Flow Synthesis

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Nitrogen-Doped Carbon Enables Heterogeneous Asymmetric Insertion of Carbenoids into Amines Catalyzed by Rhodium Nanoparticles

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Abstract: Development of stable heterogeneous catalyst systems is a crucial subject to achieve sustainable society. Though metal nanoparticles are robust species, the study of asymmetric catalysis by them has been restricted because methods to activate metal nanoparticles without causing metal leaching were limited. We developed Rh nanoparticle catalysts (NCI-Rh) supported on nitrogen-doped carbon as a solid ligand to interact with metals for asymmetric insertion of carbenoids into *N*–*H* bonds cocatalyzed by chiral phosphoric acid. Nitrogen dopants played a crucial role in both catalytic activity and enantioselectivity while almost no catalysis was observed with Rh nanoparticles immobilized on supports without nitrogen dopants. Various types of chiral α -amino acid derivatives were synthesized in high yields with high enantioselectivities and NCI-Rh could be reused in seven runs. Furthermore, we demonstrated the corresponding continuous-flow reaction using a column packed with NCI-Rh. The desired product was obtained efficiently for over 90 h through the reactivation of NCI-Rh and the chiral source could be recovered.

Heterogeneous catalysts have advantages over homogeneous catalysts with respect to their recovery and reuse. Moreover, the use of heterogeneous catalysts in continuousflow reactions can provide efficient synthetic systems, leading to enhanced environmental compatibility, efficiency, and safety.^[1] However, the development of heterogeneous chiral catalysts lags far behind than that of homogeneous chiral catalysts.^[2] Immobilization of chiral ligands on solid supports is one of the most popular methods to heterogenize chiral metal complexes (Scheme 1 a).^[3] While this method is applicable to a variety of ligands, additional synthetic processes are required to functionalize ligands and the lifetime of the catalysts depends on that of the metal complexes. In addition, it is difficult to reactivate catalysts when the complexes decompose or when catalyst poisons become attached to the metals. Therefore, these heterogeneous metal complex catalysts still suffer from a relatively short lifetime.

In contrast, heterogeneous metal nanoparticles are expected to form robust catalyst systems with long lifetimes.^[4] Such catalysts are usually used in bulk chemical synthesis as

the author(s) of this article can be found under: https://doi.org/10.1002/anie.202102506. (a) Immobilized chiral ligand with metal salt (immobilized metal complex) many choices of ligands MX_n 0~~~L* complicated preparation short life time (b) Immobilized metal nanoparticle with chiral ligand (chiral metal nanoparticle) Robustness
 Easy preparation
 Limited examples (choice of ligands) 1* C metal on innert support No siginificant activation from support (carbon black, SiO₂, Al₂O₃, etc.) This work (cooperative catalyst system with activated metal nanoparticle) 🗸 Long life time Easy preparation HA' No leaching `N N Flow reaction N-doped carbon recoverable

Scheme 1. Strategy to construct heterogeneous catalysts for asymmetric reactions.

chiral source

Acceleration by dopant

they can be easily prepared and possess high physical stability considering that they are formed at very high temperatures. Thus, heterogeneous chiral metal nanoparticle catalysts would be expected to be suitable for long-term continuousflow systems. Indeed, metal nanoparticles with chiral modifiers are applicable to asymmetric catalysis;^[5] however, examples that achieve high enantioselectivity for a wide variety of substrates are still very limited (Scheme 1b).^[6] Major challenges of metal nanoparticles for asymmetric catalysis are less flexibility in tuning of the electronic nature of the active metal species and suppression of metal leaching. Though some ligand molecules can modify the reactivity of metal nanoparticles.^[7] the available ligands are limited because strong interactions with ligands often cause metal leaching.^[6i,8] This trade-off between reactivity and stability limits the choice of chiral ligands for asymmetric metal nanoparticle catalysis.

