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Enantioselective Hydrogenation of Quinolines Catalyzed by Ir(BINAP)-Cored Dendrimers: Dramatic Enhancement of Catalytic Activity

Zhi-Jian Wang,[†,‡] Guo-Jun Deng,[†] Yong Li,[†,‡] Yan-Mei He,[†] Wei-Jun Tang,[†] and Qing-Hua Fan*[,†]

Beijing National Laboratory for Molecular Sciences, Center for Chemical Biology, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, China, and Graduate School of the Chinese Academy of Sciences, Beijing 100080, China

fanqh@iccas.ac.cn

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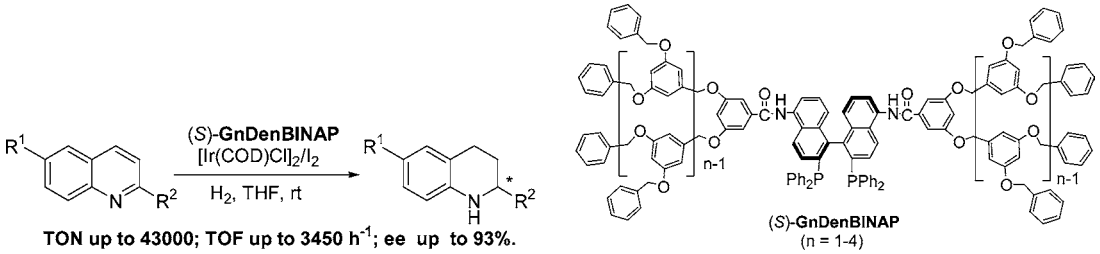
ABSTRACT



The asymmetric hydrogenation of quinolines catalyzed by chiral dendritic catalysts derived from BINAP gave the corresponding products with high enantioselectivities (up to 93%), excellent catalytic activities (TOF up to 3450 h^{-1}), and productivities (TON up to 43 000). In addition, the third-generation catalyst could be recovered by precipitation and filtration and reused at least six times with similar enantioselectivity.

The use of metallodendrimers in homogeneous catalysis is an important frontier of research in recent years.[1] Because of the well-defined molecular architecture of dendrimers, it is possible to fine-tune their catalytic properties through the systematic adjustment of their structure, size, shape, and solubility. Thus, a number of organometallic dendrimers with catalytic sites at either their core or their periphery have been reported. Among them, however, only a few reported a strong positive catalytic effect of dendrimers compared to that of monomeric species.[2,3] In the case of the core-functionalized dendrimers, it is expected that the steric shielding or blocking effect of the specific microenvironment created by the branched shell could modulate the catalytic behavior of the core. Recently, we reported a kind of BINAP-cored dendrimer for asymmetric hydrogenation of prochiral olefins.[3b]

[†] Institute of Chemistry, Chinese Academy of Sciences.

[‡] Graduate School of the Chinese Academy of Sciences.

(1) For selected reviews on dendritic organometallic catalysts, see: (a) Oosterom, G. E.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1828. (b) Astruc, D.; Chardac, F. *Chem. Rev.* **2001**, *101*, 2991. (c) van Heerbeek, R.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Chem. Rev.* **2002**, *102*, 3717. (d) Twyman, L. J.; King, A. S. H.; Martin, I. K. *Chem. Soc. Rev.* **2002**, *31*, 69. (e) Helms, B.; Fréchet, J. M. J. *Adv. Synth. Catal.* **2006**, *348*, 1125. (f) Kassube, J. K.; Gade, L. H. *Top. Organomet. Chem.* **2006**, *20*, 61.

(2) For examples of achiral dendrimer catalysts with a positive dendrimer effect, see: (a) Ropartz, L.; Morris, R. E.; Foster, D. F.; Cole-Hamilton, D. J. *Chem. Commun.* **2001**, 361. (b) Francavilla, C.; Drake, M. D.; Bright, F. V.; Detty, M. R. *J. Am. Chem. Soc.* **2001**, *123*, 57. (c) Mizugaki, T.; Murata, M.; Ooe, M.; Ebitani, K.; Kaneda, K. *Chem. Commun.* **2002**, 52. (d) Dahan, A.; Portnoy, M. *Org. Lett.* **2003**, *5*, 1197. (e) Müller, C.; Ackerman, L. J.; Reek, J. M. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2004**, *126*, 14960. (f) Ooe, M.; Murata, M.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2004**, *126*, 1604. (g) Fujihara, T.; Obora, Y.; Tokunaga, M.; Sato, H.; Tsuji, Y. *Chem. Commun.* **2005**, 4526. (h) Ouali, A.; Laurent, R.; Caminade, A.-M.; Majoral, J.-P.; Taillefer, M. *J. Am. Chem. Soc.* **2006**, *128*, 15990.

