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Nickel-Catalyzed Coupling of Azoles with Aromatic Nitriles

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Abstract

This manuscript describes the Ni-catalyzed coupling of azoles with aromatic nitriles. The use of BPh₃ promotes these arylations with electronically diverse oxazoles and benzonitriles. While the nickel catalyst is necessary for the arylations of phenyl oxazoles, arylation of benzoxazoles with some nitriles affords the arylated products even in the absence of the Ni-catalyst albeit in lower yield than the catalyzed process. The scope and rates of the Ni-catalyzed process are higher than the uncatalyzed transformation.

Graphical abstract

Diverse aromatic nitriles are relatively inexpensive, bench stable and commercially available.¹ Furthermore, the robust CN group is retained in many transition metal-catalyzed reactions, thereby enabling the late stage derivatization of this functionality in a multi-step synthesis.¹ Despite these advantages, only a few sporadic reports on biaryl synthesis using aromatic nitriles have been published.² These include Ni-catalyzed cross-couplings of aryl nitriles with aryl magnesium,^{2b} boron^{2c} or manganese reagents^{2d}. As part of our program on transition metal catalyzed arylations,³ this manuscript describes the hitherto unknown biaryl formation via Ni-catalyzed direct arylation using aromatic nitriles. These arylations expand the repertoire of electrophiles for Ni-catalyzed C–H arylations, which are thus far limited to the use of aryl halides, phenolic, and ester electrophiles.^{4,5,6,7} Importantly, previous reports on Ni-catalyzed direct arylations demonstrate the preferential functionalization of the pivalate, carbamate or chloride leaving groups in the presence of an aryl nitrile.^{5c,e} Hence, the method described herein may enable selective arylations of the pivalate (or chloride and carbamate) and nitrile leaving groups at different stages in a multi-step synthesis. Furthermore, the arylations detailed in this manuscript are a timely contribution to the recent surge in interest for the development of transformations using earth-abundant metal catalysts.^{4,8}

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The commonly proposed mechanism for nickel-catalyzed direct arylation involves three key steps: oxidative addition, C–H activation, and reductive elimination.^{4,9} Although biaryl synthesis via C–H arylation using nitriles has remained elusive, the three elementary steps in the mechanism are individually documented using nickel complexes, thereby supporting the feasibility of the proposed arylations.¹⁰

Our studies commenced with the investigation of reaction parameters for the arylation of phenyl oxazole **1** with 3-trifluoromethylbenzonitrile. These explorations began with the use of catalyst/ligand combinations that have been previously successful for Ni-catalyzed direct arylations.^{4,5} As shown in Table 1, product **1a** is obtained in moderate yield using Ni(COD)₂/dcype catalyst combination in the presence of Cs₂CO₃ as the base and diglyme as the solvent at 140 or 160 °C (entries 1 and 2). Ligands similar to dcype afford lower or comparable yields of the desired product.¹¹ Use of 1.5 equivalents of either Cs₂CO₃ or K₃PO₄ affords similar yields of **1a** (entries 1 and 3). However, increased amount of K₃PO₄ leads to enhanced yields of **1a** (entries 3 and 4). Lower catalyst loadings result in diminished yields of **1a** over 24 or 48 h (entries 5 and 6). Previous reports on Ni-catalyzed cross-couplings use Lewis acids to accelerate the transformations involving aryl nitriles.¹² Hence, a number of Lewis acids (CuF₂, ZnCl₂, Al–Me₂Cl, BPh₃) were evaluated for the formation of **1a**. This study revealed that the use of BPh₃ (40 mol %) affords **1a** with lower catalyst loadings (10 mol % Ni(COD)₂) in yields comparable to that obtained in the absence of BPh₃ with 20 mol % Ni(COD)₂ (cf. entries 4 and 10). Use of 40 or 60 mol % BPh₃ affords similar yields of **1a** (entries 10 and 11). No product is obtained in the absence of Ni(COD)₂ both in the presence and absence of BPh₃ (entries 8, 9 and 12). To obtain preliminary insight into the role of BPh₃, we monitored the reaction profile of arylations with and without BPh₃ using 10 mol % Ni(COD)₂.¹¹ These studies show that the reaction without BPh₃ levels off at about 30% yield of **1a** after 1 h. However, the arylation with BPh₃ keeps progressing even after 3 h. Importantly, there is a very small difference in the initial rates of the two transformations. Taken together these data suggest that BPh₃ might be suppressing catalyst deactivation possibly via sequestering the cyanide anion. This hypothesis is consistent with the lower yields of **1a** from the Ni-catalyzed reaction in the presence of KCN (entry 7).¹³

