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Nickel-Catalyzed Intramolecular Direct Arylation of Imines toward Diverse Indoles

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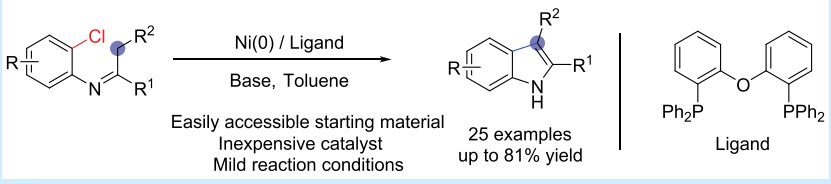
Supporting Information



ABSTRACT: An efficient nickel-catalyzed intramolecular direct arylation of imines with challenging aryl chlorides has been developed. The versatile nickel catalysis made use of easily accessible imines and delivered diversely decorated 2-arylindoles of considerable importance to biological and medicinal chemistry.

The indole core is one of the most abundant and relevant heterocycles in natural products and pharmaceuticals.[1] Specifically, the 2-arylindole derivatives are widely found in pharmaceutical compounds with a broad spectrum of biological activities.[2] For example, compound A (Figure 1) was

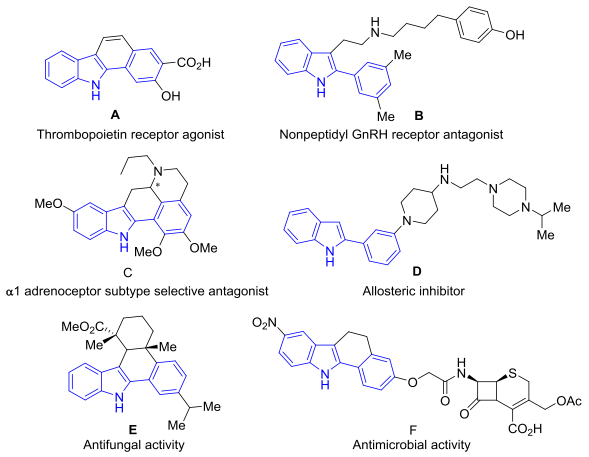


Figure 1. Examples of bioactive 2-arylindole derivatives.

identified as an effective agonist of the thrombopoietin receptor.[2a] Compounds B and C were reported to act as a nonpeptidyl GnRH receptor antagonist[2b] and a α1 adrenoceptor subtype selective antagonist,[2c] respectively. Compound D showed good biochemical activities of p97 inhibitors.[2d] Moreover, compounds E and F were identified as having an effective antifungal activity[2e] and an antimicrobial activity,[2f] respectively. Therefore, the efficient synthetic strategies for the synthesis of 2-arylindole derivatives continue to be in high demand.

The Mizoroki−Heck reaction is an invaluable coupling reaction of olefins with halides for C−C bond formation. In recent years, significant effort has been directed toward the development of intramolecular Mizoroki−Heck reactions by palladium catalysts.[3,4] Indeed, aryl chlorides would be more attractive substrates than the corresponding bromides, iodides, and triflates due to their lower cost and the significantly wider diversity of available compounds.[4c,5] However, a major limitation of the palladium-catalyzed Heck reaction is the low reactivity of aryl chlorides; therefore, sterically bulky electron-rich phosphines,[6] *N*-heterocyclic carbenes,[4k,7] or carbocyclic carbenes[8] ligands are required for the palladium catalytic system. In contrast to palladium, nickel is an abundant, low cost, and sustainable metal. Moreover, nickel catalysts can easily insert into unactivated aryl chlorides and allow them to participate in coupling reactions.[9] Recent studies have established the utility of nickel-catalyzed Heck reaction in the activation of aryl halides and pseudohalides.[10,11] However, intramolecular nickel(II)-catalyzed Heck reaction needs a reducing reagent to promote the reaction, such as manganese[12] (Scheme 1, eq 1). Thus, Desrosiers[12b] disclosed that manganese is probably involved in the catalytic cycle, while the direct use nickel(0) catalysts for the intramolecular Heck reaction is still scarce.[13] On the other hand, use of imine substrates which are prepared by condensation of the corresponding inexpensive and readily available anilines and ketones as starting materials is highly attractive because their

