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Chiral Metal Nanoparticle Systems as Heterogeneous Catalysts beyond Homogeneous Metal Complex Catalysts for Asymmetric Addition of Arylboronic Acids to α,β-Unsaturated Carbonyl Compounds

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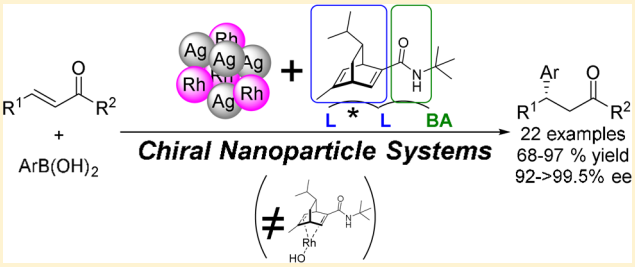
Supporting Information

ABSTRACT: We describe the use of chiral metal nanoparticle systems, as novel heterogeneous chiral catalysts for the asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds, as representative C−C bond-forming reactions. The reactions proceeded smoothly to afford the corresponding β-arylated products in high to excellent yields and outstanding enantioselectivities with wide substrate scope. Remarkably, the nanoparticle catalysts showed performance in terms of yield, enantioselectivity, and catalytic turnover that was superior to that of the corresponding homogeneous metal complexes. The catalyst can be successfully recovered and reused in a gram-scale synthesis with low catalyst loading without significant loss of activity. The nature of the active species was investigated, and we found that characteristic features of the nanoparticle system were totally different from those of the metal complex system.



INTRODUCTION

Catalytic asymmetric carbon−carbon (C−C) bond-forming reactions are useful for constructing basic carbon skeletons of target molecules with chiral centers.[1] However, applications of such reactions to industrial-scale synthesis are limited compared with those of catalytic asymmetric hydrogenation reactions.[2] In most catalytic asymmetric C−C bond-forming reactions, the catalysts are homogeneous, with relatively high catalyst loadings (generally >1 mol %), and precious metals and/or chiral ligands are difficult to recover and reuse. The use of heterogeneous catalysts would not only make catalyst recovery and reuse more straightforward but could also simplify the separation of catalysts and products and even avoid metal contamination of the products. However, the development of heterogeneous chiral catalysts has lagged far behind advances in homogeneous chiral catalysts in terms of performance and scope of reactions.[3]

To develop truly efficient chiral catalysts for asymmetric C−C bond-forming reactions, we considered heterogeneous metal nanoparticle (NP) catalysts because of their advantages such as high stability, robustness, and reusability. In addition, such systems possess unique activities and selectivities, which sometimes differ from those of reactions catalyzed by the corresponding homogeneous metal complex catalysts.[4] Although recent reports revealed that several reactions, including C−C bond-forming reactions, could be performed by using metal NP catalysts with high activities,[5] examples of asymmetric catalysis using metal NPs with a chiral molecule as a modifier, so-called chiral NPs, which showed wide substrate scope and high selectivity, were very limited.[6] We disclosed recently that nanocomposites of polystyrene-based copolymers with cross-linking moieties and carbon black successfully stabilized Rh/Ag bimetallic NPs (PI/CB Rh/Ag) and demonstrated that these heterogeneous metal NPs showed high activity and enantioselectivity for asymmetric 1,4-addition of arylboronic acids to enones in the presence of a chiral diene as a chiral modifier (Scheme 1a).[7] These results established the high potential of heterogeneous chiral NP systems; however, this system was limited to enone substrates and required relatively high metal and ligand loadings.

We thought that, in addition to the great potential of asymmetric catalysis using heterogeneous chiral NPs in terms of robustness and practicality, another strategy was required to enhance catalytic turnover and to achieve an unprecedented level of enantioselectivity with wide substrate scope. We focused on bifunctional catalysts bearing more than two active sites that were capable of interaction with substrates.[8] Recently, these strategies were successfully applied to immobilized catalysts,[9] and they were also used in the asymmetric hydrogenation of activated ketones, proceeding on a cinchona alkaloid-modified metal surface.[10] The latter systems have been of great interest for surface chemistry, and extensive studies on this reaction for more than 30 years have revealed detailed mechanisms by which interactions between substrates and modifiers on the metal surface led to enantioselective reactions. In spite of such comprehensive research efforts, applications of