We considered that the use of supports bearing coordination ability to metals could overcome these issues because interactions from the support were expected to both activate and stabilize metal nanoparticles simultaneously. Conventional supports that are used for asymmetric metal nanoparticle catalysts, such as carbon black (CB), silica, and metal oxides, were not expected to interact with the metal efficiently. We hypothesized that nitrogen-doped carbon (NDC) would be a good candidate for this purpose.^[9] We recently developed nitrogen-doped carbon-incarcerated metal nanoparticle catalysts (NCI metal) prepared from poly(4-vinylpyridine) (PVP) through a polymer-incarceration methodology, in which metal nanoparticles were encapsulated by NDC layers and stabilized.^[10] Using these catalysts, several oxidative transformations were developed. These reactions did not proceed in the absence of nitrogen dopants

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 Supporting information and the ORCID identification number(s) for

and leaching of metals was suppressed even in the presence of reactive intermediates such as radical species.^[10a] These findings inspired us to utilize NCI metal nanoparticle catalysts with an appropriate chiral source for asymmetric reactions. To our knowledge, there is no example of asymmetric catalysis using heteroatom-doped carbon-supported catalysts. In addition, a cooperative catalyst system with metal nanoparticles and chiral organic molecules that individually activate substrates would be beneficial because a rate acceleration by chiral cocatalyst systems were also less explored.^[5]

Chiral α -amino acids are essential building blocks for peptides, proteins, and many other bioactive compounds; thus, efficient and enantioselective synthetic methods to access diverse α -amino acids have been in high demand.^[11] Among synthetic routes, asymmetric insertions of carbenoids derived from diazoesters into N–H bonds are one of the most efficient methods,^[12] and cooperative systems of transitionmetal catalysts and chiral organocatalysts have been developed.^[13] Although this reaction generates only nitrogen gas as a by-product and seems to be suitable for flow systems, effective heterogeneous catalyst systems have not been established.

Herein, we report novel heterogeneous Rh nanoparticle catalysts that have high activity, enantioselectivity, and long lifetime, for the synthesis of chiral α -amino acids even under continuous-flow conditions.

We explored several kinds of heterogenous Rh nanoparticle catalysts for the asymmetric insertion of diazoesters into N-H bonds utilizing 3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diylhydrogenphosphates (TRIP) as a chiral phosphoric acid (CPA) cocatalyst that acts as a proton-transfer shuttle^[13c] (Table 1). Methyl phenyldiazoacetate (1a) and p-anisidine (2a) were selected as models. Nitrogen-doped carbon-incarcerated Rh nanoparticle catalysts (NCI-Rh A) were prepared based on our reported procedure from 1:1 (w/w) ratio of the polymer and CB.^[10b] A Rh salt was reduced to form nanoparticles in the presence of the polymer and CB. A poor solvent was then added to generate polymer encapsulated nanoparticles as precipitates, which were further pyrolyzed to give NCI catalysts (Scheme 2).

NCI-Rh A gave the desired product 3a quantitatively with low enantioselectivity (Table 1, entry 1). In contrast, almost no reaction proceeded in the presence of the previously developed Rh nanoparticle catalysts supported on polystyrene-based copolymer/carbon black (PI/CB-Rh)^[6i] or polysilane/alumina (PSi/Al₂O₃-Rh),^[6a,14] which could be used for asymmetric 1,4-addition reactions in the presence of chiral ligands (entries 2 and 3). Commercially available Rh on carbon (Rh/C) did not work well either (entry 4). CB-Rh, which was prepared without PVP by the same method used for NCI-Rh A, gave almost no product (entry 5). These results indicated that nitrogen dopants play a key role in the catalytic activity. We then examined spirobiindane diol (SPINOL)-derived chiral phosphoric acids (SCPA) as a cocatalyst based on the literature^[13c] and the product **3a** was obtained with 89.5:10.5 er (entry 6). Notably, no leaching of the metal was confirmed by inductively coupled plasma (ICP) Table 1: Screening of Rh catalysts and CPA.



[a] Determined by ¹H NMR analysis; isolated yield given in parentheses. [b] Determined by HPLC analysis. [c] Prepared without PVP in preparation of NCI-Rh **A**. [d] Prepared from nitrogen-doped carbon instead of PVP and CB.