The optimal conditions for the formation of **1a** with or without BPh₃ (Table 1, entries 4 and 10) can be applied to the arylation of electronically varied oxazoles (Scheme 2). Electron-rich, electron-neutral, and electron-deficient oxazoles afford the corresponding products in comparable yields (cf. **1a–3a**). Analogous to the formation of **1a** (Table 1), the use of BPh₃ with 10 mol % Ni(COD)₂ affords the arylated products in comparable yields to that obtained using 20 mol % Ni(COD)₂ regardless of azole electronics. Importantly, no product is obtained in the absence of Ni(COD)₂/dcype regardless of the oxazole substrate.

We next investigated the use of benzoxazoles in these arylations. Not surprisingly, the Ni-catalyzed coupling of 5-methyl benzoxazole with 3-trifluoromethyl benzonitrile affords **11a** in good yield using Cs₂CO₃ or K₃PO₄ (Table 2, entries 1–2).

Unlike the coupling of phenyl oxazoles (Scheme 2), product **11a** is formed in significant amounts (23–27% yield)^{14,15} in the absence of the nickel catalyst possibly via a S_NAr pathway (entries 4–5).¹⁶ The catalyzed arylation is significantly faster affording **11a** in 79%

yield over 8 h (versus 7% yield from the non-catalyzed process, cf. entries 6 and 7). These results suggest negligible contribution from the non-catalyzed process to the formation of **11a** in the presence of the Ni(COD)₂/dcype. Analogous to the arylations detailed in Scheme 2, the use of BPh₃ (40 mol %) enables the use of lower catalyst loadings (cf. entries 1 and 8).¹¹ Interestingly, however, BPh₃ suppresses the non-catalyzed arylation (cf. entries 4 and 9).¹⁷

These trends for the catalyzed and the non-catalyzed arylations using *meta*-trifluoromethyl benzonitrile are observed for electronically varied benzoxazoles (Scheme 3). Analogous to arylations in Scheme 2, BPh₃ promotes these arylations regardless of benzoxazole electronics. The non-catalyzed arylation affords the arylated products in yields ranging between 14–68%. In the absence of Ni(COD)₂/dcype, the highest yield (68%) of the arylated product (**17a**) is observed for the electron-deficient, fluoro-substituted benzoxazole substrate. The extent of the background reaction is diminished for electron-rich and electron-neutral azoles. The nickel catalyst is essential for the formation of product **18a** from the arylation of the less-acidic benzothiazole substrate.¹⁸

Electronically diverse aryl and heteroaryl nitriles couple with 5-methyl benzoxazole and oxazoles to afford the products in modest to good yields (Scheme 4). The lowest yield was obtained for the reaction using the *ortho*-methyl benzonitrile to afford **11j**. Interestingly, the identity of the *ortho* substituent on the nitrile is important since **11h** and **11i** were obtained in significantly higher yields. Akin to the coupling of benzoxazoles with 3-trifluoromethyl benzonitrile (Scheme 3), the non-catalyzed arylation of benzoxazoles affords significant yields of the biaryls with a few nitriles (Scheme 4). While no clear trends emerge, the nickel catalyst is necessary for the formation of biaryls using nitriles containing an ester (**11f**) or bearing a methoxy group at the *ortho*- (**11i**) or *para*-positions (**11g–h**) relative to the CN functionality. Furthermore, analogous to results in Scheme 2, no product (**1b–1d**, **1i**, **1k**) is obtained in the absence of Ni(COD)₂/dcype for arylations with phenyl oxazole regardless of the nitrile substrate. Finally, BPh₃ promotes the arylations of oxazoles and benzoxazoles with electron rich and electron deficient benzonitriles.