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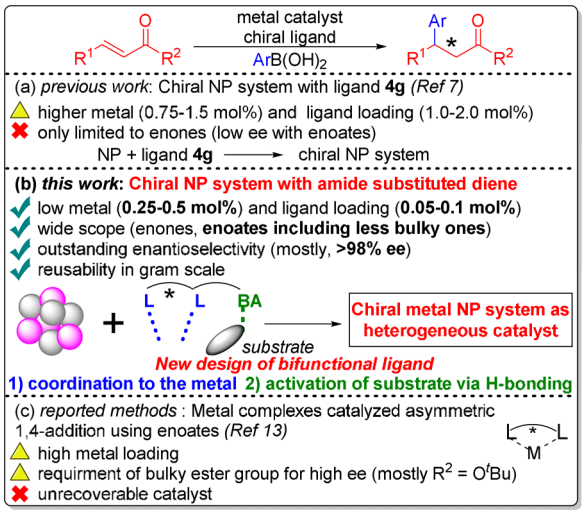
Scheme 1. Catalysts for Asymmetric 1,4-Addition Reactions



this concept were, for a long time, limited to asymmetric hydrogenation, probably because of the difficulty of tuning natural product modifiers.[11] Thus, a promising strategy would be to design a structurally diverse artificial chiral modifier with two functionalities (Scheme 1b): (1) coordination to the surface of NPs to generate active species and chiral environments, and (2) interaction with substrates to bring them close to the active centers of the catalyst and to facilitate reactions in an intramolecular fashion. Recently, a couple of research groups developed asymmetric C−C bond-formation reactions catalyzed by chiral NPs, and the results suggested an important role of hydroxyl groups in the catalytic systems.[12]

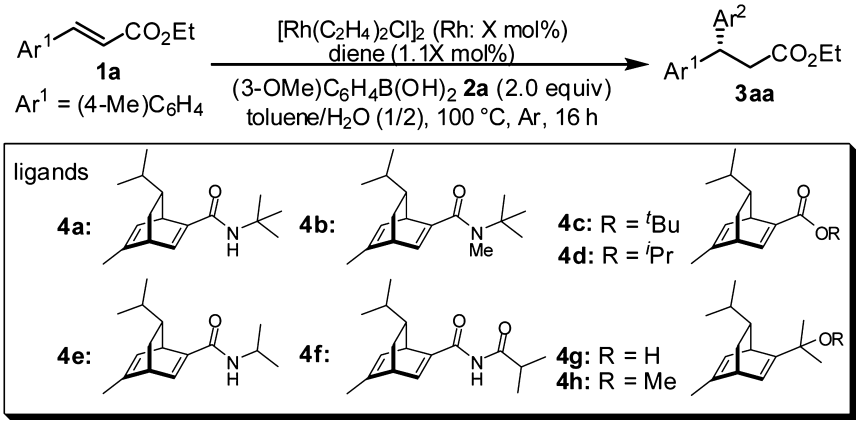
Chiral esters are one of the most useful reaction intermediates, because ester groups can be easily transformed into various functional groups. Esters with a chiral center at the β-position could be synthesized by metal-complex-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated esters.[13] However, in spite of recent progress in asymmetric 1,4-addition of arylboronic acids to electron-deficient olefins, examples involving α,β-unsaturated esters are limited to several asymmetric catalysts with homogeneous chiral Rh[13a−d,f−h] or Pd[13e] complexes (Scheme 1c). Even in these cases, high loadings of unrecoverable homogeneous catalysts (Rh: >1.5 mol %; Pd: 1 mol %) were required, and high stereoselectivities were obtained only with a limited number of substrates (bulky ester groups are required in many cases). Moreover, there have been no reports on the use of heterogeneous catalysts for this asymmetric 1,4-addition reaction. Thus, the development of efficient and practical catalytic systems for this reaction is clearly a challenging issue.

Herein, we report on chiral NP systems as heterogeneous catalysts that catalyze the asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated esters. A novel secondary amide-substituted chiral diene ligand was developed and was applied to both homogeneous complex and heterogeneous NP systems. Outstanding enantioselectivities have been achieved, with high catalytic turnover and wide substrate scope in both systems. The heterogeneous NP system showed superior performance with respect to yields, enantioselectivities, and catalytic turnover, over that of the homogeneous metal complex. We confirmed the heterogeneity of the catalytic system and the unique nature of the active species, which are distinct from those of the metal complex.

RESULTS AND DISCUSSION

Design of a Diene-Amide Chiral Bifunctional Ligand. Chiral dienes with bicyclo[2.2.2]hexadiene structure, which were studied extensively by Hayashi and Carreira, are one of the best ligands for constructing active Rh complexes for asymmetric 1,4-addition reactions because of their coordination ability, stability, and flexibly tunable structure.[14] To increase catalytic activity and enantioselectivity, we designed the

Table 1. Reaction Optimization with a Homogeneous Metal Complex



entry	X	diene	yield[a]	ee[b]	entry	X	diene	yield[a]	ee[b]
1	0.1	**4a**	94	98	7	0.1	**4g**	62	33[c]
2	0.1	**4b**	69	67	8	0.1	**4h**	42	34
3	0.1	**4c**	72	94	9	0.05	**4a**	91	98
4	0.1	**4d**	65	90	10	0.025	**4a**	76	97
5	0.1	**4e**	79	98	11	0.01	**4a**	16	96
6	0.1	**4f**	66	94	12	0.001	**4a**	NR	–

[a]Isolated yield (%). [b]Determined by HPLC analysis (% ee). [c]Reverse enantiomer was obtained.

