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Nickel N-Heterocyclic Carbene Catalyst for Cross-Coupling of Neopentyl Arenesulfonates with Methyl and Primary Alkyl Grignard Reagents

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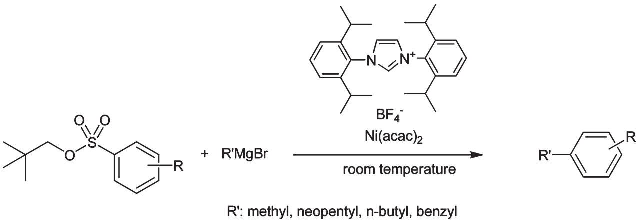

Nickel N-heterocyclic carbene (NHC) catalytic system prepared in situ by the reaction of Ni(acac)$_2$ with NHC precursor efficiently catalyzed the cross-coupling reaction of alkoxysulfonylarenes with methyl, neopentyl, and benzyl Grignard reagents at ambient temperature.

Transition metal-catalyzed cross-coupling reactions of organic electrophiles with organometallic reagents have been employed as a powerful synthetic tool for carbon−carbon bond formation in the construction of various types of organic compounds. Organic halides and pseudohalides containing a variety of sp-, sp^2-, and sp^3-hybridized C−X bonds (X = Cl, Br, I, OTf, etc.) have gained wide acceptance as electrophilic substrates in these reactions.[1]

Although tertiary phosphines still occupy a predominant place as the versatile ligands of the catalysts, more powerful electron-donating ligands have been investigated to increase the reactivity and efficiency.[2] Since Herrmann reported that palladium complexes of N-heterocyclic carbene (NHC) catalyzed the Heck reaction,[3] NHCs have emerged as attractive alternatives to phosphine ligands in catalytic transformations.[4] As NHCs, with their strong σ-donor effect combining with a shielding steric pattern, activate the oxidative addition step of transition metal-catalyzed reactions,[5] metal-NHC complexes have been recognized as highly reactive catalytic systems, especially for unactivated alkyl or aryl chlorides.[6]

Grignard reagents are one of the most widely adopted organometallic reagents[7] in the area of transition metal-catalyzed cross-coupling reactions. Accordingly, these metal-NHC complexes have often been applied for the reactions of organic electrophiles with Grignard reagents.[8] However, in reactions with NHC complexes, not only were the electrophilic compounds limited to organic halides, but also alkyl Grignard reagents have only rarely been applied.

While organosulfur compounds have not been commonly used as electrophilic substrates due to their relatively low reactivity, the recent developments of efficient catalysts and additives have begun to allow their desulfitative carbon−carbon cross-coupling reactions.[9] We previously reported that alkyloxysulfonyl moieties attached onto aromatic compounds could act as chemoselective leaving groups in reactions with aryl and primary alkyl Grignard reagents.[10] However, a large excess of Grignard reagents was still required, even at elevated temperatures, in order to overcome the low reactivity of the alkyloxysulfonyl group with common nickel catalysts. Therefore, a more electron-rich metal complex, capable of catalytic activity in an atom-economical manner at ambient temperature, is desirable.

Recently, we found that neopentyl arenesulfonates **1** readily undergo the cross-coupling reaction with relatively small amounts of methyl-, neopentyl-, and benzylmagnesium

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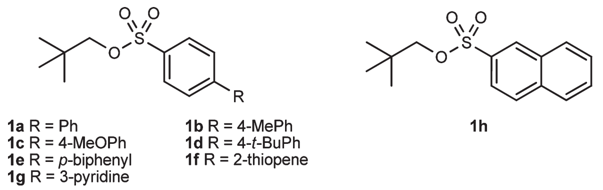
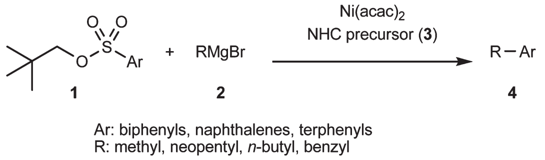


FIGURE 1. Structures of neopentyl arenesulfonates **1**.

SCHEME 1. Ni-NHC-Catalyzed Cross-Coupling Reaction of Arenesulfonates with Alkyl Grignard Reagents



bromides **2** in the presence of Ni(acac)$_2$ and NHC precursor **3** to produce the corresponding alkylarenes **4** at room temperature (Scheme 1). The results of these reactions are presented and discussed below.

