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Communication

Efficient enantioselective hydrogenation of quinolines catalyzed by conjugated microporous polymers with embedded chiral BINAP ligand

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ABSTRACT

Chiral Ir complexes were successfully used in the asymmetric hydrogenation of olefins, ketones, and quinolines. However, almost all the catalytic systems could not tolerate a high catalyst loading because of the formation of an irreversible iridium dimer and trimer during the reaction. It is expected that higher catalytic activity may be achieved if the Ir-complexes were isolated in space. The development of conjugated microporous polymers (CMPs) gives the opportunity for the spatial separation of the complexes. A series of chiral CMPs based on the chiral (*R*)-BINAP ligand (BINAP-CMPs) with different surface areas were synthesized. The BINAP ligands were separately distributed in the framework and were three times more active than the homogeneous catalyst (TOF 340 h^{-1} *VS* 100 h^{-1}) for the asymmetric hydrogenation of quinolines.

The asymmetric hydrogenation of quinolines is one of the most convenient route to synthesize enantiomerically pure tetrahydroquinoline derivatives which are important organic synthetic intermediates and structural units of alkaloids and biologically active compounds [1]. The first successful homogeneous asymmetric hydrogenation of quinolines was described by Zhou and co-workers using a Ir catalytic system [2]. Quinolines with different substituents were investigated in their following works [3–7]. Chan's group subsequently described that the air-stable and recyclable Ir-P-Phos and Ir- diphosphinite are efficient catalysts for the asymmetric hydrogenation of quinolines [8–10]. Reetz and co-workers also found that BINOL-derived diphosphonites with achiral P-ligands as additive catalyzed the same reaction [11]. Despite these important advances, a problem in the reported reaction systems was that good results were only obtained at a low substrate-catalyst ratio. The problem with a high catalyst loading was attributed to the formation of an irreversible iridium dimer and trimer during the reaction which would be pathways for catalyst deactivation [12]. Therefore, developing a highly efficient catalytic system for the asymmetric hydrogenation of quinolines is still needed.

Several attempts to avoid iridium dimer formation were tried (Scheme 1). One method is the introduction of bulky substituents onto the chiral ligands to inhibit the formation of inactive dimmers and trimers, thus promoting the catalytic activity (Scheme 1.1). Fan's group synthesized a series of dendritic dendrimer G*n*DenBINAP ligands by the condensation of the dendritic wedges G*n*-COOH with (*S*)-5,5'-diamino BINAP (*S*)-1 [13]. The G*n*DenBINAP ligands gave much higher catalytic ac-

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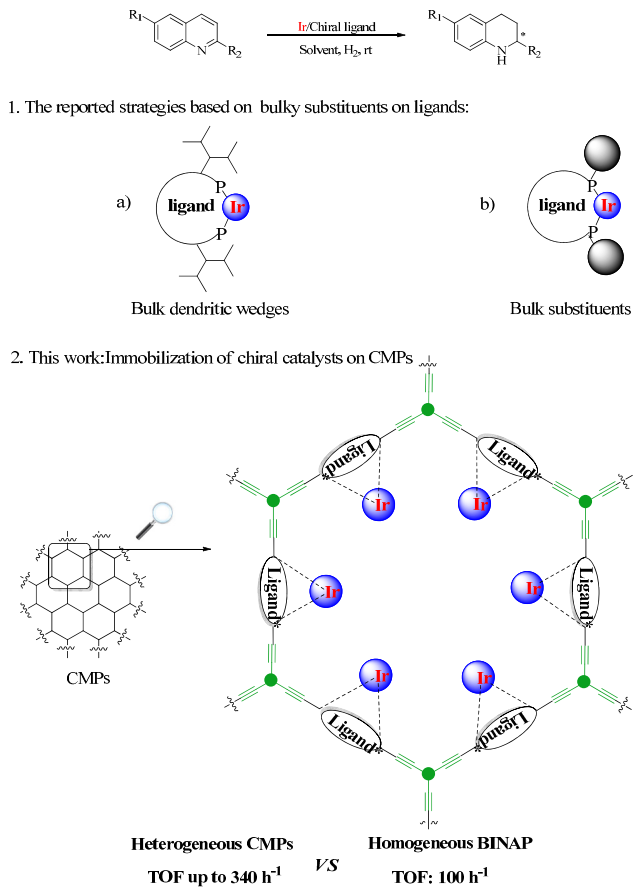


