Magnetic nanoparticle-supported proline as a recyclable and recoverable ligand for the CuI catalyzed arylation of nitrogen nucleophiles†

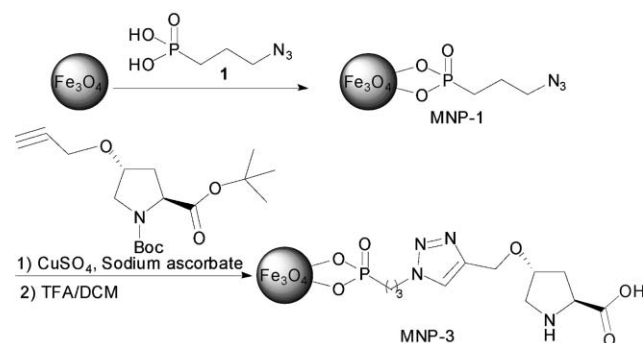Gagan Chouhan,[a] Dashan Wang[b] and Howard Alper*[a]

Magnetic nanoparticle-supported proline ligand was prepared and used for the CuI catalyzed Ullmann-type coupling reactions of aryl/heteroaryl bromides with various nitrogen heterocycles to form the corresponding N-aryl products in good to excellent yields; furthermore, this magnetic nanoparticle-supported proline ligand could be readily separated using an external magnet and reused without significant loss of activity.

Magnetic nanoparticles (MNP) have attracted much attention by researchers from a wide range of disciplines, including physics, biomedicine, biotechnology, material science and catalysis, because of their large ratio of surface area to volume, superparamagnetic behaviour and low toxicity.[1] Recently, magnetic nanoparticles have been used as a new alternative to porous materials for supporting catalytic transformations.[2] Their simple magnetically driven separation from a liquid-phase reaction, makes catalyst recovery and recycling much easier than by cross-flow filtration and centrifugation. Additionally, the MNP-supported catalysts also show high dispersion and reactivity with a high degree of chemical stability. By utilizing these advantages of magnetic nanoparticles over other supporting materials, various catalysts and ligands have been immobilized on these particles.[3] We recently examined the use of polyaminoamido (PAMAM) dendron functionalized magnetic nanoparticles as alternative homogenous materials to support Rh metal for highly selective hydroformylation reactions.[4] Herein we report the first example of the preparation of a magnetically separable proline ligand, and its application towards the filtration-free, recyclable Ullmann-type reaction between aryl/heteroaryl bromides and nitrogen heterocycles.

Ullmann-type C–N bond formation is a common strategy to prepare biologically and medicinally important N-aryl/heteroaryl heterocycles. Recently, various new systems have been developed involving copper salts and nitrogen and/or oxygen ligands such as diamines,[5] diimines,[6] 2-aminopyrimidine-4,6-diol,[7] 8-hydroxyquinoline,[8] 4,7-dimethoxy-1,10-phenanthroline,[8] as well as oxime-containing compounds,[9] and amino acids.[10] While using these ligands have led to significant results, little progress has been made to immobilize them.[11] Therefore, development of new strategies to immobilize these ligands for copper-catalyzed cross-coupling protocols is of considerable interest. Thus, we have developed a magnetic nanoparticle-supported proline ligand and evaluated its activity for the CuI catalyzed N-arylation of various nitrogen heterocycles.

Magnetite (Fe_3O_4) nanoparticles were prepared by coprecipitation of iron(II) and iron(III) ions in basic solution at 85 °C using the method described by Massart.[12] Azide functionalized magnetite (MNP-1) was prepared by treating the nanoparticles with the phosphonic acid ligand 1 as described in Scheme 1. The IR spectrum of MNP-1 clearly shows strong absorption at 2092 cm^{-1} due to azide ($-N_3$) asymmetric stretching (see ESI†). The loading of the ligand on the magnetic nanoparticles was determined by elemental analysis of nitrogen as 2.3 mmol g^{-1}. The TEM images (see ESI†) of the azide functionalized magnetic nanoparticles (MNP-1 shows slight aggregation and the size of the particles were between 6 and 15 nm. Immobilization of the proline ligand was carried out by the Cu(I)-catalyzed alkyne–azide [2 + 3] cycloaddition reaction of $CuSO_4$, sodium ascorbate and triethyl amine in a 1 : 1 mixture of tert-butyl alcohol and water at room temperature for 24 h to give the proline functionalized magnetic nanoparticles MNP-2. The IR spectrum of MNP-2 (see ESI†) showed virtual disappearance of the azide signal, and new bands at 1737 and 1693 cm^{-1} which correspond to the tert-butyl-N-Boc prolinate. The TEM images (see ESI†) shows disperse nanoparticles, suggesting that the nanoparticles are stabilized from aggregation after the click reaction with the proline ligand. The thus formed proline ligand loaded nanoparticles was further treated with trifluoroacetic acid (TFA) in dichloromethane to deprotect the tert-butyl groups from the proline ligand (see ESI† for detailed

