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Fe_3O_4 Nanoparticle-Supported Copper(I) Pybox Catalyst: Magnetically Recoverable Catalyst for Enantioselective Direct-Addition of Terminal Alkynes to Imines

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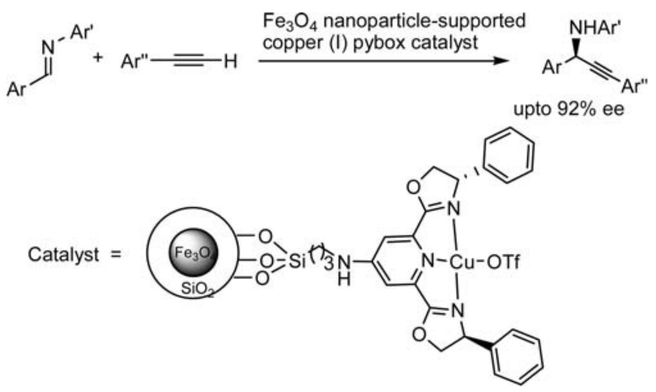
ABSTRACT



An Fe_3O_4 nanoparticle-supported copper(I) pybox catalyst, which exhibits excellent reactivity and yields products with good enantioselectivity, was developed. As a proof of concept, six optically active propargyl amines were obtained in excellent yields. The catalyst can be magnetically removed and recycled easily six times without a decrease in activity or enantioselectivity.

The use of more environmentally benign catalysts coupled with practical and efficient processes for catalyst separation and reuse provides both economical and ecological benefits.[1] Because of the ease of magnetic separation from the reaction mixture, this strategy, taking advantage of magnetic nanoparticles, is typically more effective than filtration or centrifugation as it prevents loss of the catalyst.[2] Magnetic separation of nanoparticles is simple, economical, and promising for industrial applications.[3] In recent years, the direct use of magnetic Fe_3O_4 (magnetite) nanoparticles as magnetically recoverable catalysts for organic reactions was

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developed by us and others.[4] Furthermore, Fe_3O_4 nanoparticles have emerged as robust and high-surface-area heterogeneous catalyst supports,[5] and various strategies have successfully demonstrated the applications of Fe_3O_4 nanoparticle-immobilized or -supported catalysts.[6]

Optically active propargyl amines, products of the asymmetric three-component aldehyde−alkyne−amine coupling (AA^3 coupling), are useful building blocks and important skeletons for biologically active compounds or natural products.[7] Recently, great efforts have been made to develop the methodology for generating optically active propargylamines.[8] We pioneered a highly enantioselective addition of terminal alkynes to imines to afford optically active propargylamines by using a chiral Cu(I)−bis(oxazolinyl)pyridine (pybox) complex catalyst (Figure 1).[8a,b] Pybox ligands, which demonstrate great versatility in complexation of the transition metals, were effective in a number of highly enantioselective catalytic processes. While several methods for the preparation of immobilized or supported pybox ligands have been demonstrated,[9] to the best of our knowledge, no example of magnetic nanoparticle-supported pybox complex has been reported. Herein, we wish to report a novel magnetically recoverable Fe_3O_4 nanoparticle-supported copper(I) pybox catalyst and its application in enantioselective direct-addition of terminal alkynes to imines. It was found that the Fe_3O_4 nanoparticle-supported copper(I) pybox exhibits high reactivity, yielding products with good enantioselectivity. Recovery of the catalyst by decantation of the reaction mixture in the presence of an external magnet is easy and efficient. The catalyst was recycled over six times without any significant loss in activity and enantioselectivity.

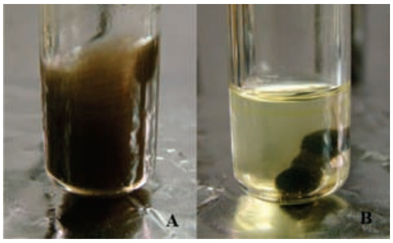
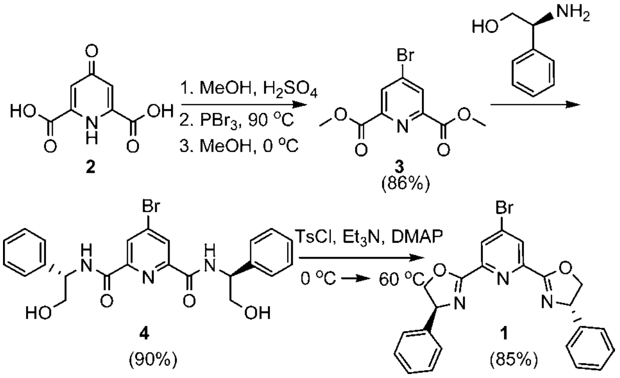


Figure 1. (A) Fe_3O_4 nanoparticle-supported copper(I) pybox catalyst dispersion in reaction solution. (B) Fe_3O_4 nanoparticle-supported copper(I) pybox catalyst adsorbed on the magnetic stirring bar.

