Selective Ni-Catalyzed Cross-Electrophile Coupling of Heteroaryl Chlorides and Aryl Bromides at 1:1 Substrate Ratio

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Supporting Information Placeholder

ABSTRACT: Nickel-catalyzed cross-electrophile coupling (XEC) reactions of (hetero)aryl electrophiles represent appealing alternatives to palladium-catalyzed methods for biaryl synthesis, but they often generate significant quantities of homocoupling and/or proto-dehalogenation side products. In this study, an informer library of heteroaryl chloride and aryl bromide coupling partners is used to identify Ni-catalyzed XEC conditions that access high selectivity for the cross-product when using equimolar quantities of the two substrates. Two different catalyst systems are identified that show complementary scope and broad functional-group tolerance, and time-course data suggest the two methods follow different mechanisms. A $NiBr_2$/terpyridine catalyst system with Zn as the reductant converts the aryl bromide into an aryl-zinc intermediate that undergoes in situ coupling with 2-chloropyridines, while a $NiBr_2$/bipyridine catalyst system with tetrakis(dimethylamino)ethylene as the reductant uses $FeBr_2$ and NaI as additives to achieve selective cross-coupling.

Introduction

Nitrogen-containing biaryls are prevalent in biologically active compounds, pharmaceuticals, and agrochemicals,[1–3] and these structures are commonly accessed by transition metal-catalyzed cross-coupling reactions.[4–17] Conventional biaryl cross-coupling features the coupling of (hetero)aryl organometallic reagents, Ar–[M] ([M] = zinc, magnesium, tin, silicon, or boron species), with (hetero)aryl electrophiles, Ar–X (X = (pseudo)halides), enabled by palladium or other transition-metal catalysts. The complementary polarity and different activation mechanisms of the nucleophilic and electrophilic coupling partners can lead to highly selective cross-coupling of the two substrates, even when used in a 1:1 stoichiometry. Nonetheless, several factors have been motivating efforts to develop new methods to access biaryl structures. Aryl-organometallic coupling partners are much less readily available than aryl electrophiles, limiting access to structural diversity. This issue is especially relevant to medicinal chemistry and high-throughput screening efforts that target rapid access to diverse compounds, but it also impacts large-scale applications arising from the higher cost and operational complexities associated with organometallic reagents. The instability of heteroaryl organometallic reagents can limit their use in cross-coupling reactions. This issue is most prominently evident in the "2-pyridyl problem", a term commonly used to describe challenges associated with preparation and use of 2-pyridyl and related heteroaryl organometallic reagents.[18,19] Finally, while palladium catalyst systems are the most widely used for cross-coupling, the increasing and fluctuating cost of palladium underlies growing interest in the development of non-precious-metal catalyst systems (**Figure 1A**).

Nickel-catalyzed cross-electrophile coupling (XEC) represents an attractive alternative to palladium-catalyzed cross-coupling for forming C(sp^2)–C(sp^2) bonds, as it directly uses stable and widely available carbon electrophiles as coupling partners, and nickel is an earth abundant, non-precious metal that is much less expensive than palladium.[20–23] A central challenge of this strategy is selectively accessing the cross-coupled product over the two homo-coupled products due to the subtle differences between two coupling partners.[24,25] Pioneering studies from the groups of Gosmini[26–28] and Léonel[29–32] laid the foundation for the development of Ni-catalyzed heteroaryl-aryl XEC reactions, demonstrating that useful yields of the cross-coupled products were possible and providing preliminary insights into the reaction mechanism. More recent advances by Lautens[33] and Watson[34] demonstrated extensions of these reactions, using new combinations of coupling partners and demonstrating enantioselective catalysis, respectively. In these precedents, optimization generally prioritized a single heteroaryl electrophile and two approaches were generally adopted to improve the yield of the cross-coupled product (**Figure 1B**). The first uses an excess of one of the coupling partners (e.g., 2–3 equiv) to improve the yield of cross-coupled products with respect to the limiting reagent. This approach, however, often generates significant quantities of homo-coupled dimers from the excess reagent, introducing undesirable waste and complicating product isolation. In the second approach, the (pseudo)halide substituents on the two electrophiles are adjusted on a case-by-case basis to identify coupling partners that show comparable reactivity and achieve optimal cross-selectivity. For instance, aryl iodides are effective with more reactive heteroaryl chlorides, while aryl bromides or chlorides can undergo selective coupling with less reactive heteroaryl chlorides. These approaches are often implemented simultaneously to maximize the yield of cross-coupled products. Ideally, one could identify catalyst systems that achieve general and selective XEC reactivity using an equimolar ratio of the coupling partners without the need to tune the halide substituents on each electrophile on a case-by-case basis (**Figure 1C**). The present study describes our efforts to achieve these goals in the context of XEC between aryl bromides and 2-chloro-substituted aromatic heterocycles, including pyridines, pyrimidines, pyrazines, and pyridazines. The latter substrates present unique challenges in conventional cross-coupling reactions with organometallic nucleophiles.[35–37]