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Scheme 1 Preparation of magnetic nanoparticle-supported proline ligand MNP-3
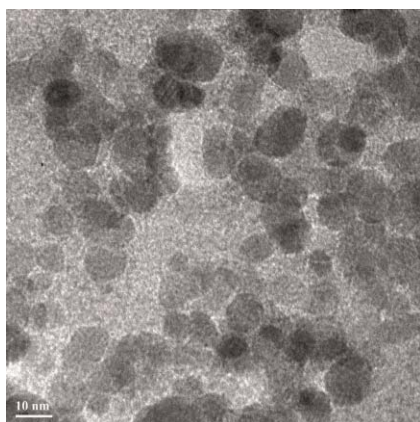
Fig. 1 TEM image of MNP-3 (scale bar 10 nm)

reaction procedure) to form the proline loaded magnetic nanoparticles **MNP-3**. The FTIR spectrum of **MNP-3** shows no *tert*-butyl or carbonyl group of the *tert*-butyl ester, and an absorption at 1620 cm^{-1} corresponds to the free acid functionality of the proline. The TEM image of the magnetite proline nanocomposite is illustrated in Fig. 1. Partially aggregated nanoparticles between 6–20 nm were obtained. Elemental analysis of the magnetite nanoparticles shows the loading of the ligand to be approximately 2 mmol g^{-1}.

The activity of the nanoparticle-supported proline ligand **MNP-3** was first evaluated for the coupling reaction of *p*-bromoacetophenone with imidazole in *N*,*N*-dimethylformamide (DMF) at 110 °C in the presence of cesium carbonate[13] and CuI (10 mol%) catalyst. Gratifyingly, **MNP-3** (at 20 mol% loading) exhibited very high activity, allowing the quantitative conversion to product (Table 1, entry 1). The efficacy of the CuI/**MNP-3** system was further demonstrated with a variety of other *N*-heterocycles such as pyrazole, indole and benzimidazole providing the corresponding *N*-aryl products in good to excellent yields (Table 1, entries 2–4). Encouraged by these results, a variety of aryl and heteroaryl bromides were also treated with various *N*-heterocycles under the standard reaction conditions (Table 1, entries 5–16). The results indicated that both aryl and heteroaryl bromides work well, with the corresponding products in moderate to excellent yields. In addition, 2-bromopyridine and 2-bromothiophene both provide good yields of coupling products with the imidazole and the pyrazole (Table 1, entries 11–12, 14–15). However, the *N*-arylation of benzimidazole with 2-bromothiophene provides the target product in a slightly lower yield compared to 2-bromopyridine (Table 1, entries 13 and 16).

The recyclability of the magnetic nanoparticle-supported proline ligand **MNP-3** were also studied. After the completion of the reaction, the reaction mixture was diluted with ethyl acetate and the ligand was easily seperated from the product by exposure to a external magnet and decantation of the reaction solution. The remaining magnetic nanoparticles were further washed with the ethyl acetate to remove residual product and dried under vacuum and subjected to the next run. The recyclability of **MNP-3** was examined for the reaction of *p*-bromoacetophenone with the imidazole. As shown in Table 2, the nanoparticle-supported proline ligand can be reused up to four runs without any significant loss of activity.

Table 1 *N*-Arylation of *N*-heterocycles with aryl and heteroaryl bromides by CuI/**MNP-3**

Ar-Br + Het-NH	MNP-3 (20 mol%) CuI(10 mol%)	Ar-N-Het

Entry[a]	Substrate	Het-NH	Product	Yield[b] (%)
1				98
2				98
3				85
4				80
5				98
6				82
7				68
8				96
9				97
10				30
11				98
12				95
13				90
14				98
15				98
16				80

[a] All reactions were performed at 110 °C for 24 h in DMF (0.2 ml) with 0.1 mmol of aryl/heteroaryl bromide, 0.11 mmol of nitrogen heterocycle, CuI (10 mol%), **MNP-3** (20 mol%) and Cs$_2$CO$_3$ (2 equiv.). [b] Determined by ^{1}H NMR spectroscopy.

