Nickel-Catalyzed Reductive Cross-Coupling of Heteroaryl Chlorides and Aryl Chlorides

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Two C−Cl Bonds

HetAr−Cl + Ar−Cl → (Ni) → Cross-Coupled Product (HetAr−Ar)

- Operationally simple
- Feedstock aryl chlorides
- Single metal catalyst
- Synergistic additive effect
- 31 examples, up to 94% yield
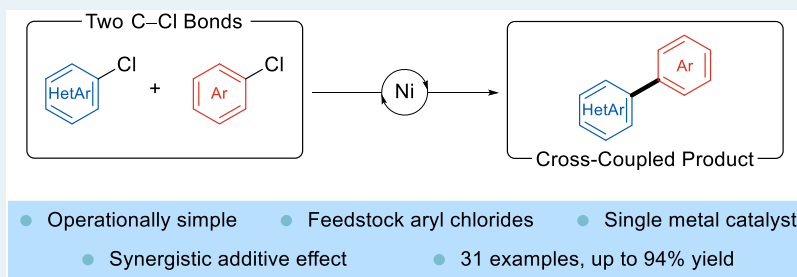
ABSTRACT: We report a nickel-catalyzed cross-electrophile coupling reaction of aryl chlorides and heteroaryl chlorides enabled by a synergistic combination consisting of halide effects and the addition of a magnesium salt. The reaction relies on the electronic difference between the aromatic and heteroaromatic coupling partners to afford the cross-coupled biaryl products using a single catalyst. A variety of heterocycles were amenable to the reaction, as well as a wide range of aryl chlorides, with electron-deficient aryl chlorides performing the best in the reaction. Preliminary mechanistic evidence demonstrates the $MgCl_2$ is essential to the reaction by accelerating the reduction of Ni(II), and that small quantities of iodide lead to improved yields.

KEYWORDS: nickel catalysis, cross-electrophile coupling, C−Cl activation, heterocycles, multicomponent reaction

Transition metal-catalyzed cross-coupling reactions remain an integral part of the synthetic chemist's toolbox to forge C−C bonds.[1] New methods demand high levels of chemo- and regioselectivity. Over the past decade, cross-electrophile coupling (XEC) has emerged as a viable alternative to the conventional palladium-catalyzed coupling of organohalides with organometallic reagents.[2] Significant advances have been made in the field of nickel-catalyzed reductive cross-coupling employing various carbon-based electrophiles. In particular, a large body of work toward $C(sp^2)−C(sp^3)$ cross-coupling has been made by the groups of Weix,[3] Gong,[4] Reisman,[5] and Jarvo and Hong,[6] enabling the use of various electrophiles and the formation of enantioenriched small molecules.
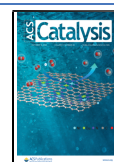
The use of an aryl and an alkyl electrophile in these reactions engenders selectivity based on the different reactivity of these components with the nickel catalyst.[7] In comparison, the nickel-catalyzed $C(sp^2)−C(sp^2)$ cross-coupling has proven to be more challenging. The use of two different $C(sp^2)$-hybridized electrophiles has the added issue of selectivity, as the similar reactivity of two aryl electrophiles can lead to competitive homocoupling. A classic solution to this problem was to utilize an excess of one of the aryl reagents to obtain synthetically useful yields. This strategy is viable in cases where one of the coupling partners is inexpensive and if the symmetrical dimers are easily separable.[7b] Electrochemical methods utilizing sacrificial metal anodes as reductants have also been used to obtain good yields of cross-coupled products.