Scheme 2. Preparation of NCI catalysts.

analysis of the crude solution. To elucidate the effect of our polymer-incarceration methodology, postdeposition of Rh to NDC was conducted as a control. The NDC was prepared by pyrolysis of a mixture of PVP and CB, and NDC-Rh was prepared from NDC instead of PVP and CB in the preparation of the NCI catalysts. Interestingly, NDC-Rh showed lower activity and enantioselectivity (entry 7), indicating that in situ formation of NDC and polymer encapsulation during the catalyst preparation was crucial for high catalytic activity. It is remarkable that the result of NCI-Rh **A** was comparable with that using the corresponding homogeneous catalyst (entry 8).

The loading of nitrogen dopant was optimized by changing the ratios of PVP to CB in NCI-Rh (Table 2). When the ratio of PVP was decreased (NCI-Rh **B**), the activity and enantioselectivity decreased slightly (entry 2). In contrast, NCI-Rh **C**, prepared from a larger amount of PVP, improved

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(a)

4

(b)

(c)

(d)

N	² H ₂ N	NCI-Rh (1 mc SCPA (1 mol	N%) (%) HN	PMP
Ph	COOMe	OMe DCM, 45 °C,	16 h Ph	COOMe
1a , 0	.3 mmol 2a , 1.0 e	q.		3a
Entry	NCI-Rh	Rh loading [m-	Yield [%] ^[b]	er ^[c]
	(PVP:CB)	$\operatorname{mol} \operatorname{g}^{-1} \operatorname{J}^{[a]}$		
1	NCI-Rh A (1:1)	0.148	82	89.5:10.5
2	NCI-Rh B (1:3)	0.158	71	88.5:11.5
3	NCI-Rh C (3:1)	0.144	90	90.5:9.5
4	NCI-Rh D (5:1)	0.150	trace	-
5	NCI-Rh E (5:1)	0.072	91	91.5:8.5
6	NCI-Rh F (7:1)	0.074	75	91:9

[a] Determined by ICP analysis. [b] Isolated yield. [c] Determined by HPLC analysis.

both yields and enantioselectivities (entry 3). Further increase in the ratio of PVP led to no activity of the catalyst (NCI-Rh D), probably because the surface area of the supports was too small to prevent aggregation of Rh nanoparticles (entry 4). When the loading of Rh was decreased, keeping the ratio of PVP:CB to 5:1, the catalyst (NCI-Rh E) gave the highest yield and enantioselectivity without causing metal leaching (entry 5). NCI-Rh F, which contained the highest ratio of PVP to CB, showed lower activity compared with NCI-Rh E (entry 6). These results proved that nitrogen dopants had highly positive effects on both catalytic activity and enantioselectivity of NCI-Rh.

To gain more insight into the effect of nitrogen dopants, we performed X-ray photoelectron spectroscopy (XPS) analysis (Figures 1 a and S2 in the Supporting Information). The binding energy of Rh 3p/2 in NCI-Rh shifted to higher energy compared with CB-Rh. The binding energy of N 1s in NCI-Rh revealed the presence of both pyrrolic and pyridinic nitrogen, with the latter being the major species (Figures S4 and S5). As both nitrogen species were suggested to work as an electron acceptor, these results indicate that electron transfer from Rh to the nitrogen dopant occurred,^[9,15] and that electron-deficient Rh species could facilitate an attack of a diazo compound on Rh to form a metal carbenoid intermediate easily. In addition, scanning transmission electron microscopy (STEM) analysis and Energy dispersive Xray spectroscopy (EDS) mapping revealed that nitrogen dopants contributed to the high dispersion of Rh nanoparticles on all of the supports (Figures 1b-d). The average size of the particles in NCI-Rh A and NCI-Rh E was 2.9 ± 0.7 and 3.0 ± 0.7 nm, respectively (N \approx 100) indicating that the amount of nitrogen dopants did not impact on the particle size significantly. On the other hand, it was difficult to determine the average Rh particle size of CB-Rh because of aggregation. We also performed XPS analysis of NDC-Rh that showed lower enantioselectivity. The binding energy of Rh 3p/2 was slightly shifted to higher energy than NCI-Rh (Figure S3) and the composition of nitrogen species was changed to be rich in pyrrolic nitrogen (Figure S6). These results indicated that the nature of nitrogen dopant significantly affected both activity and enantioselectivity. Brunauer-Emmett-Teller (BET) surface area of these catalysts was analyzed by nitrogen



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Figure 1. a) XPS analysis and b) STEM analysis of NCI-Rh E and CB-Rh c) EDS mapping of NCI-Rh E and d) CB-Rh.

adsorption methods to reveal that NCI-Rh E had a narrower surface area (158 m^2g^{-1}) than that of CB-Rh (386 m^2g^{-1}). The surface area of the catalysts seems not to have strong influences on catalytic performance.

