ORGANIC
LETTERS

2007
Vol. 9, No. 18
3495−3498

The First N-Heterocyclic Carbene-Based Nickel Catalyst for C–S Coupling

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Received May 28, 2007

ABSTRACT

We have developed the first N-heterocyclic carbene (NHC)-based transition metal catalysts for C–S coupling reactions. Ni–NHC catalysts showed good to excellent activities toward various aryl halides in C–S coupling reactions. The catalytic activities were greatly affected by the electronic and steric properties of the NHC ligands. The new catalysts were inexpensive, easy to synthesize, and environmentally friendly. They could be excellent candidates to replace Pd-organophosphanes for C–S coupling catalysis.

N-heterocyclic carbenes (NHCs) have emerged as an extremely useful class of ligands for transition-metal catalysis.[1] The striking similarity of electron-rich organophosphanes (PR_3) and NHCs, and NHCs' excellent σ-donating properties make them ligands of choice for transition metals. NHC-metal complexes have been successfully used in many processes, such as olefin metathesis,[2] C−C or C−N cross-coupling,[3] olefin hydrogenation,[4] transfer hydrogenation of ketones,[5] and also symmetric[6] or asymmetric[7] hydrosilylation reactions. However, it is surprising that no NHC-based metal catalyst has been developed for C−S coupling reactions. Organosulfur chemistry has been receiving increasing attention since sulfur-containing groups serve an important auxiliary function in organic synthetic sequences.[8] Aryl sulfides are also a common functional group in numerous pharmaceutically active compounds.[9] However, synthesis of the aryl−sulfur bond has been a challenge until the recent series of palladium organophosphane (Pd−PR_3) catalysts were developed by Migita,[10] Buchwald,[11] Hartwig,[12] and others.[13] The Pd−PR_3 catalysts suffered from some limita-

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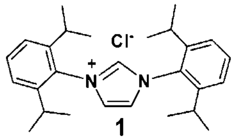
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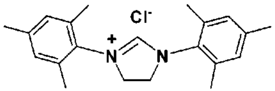
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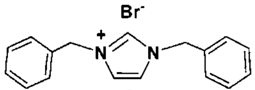
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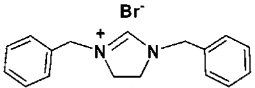
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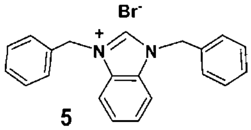
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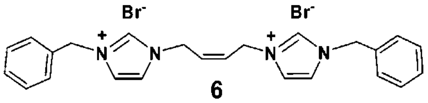
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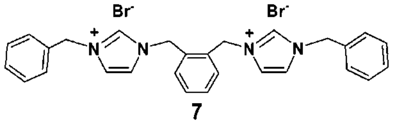
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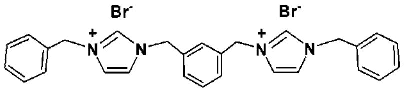
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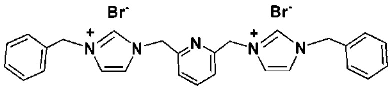
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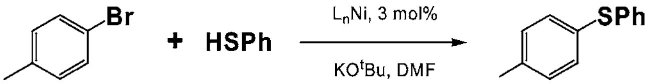
tions, including low turnover number,[10,11,13] high cost,[12] and the use of environmentally unfriendly PR_3 ligands. Several other transition-metal organophosphane-based catalysts have been developed,[14−16] but they also exhibit low activities and some other problems. For instance, the cobalt organophosphane catalyst needs excess zinc as reagent for catalyst reduction.[16] Herein we present the first NHC-ligated nickel catalyst for C−S coupling reaction. This Pd-free and PR_3-free catalyst showed excellent activities for a wide range of substrates.

