

Nickel-Catalyzed Biaryl Coupling of  
Heteroarenes and Aryl Halides/Triflates

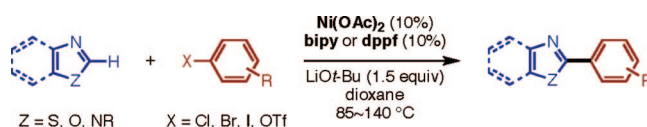
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## ABSTRACT



Ni-based catalytic systems for the arylation of heteroarenes with aryl halides and triflates have been established.  $\text{Ni}(\text{OAc})_2/\text{bipy}$  is a general catalyst for aryl bromides/iodides, and  $\text{Ni}(\text{OAc})_2/\text{dpfp}$  is effective for aryl chlorides/triflates. Thiazole, benzothiazole, oxazole, benzoxazole, and benzimidazole are applicable as heteroarene coupling partners. A rapid synthesis of febuxostat, a drug for gout and hyperuricemia, is also demonstrated.

Heterobiaryl species are omnipresent in natural products and pharmaceuticals and are frequently used in organic materials or as ligands for metals.<sup>1</sup> Therefore, the development of efficient methods to connect heteroarene and arene nuclei has been a topic of immense importance in chemical synthesis.<sup>2</sup> Although the Pd-catalyzed cross-coupling reactions of metalated arene/heteroarene and halogenated arene/heteroarene species are undoubtedly among the most important and reliable methods for making heterobiaryls,<sup>3</sup> the C–H bond arylation of heteroarenes holds significant potential to streamline overall synthetic routes.<sup>4</sup> The importance of such processes is also connected with an apparent significance of catalytic C–H bond functionalization in

chemical synthesis.<sup>5</sup> Indeed, this quest has been the driving force behind enormous efforts in the synthetic community including our group,<sup>6</sup> culminating in a wealth of useful catalytic systems employing Pd,<sup>7</sup> Rh,<sup>8</sup> Ru,<sup>9</sup> and Ir<sup>10</sup> for the C–H bond arylation of heteroarenes with aryl electrophiles.<sup>11</sup>

More recently, efforts geared toward the use of inexpensive metal catalysts have appeared. Daugulis and Miura reported independently that certain copper salts can catalyze the cross-coupling of heteroarenes with haloarenes.<sup>12</sup> These reactions are most effective with iodoarenes, but examples using moderately activated bromides and chlorides have also been demonstrated. Gaunt disclosed an interesting Cu-catalyzed indole arylation using diaryl-iodine(III) reagents.<sup>12f</sup> We also reported that  $\text{Cu}(\text{O}(\text{COCF}_3)_2)_2$  can promote the oxidative cross-coupling of electron-rich arenes and heteroarenes with arylboronic acids.<sup>6c</sup> Iron-catalyzed oxidative cross-coupling reactions of arenes and arylmetals have been developed by

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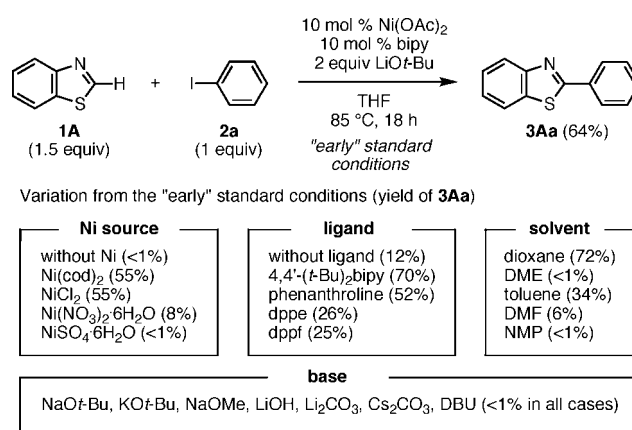
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Nakamura and Yu.<sup>13</sup> We report herein our finding that a nickel complex can catalyze the arylation of heteroarenes (azoles) with aryl halides and triflates.<sup>14,15</sup>

We began our study by examining various nickel salts, ligands, and basic additives in the reaction of benzothiazole (1A) and iodobenzene (2a). After extensive screening, we determined that Ni(OAc)<sub>2</sub>/2,2'-bipyridyl (bipy) serves as an

efficient catalyst in the presence of LiOt-Bu. For example, the cross-coupling product 2-phenylbenzothiazole (3Aa) was obtained in 64% yield when the reaction was carried out in THF at 85 °C for 18 h, representing our “early” standard conditions (Scheme 1).<sup>16</sup>