With the optimized catalyst system in hand, substrate generality of the asymmetric insertion of carbenoids into amines was examined (Scheme 3). Various types of protected amines, p-anisidine, o-anisidine, BocNH₂, FmocNH₂, and CbzNH₂, afforded the corresponding protected chiral αamino acids 3a-e smoothly. Diazo compound with ethyl or isopropyl ester gave a slightly lower yield and enantioselectivity than methyl ester (3 f, 3 g). Other diazo compounds, with substitution on the aryl ring, reacted smoothly to form N-H insertion products in high yields with high enantioselectivity, regardless of electronic effects or positions of substitutions (3h-l). 2-Naphthyl-substituted diazoester could also be utilized for this catalytic system (3m).

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Scheme 3. Substrate scope.

NCI-Rh **E** was easily recovered by centrifugation and reused for the next run of the model reaction. NCI-Rh **E** could be reused in seven runs without loss of either activity or enantioselectivity and metal leaching (see the Supporting Information). Additionally, hot filtration tests were performed showing that no further reaction took place in the filtrate obtained from the middle of the reaction. Based on the results, the possibility that trace amounts of leached Rh species catalyzed the reaction was ruled out (Table S3).

NCI-Rh E was applied to a continuous-flow system (Scheme 4). A solution of substrates and SCPA was flowed into a column packed with NCI-Rh E. Additionally, we attempted to recover the chiral source by connecting a column packed with Amberlite IR 900, which is a basic resin to trap SCPA. The product was obtained in high yields with high enantioselectivity from 4 h after starting the system, which could be run for over 65 h without significant loss of activity. The turnover number (TON) was 366 and the highest





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turnover frequency (TOF) was 5.7 h^{-1} . SCPA were recovered (48% yield) successfully from the resin by acidification and could be reused without loss of either activity or enantiose-lectivity (Scheme S2). When the recovered NCI-Rh **E** was treated at 800 °C for 2 h under Ar, restoration of reactivity was observed. Using the reactivated NCI-Rh **E**, the second run of the continuous-flow system was performed. The system gave the product in high yields with high enantioselectivity for over 25 h. The TON was 164 and the highest TOF was 6.0 h^{-1} . Through two trials of flow systems, the total TON of 530 was achieved to produce 15.3 g of the product. These results demonstrated the efficiency of the continuous-flow system and the robustness of the metal nanoparticle catalyst.

Finally, stoichiometric reactions under flow conditions were performed to confirm whether the reaction proceeded on the heterogeneous phase (Scheme 5). A solution of diazo



Scheme 5. Stoichiometric reactions under flow.

substrate 1a was flowed into a column packed with NCI-Rh E. After washing with an enough amount of dichloromethane, a solution of amine 2a and SCPA was flowed. The desired product 3a was obtained in 28% yield corresponding to Rh amounts. As a control, we examined the flow reactions using columns packed with nitrogen-doped carbon and no absorption of 1a in the column was observed. The results suggested that 1a or an intermediate derived from 1a could stay on the Rh of the heterogeneous catalyst while 1a could not be captured by the support itself. We conducted EDS mapping of NCI-Rh E treated with methyl 2-(4-bromophenyl)-2-diazoacetate to detect where the substrate located on the catalyst (Figure S7). The results showed that Br mainly placed at the same place of Rh. We think that these results supported that the reaction proceeded via heterogeneous catalysis pathway and the formation of Rh carbenoid on the solid state was proposed.