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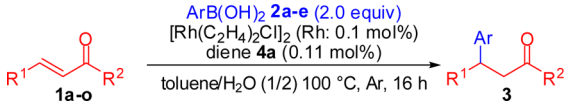
secondary amide-substituted chiral diene **4a** as a bifunctional ligand. We envisioned that the diene parts of **4a** could coordinate to Rh, and, at the same time, the relatively acidic secondary amide group of **4a** could activate an α,β-unsaturated ester through hydrogen bonding (Scheme 1b). At first, to determine whether the proposed approach was feasible, the asymmetric 1,4-addition reaction of arylboronic acid **2a** to α,β-unsaturated ester **1a** was performed with a homogeneous Rh complex (Table 1). It was found that **4a** worked well as a ligand, and excellent enantioselectivity was observed even with the ethyl ester **1a** (a less bulky ester, entry 1). On the other hand, when chiral diene **4b**, which does not bear a proton on the amide group, was used, both the yield and the enantioselectivity decreased significantly (entry 2). Whereas both the corresponding ester-substituted chiral dienes **4c** (*tert*-butyl ester) and **4d** (isopropyl ester) decreased both the yield and enantioselectivity (94% ee, 90% ee, respectively), outstanding enantioselectivity (98% ee) was maintained with less bulky isopropyl amide-substituted chiral diene **4e** (entries 3–5). These results strongly indicated that not only the bulky substituent but also the secondary amide moiety played an important role in generating the excellent yield and the outstanding enantioselectivity. Imide-substituted chiral diene **4f**, which might possess stronger hydrogen-bond donor capacity, was also tested, and relatively good enantioselectivity (94% ee) was observed even though the bulky substituent (isopropyl group) was, in this case, located far from the Rh active center (entry 6). Moreover, dienes **4g** and **4h**, which are effective for asymmetric 1,4-addition to enones,[14b] were found to be much less effective (entries 7 and 8) even though **4g** possesses a hydroxyl group, which can serve as a hydrogen-bond donor. This is probably either because formation of hydrogen bonding led to an unfavorable conformation due to a less rigid structure and easier rotation of the propan-2-ol moiety without a carbonyl group or because the low acidity of the hydroxyl group could not fix the conformation strongly. These results suggest that diene **4a** is a bifunctional ligand that can activate the substrate; however, considering relatively good results obtained in the reaction with ester-substituted chiral dienes, the other possibilities to explain outstanding performance of **4a**, such as a structurally rigid nature of the amide group that restricts the rotation of the ^{t}BuNH group to fix the favored conformation, can not be denied at this stage.

The amount of catalyst could be decreased to 0.05 mol% without significant loss of either yield or enantioselectivity (entry 9) and to 0.025 mol% with a slight decrease in yield (entry 10). The yield dropped significantly, and a slight decrease in enantioselectivity was observed when the reaction was performed in the presence of 0.01 mol% of the Rh species (entry 11).

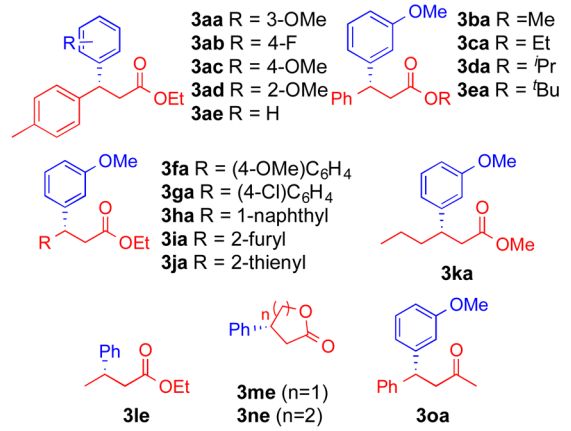
We then examined the substrate scope of the reaction by using the homogeneous Rh complex with **4a** (Table 2). Both electron-rich and electron-poor arylboronic acids afforded the desired products in high yields and with excellent enantioselectivities (entries 1–3, and 5). Only an arylboronic acid with a substituent on the *ortho*-position showed moderate reactivity, and addition of a base was necessary to improve the yield; however, the product **3ad** was obtained with outstanding enantioselectivity (entry 4). Irrespective of whether the substrates had small or bulky ester groups, excellent enantioselectivities were achieved (entries 6–9, **3ba**–**3ea**). Both electron-rich and electron-poor aromatic rings and α,β-unsaturated esters substituted with a naphthyl group could be converted into the corresponding products **3fa**–**3ha** in high yields with excellent enantioselectivities (entries 10–12). A furan-substituted substrate also gave the desired product **3ia** in high yield with excellent enantioselectivity in the presence of a catalytic amount of base (entry 13). The thienyl-substituted product **3ja** was obtained in low yield even in the presence of a base (entry 14). Aliphatic substrates and cyclic substrates were also successfully employed, affording the desired products **3ka** and **3le**–**3ne** in high yields with excellent enantioselectivities (entries 15–18). Moreover, it was found that this system could also be applied to an α,β-unsaturated ketone (**3oa**; entry 19).