Recently, Ni−NHC complexes have demonstrated that they can provide for efficient C−F and C−C bond activation.[17] It is also known that nickel complexes can catalyze C−S coupling, but good activities were only achieved with aryl iodides.[15] Ni−NHC catalyzed hydrothiolation of alkynes has also been reported.[18] With this in mind, Ni−NHC was examined as the catalyst for the coupling of thiols with aryl halides since NHCs share similar properties as organophosphanes. Thermochemical and computational studies on NHC complexes of nickel have shown that NHCs form stronger bonds to the metal center than phosphanes.[19] It was also known that the steric hindrance and strong electron-donating ligands could create more active catalysts for the Pd−PR_3 system.[12,20] Thus, we have investigated different types of NHC ligands and different NHC/Ni ratios in the coupling of 4-bromotoluene with thiophenol. The different types of Ni−NHC catalysts studied were all active in this coupling reaction. Strong electron-donating NHC generated from **3** showed the highest activity among NHCs **1**−**5** (Table 1). The catalytic activity was optimized at a NHC/Ni ratio of 2 (Table 1).[21,22]

Table 1. C−S Coupling Reactions over Ni−NHC Catalysts[a]



ligand (ligand/Ni ratio)	% yield[b]	ligand (ligand/Ni ratio)	% yield[b]
1 (1)	14	**2** (2)	54
3 (1)	56	**3** (2)	89 (56[c])
3 (3)	34	**4** (2)	65
5 (2)	52	**6** (1)	88 (65[c])
7 (1)	92 (78[c])	**8** (1)	92 (71[c])
8 (1) + **3** (1)	− (37[c])	**9** (1)	92 (68[c])

[a] Unless otherwise specified, the reaction conditions are 0.2 mmol of aryl halides, 0.22 mmol of thiols, 3 mol % of Ni catalyst, and 0.24 mmol of potassium *tert*-butoxide (KO^{t}Bu) in 1 mL of *N*,*N*-dimethylformamide (DMF), 100 °C, 16 h. [b] GC yields. [c] Reaction run using 1.5 mol % of Ni catalyst.

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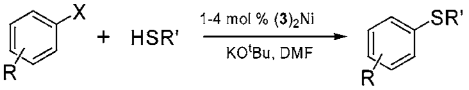
(21) Representative procedure for catalyst synthesis: $(\mathbf{3})_2$-Ni(0). An amount of 82.5 mg of $Ni(COD)_2$ (0.3 mmol) was added in a glovebox to a mixture of 195 mg of **3** (0.6 mmol) and 68 mg of KO^{t}Bu (0.6 mmol) in 10 mL of DMF. The mixture was stirred for 1 h at room temperature, and used as the catalyst stock solution for catalytic reactions.

Table 2. C−S Coupling Reactions over (**3**)$_2$-Ni(0) Catalyst[a]



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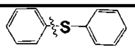
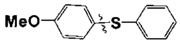
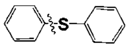
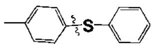
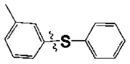
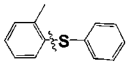
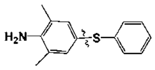
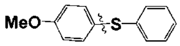
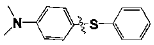
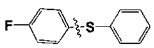
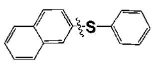
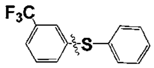
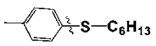
1	I	1	100		99
2	I	1.5	100		95
3	Br	3	110		99
4	Br	3	110		94
5	Br	3	110		93
6	Br	3	100		80
7	Br	4	110		96
8	Br	3	100		89
9	Br	3	100		90
10	Br	3	100		91
11	Br	3	100		94
12	Br	3	110		87
13	Br	1.5	100		78

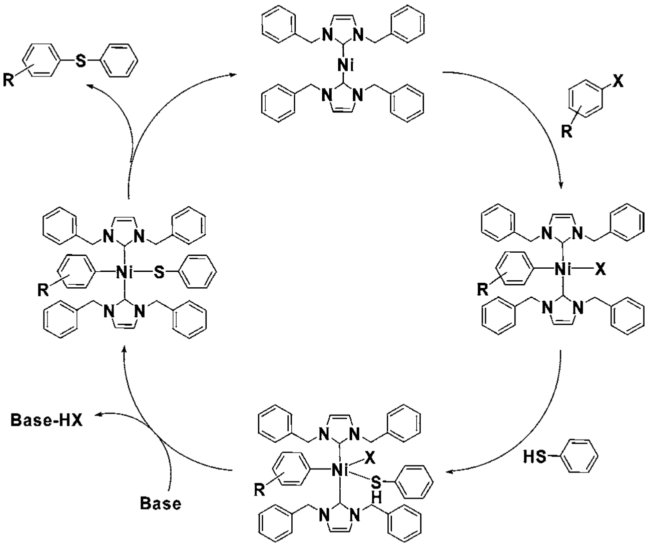
[a] Unless otherwise specified, the reaction conditions are 1 mmol of aryl halides, 1.05 mmol of thiols, 1.1 mmol of KO^{t}Bu in 5 mL of DMF, 16 h. [b] Isolated yields.

