Asymmetric Catalysis

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Chiral Nanoparticles/Lewis Acids as Cooperative Catalysts for Asymmetric 1,4-Addition of Arylboronic Acids to α,β-Unsaturated Amides

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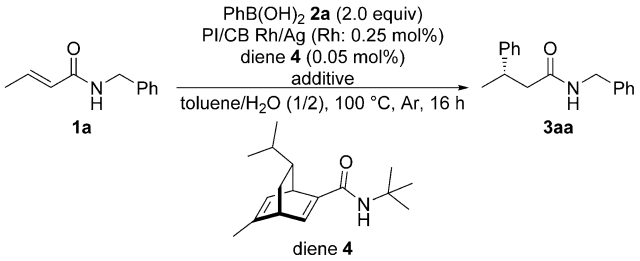
Abstract: *Cooperative catalysts consisting of chiral Rh/Ag nanoparticles and $Sc(OTf)_3$ have been developed that catalyze asymmetric 1,4-addition reactions of arylboronic acids with α,β-unsaturated amides efficiently. The reaction has been considered one of the most challenging reactions because of the low reactivity of the amide substrates. The new catalysts provide the desired products with outstanding enantioselectivities (> 98 % ee) in the presence of low loadings (< 0.5 mol %) of the catalyst.*

The development of efficient catalysts for asymmetric carbon–carbon bond (C–C bond) formation is one of the most important research themes in synthetic organic chemistry. We have focused on the use of metal nanoparticles (NPs) as novel heterogeneous catalysts because they offer advantages, such as ease of heterogenization, robustness, and unique activity.[1] The application of chiral ligand-modified metal NPs (chiral metal NPs) in asymmetric catalysis is particularly attractive. Indeed, the great potential of such chiral catalysts as an alternative to conventional metal-complex catalysts has been recognized.[2] We have also used polymer incarceration (PI) methods to construct several achiral and chiral heterogeneous NP catalysts immobilized on a nanocomposite of polystyrene-based copolymers with cross-linking moieties and carbon black (PI/CB catalyst).[3] Metal NPs in PI/CB catalysts are stabilized by weak but multiple interactions with polymer network, and cannot aggregate and leach out, resulting in high catalytic activity and robustness.

Chiral amides constitute a class of key skeletons of biologically active compounds.[4] Aryl amides that bear a chiral center at the β-position could be synthesized by asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated amides. Early examples of such reactions using Rh complexes as catalysts were reported by Hayashi and Miyaura in 2001.[5] Since then, tremendous progress in asymmetric 1,4-addition reactions has been achieved over almost two decades;[6] however, surprisingly, there have been only a few examples of the reactions with α,β-unsaturated amides.[4a,7] These reactions are challenging because of the low reactivity of amide substrates caused by higher LUMO energy compared with those of the corresponding ketones and esters.[8] Consequently, reported examples required relatively high loading (> 3 mol %) of unrecoverable homogeneous catalysts and substrate generality was limited. Herein, we report the use of chiral Rh NPs/Lewis acids as powerful heterogeneous and recoverable catalysts for asymmetric 1,4-addition reactions of arylboronic acids with α,β-unsaturated amides.

We selected *N*-benzyl crotonamide (**1a**) and phenylboronic acid (**2a**) as model compounds, and several reaction conditions were examined (Table 1). First, the reaction was conducted with a chiral metal nanoparticle system consisting of Rh/Ag bimetallic NP catalyst prepared by our polymer incarceration methods (PI/CB Rh/Ag)[9a] and secondary amide substituted chiral diene **4** under the best conditions for asymmetric 1,4-addition to α,β-unsaturated esters.[9b] Under these conditions, the desired product was obtained in low yield, although excellent enantioselectivity was obtained (Table 1, entry 1). Addition of a base improved the yield; however, a stoichiometric amount of base was necessary and the enantioselectivity decreased slightly (entries 2 and 3). Given that these unsatisfactory results were clearly ascribed to the low reactivity of the amide substrate, we then considered methods to activate the α,β-unsaturated amide by using a second catalyst.