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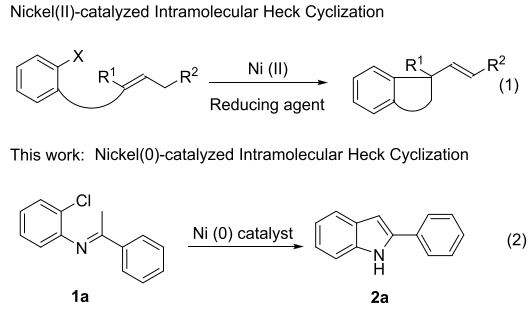
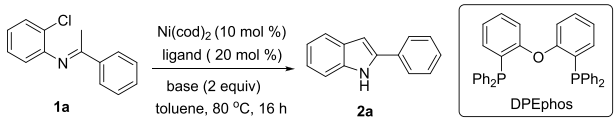
Scheme 1. Nickel-Catalyzed Intramolecular Heck Reaction



structures are useful building blocks in the synthesis of nitrogen heterocycles.[14] Herein, we envisioned that we could further exploit this ability to address the challenge of developing a method for a Heck cyclization of imines using the simple catalytic system (Scheme 1, eq 2).

At the outset of our studies, we optimized reaction conditions for the envisioned nickel-catalyzed Heck cyclization of imine **1a**. The product **2a** was obtained in moderate yield in the presence of $Ni(cod)_2$ (cod = 1,5-cyclooctadiene) as the catalyst in toluene at 80 °C (Table 1, entry 1). Utilizing ligand

Table 1. Optimization Studies for the Nickel-Catalyzed Intramolecular Heck Reaction of Imine[a]



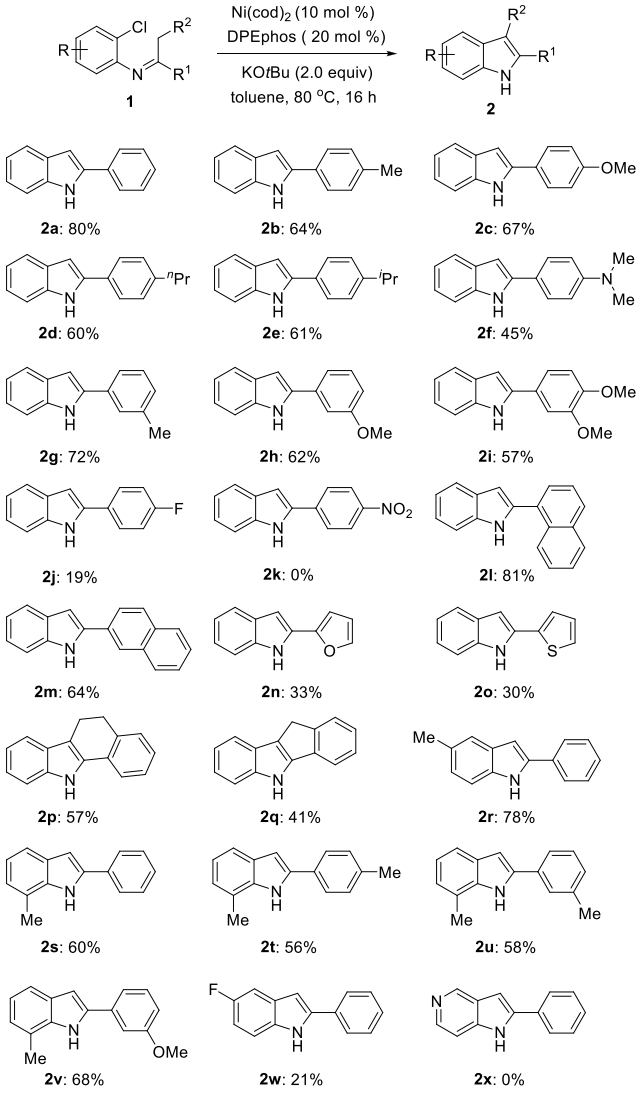
entry	catalyst	ligand	base	yield[b] (%)
1	$Ni(cod)_2$	bipyridine	KO*t*Bu	37
2	$Ni(cod)_2$	1,10-phenanthroline	KO*t*Bu	58
3	$Ni(cod)_2$	PCy_3	KO*t*Bu	30
4	$Ni(cod)_2$	PCy_3	LiO*t*Bu	8
5	$Ni(cod)_2$	dppe	KO*t*Bu	8
6	$Ni(cod)_2$	dppf	KO*t*Bu	87
7	$Ni(cod)_2$	DPEphos	KO*t*Bu	90 (80)[c]
8	$Ni(cod)_2$	DPEphos	KO*t*Bu	62[d]
9	$Ni(cod)_2$	DPEphos	NaO*t*Bu	54
10	$(DME)NiCl_2$	DPEphos	KO*t*Bu	5
11	$Ni(OTf)_2$	DPEphos	KO*t*Bu	5

[a]Reactions performed on a 0.25 mmol scale over 16 h using catalyst (10 mol %), ligand (20 mol %), base (2 equiv) and $[\mathbf{1a}]_0$ = 0.25 M in toluene at 80 °C. [b]Yield determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard. [c]The values in parentheses refer to the isolated yield. [d]Reactions carried out at 100 °C.