Furthermore, bridged bidentate NHC ligands **6**−**9** were prepared. Theoretically, the bidentate ligands would form more stable Ni complexes with a longer catalytic lifetime and prevent the formation of anionic or briding thiolate complexes (which might undergo slow reductive elimination as demonstrated in Pd−PR$_3$ systems).[12,17] Table 1 shows the catalytic results of the model reaction over catalysts with bidentate ligands derived from **6**−**9**. It was found that with 3 mol % of nickel catalysts, the activities of catalysts with bidentate ligands were similar or slightly higher than that of (**3**)$_2$-Ni (NHC/Ni = 2). However, when 1.5 mol % of nickel catalysts was used, the activities of catalysts derived from **6**−**9** were ~10 to 20% higher than that of (**3**)$_2$-Ni. No byproduct was observed over bidentate catalyst systems in contrast to ~3 to 5% symmetric byproduct obtained over (**3**)$_2$-Ni. Although the bidentate catalysts did not show significant increase in activity, they demonstrated greater stability compared to the monodentate catalysts. When more ligands were introduced in the reaction system, for instance, (**3**)$_3$-Ni or (**8** + **3**)-Ni, the catalytic activities decreased substantially. This indicated that steric hindrance from overcrowding or saturated coordination sphere of nickel center resulted in lower activities. Further modification of the steric and electronic properties of NHC ligand to balance the catalyst stability and activity would be critical toward developing superior catalytic systems.

Catalyst (**3**)$_2$-Ni was used for screening different substrates. It showed excellent activities for deactivated aryl iodides. Quantitative yields were achieved by using 1−1.5 mol % of Ni catalyst in DMF at 80 °C for thiophenol (Table 2, entries 1−2). For electron-rich aryl bromides, (**3**)$_2$-Ni also demonstrated high activities. Reactions of thiophenol with weaker bases (e.g., carbonate or phosphate) gave low conversions and undesired byproducts. When KO^{t}Bu (or NaO^{t}Bu) was used as the base, good to excellent yields were achieved for various substrates with 3−4 mol % of Ni catalyst (Table 2, entries 3−12). Good yield was also attained with alkyl thiol (Table 2, entry 13).

The mechanism of Pd−PR$_3$ catalysts in coupling reactions has been well studied.[20,23] Here, Ni−NHC catalysts are assumed to be undergoing the same oxidative addition[1c] and reductive elimination cycle (Scheme 1). Sterically hindered ligands are good in the reductive elimination step but would slow down the oxidative addition process. On the other hand,

Scheme 1



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(22) Representative experimental procedure for C−S coupling reaction (Table 2, entry 4). All reactions were performed in inert atmosphere. (**3**)$_2$-Ni solution (1 mL, 0.03 mmol of Ni), KO^{t}Bu (125 mg, 1.1 mmol), thiophenol (1.05 mmol), and 4-bromotoluene (1 mmol) were mixed with 3 mL of DMF in a reaction vial. The vial was capped, and the reaction mixture was stirred at 110 °C for 16 h. Yields were measured by gas liquid chromatography (GLC) and isolation of pure product. Products were confirmed by gas chromatography−mass spectrometry (GC−MS) and nuclear magnetic resonance (NMR).

