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**Title:** Nickel-Catalyzed construction of 2,4-disubstituted imidazoles via C–C coupling and C–N condensation cascade reactions

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COMMUNICATION

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# Nickel-Catalyzed construction of 2,4-disubstituted imidazoles *via* C–C coupling and C–N condensation cascade reactions

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**Abstract.** A convenient Ni(II)-catalyzed C−C and C−N cascade coupling reaction was developed to directly access various 2,4-disubstituted imidazoles. The reaction scope covers a variety of aryl and aliphatic substitutions, which demonstrate moderate-to-excellent yields. The tolerance of halogen and *N*-containing heterocyclic groups demonstrates the versatility of this method for further synthetic explorations.

**Keywords:** Cyano group; C−C coupling; C−N coupling; 2,4-disubstituted imidazoles; nickel catalysis

Imidazoles and their derivatives belong to an important class of aromatic heterocycles widely observed in numerous natural products, pharmaceuticals, and agro chemicals,[1] highlighting the importance of these chemical scaffolds. In particular, 2,4-disubstituted imidazoles possess both

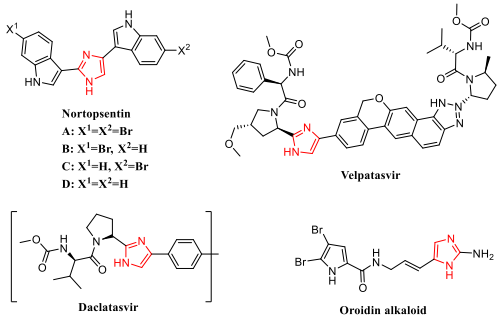


**Figure 1.** Selected examples of bioactive molecules containing 2,4-disubstituted imidazoles.

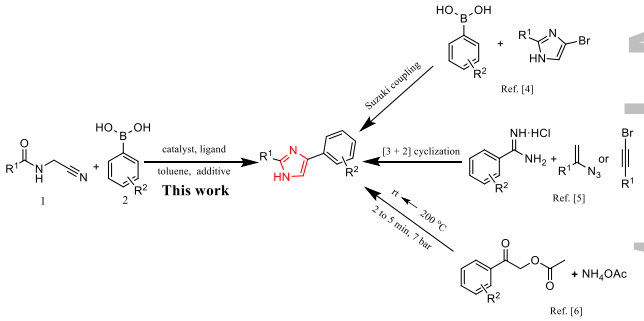


**Figure 2.** Methods for the synthesis of 2,4-disubstituted imidazoles.

hydrogen bonding acceptors and donors, which can enhance bioactivity properties. Numerous synthetic bioactive molecules and drugs comprise such modified scaffolds (Fig. 1).[2] However, synthetic pathways to 2,4-disubstituted imidazoles have not been extensively investigated, hitherto. Unprotected imidazoles remain recognized as a challenging scaffold to synthesize.[3] General routes to synthesize 2,4-disubstituted imidazoles include the Suzuki cross-coupling of haloimidazoles[4] and [3 + 2] cyclization in the presence of benzimidamides and vinyl azides or bromoacetylenes.[5] A high-temperature/high-pressure continuous flow strategy has also been described (Fig. 2).[6] Although these methods are well-established and have been developed specifically, to further improve the applicable scope

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of the methods, the bottleneck—derived from the rigorous reaction conditions and the limited accessibility of the starting materials—must be circumvented.

Over the past years, transition metal-catalyzed nitrile insertion reactions have been demonstrated as an important transformation to generate structurally diverse *N*-containing heterocyclic compounds.[7] The research by Larock [8] and Lu [9] first reported the C−C addition of nitriles catalyzed by Pd and Rh. Since their pioneering work, research by Wu, [10] Chen,[11] and our group[12] has result in Pd-catalyzed nitrile insertion to afford isoquinolines, benzofurans, indoles, quinazolines, and polysubstituted imidazoles. However, there are only a limited number of reports detailing the use of naturally abundant nickel catalysts.[13] As part of the current trend toward replacing precious metal catalysts with catalysts comprising naturally abundant metals,[14] there has been a wealth of interdependent research in developing Ni catalysts as alternatives to Pd systems.[15] Herein, this work focused on developing a novel selective synthesis method to yield 2,4-disubstituted imidazoles using less expensive nickel catalysts and readily accessible starting materials under mild conditions.