In summary, this paper describes the first example of Ni-catalyzed arylation using electronically diverse azole and benzonitriles. The use of BPh₃ for these transformations enables the use of lower catalyst loading regardless of the azole or nitrile substrates. While the nickel catalyst is necessary for the arylation of oxazoles, oxadiazole and benzothiazole substrates, arylations of benzoxazoles can proceed in the absence of Ni(COD)₂/dcype. The extent of the non-catalyzed process is dependent on the acidity of the azole and electronics nature of the benzonitrile substrates. Furthermore, the catalyzed process is significantly faster than the non-catalyzed reaction. Overall, the scope and efficiencies of the Ni-catalyzed arylation are higher than the non-catalyzed process.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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11. See SI for detailed optimization. See Scheme S1 in SI for reaction profiles for arylations with and without BPh₃.
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13. Alternatively, BPh₃ might also be promoting the oxidative addition and C-H activation steps.
14. The non-catalyzed reaction proceeds to the same extent when commercial 5-methyl benzoxazole is used with or without further recrystallization. Anhydrous Cs₂CO₃ (99.995%) and K₃PO₄ (97%) were used for these reactions. Low yield of **11a** from the non-catalyzed reaction is due to low conversions.
15. Use of stronger bases (MO^tBu, M = Li, Na or K) afford **11a** in atmost 4% yield from the non-catalyzed arylation (Table S2 in the SI).
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17. BPh₃ may inhibit the un-catalyzed reaction by complexing with the deprotonated azole. However, further studies are needed to support this hypothesis.
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Scheme 2. Scope of Oxazoles^a

[^a] Isolated yields. [^b] Ni(COD)_2 (10 mol %) and dcypc (11 mol %), and BPh_3 (40 mol %) used.

Scheme 3.

Scope of Benzoxazoles^a

^[a] Isolated yields ^[b] Yields for reactions in the absence of Ni(COD)_2 and dcype ^[c] Yields using BPh_3 (40 mol %) as additive, Ni(COD)_2 (10 mol %) and dcype (11 mol %). ^[d] Calibrated GC yields against hexadecane as the standard. ^[e] dcypT was used in place of dcype.

Scheme 4.

Scope of Nitriles^a

^[a] Isolated yields ^[b] dcyp used instead of dcype. ^[c] Yields for reactions in the absence of Ni(COD)₂ and dcype. ^[d] Yields using BPh₃ (40 mol %) as additive, Ni(COD)₂ (10 mol %), ligand (11 mol %). ^[e] Calibrated GC yields against hexadecane as the standard. ^[f] K₃PO₄ (3.0 equiv) used as the base.

Table 1

Optimization of Direct Arylation

entry	ligand	base	additive	yield of 1a (%) ⁱ
1	dcype	Cs_2CO_3	none	62
2 ^a	dcype	Cs_2CO_3	none	59
3	dcype	K_3PO_4	none	59
4 ^b	dcype	K_3PO_4	none	71
5 ^{b,c}	dcype	K_3PO_4	none	26
6 ^{b,c,d}	dcype	K_3PO_4	none	33
7 ^{b,e}	dcype	K_3PO_4	KCN	23
8 ^{b,f}	none	K_3PO_4	none	0
9 ^{b,f}	dcype	K_3PO_4	none	0
10 ^{b,c,g}	dcype	K_3PO_4	BPh_3	61
11 ^{b,c,h}	dcype	K_3PO_4	BPh_3	63
12 ^{b,f,g}	none	K_3PO_4	BPh_3	0

^a Conducted at 160 °C.^b 3.0 equiv of K_3PO_4 used.^c Ni(COD)_2 (10 mol %) and dcype (11 mol %) used.^d Reaction time was 48 h.^e KCN (1.0 equiv) added.^f General conditions, but with no Ni(COD)_2 .^g 40 mol % BPh_3 used.^h 60 mol % BPh_3 used.ⁱ Calibrated GC yields against hexadecane as the internal standard.

Table 2Arylation of 5-methyl benzoxazole^a

entry	ligand	base	time (h)	yield of 11a (%) ^a
1	dcype	Cs ₂ CO ₃	24	77
2	dcype	K ₃ PO ₄	24	71
3 ^b	dcype	Cs ₂ CO ₃	24	48
4 ^c	none	Cs ₂ CO ₃	24	27
5 ^c	none	K ₃ PO ₄	24	23
6	dcype	Cs ₂ CO ₃	8	79
7 ^c	none	Cs ₂ CO ₃	8	7
8 ^{b,d}	dcype	Cs ₂ CO ₃	24	74
9 ^{c,d}	none	Cs ₂ CO ₃	24	0

^aCalibrated GC yields against hexadecane as the internal standard.^b10 mol % Ni(COD)₂ and 11 mol % dcype used.^cIn the absence of Ni(COD)₂.^d40 mol % BPh₃ added.