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Chiral metal nanoparticle-catalyzed asymmetric C–C bond formation reactions

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Chiral ligand-modified metal nanoparticles possess an attractive potential for application in asymmetric synthesis. This article focuses on chiral-nanoparticle-catalyzed asymmetric C–C bond formation reactions and discusses the nature of the active species.

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1. Introduction

Rapid progress has been made in the field of homogeneous chiral metal complexes and many types of difficult transformations have been realized, including asymmetric C–C bond formation, to construct complicated molecular structures with high selectivity.[1,2] However, the application of these homogeneous catalysts to large-scale industrial processes is still limited.[3–9] This is because industry generally prefers heterogeneous catalysts because of their great advantages, such as low cost, reusability, avoidance of metal contamination of products, and the availability for reaction integration such as in continuous flow systems and tandem reactions.[10–14] One of the common strategies to convert homogeneous catalysts to heterogeneous catalysts is immobilization of chiral ligands on inorganic or organic supports followed by introduction of metal salts to form "immobilized chiral metal complexes."[15–19] While this strategy has already been investigated for several reactions, these systems have drawbacks, such as complicated preparation of monomeric ligands and individual fabrication of heterogeneous polymers. In addition, these catalysts themselves are not robust because of metal leaching and the instability of immobilized ligands, and it is difficult to revive their activity when the catalysts are deactivated.

Metal nanoparticles (NPs) in catalysts are of great interest in both academia and industry, not only due to their very large surface areas, producing high catalytic activity, but also due to their quantum size effect that sometimes shows high activity and unique selectivity.[20–23] Recently, several reports have shown that homogeneous metal complex-catalyzed reactions can be conducted by using immobilized metal NP catalytic systems, with the advantages of the heterogeneous catalysts mentioned above.[24] It might indicate that metal NPs possess the potential

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Hiroyuki Miyamura was born in 1982 in Saitama, Japan. He received his BS degree in pharmaceutical sciences in 2004 from The University of Tokyo. He received his MSc and PhD degrees at the same University in 2006 and 2009 under the supervision of Professor Shū Kobayashi. In 2009 just after receiving PhD, he was appointed assistant professor in the Department of chemistry at The University of Tokyo. In 2010, he received the winner of The Reaxys PhD Prize. His research interest includes metal nanocluster catalysis and reaction integration such as tandem reaction and flow synthesis.

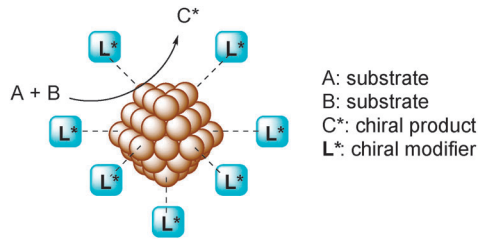

Fig. 1 Functionalized chiral NP catalysts.

for application in asymmetric synthesis, namely, the use of chiral-ligand-modified metal NPs (chiral NPs) as asymmetric catalysts (Fig. 1).

Chiral NPs themselves have attracted the attention of many researchers in various fields as they show characteristic physical properties[25–28] such as circular dichroism (CD) and metal-based electronic transitions. Furthermore, it may be possible to use them not only for asymmetric catalysis, but also as chiral nematic liquid crystals,[29–32] in chiral recognition,[33–36] *etc.*

Chiral NPs have been mainly prepared by two types of methods:[28] direct synthesis of NPs in the presence of a chiral modifier as a stabilizer (Fig. 2a) or ligand exchange from stabilized NPs (Fig. 2b). In the latter method, it is possible that chiral NPs form *in situ* simply by combining chiral modifiers and metal NPs in the reaction medium and then using them directly as chiral catalysts.

The first example of heterogeneous asymmetric catalysis using this concept was reported by Orito and co-workers in 1979, demonstrating asymmetric hydrogenation of methyl

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Shū Kobayashi studied at the University of Tokyo, receiving his PhD in 1988 working under the direction of Professor T. Mukaiyama. Following an initial period as assistant professor, he was promoted to lecturer then associate professor at Science University of Tokyo (SUT). In 1998, he moved to the Graduate School of Pharmaceutical Sciences, the University of Tokyo, as full professor. In 2007, he was appointed to his current position as professor of organic chemistry in the Department of Chemistry, Faculty of Science, The University of Tokyo. He has held various visiting professorships, including the Universite Louis Pasteur, Strasbourg (1993), Kyoto University (1995), Nijmegen University (1996), Philipps-University of Marburg (1997), Paris-Sud (2010). Professor Kobayashi has wide-ranging research interests that include the development of new synthetic methods and novel catalysts, organic reactions in water, solid-phase synthesis, total synthesis of biologically interesting compounds, and organometallic chemistry.

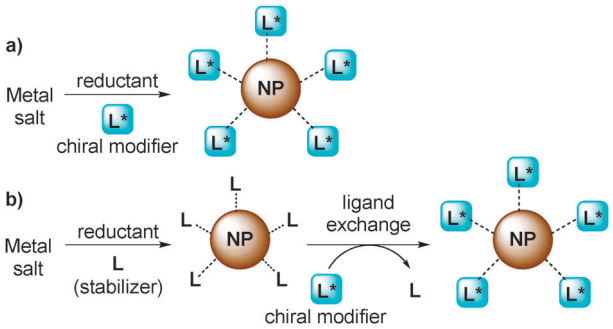
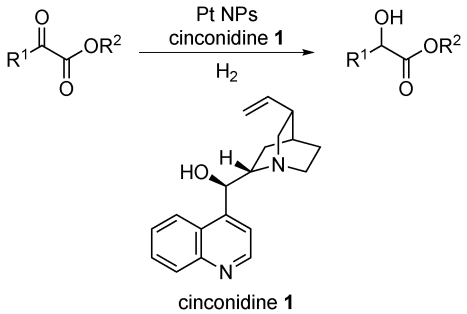


Fig. 2 (a) Direct synthesis of chiral NPs; (b) synthesis of chiral NPs *via* ligand exchange.