Table 2. Substrate Scope under Homogeneous Conditions



entry	product	yield[a]	ee[b]	entry	product	yield[a]	ee[b]
1	**3aa**	94	98	11	**3ga**	94	99
2	**3ab**	96	99	12	**3ha**	91	99
3	**3ac**	93	97	13[d]	**3ia**	91	97
4[c]	**3ad**	73	>99.5	14[d]	**3ja**	37	91
5	**3ae**	96	97	15[d]	**3ka**	80	96
6[d]	**3ba**	93	99	16[e]	**3le**	81	96
7	**3ca**	96	99	17	**3me**	85	99
8	**3da**	88	99	18	**3ne**	66	92
9[e]	**3ea**	76	99	19	**3oa**	92	96
10	**3fa**	92	99				

[a]Isolated yield (%). [b]Determined by HPLC analysis (% ee). [c]K_2CO_3 (1.0 equiv) was used. [d]K_2CO_3 (0.1 equiv) was used. [e]$[Rh(C_2H_4)_2Cl]_2$ (0.1 mol %) and **4a** (0.22 mol %) were used.



Development of Chiral Rh/Ag NP Systems with Amide-Substituted Chiral Dienes. We then employed **4a** in a heterogeneous Rh/Ag NP system with PI/CB Rh/Ag. It was assumed that Rh atoms that make up the core of the NPs cannot participate in catalysis. Therefore, in our experiments, we first employed a large loading of Rh (1.5 mol%) compared with the loading of **4a** (0.1 mol%). Interestingly, the reaction of **1a** with **2a** proceeded smoothly to afford the desired compound **3aa** in high yield with outstanding enantioselectivity by using the heterogeneous NP system (Table 3A, entry 1). When **4b**, which does not have a proton on the amide group, was used, a significant drop in both the yield and enantioselectivity was observed (entry 2). These results indicate that in the heterogeneous NP system, Rh and a Brønsted acidic amide group are both essential for obtaining excellent yield and outstanding enantioselectivity. Moreover, the previous catalytic

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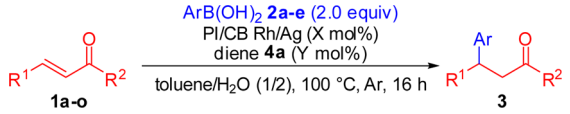
Table 3. Results of Asymmetric 1,4-Addition Reactions in the Heterogeneous NP System



(A) optimization (product = **3aa**)

entry	X	Y	yield[a]	ee[b]	entry	X	Y	yield[a]	ee[b]
1	1.5	0.1	92	99	6	1.5	0.01	45	97
2[c]	1.5	0.1	59	66	7	0.25	0.05	94	99
3[d]	1.5	0.1	62	33[e]	8	0.10	0.05	91	99
4	1.5	0.05	95	99	9	0.05	0.05	71	99
5	1.5	0.025	73	99					

(B) substrate scope (X = 0.25, Y = 0.05)

entry	product	yield[a]	ee[b]	entry	product	yield[a]	ee[b]
1	**3aa**	94	99	11	**3ga**	95	99
2	**3ab**	97	99	12	**3ha**	90	99
3	**3ac**	90	99	13[g,h]	**3ia**	80	98
4[f]	**3ad**	85	>99.5	14[g,h]	**3ja**	80	92
5	**3ae**	97	99	15[h]	**3ka**	85	99
6[g]	**3ba**	83	99	16[g]	**3le**	85	99
7	**3ca**	83	99	17[g,i]	**3me**	85	99
8	**3da**	88	99	18[g]	**3ne**	68	93
9[g]	**3ea**	78	99	19	**3oa**	95	97
10	**3fa**	86	98				