In conclusion, we have developed NCI-Rh for the asymmetric insertion of carbenoids derived from diazoesters into N–H bonds. Nitrogen dopants played a crucial role in both activity and enantioselectivity, and that the polymerencapsulation protocol for the catalyst preparation was also important. By employing SCPA as cocatalysts, various types of α -amino acid derivatives were synthesized in high yields with high enantioselectivity. In a batch system, NCI-Rh could be reused for seven runs without any loss of either activity or enantioselectivity. Furthermore, NCI-Rh was applied successfully to a flow system. This system worked efficiently for over 90 h through the reactivation of the catalyst and chiral α -

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amino acid derivatives could be produced at approximately 4 g per day on a laboratory scale. Several control studies and analyses proposed the formation of intermediates derived from diazo compounds on the surface of Rh and the heterogeneous nature of the reaction system. This work not only establishes an efficient synthetic system, but also opens the door to asymmetric reactions catalyzed by metal nanoparticles.

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Conflict of interest

The authors declare no conflict of interest.

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- [1] S. Kobayashi, Chem. Asian J. 2016, 11, 425-436.
- [2] a) T. Yu, Z. Ding, W. Nie, J. Jiao, H. Zhang, Q. Zhang, C. Xue, X. Duan, Y. M. A. Yamada, P. Li, *Chem. Eur. J.* **2020**, *26*, 5729–5747; b) D. Zhao, K. Ding, *ACS Catal.* **2013**, *3*, 928–944.
- [3] a) B. Altava, M. I. Burguete, E. García-Verdugo, S. V. Luis, *Chem. Soc. Rev.* 2018, 47, 2722–2771; b) P. McMorn, G. J. Hutchings, *Chem. Soc. Rev.* 2004, 33, 108–122.
- [4] D. Astruc, F. Lu, J. R. Aranzaes, Angew. Chem. Int. Ed. 2005, 44, 7852–7872; Angew. Chem. 2005, 117, 8062–8083.
- [5] a) F. Meemken, A. Baiker, *Chem. Rev.* 2017, *117*, 11522–11569;
 b) T. Yasukawa, H. Miyamura, S. Kobayashi, *ACS Catal.* 2016, *6*, 7979–7988; c) T. Yasukawa, H. Miyamura, S. Kobayashi, *Chem. Soc. Rev.* 2014, *43*, 1450–1461.
- [6] a) H. Miyamura, T. Yasukawa, Z. Zhu, S. Kobayashi, Adv. Synth. Catal. 2020, 362, 353-359; b) J. Zhu, X.-T. Sun, X.-D. Wang, L. Wu, ChemCatChem 2018, 10, 1788-1792; c) M. Y. Chen, Z. Xu, L. Chen, T. Song, Z. J. Zheng, J. Cao, Y. M. Cui, L. W. Xu, ChemCatChem 2018, 10, 280-286; d) H. Miyamura, K. Nishino, T. Yasukawa, S. Kobayashi, Chem. Sci. 2017, 8, 8362-8372; e) H.-C. Ma, J.-L. Kan, G.-J. Chen, C.-X. Chen, Y.-B. Dong, Chem. Mater. 2017, 29, 6518-6524; f) T. Yasukawa, Y. Saito, H. Miyamura, S. Kobayashi, Angew. Chem. Int. Ed. 2016, 55, 8058-8061; Angew. Chem. 2016, 128, 8190-8193; g) T. Yasukawa, T.

Kuremoto, H. Miyamura, S. Kobayashi, Org. Lett. **2016**, 18, 2716–2718; h) T. Yasukawa, A. Suzuki, H. Miyamura, K. Nishino, S. Kobayashi, J. Am. Chem. Soc. **2015**, 137, 6616–6623; i) T. Yasukawa, H. Miyamura, S. Kobayashi, J. Am. Chem. Soc. **2012**, 134, 16963–16966; j) K. V. S. Ranganath, J. Kloesges, A. H. Schäfer, F. Glorius, Angew. Chem. Int. Ed. **2010**, 49, 7786–7789; Angew. Chem. **2010**, 122, 7952–7956.

