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Enantioselective Hydrogenation of *N*-heteroaromatics Catalyzed by Chiral Diphosphines Modified Binaphthyl Palladium Nanoparticles

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The first application of binaphthyl-stabilized palladium nanoparticles (BIN-PdNPs) with chiral modifiers in asymmetric hydrogenation of *N*-heteroaromatics is revealed. With an appropriate ratio of *R*-BINAP/Bin-PdNPs used, the pre-prepared chiral nanocatalyst achieves asymmetric hydrogenations of 2-substituted quinolines with good to excellent yields and moderate enantioselectivities, which showed superior catalytic properties over that of *R*-BINAP/Pd complex. Moreover, this protocol is also applicable to 2-substituted indoles.

Metal nanoparticles as active sites in organic transformations have attracted extensive interest to academic and industrial communities for several decades.[1] Metal nanoparticles possessing large surface-to-volume ratio, dominantly facilitate higher catalytic efficiency compared to that of bulky metals or metal complexes. Contrarily, the unpassivated active sites tend to aggregate and precipitate during the catalytic cycle. In order to prevent the aggregation and improve the reusability, organic stabilizers or inorganic supports are usually utilized based on either coordination effects or physical disjunction.[1]

In terms of organic stabilizers, organic molecules bearing coordinating groups of O, N, P, or S atoms represent the prevalent strategies.[2] For pioneering contributions in asymmetric catalysis, the Orito's platinum catalytic systems (cinchonidine modified platinum nanoparticles)[3] and tartaric acid-modified nickel nanoparticles[4] were widely recognized as two classical systems for asymmetric hydrogenation (AH) of C=O bonds (Scheme 1a). Afterwards, varieties of metal nanoparticles, chiral ligands and immobilization methods, including polymers, magnetic Fe_3O_4, SiO_2, and CNTs (carbon nanotubes), were developed.[5] Notably, AH with nanocatalysts has long been limited to the two systems, albeit much efforts have been devoted.[6] Intriguingly, in 2014, an elegant study was revealed by Xiao and co-workers, who reported the first chiral N,P-macrocyclic ligands stabilized iron nanoparticles for asymmetric hydrogenation of ketones with excellent enantioselectivities.[7] However, compared to the blooming of asymmetric C-X, C-C formations,[8] the AH achieved by metal nanoparticles are still underdeveloped, thus, it is highly desirable to develop novel nanocatalysts and expand applications to enrich this chemistry.

The asymmetric hydrogenation of quinolines and indoles, representative families of *N*-heteroaromatics, provided a powerful tool for the synthesis of enantiopure tetrahydroquinolines and tetrahydroindoles, which were widely found in natural-occurring or synthetic bioactive compounds.[9] Leading scientists, such as Zhou, Fan and Kuwano, have made great achievements in this process with transition metal complexes of Ru, Rh, Ir and Pd.[10] Among which, in 2014, the first palladium-catalyzed AH of quinoline derivatives was developed by Zhou *et al*, with substrates bearing 3-phthalimido substitution.[10h] To be noted, to the best of our knowledge, palladium nanoparticles has never been applied in AH of quinolines and indoles so far.[11]

It has to mention that the aforementioned coordinative ligands-stabilized nanocatalyst are widely accepted as "semi-heterogeneous",[1f] which is usually accompanied by a homogeneous catalytic process, deriving from metal leaching from the nanoparticles surface. This phenomenon might be acceptable to non-asymmetric reactions, but lethal to asymmetric ones, since the homogeneous metal species would disturb the catalytic process. Therefore, the design of nanocatalyzed asymmetric reactions would be a challenging issue to distinguish the heterogeneous process from homogeneous, but attractive. As a breakthrough of stabilization model, the first metal-carbon bond stabilized gold and platinum nanoparticles was report by Mirhalaf in 2006,[12] which exhibited higher bond energy than that of traditional metal-nitrogen or metal-sulfur bonds, offering a clearly heterogeneous catalysis mode. To date, varieties of organic transformations have been achieved with metal-carbon bond stabilized palladium nanoparticles (MCBS-PdNPs).[13] Our group has also advanced a serial of MCBS-PdNPs for hydrogenation and dehydrogenation of *N*-heterocycles,[14] in which covalent binaphthyl stabilization was found to be the most efficient way.[14a] It has been exemplified that the strong covalent metal-carbon bonds would be easier to keep heterogeneous during the catalytic cycle, providing a distinct catalytic pattern from