The 4-bromo-substituted phenyl-pybox ligand **1**, generated from chelidamic acid **2**, was selected as a suitable derivative for further functionalization. Chelidamic acid **2** was transformed to dimethyl 4-bromopyridine-2,6-dicarboxylate **3** in high yield (Scheme 1).[9b]

Scheme 1. Synthesis of 4-Bromo-Substituted Phenyl-Pybox



Reaction of **3** and (*S*)-phenylglycinol generated diamide **4**, which was transformed into **1** in 85% yield. The Fe_3O_4

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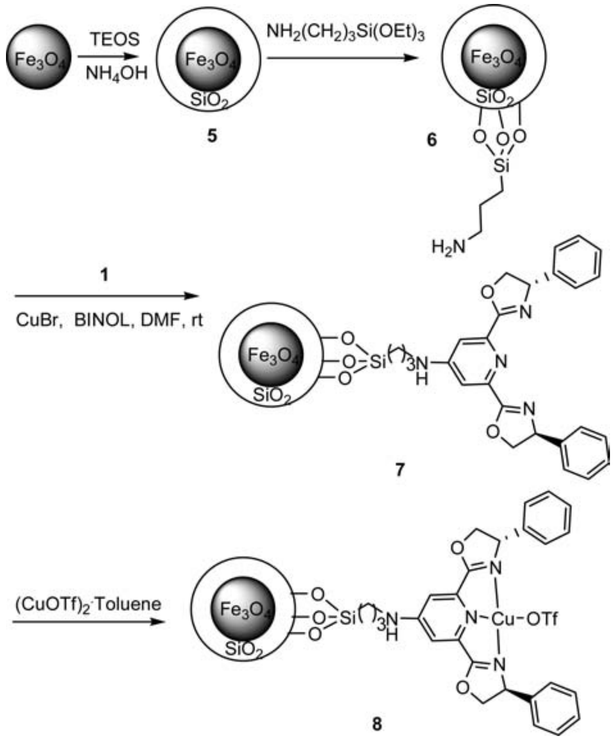
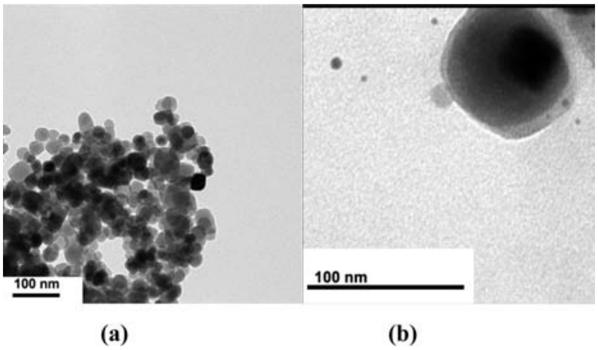
Scheme 2. Preparation of Fe_3O_4 Nanoparticle-Supported Copper(I) Pybox Catalyst



nanoparticle-supported copper(I) pybox was prepared by the concise route schematically illustrated in Scheme 2. Magnetite (Fe_3O_4) NPs (<50 nm particle size (TEM)) were purchased from Sigma-Aldrich (Figure 2). The NPs were then coated with a silica layer to generate **5**.[10] This step was carried out to protect the Fe_3O_4 NP cores, considering the potential particle oxidation and aggregation of Fe_3O_4 NPs and the potential interactions between Fe_3O_4 and copper(I) pybox complex or reaction intermediates. Treatment of the silica-coated nanoparticles with excess 3-aminopropyltriethoxysilane in toluene at room temperature afforded silica nanospheres functionalized with amine groups **6**.[10] CuBr/BINOL(1,1′-binaphthyl-2,2′-diol)-catalyzed *N*-arylation reaction of ligand **1** and NPs **6** afforded **7**.[11] The application of this CuBr/BINOL-catalyzed *N*-arylation method was confirmed by reaction of **1** and 2-phenylethanamine, which gave a high yield (81%, yield based on **1**). In this reaction, the pybox ligand remained stable under the mild reaction conditions of 50 °C and the presence of K_3PO_4 as the base. It is worth noting that a control experiment indicated the stability of the secondary aromatic amine under reaction conditions of copper(I) pybox catalyzed enantioselective direct addition of terminal alkynes to imines (and secondary aromatic amine is also the desired product of this reaction), suggesting that this secondary amine linker remains intact throughout the reactions. Compound **7** was washed with solvents and aqueous EDTA solution several times to eliminate copper residue[12] and then stirred with a dichloromethane solution of $(CuOTf)_2$•toluene, filtered, and washed, yielding the magnetically recoverable Fe_3O_4 nanoparticle-supported copper(I) pybox catalyst **8**. The loading process proceeded cleanly (0.20 mmolg^{-1} loading, calculated by ICP-AES test of Cu), and transmission electron microscopy (TEM) demonstrated that in the core−shell structure of the nanoparticles there are small Fe_3O_4 nanoparticle clusters encapsulated within the silica in the core/shell Fe_3O_4@SiO_2 nanoparticles.

