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"*In situ* immobilization" of a multicomponent chiral catalyst (MCC) *via* non-covalent interactions for heterogeneous asymmetric hydrogenation reactions†

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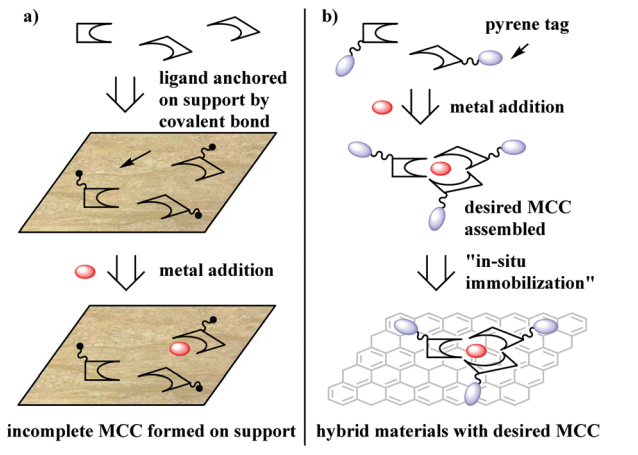
We have developed a practical "*in situ* immobilization" strategy where pyrene-tagged, multicomponent chiral catalysts (MCCs) are anchored onto graphene materials *via* π–π stacking interactions. The resulting novel hybrid catalysts showed excellent catalytic activity and enantioselectivity towards the hydrogenation of dehydroamino acid esters. Moreover, the catalysts demonstrated enhanced stability as they can be readily recycled and reused for up to thirteen runs without obvious deterioration of reactivity or enantioselectivity.

Asymmetric homogeneous catalysis has prevailed in the field of chiral synthesis and has provided enantiomerically-enriched molecules that serve as precursors for the pharmaceuticals, agrochemicals, and fine chemical industries. Immobilization of chiral transition metal catalysts has attracted the interest of chemists because it can facilitate the recovery and separation of expensive and often toxic metal catalysts from products, eliminate economic and environmental barriers, and therefore broaden their applications in commercial and industrial processes.[1–4] Multicomponent chiral catalysts (MCCs), which contain mixtures of several chemical entities (*e.g.*, ligands, metals, and other functional moieties), mimic enzymes by using the synergistic cooperation between each active site to promote various regio and stereoselective reactions. However, immobilization of MCC systems has been a challenge.[5,6] In the traditional immobilization approach (Scheme 1a), ligands are randomly anchored by covalent bonds onto an irregular surface of a solid support (*e.g.*, polystyrene resin), followed by the introduction of active metals. This process may prevent the formation of an MCC with the desired structure due to the constraints imposed by the distance between each fixed component (such as ligands and metals), which can lead to reduced catalytic performance of the resulting materials. Currently, very few methods for heterogenization of MCCs have been developed which limit their potential uses in industrial applications. Therefore, development of a new strategy for MCC immobilization is highly desirable.

The use of non-covalent interactions as a practical alternative to covalent-based chemistry has been recognized as one of the most important tools in the design and fabrication of complex functional systems.[4,7,8] Graphene materials, because



Scheme 1 (a) The traditional polymer-supported catalyst with an incomplete MCC. (b) Preparation of hybrid graphene catalysts *via* the "*in situ* immobilization" strategy.