[a]Isolated yield (%). [b]Determined by HPLC analysis (% ee). [c]**4b** was used instead of **4a**. [d]**4g** was used instead of **4a**. [e]Reverse enantiomer was obtained. [f]K_2CO_3 (1.0 equiv) was used. [g]X = 0.5, Y = 0.1. [h]K_2CO_3 (0.1 equiv) was used. [i]The ratio of toluene to water was 2:1.

system with **4g**,[7] which was effective for asymmetric 1,4-addition of arylboronic acids to enones, gave a moderate yield with low enantioselectivity (entry 3). It is assumed that the ester of the substrate is fixed rigidly by the **4a**-modified NP catalytic system, leading to the excellent yield and to the outstanding enantioselectivity. On the other hand, the coordination of the ester is considered to be more flexible because of the steric repulsion between the NMe amide and the ester groups, which decreased both the yield and the selectivity when **4b** was employed. When the previous catalytic system with **4g** was used, the product was obtained with reverse enantioselectivity. In this case, coordination of the ester was expected to be much more flexible, leading to much lower enantioselectivity. The chiral NP system with **4a** is clearly distinguishable from the other two catalytic systems, even though all three catalysts consist of Rh/Ag NPs and chiral diene ligands.

We further optimized the reaction conditions and found that the amount of **4a** could be reduced to 0.05 mol% without loss of yield while maintaining the enantioselectivity (Table 3A, entry 4). Even in the presence of 0.01 mol% **4a**, a reasonable yield was obtained with excellent enantioselectivity (entry 6), whereas a similar low loading of the corresponding homogeneous Rh complex gave a poor yield (Table 1, entry 11). It is noted that the heterogeneous chiral NP system showed superior performance to the homogeneous system and that the heterogeneous chiral NP system achieved excellent reactivities and enantioselectivities (*vide infra*). The amount of PI/CB Rh/Ag could be decreased to 0.25 mol% with excellent yield and outstanding enantioselectivity (Table 3A, entry 7). Furthermore, the use of 0.1 mol% of PI/CB Rh/Ag gave a similar excellent result, albeit with slightly decreased yield (entry 8). When the ratio of Rh to **4a** was 1:1, the yield decreased, probably because not all the chiral diene could contribute to catalysis because of the reduced number of exposed Rh atoms on the surface (entry 9).

The substrate scope of the reaction with the heterogeneous chiral Rh/Ag NP system as a catalyst was then examined. A wide range of arylboronic acids and aromatic unsaturated esters, including heteroarenes, was successfully employed in this system to afford the desired products in high to excellent yields with outstanding enantioselectivities (Table 3B). Remarkably, the heterogeneous chiral NP system showed superior performance to the homogeneous metal complexes in most cases, even with less **4a** (0.05 vs 0.11 mol%). For example, the moderate yield of the *ortho*-substituted arylboronic acid (Table 2, entry 4) was improved by using the heterogeneous chiral NP system (Table 3B, entry 4). A thienyl-substituted ester gave a high yield of the desired product (Table 3B, entry 14) by using the chiral NP system, whereas the same substrate gave only 37% yield by using the corresponding homogeneous system (Table 2, entry 14). Moreover, the enantioselectivities were improved or maintained at outstanding levels (mostly 99% ee or >99.5% ee) by using the heterogeneous chiral NP system, compared with those obtained by using the homogeneous metal complexes in all 19 examples tested. In particular, the reactions with aliphatic α,β-unsaturated esters showed increased enantioselectivities under the heterogeneous conditions compared with those under the homogeneous conditions (Table 3B, entries 15, 16 vs Table 2, entries 15, 16), and cyclic substrates and α,β-unsaturated ketone also gave similar excellent results (entries 17–19). Moreover, tolerance to various functional groups, such as amide, nitrile, bromide, and alcohol, was confirmed from an additive-based approach, "robustness screen," which was proposed by Glorius.[15,16] Even in the presence of functional groups that inhibited the reactions, outstanding enantioselectivity was maintained. These

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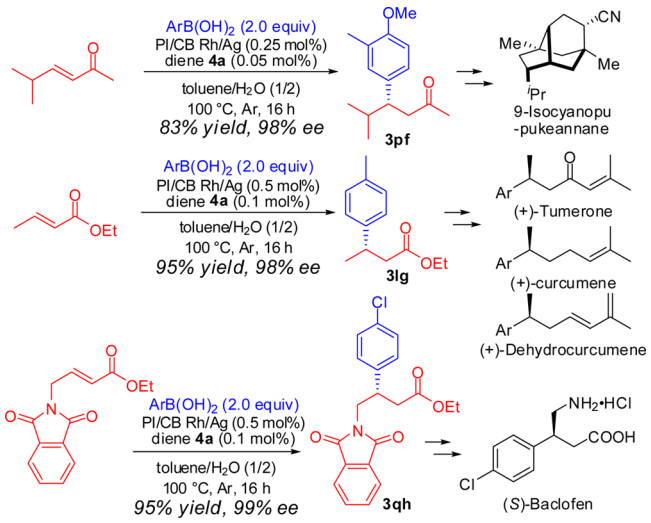
results indicate the stability and robustness of the catalytically active species of the heterogeneous chiral Rh/Ag NP system.