Pioneering reports by Gosmini[8] have proven the viability of this strategy in $C(sp^2)−C(sp^2)$ cross-coupling reactions catalyzed by nickel. The proposed mechanism of these reactions involves the formation of organometallic reagents at the surface of the anode.[8a] More recent reports by Léonel[9] have expanded the scope of substrates suitable for electrochemical XEC reactions. The Reisman group has also utilized an electroreductive strategy to enable enantioselective $C(sp^2)−C(sp^3)$ cross-electrophile coupling.[10]
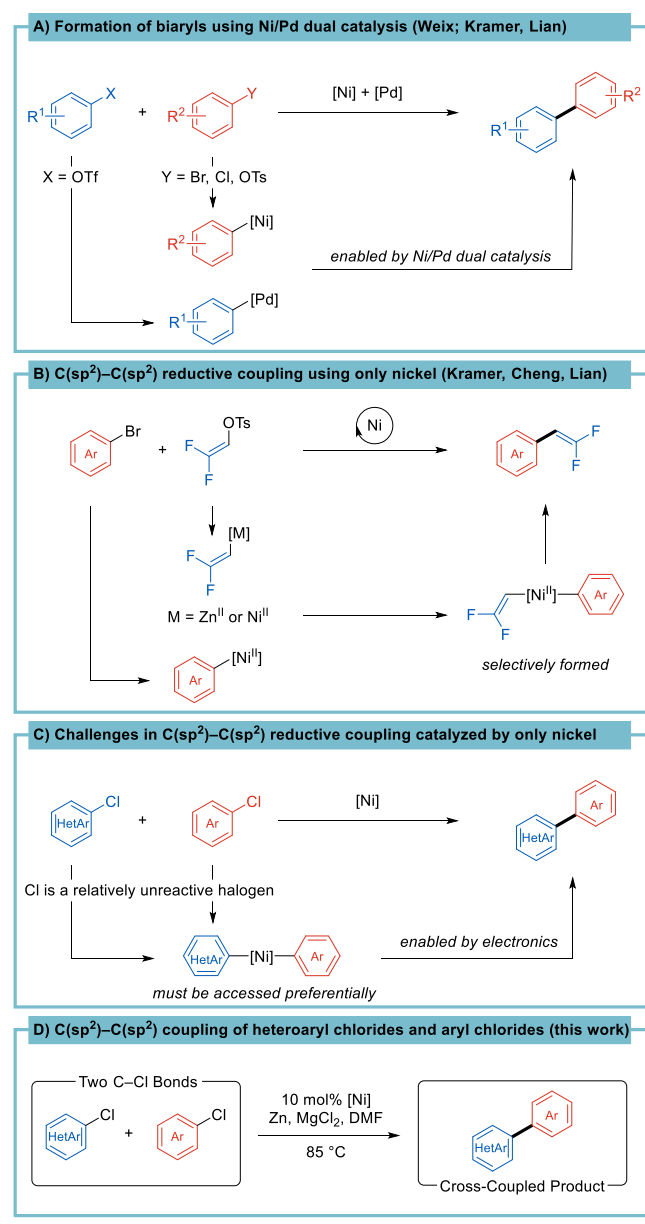
In 2015, the Weix group developed a Ni/Pd dual catalytic system to address the inherent selectivity limitation in $C(sp^2)−C(sp^2)$ reductive couplings (Scheme 1A).[11] This strategy relied on the selective oxidative addition of two catalysts into each of the aryl electrophiles; the nickel catalyst favored oxidative addition into the C−Br bond, while the palladium catalyst favored oxidative addition into the C−OTf bond. The use of multimetallic catalyst systems have since been developed to address challenges associated with $C(sp^2)−C(sp^2)$ cross-coupling.[12]

Scheme 1. Strategies for C(sp²)–C(sp²) Reductive Cross-Coupling

A) Formation of biaryls using Ni/Pd dual catalysis (Weix; Kramer, Lian)

B) C(sp²)–C(sp²) reductive coupling using only nickel (Kramer, Cheng, Lian)

C) Challenges in C(sp²)–C(sp²) reductive coupling catalyzed by only nickel

D) C(sp²)–C(sp²) coupling of heteroaryl chlorides and aryl chlorides (this work)

More recently, metal/photoredox[13] and directing group strategies[14] have been developed to achieve selective cross-coupling of sp²-hybridized electrophiles. The groups of Kramer, Cheng, and Lian have disclosed the C(sp²)–C(sp²) cross-coupling of 2,2-difluorovinyltosylate with various aryl bromides,[15] where the difference in the electronic parameters of the two electrophiles presumably enabled the reaction to proceed using only nickel (Scheme 1B).

Our ongoing interest in base metal catalysis[16] has resulted in a nickel-catalyzed XEC reaction to form a C(sp²)–C(sp²) bond. This strategy uses abundant aryl chlorides[17] in the reductive cross-coupling (Scheme 1C). To overcome the challenges associated with competitive oxidative addition, we identified heteroaryl chlorides as one of the desired coupling partners.[18] The advantages of this strategy are twofold: the use of commercially available aryl and heteroaryl chlorides allows for a more attractive starting point for synthesis compared to the currently available protocols. In addition, the difference in

the electronics of the heteroaryl chloride compared to the aryl chloride led to the desired cross-Ullmann products without needing to include a palladium co-catalyst. Herein, we report details of a reductive cross-coupling of heteroaromatic chlorides with aryl chlorides under nickel catalysis, where a synergistic effect of iodide ions and a magnesium salt was crucial for high yields of the reaction (Scheme 1D).