**Scheme 1.** Discovery of Ni Catalysis and Influence of Parameters



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Listed in Scheme 1 are some examples of variations from the “early” standard conditions. In the absence of nickel, essentially none of the desired coupling was observed. Nickel complexes such as Ni(cod)<sub>2</sub> (55%) and NiCl<sub>2</sub> (55%) were moderately effective, but Ni(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O and NiSO<sub>4</sub>·6H<sub>2</sub>O were by far less effective. We also determined that bidentate nitrogen-based ligands furnish efficient catalysts. Whereas bipy (64%), 4,4'-(*t*-Bu)<sub>2</sub>bipy (70%), and phenanthroline (52%) promoted the coupling, diphosphines such as dppe<sup>17</sup> and dppf<sup>17</sup> were less efficient under these conditions. The coupling proceeded slightly better in dioxane (72%), but DME, toluene, DMF, and NMP were unsuitable solvents. The choice of basic additive turned out to be most critical: when LiOt-Bu was replaced by other bases such as NaOt-Bu, KOt-Bu, NaOMe, LiOH, Li<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, and DBU, essentially none of the target product was produced. A dramatic difference between LiOt-Bu and its sodium and potassium analogues is notable. In view of efficiency, cost, simplicity, and stability, we identified Ni(OAc)<sub>2</sub>/bipy/LiOt-

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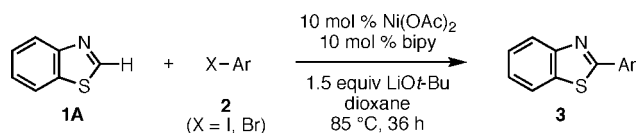
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Bu/dioxane/85 °C as our standard conditions for the coupling using aryl iodides and bromides.

With an efficient Ni(OAc)<sub>2</sub>/bipy catalyst in hand, the scope of applicable aryl electrophiles was examined (Table 1).

**Table 1.** Ni(OAc)<sub>2</sub>/bipy-Catalyzed Arylation of Benzothiazole with Aryl Bromides and Iodides<sup>a</sup>



entry	2	X	3 (isolated yield)
1		X = I	<b>3Aa</b> (80%)
2		X = I	<b>3Aa</b> (51%) <sup>b</sup>
3		X = Br	<b>3Aa</b> (62%)
4		X = I	<b>3Ab</b> (90%)
5		X = Br	<b>3Ab</b> (82%)
6		X = I	<b>3Ac</b> (71%)
7		X = Br	<b>3Ac</b> (63%)
8		X = I	<b>3Ad</b> (69%)
9		X = Br	<b>3Ad</b> (48%)
10			<b>3Ae</b> (91%)
11		<i>o</i> -	<b>3Af</b> (65%)
12		<i>p</i> -	<b>3Ag</b> (70%)
13		<i>m</i> -	<b>3Ah</b> (75%)
14		<i>p</i> -	<b>3Ai</b> (68%)
15			<b>3Aj</b> (78%)
16			<b>3Ak</b> (51%)
17			<b>3Al</b> (61%)
18			<b>3Am</b> (91%)
19			<b>3An</b> (57%)
20			<b>3Ao</b> (74%)
21			<b>3Ap</b> (58%)

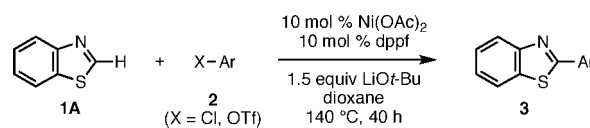
<sup>a</sup> Conditions: **1A** (0.75 mmol), **2** (0.50 mmol), Ni(OAc)<sub>2</sub> (0.05 mmol), 2,2'-bipyridyl (0.05 mmol), LiOt-Bu (0.75 mmol), dioxane (2 mL), 85 °C, 36 h. <sup>b</sup> Reaction at 100 °C for 48 h with 1 mol % of Ni catalyst.

Various electronically and structurally diverse aryl iodides and bromides reacted with **1A** to give the corresponding heterobiaryls **3** in moderate to excellent isolated yields.<sup>18</sup> Both electron-rich and electron-deficient aryl iodides/

bromides can be used as aryl electrophiles. Severe steric hindrance imposed by *ortho*-substitution is tolerated. Heteroaryl iodides and bromides are also reactive. The reaction also takes place with catalyst loading as low as 1 mol % of Ni (entry 2).