Scheme 1 Orito-type reactions.

pyruvate or methyl benzoylformate catalyzed by cinchonidine-modified Pt on carbon (Scheme 1).[37,38] Although the first Orito-type reaction was reported more than 30 years ago, this type of reaction is still being studied.[39–43] Recently, studies were carried out to improve the catalyst system[44–61] and to reveal its detailed mechanism.[62–67] It is generally accepted that the chemisorption layer, through the formation of individual 1 : 1 diastereomeric complexes from substrates and chiral modifiers, is the key to inducing chirality in this reaction.[62] Very recently, Maeda, Baiker and co-workers proposed a possible intermediate and complex between a substrate and a modifier formed by multiple hydrogen bonds.[64] Based on this chiral NP system, other types of chiral NP catalysts for asymmetric hydrogenation reactions, for example nickel-boride NPs,[68] Pd NPs,[69–85] Ru NPs,[86–90] Rh NPs,[88,91–96] Ir NPs,[88,97–99] and Fe NPs,[100] have been widely investigated. Several reviews illustrate examples of heterogeneous asymmetric hydrogenation reactions.[17,101–104]

On the other hand, asymmetric C–C bond formation reactions catalyzed by chiral NPs are a challenging topic and less well developed, judging from the mechanism of the corresponding homogeneous metal complex system. The mechanism of chiral induction is more complicated and multicoordination of both chiral modifier and substrates to NPs is required in transition states. Moreover, this type of multicoordination may easily cause the metal to leach from supports or the decomposition of NPs to form molecular complexes. For these reasons, the nature of the active species should be examined carefully because it is also possible that such a homogeneous molecular complex is a real active species.[105–108] However, lack of fair observation and

discussion about heterogeneity is sometimes found. Widely accepted tests to confirm heterogeneity, for example, the mercury-poisoning test, hot filtration test (filtrate transfer test), and three-phase test, are usually conducted.[105]

In this review, we focus on chiral NP-catalyzed asymmetric C–C bond formation. Although the detailed mechanism and active species are still unclear, some reports describe the specific nature of chiral NPs catalysts, which showed different catalyst behavior from the corresponding homogeneous molecular complex catalysts.

2. Palladium nanoparticles

2.1 Asymmetric allylic alkylation

Palladium-catalyzed asymmetric allylic alkylation reactions are one of the most powerful tools to construct asymmetric C–C bonds and have been widely investigated in homogeneous Pd complex systems.[109,110] Several groups have reported that chiral palladium NPs catalyzed this reaction using various chiral modifiers and, interestingly, the assumed nature of the active species was different for each of the catalyst systems.

In general, stabilization methods for metal NPs are crucial to develop efficient catalysts. In this context, Kobayashi and co-workers developed microencapsulated (MC) catalysts.[111–114] Microcapsules have been used for coating and isolating substances until their activity is required, and their applications in medicine and pharmacy have been extensively studied.[115] This microencapsulation technique was applied to the immobilization of metal NP catalysts into polymers. That is, catalysts would be physically enveloped by polymer backbones and, simultaneously, immobilized by the interaction between the π electrons of the benzene rings of the polystyrene used as a polymer support and vacant orbitals of the catalysts (metal NPs) (Fig. 3).

In 2002, Kobayashi *et al.* stabilized Pd(0) by the microencapsulation technique, and the thus prepared MC Pd(0) (MC Pd(PPh_3)) was applied to a catalytic asymmetric allylation reaction (Scheme 2).[116] The reaction of 1,3-diphenyl-2-propen-1-yl

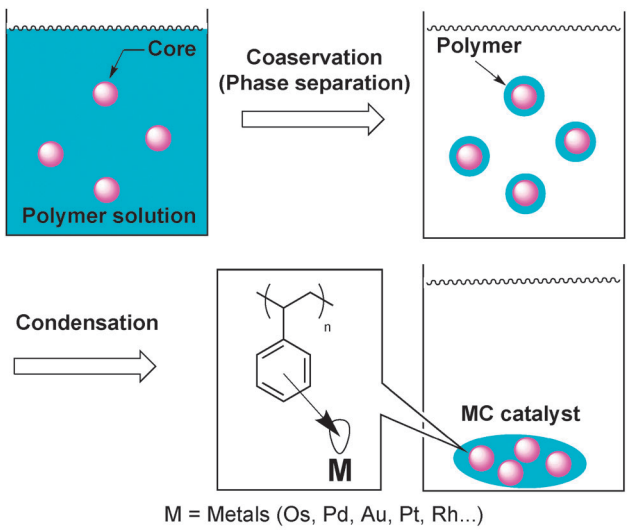
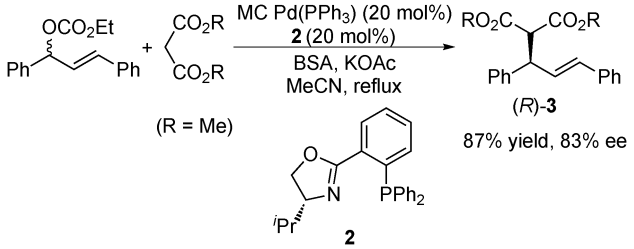


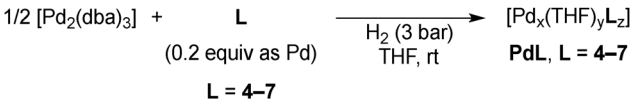
Fig. 3 Microencapsulation technique.