We began our investigation with 2-chlorobenzimidazole derivatives since they are privileged structures in natural products and bioactive small molecules,[19] as well as in materials (Table 1).[20] The use of NiI_2 (10 mol %), bipyridine (bipy) (15 mol %), Zn (2 equiv), and $MgCl_2$ (2 equiv) in dimethylformamide (DMF) at 85 °C for 24 h with a slight excess of aryl chloride were the optimal conditions for the reductive coupling (entry 1), giving the product in 90% isolated yield, with minimal amounts of the homocoupled products being observed (see the Supporting Information for the complete optimization). Reducing the amount of $MgCl_2$ led to a reduction in yield (entry 2), while increasing the amount did not lead to a noticeable difference in product formation (entry 3). Attempts to use a 1:1 ratio of **1a** and **2a** led to a significant reduction in product yield. Other solvents and nickel sources were not as efficient in the reaction (entries 5 and 6), and control experiments confirmed the necessity of both the nickel catalyst and Zn (entries 7 and 8).

The generality of the method was explored by varying the identity of heteroaryl chloride (Scheme 2). The reaction was tolerant of benzimidazoles containing various nitrogen substitutions (**3aa**, **3ba**, **3da**) and even products with the unprotected benzimidazole (**3ca**) could be isolated in 54% yield. Other heterocycles, containing a benzoxazole (**3ea**) or a quinazolinone (**3fa**), were obtained in 70 and 55% yield, respectively. Pyridines bearing various substitution patterns were competent coupling partners (**3ga-3ia**). Notably, 2-substituted pyridines could be obtained in 85% yield (**3ha**) from the corresponding 2-chloropyridine. The 2-pyridyl unit has traditionally been a capricious cross-coupling partner, partially due to the instability of the corresponding organometallic reagents.[21] A densely functionalized pyridine could also be used in the reaction with good efficiency (**3ia**). Furthermore, a fully substituted imidazole containing a reactive aldehyde was obtained in 52% yield (**3ja**). Imidazoles of this type have previously been shown to act as potent angiotensin converting enzyme (ACE) inhibitors.[22] Purine and deazapurine coupled products could be obtained, albeit in significantly reduced yields (**3ka−3la**). Although the yields are not high, the products can be easily purified and obtained in quantities needed for subsequent manipulations.

Next, we investigated a range of aryl chlorides. The performance of the reaction was sensitive toward the electronics of the aryl coupling partner. In general, the reaction performed best when using aryl chlorides bearing electron-withdrawing substituents (**3ma−3rab**, **3za**, **3db−3eb**). Tertiary (**3pa**), and even the relatively acidic secondary (**3na**) and primary (**3oa**) sulfonamides were all tolerated in the reaction. An electron-withdrawing ester in the 3-position of aryl chloride delivered the product in 94% yield. Although it is expected that more reactive halogens (Br, I) would lead to competitive oxidative addition and potential homocoupling, fluorine atoms could be easily incorporated (**3ma**, **3ra**, **3za**). Electron-neutral and electron-donating aryl chlorides were poor substrates in the reaction, likely owing to a more challenging oxidative addition.[23,24] This limitation is one that is

Table 1. Optimization of the Nickel-Catalyzed Reductive Cross-Coupling[a]

entry	variation	yield 3aa (%)[b]
1	none	96 (90)
2	1 equiv MgCl$_2$ instead	54
3	4 equiv MgCl$_2$ instead	90
4	1 equiv 2a	45
5	DMPU instead of DMF	48
6	NiCl$_2$(dme) instead	48
7	without NiI$_2$	0
8	without Zn	0

[a]Reactions were carried out on 0.2 mmol scale with a 1:1.5 ratio of 1a:2a. [b]Yield was determined by ^{1}H NMR analysis of the crude reaction mixture following workup using 1,3,5-trimethoxybenzene as the internal standard. Isolated yields are given in parentheses.