Our group has focused on the development of novel transition metal-catalyzed C−C and C−N cascade coupling reactions using nitrile reagents.[12, 13d] As part of continuous efforts, herein, we report an efficient and convenient nickel-catalyzed synthetic strategy to afford 2,4-disubstituted imidazoles, which is compatible with a wide variety of substrates.

At the outset, *N*-(cyanomethyl)acetamide **1a** (0.6 mmol) and phenylboronic acid **2a** (1.2 mmol) are fixed reactant entities during the investigation of the reaction conditions (Table 1). The reaction was performed in the presence of $Ni(acac)_2$ (10 mol%) and ligand **L1** (10 mol%) in toluene (3.0 mL) at 120 °C for 12 h (Table 1, entry 1). As expected, the desired product **3a** was obtained in 45% yield. Prolonging the reaction time led to a significant improvement in yield (71%, entry 2). Despite the modest yield, the complete conversion of **1a** was not achieved. Inspired by the research of the Bathula group,[16] the water produced during the intramolecular cyclization process was proposed to hamper the conversion rate. Therefore, molecular sieves, or sodium sulfate, were added to remove the water, which resulted in the yield of **3a** to increase to 80% in the presence of 5.0 mmol of $Na_2SO_4$ (entries 3 and 4). A series of Ni catalysts (entries 4-8) were then screened with $Ni(PPh_3)_2Br_2$ giving the highest yield (83%, entry 8). To further improve the yield, a variety of ligands (**L1-L8**, entries 8-15) were screened. Among all the bidentate nitrogen ligands, 5,5′-dimethyl-2,2′-bipyridine (**L6**) was observed to efficiently promote the reaction—generating **3a** in 87% yield (entry 13). Decreasing catalyst or phenylboronic acid **2a** amount resulted in the loss of yield. (entries 16 and 17). Control experiments demonstrated that the reaction barely proceeded in the absence of any ligand (entry 18).

With optimal conditions in hand, the influence of boronic acids to the reaction scope were studied (Scheme 1). As illustrated in the scheme, the electronic effect influenced, to varying degrees, the reaction yield. Furthermore, acrylic acids bearing electron-donating groups (**3b-h**) gave better yields compared with

