CH_3$;
(*S*),(*S*,*S*)-**1c:** Ar = 4-MeC_6H_4; $R^1 = R^2 = CH_3$;
(*S*),(*S*,*S*)-**1d:** Ar = 3,5-$Me_2C_6H_3$; $R^1 = R^2 = CH_3$;
(*S*),(*S*,*S*)-**1e:** Ar = 3,5-(*t*-Bu)$_2C_6H_3$; $R^1 = R^2 = CH_3$;
(*S*),(*S*,*S*)-**1f:** Ar = 4-MeO-3,5-(*t*-Bu)$_2C_6H_2$; $R^1 = R^2 = CH_3$.

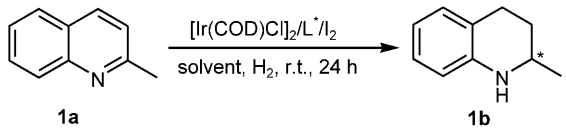
Scheme 1. C_3-TunePhos and C_3*-TunePhos.

The direct catalytic asymmetric hydrogenation of quinolines constitutes the most convenient route to enantiomerically pure tetrahydroquinolines,[1] which are not only useful synthetic intermediates[2] but also structural moieties in alkaloids which are natural products and biologically active compounds.[3] The first example of asymmetric hydrogenation of quinolines was reported by Zhou[4a] and co-workers, and some progresses has been achieved thereafter.[4–6] However, the challenges of developing easily accessible, air-stable, chiral ligands and their application in the direct asymmetric hydrogenation of highly substituted quinolines still remain.

In previous communications, we have developed a practical and convenient synthetic route to prepare a series of air-stable, modular, biaryl chiral diphosphine ligands C_3*-TunePhos (Scheme 1).[7] These ligands were designed to achieve superior enantioselectivities for asymmetric hydrogenations utilizing the highly modular nature of their unique steric and electronic properties and they have been demonstrated to be highly effective in the hydrogenation *N*-substituted allylphthalimides,[7g] β-keto esters[7h] and unfunctionalized ketones.[7i] Chan et al. demonstrated the catalytic capability of (*S*),(*S*,*S*)-**1b** for the iridium-catalyzed reduction of some heteroaromatic compounds,[7j] however, hard modifications on P-aryl groups restrict their potential applications, since for atropisomeric biaryldiphosphines, a small variation of the dihedral angle of the ligands can have a significant impact on the reactivity and selectivity of the reaction. Thus, to screen the catalytic performance of C_3*-TunePhos families and illustrate their potential utilities, we summarized our efforts in the iridium-catalyzed asymmetric hydrogenation of highly substituted quinoline derivatives.

Our initial study began with hydrogenation of 2-methylquinoline **1a** as the model substrate and a brief screening of the performance of different catalysts. Key results are shown in Table 1. First, different iridium precursors were screened using C_3-TunePhos as the ligand. It was shown that the neutral precursor $[Ir(COD)Cl]_2$ was superior to the cationic iridium species with BF_4 and BARF {tetrakis[3,5-bis(trifluorome-

Table 1. Catalytic asymmetric hydrogenation of **1a**.[a]



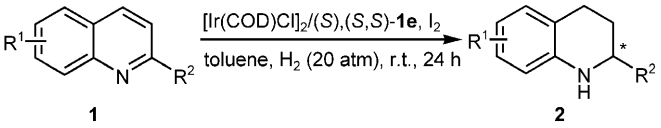
Entry	Metal precursor	Ligand L*	Solvent	Conv. [%][b]	*ee* [%][c]
1	$[Ir(COD)Cl]_2$	(*S*),(*S*,*S*)-**1a**	toluene	96	84
2	$Ir(COD)_2BARF$	(*S*),(*S*,*S*)-**1a**	toluene	99	70
3	$Ir(COD)_2BF_4$	(*S*),(*S*,*S*)-**1a**	toluene	99	62
4	$[Ir(COD)Cl]_2$	(*S*),(*S*,*S*)-**1b**	toluene	99	90
5	$[Ir(COD)Cl]_2$	(*S*),(*S*,*S*)-**1c**	toluene	98	91
6	$[Ir(COD)Cl]_2$	(*S*),(*S*,*S*)-**1d**	toluene	98	88
7	$[Ir(COD)Cl]_2$	(*S*),(*S*,*S*)-**1e**	toluene	97	93
8	$[Ir(COD)Cl]_2$	(*S*),(*S*,*S*)-**1f**	toluene	98	91
9	$[Ir(COD)Cl]_2$	(*S*),(*S*,*S*)-**1e**	THF	92	64
10	$[Ir(COD)Cl]_2$	(*S*),(*S*,*S*)-**1e**	CH_2Cl_2	96	82
11	$[Ir(COD)Cl]_2$	(*S*),(*S*,*S*)-**1e**	AcOEt	95	86
12	$[Ir(COD)Cl]_2$	(*S*),(*S*,*S*)-**1e**	*i*-PrOH	95	84
13[d]	$[Ir(COD)Cl]_2$	(*S*),(*S*,*S*)-**1e**	toluene	98	93
14[e]	$[Ir(COD)Cl]_2$	(*S*),(*S*,*S*)-**1e**	toluene	99	91