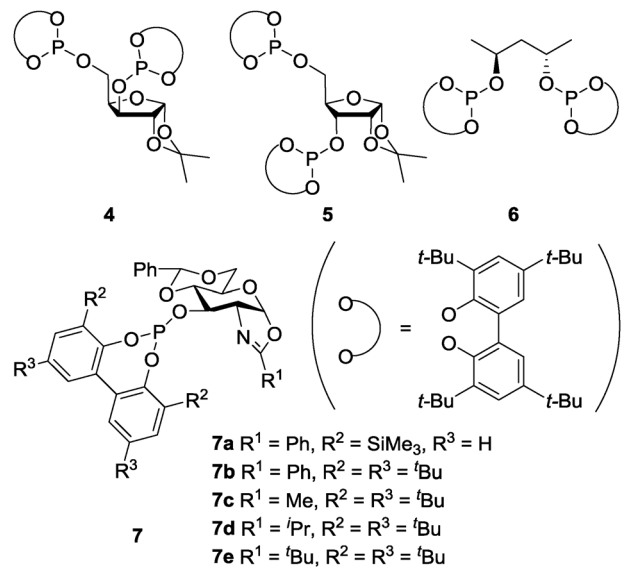
Scheme 2 MC Pd-catalyzed asymmetric allylation.

ethyl carbonate (1.0 equiv.) with dimethyl malonate (3.0 equiv.) was performed in the presence of MC Pd(PPh_3) (20 mol%), chiral phosphine-oxazoline **2** (20 mol%), bis(trimethylsilyl)-acetamide (BSA) (3.0 equiv.), and potassium acetate (0.10 equiv.) under reflux conditions in acetonitrile. The allylation adduct (*R*)-**3** was obtained in 87% yield with 83% ee.

In 2004, Gómez, Philippot, Chaudret and co-workers reported asymmetric allylic alkylation reactions catalyzed by chiral diphosphite **4** with xylose-backbone-modified colloidal Pd NPs (Schemes 3 and 4).[117] The reactivity of a molecular Pd complex (referred to as **Mol. 4**), which was generated *in situ* by the reaction of $[Pd(C_3H_5)Cl]_2$ with **4**, was compared with that of NP catalysts. A significant difference was observed (Table 1). In the presence of a NP catalyst (**Pd4**), the reaction mainly proceeded with one enantiomer of the racemic **8** and, consequently, a very high degree of kinetic resolution was demonstrated, while no kinetic resolution was observed in the presence of **Mol. 4**. The relative rates of alkylation of the two enantiomers of **8** in two catalyst systems

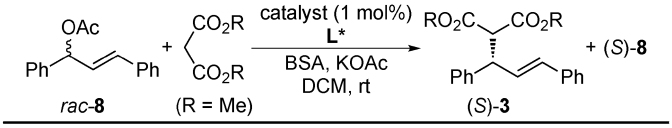


Scheme 3 Synthesis of chiral Pd NPs.



Scheme 4 Chiral diphosphite ligands.

Table 1 Asymmetric allylic alkylation of *rac*-**8** with dimethyl malonate by a Pd catalyst

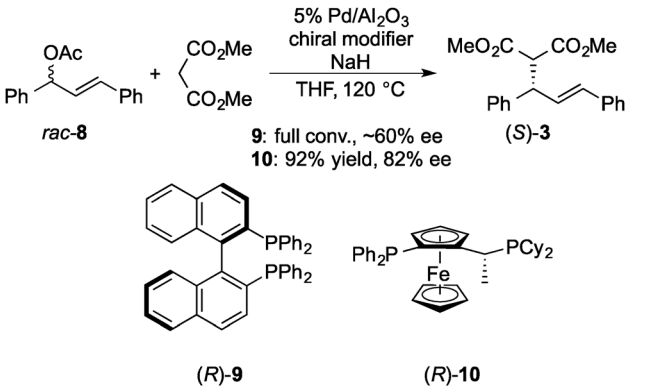


Entry	Catalyst	Pd/**L***	Time (*h*)	Conv. (%)	ee of **3** (%)	ee of **8** (%)
1	**Pd4**	1/0.2	24	56	97	89
2	**Pd4**	1/0.2	168	59	97	89
3	**Pd4**	1/1.05	168	61	97	89
4	**Mol. 4**	1/1	1.5	95	90	0

were studied. The kinetic preference for the *R*-**8** was only a factor of 2 in the **Mol. 4** system, whereas it was clearly higher (12–20) in the **Pd4** system.

In 2007, the same group reported detailed studies of this reaction and showed higher sensitivity of NP catalyst systems upon adjustment of the metal, the chiral modifier and the substrate than that of molecular catalysts.[118] For example: (i) **Pd5** showed a remarkable difference in stability and decomposed into molecular species, while **Pd4** did not, and (ii) alkyl-substituted allyl acetates were not alkylated by using **Pd4** or **Pd6**, while the corresponding molecular catalyst systems gave high conversions. In 2008, Diéguez, Gómez, Leeuwen and co-workers reported modified Pd NPs systems with chiral oxazolinyl-phosphite ligands **7a–7e** for the same reaction.[119] The nature of the active species was carefully studied by continuous-flow membrane reactor experiments, transmission electron microscopy observations, classical poisoning experiments, and kinetic measurements. The results proved the molecular nature of the true catalysts, which were leached, as measured by inductively coupled plasma atomic emission spectrometry (ICP-AES) analysis.

In 2005, Felpin and Landais reported a heterogeneous Pd catalyst with a chiral modifier that promoted asymmetric allylic alkylation.[120] Pd/C and (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) **9** were used as catalysts for the reaction of racemic **8** with diethylmalonate in water, and high enantioselectivity (80% ee) was achieved in spite of low yield (21%). Subsequently, in 2007, Baiker and co-workers reported **9** modified Pd/Al_2O_3 catalyst systems for the reaction of racemic **8** with the sodium salt of dimethyl malonate (Scheme 5).[121] Reductive treatment of Pd/Al_2O_3 in hydrogen before the reaction was required for obtaining reproducibility and, as a result, good chemoselectivity (94%) and moderate enantioselectivity (~60% ee) were obtained. The enantioselectivity of this system was independent of the reaction temperature (60 and 120 °C), while the corresponding homogeneous complex system afforded poor enantioselectivity to give the opposite enantiomer of the product (*R*-**3**) at 60 °C or above. In a report from the same group in 2008, the enantioselectivity of this system was improved (82% ee) by changing the chiral modifier to a ferrocenyl phosphine ligand **10**.[122] As in the case of the Pd/Al_2O_3–BINAP system, no dependence of enantioselectivity on temperature was observed (60 and 120 °C), while the enantioselectivity was decreased by increasing the reaction temperature from 85% ee at 60 °C to 55% ee at 120 °C in the



Scheme 5 Asymmetric allylic alkylation of *rac*-**8** with dimethyl malonate by Pd catalyst.