Table 1: Optimization of reaction conditions of asymmetric 1,4-addition.



Entry	Additive [mol %]	Yield [%][a]	*ee* [%][b]	Rh leaching [%][c]
1	–	37	98	ND
2	K_2CO_3 (10)	42	97	ND
3	K_2CO_3 (100)	74	96	ND
4	$Sc(OTf)_3$ (1)	79	99	ND
5	$Cu(OTf)_2$ (1)	63	98	–
6[e]	Other $M(OTf)_n$ (1)	27–49[d]	97–99	–
7[f]	$Sc(OTf)_3$ (1)	93	98	ND

[a] Isolated yield. [b] Determined by HPLC analysis. [c] Determined by ICP analysis (ND = not detected). The values express the percentage of the total amount of Rh that was employed in the reaction. Detection limit of Rh leaching was 0.3–0.4 %. [d] Determined by ^{1}H NMR analysis. [e] M = Mg, Ca, Ba, La, Ce, Sm, Y, Yb. [f] Reaction time was 24 h and **4** (0.1 mol %) was used.

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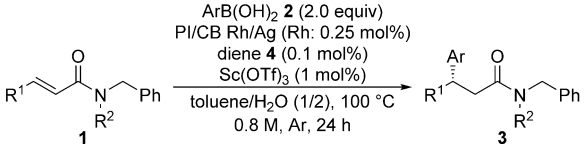
When two or more catalysts are applied together to a reaction system, the catalytic performance is sometimes enhanced by a synergistic effect to give a better result. This strategy has been explored for several combinations of catalysts such as metal complexes and non-metal catalysts.[10] In contrast, this approach has been less well explored for metal NP catalysts,[11] probably because these catalysts are often incompatible with other catalysts.[12] To our knowledge, there had been no example of synergistic effects between chiral NP catalysts and other types of catalyst. Quite recently, our group reported a synergistic effect between Au/Pd bimetallic NP catalysts and metal Lewis acid catalysts for hydrogen autotransfer processes.[13] From these findings, we envisioned that cooperative catalyst systems of chiral metal NP catalysts and metal Lewis acids may give a new opportunity to develop highly active asymmetric catalysis.

We then examined the use of metal Lewis acid cocatalysts to activate the amide substrate. After screening several Lewis acids, it was found that $Sc(OTf)_3$ gave the best result (Table 1, entries 4–6); when 1 mol% $Sc(OTf)_3$ was employed, the yield improved dramatically (entry 4). It is remarkable that chiral NPs were compatible with $Sc(OTf)_3$ and a synergistic effect was found to enhance the catalytic performance significantly. This is in marked contrast to the fact that acidic additives sometimes inhibit these types of reactions using Rh-BINAP complex systems[5b] and that most Rh-catalyzed asymmetric 1,4-addition reactions tend to be performed under either basic conditions. This result may be ascribed to the unique character of $Sc(OTf)_3$.[14] We expected that $Sc(OTf)_3$ lowered the LUMO level of the amide substrate to accelerate the C–C bond-forming step. At the same time, a second role of $Sc(OTf)_3$, such as acceleration of a protonation (product release and catalyst regeneration) step by inner-sphere water ligands of the water-compatible Lewis acid, was also assumed.[14] When the loading of the chiral diene was increased and the reaction time was extended, the desired 1,4-addition product was obtained in 93% yield with 98% *ee* (entry 7). Notably, no metal leaching was identified by ICP analysis under any of the conditions.