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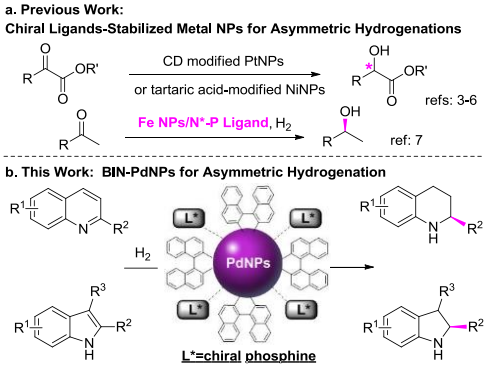
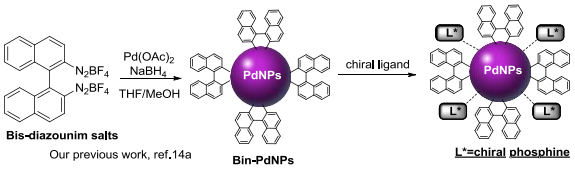
the ligands/polymers-stabilized nanocatalysts or metal complexes. Interestingly, this type of metal nanoparticles has never been investigated in asymmetric reactions. Herein, as our continuing interest in nanocatalysis,[14,15] we will disclose the first application of binaphthyl-stabilized palladium nanoparticles (**Bin-PdNPs**) in AH of 2-substituted quinolines and indoles (Scheme 1, b).

Scheme 1 Representative Metal Nanoparticles for Asymmetric Hydrogenation (a); and This Work (b).



The **Bin-PdNPs**, consisting of Pd(0) and Pd(II), was prepared by *in-situ* reduction of palladium acetate and 1,1'-binaphthyl-2,2'-bis(diazonium-tetrafluoroborate (denoted as Bis-diazonium salts) according to our reported "one-phase reduction" procedures with a size distribution of 2.5±0.5 nm.[14a] The resulting nanocatalyst was then coordinated with (R)-BINAP (**L1**) in acetone (the size distribution was not changed after coordination, see details in the Supporting Information) before being applied in the AH of 2-methyl-quinoline. The coordination status of **Bin-PdNPs** and (R)-BINAP were monitored by ^{31}P-NMR spectroscopy. Table 1 described the *in-situ* coordination labelings of phosphine ligands. Free (R)-BINAP lied in -15.64 ppm, but changed to 28.64 ppm after being decorated on the particles surface. According to the integration ratios of free ligands and coordinated ones on ^{31}P-NMR spectra, the percentages of (R)-BINAP decorated PdNPs could be calculated (see details in S.I.). With 1.2 equivalents (R)-BINAP used, the chiral ligands occupied 34% of the nanoparticles surface (Table 1, entry 3), which reflected an average value of chirally modified sites over non-chiral ones on PdNPs surface. Higher loading of phosphine ligand would decrease the percentage accordingly, which might be ascribed to the result of π-π repulsion.[16]

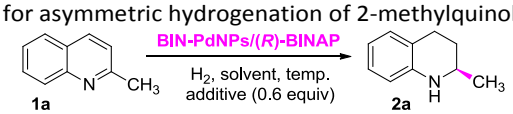
Table 1 ^{31}P-NMR monitored coordination of (R)-BINAP with **Bin-PdNPs**.[a]



Entry	**L1**/**Bin-PdNPs** (molar ratio)	Integration ratio	Percentage on **Bin-PdNPs**
1	0.5:1	1:1	26%
2	0.75:1	0.6:1	28%
3	**1.2:1**	**0.4:1**	**34%**
4	1.5:1	0.2:1	25%

