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Asymmetric Arylation of Imines Catalyzed by Heterogeneous Chiral Rhodium Nanoparticles

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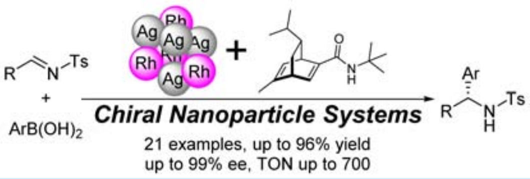
S *Supporting Information*

ABSTRACT: Asymmetric arylation of aldimines catalyzed by heterogeneous chiral rhodium nanoparticles has been developed. The reaction proceeded in aqueous media without significant decomposition of the imines by hydrolysis to afford chiral (diarylmethyl)amines in high yields with outstanding enantioselectivities. This catalyst system exhibited the highest turnover number (700) in heterogeneous catalysts reported to date for these reactions. The reusability of the catalyst was also demonstrated.



Chiral (diarylmethyl)amines are important compounds that are found in many pharmaceutical skeletons.[1] Asymmetric arylation of aldimines can afford such compounds, and the use of organoboron reagents as aryl donors is one of the most promising strategies for the synthesis of these compounds because of the stability, mild reactivity, and ease of handling of organoboron reagents.[2] Since the first examples of asymmetric addition of arylboronic acids to aryl tosylimines catalyzed by chiral Rh complexes were reported in 2004,[3] numerous efforts for the development of this type of reaction have focused on improving the catalytic activities and substrate diversity to include aliphatic imines and various types of protected aldimines.[1b,4] As alternatives to Rh catalysis, other metals such as Pd[5] and Ru[6] catalyst systems were also investigated. Despite great advances in the development of this reaction, the catalysts have all been homogeneous metal complexes and less attention has been focused toward the development of heterogeneous catalysts. This is a crucial issue for further applications of the reaction considering the advantages of heterogeneous catalysts, such as ease of recovery, reusability, and prevention of metal contamination in the final products.[7] Quite recently, heterogeneous Rh complex catalysts embedded on chiral diene-based metal−organic frameworks were developed, and asymmetric arylation of aldimines was demonstrated.[8] Although these reactions achieved a high turnover number (TON = 275), a large catalyst loading was necessary to obtain a quantitative yield (3 mol %) and to maintain the activity upon reuse of the catalyst (6 mol %). Therefore, more active heterogeneous catalysts for this reaction are still required.

Chiral ligand-modified metal nanoparticles (chiral metal NPs) provide promising strategies to construct active and robust asymmetric catalyst systems as an alternative to conventional metal complex catalysts.[9] Metal NPs can be easily immobilized on solid supports to form heterogeneous catalysts, and our laboratory has also established polymer incarceration methods to immobilize various metal NP catalysts on a nanocomposite of polystyrene-based copolymers with cross-linking moieties and carbon black.[10] We successfully developed Rh/Ag bimetallic NP catalysts (PI/CB Rh/Ag), which were utilized for asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds in the presence of a chiral diene as a modifier.[11] Notably, this heterogeneous chiral Rh NP system showed superior performance over the corresponding homogeneous metal complex for some substrates, and the unique nature of the active species was found to be distinct from that of a metal complex.[11a] These results demonstrated the great potential of chiral metal NP catalysts. Herein, we report the application of heterogeneous chiral Rh NP catalyst systems for asymmetric arylation of aldimines.

We selected aryltosylimine (**1a**) and phenylboronic acid (**2a**) as model substrates, and reaction conditions were optimized (Table 1). Initially, the reaction was conducted with a chiral metal NP system consisting of PI/CB Rh/Ag and secondary amide-substituted chiral diene **4**[12] under the optimal conditions for asymmetric 1,4-addition to α,β-unsaturated esters.[11a] Under these conditions, the desired product was obtained with excellent enantioselectivity but in moderate yield (entry 1). Aldehyde **5** and a significant amount of diarylmethanol adduct **6** were also observed, indicating that decomposition of **1a** to **5** occurred in the presence of water with subsequent arylation of **5**. The solvent ratio was then examined in an attempt to suppress the hydrolysis of **1a** (entries 2−6). When the ratio of toluene and water was 4:1 or 8:1, the yield of **3aa** was improved (entries 2 and 3). Further decreases in the amount of water led to a dramatic reduction in the catalytic activity (entries 4−6). The presence of water might play a key role in accelerating part of the catalytic cycle such as the catalytic turnover step, that is, hydrolysis of a reaction intermediate after addition of an aryl group to an imine to give the product. When water was replaced by ethanol, formation of **6** was suppressed; however, the yield was not improved (entry 3 vs 7). The inclusion of