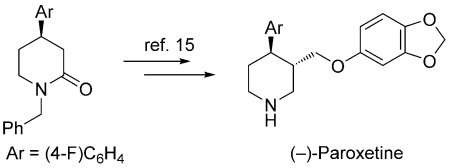
Substrate generality was surveyed under the optimized conditions (Table 2). Arylboronic acids with either electron-donating or electron-withdrawing groups were tested for the reaction with **1a** (Table 2, entries 1–8). The presence of a substituent at the *ortho*-position decreased the reactivity significantly, but an increase in the catalyst loading gave the product in high yield with outstanding enantioselectivity (entry 2). The reactions with arylboronic acids bearing an electron-donating substituent at the *meta*- or *para*-position proceeded smoothly to afford the products in high yields with excellent enantioselectivities (entries 4–6). The reactions with arylboronic acids bearing an electron-withdrawing substituent also afforded the products in high yields with excellent enantioselectivities, when the catalyst loading was slightly increased (entries 3, 7, and 8). Notably, the primary amide could be applied directly, and the desired product was obtained in 61% yield with 98% *ee* when a toluene major cosolvent system was used (entry 9). Several *N*-benzyl unsaturated amides, including aliphatic substrate **1c**, aromatic substrate **1d**, sterically bulky isopropyl group-substituted substrate **1e**, and cyclic substrate with a six-membered ring **1f**, were converted into the corresponding 1,4-addition products in good yields with outstanding enantioselectivities (entries 10–13). The application of the reaction conditions to the formal synthesis of a pharmacologically important compound, Paroxetine,[15] was demonstrated by the reaction of **1f** with 4-fluorophenylboronic acid (Scheme 1). The product **3fh**, which can be converted into Paroxetine by using a reported method,[15] was obtained in 72% yield with 99% *ee* (entry 14). On the other hand, conducting the reaction with **1g**, a cyclic substrate with a five-membered ring, gave the desired product in 35% yield with 99% *ee* (entry 15). In this reaction, formation of *ortho*-disubstituted benzene side product **5** was observed, which was presumably generated through sequential 1,4-addition to **1g**, 1,4-migration of Rh,[16] and further 1,4-addition to another molecule of **1g**. In this

Table 2: Substrate scope.



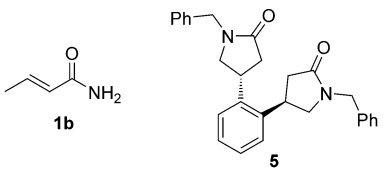
Entry	R^1, R^2	Ar	3	Yield [%][a]	*ee* [%][b]
1	CH_3, H (**1a**)	Ph	**3aa**	93	98
2[c]	CH_3, H	(2-OMe)C_6H_4	**3ab**	88	>99.5
3[d]	CH_3, H	(3-OMe)C_6H_4	**3ac**	85[e]	98
4	CH_3, H	(4-OMe)C_6H_4	**3ad**	90[e,f]	98
5	CH_3, H	(3-Me)C_6H_4	**3ae**	85	99
6	CH_3, H	(4-Me)C_6H_4	**3af**	84	98
7[d]	CH_3, H	(4-Cl)C_6H_4	**3ag**	77	99
8[d]	CH_3, H	(4-F)C_6H_4	**3ah**	81	98
9[g]	CH_3, H (**1b**)[h]	Ph	**3ba**	61	98
10	$^nC_5H_{11}$, H (**1c**)	Ph	**3ca**	88[e]	99
11[d]	(4-Me)C_6H_4, H (**1d**)	Ph	**3da**	69[e]	99
12[i]	$^iC_3H_7$, H (**1e**)	Ph	**3ea**	72[e]	99
13	-$(CH_2)_2$- (**1f**)	Ph	**3fa**	56[e]	99
14[d]	-$(CH_2)_2$-	(4-F)C_6H_4	**3fh**	72	99
15[d,j]	-$(CH_2)_1$- (**1g**)	Ph	**3ga**	35[e]	99

[a] Isolated yield. [b] Determined by HPLC analysis. [c] PI/CB Rh/Ag (Rh: 1 mol%) and **4** (0.4 mol%) were used. [d] PI/CB Rh/Ag (Rh: 0.5 mol%) and **4** (0.2 mol%) were used. [e] Calculated by ^{1}H NMR analysis after isolation of the mixture of the product and the starting material. [f] 1.07 M. [g] Toluene/H_2O = 3:1 and 0.36 M. [h] Crotonamide (**1b**) was used. [i] 1.6 M. [j] Toluene/H_2O = 2:1 and 0.4 M. The concentrations were calculated based on the amount of toluene.