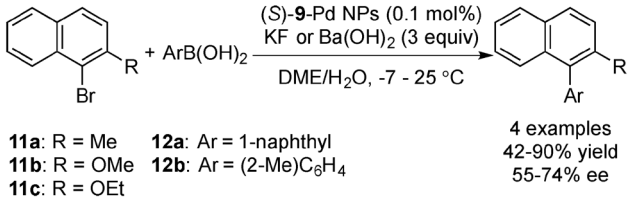
corresponding homogeneous complex system. Here, the same enantiomer of the product (*S*-**3**) was produced. To confirm the metal leaching in the reaction mixture, the catalytic activity in the filtrate with additional substrates was examined after the first reaction was conducted at 120 °C for 6 h and the catalyst was removed by centrifugation. The reaction was continued for a further 6 h and gave the additional product in 19% yield, while the yield in the blank experiment, which was conducted in the absence of Pd/Al_2O_3, was 10%.

In 2010, the same group reported a detailed study of the nature of the active species in the Pd/Al_2O_3–BINAP system and emphasized heterogeneity.[123] The oxidation state of Pd was investigated by *in situ* X-ray absorption near-edge structure analysis of the reaction mixture. They did not observe oxidized Pd in the supernatant solution and hence proposed that the molecules in the reaction mixture, such as the solvent and sodium dimethyl malonate, were able to reduce Pd atoms on the surface of Pd NPs and to maintain the reduced state during the reaction. They also pointed out that addition of a chlorinated solvent, such as chloroform, favored dissolution of metallic Pd to form homogeneous catalysis. After the first reaction at 120 °C for 3 h, the reaction mixture was cooled. The catalyst was removed by centrifugation and the supernatant with additional sodium malonate did not give further conversion at room temperature over 18 h in the case of pure THF as solvent, while a small conversion was observed in a similar control experiment in the presence of chloroform.

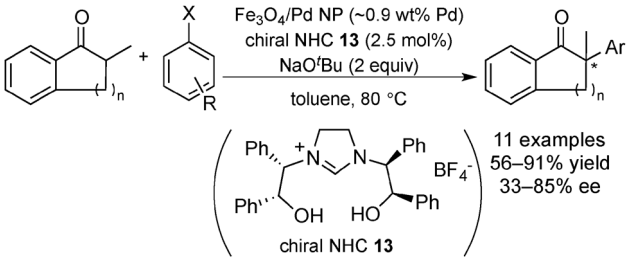
2.2 Asymmetric cross-coupling reactions

Palladium-catalyzed cross-coupling reactions are one of the biggest breakthroughs in transition metal-catalyzed C–C bond formation reactions.[124] Not only have homogeneous catalysts been developed, but also many heterogeneous catalyst systems.[107,108,125] Among these systems, a couple of examples of asymmetric cross-coupling systems were reported recently.

In 2008, Fujihara and co-workers succeeded in preparing the optically active mono- and bisphosphine-modified chiral Pd NPs and applying these NPs to asymmetric Suzuki–Miyaura coupling reactions (Scheme 6).[126] The zero oxidation state of the chiral Pd NPs was confirmed by X-ray photoelectron



Scheme 6 Asymmetric Suzuki–Miyaura coupling reactions catalyze by chiral Pd NPs.



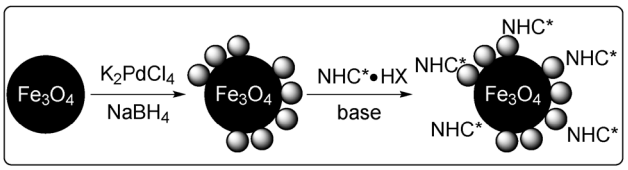
Scheme 8 The asymmetric α-arylation of ketones with aryl halides.

spectroscopy (XPS) analysis, and CD spectra of the chiral Pd NPs showed negative Cotton effects. It was demonstrated that (*S*)-BINAP-modified chiral Pd NPs could catalyze the coupling reactions with naphthyl halides and arylboronic acids to afford axially chiral biaryl compounds in good enantioselectivity at low temperature (−7 to 25 °C), although reported syntheses of binaphthalenes catalyzed by a chiral Pd–bisphosphine complex required high temperatures to obtain acceptable yields. The latter showed low enantioselectivity.

In 2009, Yamashita and co-workers reported the BINAP-modified core–shell structured bimetallic Fe/Pd NP-catalyzed asymmetric Suzuki–Miyaura coupling reaction.[127] The Fe/Pd NPs with an Fe-rich core and a Pd-rich shell were synthesized by thermal decomposition of $Fe(CO)_5$ and subsequent reduction of $Pd(acac)_2$ in the presence of oleic acid and oleylamine, and BINAP-modified NPs were formed through a simple ligand exchange procedure. X-ray absorption measurements revealed that most Pd atoms existed in a metallic form while Fe atoms existed in an oxidized form. The optically active BINAP-modified Fe/Pd NPs showed catalytic activity for the coupling reaction between halide **11b** and boronic acid **12a** with moderate enantioselectivity (up to 48% ee). The NPs were recovered easily by applying an external magnet and could be reused, while maintaining identical enantioselectivity without an external addition of chiral modifier. A hot filtration test was conducted and the reaction hardly occurred in the filtrate after removal of the catalyst.