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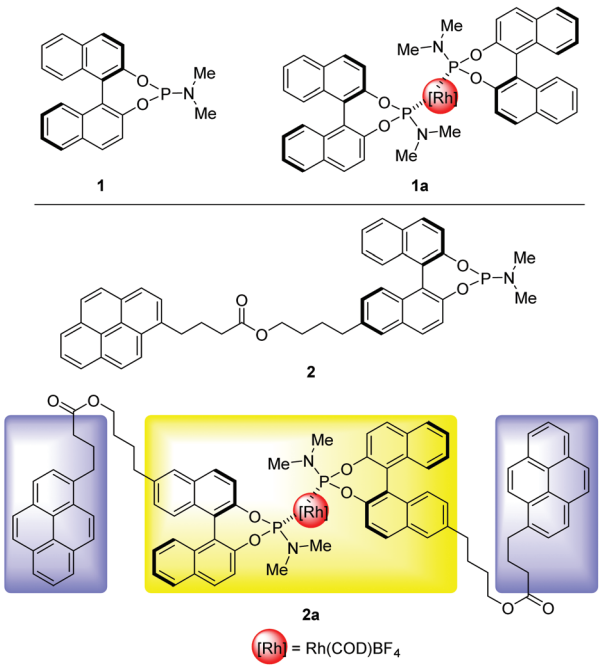
of their chemical inertness, extremely high surface area, and mechanical stability, offer a unique opportunity for non-covalent modifications by π–π stacking interactions with molecules containing polycyclic aromatic hydrocarbons, such as pyrene units.[9–11] Various catalysts have been modified and anchored onto graphene (including other types of carbon materials such as charcoal, fullerene, and carbon nanotubes) with the goal of facilitating the recovery and reuse of the catalyst.[12–18] Although significant advances have been achieved, such hybrid catalysts still have some limitations. For example, the reactivity and selectivity gradually drop in recycling experiments after few runs. This indicates that the heterogenization of chiral metal catalysts *via* non-covalent interactions is still a challenge.

With these considerations in mind, it was reasoned that a well-organized MCC modified with a pyrene unit, which is assembled initially through ligand-to-metal coordination interactions in a homogeneous solution, is expected to be adsorbed spontaneously onto graphene through π–π stacking interactions. During this process, the well-defined structural features of MCC will be maintained completely (Scheme 1b). Additionally, this "*in situ* immobilization" approach avoids the need for extra chemical modifications of both moisture-sensitive metal complex catalysts and support materials, and thus high intrinsic catalytic reactivity and enantioselectivity can be realized under heterogeneous reaction conditions. Based on these premises, and the importance of asymmetric hydrogenation both in academia and industry, here we report an "*in situ* immobilization" strategy of MCC *via* π–π stacking. The resulting hybrid graphene materials demonstrate excellent asymmetric induction in the catalytic hydrogenation of dehydroamino acid derivatives, and can be easily recycled without leaching toxic metal ions into the products.

Feringa's MonoPhos **1**/Rh(I) complex **1a**[19–21] (Scheme 2a) has been shown to catalyze the hydrogenation of many different substrates with excellent enantioselectivity and reactivity. A mechanistic study indicated that the active catalytic species **1a** contains two phosphorus ligands **1** and one rhodium(I), thus it is an example of a MCC system that uses the above-mentioned strategy. Pyrene-tagged MonoPhos ligand **2** was readily synthesized in high yield by integration of commercially-available 1-pyrenebutyric acid and known (R)-[1,1′-binaphthalene]-2,2′-dimethoxy-6-butanol[22] in the presence of DCC and DMAP, followed by deprotection to reveal the free hydroxyl groups which then reacted with hexamethyltriamidophosphite (HMPT) (see the ESI† for details).

The structure of the resulting ligand **2** has been characterized and confirmed by ^{1}H and ^{31}P NMR spectroscopy, optical rotation, Fourier-transform infrared spectroscopy (FTIR), and high-resolution mass spectroscopic (HRMS) analysis. ^{31}P NMR analysis showed the sole formation of the desired phosphoramidite ligand **2** (δ 148.8 ppm). The product is soluble in common organic solvents (*e.g.*, tetrahydrofuran and ethyl acetate), is air stable, and may be stored indefinitely under argon.



Scheme 2 (a) MonoPhos ligand **1** and metal complex **1a** and (b) pyrene modified ligand **2** and metal complex **2a**.