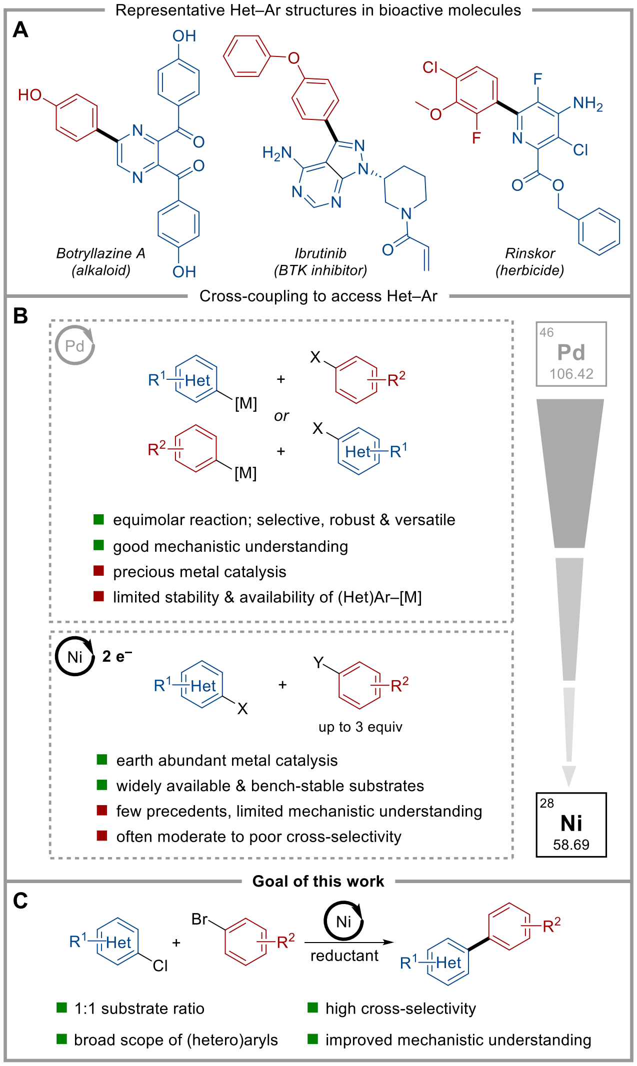


Figure 1. Heteroaryl-aryl core structures are commonly encountered in bioactive molecules (A). Existing coupling methods typically use Pd-based catalyst, but Ni-catalyzed methods would offer compelling alternatives, if they could overcome selectivity challenges (B). This study targets the development of Ni-catalyzed cross-electrophile coupling methods that are compatible with equimolar substrate ratios (C).