As shown in Table 2, preliminary results indicated that the ratios of **Bin-PdNPs**/(R)-BINAP, solvents, additive, hydrogen pressure, and reaction temperature dramatically affect the enantioselectivity of the hydrogenated product. Though not distinct, reactions in aprotic solvents exhibited better enantio-control. Most importantly, the reactions in water with less ratio of (R)-BINAP gave the racemic product **2a** (entries 1-2), to our delight, 6% *e.e.* was detected while enhancing the phosphine ligand loading (entry 3). We reasoned that, the percentages of coordinated nanoparticles in Table 1 keep well consistent with the preliminary results. With less ligand used, the spare active sites would lead to the racemic product;[14a] on the contrary, excess ligands competitively occupied the active sites against the coordination of substrates with particle surface, thus impairing the catalytic efficiency. Consequently, the pre-prepared chiral nanocatalyst with a ratio of Pd/BINAP (1:1.2) was utilized for further optimizations. With trifluoroacetic acid (TFA) as an additive in dichloromethane, the *ee* value could be improved to 70% (entry 9). It is worthy to mention that the probable acidolysis of **Bin-PdNPs**/(R)-BINAP upon TFA into the Pd(TFA)$_2$/(R)-BINAP complex can be ruled out, since the homogeneous palladium complex has been proven to be ineffective in asymmetric hydrogenation of 2-methylquinoline.[10h] Other optimizations by altering hydrogen pressure, amount of additive, reaction temperature and phosphine ligands (**L2**-**L9**) were screened (in S.I.). Bidentate chiral phosphines (**L2**-**L6**) rended either better yields or enantioselectivties than mondentate phosphines, but worse than the performance of **L1** (entries 10-14), probably due to the match or mismatch of ligand dihedral angle,[17] coordination sits and substrate. Intriguingly, the reported (R)-BINAP-stabilized palladium nanoparticles [(R)-BINAP-PdNPs][8a,8b] gave 85% yield for this transformation under the optimized conditions, but with only 8% *e.e.* (entry 15). The **Bin-PdNPs** itself was used as comparison in the absence of chiral phosphine, which delivered no difference in reactivity (entry 16 vs 9). Moreover, chiral covalent binaphthyl-stabilized PdNPs (prepared from the corresponding R- and S- Bis-diazonium salts, respectively) presented identical enantio-control with the racemic one (entries 17, 18). Eventually, a homogeneous counterpart, Bis-diazonium salts/Pd(TFA)$_2$/**L1**, furnished only trace amount of the hydrogenated product (entry 19), confirming the heterogeneous nature of our catalyst. These results collectively pointed to a fact that the covalent binaphthyl groups and chiral ligands play synergistic roles on the reactivity and enantioselectivity.

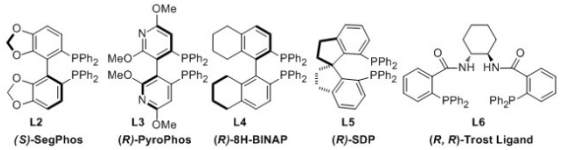
Table 2 The effects of solvents and ratios of **Bin-PdNPs**/(R)-BINAP for asymmetric hydrogenation of 2-methylquinoline.[a]



Entry	Catalyst/ Ligand (mol%)	Solvent/ Additive	H_2 pressure /temp (°C)	Yield /*ee*(%)
1	2/0.5 (**L1**)	H_2O/-	balloon/25	>95/0
2	1/0.5 (**L1**)	H_2O/-	balloon/25	>95/0
3	1/1 (**L1**)	H_2O/-	balloon/25	>95/6
4	1/1 (**L1**)	toluene/-	balloon/25	>95/5
5	1/1 (**L1**)	ether/-	balloon/25	>95/8
6	1/1 (**L1**)	CH_2Cl_2/-	balloon/25	>95/12
7	1/2 (**L1**)	CH_2Cl_2/-	balloon/25	56/0
8	5/6 (**L1**)	CH_2Cl_2/-	30 atm/60	>95/8
9	**5/6 (L1)**	**CH_2Cl_2/TFA**	**30 atm/60**	**>95/70**
10	5/6 (**L2**)	CH_2Cl_2/TFA	30 atm/60	55/-21
11	5/6 (**L3**)	CH_2Cl_2/TFA	30 atm/60	52/6
12	5/6 (**L4**)	CH_2Cl_2/TFA	30 atm/60	56/21
13	5/6 (**L5**)	CH_2Cl_2/TFA	30 atm/60	90/0

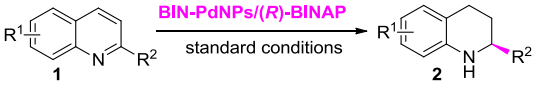
14	5/6 (**L6**)	CH_2Cl_2/TFA	30 atm/60	88/0
15[c]	5	CH_2Cl_2/TFA	30 atm/60	85/8
16	**Bin-PdNPs**	CH_2Cl_2/TFA	30 atm/60	>95/0
17	(R)-**Bin-PdNPs/L1**	CH_2Cl_2/TFA	30 atm/60	>95/70
18	(S)-**Bin-PdNPs/L1**	CH_2Cl_2/TFA	30 atm/60	>95/70
19[d]	**Bis-diazonium salts**/$Pd(TFA)_2$/**L1**	CH_2Cl_2/TFA	30 atm/60	trace

[a] 2-methylquinoline (**1a**, 0.1 mmol), 3 mL solvent, **Bin-PdNPs**/(R)-BINAP, 36 h; [b] Yields and *e.e.* values were determined by ^{1}HNMR and HPLC equipped with a chiral OJ-H column, respectively; [c] (R)-BINAP-PdNPs as catalyst; [d] Bis-diazonium salts (6.7 mg, 1.8 mol%), 5 mol% $Pd(TFA)_2$, 6 mol% (R)-BINAP.