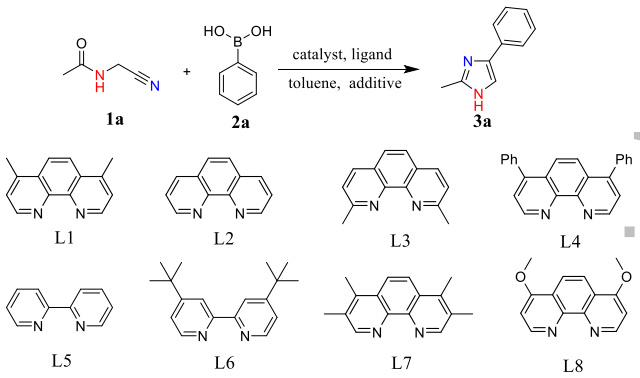


**Table 1.** Optimization of reaction conditions. [a]

| Entry | Catalyst | Ligand | Desiccants | Yield[b] (%) |
|---|---|---|---|---|
| 1[c] | $Ni(acac)_2$ | L1 | | 45 |
| 2[d] | $Ni(acac)_2$ | L1 | | 71 |
| 3[e] | $Ni(acac)_2$ | L1 | molecular sieves | 76 |
| 4 | $Ni(acac)_2$ | L1 | $Na_2SO_4$ | 80 |
| 5 | $Ni(acac)_2$ | L1 | $Na_2SO_4$ | 80 |
| 6 | $NiCl_2$ | L1 | $Na_2SO_4$ | 73 |
| 7 | $NiBr_2$ | L1 | $Na_2SO_4$ | 80 |
| 8 | $Ni(PPh_3)_2Br_2$ | L1 | $Na_2SO_4$ | 83 |
| 9 | $Ni(PPh_3)_2Br_2$ | L2 | $Na_2SO_4$ | 79 |
| 10 | $Ni(PPh_3)_2Br_2$ | L3 | $Na_2SO_4$ | trace |
| 11 | $Ni(PPh_3)_2Br_2$ | L4 | $Na_2SO_4$ | 81 |
| 12 | $Ni(PPh_3)_2Br_2$ | L5 | $Na_2SO_4$ | 57 |
| **13** | **$Ni(PPh_3)_2Br_2$** | **L6** | **$Na_2SO_4$** | **87** |
| 14 | $Ni(PPh_3)_2Br_2$ | L7 | $Na_2SO_4$ | 78 |
| 15 | $Ni(PPh_3)_2Br_2$ | L8 | $Na_2SO_4$ | 20 |
| 16 [f] | $Ni(PPh_3)_2Br_2$ | L6 | $Na_2SO_4$ | 71 |
| 17 [g] | $Ni(PPh_3)_2Br_2$ | L6 | $Na_2SO_4$ | 75 |
| 18 [h] | $Ni(PPh_3)_2Br_2$ | | $Na_2SO_4$ | < 5 |

[a] Reaction conditions: unless otherwise stated, all reactions were carried out with a catalyst/ligand ratio of 1:1 (10 mol%), **1a** (0.6 mmol), **2a** (1.2 mmol, 2.0 equiv.), $Na_2SO_4$ (3.0 mmol, 5.0 equiv.), and anhydrous toluene (3.0 mL) as the solvent. The mixture was stirred at 120 °C, in air, in a sealed tube for 24 h.
[b] Isolated yield based on **1a**.
[c] Reaction time was 12 h without drying agent.
[d] No drying agent.
[e] Molecular sieves as desiccants.
[f] $Ni(PPh_3)_2Br_2$ (0.03 mmol, 5.0 mol%) and **L6** (0.03 mmol, 5.0 mol%).
[g] **2a** (0.9 mmol, 1.5 equiv.).
[h] In the absence of any ligand.

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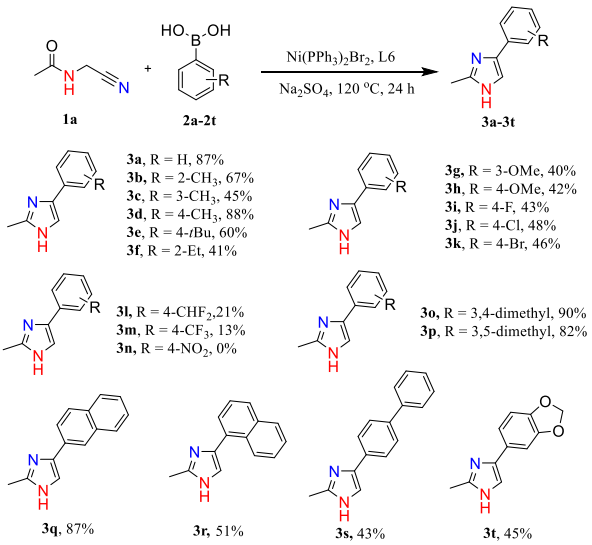
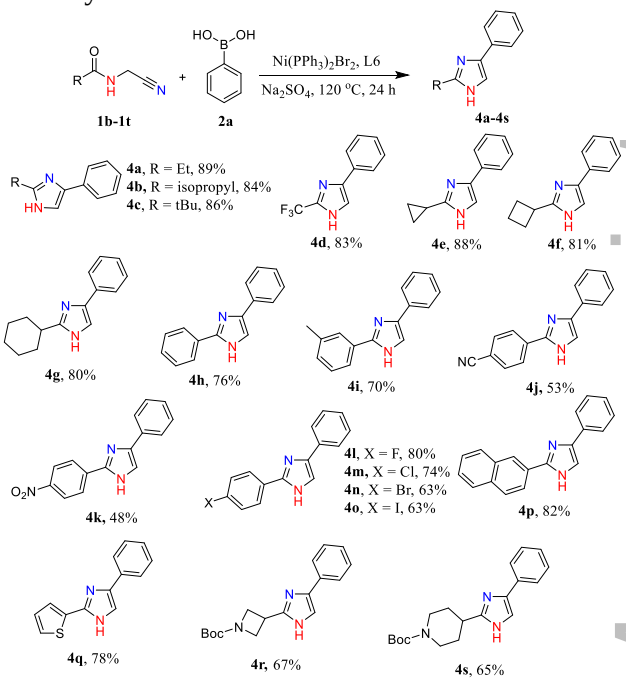
strongly electron-withdrawing groups (**3l-n**). Interestingly, arylboronic acids bearing methoxy substituents at the 3- and, 4- positions (**3g** and **3h**) afforded the corresponding products in lower yields compared with other moieties bearing other electron-donating groups.[17] The introduction of moderately electron-withdrawing groups, such as halogens (**3i-k**), were tolerated in this reaction, achieving moderate yields (43-48%). Introducing strongly electron-withdrawing groups, such as diflouromethyl and