Results and Discussion

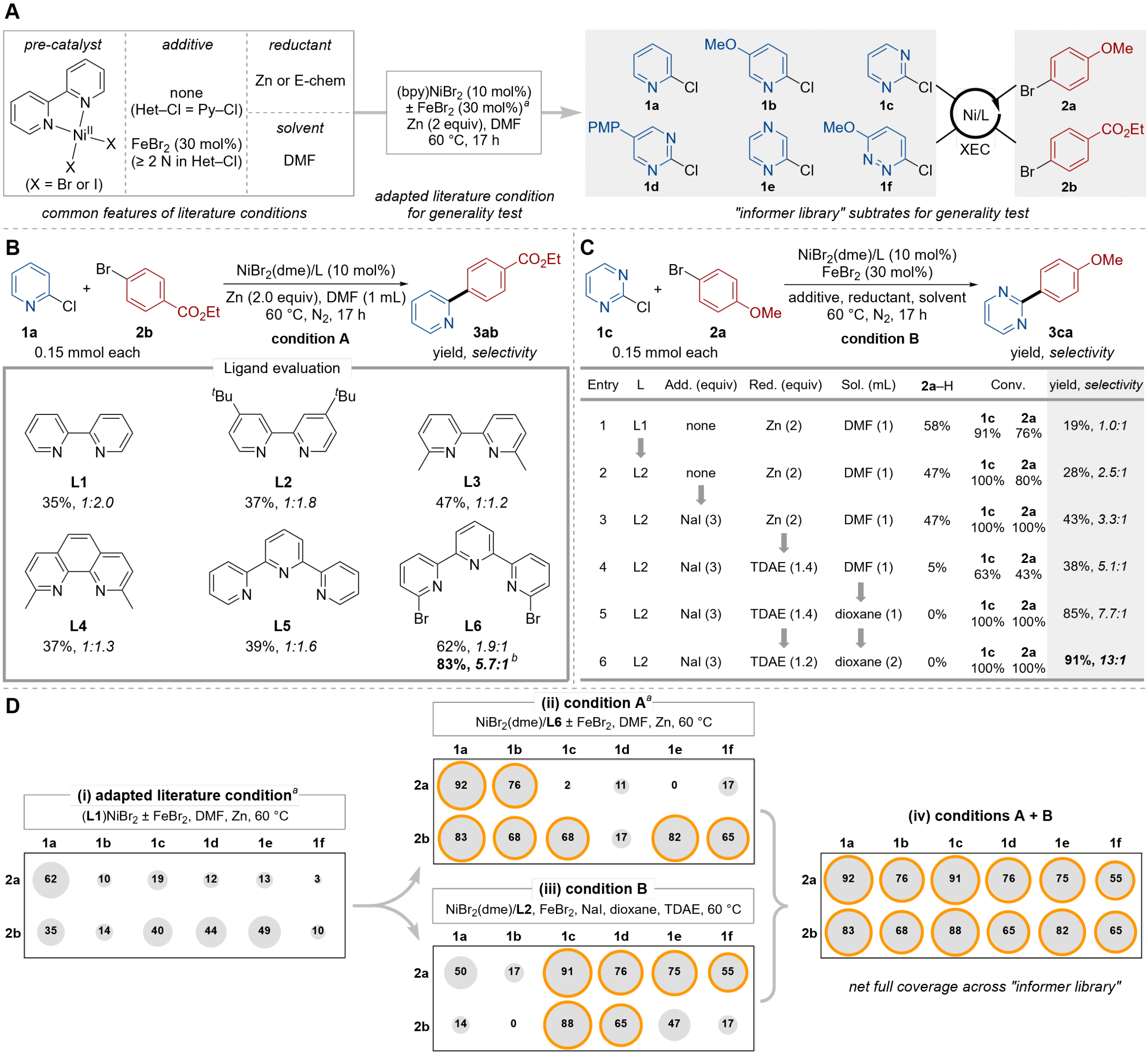
Reaction optimization using an informer library. Precedents for Ni-catalyzed heteroaryl-aryl XEC reactions show strong similarity among the catalyst systems employed. Early studies by Gosmini[26–28] and subsequent studies by Léonel[29–32] utilized electrochemical reduction, while more recent reports by Lautens[33] and Surgenor[38] used Zn or Mn chemical reductants. Each of these reports used NiX_2/bpy (X = Br or I, bpy = 2,2′-bipyridine) catalyst systems. Gosmini and Léonel noted a beneficial effect of $FeBr_2$ on reactions with heteroaryl electrophiles that contain two or more nitrogen atoms in the ring (e.g., pyrimidine, pyrazine, and pyridazine), wherein $FeBr_2$ was proposed to limit catalyst poisoning by the heterocycle through coordination to Ni.[27]