- [7] a) M. A. Ortuño, N. López, *Catal. Sci. Technol.* 2019, *9*, 5173–5185; b) R. Ye, A. V. Zhukhovitskiy, R. V. Kazantsev, S. C. Fakra, B. B. Wickemeyer, F. D. Toste, G. A. Somorjai, *J. Am. Chem. Soc.* 2018, *140*, 4144–4149; c) M. Guo, H. Li, Y. Ren, X. Ren, Q. Yang, C. Li, *ACS Catal.* 2018, *8*, 6476–6485; d) L. Jin, B. Liu, S. Duay, J. He, *Catalysts* 2017, *7*, 44; e) J. B. Ernst, C. Schwermann, G.-I. Yokota, M. Tada, S. Muratsugu, N. L. Doltsinis, F. Glorius, *J. Am. Chem. Soc.* 2017, *139*, 9144–9147; f) A. Fedorov, H.-J. Liu, H.-K. Lo, C. Copéret, *J. Am. Chem. Soc.* 2016, *138*, 16502–16507; g) J. B. Ernst, S. Muratsugu, F. Wang, M. Tada, F. Glorius, *J. Am. Chem. Soc.* 2016, *138*, 10718–10721.
- [8] a) D. B. Eremin, V. P. Ananikov, *Coord. Chem. Rev.* 2017, 346, 2–19; b) S. Reimann, J. Stötzel, R. Frahm, W. Kleist, J.-D. Grunwaldt, A. Baiker, *J. Am. Chem. Soc.* 2011, 133, 3921–3930; c) V. P. Ananikov, K. A. Gayduk, I. P. Beletskaya, V. N. Khrustalev, M. Y. Antipin, *Eur. J. Inorg. Chem.* 2009, 1149–1161.
- [9] L. He, F. Weniger, H. Neumann, M. Beller, Angew. Chem. Int. Ed. 2016, 55, 12582–12594; Angew. Chem. 2016, 128, 12770– 12783.
- [10] a) T. Yasukawa, S. Kobayashi, Bull. Chem. Soc. Jpn. 2019, 92, 1980–1985; b) T. Yasukawa, X. Yang, S. Kobayashi, Org. Lett. 2018, 20, 5172–5176.
- [11] a) Y. P. Xue, C. H. Cao, Y. G. Zheng, *Chem. Soc. Rev.* 2018, 47, 1516–1561; b) C. Nájera, J. M. Sansano, *Chem. Rev.* 2007, 107, 4584–4671.
- [12] A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* 2015, 115, 9981–10080.
- [13] a) M.-L. Li, J.-H. Yu, Y.-H. Li, S.-F. Zhu, Q.-L. Zhou, Science 2019, 366, 990–994; b) Y. Zhu, X. Liu, S. Dong, Y. Zhou, W. Li, L. Lin, X. Feng, Angew. Chem. Int. Ed. 2014, 53, 1636–1640; Angew. Chem. 2014, 126, 1662–1666; c) B. Xu, S.-F. Zhu, X.-L. Xie, J.-J. Shen, Q.-L. Zhou, Angew. Chem. Int. Ed. 2011, 50, 11483–11486; Angew. Chem. 2011, 123, 11685–11688; d) B. Liu, S.-F. Zhu, W. Zhang, C. Chen, Q.-L. Zhou, J. Am. Chem. Soc. 2007, 129, 5834–5835.
- [14] H. Miyamura, A. Suzuki, T. Yasukawa, S. Kobayashi, J. Am. Chem. Soc. 2018, 140, 11325-11334.
- [15] a) R. E. Ambrusi, M. E. Pronsato, *Appl. Surf. Sci.* 2019, 464, 243–254; b) Z. He, B. Dong, W. Wang, G. Yang, Y. Cao, H. Wang, Y. Yang, Q. Wang, F. Peng, H. Yu, *ACS Catal.* 2019, 9, 2893–2901; c) C. P. Deming, R. Mercado, J. E. Lu, V. Gadiraju, M. Khan, S. Chen, *ACS Sustainable Chem. Eng.* 2016, 4, 6580–6589.

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R. Masuda, T. Yasukawa,* Y. Yamashita, S. Kobayashi* _____ **IIII**-IIII

Nitrogen-Doped Carbon Enables Heterogeneous Asymmetric Insertion of Carbenoids into Amines Catalyzed by Rhodium Nanoparticles



Rh nanoparticle catalysts supported on nitrogen-doped carbon were developed for asymmetric insertions of carbenoids derived from diazoesters into N-H bonds cocatalyzed by chiral phosphoric acid. The nitrogen dopants are essential to promote the reactions. The catalyst could be reused several times and was applicable for a continuous-flow reaction system that produced the desired chiral amine for over 90 h through reactivation of the catalyst.

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