commonly observed in C(sp²)−C(sp²) XEC and few methods, utilizing Ni/Pd co-catalysis, have been reported to be broadly applicable to this substrate class.[3a,12b] Under our conditions, these substrates could be used; however, the products were obtained in poor yields (3sa−3ya, 3aa−3bb). This issue was somewhat circumvented using the corresponding aryl bromide substrates, giving the products in acceptable yields, highlighted by sterically hindered *ortho*-tolyl (3wa) and xylyl (ab) substrates. The methodology was also amenable to an intramolecular XEC reaction to afford the tetracyclic product in 48% yield (3cb). In this case, the coupling occurs efficiently with an aryl chloride containing an electron-donating functional group. Of note, intramolecular XEC reactions forging C(sp²)−C(sp²) bonds are relatively rare in the literature. A product containing five Lewis-basic heteroatoms (3db) was amenable to the reductive coupling and an electron-deficient aryl chloride containing a protected carbohydrate was obtained without loss of the acetonide protecting groups (3eb).
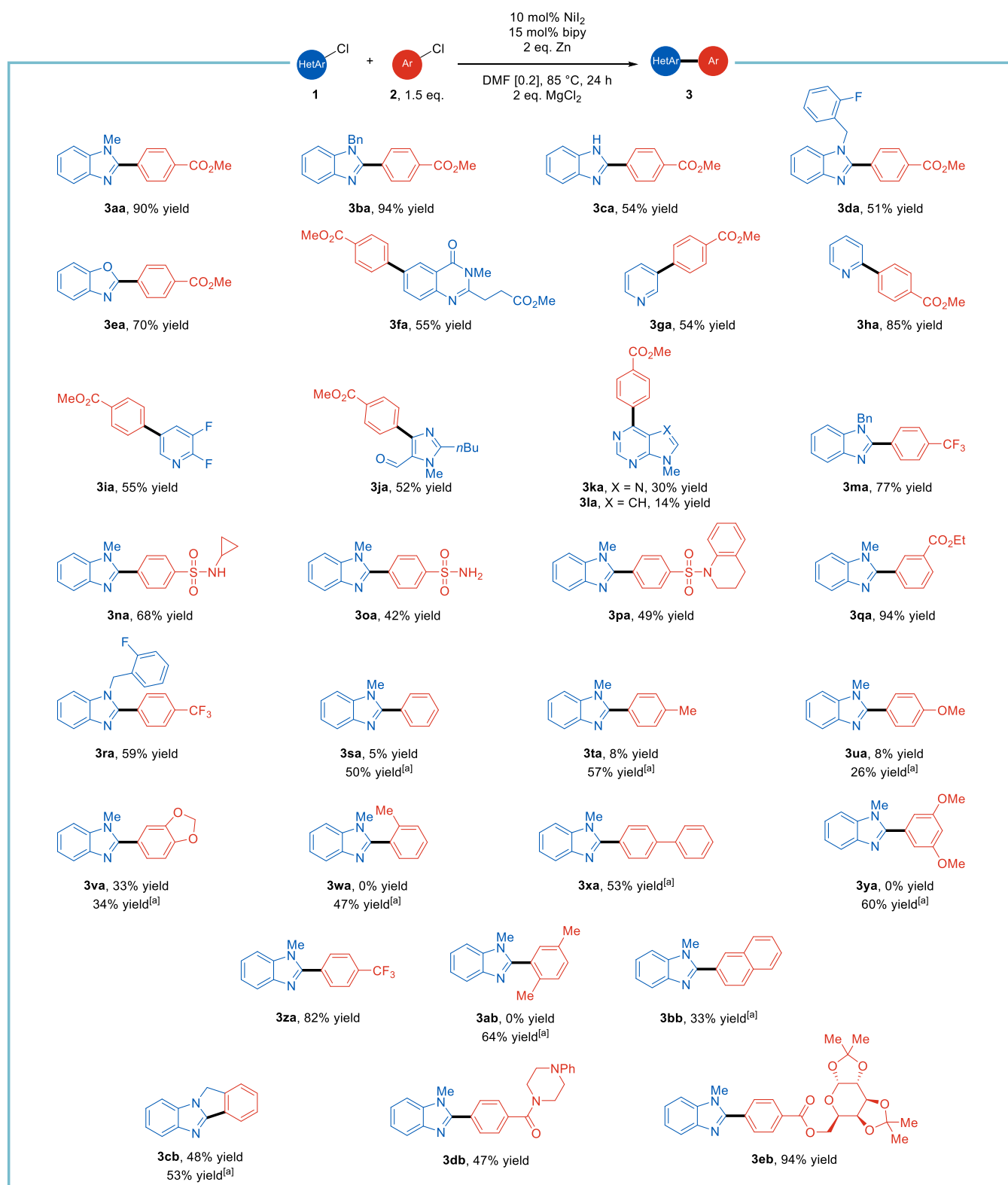
Mechanistically, we envisioned that the reaction could proceed through three possible pathways: (1) a radical-polar crossover that involves the formation of an aryl radical, (2) a sequential oxidative addition mechanism that involves oxidative addition at Ni(0) and Ni(I), and (3) a bimetallic pathway that involves a transmetalation event between two organonickel intermediates (potentially mediated by zinc).