Building on these reports, we initiated reactivity studies with a reaction system comprising a (bpy)$NiBr_2$ catalyst (10 mol%), Zn as the reductant, and DMF as the solvent (**Figure 2A**). A panel of six different heteroaryl chlorides (Het–Cl, **1a**–**1f**) and two aryl bromides (Ar–Br, **2a** and **2b**) were used as an "informer library"[39] to evaluate XEC reactivity with equimolar quantities of the Het–Cl and Ar–Br substrates. With the diazaheteroaryl substrates **1c**–**1f**, 30 mol% $FeBr_2$ was included in the reaction (see Section 2.1 of the Supporting Information for full screening data). The majority of the reactions led to poor or modest yields of the desired XEC (**Figure 2D-i**), with more than half affording <20% yields. The reactions typically proceed to high conversion, but they favor formation of homo-coupled dimers and/or proto-dehalogenation byproducts (Table S1). This outcome highlights the predominant challenge facing such reactions, particularly when using a 1:1 ratio of the electrophilic coupling partners.

Results from XEC reactions using the adapted literature conditions highlight the need for new catalyst systems. We initiated the reaction optimization by evaluating a series of nitrogen-based ligands for the coupling of 2-chloropyridine (**1a**) with ethyl 4-bromobenzoate (**2b**) (**Figure 2B**). Reactions catalyzed by Ni complexed with bidentate nitrogen ligands showed that a hindered ligand, 6,6′-dimethyl-2,2′-bipyridine (**L4**), slightly increased the yield of the cross-coupled product **3ab**, compared to other bipyridine or phenanthroline ligands evaluated (**L1** to **L4**; see full ligand screening in Table S2). Tridentate nitrogen ligands were also evaluated. The parent terpyridine (tpy) ligand **L5** exhibits performance similar to the bidentate ligands. Among other tridentate ligands, the dibromo-substituted tpy derivative **L6** led to the best yield of **3ab** (62%). Reducing the Ni/**L6** catalyst loading to 7 mol% further improved the result (83%). The effectiveness of this ligand is rather unexpected because it has heteroaryl bromide groups that are potentially reactive. While the origin of the beneficial effect of **L6** is not yet understood, the reaction shows nearly quantitative mass balance with respect to **1a** and **2b** and their associated products, suggesting that the ligand does not undergo XEC with the substrates. In addition, analysis of the reaction mixture by MALDI-MS reveals peaks associated with the Ni/**L6** complex after the reaction (see Section 5 of the Supporting Information for additional data).

Use of the Ni/**L6** catalyst system results in more than a ten-fold increase in the cross-selectivity relative to the original Ni/**L1** catalyst (from 1:2.0 to 5.7:1). This catalyst system, designated "condition A", was then evaluated with the other substrates in the informer library (using 30 mol% $FeBr_2$ with **1c**–**1f**). Significantly improved outcomes were observed for many of the substrate pairs, with good-to-excellent results obtained from XEC of 2-chloropyridines **1a** and **1b** with **2a** and **2b**, and from the reactions of pyrimidine **1c**, pyrazine **1e**, and pyridazine **1f** with **2b** (**Figure 2D-ii**). The reduced yields in the remaining reactions correlated with formation of significant quantities of proto-dehalogenation byproducts (Table S4).