[a] All reactions were performed on a 0.5-mmol scale: iridium/ligand/I_2 = 0.5/1.05/5, 1 mol% iridium catalyst, 2.5 mL solvent, 50 atm H_2 pressure, room temperature, 24 h.
[b] Determined by GC analysis.
[c] The *ee* was determined by chiral GC analysis or chiral HPLC analysis (see the Supporting Information). The absolute configuration of product is assigned by comparison of optical rotation with literature data.
[d] 20 atm H_2 pressure.
[e] 10 atm H_2 pressure.

thyl)phenyl]borate} counterions, and afforded 96% conversion and 84% *ee* (Table 1, entries 1–3). Further studies showed that the reactions proceeded smoothly with high conversions and *ee* values when switching to the C_3*-TunePhos ligand family with various aryl substituents on the phosphine moiety (entries 4–8). To our delight, the highest enantioselectivity of 93% *ee* was achieved by applying the di-*t*-Bu-phenyl-substituted ligand (*S*),(*S*,*S*)-**1e** (entry 7). Greater than 90% conversions were achieved in all solvents examined, either protic or aprotic solvents (entries 9–12). But the use of THF as solvent resulted in low enantioselectivity and somewhat a slightly lower conversion (entry 9). Compared with other solvents, toluene was more effective. The best result was obtained under 20 atm H_2 and the *ee* value remained the same under the milder conditions (entries 13 and 14). Considering the crucial influence of additives on reactivity,[8] we further evaluated a number of additives including KI, NaI, LiI, tetrabutylammonium iodide and some organic and inorganic acids, such as CF_3SO_3H, CF_3COOH, CH_3COOH, HCl and H_2SO_4, etc., I_2 was found to be essential and the most effective additive.

Despite the recent progresses in the asymmetric hydrogenation of quinolines, highly enantioselective hydrogenation of various functionalized quinolines still remains as a challenging task. However, reactivity and enantioselectivity are often substrate-dependent: subtle variations of steric and electronic properties of the substituents could lead to significant changes in reactivity and enantioselectivity. Nevertheless, previous reports on the hydrogenation of quinolines have mainly focused on 2- or 6-substituted analogues, and a systematic examination of the substrate scope of substituted quinolines is rare. Thus, under the optimized conditions, the generality of the iridium-C_3*-TunePhos catalyst was further investigated, and the results are summarized in Table 2. Slightly decreased conversion and *ee* values were observed in the hydrogenation of substrate **1b** which bears a more bulky alkyl group (Table 2, entry 2). However, changing the alkyl group at the 2-position to a phenyl group resulted in significant erosion of the enantioselectivity (entry 3). On the other hand, this hydrogenation could tolerate various substituents at the 6- or 7-position, including fluoro, chloro, bromo, methyl and methoxy groups (entries 4–11). However, a nitro-substituted substrate afforded lower enantioselectivity (75% *ee*; entry 9), possibly due to the strong electronic property of the nitro group. When switching to 8-

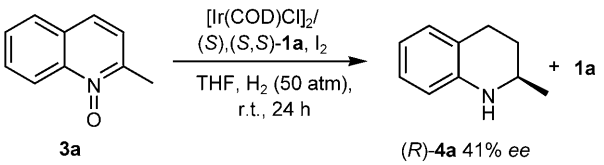
Table 2. Catalytic asymmetric hydrogenation of quinoline derivatives.[a]



1 2

Entry	R^1/R^2 of **1**	Product	Conv. [%][b]	*ee* [%] (config.)[c]
1	H/Me (**1a**)	**2a**	98	93 (*S*)
2	H/Et (**1b**)	**2b**	94	88 (*S*)
3	H/Ph (**1c**)	**2c**	98	73 (*S*)
4	6-F/Me (**1d**)	**2d**	97	91 (*S*)
5	6-Cl/Me (**1e**)	**2e**	99	90 (−)
6	6-Br/Me (**1f**)	**2f**	99	90 (−)
7	6-Me/Me (**1g**)	**2g**	95	92 (*S*)
8	6-MeO/Me (**1h**)	**2h**	84	89 (*S*)
9	6-NO_2/Me (**1i**)	**2i**	98	75 (−)
10	7-F/Me (**1j**)	**2j**	99	92 (−)
11	7-Cl/Me (**1k**)	**2k**	99	90 (−)
12	8-Cl/Me (**1l**)	**2l**	99	56 (−)