We hypothesized that the formation of a relatively unstable aryl radical was unlikely and that a radical scavenger would not inhibit the reaction. The addition of TEMPO to the standard reaction led to significantly reduced yields. The poisonous effect of TEMPO in nickel catalysis is well-established,[25] so other radical scavengers were tested (Table 2). The addition of butylated hydroxytoluene (BHT) or 1,1-diphenylethylene (DPE) did not lead to a significant reduction in the product yield, indicating that radicals are likely not involved in the reaction mechanism.

Recent reports have shown that the reductive cross-coupling of C(sp²)-based electrophiles can occur via formation of in situ generated Negishi reagents.[12b,15] To test for this possibility, we separately reacted both 1a and 2a with Zn metal in DMF at 85 °C for 24 h.[26] Quenching the reaction mixture with I$_2$ did not lead to the formation of the corresponding iodinated compounds, suggesting that this pathway is not operative. Instead, we observed decomposition of both 1a and 2a under

these conditions. Interestingly, the presence of 2 equiv of MgCl$_2$ prevented the decomposition of 1a but accelerated the decomposition of 2a, justifying the need for a slight excess of aryl chloride (Table 1, entry 4). We additionally performed reaction monitoring studies in the absence and presence of MgCl$_2$ (see the Supporting Information, Section 5.7). The reaction proceeds almost immediately when MgCl$_2$ is included as an additive; conversely, there is an induction period that occurs in its absence. This suggests that MgCl$_2$ is facilitating the reduction of nickel(II). Previous reports that have found that magnesium salts can aid in the reduction of the nickel catalyst,[4e] which in some cases can be the turnover limiting step.[27] Since the starting materials slowly decompose under the reaction conditions, an induction period is detrimental to reaction success.

The Weix group has previously shown that the presence of a catalytic amount of iodide or bromide ions, regardless of how they are introduced in the reaction, can lead to significantly improved reaction rates.[3a] We sought to determine if the iodide in the nickel precatalyst was influencing the reaction (Table 3, see the Supporting Information for halogen exchange experiments). Changing from NiI$_2$ to NiCl$_2$(dme) led to a significant reduction in yield, affording only 48% of 3aa (Table 1, entry 6). We then replaced MgCl$_2$ with MgI$_2$ under the standard reaction conditions to confirm that it was a competent additive in the reductive cross-coupling (Table 3, entry 1). The use of both NiCl$_2$(dme) as the precatalyst and MgI$_2$ as an additive led to the formation of 3aa in 74% yield (Table 3, entry 2), markedly higher than when iodide was absent. Salt concentrations chosen to mimic those in the standard conditions gave the desired product in 76% yield (Table 3, entry 3). The inclusion of iodide via the addition of 20 mol % I-2a using NiCl$_2$(dme) similarly led to improved yields (Scheme 3A). We considered that I-2a might be formed in small amounts during the course of the reaction. Halogen exchange experiments did not lead to the formation of I-2a, and it was not observed during the course of the reaction. The use of a nickel(0) precatalyst in the absence of added iodide provided the desired product in good yields, but addition of 10 mol % MgI$_2$ gave significantly better results (Scheme 3B). Although we were unable to confirm the precise role of iodide, we suspect that it is assisting in the reduction of nickel(II) species or breaking catalytically inactive polymeric structures.

Scheme 2. Scope of the Nickel-Catalyzed Reductive Cross-Ullman Coupling[a]

3aa, 90% yield

3ba, 94% yield

3ca, 54% yield

3da, 51% yield

3ea, 70% yield

3fa, 55% yield

3ga, 54% yield

3ha, 85% yield

3ia, 55% yield

3ja, 52% yield

3ka, X = N, 30% yield
3la, X = CH, 14% yield

3ma, 77% yield

3na, 68% yield

3oa, 42% yield

3pa, 49% yield

3qa, 94% yield

3ra, 59% yield

3sa, 5% yield
50% yield[a]

3ta, 8% yield
57% yield[a]

3ua, 8% yield
26% yield[a]

3va, 33% yield
34% yield[a]

3wa, 0% yield
47% yield[a]

3xa, 53% yield[a]

3ya, 0% yield
60% yield[a]

3za, 82% yield

3ab, 0% yield
64% yield[a]

3bb, 33% yield[a]

3cb, 48% yield
53% yield[a]

3db, 47% yield

3eb, 94% yield

[a]Aryl bromide was used in place of aryl chloride.