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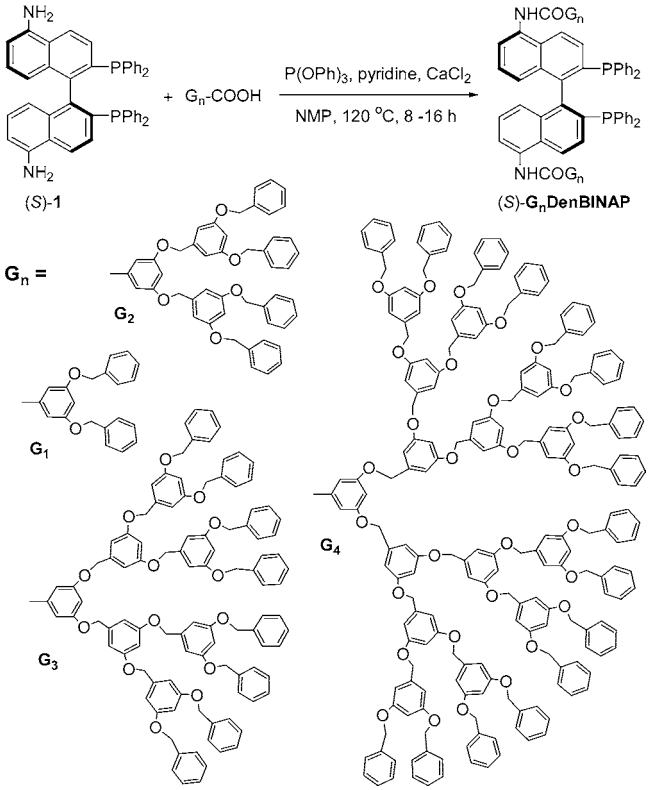
It was found that the rate of the reaction increased using the higher-generation dendritic catalysts. In contrast, dendritic catalysts with a chiral diphosphine pyrphos located at the focal point showed a dramatic decrease in catalytic activity on going from generation 3 to generation 4.[4] This negative effect might be due to the steric shielding effect of the dendritic shell. Here, we wish to report a strong positive dendrimer effect in the Ir-catalyzed asymmetric hydrogenation of quinolines by using our BINAP-cored dendrimers.

Asymmetric hydrogenation of quinolines constitutes the most convenient route to enantiomerically pure 1,2,3,4-tetrahydroquinolines, compounds which not only are useful synthetic intermediates but also are the structural units in naturally occurring alkaloids.[5] Although a variety of chiral Rh, Ru, and Ir complexes have been demonstrated to be highly efficient and enantioselective in the hydrogenation of prochiral olefins, ketones, and imines,[6] most of these catalysts failed to give satisfactory results in the asymmetric hydrogenation of heteroaromatic compounds.[7−9] Successful examples in the asymmetric hydrogenation of quinolines are rare.[8,9] Recently, Zhou and co-workers found that the iridium complex generated in situ from $[Ir(COD)Cl]_2$ and (*R*)-MeO-BIPHEP or the ferrocenyloxazoline-derived P,N-ligand is effective in the hydrogenation of 2-substituted quinolines with high enantioselectivities and reaction yields.[8a,c] Similar results were subsequently described by Fan and Chan et al. with the air-stable and recyclable Ir-P-Phos catalyst system.[9a] More recently, Fan and Chan et al. further reported that the iridium complexes prepared from the easily available chiral phosphinite H8-BINAPO or spiro diphosphinite were able to catalyze the enantioselective hydrogenation of quinolines with high enantioselectivities and very good yields.[9b,c] Reetz and co-workers also demonstrated BINOL-derived diphosphonites with achiral P-ligands as additives to be highly efficient for the same reactions.[9d] However, almost all these catalytic systems suffered from low catalyst efficiency as evidenced by the fact that good results could only be obtained at a low substrate−catalyst ratio of 100. Although the mechanism of this reaction is not clear at this moment, it is believed that the high catalyst loading may be due to the catalyst deactivation during the reaction. Recently, it was reported that the Ir complexes were effective in the asymmetric hydrogenation of imines.[10] However, the formation of an irreversible iridium dimer could retard the reaction, as it was a pathway for catalyst deactivation.[11] Therefore, we anticipated that the encapsulation of such an iridium complex into a dendrimer framework would reduce dimerization and therefore enhance the productivity of the catalyst.