To determine the nature of the π–π stacking interactions between complex **2a** and graphene materials, pyrene-tagged ligand **2** (8.7 mg, 1.2×10^{-2} mmol) was first mixed with $[Rh(cod)_2]BF_4$ (2.5 mg, 0.6×10^{-2} mmol) in a 2 : 1 ratio in 5 mL ethyl acetate (Fig. 1, left). The resulting homogeneous solution displayed a typical orange color, indicating the formation of **2a** by metal-to-ligand coordination between one rhodium(I) atom and two phosphorus ligands **2**. Subsequently, the adsorption of complex **2a** onto graphene was studied. The above solution was mixed with graphene (20 mg) and stirred for 30 minutes. The original orange color of the solution became colorless, indicating that complex **2a** was anchored onto the graphene surface (Fig. 1, middle). The screening of various solvents showed that ethyl acetate was the best solvent for both adsorption and catalytic performance. The resulting hybrid material

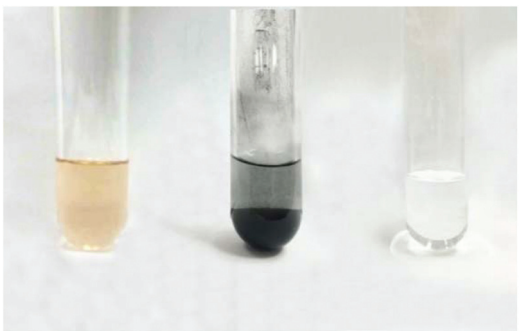


Fig. 1 The adsorption of chiral catalyst **2a** onto graphene in EtOAc. Homogeneous complex solution (left), the mixture with graphene (middle), and the filtrate (right).

2a@graphene was filtered and washed with ethyl acetate (Fig. 1, right). The ^{1}H NMR spectrum of the filtrate revealed the absence of any traces of complex **2a** in the solution which further confirmed the quantitative deposition of **2a** onto graphene. Furthermore, the control experiment of a mixture of the pyrene-free complex **1a** with graphene under the same conditions showed that complex **1a** remained in the solution, which confirmed that the pyrene unit is responsible for the adsorption. Thus, the formation of hybrid catalyst materials by "orthogonal" non-covalent interactions (metal-to-ligand coordination and π–π stacking) is confirmed. The new hybrid material **2a**@graphene was subjected to elemental mapping analysis by energy-dispersive X-ray spectroscopy (EDS) performed on a transmission electron microscope (TEM), which showed the homogeneous distribution of rhodium(I) on the material (Fig. 2b). The rhodium(I) loading was calculated to be 3×10^{-4} mmol mg^{-1} on graphene (3.1 wt%). The analysis of the surface area of materials was performed by argon sorption analysis at 77 K. The BET area for **2a**@graphene was 360.4 m^2 g^{-1}, which is significantly lower than that of raw graphene (734.6 m^2 g^{-1}).

Comparison of the chemical shifts in the solid-state ^{31}P cross-polarization magic-angle spinning (CP-MAS) NMR spectra of pyrene-tagged ligand **2** and the hybrid graphene material **2a**@graphene with those of MonoPhos **1** and its rhodium(I) complex **1a** clearly demonstrates a similar coordination pattern in the materials (Fig. 3). The ^{31}P CP-MAS NMR spectrum of MonoPhos **1** showed a broad peak centered at 149.5 ppm, which moved upfield to 135.3 ppm once the rhodium(I) complex **1a** was formed. Similarly, the resonances for pyrene-tagged ligand **2** and hybrid **2a**@graphene shifted from 146.5 ppm to 135.9 ppm, respectively. These data suggested that the well-defined structural motif in pyrene-tagged complex **2a** was successfully adsorbed onto the graphene surface without changing the coordination pattern.