To demonstrate the utility of the chiral NP systems as chiral catalysts, formal syntheses of biologically important compounds were undertaken (Scheme 2). Ketone **3pf**, which is known as

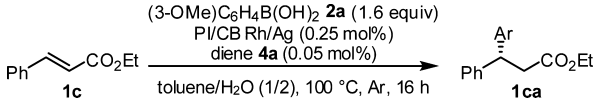
Scheme 2. Formal Synthesis of Biologically Important Compounds



an intermediate for the synthesis of the natural product 9-isocyanopupukeannane,[17] was synthesized by using the chiral NPs in 83% yield with 98% ee. Ethyl crotonate reacted with *p*-tolylboronic acid in the presence of the chiral NPs to afford **3lg** in 95% yield with 98% ee. Ester **3lg** can be converted into various anticancer and antimicrobial natural products such as bisabolane sesquiterpenes.[18] Moreover, the aminobutyric acid derivative **3qh**, which can be converted into (*S*)-Baclofen as an antispasmodic agent,[19] was also prepared in excellent yield with outstanding enantioselectivity.

PI/CB Rh/Ag could be recovered and reused without significant loss of activity (Table 4). After the reaction, the

Table 4. Reuse of Heterogeneous NP Catalyst in Gram-Scale Synthesis



run	first	second	third	fourth	fifth	sixth
yield[a]	92 (1.05 g)	94	90	87	86	94
ee[b]	99	99	99	99	99	99

[a]Isolated yield (%). [b]Determined by HPLC analysis (% ee).

catalyst was filtered, washed, dried, and reused in the next reaction. We used the catalyst six times in gram-scale syntheses and confirmed that high yields and outstanding enantioselectivities were obtained in all cases.

Mechanistic Study. For the heterogeneous NP system, it is crucial to establish whether the active species are leached homogeneous Rh species or not. To clarify this point, metal leaching was examined under the conditions detailed in Table 3A, entry 7. No leaching was observed by inductively coupled plasma (ICP) analysis of the crude mixture. A hot filtration test[20] was carried out, and it was confirmed that no reaction proceeded in the filtrate that was obtained in the middle of the reaction at two different times (Figure 1). The catalytic activity

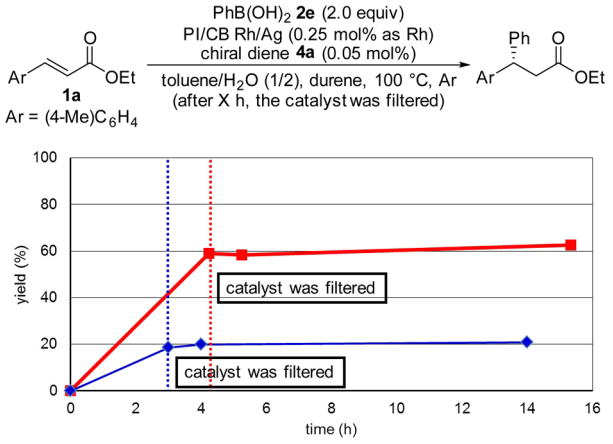


Figure 1. Hot filtration test. The initial concentration of ($[\mathbf{1a}]_0$) was 0.8 M; dark-blue line, X = 3 h, and red line, X = 4.25 h.

of the remaining PI/CB Rh/Ag after hot filtration was also confirmed.[16] Given that the heterogeneous NP system showed higher activity at low loadings of the catalysts compared with the homogeneous metal complex system, which showed no activity in low concentrations (Table 1, entries 11 and 12), it is clear that the active species in the heterogeneous NP system are not leached homogeneous Rh complexes.