[a] All reactions were performed on a 0.5-mmol scale: $[Ir(COD)Cl]_2$ 0.5 mol%, (*S*),(*S*,*S*)-**1e** 1.05 mol%, I_2 5 mol%, H_2 20 atm, toluene 2.5 mL, room temperature, 24 h.
[b] Determined by GC analysis.
[c] The *ee* was determined by chiral GC analysis or chiral HPLC analysis (see the Supporting Information). The absolute configuration of product is assigned by comparison of rotation sign with literature data.



Scheme 2. Catalytic asymmetric hydrogenation of quinoline *N*-oxide.

substituted substrate **1l**, a dramatic drop of *ee* was observed (entry 12), In this case, the lower enantioselectivity may be attributed to the steric hindrance of the substituent. Additional attempts to examine 3- or 4-substituted quinolines exhibited no effect, and the result is consistent with Zhou's finding with the iridium-MeOBIPHEP catalyst system.[4a]

The above results encouraged us to extend our investigation of asymmetric hydrogenation to other related substrates by applying the iridium-C_3*-TunePhos catalyst. We envisioned that our approach could be applied to enantioselectively reduce quinoline *N*-oxide derivatives. Utilizing substrate **3a** as a model substrate, the reaction conditions were optimized to achieve this goal (Scheme 2). The best result was achieved in THF under 50 atm H_2. The reaction produced a 9:1 ratio of (*R*)-2-methyl-1,2,3,4-tetrahydroquinoline **4a** with 41% *ee* and 2-methylquinoline (>99% conversion). We envisioned one pathway of this transformation might have proceeded in two sequential steps, involving an iridium-catalyzed reduction of quinoline *N*-oxide step which afforded the key intermediate **1a**, followed by an asymmetric hydrogenation step to form the final product **4a** with the opposite configuration. We also believe that there exist other hydrogenation pathways because of the only moderate enantioselectivity and more importantly the fact that the opposite configuration was obtained in product **4a**. To our best knowledge, this preliminary study is the first report of homogeneous catalytic asymmetric hydrogenation of quinoline *N*-oxides.

In conclusion, we have developed an efficient enantioselective hydrogenation of a wide range of functionalized quinoline derivatives using the iridium-(*S*)-C_3*-TunePhos catalyst. This method provided an efficient access to a variety of optically active tetrahydroquinolines with good to excellent enantioselectivities (up to 93% *ee*). Further studies on the hydrogenation of other heteroaromatic compounds and development of new catalytic systems for asymmetric hydrogenation of heteroaromatic *N*-oxides are under way and will be reported in due course.

Experimental Section

General Procedure for Asymmetric Hydrogenation of Quinolines

A mixture of $[Ir(COD)Cl]_2$ (1.7 mg, 0.0025 mmol) and (*S*),(*S*,*S*)-**1e** (5.6 mg, 0.00525 mmol) in toluene (1 mL) was stirred at room temperature for 10 min in a glovebox, then I_2 (6.4 mg, 0.025 mmol) and substrate (0.5 mmol) together with 1.5 mL of toluene were added and the solution was stirred for another 10 min. The hydrogenation was performed under 20 atm H_2 at room temperature for 24 h. After the hydrogen had been carefully released, the reaction solution was purified on a silica gel column to give the product, which was then analyzed by chiral GC to determine the conversions and enantiomeric excesses.

(−)-7-Chloro-2-methyl-1,2,3,4-tetrahydroquinoline (2k): 99% conversion; 90% *ee*; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.76 (d, J = 4.0 Hz, 1H), 6.47–6.44 (m, 1H), 6.34 (s, 1H), 3.62 (s, 1H), 3.32–3.27 (m, 1H), 2.67–2.60 (m, 2H), 1.85–1.80 (m, 1H), 1.49–1.43 (m, 1H), 1.11 (d, J = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 145.7, 131.9, 130.2, 119.4, 116.6, 113.3, 47.0, 29.8, 26.1, 22.5; IR (neat): ν = 1602, 1494, 1330, 1296, 1139, 1081, 933, 820, 756 cm^{-1}; chiral GC (Gamma Dex 225, 30 m × 0.25 mm, column temperature: 130 °C, carrier gas: He, 1.0 mL min^{-1}): t_1 = 81.12 min, t_2 = 83.83 min; HR-MS: m/z = 182.0741, calcd. for $C_{10}H_{13}ClN$ $[M+H]^+$: 182.0737; $[\alpha]_D^{20}$: −68.5 (*c* 0.5, $CHCl_3$).