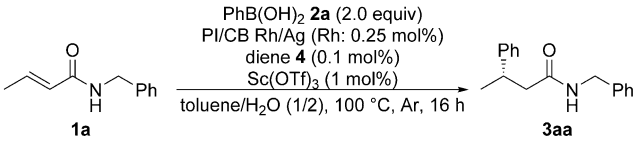
Scheme 1. Formal synthesis of pharmacologically important compound.

substrate survey, it is noted that outstanding enantioselectivities (>98% *ee*) were obtained under any of the conditions.



It was confirmed that the asymmetric 1,4-addition reaction could be successfully conducted on a gram scale (Table 3, run 1). The PI/CB Rh/Ag catalyst was then recovered by simple filtration. After washing with organic solvents and water followed by heating at 150 °C, the recovered catalyst

Table 3: Recovery and reuse of the catalyst.



Parameter	Run				
	1[c]	2[d]	3[d]	4[e]	5[e]
Yield (%)[a]	87 (1.32 g)	82	53	75	75
ee (%)[b]	99	99	98	99	99

[a] Isolated yield. [b] Determined by HPLC analysis. [c] 40 h. [d] The recovered catalyst was washed with water and THF then heated at 150 °C for 3 h before use. [e] The recovered catalyst was first washed with THF/1 M TfOH aq. = 99:1, water, and THF and heated at 150 °C for 3 h before use. New portions of diene **4** and $Sc(OTf)_3$ were added in every run.

was reused in the same reaction of **1a** and **2a** with new portions of chiral diene **4** and $Sc(OTf)_3$ to afford the desired product **3aa** with similar yield and enantioselectivity (run 2). The same recovery and reuse experiments were then continued further. Whereas the yield decreased in the 3rd run (run 3), the catalyst was successfully reactivated by treatment with trifluoromethanesulfonic acid,[17] and good yields and excellent enantioselectivities were observed again in the 4th and 5th runs (runs 4 and 5).

We have some information on the structure of the key cooperative catalysts consisting of chiral Rh/Ag NPs and $Sc(OTf)_3$. We assumed that $Sc(OTf)_3$ was easily accessible into amphiphilic polymer matrix consisting of benzene rings and polyethylene glycol moieties to locate closely to Rh/Ag NPs, creating efficient asymmetric environments for catalysis. Indeed, it was confirmed that the Rh/Ag NPs/$Sc(OTf)_3$ cooperative catalyst gave a higher yield than simple combination of a homogeneous Rh complex and $Sc(OTf)_3$ (Table S2, in the Supporting Information). When an excess amount of $Sc(OTf)_3$ was added to a reaction system, Rh leaching was observed (Table S1) suggesting that the stabilization of $Sc(OTf)_3$ from polymer matrix may be competitive with that of Rh/Ag NPs.[18] Further investigations to clarify the structure of the cooperative catalysts are ongoing.

In summary, we have developed cooperative catalysts consisting of chiral Rh/Ag NPs and $Sc(OTf)_3$ for asymmetric 1,4-addition reactions of arylboronic acids with α,β-unsaturated amides. The reactions with unreactive amide substrates were successfully conducted by using the new catalyst, and the desired products were obtained in high yields with outstanding enantioselectivities (>98% *ee*) in the presence of low catalyst loading (<0.5 mol%). The catalyst could be recovered and reused by a simple procedure without significant loss of activity. No metal leaching occurred, which was carefully confirmed by ICP analysis. In addition to a remarkable activity of the cooperative catalyst, it is notable that, whereas most homogeneous rhodium-complex-catalyzed asymmetric arylation reactions are performed under basic conditions, the chiral Rh/Ag NPs reported herein showed compatibility with a Lewis acid. Furthermore, it was found that the heterogeneous NP catalyst system enhanced the efficiency of the cooperative catalysis. These cooperative catalysts may provide new possibilities for asymmetric catalysis and heterogeneous NP catalysis.