We continued our investigation into the mechanism by probing for potential side reactions that would lead to undesired homocoupling products. Subjecting **1a** to the reaction conditions in the absence of **2a** led to complete decomposition without the formation of the dimer (Scheme 4A), suggesting that heteroaryl chloride is unable to undergo homocoupling. No homocoupled products arising from any of the heteroaryl chlorides were observed during the course of our investigation. Conversely, treating **2a** under the standard

Table 2. Effect of Radical Scavengers on the Reaction[a]
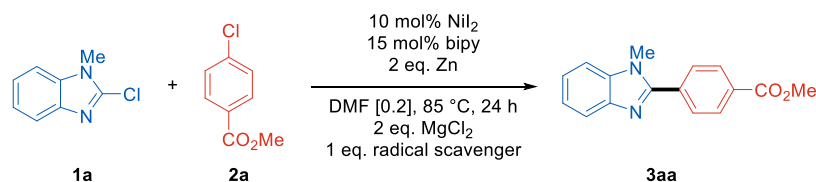
| entry	radical scavenger	yield 3aa (%)[b]
1	TEMPO	15
2	BHT	98
3	DPE	72

[a]Reactions were carried out on 0.2 mmol scale with a 1:1.5 ratio of **1a:2a**. [b]Yield was determined by ^{1}H NMR analysis of the crude reaction mixture following workup using 1,3,5-trimethoxybenzene as the internal standard.

Table 3. Effect of Iodide on the Reaction[a]
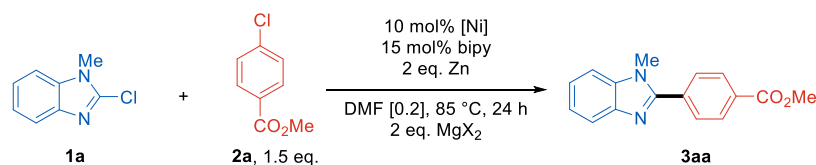
entry	nickel source	MgX$_2$	yield 3aa (%)[b]
1	NiI$_2$	MgI$_2$	93
2	NiCl$_2$(dme)	MgI$_2$	74
3	NiCl$_2$(dme)	1.9 equiv MgCl$_2$ and 0.1 equiv MgI$_2$	76

[a]Reactions were carried out on 0.2 mmol scale with a 1:1.5 ratio of **1a:2a**. [b]Yield was determined by ^{1}H NMR analysis of the crude reaction mixture following workup using 1,3,5-trimethoxybenzene as the internal standard.