Nonlinear effect (NLE) analysis is a powerful tool with which to obtain information about the structure of active species.[21] We therefore used this approach on both the homogeneous metal complex system and on the heterogeneous NP system (Figure 2). Interestingly, a positive NLE was observed in the

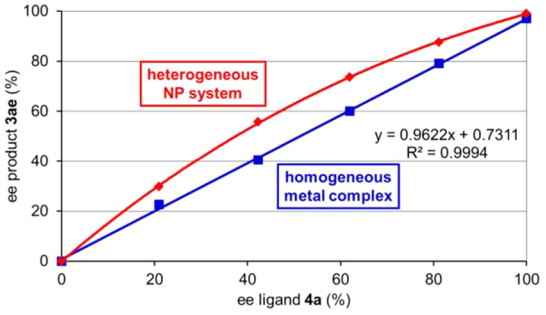


Figure 2. Nonlinear effects on both systems.

heterogeneous NP system, whereas a linear relationship between the enantiomeric excess of ligand and that of product was observed in the homogeneous metal complex system.[22] These results clearly demonstrated the different nature of the active species involved in the two systems.

The reaction profiles of the two systems were also compared (Figure 3). A faster initial reaction rate in the homogeneous system compared with that in the heterogeneous NP system was observed, and almost quantitative yield was observed in both systems when the initial concentration ($[\mathbf{1a}]_0$) was 0.8 M. Interestingly, a long induction period was observed only in the case of the heterogeneous system. When the initial concentration ($[\mathbf{1a}]_0$) was diluted to 0.4 M, although the initial rate of the reaction was still faster in the homogeneous system, the reaction essentially stopped at the point of approximately 60%

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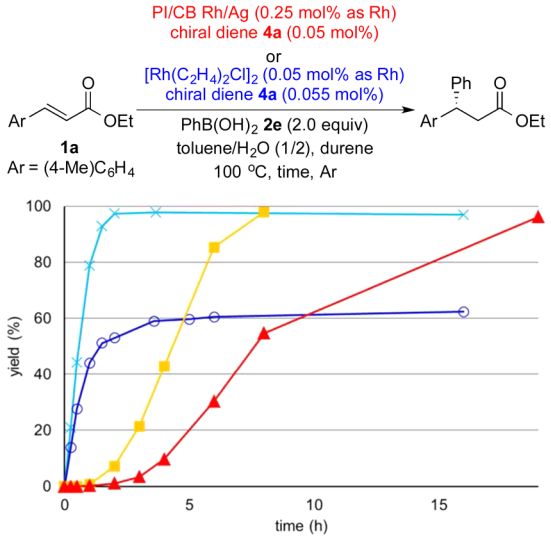

Figure 3. Reaction profiles; homogeneous complex vs heterogeneous NP system. Homogeneous complex systems: light-blue line, ($[\mathbf{1a}]_0$ = 0.8 M), and dark-blue line, ($[\mathbf{1a}]_0$ = 0.4 M). Heterogeneous NP systems: yellow line, ($[\mathbf{1a}]_0$ = 0.8 M), and red line, ($[\mathbf{1a}]_0$ = 0.4 M). Durene was used as an internal standard.

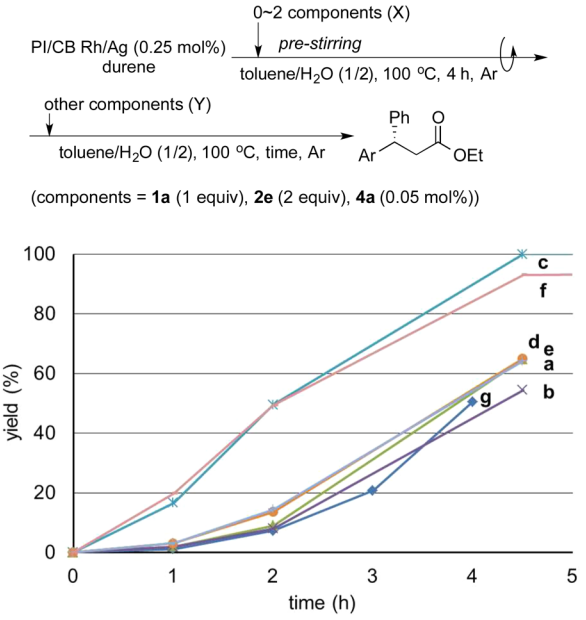

Figure 4. Effect of pre-stirring with reaction components. Plots were started after 4 h pre-stirring except for plot g. (a) No component was added during pre-stirring. (b) X = **1a**, Y = **2e**, **4a**; (c) X = **2e**, Y = **1a**, **4a**; (d) X = **4a**, Y = **1a**, **2e**; (e) X = **1a**, **4a**, Y = **2e**; and (f) X = **2e**, **4a**, Y = **1a**. (g) Prestirring was not conducted. Durene was used as an internal standard.

yield. Under these conditions, with such a low concentration, the yield hardly improved even though an additional portion of **2e** was employed after the reaction stopped (4 h).[16] This result indicated that the catalyst had either decomposed or had been deactivated after several hours. With the heterogeneous NP system, on the other hand, although the reaction proceeded slowly due to the longer induction period, the process could continue until almost quantitative yield was produced even with a low concentration of substrate. These results suggest that one of the factors that led to the superior performance of the heterogeneous NP system could be the stability of active species. In addition, these experiments clearly indicate that the active species in the heterogeneous NP system were distinct from those of the homogeneous complex.