On the basis of these findings, we next aimed to extend the scope of aryl electrophiles to more challenging aryl chlorides and triflates. Interestingly, the Ni(OAc)<sub>2</sub>/dppf system, which was found to be less effective for iodobenzene at 85 °C (Scheme 1), is able to catalyze the arylation of benzothiazole with aryl chlorides and triflates in dioxane at 140 °C, whereas the Ni(OAc)<sub>2</sub>/bipy system is ineffective for these substrates even at 140 °C.<sup>19</sup> Preliminary results are shown in Table 2.<sup>18,20</sup>

**Table 2.** Ni(OAc)<sub>2</sub>/dppf-Catalyzed Arylation of Benzothiazole with Aryl Chlorides and Triflates<sup>a</sup>



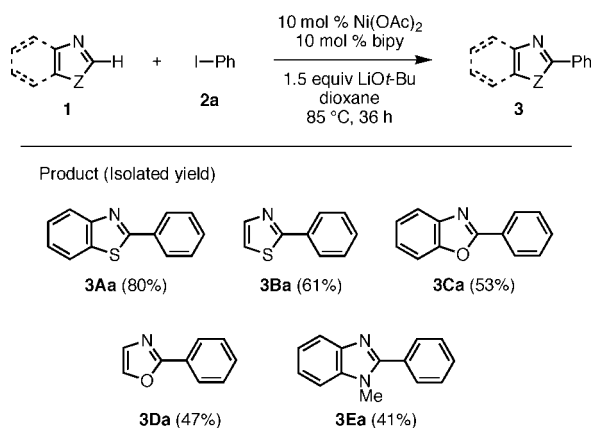
entry	2	X	3 (isolated yield)
1		X = Cl	<b>3Aa</b> (74%)
2		X = OTf	<b>3Aa</b> (48%)
3			<b>3Ab</b> (85%)
4			<b>3Aq</b> (65%)
5			<b>3Ao</b> (58%)

<sup>a</sup> Conditions: **1A** (0.75 mmol), **2** (0.50 mmol), Ni(OAc)<sub>2</sub> (0.05 mmol), dppf (0.05 mmol), LiOt-Bu (0.75 mmol), dioxane (2 mL), 140 °C, 40 h.

The scope of applicable heteroarenes (azoles) under Ni(OAc)<sub>2</sub>/bipy catalysis is presented in Scheme 2. Other than benzothiazole, thiazole (**1B**), benzoxazole (**1C**), oxazole (**1D**), and *N*-methylbenzimidazole (**1E**) were found to be arylated at the 2-position in moderate yields. In the case of thiazole and oxazole, only the monoarylated product was obtained.<sup>21</sup>

Although the mechanism of these reactions remains unknown, one possibility involves Ni<sup>0</sup>/Ni<sup>II</sup> redox catalysis via (i) oxidative addition of an aryl electrophile (Ar-X) to Ni<sup>0</sup> (generated in situ) to form Ar-Ni<sup>II</sup>-X, (ii) metalation of a heteroarene (Het-H) generating Ar-Ni<sup>II</sup>-Het, and (iii) reductive elimination of a heterobiaryl (Het-Ar) with the regeneration of Ni<sup>0</sup> species. The heteroarene nickelation (step ii) could be either (a) deprotonation of heteroarene with LiOt-Bu, followed by transmetalation with Ar-Ni<sup>II</sup>-X or (b) concerted metalation–deprotonation of heteroarene with Ar-Ni<sup>II</sup>-Ot-Bu, which could possibly be generated from Ar-Ni<sup>II</sup>-X and LiOt-Bu. If the former mechanism is operative, the current biaryl coupling would be tantamount to an in situ cross-coupling

## Scheme 2. Scope of Heteroarene Coupling Partners<sup>a</sup>

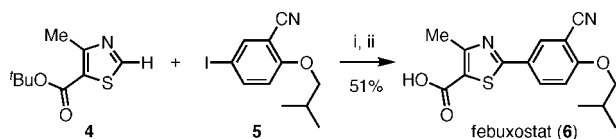


<sup>a</sup> Conditions: **1** (0.75 mmol), **2a** (0.50 mmol), Ni(OAc)<sub>2</sub> (0.05 mmol), 2,2'-bipyridyl (0.05 mmol), LiOt-Bu (0.75 mmol), dioxane (2 mL), 85 °C, 36 h.

of heteroaryllithiums and aryl electrophiles. Considering the limited success in applying organolithium reagents to cross-coupling processes, the system described herein should hold considerable synthetic potential.<sup>22</sup>

To demonstrate the synthetic utility of the present Ni-catalyzed biaryl coupling, a rapid synthesis of febuxostat (**6**) was examined (Scheme 3). Febuxostat is a novel, nonpurine,

## Scheme 3. Rapid Synthesis of Febuxostat<sup>a</sup>



<sup>a</sup> Conditions: (i) **4** (1.5 equiv), **5** (1.0 equiv), Ni(OAc)<sub>2</sub> (10 mol %), bipy (10 mol %), LiOt-Bu (1.5 equiv), dioxane, 100 °C, 40 h; (ii) CF<sub>3</sub>CO<sub>2</sub>H, CH<sub>2</sub>Cl<sub>2</sub>.

selective inhibitor of xanthine oxidase, which is effective for the treatment of gout and hyperuricemia.<sup>23,24</sup> Under the

(16) Typically, anhydrous Ni(OAc)<sub>2</sub> is generated by the dehydration of Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O, which is more inexpensive.<sup>18</sup> When Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O was used without pretreatment, **3Aa** was obtained in 23% yield.