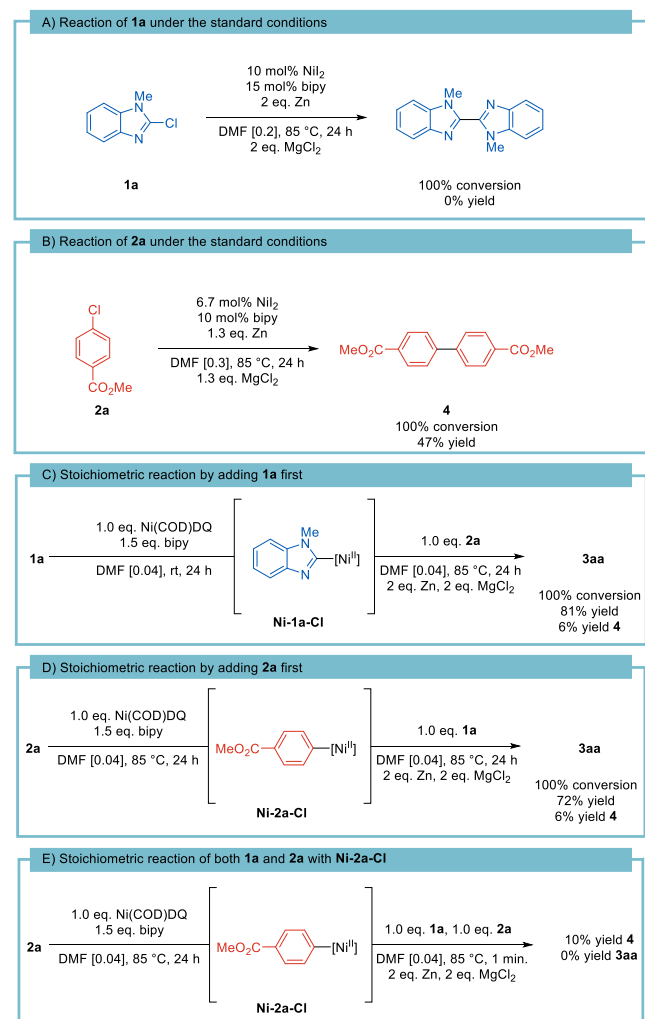## Scheme 3. Further Evaluation of Iodide on the Reaction
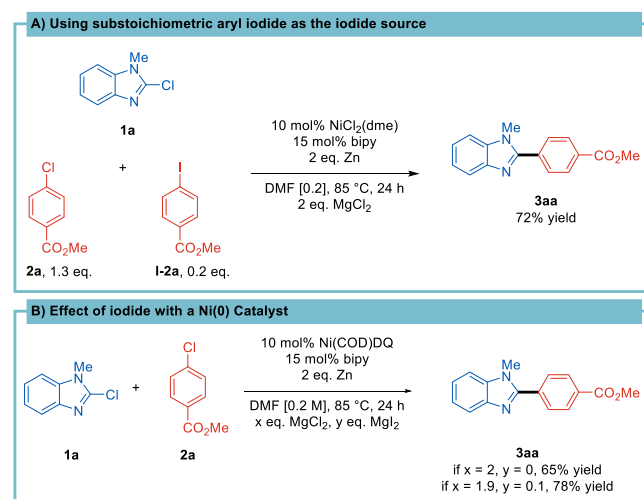
reaction conditions led to the formation of the homocoupled biaryl **4** in 47% yield (Scheme 4B).

Finally, we set out to determine if the double oxidative addition mechanism was operative. Attempts to access (hetero)arylnickel complexes in situ using nickel(II) salts were unsuccessful (see the Supporting Information for more details). We reasoned that the inclusion of Zn or MgCl$_2$ resulted in decomposition, and so we opted to use Ni(COD)-DQ[28,29] to preclude the need for these reagents. A stoichiometric reaction of **1a** with the nickel catalyst led the formation of a dark solution, presumed to be the oxidative addition complex, **Ni-1a-Cl**. Subsequent addition of **2a** led to the formation of **3aa** in 81% yield (Scheme 4C). The addition of **2a** to Ni(COD)DQ should give a solution of **Ni-2a-Cl**. The
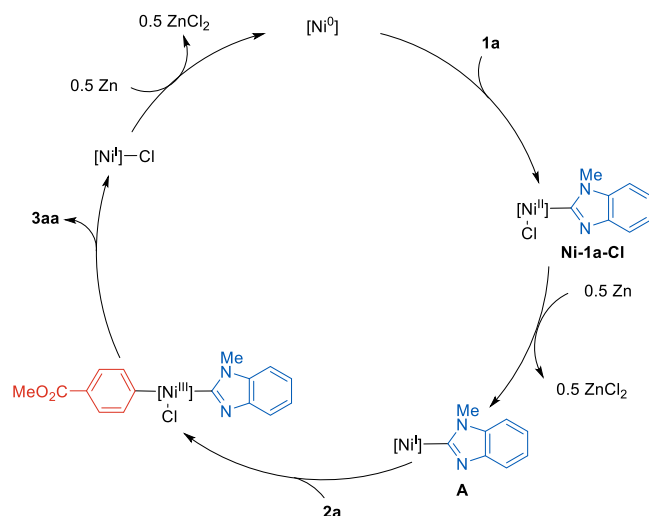
addition of **1a** to **Ni-2a-Cl** led to the formation of **3aa**, though in diminished yields (Scheme 4D). Further stoichiometric studies suggest that **Ni-1a-Cl** is unable to engage with another equivalent of **1a**, while **Ni-2a-Cl** can react with either heteroaryl chloride to form the desired product or aryl chloride to form **4** (see the Supporting Information for more details). These experiments show that the homocoupled aryl chloride can be formed when heteroaryl chloride is not present, but the dimerization product of **1a** was never observed, even in the absence of another coupling partner. The key to our understanding of the reaction is to identify which halide reacts with the nickel catalyst first, since both nickel(II) oxidative addition complexes are competent intermediates. We reacted a solution of **Ni-2a-Cl** with a mixture of **1a** and **2a** in a 1:1:1 ratio and stopped the reaction at low conversions. After 1 min, the homocoupled biaryl product, **4**, was observed in 10% yield and **3aa** was not observed. This outcome suggests that **Ni-2a-Cl** reacts with **2a** faster than with **1a**. Since the homocoupling is only formed in small amounts in the reaction, this implies that **Ni-2a-Cl** is unlikely to be formed during the course of the reaction. The available evidence supports that the nickel catalyst preferentially inserts into heteroaryl chloride.