1,10-phenanthroline increased the reactivity of the catalytic system (entry 2). A series of representative phosphorus ligands were also analyzed (entries 3−7), revealing that phosphorus ligand could be used as an additional handle for modulating reaction efficiency. In particular, the DPEphos ligand delivered the desired product **2a** in good isolated yield (entry 7). A subsequent investigation on the effect of temperature revealed that the reaction gave the best result at 80 °C, while the weak base NaO*t*Bu reduced the reactivity (entry 9). Different nickel(II) catalysts were also explored, but no better results were obtained (entries 10 and 11). Finally, the best reaction conditions were eventually finalized with 10 mol % of $Ni(cod)_2$ as the catalyst and 20 mol % of DPENphos as the ligand.

With the optimization conditions in hand, we set out to investigate the scope of the transformation. As shown in Scheme 2, the presence of a range of substituents is compatible

Scheme 2. Scope of the Nickel-Catalyzed Intramolecular Heck Reaction



with the reaction. *Para*- or *meta*-substituted compounds with electron-donating groups on the acetophenone-derived moieties were well tolerated, affording the corresponding products in moderate to good yields (**2b−i**). However, an electron-withdrawing substituent at the 4-position was sluggish in this reaction, resulting in a low yield (**2j**). Substitution with 1-naphthyl at the 2-position gave better results than with 2-naphthyl, probably due to steric effects (**2l**,**m**). In addition, the reaction was compatible with heteroaryl frameworks, as shown in the synthesis of the furyl- and thiophenyl-substituted indoles, although the formation of **2n** and **2o** was slightly more sluggish. Remarkably, the chemistry can be successfully extended to synthesize biological tetracyclic core indole derivatives compounds[15] in a single step with good yields and high regioselectivities (**2p**,**q**). Furthermore, the scope of the reaction with respect to the aniline-derived moieties was

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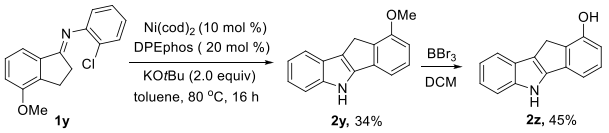
also explored. The presence of an electron-donating group of substituents were well tolerated (**2r**–**v**). However, an attempt to generate substituted 4-azaindole derivative was not successful (**2x**).

To demonstrate the utility of the current procedure, a transformation was performed. As shown in Scheme 3,

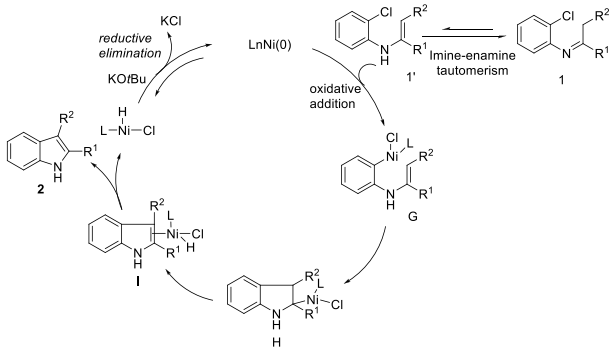
Scheme 3. Derivatization of the Cyclization Product



cyclization of substrate **1y** proceeded under the standard conditions to afford the product **2y**. Subsequently, demethylation of **2y** produced **2z** with moderate yield, which could serve as an inhibitor of carbononic anhydrase.[15c,d]

A plausible mechanism based on literature precedence[9,16] and our mechanistic studies (Supporting Information) is proposed in Scheme 4. Initially, the nickel(0) catalyst attacks

Scheme 4. Proposed Mechanism



the enamine **1′**, which is generated in situ by tautomerization of imine **1**, affording intermediate **G**. Subsequently, an intramolecular carbonickelation generates species **H**, which undergoes subsequent *β*-hydride elimination to furnish the desired product **2**, followed by a base-mediated reductive elimination regenerates the catalytically competent nickel(0) species.

In summary, we have discovered a nickel-catalyzed intramolecular Mizoroki–Heck direct arylation of imines with challenging aryl chlorides. The direct arylation proceeded under mild conditions with tolerance for various functional groups, providing synthetically meaningful building blocks for the synthesis of 2-arylindole scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00600.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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