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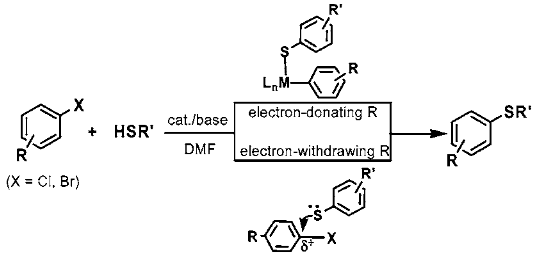
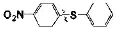
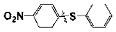
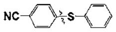
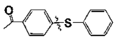
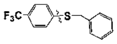
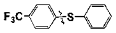
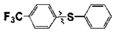
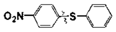
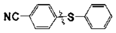
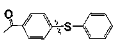
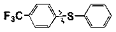
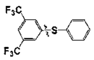
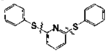
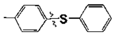
strong electron-donating ligands may help the oxidative addition of aryl halides but are not good in reductive elimination. Thus, tuning the steric hindrance and electron-donating properties of ligands is important for catalyst development.

Table 3. C−S Coupling of Electron-Poor Aryl Halides[a]



entry	X	catalyst (mol %)[c]	product	temp (°C)	base	time (h)	yield (%)[b]
1	Cl	Pd-xantphos (5)		> 100	Cs_2CO_3	15	85[13b]
2	Cl	—		80	Na_2CO_3	1	98
3	Cl	—		80	Na_2CO_3	1	97
4	Cl	—		80	NaO^{t}Bu	15	94
5	Cl	—		80	KO^{t}Bu	4	97
6	Cl	—		100	KO^{t}Bu	16	65
7	Cl	**3**-Ni (1.5)		80	KO^{t}Bu	16	87
8	Br	—		80	Cs_2CO_3	1	96
9	Br	—		80	NaO^{t}Bu	1	95
10	Br	—		80	NaO^{t}Bu	6	97
11	Br	—		100	KO^{t}Bu	16	95
12	Br	—		100	KO^{t}Bu	16	94
13	Br	—		100	KO^{t}Bu	16	95
14	Br	—		100	NaO^{t}Bu	16	0

[a] Unless otherwise specified, the reaction conditions are 1 mmol of aryl halides, 1.05 mmol of thiols, 1.1 mmol of KO^{t}Bu in 5 mL of DMF. [b] Isolated yields. [c] No catalyst was used in entries 2−6, 8−14.

Although it is known that activated aryl chlorides, such as *p*-nitrile chlorobenzene, can follow the nucleophilic substitution mechanism to form a C−S coupling product and do not need a catalyst, the competition between nucleophilic substitution and metal-catalyzed reductive elimination pathways to certain substrates remains unclear. A number of publications have reported that metal complexes catalyzed coupling of electron-poor aryl halides[13b,e,f,16] with thiols.[13g] However, we have found that control reactions between these aryl halides with thiols also gave good to quantitative yields of C−S coupling products under similar reaction conditions (Table 3). Under our reaction conditions, the rate of nucleophilic substitution pathway on most electron-poor sp^2 carbon was competitive with or higher than that of metal-catalyzed reductive elimination pathway. As shown in Table 3, reactions between 1-chloro(bromo)-4-nitrobenzene or 4-chloro(bromo)benzonitrile with thiols gave quantitative thioether in 1 h under relatively mild conditions (entries 1−3 and 8−9). This was obviously different from the literature report.[13b] Reactions between 4-chloro(bromo)acetophenone, 2,6-dibromopyridine, and 3,5-bis(trifluoromethyl)bromobenzene with thiophenol also gave quantitative yields in 8−16 h with a strong base. 4-Chloro(bromo)benzotrifluoride with thiophenol showed competitive reaction rates by two different reaction pathways. The reaction between 4-chlorobenzotrifluoride and benzylthiol with base was much faster (Table 3, entry 5). Without metal catalysts, no desired products were observed for reactions between electron-rich chloro(bromo)arenes with thiols (Table 3, entry 14).

In conclusion, the first NHC-based transition-metal catalysts have been developed for C−S coupling reactions. Ni−NHC catalysts showed good to excellent activities toward various aryl halides in C−S coupling reactions. The new catalysts were inexpensive, easy to synthesize, and environmentally friendly. They could be excellent candidates to replace Pd−PR_3 for this reaction. It was also found that the electronic and steric characteristics of NHC ligand greatly affected the catalytic activities. Further fine-tuning of NHC ligand to improve the catalyst performance and full characterization of the new system are in progress.

Acknowledgment. This work was supported by the Institute of Bioengineering and Nanotechnology (Biomedical Research Council, Agency for Science, Technology and Research, Singapore).

Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL071248X