Fréchet-type polyaryl ether dendrons were chosen for this study owing to their chemical inertness and inability to coordinate iridium.[12] The synthesis and structures of the dendritic ligands were outlined in Scheme 1. According to

Scheme 1. Synthesis and Structures of Dendritic **G_nDenBINAP** Ligands



our previous study,[3b] the chiral dendrimer ligands **G_nDenBINAP** were synthesized by condensation of the dendritic wedges G_n-COOH with (*S*)-5,5′-diamino BINAP (*S*)-**1** in the presence of triphenylphosphite, pyridine, and calcium chloride in *N*-methyl-2-pyrrolidone (NMP) at 120 °C overnight in more than 80% reaction yield, respectively. These ligands were fully characterized by ^1H, ^{13}C, and ^{31}P NMR spectroscopy, MALDI-TOF mass spectrometry, and elemental analysis. All results are in full agreement with the compounds synthesized.

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(5) For a review on 1,2,3,4-tetrahydroquinolines, see: Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031.

(6) For reviews, see: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley: New York, 2000. (c) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2. (d) Lin, G. Q.; Li, Y. M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*; Wiley-Interscience: New York, 2001.

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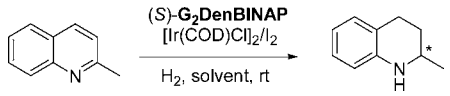
With these dendritic ligands in hand, we initially focused on the examination of reaction parameters. The effects of the solvents, temperature, hydrogen pressure, and additive on the activity and enantioselectivity were investigated by using the second-generation dendrimer catalyst, which was generated in situ from **G_2DenBINAP** and $[Ir(COD)Cl]_2$ (Table 1).

Table 1. Asymmetric Hydrogenation of Quinaldine (**2a**) Catalyzed by Dendritic Ir(**G_2DenBINAP**) Catalyst[a]



entry	solvent	time (h)	conversion (%)[b]	ee (%)[c]
1	toluene	20	>95	81
2	CH_2Cl_2	20	>95	85
3	1,4-dioxane	20	>95	88
4	THF	20	>95	89
5	THF/MeOH (4:1)	20	70	88
6	THF	1.5	>95	89
7[d]	THF	1.5	>95	88
8[e]	THF	6	>95	90
9[f]	THF	1.5	71	86
10[g]	THF	1.5	50	85
11[h]	THF	1.5	>95	89
12[i]	THF	1.5	>95	86
13[j]	THF	20	< 5	nd

[a] Reaction conditions: 0.25 mmol of quinaldine (**2a**) in 1.25 mL of solvent, 0.5 mol % of $[Ir(COD)Cl]_2$, 1.1 mol % of (*S*)-**G_2DenBINAP**, I_2/catalyst = 10 (mol/mol), 45 atm H_2, 15∼20 °C. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Determined by HPLC analysis with a Chirapak OJ-H column. The predominated product was in the *S*-configuration. [d] Reaction temperature = 50 °C. [e] Reaction temperature = 0 °C. [f] H_2 = 100 atm. [g] H_2 = 10 atm. [h] I_2/catalyst = 5 (mol/mol). [i] I_2/catalyst = 1 (mol/mol). [j] I_2 = 0 mol %.

It is interesting to find that the dendritic catalyst is effective in the asymmetric hydrogenation of **2a** with I_2 as an additive. A series of organic solvents were tested, and THF was found to be the best choice in terms of both conversion and enantioselectivity (entries 1−5). The use of alcoholic solvent such as methanol resulted in much lower catalytic activity (entry 5 vs 6). The enantioselectivity of the reaction was slightly increased at low temperature, but the reaction could be completed at prolonged time (entry 8). Notably, low conversion and enantioselectivity were observed under both higher and lower hydrogen pressure (entries 9 and 10). The reaction could not proceed without iodine as an additive (entry 13).

On the basis of the optimized reaction conditions, the asymmetric hydrogenation of **2a** was also used to assess the minimum amount of the dendritic catalysts. In sharp contrast to the small diphosphine ligands,[8,9] the dendritic catalyst was found to be highly effective even at extremely high substrate/catalyst ratio (Table 2). Most importantly, the enantioselectivity did not decrease under low catalyst loading. For example, in the presence of 0.01 mol % of **G_2DenBINAP**-Ir, the reaction proceeded smoothly upon prolonged reaction time, giving 88% ee and more than 95% conversion (entry 6). It was worthy to note that the reaction performed well under rather low catalyst loading on a large scale, giving a TON of 43 000, which is the highest TON reported to date.