Arenesulfonates **1** were prepared according to the procedure of our previous report (Figure 1).[11] The neopentyl group was selected to avoid the competitive substitution or elimination of arenesulfonate moiety in the reactions with alkyl Grignard reagents. NHC precursors **3**, 1,3-bis(2,6-diisopropylphenyl)imidazolium trifluoroborate (**3a**), and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (**3b**), and bis[1,3-di(2′,6′-diisopropylphenyl)imidazolin-2-ylidene]nickel(0) (Ni(IPr)$_2$, **5**) were prepared by a modified version of the literature procedure (Figure 2).[12]

The reaction of 4-biphenylsulfonate **1a** with methylmagnesium bromide (**2a**) was initially investigated in order to determine the optimum reaction conditions (Table 1). While the reaction gave a good yield in the presence of dppeNiCl$_2$ or dppfNiCl$_2$ (entries 1−2),[10] Ni(acac)$_2$ alone was a poor catalyst even at the elevated temperature (entry 3). However, its activity was dramatically increased by the addition of **3a** to facilitate the reaction to proceed at room temperature (entry 4). This indicated that the reactive Ni-NHC catalyst is generated in situ from Ni(acac)$_2$ and **3a**.

Although the NHC-coordinated metals were generally prepared and isolated prior to the coupling reactions, the catalytic complexes generated in situ from the transition metals and NHC precursors were also efficient in some coupling reactions.[13] Herrmann et al. first demonstrated the ability of the in situ generated Ni-NHC complexes to successfully mediate the cross-coupling reactions of aryl chlorides with arylmagnesium brimides and thereby afford unsymmetrical biaryls.[12b] Fort et al. also disclosed in situ preparation of Ni-NHC.[14]

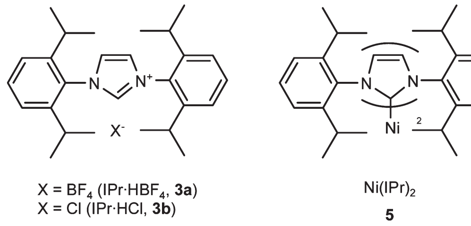
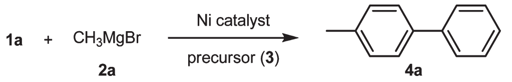


FIGURE 2. Structures of NHC precursors **3** and Ni-NHC catalyst **5**.

TABLE 1. Effect of Reaction Conditions on the Cross-Coupling of 1a with 2a[a]



entry	catalyst[b]	**2a** (equiv)	**3**	solvent	temp (°C)	yield (%)[c]
1	dppeNiCl$_2$	5	none	THF	67	92
2	dppfNiCl$_2$	5	none	THF	67	86
3	Ni(acac)$_2$	5	none	THF	67	22
4	Ni(acac)$_2$	5	**3a**	THF	25	99
5	none	5	**3a**	THF	67	no rxn
6	Ni(acac)$_2$	3	**3a**	THF	25	98
7	Ni(acac)$_2$	1.5	**3a**	THF	25	98
8	Ni(acac)$_2$	1.5	**3a**	DME	25	87
9	Ni(acac)$_2$	1.5	**3a**	Et$_2$O	25	84
10	Ni(acac)$_2$	1.5	**3b**	THF	25	96
11	**5**	1.5	none	THF	25	92
12	Ni(acac)$_2$	1.5	**3a**[d]	THF	25	85

[a] Reactions of **1a** (0.300 mmol) with **2a** were carried out in the indicated solvent (10 mL) by using the indicated catalyst (0.015 mmol) and **3** (0.015 mmol) at the indicated temperature for 12 h. [b] dppe = 1,2-bis(diphenylphosphino)ethane, dppf = 1,1′- bis(diphenylphosphino)-ferrocene. [c] Yields were determined by GC analyses, using naphthalene as an internal standard. [d] 0.0300 mmol of **3a** was used.

With only **3a**, the reaction did not proceed without a nickel catalyst (entry 5). Addition of 1.5 equiv of **2a** was sufficient for reaction completion (entry 7) because additional **2a** did not improve the reaction conversion by a meaningful margin (entries 4 and 6). THF was the best ethereal solvent in this catalytic system (entries 7−9). The counteranion of the salt **3** did not greatly influence the catalytic power of the resulting Ni-NHC catalyst, although the catalytic system with **3b** was slightly less efficient than that system with **3a** (entry 10).

The use of **5** prepared in advance exhibited a lower efficiency (entry 11). This was consistent with the superiority of the 1:1 mixture of Ni(acac)$_2$ and **3a** compared to the 1:2 mixture (entry 12). The zerovalent nickel coordinated by only one NHC ligand has been postulated as the catalytically active species.[12,14] In summary, the best results in the optimization studies were obtained by using 1.5 equiv of **2a** in the presence of Ni(acac)$_2$ and **3a** in THF at room temperature.

