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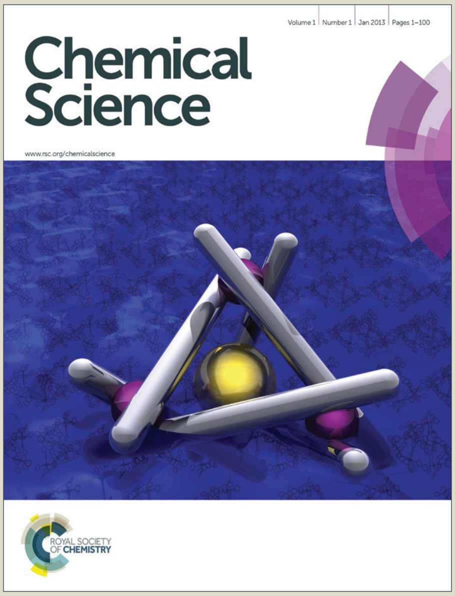

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ARTICLE

Integration of Aerobic Oxidation and Intramolecular Asymmetric *aza*–Friedel–Crafts Reactions with a Chiral Bifunctional Heterogeneous Catalyst†

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A new class of chiral bifunctional heterogeneous materials bearing Au/Pd nanoparticles and chiral phosphoric acid as active orthogonal catalysts was prepared by utilizing a facile pseudo-suspension co-polymerization method. It was found that this heterogeneous catalyst was capable of facilitating the sequential aerobic oxidation-asymmetric intramolecular *aza*-Friedel-Crafts reaction between benzyl alcohols and *N*-aminoethylpyrroles. Moreover, this designed chiral heterogeneous catalyst could be recovered and reused several times without significant loss of activity and enantioselectivity.

Introduction

Multicatalyst-promoted asymmetric tandem reactions[1] are an emerging subset in the family of one-pot processes[2] that can provide access to complex organic substrates of high enantiopurity in an efficient and practical manner. Despite the promise of these reactions, one of the major challenges, which have limited its development, is the problem associated with catalyst incompatibility. A potential strategy to overcome this obstacle is by applying the principle of site separation to prevent mutual deactivation of catalysts, and successful tandem asymmetric processes have been achieved with chiral catalysts immobilized or encapsulated on polymers[3] and sol-gel materials.[4] Another challenge faced in multicatalyst-promoted tandem reactions is the unselective interaction of starting materials and reaction intermediates with the catalysts to generate unwanted by-products. While it is difficult to achieve catalyst selectivity in one-pot reaction process, the use of heterogeneous catalysts in continuous-flow systems is a potential solution to overcome this problem.[5]

Our group has a long-standing interest in the immobilization of metal nanoparticles (NPs) onto polymer supports[6] and its application to tandem oxidation processes (TOPs) with oxygen gas as the terminal oxidant.[7] Previously, we reported the fabrication of a layered heterogeneous bifunctional chiral catalyst consisting of Au/Pd NPs and a Jørgensen-Hayashi-type organocatalyst supported on separate polymeric materials (PI(Au/Pd)-CO, polymer-incarcerated Au/Pd NP-coated organocatalyst), and its application as a catalyst for the sequential aerobic oxidation-asymmetric Michael reactions of primary allylic alcohols and dibenzyl malonate (Scheme 1a).[3c] While we were able to demonstrate that our fabrication method prevented catalyst deactivation between the Au/Pd NPs and the chiral organocatalyst to enable the asymmetric TOP, it was discovered that the chiral secondary amine catalyst was neutralized under aerobic conditions and that the heterogeneous catalyst could not be reused. Based on our preliminary experimental studies and related literatures,[8] we concluded that the use of chiral heterogeneous secondary amines as organocatalysts for asymmetric TOPs was not a viable strategy due to the propensity of its covalent intermediates to undergo aerobic oxidation and become degraded. Therefore, we hypothesized that the use of chiral organocatalysts, which activated the organic substrates through non-covalent interactions, would lead to a more robust heterogeneous system that could be recovered and reused even under aerobic conditions.

Over the past decade, chiral phosphoric acids (CPAs) have been proven to be highly efficient catalysts for a wide range of asymmetric transformations.[9,10] Of particular note is their ability to activate imine derivatives, via hydrogen bonding or ion pair interactions (non-covalent interactions), and to promote high levels of stereoinduction of the prochiral electrophiles. Based on these considerations, we rationalized that CPAs might represent the ideal chiral component for a recyclable heterogeneous catalyst that could facilitate asymmetric TOPs. Herein, we report the preparation of a heterogeneous chiral bifunctional catalyst, consisting of Au/Pd NPs and a CPA, and its application for the sequential aerobic oxidation-asymmetric *aza*-Friedel-Crafts (FC) reaction (Scheme 1b).