To achieve effective coupling of the substrates that reacted poorly under condition A, we explored new modified reaction conditions for the XEC of 2-chloropyrimidine (**1c**) and 4-bromoanisole (**2a**) (**Figure 2C**; see Tables S5–S8 for additional screening data). Switching the ligand from **L1** to **L2** slightly



Entry	L	Add. (equiv)	Red. (equiv)	Sol. (mL)	**2a**–H	Conv.	yield, *selectivity*
1	L1	none	Zn (2)	DMF (1)	58%	**1c** 91% **2a** 76%	19%, *1.0:1*
2	L2	none	Zn (2)	DMF (1)	47%	**1c** 100% **2a** 80%	28%, *2.5:1*
3	L2	NaI (3)	Zn (2)	DMF (1)	47%	**1c** 100% **2a** 100%	43%, *3.3:1*
4	L2	NaI (3)	TDAE (1.4)	DMF (1)	5%	**1c** 63% **2a** 43%	38%, *5.1:1*
5	L2	NaI (3)	TDAE (1.4)	dioxane (1)	0%	**1c** 100% **2a** 100%	85%, *7.7:1*
6	L2	NaI (3)	TDAE (1.2)	dioxane (2)	0%	**1c** 100% **2a** 100%	**91%, *13:1***

(i) adapted literature condition[a]
(**L1**)NiBr$_2$ ± FeBr$_2$, DMF, Zn, 60 °C

	1a	1b	1c	1d	1e	1f
2a	62	10	19	12	13	3
2b	35	14	40	44	49	10

(ii) condition A[a]
NiBr$_2$(dme)/**L6** ± FeBr$_2$, DMF, Zn, 60 °C

	1a	1b	1c	1d	1e	1f
2a	92	76	2	11	0	17
2b	83	68	68	17	82	65

(iii) condition B
NiBr$_2$(dme)/**L2**, FeBr$_2$, NaI, dioxane, TDAE, 60 °C

	1a	1b	1c	1d	1e	1f
2a	50	17	91	76	75	55
2b	14	0	88	65	47	17

(iv) conditions A + B

	1a	1b	1c	1d	1e	1f
2a	92	76	91	76	75	55
2b	83	68	88	65	82	65

Figure 2. Reaction optimization. See Section 2 of the Supporting Information for experimental details. Yields were determined by ^{1}H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. Cross-selectivity ratio reflects ^{1}H NMR yields of cross-coupled product:(heteroaryl dimer + aryl dimer). (A) Illustration of (adapted) literature conditions and informer library substrates. (B) Optimization of XEC of **1a** with **2b**. (C) Optimization of XEC of **1c** with **2a**. (D) Use of informer library to test the generality of the adapted literature condition, condition A, and condition B. [a] Used 10 mol% Ni catalyst and added 30 mol% FeBr$_2$ when **1** contains more than one nitrogen atom in the ring. [b] 7 mol% Ni catalyst.

increased the yield from 19% to 28% (entries 1 and 2). Addition of 3 equiv of NaI enhanced the aryl bromide conversion and led to a higher yield of **3ca** (43%, entry 3), but a significant quantity of the proto-dehalogenation byproduct of **2a** (**2a**–H) was observed. This side reaction was attributed to the use of Zn as the reductant, as soluble Zn^{II} salts generated during the reaction could form protolytically sensitive aryl-zinc species *in situ*.[40,41] Formation of the proto-debromination byproduct **2a**–H was suppressed upon replacing Zn with tetrakis(dimethylamino)-ethylene (TDAE), a mild organic reductant,[42] and changing from DMF to dioxane as the solvent led to an 85% yield of **3ca**, with full conversion of both coupling partners (entries 4 and 5). Reducing the TDAE loading and reaction concentration led to the optimal yield (91%, entry 6), and these conditions were designated "condition B". No product was observed when replacing TDAE with Zn or replacing **L2** with **L6** under optimized condition B (Table S8), implicating key differences between conditions A and B, as elaborated below. The condition B catalytic method was then evaluated with the other substrates in the informer library (Table S9). The yields obtained from the reaction of **2a** with **1c**–**1f** and **2b** with **1c**–**1d** showed significant enhancement under condition B (**Figure 2D-iii**). Collectively, the informer library data show that conditions A and B exhibit complementary reactivity, enabling successful outcomes with all 12 XEC reactions (**Figure 2D-iv**).