Cross-coupling reactions were performed between various arenesulfonates **1** and alkyl Grignard reagents **2** under the optimized conditions, and the results are summarized in Table 2. Arenesulfonates **1** underwent reaction with **2a** to produce the corresponding methylarenes, **4a−h**, in high yields within 12 h at ambient temperature (entries 1−8). Neopentylmagnesium bromide (**2b**), not possessing a β-hydrogen to magnesium, also showed high reactivity toward the arensulfonates **1a−c** and **1e** to produce the

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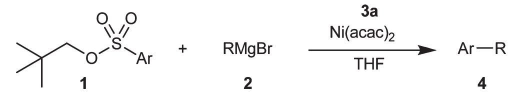
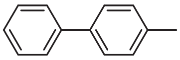
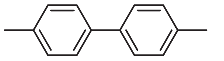
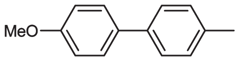
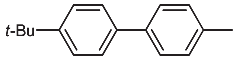
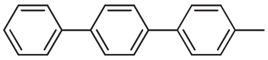
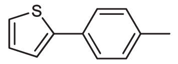
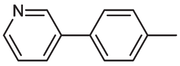
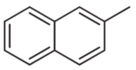
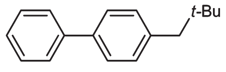
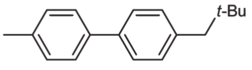
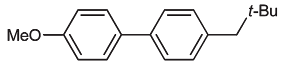
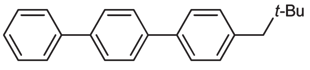
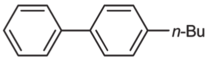
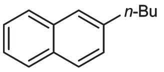
TABLE 2. Coupling Reactions of 1 with 2[a]



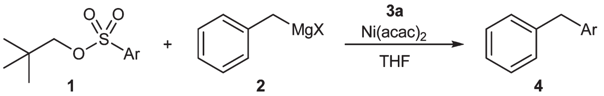
entry	1	2[b]	product 4		yield (%)[c]
1	**1a**	**2a**		**4a**	92
2	**1b**	**2a**		**4b**	94
3	**1c**	**2a**		**4c**	93
4	**1d**	**2a**		**4d**	92
5	**1e**	**2a**		**4e**	90
6	**1f**	**2a**		**4f**	85
7	**1g**	**2a**		**4g**	83
8	**1h**	**2a**		**4h**	97[d]
9	**1a**	**2b**		**4i**	84
10	**1b**	**2b**		**4j**	86
11	**1c**	**2b**		**4k**	76
12	**1e**	**2b**		**4l**	78
13	**1a**	**2c**		**4m**	15[d]
14	**1h**	**2c**		**4n**	13[d]

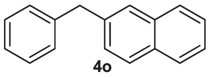
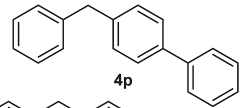
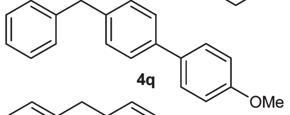
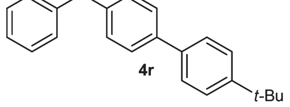
[a] Reactions of sulfonates **1** (0.300 mmol) with **2** (0.450 mmol) were carried out in THF (10 mL) by using Ni(acac)$_2$ (0.015 mmol) and **3a** (0.015 mmol) at room temperature for 12 h. [b] **2a** = methylmagnesium bromide; **2b** = neopentylmagnesium bromide; **2c** = *n*-butylmagnesium chloride. [c] Yields based on **1**. [d] Yields were determined by GC analyses, using *p*-terphenyl as an internal standard.

neopentylarenes **4i**−**l** in good yields (entries 9−12). However, reactions of *n*-butylmagnesium chloride (**2c**) with **1a** and neopentyl 2-naphthalenesulfonate (**1h**) proceeded via the competition between the cross-coupling reaction and the hydrogenolysis, with the latter dominating by a 5-fold factor, presumably due to the β-hydride elimination (entries 13 and 14).

Cross-coupling reactions between **1** and benzyl Grignard reagents **2d**,**e**, which showed low reactivity toward dppe-NiCl$_2$ in our previous report,[10a] were performed with this catalytic system (Table 3). Although 1.5 equiv of benzylmagnesium bromide (**2d**) was insufficient to complete the reaction (entry 1), the reaction with 3 equiv of **2d** afforded a good yield within 3 h under the standard reaction condition (entry 2). Benzylmagnesium chloride (**2e**) was less reactive than **2d** (entry 3). When three arenesulfonates, **1a**, **1c**, and **1d**, were allowed to react with **2d**, the corresponding coupled products **4p**−**r** were produced in good yields (entries 4−6). Their low reactivity toward traditional nickel catalysts supports the potential value of this Ni-NHC catalytic system.