In summary, we have prepared a magnetic nanoparticle-supported proline ligand and demonstrated its application for the CuI catalyzed arylation of the nitrogen nucleophiles. This magnetic nanoparticle-supported proline ligand can easily be prepared by a click chemistry approach. Furthermore, it can be

Table 2 Recycling of **MNP-3** for the coupling reaction of *p*-bromoacetophenone with imidazole

Entry[a]	Recycle	Yield[b] (%)
1	1st	98
2	2nd	98
3	3rd	95
4	4th	93

[a] All reactions were performed at 110 °C for 24 h in DMF (0.2 ml) with 0.1 mmol of *p*-bromoacetophenone, 0.11 mmol of imidazole, CuI (10 mol%), **MNP-3** (20 mol%) and Cs_2CO_3 (2 equiv.). [b] Determined by ^{1}H NMR spectroscopy.

efficiently recovered from the reaction by decantation of the reaction mixture in the presence of the external magnet and used in up to four runs with little loss of activity. We believe that this magnetic nanoparticle-supported proline ligand can also be useful in biomedicine/biotechnology and drug delivery by acting as an anchor to further immobilized biomolecules and drug candidates. New investigations of magnetic nanoparticle-supported proline ligands are underway.

Notes and references

1 For recent reviews, see: (*a*) A.-H. Lu, E. L. Salabas and F. Schüth, *Angew. Chem., Int. Ed.*, 2007, **46**, 1222; (*b*) J. Fan and Y. Gao, *J. Exp. Nanosci.*, 2006, 457; (*c*) Y.-W. Jun, J.-S. Choi and J. Cheon, *Chem. Commun.*, 2007, 1203.

2 (*a*) D. Lee, J. Lee, H. Lee, S. Jin, T. Hyen and B. M. Kin, *Adv. Synth. Catal.*, 2006, **348**, 41; (*b*) S. Ding, Y. Xing, M. Radosz and Y. Shen, *Macromolecules*, 2006, **39**, 6399; (*c*) Y. Zheng, P. D. Stevens and Y. Gao, *J. Org. Chem.*, 2006, **71**, 537; (*d*) P. D. Stevens, G. Li, J. Fan, M. Yen and Y. Gao, *Chem. Commun.*, 2005, 4435.

3 (*a*) C. Ó. Dálaigh, S. A. Corr, Y. Gunko and S. J. Connon, *Angew. Chem., Int. Ed.*, 2007, **46**, 4329; (*b*) M. Kawamura and K. Sato, *Chem. Commun.*, 2006, 4718; (*c*) A. Hu, G. T. Yee and W. Lin, *J. Am. Chem. Soc.*, 2005, **127**, 12486; (*d*) L. Bromberg and T. A. Halton, *Ind. Eng. Chem. Res.*, 2005, **44**, 7991; (*e*) T.-J. Yoon, W. Lee, Y.-S. Oh and J.-K. Lee, *New J. Chem.*, 2003, **27**, 227.

4 R. Abu-Rezig, H. Alper, D. Wang and M. L. Post, *J. Am. Chem. Soc.*, 2006, **128**, 5279.

5 (*a*) J. C. Antilla, A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 11684; (*b*) A. Klapras, J. C. C. Antilla, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 7727.

6 (*a*) E. Alcalde, I. Dinares, S. Rodriguez and C. G. deMiguel, *Eur. J. Org. Chem.*, 2005, 1637; (*b*) E. K. Bekedam, G. M. Visser, A. van den Hoogenband, J. W. Terpstra, P. C. J. Kamer, P. W. N. M. van Leeuwena and G. P. F. van Srtijdoncka, *Tetrahedron lett.*, 2005, **46**, 2405.

7 Y. Xie, S. Pi, J. Wang, D. Yin and J. Li, *J. Org. Chem.*, 2006, **71**, 8324.

8 R. A. Altman and S. L. Buchwald, *Org. Lett.*, 2006, **8**, 2779.

9 H.-J. Cristau, P. P. Cellier, J.-F. Spindler and M. Taillefer, *Chem.–Eur. J.*, 2004, **10**, 5607.

10 (*a*) D. Ma and Q. Cai, *Synlett*, 2004, 128; (*b*) H. Zhang, Q. Cai and D. Ma, *J. Org. Chem.*, 2005, **70**, 5164; (*c*) X. Lu, Z. Wang and W. Bao, *Tetrahedron*, 2006, **62**, 4756.

11 L. Zhu, L. Cheng, Y. Zhang, R. Xie and J. You, *J. Org. Chem.*, 2006, **72**, 2737.

12 R. Massart, *IEEE Trans. Magn.*, 1981, **17**, 1247.

13 Other bases such as K_2CO_3, Na_2CO_3 and K_3PO_4 were found to be less effective compared to Cs_2CO_3.