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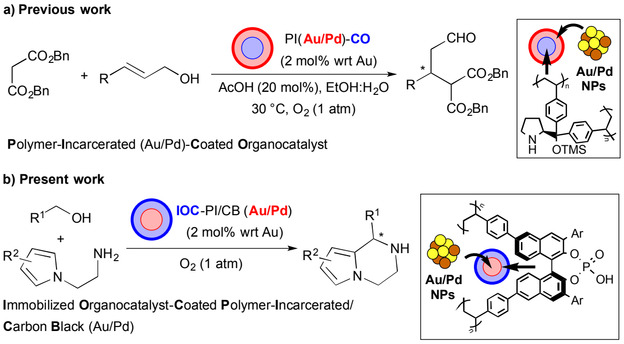
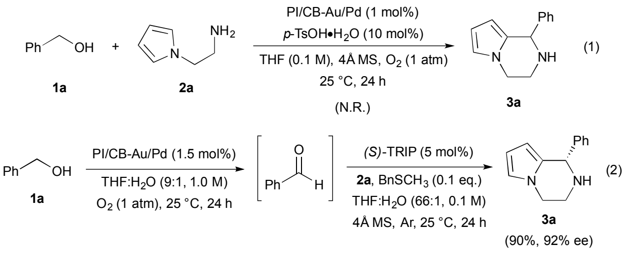


Scheme 1 Chiral bifunctional heterogeneous catalysts for TOPs

Results and discussion

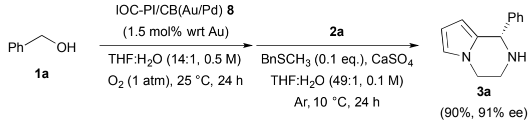
We began our investigations by examining the feasibility of a TOP that integrated aerobic oxidation with the *aza*-FC reaction using benzyl alcohol (**1a**) and *N*-aminoethylpyrrole (**2a**) as model substrates, and PI/CB-Au/Pd and *p*-toluenesulfonic acid as co-catalysts (Scheme 2, eqn 1). It was found that the expected piperazine **3a** was not obtained under our initial conditions. This was unexpected given that control studies showed that both the aerobic oxidation of **1a** and the *aza*-FC reaction between **2a** and benzaldehyde occurred in good yields under these initial conditions.[11] It was later revealed that the aerobic oxidation of **1a** did not occur in the presence of **2a**, most likely due to the strong coordination of the primary amine moiety of **2a** to the Au/Pd NPs, to cause catalyst deactivation. To overcome this limitation, we found that by performing the TOP through a one-pot, sequential addition process, in which the aerobic oxidation of **1a** was allowed to proceed prior to the addition of **2a**, was key to successfully obtain **3a**. Optimization of the aerobic oxidation step and the asymmetric TOP using *(S)*-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'diyl hydrogenphosphate (*(S)*-TRIP)[12] as the CPA was performed in order to improve the yield and enantioselectivity of the desired chiral piperazine **3a**. It was found that water was essential to promote the aerobic oxidation of **1a**, while the introduction of BnSCH$_3$ as an additive to deactivate the Au/Pd NPs was important to prevent oxidation of **3a** to its imine form. Based on these two major modifications, the asymmetric TOP proceeded well to deliver chiral piperazine **3a** in high yield and enantioselectivity (Scheme 2, eqn 2).



Scheme 2 Reaction integration of aerobic oxidation with *aza*-FC reaction

With these results in hand, we began the process of fabricating chiral bifunctional heterogeneous catalysts that would be capable of facilitating the sequential aerobic oxidation-asymmetric *aza*-FC reaction. We began by developing a reliable synthetic route for *(S)*-TRIP-type monomer **4**,[13] and then utilize this as a chiral feedstock to construct the chiral composite material **8** through a pseudo-suspension co-polymerization method (Fig 1a). With this heterogeneous bifunctional chiral catalyst in hand, we examined the asymmetric TOP between benzyl alcohol (**1a**) and *N*-aminoethylpyrrole **2a** (Scheme 3). It was found that after slight modification of the optimized reaction conditions previously determined for the combined catalyst system of PI/CB-Au/Pd and *(S)*-TRIP, the desired piperazine **3a** could be obtained in excellent yield and enantioselectivity. We also examined our model reaction using the layered heterogeneous catalyst **10** with the inversed placement of the Au/Pd NPs and CPA (Fig 1c), and it was found to catalyze the asymmetric TOP with similar results (85%, 88% ee of **3a**).