TABLE 3. Coupling Reactions of 1 with Benzyl Grignard Reagents[a]



entry	1	2[b]	product 4	yield (%)[c]
1[d]	**1h**	**2d**	 **4o**	46
2	**1h**	**2d**	**4o**	88
3	**1h**	**2e**	**4o**	68
4	**1a**	**2d**	 **4p**	82
5	**1c**	**2d**	 **4q**	78
6	**1d**	**2d**	 **4r**	83

[a] Reactions of sulfonates **1** (0.300 mmol) with **2** (0.900 mmol) were carried out in THF (10 mL) by using Ni(acac)$_2$ (0.015 mmol) and **3a** (0.015 mmol) at room temperature for 12 h . [b] **2d**: X = Br; **2e**: X = Cl. [c] Yields based on **1**. [d] 0.450 mmol of **2** was used.

In summary, the Ni-NHC catalyst generated in situ by the reaction of Ni(acac)$_2$ with NHC precursor efficiently catalyzed the cross-coupling reaction of alkoxysulfonylarenes with methyl, neopentyl, and benzyl Grignard reagents. The reactions rapidly proceeded to afford high yields with only 1.5 equiv of methyl and neopentyl nucleophiles at room temperature. Moreover, 3 equiv of benzyl Grignard reagents, which showed low reactivity toward traditional catalysts, successfully underwent reaction at room temperature. This reaction provides an efficient synthetic route for alkylarenes, via the mild and versatile transformation of various arenesulfonates. The application of this catalytic system to solid-phase organic synthesis is currently under investigation.

Experimental Section

General Procedure for the Preparation of Arenesulfonates. To 2,2-dimethyl-1-propanol (58.7 mmol) in chloroform (50 mL) at 0 °C were added pyridine (9.28 g, 117 mmol) dropwise over a period of 20 min and arenesulfonyl chloride (39.0 mmol) in small portions. The reaction mixture was stirred at room temperature for 12 h and diluted with EtOAc. The organic layer was washed with 1% aqueous HCl, water, and brine, dried over MgSO$_4$, and concentrated in vacuo. The crude sulfonates were purified by recrystallization.

General Procedure for the Preparation of Neopentyl Biphenylsulfonates (1). To the solution of neopentyl 4-bromobenzenesulfonate (5.22 mmol) and Pd(PPh$_3$)$_4$ (0.157 mmol) in toluene (12.0 mL) was added 2.0 M aqueous Na$_2$CO$_3$ (6.0 mL) under Ar atmosphere. To the resulting mixture was added arylboronic acid (5.74 mmol), which was dissolved in ethanol (3.0 mL). The reaction mixture was heated at reflux for 7 h with vigorous stirring and diluted with EtOAc (100 mL). The organic layer was washed with 1% aqueous HCl, water, and brine, dried over

$MgSO_4$, filtrated through a small pad of silica gel in a sintered glass filter, and concentrated in vacuo. The crude compound was purified by recrystallization from *n*-hexane to give **1** as a white solid. The sulfonates **1a**−**c** and **1e** were identified according to the literature.[11]

General Procedure for Cross-Coupling Reactions of 1 with 2a, 2b, and 2c. To a stirred solution of **1** (0.300 mmol), Ni(acac)$_2$ (0.0150 mmol), and **3a** (0.0150 mmol) in THF (10.0 mL) was slowly added Grignard reagents **2** (0.450 mmol) at room temperature under an Ar atmosphere. The reaction mixture was stirred at room temperature for 12 h. The resulting mixture was diluted with Et_2O. The organic layer was washed with 1% aqueous HCl, water, and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude biphenyls **4** were purified by column chromatography.

General Procedure for Cross-Coupling Reactions of 1 with 2d and 2e. To a stirred solution of **1** (0.300 mmol), Ni(acac)$_2$ (0.0150 mmol), and **3a** (0.0150 mmol) in THF (10.0 mL) was slowly added Grignard reagents **2** (0.900 mmol) at room temperature under an Ar atmosphere. The reaction mixture was stirred at room temperature for 3 h. The resulting mixture was diluted with Et_2O. The organic layer was washed with 1% aqueous HCl, water, and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude products **4** were purified by recrystallization in 2-propanol.

Supporting Information Available: Synthetic procedures, characterization data, and copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.