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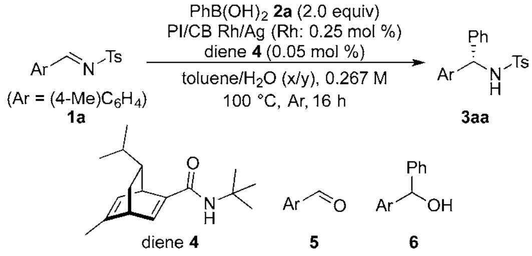
Table 1. Reaction Optimization

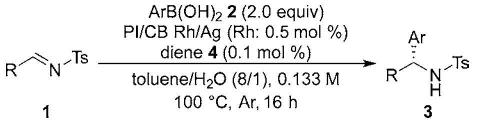


1a **3aa** diene **4** **5** **6**

entry	x/y	yield (%)[a]			ee (%)[b]
		3aa	5	6	3aa
1	1:2	45	6	38	99
2	4:1	71	12	7	99
3	8:1	77	<1	16	99
4	16:1	29	22	<1	99
5	100:1	4	15	<1	99
6	1:0	3	<1	2	–
7[c]	1:0	77	8	2	99
8[d]	8:1	<1	71	<1	–
9[e]	8:1	96 (87)[f]	2	5	99
10[g]	8:1	74 (70)[f]	8	10	99

[a] Determined by ^{1}H NMR analysis. [b] Determined by HPLC analysis. [c] Toluene/EtOH (8:1) cosolvent system was used. [d] K_2CO_3 (1 equiv) was added. [e] PI/CB Rh/Ag (Rh: 0.5 mol %) and **4** (0.1 mol %) were used, and the concentration was 0.133 M. The concentration was calculated based on the total amount of both solvents. [f] Isolated yield. [g] PI/CB Rh/Ag (Rh: 0.1 mol %) and **4** (0.1 mol %) were used, and the reaction time was 48 h.

Table 2. Substrate Scope



1 **3**

entry	R	Ar	3	yield (%)[a]	ee (%)[b]
1	(4-Me)C_6H_4 (**1a**)	C_6H_5	**3aa**	87	99
2	(3-Me)C_6H_4 (**1b**)	C_6H_5	**3ba**	85	99
3	(2-Me)C_6H_4 (**1c**)	C_6H_5	**3ca**	91	96
4	(4-F)C_6H_4 (**1d**)	C_6H_5	**3da**	79	99
5	(4-Cl)C_6H_4 (**1e**)	C_6H_5	**3ea**	84	99
6[c]	(4-Br)C_6H_4 (**1f**)	C_6H_5	**3fa**	84	99
7	(4-OMe)C_6H_4 (**1g**)	C_6H_5	**3ga**	86	99
8	C_6H_5 (**1h**)	(4-Me)C_6H_4	**3hb**	75	99
9	(4-Me)C_6H_4 (**1a**)	(3-Me)C_6H_4	**3ac**	81	99
10[c]	(4-Me)C_6H_4 (**1a**)	(2-Me)C_6H_4	**3ad**	84	95
11	(4-Me)C_6H_4 (**1a**)	(4-F)C_6H_4	**3ae**	93	99
12	(4-Me)C_6H_4 (**1a**)	(4-Cl)C_6H_4	**3af**	77	99
13	(4-Me)C_6H_4 (**1a**)	(4-Br)C_6H_4	**3ag**	80	99
14	(4-Me)C_6H_4 (**1a**)	(4-OMe)C_6H_4	**3ah**	86	99
15	1-naphthyl (**1i**)	C_6H_5	**3ia**	96	99
16	2-naphthyl (**1j**)	C_6H_5	**3ja**	93	99
17	2-furyl (**1k**)	C_6H_5	**3ka**	73	99
18	2-thienyl (**1l**)	C_6H_5	**3la**	89	99
19[c,d]	^{t}Bu (**1m**)	C_6H_5	**3ma**	33	99
20[c,d]	Cy (**1n**)	C_6H_5	**3na**	19	99
21	(4-Me)C_6H_4 (**1o**)[e]	C_6H_5	**3oa**	33	99

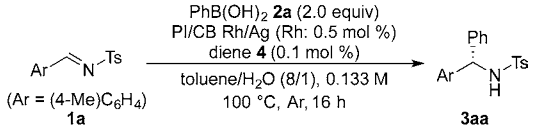
[a] Isolated yield. [b] Determined by HPLC analysis. [c] PI/CB Rh/Ag (Rh: 1.0 mol %) and **4** (0.2 mol %) were used. [d] The reaction mixture before **1k** and **4** were added was heated at 100 °C for 6 h. [e] 4-Nitrobenzenesulfonyl-protected imine was used.

either acidic or basic additives did not work well and led to decomposition of **1a** (entry 8; see also the Supporting Information). Finally, reducing the concentration and increasing the catalyst loading gave both satisfactory yield and outstanding enantioselectivity (entry 9). The highest TON (700) was achieved when the catalyst loading was 0.1 mol % (entry 10). Notably, the catalytic activity of the present chiral NP catalyst system was higher than that of the reported heterogeneous catalysts,[8] although a similar type of chiral ligand, secondary amide-substituted chiral dienes with a bicyclo[2.2.2]octadiene structure,[11a] was used.