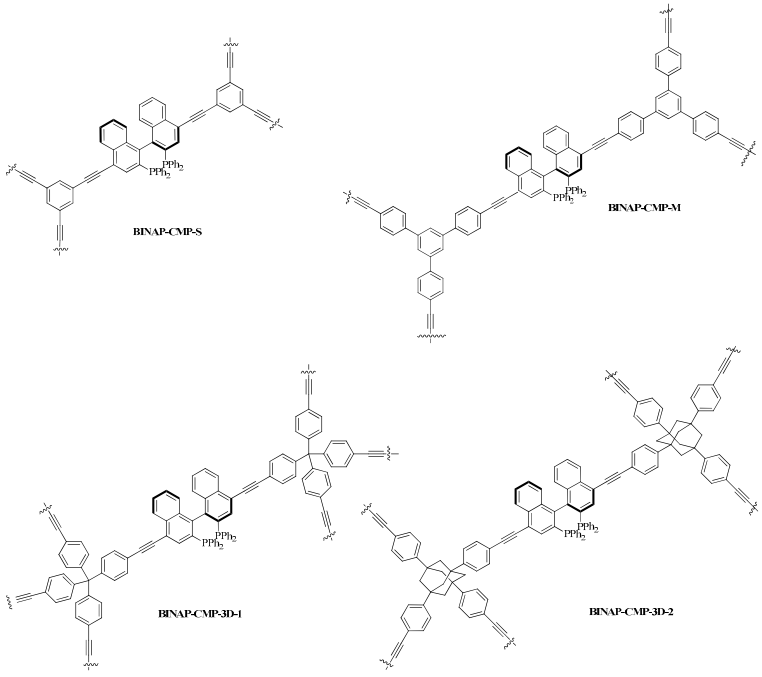
Scheme 1. Strategies for inhibiting the dimerization of the Ir-complex in the hydrogenation of quinolone.

tivity than BINAP through the steric shielding effect of the bulky dendritic wedges to reduce dimerization (Scheme 1.1(a)). Zhou and coworkers reported that introducing bulky groups onto the coordination phosphorus atoms effectively blocked the formation of inactive dimer and trimer species and improved the activity of the Ir catalysts [14] (Scheme 1.1(b)).

Recently, we reported the synthesis of a series of CMPs by embedding the chiral BINAP ligand into CMP networks. These solid materials are efficient catalysts for the asymmetric hydrogenation of *β*-keto esters [15]. Because all the BINAPs are embedded on the pore structure of the networks separately, we envisioned that these heterogeneous catalysts [16–18] with an inherent isolation effect can perform the asymmetric hydrogenation of quinoline with high activity through preventing the formation of dimers and trimers. (Scheme 1.2) Here, we reported the results.

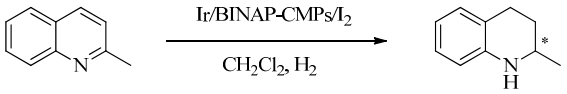
A typical strategy for synthesizing **BINAP-CMP-3D-2** was as follows: 1,3,5,7-Tetrakis(4-ethynylphenyl) adamantine, (*R*)-4,4-DibromoBINAPO, tetrakis-(triphenylphosphine) palladium, and copper iodide were dissolved in a mixture of dioxane and Et_3N. The reaction mixture was heated to 80 °C and stirred for 72 h under a nitrogen atmosphere. The precipitate was filtered and washed with solvent. After reducing with $HSiCl_3$, **BINAP-CMP-3D-2** was obtained.

We began by examining the hydrogenation of 2-methylquinoline **1a** with an iridium catalyst in the presence of different BINAP-CMPs. We were pleased to find that the hydrogenation catalyzed by the BINAP-CMPs proceeded smoothly and afforded the product with moderate enantioselectivity (Table 1, entries 1–4). In sharp contrast, the homogeneous hydrogenation catalyzed by BINAP gave trace product under same reaction conditions (Table 1, entry 5). Moreover, the catalytic activity gradually increased with increasing surface area and pore volume of the BINAP-CMPs. CMPs with larger surface area and pore volume benefit the diffusion of substrate and product, which makes it easier to access the active center and improve the activity.



Scheme 2. Structure of BINAP-CMPs.

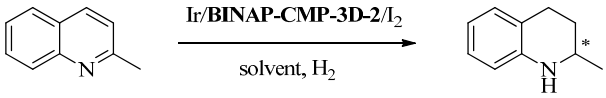
Table 1
Comparison of catalytic activity of the synthesized BINAP-CMPs.