In 2010, Glorius and co-workers reported the first successful application of chiral N-heterocyclic carbene (NHC) as a chiral modifier of magnetite supported Pd NPs (Scheme 7) in the asymmetric α-arylation of ketones with aryl halides (Scheme 8).[128] Chiral Pd NPs were prepared by addition of a NHC precursor and a base in the presence of Fe_3O_4/Pd. A zero-oxidation state of Pd was confirmed, even after surface modification, by XPS analysis. The presence of a NHC-modified surface was supported by differences between spectra of the free salt **13** and that of Fe_3O_4/Pd/**13** in attenuated total reflection infrared spectroscopy analysis. Various ketones and aryl halides could be employed for asymmetric α-arylation reactions, including intramolecular reactions, to afford the corresponding α-arylated ketones in moderate-to-good enantioselectivity. The paramagnetic catalyst could be recovered using a magnet and then reused five times without significant loss of activity and selectivity. The heterogeneous nature of active species was indicated by several experiments, such as the hot filtration test, mercury-poisoning test and trace metal analysis. Moreover, dramatically low selectivity was exhibited by several homogeneous complex systems, which afforded the racemic α-arylated product, biphenyl, and other side products. The same research group also developed a homogeneous Pd catalyst system with quinine for this asymmetric α-arylation reaction and achieved excellent substrate generality and enantioselectivity.[129] A combination of Fe_3O_4/Pd and quinine as a chiral modifier was also examined. The heterogeneous nature of the real active species was indicated by the mercury-poisoning test and hot filtration test. The results emphasized the important role of chiral NHC for both stability and activity of the Pd NPs as catalysts.

In 2011, Glorius and co-workers further developed immobilized Pd catalysts with NHC.[130] From magnetite-supported NHC **14**, a molecular Pd catalyst **15** was prepared with $Pd(OAc)_2$, while a Pd NP catalyst **16** was also prepared by the reduction of K_2PdCl_4 (Scheme 9). These catalysts were characterized by XPS analysis to confirm the formation of a Pd complex or Pd(0), respectively, and the catalytic activities of these two Pd catalysts were tested in the asymmetric allylation of 4-nitrobenzaldehyde with allyltributyltin (Scheme 10). The NP catalyst **16** provided improved allylation results for both yield and enantioselectivity, and, surprisingly, the product was obtained with the opposite absolute configuration to the one formed with the molecular catalyst **15**.



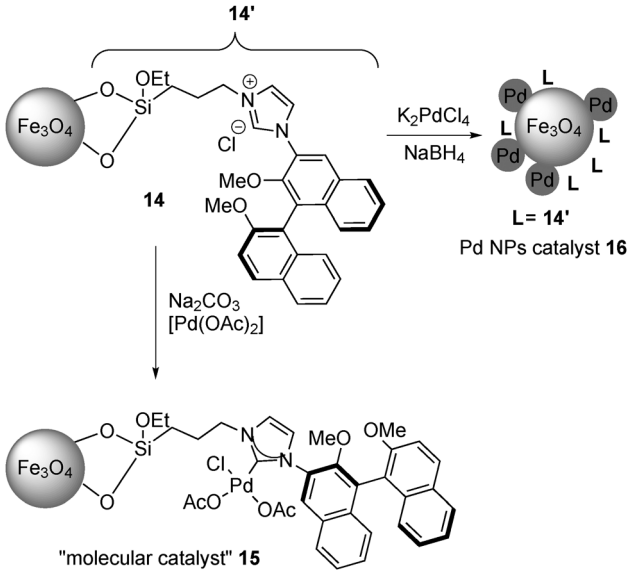
Scheme 7 Preparation of Fe_3O_4/Pd NPs modified by chiral NHC **13**.

3. Rhodium nanoparticles

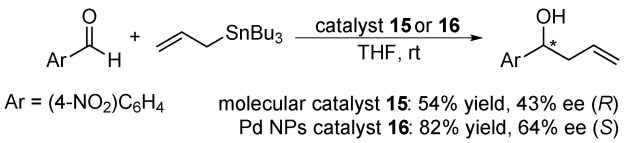
3.1 Hydroformylation

Asymmetric hydroformylation of olefins using chiral Rh complexes in the presence of syngas is a useful method to synthesize optically active aldehydes with excellent regioselectivity and enantioselectivity.[131] Despite extensive development of homogeneous catalysis and recent advances in Rh NP catalysts,[132] heterogeneous asymmetric hydroformylation is still a challenging topic.[133]

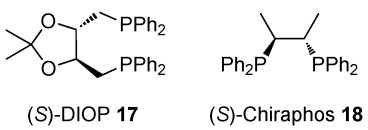
In 2000, Anderson and co-workers reported styrene hydroformylation over chiral-ligand-modified $Rh/SiO_2{\cdot}Al_2O_3$. Chiral induction was achieved by using DIOP **17** or chiraphos **18** (Scheme 11) as a chiral modifier although selectivity was very



Scheme 9 Preparation of a molecular catalyst and a Pd NP catalyst on Fe_3O_4.

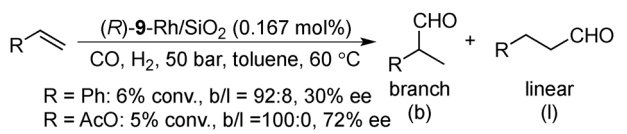


Scheme 10 Asymmetric allylation of 4-nitrobenzaldehyde with allyltributyltin.

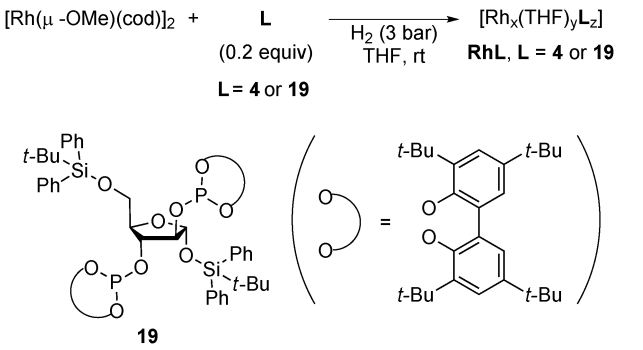


Scheme 11 Chiral diphosphine ligands.