After establishing the optimal reaction conditions for the sequential aerobic oxidation-asymmetric *aza*-FC reaction, we



Scheme 3 Sequential aerobic oxidation of **1a**-asymmetric *aza*-FC reaction with **2a** catalyzed by IOC-PI/CB(Au/Pd) **8**

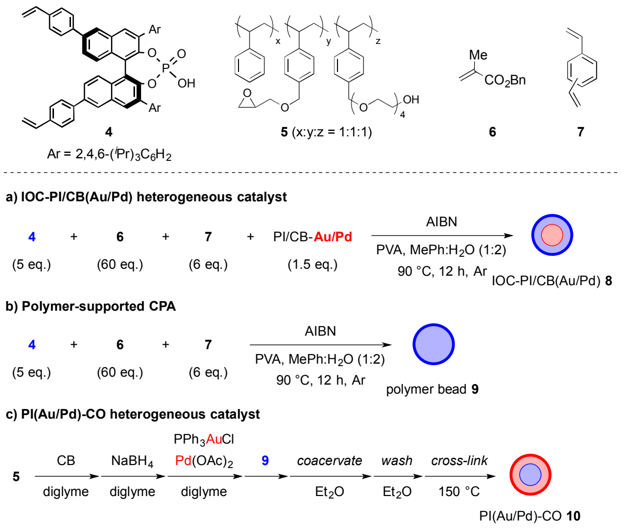


Fig 1 Fabrication procedure for a) IOC-PI/CB(Au/Pd) **8**; b) polymer-supported CPA **9**; c) PI(Au/Pd)-CO **10**. Blue represents the layer containing CPA while the red represents the layer containing Au/Pd NPs

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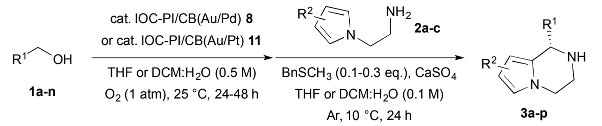
examined the substrate scope for this one-pot process (Table 1). It was found that substituted benzyl alcohols **1a-h**, bearing electron-donating substituents, could be utilized for the asymmetric TOP to furnish the desired chiral piperazines **3a-h** in good yields and enantioselectivities (entries 1-8). On the otherhand, when we examined 4-fluorobenzyl alcohol (**1i**) as a substrate, only a trace amount of the expected product **3i** was detected under the current reaction conditions. Control studies revealed that the origin of this problem was the aerobic oxidation step, and we found that Au/Pt NPs in DCM:H_2O (1:1) was more effective for the aerobic oxidation of benzyl alcohols possessing electron-withdrawing substituents. Thus, we prepared a new chiral bifunctional heterogeneous catalyst, IOC-PI/CB(Au/Pt) **11**, and found that this new chiral composite material could effectively catalyze the sequential oxidation-asymmetric *aza*-FC reaction for 4-substituted benzyl alcohols with a wide range of functional groups, such as F, Cl, CF_3, CO_2Me, and CN, to furnish the corresponding chiral piperazines **3i-n** in good yields and enantioselectivities (entries 9-14). We also examined the asymmetric TOP with methyl substituted *N*-aminoethylpyrroles **2b-c**, and it was found that these substrates were also suitable to provide chiral bicyclic heterocycles **3o-p** with high yields and enantioselectivities (entries 15-16).

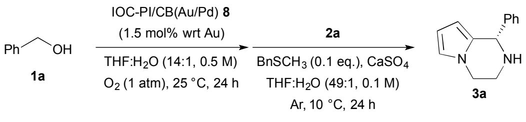
Table 1 Substrate scope for the IOC-PI/CB(Au/Pd) **8** or IOC-PI/CB(Au/Pt) **11**-catalyzed asymmetric TOP between benzyl alcohols **1a-n** and *N*-aminoethylpyrroles **2a-c**[a]