The hybrid material **2a**@graphene provides an excellent opportunity for conducting heterogeneous asymmetric reactions. As shown in Table 1, asymmetric hydrogenation of α-dehydroamino acid derivatives catalyzed by **2a**@graphene (1 mol% Rh loading) proceeded smoothly with complete conversion under standard conditions at 20 atm hydrogen pressure for 2 h. In contrast, the supernatant of **2a**@graphene did not give further hydrogenation product under identical

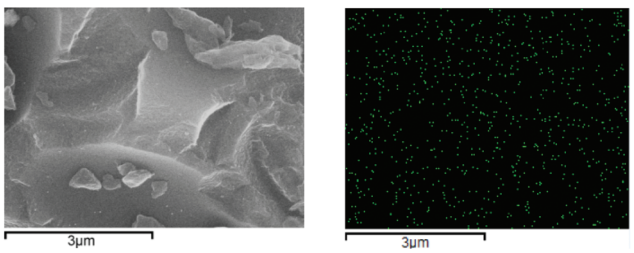


Fig. 2 STEM images of **2a**@graphene (left) and EDS elemental mapping image showing the homogeneous distribution of rhodium (right).

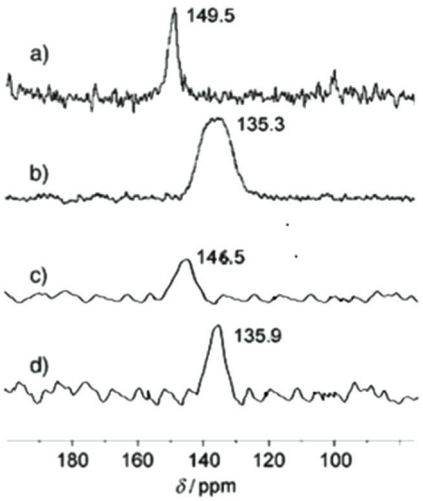
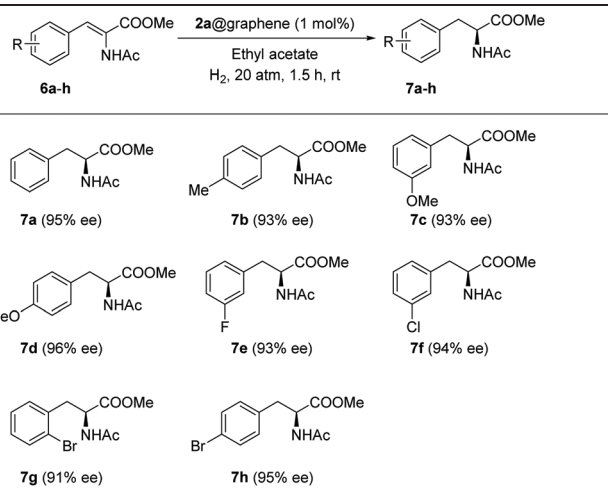


Fig. 3 ^{31}P CP-MAS NMR spectra: (a) MonoPhos ligand **1**; (b) metal complex **1a**; (c) ligand **2**; (d) metal complex **2a**@graphene.

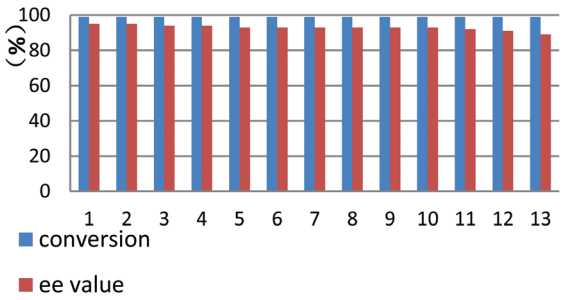
Table 1 Asymmetric hydrogenation of **6a–h** catalyzed by **2a**@graphene



All reactions were conducted in ethyl acetate under 20 atm of H_2 and **6** (0.5 mmol, 1.0 M). Conversions were >99% as determined by ^{1}H NMR spectroscopy.