Table 2. Minimum Amount of Dendritic Ir(**G_2DenBINAP**) Catalysts[a]

entry	sub./cat.	time (h)	TON	conversion (%)[b]	ee (%)[c]
1	400	1.5	400	>95	89
2	1000	5	1000	>95	89
3	2000	5	2000	>95	89
4	5000	5	4550	91	88
5	10000	5	7450	75	88
6	10000	20	10000	>95	88
7[d]	50000	48	43000	86	88

[a] Reaction conditions: 0.2∼0.5 mmol of quinaldine (**2a**) in THF, 1.25∼5.0 mol % of I_2, 45 atm H_2, 15∼20 °C. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Determined by HPLC analysis. [d] Substrate = 17.875 g, 1.25 mol % of I_2, 60 mL of THF, 45 atm H_2, 15∼20 °C.

Next, we investigated the effect of dendrimer generation on the catalyst performance (Table 3). It was found that the catalytic activity gradually increased with increasing dendrimer generation. Under low catalyst loading, the high-generation catalysts gave only slightly lower enantioselectivities. The maximum initial TOF thus reached 3450 (entry 6) which, to our knowledge, is the highest TOF obtained so far for the asymmetric hydrogenation of quinolines. In contrast, BINAP-Ir catalyst gave much lower enantioselectivity and catalytic activity (entries 5 and 7). The rate enhancement of the dendritic catalysts was further demonstrated by the results of the time-conversion curves (Figure 1). Although the nature of the observed strong dendrimer effect is not clear, the isolation effect of the steric dendritic shell might be responsible for this rate enhancement.

Table 3. Effect of Dendrimer Generation[a]

entry	ligand	TOF (h^{-1})[b]	conversion (%)[c]	ee (%)[d]
1	**G_1DenBINAP**	1000	50	89 (90)[e]
2	**G_2DenBINAP**	1500	75	89 (89)[e]
3	**G_3DenBINAP**	1580	79	88 (90)[e]
4	**G_4DenBINAP**	>1900	>95	87 (89)[e]
5[f]	BINAP	430	43	71 (75)[e]
6[f,g]	**G_3DenBINAP**	3450	23	87
7[f,h]	BINAP	625	25	71

[a] Reaction conditions: 2.5 mmol of quinaldine (**2a**) in 5 mL of THF, sub./cat. = 10 000 (mol ratio), 1.25 mol % of I_2, 45 atm H_2, 15∼20 °C, 5 h. [b] Average TOF over the reaction time. [c] Determined by ^{1}H NMR analysis of the crude product. [d] Determined by HPLC analysis. [e] Data in brackets were obtained with 1 mol % of catalyst, and complete conversion was observed. [f] Sub./cat. = 5000. [g] Reaction time = 20 min. [h] Reaction time = 2 h.

Encouraged by these excellent results, we decided to further investigate the applications of the dendritic catalyst in the asymmetric hydrogenation of other 2-substituted quinoline derivatives using **G_2DenBINAP** as the ligand

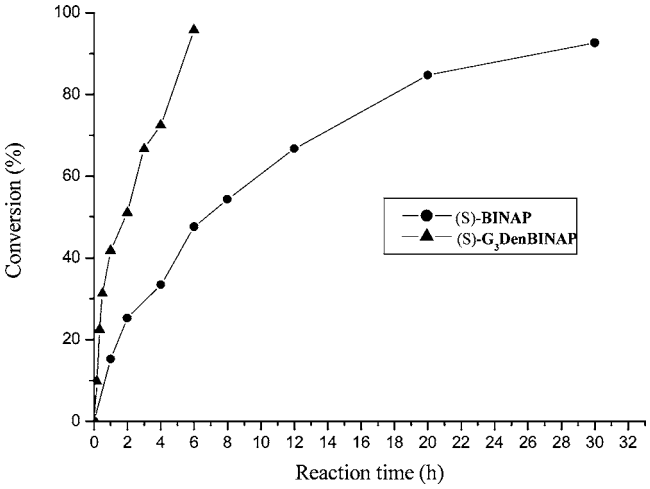
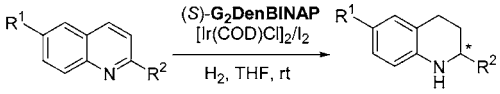


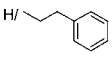
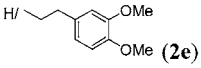
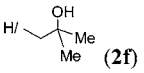
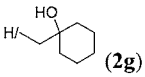
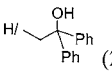
Figure 1. Time course curves of the hydrogenation of **2a** for Ir(**G_3DenBINAP**) and Ir(BINAP) catalysts (reaction conditions: 0.25 mmol of **2a** in THF, sub./cat. = 5000, 5.0 mol % of I_2, 45 atm H_2, 25 °C).