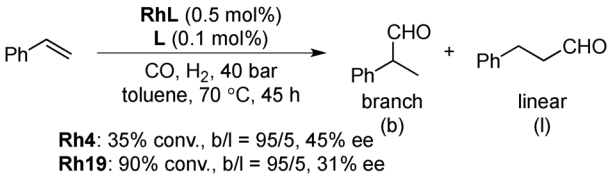
low (up to 9% ee).[134] In 2006, Li and co-workers reported the asymmetric hydroformylation of styrene or vinyl acetate catalyzed by BINAP-modified Rh/SiO_2 (Scheme 12).[135] To achieve chiral induction, an optimized ratio of Rh and modifier was close to 1.0 and, as a result, up to 72% ee and 100% selectivity of a branched aldehyde for the hydroformylation was obtained, although conversion was very low (<10%). It was noted that the DIOP **17**-modified Rh/SiO_2 catalyst showed higher turnover frequency (TOF) for the hydroformylation of vinyl acetate (128 h^{-1}) than that of unmodified Rh/SiO_2 (90 h^{-1}), while other diphosphine ligands decreased the catalytic activity. ^{31}P magic angle spinning nuclear magnetic resonance (MAS NMR) analysis



Scheme 12 Asymmetric hydroformylation of olefins by BINAP-Rh/SiO_2.



Scheme 13 Synthesis of chiral Rh NPs **4** and **19**.



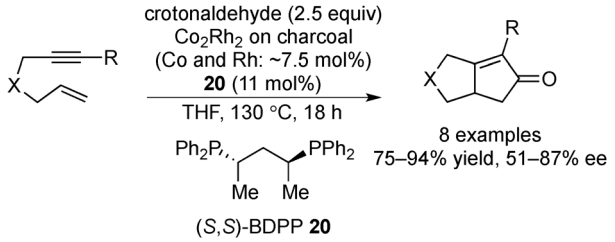
Scheme 14 Asymmetric hydroformylation of styrene by Rh NPs.

and IR spectra of adsorbed CO indicated the existence of a strong interaction between the P atoms of the chiral modifier and the surface Rh sites. In 2008, the same group reported a different method to prepare modified Rh NPs, by one-pot chemical reduction of aqueous rhodium chloride dispersed in toluene in the presence of amphiphilic tetraoctylammonium bromide and (*R*)-BINAP.[136] These BINAP-modified Rh NPs could also be immobilized on SiO_2 in a vacuum by adsorption; however, no significant improvement of catalytic performance was observed.

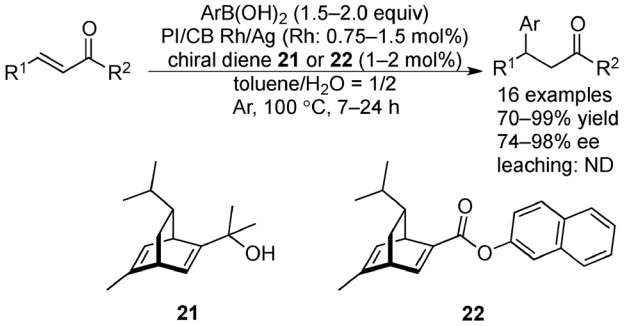
In 2008, Axet, Claver and Philippot reported that carbohydrate-derived diphosphite-ligand-modified colloidal Rh NPs (Scheme 13) catalyzed the asymmetric hydroformylation of styrene.[137] With the addition of an excess amount of the ligand, high conversion, high regioselectivity, and moderate enantioselectivity were observed in the presence of **Rh19** NPs (Scheme 14). The catalytic activities of molecular complexes, which were prepared from [Rh(acac)$(CO)_2$] and the corresponding chiral ligands, were examined. The enantioselectivities in the molecular systems were slightly lower (~10% ee difference) than those in the respective colloidal systems. As results of experiments carried out with dilute solutions and poisoning tests were not conclusive, *in situ* high-pressure NMR spectroscopic studies under catalytic conditions in the presence of **Rh4** NPs were conducted and the well-known hydridorhodium diphosphite complex [RhH$(CO)_2$(**4**)] was detected after a reaction time of 45 h. The results indicated that molecular species generated from NPs are real active species. Given the difference in enantioselectivity between the molecular complex system and the NPs system, the possibility that some activity comes from NPs cannot be excluded.

3.2 Pauson–Khand reaction

The Pauson–Khand reaction is a [2+2+1] cycloaddition of an alkyne, an alkene, and carbon monoxide to construct a



Scheme 15 Co/Rh NP-catalyzed asymmetric Pauson–Khand type reactions.



Scheme 16 Rh/Ag NP-catalyzed asymmetric 1,4-addition reactions.

cyclopentanone skeleton. In early studies of this reaction, a dicobalt octacarbonyl complex was used as the catalyst,[138,139] but further developments revealed that several other transition metal complexes[138,140] or cobalt NPs[141] could be used for this reaction. Moreover, the use of heterobimetallic NP catalysts has attracted more attention due to their high catalytic activity.[141,142] In 2005, Park and Chung reported charcoal-immobilized Co/Rh heterobimetallic NP-catalyzed asymmetric Pauson–Khand-type reactions with a chiral modifier.[143] In the presence of the Co/Rh NP catalyst and chiral diphosphine modifier **20**, the reactions of several enynes with crotonaldehyde as an alternative CO source proceeded, and the corresponding bicyclic cyclopentanones were obtained in high yields with moderate-to-good enantioselectivities (Scheme 15). The catalyst could be recovered by filtration and then reused five times with the addition of a new chiral modifier without significant loss of yield and enantioselectivity. Although elemental analysis of the reaction mixture by ICP-AES after three cycles detected 3.9 ppm of Co and 0.3 ppm of Rh species, results of the mercury-poisoning test supported a heterogeneous nature of the active species as Hg(0) completely eliminated further catalysis after the addition of Hg(0) to the reaction mixture.