Experimental Section

Typical procedure (Table 2, entry 5): (*E*)-*N*-Benzylbut-2-enamide **1a** (52.4 mg, 0.3 mmol), 3-methylphenylboronic acid **2e** (70.8 mg, 0.6 mmol), PI/CB Rh/Ag (4.3 mg, Rh: 0.25 mol%) and chiral diene **4** (3.93 mg mL^{-1} in toluene, 0.02 mL) were combined in a Carousel tube, toluene (0.375 mL) was added and the mixture was stirred for 1 min. $Sc(OTf)_3$ (14.8 mg mL^{-1} in water, 0.1 mL) and water (0.65 mL) were added and the mixture was stirred and heated to 100 °C under an Ar atmosphere for 24 h. The mixture was allowed to cool and diethyl ether was added to quench the reaction. The mixture was filtered through a membrane filter to remove residual solids and the solution was transferred to a separating funnel. The aqueous layer was extracted with diethyl ether and the organic layer was washed with brine. The combined organic layer was dried over sodium sulfate and the conversion of **1a** and the yield of **3ae** were determined by ^{1}H NMR analysis with reference to 1,1,2,2-tetrachloroethane as internal standard. The crude product was purified by preparative TLC (dichloromethane/acetone = 49:1) to afford 68.4 mg (85% yield) of **3ae**. The *ee* of the product was determined by chiral HPLC analysis.

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Keywords: cooperative effects · heterogeneous catalysis · Lewis acid · nanoparticles · Rh catalysis

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[1] a) L. L. Chng, N. Erathodiyil, J. Y. Ying, *Acc. Chem. Res.* **2013**, *46*, 1825; b) H. Cong, J. A. Porco, *ACS Catal.* **2012**, *2*, 65; c) D. Astruc, *Nanoparticles and Catalysis*, Wiley-VCH, Weinheim, **2007**.

[2] a) T. Yasukawa, H. Miyamura, S. Kobayashi, *Chem. Soc. Rev.* **2014**, *43*, 1450; b) K. V. S. Ranganath, J. Kloesges, A. H. Schäfer, F. Glorius, *Angew. Chem. Int. Ed.* **2010**, *49*, 7786; *Angew. Chem.* **2010**, *122*, 7952; c) K. Ding, Y. Uozumi, *Handbook of Asymmetric Heterogeneous Catalysis*, Wiley-VCH, Weinheim, **2008**, pp. 1 – 24; d) B. M. Choudary, K. V. S. Ranganath, U. Pal, M. L. Kantam, B. Sreedhar, *J. Am. Chem. Soc.* **2005**, *127*, 13167; e) S. Jansat, M. Gómez, K. Philippot, G. Muller, E. Guiu, C. Claver, S. Castillon, B. Chaudret, *J. Am. Chem. Soc.* **2004**, *126*, 1592; f) M. Tamura, H. Fujihara, *J. Am. Chem. Soc.* **2003**, *125*, 15742; g) Y. Orito, S. Imai, S. Niwa, G. H. Nguyen, *J. Synth. Org. Chem. Jpn.* **1979**, *37*, 173.

[3] a) S. Kobayashi, H. Miyamura, *Aldrichimica Acta* **2013**, *46*, 3; b) R. Akiyama, S. Kobayashi, *Chem. Rev.* **2009**, *109*, 594.

[4] a) Z.-T. He, Y.-B. Wei, H.-J. Yu, C.-Y. Sun, C.-G. Feng, P. Tian, G.-Q. Lin, *Tetrahedron* **2012**, *68*, 9186; b) V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471; c) E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606; d) A. Enz, D. Feuerbach, M. U. Frederiksen, C. Gentsch, K. Hurth, W. Müller, J. Nozulak, B. L. Roy, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1287.

[5] a) T. Senda, M. Ogasawara, T. Hayashi, *J. Org. Chem.* **2001**, *66*, 6852; b) S. Sakuma, N. Miyaura, *J. Org. Chem.* **2001**, *66*, 8944.