With the optimal conditions in hand, we then evaluated the generality of this protocol for various 2-substituted quinolines. For 2-methyl substituted ones, electron-rich and electron-deficient substituents, such as methyl, methoxy, and fluoro at 6-positions, were well tolerated, affording the hydrogenated products with good to excellent yields, along with moderate *e.e.* values (Table 3, entries 2-5). It is noticed that, asymmetric hydrogenation of methyl 2-methyl-quinoline-6-carboxylate (**1e**) furnished **2e** with higher yield and enantioselectivity than that of palladium complex (entry 5, e.e.: 59% vs 27%).[10h] In particular, substrates with 2-ethyl and 2-aryl substituents were viable to the nanocatalytic system with good yields, along with moderate *e.e.* values ranged from 52-66%. To our delight, these are the best results in palladium-based catalytic protocol for asymmetric hydrogenation of 2-arylsubstituted quinolines, which has not been achieved for palladium complex yet.

Table 3 Substrate scope of quinolines.[a]

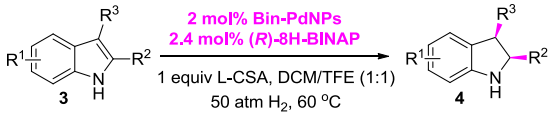


Entry	R^1	R^2	Yield/*e.e.* (**2**, %)[b]
1	H	Me (**1a**)	93/70(R)
2	6-Me	Me (**1b**)	95/62(R)
3	6-MeO	Me (**1c**)	95/46(R)
4	6-F	Me (**1d**)	71/54(R)
5	6-COOMe	Me (**1e**)	63/59(R)
6	H	Et (**1f**)	86/66(R)
7	H	Phenyl (**1g**)	91/56(S)
8	H	*o*-tolyl (**1h**)	84/46(S)
9	H	2,4-dimethylphenyl (**1i**)	82/52(S)
10	H	2-Naphthyl (**1j**)	76/53(S)

[a] Isolated yield; *e.e.* values were determined on HPLC.

Our protocol can also be applied to the asymmetric hydrogenation of indole derivatives. Nevertheless, the optimal conditions developed for quinolines were not applicable herein. Systematical conditions screening revealed that, with 2 mol% **BIN-PdNPs**/2.4 mol% (R)-8H-BINAP as catalyst, dichloro-methane/trifluoroethanol (1:1) as solvent, L-CSA as additive, and 50 atm H_2, 2-methylindole underwent hydrogenation smoothly (see more details in the S.I.). As depicted in Table 4, 2 or 2,3-substituted indoles proceeded with good to excellent yields of hydrogenated products (**4a**-**4k**), albeit with moderate *e.e.* values ranged from 47-55%. Moreover, owing to the heterogeneous nature, only *cis*-products were detected for 2,3-substituted indoles (**3d**-**3h**). Although this protocol exhibited worse enantiocontrol for 2-alkyl substitutions than that of palladium complex, we delightfully found that, for more challenging substrates with 2-aryl substitutions (**3l**-**3n**), our system gave good to excellent yields with *e.e.* values above 30%, whereas only <5% yield of the hydrogenated product was detected in $Pd(TFA)_2$/(R)-8H-BINAP system.[10j] Besides, the results for 2-aryl-substituted indoles were comparable to the recent case of ruthenium-DPEN complexes.[18]

Table 4 Substrate scope of indoles.[a]



Entry	R^1	R^2	R^3	Yield/*e.e.* (**4**, %)[b]
1	H	Me	H (**3a**)	85/64(R)
2	5-F	Me	H (**3b**)	81/50(R)
3	5-Me	Me	H (**3c**)	92/47(R)
4	H	Me	Me (**3d**)	95/51(R)[c]
5	H	Me	4-F-benzyl (**3e**)	83/48(R) [c]
6	H	Me	4-MeO-benzyl (**3f**)	86/54(R) [c]
7	H	Me	4-Me-benzyl (**3g**)	92/55(R) [c]
8	H	Me	benzyl (**3h**)	90/53(R) [c]
9	H	4-Me-benzyl	H (**3i**)	81/55(R)
10	H	3-Me-benzyl	H (**3j**)	86/53(R)
11	H	benzyl	H (**3k**)	93/54(R)
12	H	Phenyl	H (**3l**)	76/31(S)
13	H	*p*-tol	H (**3m**)	93/32(S)
14	H	*p*-F-C_6H_4	H (**3n**)	51/35(S)
15	H	*p*-MeO-C_6H_4	H (**3o**)	86/22(S)

[a] indole (**3**, 0.25 mmol), 3 mL DCM/TFA(1:1), **Bin-PdNPs**/(*R*)-8H-BINAP (2 mol%/2.4 mol%), 1 equiv L-CSA, 50 atm H_2, 24 h. [b] Isolated yield, *e.e.* values were determined on HPLC. [c] *Cis*-configuration.