Substrate generality was then surveyed by using the optimized conditions (Table 2). Substituents including electron-donating or -withdrawing groups on aryl tosylimines did not affect the reactivity significantly; all the products were obtained in high yields and with outstanding enantioselectivities, irrespective of the position of the substituents (entries 1–7). Whereas arylboronic acids bearing substituents on the *meta*- or *para*-position could be utilized without a decrease in yields (entries 8 and 9), the use of *o*-tolylboronic acid required a slight increase in the catalyst and ligand loadings to achieve a high yield (entry 10). Arylboronic acids with either electron-donating or -withdrawing groups reacted smoothly to afford the desired products in high yields with outstanding enantioselectivities (entries 11–14). A range of aryl tosylimines including naphthyl imines (entries 15 and 16) and heteroarenes (entries 17 and 18) were also suitable for this catalytic system, and the desired products were obtained in high yields and with outstanding enantioselectivities under the standard conditions. The reaction with an aliphatic imine under the optimized conditions was unsuccessful, presumably because aliphatic imines are generally more sensitive to water than aromatic imines. Therefore, we changed the reaction procedure to improve the yield. In our previous study of chiral NP catalyst systems for asymmetric 1,4-addition to *α*,*β*-unsaturated esters, an induction period was observed that could be shortened by heating PI/CB Rh/Ag at 100 °C for several hours in the presence of arylboronic acid and solvents before starting the reaction.[11a,13] It was assumed that most aliphatic imines might decompose during the induction period and the “preheating” treatment described above might minimize this effect. Indeed, when a mixture of the catalyst and arylboronic acid was heated at 100 °C for 6 h prior to the addition of imine **1m** to diene **4**, the desired product was obtained in 33% yield with 99% ee (entry 19). The same protocol was applied to more unstable aliphatic imine **1n**, and the product was obtained in excellent enantioselectivity despite the low yield (entry 20). Notably, the chiral NP system could be used to catalyze the reaction with a relatively unstable aliphatic imine in aqueous media. Finally, the effect of protecting groups on the nitrogen was surveyed. The reactivity of 4-nitrobenzenesulfonyl group-protected imine **1o** was relatively lower than that of tosyl imines under the optimized conditions, and the product was obtained in low yield with excellent enantioselectivity (entry 21). We also tested *tert*-butoxycarbonyl protected imine; however, no desired product was observed probably due to rapid hydrolysis of the imine.

The recovery and reuse of the heterogeneous NP catalyst were examined (Table 3). The catalyst was readily recovered by simple filtration, and a new portion of chiral diene **4** was added

Table 3. Recovery and Reuse of the Catalyst



cycle	1	2	3[c]	4[c]	5[c]
yield (%)[a]	85(92)	77(80)	94(97)	88(92)	85(89)
ee (%)[b]	99	99	99	99	99

[a]The yield was determined by isolation from a small fraction of a crude mixture. The yield determined by ^{1}H NMR analysis was shown in parentheses. [b]Determined by HPLC analysis. [c]The recovered catalyst was heated at 150 °C for 6 h before use.

in every cycle. The yield decreased slightly in the second cycle after washing the recovered catalyst with water and an organic solvent followed by drying. The recovered catalyst was then reactivated by heating at 150 °C for 6 h, which resulted in the high yield and outstanding enantioselectivity being maintained for the following three cycles (cycles 3−5).

In summary, heterogeneous chiral Rh NP catalysts for asymmetric addition of arylboronic acids to aldimines have been developed. The catalyst worked efficiently in aqueous media, and the highest TON (700) in heterogeneous catalysts yet described for this reaction was achieved. A wide variety of substrates could be utilized to afford the desired products in high yields and with outstanding enantioselectivities. Remarkably, in spite of the aqueous conditions, even water-unstable aliphatic imines could be converted into the desired products with excellent enantioselectivities. Moreover, the reusability of the catalyst was confirmed and a simple heating treatment could be used to maintain the catalytic activity for five cycles. We believe that heterogeneous chiral NPs are active and practical catalyst systems for the synthesis of important chiral amine compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01172.

Experimental procedures, characterization data, and copies of NMR and HPLC charts (PDF)

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Notes

The authors declare no competing financial interest.

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(12) The structure of the chiral diene was previously optimized in the asymmetric 1,4-addition to α,β-unsaturated esters. See ref 11a.

(13) We assumed that a redox process between Rh/Ag NP and arylboronic acids might occur during the "preheating" stage to generate active species. A similar shorter induction period was observed when preheating was carried out in the presence of the catalyst and a catalytic amount of sodium citrate (5 mol%) as a reductant. See ref 11a for more details.