[6] a) P. Tian, H.-Q. Dong, G.-Q. Lin, *ACS Catal.* **2012**, *2*, 95; b) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829; c) Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579.

[7] a) N. Kuuloja, M. Vaismaa, R. Franzén, *Tetrahedron* **2012**, *68*, 2313; b) C. Shao, H.-J. Yu, N.-Y. Wu, P. Tian, R. Wang, C.-G. Feng, G.-Q. Lin, *Org. Lett.* **2011**, *13*, 788; c) S. Oi, A. Taira, Y. Honma, T. Sato, Y. Inoue, *Tetrahedron: Asymmetry* **2006**, *17*, 598; d) R. Shintani, T. Kimura, T. Hayashi, *Chem. Commun.* **2005**, 3213; e) M. Pucheault, V. Michaut, S. Darses, J. P. Genet, *Tetrahedron Lett.* **2004**, *45*, 4729; f) C. Defieber, J.-F. Paquin, S. Serna, E. M. Carreira, *Org. Lett.* **2004**, *6*, 3873.

[8] a) A. K. Schoonen, M. Angeles Fernandez-Ibanez, M. Fananas-Mastral, J. F. Teichert, B. L. Feringa, *Org. Biomol. Chem.* **2014**, *12*, 36; b) S. Matsunaga, T. Kinoshita, S. Okada, S. Harada, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 7559.

[9] a) T. Yasukawa, H. Miyamura, S. Kobayashi, *J. Am. Chem. Soc.* **2012**, *134*, 16963; b) T. Yasukawa, A. Suzuki, H. Miyamura, K. Nishino, S. Kobayashi, *J. Am. Chem. Soc.* **2015**, *137*, 6616. Since it was assumed that Rh atoms that make up the core of the NPs could not participate in catalysis, we employed a higher loading of Rh than of diene **4**.

[10] a) S. M. Inamdar, V. S. Shinde, N. T. Patil, *Org. Biomol. Chem.* **2015**, *13*, 8116; b) A. Gualandi, L. Mengozzi, C. M. Wilson, P. G. Cozzi, *Chem. Asian J.* **2014**, *9*, 984; c) D.-F. Chen, Z.-Y. Han, X.-L. Zhou, L.-Z. Gong, *Acc. Chem. Res.* **2014**, *47*, 2365; d) A. E. Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, *3*, 633.

[11] a) D.-T. D. Tang, K. D. Collins, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 7450; b) H. Yuan, W.-J. Yoo, H. Miyamura, S. Kobayashi, *J. Am. Chem. Soc.* **2012**, *134*, 13970.

[12] H. Miyamura, G. C. Y. Choo, T. Yasukawa, W.-J. Yoo, S. Kobayashi, *Chem. Commun.* **2013**, *49*, 9917.

[13] G. C. Y. Choo, H. Miyamura, S. Kobayashi, *Chem. Sci.* **2015**, *6*, 1719.

[14] a) S. Kobayashi, *Eur. J. Org. Chem.* **1999**, 15; b) S. Kobayashi, S. Nagayama, T. Busujima, *J. Am. Chem. Soc.* **1998**, *120*, 8287.

[15] M. S. Yu, I. Lantos, Z.-Q. Peng, J. Yu, T. Cacchio, *Tetrahedron Lett.* **2000**, *41*, 5647.

[16] S. Ma, Z. Gu, *Angew. Chem. Int. Ed.* **2005**, *44*, 7512; *Angew. Chem.* **2005**, *117*, 7680.

[17] T. Yasukawa, H. Miyamura, S. Kobayashi, *Chem. Sci.* **2015**, *6*, 6224.

[18] Direct interaction between $Sc(OTf)_3$ and the oxygen sites on the surface of Rh/Ag NPs can also be considered. Since the catalyst was heated at high temperature under air during preparation, the surface of Rh NPs might be partially oxidized. The detection of Rh oxide by XPS analysis in a similar RhNP catalyst was reported previously (see Ref. [17]).

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