3.3 1,4-Addition reaction

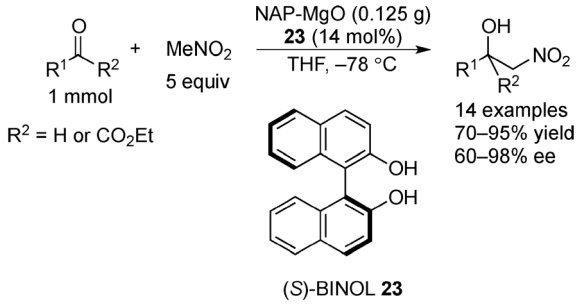
Since the development of the rhodium-catalyzed asymmetric 1,4-addition of boron compounds to α,β-unsaturated carbonyl compounds by Hayashi and Miyaura,[144] both academic research[145–147] and large-scale processes[148–150] (the largest example being 20 kg) of this reaction have been widely demonstrated; however, due to the high cost of Rh, reusable and robust chiral heterogeneous Rh catalysts are required.

In 2012, Kobayashi and co-workers developed chiral Rh NPs and Rh/Ag bimetallic NPs, which were immobilized on a mixture of polystyrene-based copolymer with a cross-linking moiety and carbon black (PI/CB Rh and PI/CB Rh/Ag), and used them in the asymmetric 1,4-addition of boronic acids to α,β-unsaturated ketones (Scheme 16).[151] In the presence of PI/CB Rh and (*S*)-BINAP as a chiral modifier, a significant amount of Rh leaching was observed during the reaction between a cyclic substrate and phenylboronic acid. When changing the chiral modifier to optically active chiral diene **21**, Rh leaching in a crude mixture was dramatically suppressed to the detection limit of ICP-AES, and the desired product was obtained in high yield and excellent enantioselectivity. The low catalytic activity of PI/CB Rh towards acyclic substrates was improved after the formation of bimetallic NPs with Ag; various substrates were applicable and the desired β-arylated ketones were obtained in high yields and high enantioselectivities by using PI/CB Rh/Ag and chiral modifiers **21** or **22**, without leaching of the metals. Scanning transmission electron microscopy (STEM) analysis and energy dispersive X-ray spectroscopy (EDS) mapping showed that Ag formed alloy NPs with Rh that could prevent the aggregation of Rh NPs, to enhance the catalytic activity. PI/CB Rh/Ag could be recovered by filtration and then reused. High yields and high enantioselectivities could be maintained for eight reactions. The deactivated catalyst, after repeated use, could be restored fully simply by heating. Fourteen cycles were demonstrated. Furthermore, a hot filtration test confirmed that after the reaction the filtrate did not catalyze the 1,4-addition reaction, indicating that the reaction is not catalyzed by homogeneous leached species. A one-pot aerobic oxidation-asymmetric 1,4-addition reaction of an allyl alcohol and an arylboronic acid was also demonstrated by combining with PI/CB Au as an aerobic oxidation catalyst.

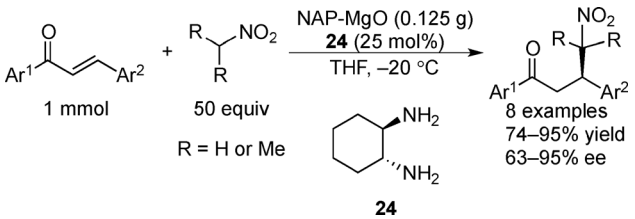
4. Other metal nanoparticles

4.1 Nanocrystalline magnesium oxide

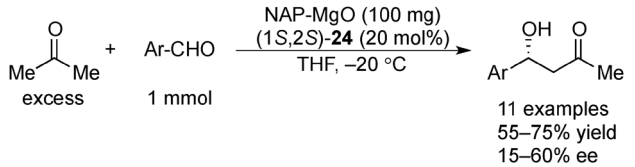
Examples of asymmetric catalysis by chiral modifiers and nontransition metal NPs are rather limited. In 2005, Choudary *et al.* reported several asymmetric reactions using aerogel-prepared nanocrystalline MgO (NAP–MgO), which is commercially available and possesses a large surface area (590 $m^2\ g^{-1}$) and a three-dimensional polyhedral structure.[152] The NAP–MgO was used for asymmetric Henry reactions with aldehydes or α-ketoesters in the presence of (*S*)-BINOL **23** (Scheme 17) and asymmetric Michael reactions with nitroalkanes in the presence of optically active chiral diamine **24** (Scheme 18). In both reactions, high yields and high enantioselectivities were achieved for several substrates, and NAP–MgO could be reused five times after heating at 250 °C for 1 h without loss of activity and enantioselectivity. The control experiments using silylated MgO or protected hydroxyls of **23** indicated that the hydrogen bond interaction between the hydroxy groups of **23** and the hydroxy groups of partially hydrated MgO are essential for obtaining high enantioselectivity. In 2006, the same group reported that



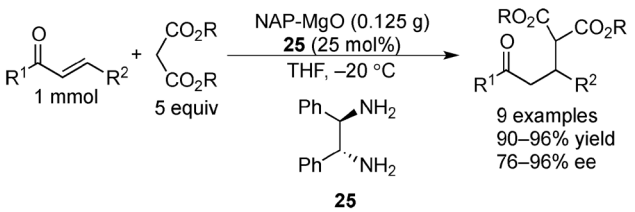
Scheme 17 NAP–MgO-catalyzed asymmetric Henry reactions.



Scheme 18 NAP–MgO-catalyzed asymmetric Michael reactions with nitroalkanes.



Scheme 19 NAP–MgO-catalyzed asymmetric aldol reactions.



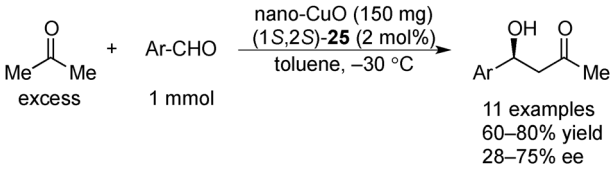
Scheme 20 NAP–MgO-catalyzed asymmetric Michael reactions with malonates.