Acknowledgements

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References

[1] a) Y.-G. Zhou, *Acc. Chem. Res.* **2007**, *40*, 1357–1366; b) J. Wu, A. S. C. Chan, *Acc. Chem. Res.* **2006**, *39*, 711–720.

[2] J. D. Keay, in: *Comprehensive Organic Synthesis*, (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, Vol. 8, pp 579–601.

[3] a) *Comprehensive Natural Products Chemistry*, Vols. 1–9 (Eds.: D. H. R. Barton, K. Nakanishi, O. Meth-Cohn), Elsevier, Oxford, **1999**; b) I. Jacquemond-Collet, S. Hannedouche, N. Fabre, I. Fouraste, C. Moulis, *Phytochemistry* **1999**, *51*, 1167–1169; c) J. H. Rokotoson, N. Fabre, I. Jacquemond-Collet, S. Hannedouche, N. Fabre, I. Fouraste, C. Moulis, *Planta Med.* **1998**, *64*, 760–762; d) P. J. Houghton, T. Z. Woldemariam, Y. Watanabe, M. Yates, *Planta Med.* **1999**, *65*, 250–254; e) M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341–3370.

[4] a) W.-B. Wang, S.-M. Lu, P.-Y.; Yang, X.-W. Han, Y.-G. Zhou, *J. Am. Chem. Soc.* **2003**, *125*, 10536–10537; b) S.-M. Lu, X.-W. Han, Y.-G. Zhou, *Adv. Synth. Catal.* **2004**, *346*, 909–912; c) S.-M. Lu, Y.-Q.; Wang, X.-W. Han, Y.-G. Zhou, *Angew. Chem.* **2006**, *118*, 2318–2321; *Angew. Chem. Int. Ed.* **2006**, *45*, 2260–2263; d) X.-B. Wang, Y.-G. Zhou, *J. Org. Chem.* **2008**, *73*, 5640–5642; e) D.-W.

Wang, X.-B. Wang, ; D.-S. Wang, S.-M. Lu, Y.-G. Zhou, Y.-X. Li, *J. Org. Chem.* **2009**, *74*, 2780–2787; f) L. J. Xu, K. H. Lam, J. X. Ji, Q.-H. Fan, W.-H. Lo, A. S. C. Chan, *Chem. Commun.* **2005**, 1390–1392; g) K. H. Lam, L. J. Xu, L. C. Feng, Q.-H. Fan, F. L. Lam, W.-H. Lo, A. S. C. Chan, *Adv. Synth. Catal.* **2005**, *347*, 1755–1758; h) W.-J. Tang, S.-F. Zhu, L.-J. Xu, Q.-L. Zhou, Q.-H. Fan, H.-F. Zhou, K. Lam, A. S. C. Chan, *Chem. Commun.* **2007**, 613–615; i) M. T. Reetz, X.-G. Li, *Chem. Commun.* **2006**, 2159–2160; j) N. Mrsic, L. Lefort, J. A. F.; Boogers, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *Adv. Synth. Catal.* **2008**, *350*, 1081–1089; k) Z.-J. Wang, G.-J. Deng, Y. Li, Y.-M. He, W.-J. Tang, Q.-H. Fan, *Org. Lett.* **2007**, *9*, 1243–1246.

[5] a) Z.-W. Li, T.-L. Wang, Y.-M. He, Z.-J. Wang, Q.-H. Fan, J. Pan, L.-J. Xu, *Org. Lett.* **2008**, *10*, 5265–5268; b) H.-F. Zhou, Z.-W. Li, Z.-J. Wang, T.-L. Wang, L.-J. Xu, Y.-M. He, Q.-H. Fan, J. Pan, L.-Q. Gu, A. S. C. Chan, *Angew. Chem.* **2008**, *120*, 8592–8595; *Angew. Chem. Int. Ed.* **2008**, *47*, 8464–8467; c) S.-M. Lu, C. Bolm, *Adv. Synth. Catal.* **2008**, *350*, 1101–1105; d) C. Wang, C.-Q. Li, X.-F. Wu, A. Pettman, J.-L. Xiao, *Angew. Chem.* **2009**, *121*, 6646–6650; *Angew. Chem. Int. Ed.* **2009**, *48*, 6524–6528.