**Scheme 1.** Scope of boronic acid. Standard reaction conditions: **1a** (0.6 mmol), boronic acid (1.2 mmol, 2.0 equiv.), $Ni(PPh_3)_2Br_2$ (0.06 mmol, 10 mol%), ligand (0.06 mmol, 10 mol%), $Na_2SO_4$ (3 mmol, 5.0 equiv.), and anhydrous toluene (3.0 mL), sealed, 120 °C for 24 h; isolated yield based on **1a.**

triflourmethy moieties, only gave low yields (**3l** and **3m**). The reaction barely proceeded (**3n**) when (4-nitrophenyl)boronic acid, with a strong electron-withdrawing group, was used. The steric effects also influenced the outcome of the reaction. For example, the yield was observed to significantly decrease with methyl group at the *ortho*-position (**3b**). Increasing the size of the *ortho*-substitution moiety further decreased the yield (**3f**). Disubstituted substrates were also incorporated. **3o** and **3p** were obtained in excellent yields. Surprisingly, functional groups, such as naphthyl (**3q** and **3r**) and biphenyl (**3s**) were also tolerated with observed yields ranging from 43% to 87%. Additionally, the 3,4-methylenedioxyphenyl fused ring was also successfully transformed when subjected to the reaction condition (**3t**).

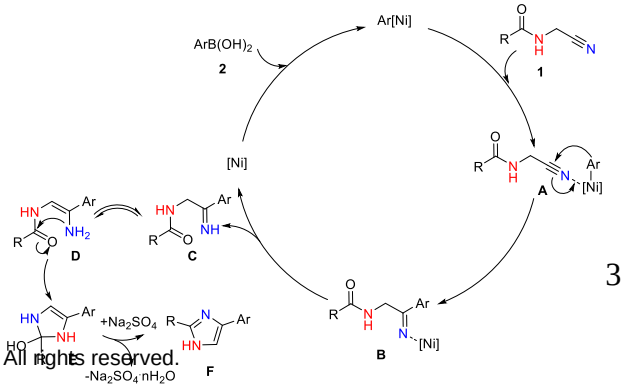
Furthermore, the variation of different substituted *N*-cyanomethyl-acetamides were examined (Scheme 2). Substrates bearing alkyl groups were observed to be well tolerated with yields from 80% to 89% (**4a-g**). Regarding aryl substitutions, *N*-cyanomethylbenzamide gave the corresponding product in 76% yield (**4h**). Both electron-donating (e.g., –Me) and electron-withdrawing (e.g., $–NO_2$) groups on the aromatic rings were compatible with this reaction. In general, *N*-cyanomethyl-acetamide bearing an electron-donating substituent (**4i**), produced a slightly higher product yield compared with the corresponding electron-withdrawing substituent analogues (**4j** and **4k**). Notably, the CN group remained intact and no nickel-catalyzed boron addition to the group was observed (**4j**). The reaction proceeded well in the presence of the halogen groups (**4l-o**) with 63-80% yields, demonstrating the potential of this method across a wide application base after further cross-coupling reactions. Notably, fused-aryl