(Table 4). In general, all substituted quinolines studied were hydrogenated with good enantioselectivities and conversions.

Table 4. Catalytic Asymmetric Hydrogenation of Quinoline Derivatives[a]



2 (2a~2k) **3 (3a~3k)**

entry	R^1/R^2 (substrates)	convn (%)[b]	ee (%)[c]	config[d]
1	H/Me (**2a**)	>95 (>95)[e]	90 (89)[e]	S
2	H/Et (**2b**)	>95 (82)[e]	89 (87)[e]	*S*
3	H/n-Pr (**2c**)	>95 (>95)[e,f]	89 (86)[e]	*S*
4	 (**2d**)	>95 (78)[e]	84 (82)[e]	*S*
5	 (**2e**)	83 (37)[e]	82 (76)[e]	*R*
6	 (**2f**)	>95 (38)[e]	92 (93)[e]	*R*
7	 (**2g**)	>95 (35)[e]	93 (92)[e]	*R*
8	 (**2h**)	77	76	*R*
9	MeO/Me (**2i**)	87	89	*S*
10	Me/Me (**2j**)	77	87	*S*
11	F/Me (**2k**)	>95	87	*S*

[a] Reaction conditions: 0.25 mmol of substrate in 1.25 mL of THF, 0.25 mol % of Ir(**G_2DenBINAP**) catalyst, 5 mol % of I_2, 20~25 °C, 1.5 h. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Determined by HPLC analysis with Chirapak OJ-H (**2a**~**2c**, **2i**, and **2j**), AS-H (**2d** and **2e**), and OD−H (**2f**~**2h** and **2k**) columns. [d] The absolute configuration is assigned by comparison of the HPLC retention time with those reported in the literature data. [e] Data in brackets were obtained by using 0.01% catalyst under the following conditions: 2.5 mmol of substrate in 5 mL of THF, 1.25 mol % of I_2, 20~25 °C, 24 h. [f] Reaction time = 36 h.

The reaction is relatively insensitive to the length of the 2-alkylated side chain of quinolines, and high enantioselectivities and good yields have been consistently obtained (entries 1−3). 2-Arenethyl-substituted quinolines gave slightly low enantioselectivity (entries 4 and 5). The asymmetric hydrogenation of quinolines bearing hydroxyl groups proceeded smoothly, affording good to high enantioselectivities (entries 6−8). With 6-substituted quinolines (entries 9−11), slightly low enantioselectivities and conversions were observed. Notably, under low catalyst loading, the reactions performed well, affording similar enantioselectivities, albeit low catalytic activities (entries 1−7).

Having established the efficacy of the dendritic catalysts, we then investigated their recyclability (Table 5).

Table 5. Recovery and Recycling of Ir(**G_3DenBINAP**) Catalyst[a]

cycle	run 1	run 2	run 3	run 4	run 5	run 6
conversion (%)[b]	>95	>95	>95	>95	80	80
ee (%)[c]	87	85	86	85	85	85

[a] Reaction conditions: 2.5 mmol of quinaldine (**1a**) in 1.25 mL of THF, sub./cat. = 1000 (mol ratio), 0.5 mol % of I_2, 45 atm H_2, 25~30 °C, 8 h for runs 1~3, 16 h for runs 4 and 5, and 32 h for run 6. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Determined by HPLC analysis.

G_3DenBINAP-Ir-catalyzed asymmetric hydrogenation of **2a** was chosen as the standard reaction. Upon the completion of the reaction, the catalyst was quantitatively precipitated by the addition of hexane and reused at least six times with similar enantioselectivities but at the expense of relatively low catalytic activities. The leaching of iridium was measured by ICP−XRF at the second cycle and found to be no more than 0.024 ppm.

In conclusion, we have demonstrated for the first time the importance of the dendritic wedges on the catalytic activity in the Ir-catalyzed asymmetric hydrogenation of quinolines. Good to high enantioselectivities with significantly high catalytic activities (TOF up to 3450 h^{-1}) and productivities (TON up to 43 000) have been obtained in this challenging reaction. Such dendritic enhancement is very rare in the field of dendrimer chemistry. Current work is aiming at detailed insight of the nature of the strong dendrimer effect and the exploration of these dendritic catalysts in other asymmetric hydrogenations of heteroaromatic compounds.

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Supporting Information Available: General experimental methods, preparation and characterization data for dendritic ligands **G_nDenBINAP**, and ^{1}H and ^{13}C NMR spectral data for the reduced products. This material is available free of charge via the Internet at http://pubs.acs.org.

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