Reaction scope. With the optimal conditions in hand, we examined the coupling of a variety of heteroaryl chlorides and aryl bromides containing an array of functional groups and steric environments (**Figure 3**). Coupling reactions of 2-chloropyridine (**1a**) with aryl bromides bearing different substituents, ranging from electron-rich (–NMe$_2$) to electron-deficient (–CF$_3$), were all effective under condition A, affording the cross-coupled products in high yields (**3aa**–**3af**). The

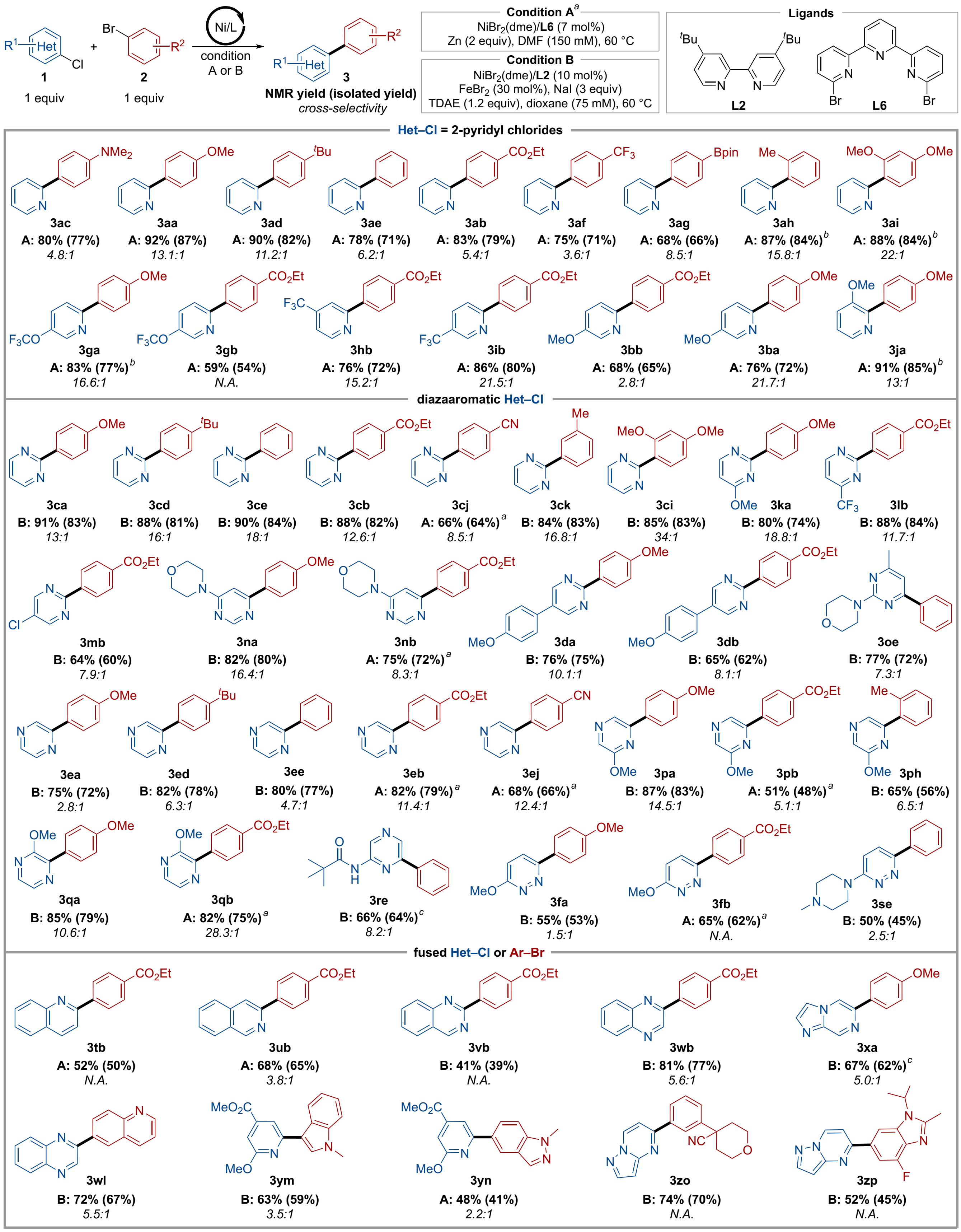


Figure 3. Synthetic scope of heteroaryl chlorides coupling with aryl bromides with conditions A and B. Yields were determined by ^{1}H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard; isolated yields are shown in parentheses. Cross-selectivity ratio reflects ^{1}H NMR yields of cross-coupled product:(heteroaryl dimer + aryl dimer). See Section 3 of the Supporting Information for experimental details. [a] Used 10 mol% Ni catalyst and added 30 mol% FeBr$_2$ when **1** contains two or more nitrogen atoms in the ring. [b] **L3** instead of **L6**, 10 mol% Ni catalyst. [c] Added 2 equiv LiCl.

tolerance of the boronic ester allows room for further diversification (**3ag**). Sterically hindered aryl bromide **2h** was smoothly coupled with **1a**, using 10 mol% Ni complexed with **L3** instead of **L6**. Electron-donating and -withdrawing groups at different positions of the pyridine ring were compatible with the reaction conditions (**3ai**, **3ga**, **3gb**, **3hb**, **3ib**, **3bb**, **3ba**, **3ja**).

The reaction also shows broad scope with diazaheteroaryl chlorides. Unsubstituted 2-chloropyrimidine (**1c**) and 2-chloropyrazine (**1e**) can be coupled with an array of electronically diverse para-substituted aryl bromides (**2a**, **2b**, **2d**, **2e**, **2j**). Ortho- and meta-substituted aryl bromides were also effective (**3ck**, **3ci**, **3ph**). Exclusive activation of the C–Cl bond at the C2 position of **1m** showed the great site-selectivity of this method. Variations of substituents on the 2-chloropyrimidine or 2-chloropyrazine ring were tolerated (**3ka**, **3lb**, **3mb**, **3da**, **3db**, **3pa**, **3pb**, **3qa**, **3qb**). 