Finally, to determine which reaction component causes the induction period in the heterogeneous NP system, the effect of "pre-stirring" was examined (Figure 4). When all reaction components (**1a**, **2e**, and **4a**) were added after the mixture of PI/CB Rh/Ag and solvent was stirred for 4 h at 100 °C as a "pre-stirring" process (Figure 4a), no dramatic change of the reaction profile was observed compared with those observed under the standard conditions without pre-stirring (g). Various reaction profiles were examined in the presence of the catalyst and one or two reaction components during pre-stirring (Figure 4b–f). It was found that the induction period could be shortened only when arylboronic acid was combined during pre-stirring (Figure 4c,f). The reaction hardly proceeded in a filtrate that was obtained after the pre-stirring with **2e** by hot filtration, indicating no leaching of the active species during the induction period.[16] A similar shorter induction period was observed when pre-stirring was carried out in the presence of the catalyst and a catalytic amount of sodium citrate (5 mol %).[16] Given that sodium citrate and arylboronic acids have been reported to work as a reductant of metal,[23,24] a redox process between Rh/Ag NP and additives might occur in the pre-stirring stage to generate the active species.[25,26] A similar redox process would be expected to occur during the induction period of the heterogeneous NP system (Figure 3). Indeed, biphenyl formed via an oxidative homocoupling of **2e** after the mixture of the catalyst and **2e** was heated for 4 h at 100 °C. This observation supported the hypothesis.[16]

Based on these results, a proposed mechanism concerning the generation of active species from PI/CB Rh/Ag was described (cf. Figure S4).[16] First, a redox process between the surface of Rh/Ag NPs and arylboronic acids generates a reduced surface. From this stage, there might be two possible pathways: (1) the ligands coordinated to the reduced surface to generate the active sites and the reaction occurred on these sites, and (2) the coordination of the ligands dissociates Rh NPs to generate small active nanoclusters and PI/CB Rh/Ag acts as a metal reservoir.[27] In the latter case, the active species might aggregate to reconstitute larger NPs to stay inside the polymer matrix, and consequently no leaching was observed. Although it is difficult to elucidate the true pathway at this stage, the distinct nature of the active species in the heterogeneous NP systems might exclude the possibility of the leached homogeneous metal complexes as active species.

■ CONCLUSION

We have developed the secondary amide-substituted, chiral diene-modified Rh/Ag NP systems as novel heterogeneous catalysts. The catalyst systems were successfully employed in the asymmetric 1,4-addition of arylboronic acids to *α,β*-unsaturated carbonyl compounds to afford the corresponding arylated products in high to excellent yields and outstanding enantioselectivities. The chiral Rh/Ag NP systems were prepared from Rh nanocomposites of polystyrene-based copolymers with cross-linking moieties and carbon black and the newly designed chiral ligand **4a**, which was suggested as a bifunctional ligand. The ligand **4a** was also successfully used to generate homogeneous chiral metal complex systems; however, the heterogeneous NP systems showed superior performance in terms of yield, enantioselectivity, and catalytic turnover

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compared with the corresponding homogeneous metal complexes.[28] As notable examples of the superior performance of the chiral NP systems as heterogeneous chiral catalysts, the reactions of a wide range of arylboronic acids and α,β-unsaturated esters, which are known to be difficult to obtain with high selectivity,[13] were conducted with remarkably high enantioselectivities (>98% ee of 19 examples in 22 examples tested). Based on the results of ICP analysis and of hot leaching tests, we ruled out the possibility that leached Rh-diene complexes function as the active species in the heterogeneous NP system. Furthermore, various unique phenomena in the heterogeneous NP system were observed by NLE analysis of the reaction, by measuring the reaction profiles, and by determining the effect on the length of the induction periods of pre-stirring with reductive compounds. These experimental results demonstrate that there is a clear difference between the nature of active species in the heterogeneous NP system and the active species in the homogeneous metal complex system. Chiral NP systems offer engineering flexibility and have the potential to be applied to many other reactions promoted by asymmetric catalysts. We believe the concept of chiral NP systems as heterogeneous chiral catalysts opens the door to a new generation of asymmetric catalysts and expect that this approach will play a central role in this important field.

■ ASSOCIATED CONTENT

Supporting Information

Reaction procedures and spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02213.

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Notes

The authors declare no competing financial interest.

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