experimental conditions, which demonstrated the heterogeneous nature of the present catalytic system. Expanding the scope of the catalyst system to a couple of aromatic α-dehydroamino acid derivatives containing electron-withdrawing and electron-donating groups gave excellent results (>95% ee) in all cases, comparable to the values for the homogeneous system **1a**. The high reactivity and high enantioselectivity are best attributed to the "*in situ* immobilization" strategy, based on our expectation that the well-defined orientation structure of MonoPhos/Rh^{I} is maintained during the adsorption process. Additionally, the graphene material has no detrimental effect on the micro chiral environment around the catalytic rhodium(I) metal provided by the chiral ligand. Since π–π interactions only take place between the pyrene unit

Table 2 Reuse of **2a**@graphene in the asymmetric hydrogenation of **6a**



All reactions conducted in ethyl acetate under 20 atm of H_2, **6a** (2.0 mmol, 1.0 M), and **2a**@graphene (0.01 M, based on the $(MonoPhos)_2$/Rh unit).

and graphene, the MonoPhos/Rh(I) complex unit is not attached to the graphene surface directly. It is probably in a homogeneous-like state *via* a long aliphatic chain anchored to graphene, therefore the catalytic activity of **2a**@graphene is comparable to its homogeneous counterparts.

The advantage of the hybrid **2a**@graphene material over its homogeneous counterparts lies in its facile recovery and reusability. After the hydrogenation reaction is complete, simple cannula filtration under argon in a glove box allows the separation of **2a**@graphene from the solution containing the product. The isolated **2a**@graphene is then simply recharged with solvent and substrates, and reloaded into the autoclave for the next run. The reusability of the catalyst system is exemplified by the hydrogenation of phenyl α-dehydroamino acid ester (**6a**). As shown in Table 2, the hydrogenation proceeded with near-quantitative conversion and constant enantioselectivity (96–92% ee) for at least 13 cycles with the same catalyst. However, it was observed that it was necessary to extend the reaction time from 2 hours to 10 hours to achieve a complete conversion of the substrate after recycling the catalyst 7 times. This indicated that the catalyst's reactivity to **2a**@graphene declined gradually during consecutive hydrogenations. Importantly, the leaching of Rh metal in the combined products for 13 recycling reactions of the catalyst is found to be 2.87 ppm, as determined by ICP spectroscopy. Thus, the total Rh leaching in the product solution is 1.7% of that in the original catalyst. Our earlier studies suggested that the partial MonoPhos/Rh(I) complex decomposed during the recycling process due to the instability of the intermediate catalyst species when not under a hydrogen atmosphere.[23,24]

Conclusions

In summary, the immobilization of a multicomponent chiral catalyst based on non-covalent π–π stacking interactions between pyrene units and graphene materials has been achieved, and the resulting hybrid materials were characterized by various techniques. The **2a**@graphene catalyst showed excellent asymmetric induction during the hydrogenation of dehydroamino acid derivatives (up to >95% ee and >99% yield) and could be readily recycled and reused. Notably, the strategy presented here will stimulate future research aimed at developing other heterogeneous hybrid chiral catalysts for asymmetric reactions based on non-covalent interactions.

Experimental section

The catalyst was prepared *in situ* by mixing $[Rh(COD)_2]BF_4$ (2.0 mg, 0.005 mmol) and ligand **2** (7.0 mg, 0.01 mmol) in dry ethyl acetate (5 mL) for 10 min. To the above solution was added graphene (20 mg) and stirred for 30 minutes. Then the mixture was transferred into a 50 mL stainless steel autoclave equipped with a glass liner, which contained a dehydroamino acid derivative (0.5 mmol) and a magnetic stirring bar. The reactor was charged with hydrogen gas, and the solution was stirred at the required temperature for a predetermined period of time. After the reaction was complete, the hydrogen gas was released and the ee value of the product was measured directly using the reaction mixture without further purification.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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