[6] a) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 3765–3768; *Angew. Chem. Int. Ed.* **2006**, *45*, 3683–3686; b) M. Rueping, T. Theissmann, S. Raja, J. W. P. Bats, *Adv. Synth. Catal.* **2008**, *350*, 1001–1006; c) Q.-S. Guo, D.-M. Du, J. Xu, *Angew. Chem.* **2008**, *120*, 771–774; *Angew. Chem. Int. Ed.* **2008**, *47*, 759–762; d) Y.-M. He, Q.-H. Fan, *Org. Biomol. Chem.* **2010**, *11*, 2497–2504; e) D.-S. Wang, Y.-G. Zhou, *Tetrahedron Lett.* **2010**, *51*, 3014–3017; f) D.-S. Wang, J. Zhou, D.-W. Wang, Y.-L. Guo, Y.-G. Zhou, *Tetrahedron Lett.* **2010**, *51*, 525–528; g) W.-J. Tang, J. Tan, L.-J. Xu, K.-H. Lam, Q.-H. Fan, A. S. C. Chan, *Adv. Synth. Catal.* **2010**, *352*, 1055–1062; h) W. Tang, Y. Sun, L. Xu, T. Wang, Q. Fan, K.-H. Lam, A. S. C. Chan, *Org. Biomol. Chem.* **2010**, *15*, 3464–3471; i) P.-C. Yan, J.-H. Xie, G.-H. Hou, L.-X. Wang, Q.-L. Zhou, *Adv. Synth. Catal.* **2009**, *351*, 3243–3250; j) Z.-J. Wang, H.-F. Zhou, T.-L. Wang, Y.-M. He, Q.-H. Fan, *Green Chem.* **2009**, *6*, 767–769; k) M. Eggenstein, A. Thomas, J. Theuerkauf, G. Franciò, W. Leitner, *Adv. Synth. Catal.* **2009**, *351*, 725–732; l) H. Tadaoka, D. Cartigny, T. Nagano, T. Gosavi, T. Ayad, J.-P. Genêt, T. Ohshima, V. Ratovelomanana-Vidal, K. Mashima, *Chem. Eur. J.* **2009**, *15*, 9990–9994; m) C. Deport, M. Buchotte, K. Abecassis, H. Tadaoka, T. Ayad, T. Ohshima, J.-P. Genêt, K. Mashima, V. Ratovelomanana-Vidal, *Synlett* **2007**, *17*, 2743–2747.

[7] a) X. Zhang, U.S. Patent 6,521,769, **2000**; b) Z. Zhang, H. Qian, J. Longmire, X. Zhang, *J. Org. Chem.* **2000**, *65*, 6223–6226; c) S. Wu, W. Wang, W. Tang, M. Lin, X. Zhang, *Org. Lett.* **2002**, *4*, 4495–4497; d) C. Wang, X. Sun, X. Zhang, *Angew. Chem.* **2005**, *117*, 5013–5015; *Angew. Chem. Int. Ed.* **2005**, *44*, 4933–4935; e) X. Sun, L. Zhou, C. Wang, X. Zhang, *Angew. Chem.* **2007**, *119*, 2677–2680; *Angew. Chem. Int. Ed.* **2007**, *46*, 2623–2626; f) X. Sun, W. Li, L. Zhou, X. Zhang, *Chem. Eur. J.* **2009**, *15*, 7302–7305; g) X. Sun, L. Zhou, W. Li, X. Zhang, *J. Org. Chem.* **2008**, *73*, 1143–1146; h) W. Li, X. Sun, L. Zhou, G. Hou, S. Yu, X. Zhang, *J. Org. Chem.* **2009**, *74*, 1397–1399; i) X. Sun, W. Li, G. Hou, L. Zhou, X. Zhang, *Adv. Synth. Catal.* **2009**, *351*, 2553–2557; j) L. Qiu, F. Y. Kwong, J. Wu, W. H. Lam, S. Chan, W.-Y. Yu, Y.-M. Li, R. Guo, Z. Zhou, A. S. C. Chan, *J. Am. Chem. Soc.* **2006**, *128*, 5955–5965.

[8] For reviews, see: a) K. Fagnou, M. Lautens, *Angew. Chem.* **2002**, *114*, 26–49; *Angew. Chem. Int. Ed.* **2002**, *41*, 26–47; b) E. M. Vogl, H. Groeger, M. Shibasaki, *Angew. Chem.* **1999**, *111*, 1672–1680; *Angew. Chem. Int. Ed.* **1999**, *38*, 1570–1577; c) D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* **1995**, *107*, 1159–1171; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059–1070.

