Recyclable NHC-Ni Complex Immobilized on Magnetite/Silica Nanoparticles for C–S Cross-Coupling of Aryl Halides with Thiols

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Abstract: A new type of magnetite/silica nanoparticle-supported N-heterocyclic carbene nickel catalyst (Mag-NHC-Ni) was developed from imidazolium with *N*-picolyl moieties and used as an efficient catalyst in the C–S coupling of various aryl halides with thiols. Moreover, the catalyst was easily recovered from the reaction mixture by simple filtration and recycled with almost consistent activity.

Key words: heterogeneous catalysis, cross-coupling, magnetic nanoparticle, nickel

The formation of carbon–sulfur bonds is one of the important reactions in synthetic organic chemistry since aryl sulfides and their sulfur-containing derivatives show significant biological and pharmaceutical activities,¹ for example, as inhibitors of Alzheimer's and Parkinson's diseases,² anticancer reagents,³ and as a HIV-1 protease inhibitor.⁴

Although numerous synthetic methods have been developed in the past decades, traditional methods for the formation of carbon–sulfur bonds often require strong basic and harsh reaction conditions. To overcome these difficulties, many research activities have focused on the development of catalytic systems. Recently, transition-metalcatalyzed carbon–sulfur cross-coupling reactions have emerged as one of the most powerful approaches.⁵ Generally, palladium-,⁶ copper-,⁷ nickel-,⁸ and cobalt-based⁹ catalytic systems with appropriate ligands have been used for cross-coupling between aryl halides and thiols under basic conditions (Scheme 1). Also, iron-,¹⁰ indium-¹¹ and lanthanum-based¹² catalysts have been reported as effective systems very recently.



Scheme 1 Transition-metal-catalyzed C–S coupling reaction

However, the high cost and air sensitivity of Pd catalysts, and the often tedious procedure for the preparation of spe-

SYNLETT 2010, No. 16, pp 2518–2522 Advanced online publication: 26.08.2010 DOI: 10.1055/s-0030-1258545; Art ID: U06210ST © Georg Thieme Verlag Stuttgart · New York cially designed phosphine ligands, restrict their largescale application. Cu-mediated reaction systems sometimes require the use of copper salts at a higher than stoichiometric amount, at high temperature (>200 °C) and for a long reaction time. Co and Ni catalysts have common problems such as metal toxicity, low turnover number and the use of excess reagents. Moreover, most transitionmetal-catalyzed C–S coupling reactions are performed as a homogeneous process. Their tedious workup and catalyst non-recyclability have limited their applicability due to the high cost and limited scope of the reaction.

Consequently, there is a need to develop alternative, efficient and facile heterogeneous catalytic systems for simplified product isolation, easy recovery, thermal and air stability and recyclability. We have recently reported the preparation of a wide range of supported transition metals (e.g. Pd, Cu, Gd and Os) on polymers or silica materials as catalysts in a variety of reactions.¹³

Our interest in this area has led us to explore the immobilization of N-heterocyclic carbene-nickel (NHC-Ni) complex on magnetite/silica nanoparticles. Magnetic nanoparticles (MNPs) have been widely studied in various biological and medical applications. Furthermore, the use of MNPs as a support for catalysts¹⁴ is an emerging field due to their high surface area to volume ratios, the ability of easy dispersion and recovery from solution, high thermal stability, and the capability of surface modifications.15 NHCs have been widely applied to a number of organic transformations as alternatives to phosphine ligands due to their excellent σ -donor properties, ease of synthesis and variable bulkiness.¹⁶ However, as of yet, the NHCmetal complex-catalyzed C-S coupling reaction has not been well studied.¹⁷ To the best of our knowledge, this is the first report on the heterogeneous NHC-metal complex-catalyzed C-S coupling reaction of aryl halide with thiols for the formation of aryl sulfides.