Based on these results and previous literature precedent, we believe that the reaction occurs via sequential oxidative addition (Scheme 5), beginning with oxidative addition of a nickel(0) complex into the heteroaryl[30,31] chloride to form a nickel(II) complex (**Ni-1a-Cl**). Following reduction by zinc, the resultant nickel(I) complex (**A**) performs a second oxidative addition into the aryl chloride to generate the nickel(III)−biaryl complex. Subsequent reductive elimination forms the desired product and a zinc-mediated reduction reforms the active nickel(0) catalyst. The second oxidative

Scheme 4. Mechanistic Studies

A) Reaction of **1a** under the standard conditions

10 mol% NiI$_2$
15 mol% bipy
2 eq. Zn
DMF [0.2], 85 °C, 24 h
2 eq. MgCl$_2$

1a

100% conversion
0% yield

B) Reaction of **2a** under the standard conditions

6.7 mol% NiI$_2$
10 mol% bipy
1.3 eq. Zn
DMF [0.3], 85 °C, 24 h
1.3 eq. MgCl$_2$

2a

4
100% conversion
47% yield

C) Stoichiometric reaction by adding **1a** first

1.0 eq. Ni(COD)DQ
1.5 eq. bipy
DMF [0.04], rt, 24 h

1a → [Ni^{II}] **Ni-1a-Cl**

1.0 eq. **2a**
DMF [0.04], 85 °C, 24 h
2 eq. Zn, 2 eq. MgCl$_2$

3aa
100% conversion
81% yield
6% yield **4**

D) Stoichiometric reaction by adding **2a** first

1.0 eq. Ni(COD)DQ
1.5 eq. bipy
DMF [0.04], 85 °C, 24 h

2a → MeO$_2$C–[Ni^{II}] **Ni-2a-Cl**

1.0 eq. **1a**
DMF [0.04], 85 °C, 24 h
2 eq. Zn, 2 eq. MgCl$_2$

3aa
100% conversion
72% yield
6% yield **4**

E) Stoichiometric reaction of both **1a** and **2a** with **Ni-2a-Cl**

1.0 eq. Ni(COD)DQ
1.5 eq. bipy
DMF [0.04], 85 °C, 24 h

2a → MeO$_2$C–[Ni^{II}] **Ni-2a-Cl**

1.0 eq. **1a**, 1.0 eq. **2a**
DMF [0.04], 85 °C, 1 min.
2 eq. Zn, 2 eq. MgCl$_2$

10% yield **4**
0% yield **3aa**

Scheme 5. Proposed Mechanism

addition from **A** would be more facile with electron-deficient aryl chlorides and lead to improved yields. Conversely, electron-neutral and electron-rich aryl chlorides would suffer from a slower oxidative addition, leading to increased levels of decomposition and consequently lower yields since the starting

materials are unstable to the reaction conditions. Under this premise, we suspected that using a more activated aryl electrophile (i.e., aryl bromides) would increase the rate of oxidative addition and lead to improved yields.

In conclusion, a nickel-catalyzed XEC coupling of C(sp^2)-hybridized electrophiles containing relatively unreactive C–Cl bonds has been developed. The difference between the heteroaryl and aryl chloride enables the coupling to occur without the use of a palladium co-catalyst. The relatively mild reaction conditions allow for broad functional group tolerance and a variety of heterocycles can be obtained in good yields. The inclusion of MgCl$_2$ to facilitate the reduction of nickel(II) and catalytic amounts of iodide are sufficient to enable the reductive coupling. Furthermore, preliminary mechanistic studies suggest that the nickel catalyst first oxidatively adds into the heteroaryl chloride over the aryl chloride. Although a complete mechanistic understanding has not yet been completed, we expect that the current results will enable the development of further C(sp^2)–C(sp^2) cross-electrophile couplings.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02307.

> Preparation of starting materials, optimization tables, control experiments, experimental procedures, and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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