NAP–MgO systems modified with chiral diamine **24** were applicable for asymmetric aldol reactions with moderate yields and enantioselectivities (Scheme 19).[153]

Kantam and co-workers also investigated the NAP–MgO-mediated asymmetric Michael reactions with malonates. The desired products were obtained in high yields and high enantioselectivities in the presence of optically active chiral diamine **25** (Scheme 20).[154]

4.2 Copper nanoparticles

In 2008, Kantam and co-workers found that nanocrystalline CuO (nano-CuO) could also be utilized for the asymmetric aldol reactions of acetone with arylaldehydes in the presence



Scheme 21 Nano-CuO-catalyzed asymmetric aldol reactions.

of chiral diamine **25** as a chiral modifier (Scheme 21).[155] Nano-CuO had a higher large surface area (136 m^2 g^{-1}) and smaller crystal size (7–9 nm) and showed higher activity and enantioselectivity compared with commercial CuO. Nano-CuO could be reused for four cycles without significant loss of activity, and no structure or morphology change was observed after the reaction, as confirmed by X-ray diffraction (XRD) analysis. The filtrate, which was obtained after removal of the solids, did not promote the reaction, and the absence of copper in the filtrate was confirmed by atomic absorption spectrometry studies.

4.3 Gold nanoparticles

Although gold NPs as catalysts, such as in aerobic oxidation, have been extensively studied,[156–160] asymmetric catalysis with gold NPs had not been reported until very recently. In 2013, Toste, Somorjai and co-workers investigated enantioselective heterogeneous Au NP catalysts for the asymmetric cyclopropanation reaction by immobilization of a chiral self-assembled monolayer (SAM) on the surface of a mesoporous silica support.[161] After amino acids, as chiral modifier, were attached to the surface of mesoporous SiO_2 (MCF-17) through the OH terminal, Au ions were introduced, and the encapsulated Au ions were reduced to NPs by exposure to H_2 (Fig. 4).

The obtained Au NPs catalyst (Au@SAM/MCF) was used for the intermolecular cyclopropanation reaction of styrene with propargyl pivalate in the presence of an oxidizer (Scheme 22). The desired product **26** was obtained in good diastereoselectivity and moderate enantioselectivity, when peptide **28** was immobilized on the surface of mesoporous SiO_2. The same catalyst could also be used for the asymmetric intramolecular cyclopropanation reaction although, there, moderate conversion and moderate enantioselectivity were observed (Scheme 23). The corresponding homogeneous system using $AuCl_3$ and unsupported diproline in the intermolecular reaction produced low yield and no enantioselection. While ICP analysis showed no leaching of Au ions to the solution phase due to the repulsion forces between hydrophilic catalyst and hydrophobic solvent, *in situ* near-edge X-ray adsorption fine structure measurements carried out under reaction conditions proved that the formation

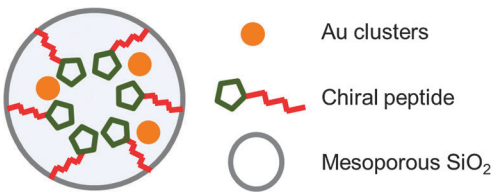
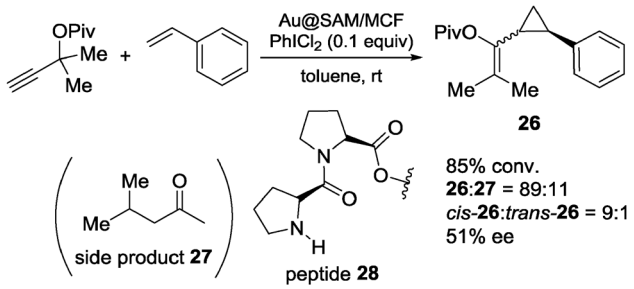
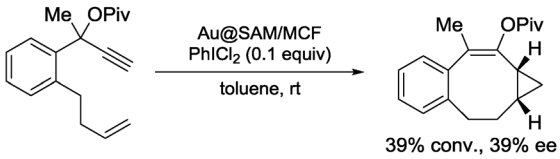


Fig. 4 Au NPs encapsulated in chiral SAM/mesoporous MCF-17 support.



Scheme 22 Au@SAM/MCF-17-catalyzed asymmetric intermolecular cyclopropanation.



Scheme 23 Au@SAM/MCF-17-catalyzed asymmetric intramolecular cyclopropanation.

of Au(III) ions, which were generated from Au(0) NPs by oxidation with $PhICl_2$, were the active species. Spectroscopic measurements revealed that the enantioselectivity was correlated with the stability of SAM, by the formation of a hydrogen bonding network. Although, in this study, the active species was proved to be not the NPs themselves, the advantages of the surrounding chiral SAM for the formation of a mesoscale enantioselective catalyst were noted.

5. Conclusion

The recent reports that we reviewed clearly showed the potential of chiral NP catalysts not only for asymmetric hydrogenation, but also for various types of asymmetric C–C bond formation reactions. Chiral NPs can be easily generated from metal precursors and chiral modifiers. The obtained NPs can be immobilized on several insoluble supports, such as metal oxides, polymers and magnetic NPs, to form heterogeneous catalysts. It was demonstrated that such catalysts could be recovered by simple operations and reused several times, without significant loss of activities and selectivities. The enantioselectivities in chiral NP catalyst systems were comparable to those in the corresponding homogeneous catalytic systems, and some chiral NP catalyst systems showed different selectivities compared with homogeneous catalytic systems. These facts indicate that chiral NP catalysts are not just "immobilized homogeneous catalysts;" they should be considered as distinct active species. The choice of the chiral modifier is a critical key not only to control enantioselectivity, but also to stabilize the NP catalyst itself. A wrong choice of chiral modifier can lead to the decomposition of NP catalyst to a corresponding homogeneous catalyst.

Given these aspects, we should be careful when discussing the real active species. Although the heterogeneity was confirmed by several traditional experiments, such as the poisoning test, hot filtration test, three-phase test, and ICP analysis in a reaction mixture, it is still unclear how the chiral environment is constructed around the NPs and how chiral modifiers and substrates interact with the surface of NPs or any other active species.

It is important to clarify the chiral active species and the mechanism of specific selectivities in chiral NP-catalyzed reactions. This is an emerging area of research. Further studies should lead to achievement of more efficient and unique chiral NP-catalyzed reactions.

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