Based on our experimental results and previous reports,[14a,19] a catalytic mechanism is proposed in **Fig. 1**. The protonated quinoline (**1a**) docks on the **Bin-PdNPs** surface by π-π stacking with covalent binaphthyl group and the coordination of nitrogen with palladium(0) atoms. Subsequently, asymmetric hydrogenation occurs on C=N bond at the proximal zero-palladium site modified with chiral phosphine. This dual interaction mode clarifies the worse chiral induction for individual (R)-BINAP-PdNPs[8a,8b] and the identical results catalyzed by (R)-/(S)-**Bin-PdNPs** (Table 1, entries 17, 18). Considering the percentage of chiral ligands modified surface (34%), a competing mode of flat absorption of the quinoline moiety onto the metal surface leads to the racemic product, which can explain the moderate enantioselectivities obtained in this protocol.

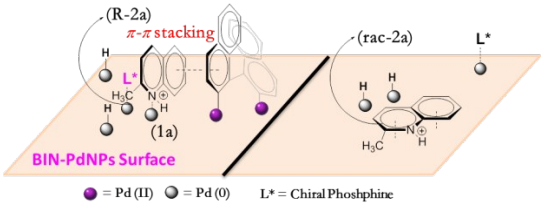


Fig. 1 Proposed Catalytic Mechanism.

In summary, we revealed here the first application of binaphthyl-stabilized palladium nanoparticles (**Bin-PdNPs**) with chiral modifiers in asymmetric hydrogenation of *N*-heteroaromatics. The effects of organic shell and chiral ligand density on the reactivity and enantioselectivity were explained by ^{31}P-NMR spectroscopy and experimental facts. With the appropriate ratios of **Bin-PdNPs** and chiral phosphine ligands used, asymmetric hydrogenations of 2-substituted quinolines and 2-arylindoles were achieved with good to excellent yields and moderate enantioselectivities, which showed superiority to that of palladium complex. Further application of this protocol into other asymmetric reactions is ongoing in our laboratory.

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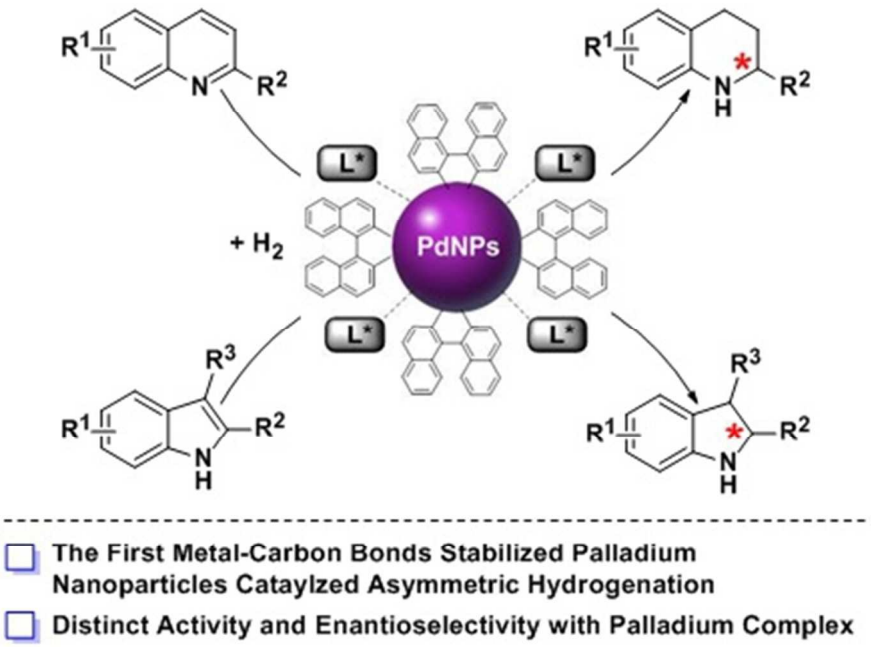

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