Entry	BINAP-CMPs	A_{BET} [a] (m^2/g)	V_{total} [b] (cm^3/g)	Conversion [c] (%)	TOF [d] (h^{-1})	ee [e] (%)
1	BINAP-CMP-S	170	0.37	9	180	48
2	BINAP-CMP-M	318	0.46	10	200	50
3	BINAP-CMP-3D-1	279	0.76	12	240	54
4	**BINAP-CMP-3D-2**	398	0.77	17	340	54
5	BINAP	—	—	5	100	70

Reaction conditions: quinaldine 0.25 mmol, CH_2Cl_2 3 mL, $[Ir(COD)Cl]_2$ 0.000125 mmol, I_2 0.05 mmol, 1.5 MPa H_2, 25 °C, 0.5 h. [a] Surface area calculated from the N_2 adsorption isotherm using the BET method. [b] Total pore volume at p/p_0 = 0.99. [c] Determined by ^1H NMR analysis of the crude product. [d] Average TOF over the reaction time. [e] Determined by HPLC analysis with a Chiralpak OJ-H column.

Table 2
Asymmetric hydrogenation of quinaldine (**1a**) catalyzed by the **BINAP-CMP-3D-2** catalyst.



Entry	Solvent	Conversion [a] (%)	ee [b] (%)
1	THF	99	34
2	CH_2Cl_2	99	60
3	MeOH	88	29
4	toluene	99	40
5	benzene	99	38
6	dioxane	99	39
7	CH_2Cl_2/THF 1:2	99	56
8	CH_2Cl_2/toluene 1:2	99	51
9 [c,d]	CH_2Cl_2	99	69
10 [c,e]	CH_2Cl_2	99	70
11 [c]	CH_2Cl_2	99	70
12 [c,f]	CH_2Cl_2	93	70
13 [c,g]	CH_2Cl_2	95	73
14 [c,h]	CH_2Cl_2	99	69

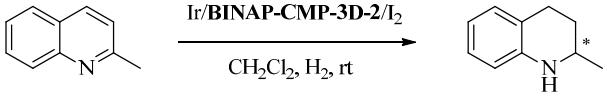
Reaction conditions: quinaldine 0.25 mmol, CH_2Cl_2 3 mL, $[Ir(COD)Cl]_2$ 0.000125 mmol, I_2 0.05 mmol, 4 MPa H_2, 25 °C, 18 h. [a,b] See Table 1. [c] $[Ir(COD)Cl]_2$ 0.00125 mmol, 2 h. [d] 6.5 MPa H_2. [e] 5 MPa H_2. [f] 1.5 MPa H_2. [g] 0 °C. [h] 50 °C.

To obtain higher enantioselectivity, the effects of the solvent, temperature and pressure were investigated by using **BINAP-CMP-3D-2** as the catalyst (Table 2). A series of organic solvents were investigated. CH_2Cl_2 was the best in terms of both conversion and enantioselectivity (Table 2, entries 1–8). The enantioselectivity of the reaction was slightly increased at low temperature with incomplete conversion (Table 2, entry 13). Also, the reaction did not reach completion under a low pressure(Table 2 entry 12).

Using the optimized reaction conditions, the limit of catalyst activity was also investigated. The **BINAP-CMP-3D-2** catalyst was found to be highly effective even at a high substrate/catalyst ratio although the enantioselectivity decreased with a low catalyst loading (Table 3).

Using the optimal conditions, we demonstrated the scope of quinoline for this heterogeneous hydrogenation (Table 4). All substituted quinolines used here were hydrogenated with good conversion and modest enantioselectivity. The reaction was relatively insensitive to the length of the 2-alkylated side chain

Table 3
Minimum amount of Ir/**BINAP-CMP-3D-2** catalyst that can be used.



Entry	Time (h)	Substrate/Catalyst	Conversion [a] (%)	ee [b] (%)
1	2	100:1	99	70
2	2	500:1	99	64
3	2	1000:1	99	60
4 [d]	6	2000:1	99	53
5 [e]	24	5000:1	93	42

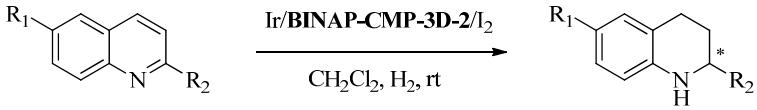
Reaction conditions: quinaldine (**1a**) 0.25–5 mmol, CH_2Cl_2 3 mL, I_2 0.05 mmol, 4 MPa H_2, 25 °C. [a,b] See Table 1.

of the quinoline. It was interesting that with increasing length of the side chain of R_2, the enantioselectivity obtained with **BINAP-CMP-3D-2** increased from being slightly less than to be obviously higher than the enantioselectivity of the homogeneous Ir/BINAP catalyst (Table 4, entries 1–5). The conversion decreased with the increasing of steric hindrance (Table 4, entries 4–6), which may be due to that bulky substituted quinolines suffer more diffusion resistance when diffusing through the pore structure of the polymer. With 6-substituted quinolines as the substrate (Table 4, entries 7–9), low enantioselectivity with complete conversion were observed.