Magnetic nanoparticles (MNPs) were readily prepared by a conventional co-precipitation procedure.¹⁸ Then, particles were coated with a thin layer of silica in order to prevent the aggregation of nanoparticles and the surface of MNPs having plenty of hydroxyl groups was easily modified with alkoxysilane reagents. As shown in Scheme 2, further modification of the surface of silica-coated MNPs



Scheme 2 Preparation of magnetite/silica nanoparticle-supported NHC-Ni catalyst

2 with excess imidazolinyl-functionalized triethoxysilane in refluxed toluene afforded **3**. Reaction mixtures were magnetically concentrated and washed with toluene and ethanol. As a chelate-carbene ligand, pyridinyl imidazole-2-ylidene ligand toward nickel ions has been reported recently¹⁹ due to the presence of a strong coordinating pyridinyl donor. Thus, we focused our attention on comparing two different substituent groups based on nitrogenous pyridine and normal benzene.

Simply, the appropriate imidazolinyl-functionalized MNPs were redispersed and mixed with 2-picolyl chloride or benzyl chloride at 80 °C in chloroform for 12 hours, thus affording **4** and **6**, respectively.



Figure 1 HR-TEM images (a) MNPs; (b) imidazolinyl functionalized on silica-coated MNPs (MNP-Si); (c) nickel complex immobilized MNPs, catalyst 5 [MNP-Si-NHC(Pyr)-Ni]; (d) catalyst 7 [MNP-Si-NHC(Bz)-Ni]

After washing, the loadings of imidazoles on MNP-Si were determined by their nitrogen contents by elementary analysis (**4**, 0.47 mmol/g; **6**, 0.67 mmol/g).

The procedure for the preparation of supported nickel catalyst was carried out by mixing the NHC ligand functionalized MNPs with Ni(acac)₂ at 60 °C in DMSO under basic conditions (Scheme 2).²⁰ High-resolution transmission electron microscopy (HRTEM) confirmed that the morphology of MNPs-based catalysts **5** and **7** was as shown in Figure 1.

It was observed that the silica shell was completely coated with MNPs, and that the morphology of the silica-coated MNPs was not changed during the preparation of Ni-immobilized catalyst. The existence of Ni was confirmed by EDX spectroscopy (data not shown). It was further analyzed by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) to confirm that the nickel content was 0.40 mmol/g for catalyst **5** [MNP-Si-NHC(Pyr)-Ni] and 0.26 mmol/g for catalyst **7** [MNP-Si-NHC(Bz)-Ni].

We explored the catalytic ability of catalyst **5** and catalyst **7** in the carbon–sulfur cross-coupling reaction of aryl halides with thiols, and the results are summarized in Table 1. Catalyst **5** underwent the C–S cross-coupling reaction with thiophenol, 4-methylbenzenethiol, and 4-methoxybenzenethiol (entries 1–3), affording the corresponding products in an 89–92% yield, whereas catalyst **7** mediated the same reaction with a yield of 86–88% after 10–12 hours. Furthermore, the reaction of thiophenol with aryl halides having electron-donating and -withdrawing substituent was investigated (entries 4–7) and afforded aryl sulfides with excellent yields. It should be noted that the reaction yield was not greatly influenced by the electronic properties of the substituent on the aryl halides or thiol substrates.



^a Reaction conditions: MNP-Si-NHC-Ni catalyst (10 mol%), aryl halide (1 mmol), thiol (1 mmol), Cs₂CO₃ (2 mmol), 100 °C in DMF (1 mL).

^b Isolated yield.

^c Catalyst **5** [MNP-Si-NHC(Pyr)-Ni] was used.

^d Catalyst 7 [MNP-Si-NHC(Bz)-Ni] was used.

However, as shown in Table 1, catalyst **5** was more effective in the reaction, and produced the desired product with good yield, whereas catalyst **7** showed comparatively lower catalytic activity. It was found that N-donor ligand with pyridine group can significantly enhance the catalyt-

ic activities of NHC-nickel complexes in the C–S crosscoupling reaction. Until recently, reported homogeneous catalyst was used only once, and could not be recycled. However, development of recoverable and reusable catalytic system has received a great deal of research attention. Thus, a reuse test of MNP-Si-NHC(Pyr)-Ni catalyst **5** was also performed for the reaction.

We chose the cross-coupling of 4-iodoacetophenone and thiophenol as the model reaction.