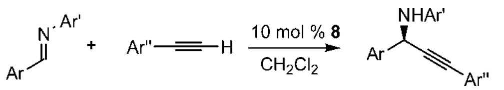


(a) (b)

Figure 2. TEM images of (a) Fe_3O_4 and (b) core/shell Fe_3O_4@SiO_2 nanoparticles.

To evaluate the efficiency of the Fe_3O_4 nanoparticle-supported copper(I) pybox catalyst, it was tested in enantioselective direct-addition reactions of terminal alkynes to imines. Our experiments revealed that **8** exhibits high reactivity and good enantioselectivity. For example, the reaction of 1.5 equiv of phenylacetylene with *N*-(4-bromobenzylidene)aniline in dichloromethane in the presence of 10 mol % of catalyst at 35 °C for 36 h under argon atmosphere afforded the adduct in 92% yield and 92% ee (entry 2, Table 1). The optical rotation of the product showed the same sign as the one obtained from the homogeneous

Table 1. Fe_3O_4 Nanoparticle-Supported Copper(I) Pybox-Catalyzed Enantioselective Direct-Addition Reactions of Terminal Alkynes to Imines[a]



entry	aldehyde	aniline	akyne	yield (%)	ee (%)
1	PhCHO	$PhNH_2$	PhCCH	91	86
2	4-BrC_6H_4CHO	$PhNH_2$	PhCCH	92	92
3	4-ClC_6H_4CHO	$PhNH_2$	PhCCH	90	92
4	4-$CF_3C_6H_4CHO$	$PhNH_2$	PhCCH	80	86
5	PhCHO	4-$BrC_6H_4NH_2$	PhCCH	94	84
6	PhCHO	$PhNH_2$	4-MeC_6H_4CCH	93[b]	85

[a] Isolated yield of analytically pure product, reaction conditions: 10 mol % catalyst, CH_2Cl_2 (0.5 mL), aldehyde (0.2 mmol), aniline (0.24 mmol), alkyne (0.3 mmol), 35 °C, 36 h, under argon atmosphere. [b] Reacted for 2 days.

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catalyst.[8a] A variety of substrates were examined, the results of which are summarized in Table 1. In all cases, the reactions took place smoothly, giving propargylamines in high yields and good enantioselectivity. The most probable reason for the higher reactivity of Fe_3O_4 nanoparticle-supported copper(I) pybox catalyst over other solid-phase supported pybox catalysts is that nanoparticles have a much larger surface area to volume ratio, which can provide a higher catalytic activity.[9] Separate experiments demonstrated that $(CuOTf)_2$•toluene catalyzed this reaction (substrates in entry 1, Table 1) to afford only trace amounts of racemic products, and **1** is not catalytically active in this addition reaction. It can therefore be assumed that the Fe_3O_4 nanoparticle-supported copper(I) pybox complex **8** is responsible both for the activity as well as the enantioselectivity.

Recovery of the catalyst is easy and efficient. When the magnetic stirring was stopped, the Fe_3O_4 nanoparticle-supported copper(I) pybox catalyst adsorbed onto the magnetic stirring bar. The catalyst was recovered by decantation of the reaction mixture in the presence of an external magnet. The catalyst was then washed with dichloromethane, dried under high vacuum, and used directly for the next round of reaction without further purification. The ease of recovery, combined with the intrinsic stability of both the copper(I) pybox (under argon atmosphere) and silica-protected Fe_3O_4 nanoparticle components, allows the catalyst to be recycled over six times in reactions without any significant loss in activity and enantioselectivity (Table 2). The possible reason for the slight ee (%) reduction is that a small amount of pybox ligand decomposed after several cycles.

In summary, we have developed an Fe_3O_4 nanoparticle-supported copper(I) pybox catalyst which exhibits excellent reactivity in asymmetric aldehyde–alkyne–amine coupling, yielding products with good enantioselectivity. The catalyst can be synthesized from readily available starting materials or directly on the solid phase easily and remains intact throughout the reactions. Recovery of the catalyst by decantation of the reaction mixture in the presence of an external magnet is easy and efficient. The catalyst was recycled over six times in reactions without any obvious loss in activity and enantioselectivity. Several optically active propargylamines were obtained in excellent yields. Further study on the wider applications of this efficient strategy is under investigation in our laboratory.

Table 2. Recycling of the Fe_3O_4 Nanoparticle-Supported Copper(I) pybox Catalyst[a]

cycle	yield (%)	ee (%)	cycle	yield (%)	ee (%)
1	89	87	4	92	85
2	90	86	5	90	84
3	92	86	6	82	81

[a] Isolated yield of analytically pure product, reaction conditions: 10 mol % catalyst, CH_2Cl_2 (0.5 mL), benzaldehyde (0.2 mmol), aniline (0.24 mmol), phenylacetylene (0.3 mmol), 35 °C, 36 h, under argon atmosphere.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The Cu(I)Br will reduce the enantioselectivity of the products.[8a]