(17) dppe = 1,2-bis(diphenylphosphino)ethane; dppf = 1,1'-bis(diphenylphosphino)ferrocene.

(18) **General Procedure.** A 20-mL glass vessel equipped with J. Young O-ring tap containing a magnetic stirring bar and Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O (10.6 mg, 0.05 mmol) was dried with a heatgun under vacuum and filled with argon after cooling to room temperature. To this vessel were added bipy or dppe (0.05 mmol), LiOt-Bu (60.0 mg, 0.75 mmol), heteroarene **1** (0.75 mmol), and haloarene **2** (0.50 mmol), followed by dry 1,4-dioxane (2.0 mL). The vessel was sealed with an O-ring tap and then heated (85–140 °C) in an eight-well reaction block with stirring. After cooling to room temperature, the mixture was passed through a short silica gel pad (EtOAc). The filtrate was concentrated, and the residue was subjected to preparative thin-layer chromatography (hexane/EtOAc) to afford a coupling product **3**.

influence of the Ni(OAc)<sub>2</sub>/bipy catalyst and LiOt-Bu, thiazole **4** and iodoarene **5** underwent cross-coupling in dioxane at 100 °C, furnishing the corresponding coupling product. Subsequent treatment with CF<sub>3</sub>CO<sub>2</sub>H afforded febuxostat (**6**) in 51% overall yield. The synthesis is extremely efficient, as both of the coupling components (**4** and **5**) can be quickly derivatized in one step from commercially available 4-methyl-5-thiazolecarboxylic acid and 2-fluoro-5-iodobenzonitrile, respectively (see Supporting Information).

In summary, we have uncovered nickel catalysis for the coupling of heteroarenes (azoles) and aryl electrophiles. Selective coupling of aryl bromides/iodides can be realized with Ni(OAc)<sub>2</sub>/bipy, whereas Ni(OAc)<sub>2</sub>/dppf is effective for the reaction using aryl chlorides/triflates. Regardless of the mechanism of action, the present method has the significant advantage that it employs inexpensive, air-stable Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O as the catalyst precursor.<sup>25</sup> The successful rapid synthesis of febuxostat speaks well for the potential of the present Ni catalysis in a range of synthetic applications.

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

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(19) Ni(OAc)<sub>2</sub>/dppf is effective for aryl iodides/bromides at 140 °C.

(20) In entries 3–5, **3Aa** (a phenyl group transfer product from dppe) was not observed.

(21) Under current conditions, the following heteroarenes proved to be unreactive: 1-methylpyrrole, 1-phenylpyrazole, 3-methoxythiophene. A full scope of applicable (hetero)arenes will be reported in due course.

(22) For successful/unsuccessful examples of organolithium cross-coupling, see: (a) Murahashi, S.-I. *J. Organomet. Chem.* **2002**, 653, 27. (b) Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc.* **1977**, 99, 4833. (c) Bumagin, N. A.; Ponomaryov, A. B.; Beletskaya, I. P. *J. Organomet. Chem.* **1985**, 291, 129. (d) Pelter, A.; Rowlands, M.; Clements, G. *Synthesis* **1987**, 51. (e) Negishi, E.-I.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, 109, 2393. (f) Itami, K.; Mineno, M.; Muraoka, N.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, 126, 11778. (g) Jhaveri, S. B.; Carter, K. R. *Chem.-Eur. J.* **2008**, 14, 6845.

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(24) Febuxostat has already been approved for use in Europe, and the FDA's Arthritis Advisory Committee has recently recommended approval for use in the U.S. If approved, febuxostat will be the first new treatment for the management of gout-associated hyperuricemia in more than 40 years.

(25) The price of representative catalyst precursors in arene arylation (Strem Chemicals, Inc.): Ni(OAc)<sub>2</sub>·4H<sub>2</sub>O (\$126 for 1 kg), CuI (\$102 for 500 g), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (\$116 for 5 g), Pd(OAc)<sub>2</sub> (\$678 for 25 g), [RhCl(CO)<sub>2</sub>]<sub>2</sub> (\$610 for 2 g).