Entry	**1**: R^1; **2**: R^2	**3**	Yield (%)[d]	ee (%)[e]
1	**1a**: Ph; **2a**: H	**3a**	89	94
2	**1b**: 4-Me-C_6H_4; **2a**: H	**3b**	89	84
3	**1c**: 2-Me-C_6H_4; **2a**: H	**3c**	91	92
4	**1d**: 4-MeO-C_6H_4; **2a**: H	**3d**	80	80
5[b]	**1e**: 3-MeO-C_6H_4; **2a**: H	**3e**	83	93
6[b]	**1f**: 2-MeO-C_6H_4; **2a**: H	**3f**	85	91
7	**1g**: piperonyl; **2a**: H	**3g**	84	73
8[b]	**1h**: 1-naphthyl; **2a**: H	**3h**	85	93
9[c]	**1i**: 4-F-C_6H_4; **2a**: H	**3i**	91	90
10[c]	**1j**: 2-F-C_6H_4; **2a**: H	**3j**	88	91
11[c]	**1k**: 4-Cl-C_6H_4; **2a**: H	**3k**	83	90
12[c]	**1l**: 4-CF_3-C_6H_4; **2a**: H	**3l**	82	86
13[c]	**1m**: 4-CN-C_6H_4; **2a**: H	**3m**	89	95
14[c]	**1n**: 4-CO_2Me-C_6H_4; **2a**: H	**3n**	84	90
15	**1a**: Ph; **2b**: 2-Me	**3o**	91	85
16	**1a**: Ph; **2c**: 2,4-$(Me)_2$	**3p**	83	70

[a] Reaction conditions: benzyl alcohol **1** (0.3 mmol), IOC-PI/CB(Au/Pd) **8** (1.5 mol% wrt Au) in THF:H_2O (v:v = 0.56:0.04 mL) under a balloon of oxygen gas at room temperature for 24 h (aerobic oxidation step). Then *N*-aminoethylpyrrole **2** (0.2 mmol), $CaSO_4$ (200 mg), $BnSCH_3$ (2.8 mg) and THF (1.4 mL) were added under a balloon of Ar at 10 °C for 24 h (*aza*-FC step). [b] Standard reaction conditions except for the use of IOC-PI/CB(Au/Pd) **8** (3.0 mol% wrt Au) for 48 h (aerobic oxidation step) and $BnSCH_3$ (5.6 mg) (*aza*-FC step). [c] Standard reaction conditions except for the use of IOC-PI/CB(Au/Pt) **11** (3.0 mol% wrt Au) in DCM:H_2O (v:v = 0.54:0.06 mL) (aerobic oxidation step) and $BnSCH_3$ (5.6 mg) (*aza*-FC step). [d] Isolated yield based on **2a-c** and determined by weight of the isolated product **3a-p**. [e] The ee value was determined by chiral HPLC analysis.

Finally, we examined the possibility of recycling our chiral bifunctional heterogeneous catalyst, and found that it could be recovered and reused several times without significant loss in yield and enantioselectivity for the asymmetric TOP with benzyl alcohol **1a** and *N*-aminoethylpyrrole **2a** as substrates (Scheme 4). The key to recycling the heterogeneous catalyst was the treatment of the spent IOC-PI/CB(Au/Pd) **8** with an aqueous solution of H_2O_2 to remove $BnSCH_3$ and reactivate the Au/Pd NP catalyst.



1st: 92%, 89% ee, **2nd**: 90%, 88% ee, **3rd**: 90%, 88% ee, **4th**: 87%, 87% ee
5th: 88%, 88% ee, **6th**: 85%, 84% ee

Scheme 4 Recovery and reuse of IOC-PI/CB(Au/Pd) **8**

Conclusions

In conclusion, we have developed a new chiral bifunctional heterogeneous catalyst, composed of metal NPs and CPAs, that was capable of performing the sequential, one-pot aerobic oxidation-intramolecular asymmetric *aza*-FC reaction to provide chiral 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazines **3a-p** in high yields and enantioselectivities. Interestingly, we found a chemical system (H_2O_2/$BnSCH_3$) to switch on/off the catalytic activity[14] of the Au/Pd and Au/Pt NPs. By controlling the catalytic activity of the heterogeneous catalyst through the use of a chemical modifier, the undesired oxidation of chiral piperazines **3a-p** was avoided, and the facile reactivation of the deactivated catalyst enabled the chiral composite material to be recovered and reused several times without significant losses in yields and enantioselectivities of the desired product **3a**. Moreover, we were able to demonstrate that heterogeneous CPAs could retain its catalytic ability in the presence of metal NPs under oxidative conditions (O_2 and H_2O_2). Further investigations into the use of these robust chiral heterogeneous catalysts in other types of asymmetric TOPs are currently underway in our laboratory.

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