After completion of the each reaction, the catalyst was easily recovered by an external magnet (Figure 2), which was washed with ethyl acetate and reused directly in the next run. The catalytic activity of catalyst, **5** was almost unchanged during three repeated cycles.²²

In summary, we have described a simple and efficient catalytic reaction system for the C–S cross-coupling of aryl halides with thiols using NHC-nickel catalyst immobilized on magnetite/silica-nanoparticles. Product separation and catalyst isolation are easier and much simpler with the assistance of an external magnet, and the recovered catalyst was recycled up to three times without significant loss of catalytic activity.

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Figure 2 Magnetic separation and recycling of catalyst 5: (a) the reaction mixture; (b) recovery of catalyst 5 by an external magnet

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- (18) Synthesis of Silica-Coated Magnetic Particles: A twonecked round-bottomed flask (RBF) containing NH4OH (250 mL) and deionized (DI) H₂O (250 mL) was vigorously stirred with an overhead stirrer at 500 rpm. A freshly prepared aq solution of iron chloride (100 mL) containing FeCl₂·4H₂O (2.57 g, 12.93 mmol) and FeCl₃·6H₂O (6.18 g, 22.6 mmol) was dropwise mixed with NH₄OH solution for 30 min. The resultant mixture was stirred for additional 1 h at r.t., then the formed MNPs were separated using a magnet (4000 gauss). The MNPs were washed with DI $H_2O(20 \times)$ and MeOH $(5 \times)$ by repeating magnet separation and decantation. The MNPs (1.35 g) dried in vacuo were treated with 1% 3-aminopropyltriethoxysilane in CHCl₃ (80 mL) at 60 °C for 4 h. The aminated MNPs were washed with CHCl₃ $(10 \times)$ and MeOH $(5 \times)$ by repeating magnet separation and decantation. The MNPs (1 g) dried in vacuo (elemental analysis, N%: 0.382%, 0.27 mmol/g) were treated with 2% TEOS (tetraethyl orthosilicate) in EtOH and shaken at 30 °C for 12 h. The particles were washed with EtOH ($6 \times$) repeating magnet separation and decantation.
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- (20) Preparation of Catalyst 5 [MNP-Si-NHC(Pyr)-Ni] and Catalyst 7 [MNP-Si-NHC(Bz)-Ni]: The aforementioned magnetic nanoparticles (MNPs) were redispersed in toluene and the resulting solution was heated to reflux. Then, 1-(3triethoxysilylpropyl)-2-imidazoline was added. After 24 h, the solution was cooled to r.t. MNPs were concentrated magnetically by using an external permanent magnet and washed with toluene and EtOH. Imidazolinyl-functionalized MNPs were redispersed and reacted with 2-picolyl chloride or benzyl chloride at 80 °C in CHCl₃ for 12 h, affording 4 and 6. After washing, the loadings of imidazoles on MNP-Si were determined by their nitrogen contents by elementary analysis (4, 0.47 mmol/g; 6, 0.67 mmol/g). The NHC ligand functionalized MNPs were then redissolved in a mixture of Ni(acac)₂ at 60 °C in DMSO under basic conditions (Scheme 2). After 12 h, the mixture was cooled to r.t., and then catalyst 5 [MNP-Si-NHC(Pyr)-Ni] or catalyst 7 [MNP-Si-NHC(Bz)-Ni] were magnetically separated by using the external magnet. The prepared catalysts were washed with CHCl₃, EtOH, and H₂O subsequently.
- (21) General Procedure for C–S Cross-Coupling Reaction: To a mixture of 10 mol% of catalyst in DMF (1 mL) and Cs₂CO₃ (2 mmol) were added an aryl halide (1 mmol) and a thiol

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(1 mmol). The temperature was raised to 100 °C. After 10 h, the mixture was cooled to r.t. The used catalysts were removed magnetically by using an external permanent magnet and dried for reuse in the next round of reactions. The desired products were washed with H_2O and extracted with EtOAc. Then, the organic phase was evaporated in

vacuo and the residues were subjected to flash column chromatography purification.

(22) After the 4th run, unfortunately the coupling yields were decreased (ca. 10%) and leaching of nickel species was detected from the filtrates after the 4th run and the 5th run (14% and 18%, by ICP–AES analysis of the filtrate).