**Scheme 2.** Scope of substituted *N*-cyanomethyl-acetamides. Standard reaction conditions: **1b-t** (0.6 mmol), boronic acid (1.2 mmol, 2.0 equiv.), $Ni(PPh_3)_2Br_2$ (0.06 mmol, 10 mol%), ligand (0.06 mmol, 10 mol%), $Na_2SO_4$ (3.0 mmol, 5.0 equiv.), and anhydrous toluene (3.0 mL), sealed, 120 °C for 24 h; isolated yield based on **4a-s**.

(**4p**) and heteroaryl (**4q**) substitutions also proceeded smoothly resulting in desired products in moderate-to- good yields. Additionally, the reaction was also proved suitable for various *N*-Boc-cycloalkanes and gave the desired products in moderate yields (**4r** and **4s**).

A tentative mechanism has been proposed (Scheme 3) based on previously published relevant reports.[8c, 9a, 10e] The reaction proceeds by forming aryl nickel species generated from the transmetalation process derived from the Ni(II) catalyst and arylboronic acid. Thereafter, nitrile coordination to Ni[Ar] affords the intermediate **A**, which undergoes an intramolecular



insertion of the nitrile group to yield the corresponding ketimine complex **B**. Further, the above complex **B**

**Scheme 3.** Proposed Mechanism.

afforded the ketimine intermediate **C**, and thus regenerates the Ni(II) catalyst. The ketamine intermediate **C** undergoes tautomerization to afford **D**, which is followed by intramolecular condensation to yield the corresponding desired product **F**.

In summary, an efficient nickel(II)-catalyzed coupling cascade reaction has been developed to synthesize structurally diverse 2,4-disubstituted imidazoles. The reaction involves C−C coupling followed by intramolecular C−N bond formation. The method exhibits remarkable selectivity across a broad substrate scope. Notably, halogen and *N*-containing heterocyclic substituents are amenable to the reaction to further contribute to product diversity. Further studies are ongoing with respect to extending this methodology for the synthesis of various heterocycles.

## Experimental Section

**General procedure for the synthesis of 2,4-disubstituted imidazoles**

Anhydrous toluene (3.0 mL) was added to an over-dried 5 mL sealed tube, equipped with a stirrer bar, containing aminoacetonitrile **1a** (0.6 mmol), phenylboronic acid **2a** (1.2 mmol), $Ni(PPh_3)_2Br_2$ (10 mol%), 4,4'-di-*tert*-butyl-2,2'-bipyridine (10 mol%), and anhydrous $Na_2SO_4$ (3.0 mmol). The mixture was stirred at 120 °C for 24 h. After completion of the reaction, the solvent was removed under reduced pressure. Thereafter, the mixture was diluted with EtOAc and washed with brine. The organic layer was dried over anhydrous $Na_2SO_4$ and evaporated under vacuum, after which the residue was purified by column chromatography using 2 vol.% methanol in dichloromethane to give the desired product **3a**.

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[17] Similar phenomena can be observed in other previous reports regarding transition metal-catalyzed nitrile insertion reactions, see: ref.10 a), ref.11, and ref.13 d). On the basis that in transition metal-catalyzed reactions, some nitrogen or sulfur atoms present in heterocyclic substrates will coordinate strongly with metal catalysts, we propose that the oxygen atom in the substrates may hamper the transformation in a similar way.

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# Nickel-Catalyzed construction of 2,4-disubstituted imidazoles *via* C–C coupling and C–N condensation cascade reactions

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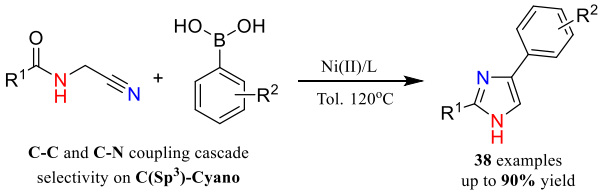


**C-C** and **C-N** coupling cascade selectivity on **C(Sp$^3$)-Cyano**

**38** examples up to **90%** yield