The recyclability of the **BINAP-CMP-3D-2** catalyst was also investigated (Table 5). Upon completion of the reaction, the Ir/**BINAP-CMP-3D-2** catalyst was easily recovered by centrifugation and a regular filter. The colorless filtrate from the asymmetric hydrogenation of quinaldine (**1a**) did not afford any additional product, showing the heterogeneous nature of the reaction system. After washing with CH_2Cl_2 and heating under vacuum, the solid catalyst was reused for the next cycle. We did not see any significant deterioration in the activity for the recovered catalyst even after five cycles.

In summary, we synthesized a series of BINAP-CMPs with different surface areas, which gave high activity and modest enantioselectivity in the Ir-catalyzed asymmetric hydrogenation of quinolines. The catalytic activity was related to the structural properties of the BINAP-CMPs. The CMP with a higher surface area and pore volume gave better asymmetric hydrogenation results. Through preventing the formation of

Table 4
Catalytic asymmetric hydrogenation of quinoline derivatives.

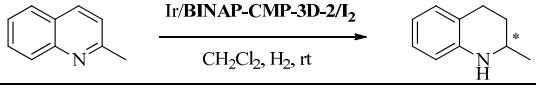


1 (1a-1i) **2 (2a-2i)**

Entry	R_1/R_2 (substrates)	Conversion [a] (%)		ee [b] (%)		Configuration [c]
		Ir/**BINAP-CMP-3D-2**	Ir/BINAP	Ir/**BINAP-CMP-3D-2**	Ir/BINAP	
1	H/Me (**1a**)	99	24	70	72	*R*
2	H/Et (**1b**)	99	23	77	78	*R*
3	H/*n*-Pr (**1c**)	99	16	78	74	*R*
4	H/*n*-Bu (**1d**)	80	18	77	75	*R*
5	H/*i*-Pr (**1e**)	83	13	79	75	*R*
6	H/Ph (**1f**)	84	34	44	50	*R*
7	F/Me (**1g**)	99	23	63	77	*S*
8	Me/Me (**1h**)	99	16	67	76	*R*
9	MeO/Me (**1i**)	97	9	70	78	*R*

Reaction conditions: quinoline 0.25 mmol, CH_2Cl_2 3 mL, $[Ir(COD)Cl]_2$ 0.00125 mmol, I_2 0.05 mmol, 4 MPa H_2, 25 °C, 2 h. [a,b] See Table 1. [d] The absolute configuration is assigned by comparison of the HPLC retention time with those reported in the literature data.

Table 5
Recycling experiment of the **BINAP-CMP-3D-2** catalyst.



Cycle	0	1	2	3	4	5	6
Conversion [a] (%)	99	99	99	99	99	99	90
ee [b] (%)	72	72	71	70	70	70	69

Reaction conditions: quinaldine 0.5 mmol, CH_2Cl_2 3 mL, $[Ir(COD)Cl]_2$ 0.00125 mmol, I_2 0.05 mmol, 4 MPa H_2, 25 °C, 2 h. [a,b] See Table 1.

dimmers by the spatial isolation effect of the CMP, the BINAP-CMPs gave much higher activity than the homogeneous BINAP ligand.

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Graphical Abstract

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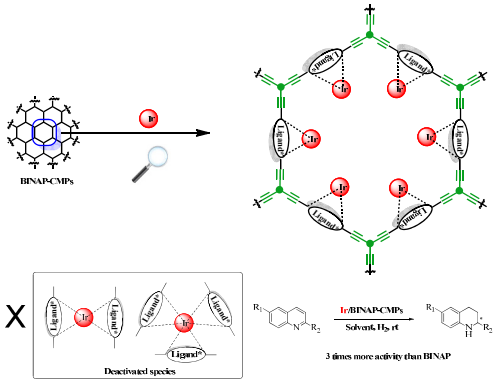

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