4-Chloropyrimidine and 3-chloropyridazine derivatives can be coupled with electron-rich, -neutral, and -deficient aryl bromides under condition A or B (**3na**, **3nb**, **3re**, **3fa**, **3fb**, **3se**).

The coupling of **1n** with **2a** was effective under condition A, while its coupling with **2b** was effective under condition B. Several more examples showcased this complementary reactivity accessible with conditions A and B (cf. **3pa** and **3pb**, **3qa** and **3qb**, **3fa** and **3fb**).

The reaction conditions can be extended to the XEC of heteroaryl chlorides with aryl bromides in which one or both substrates features a fused bicyclic structure. Multi-substituted 2-chloropyridines can be coupled with fused aryl bromides (**3ym**, **3yn**). The reactions of electron-deficient and -rich aryl bromides with fused bicyclic heteroaryl chlorides afforded the cross-coupled products in moderate to high yields (**3tb**, **3ub**, **3vb**, **3wb**, **3xa**, **3wl**). Heteroaryl chlorides with multiple nitrogen atoms in the ring can increase the likelihood of catalyst poisoning, but three such structures were shown to undergo effective coupling (**3xa**, **3zo**, **3zp**).

Overall, an average isolated yield of 70 ± 12% was achieved across 55 products containing 12 heteroaryl core structures, highlighting the efficacy and generality of conditions A and B for heteroaryl-aryl XEC. These optimized conditions were evaluated without further optimization in reactions with other electrophiles such as heteroaryl bromides and aryl sulfonate esters.[43,44] These reactions proved much less successful (see Section 4 of the Supporting Information for full details); however, the workflow introduced provides the basis for development of new catalyst systems for the reactions of other electrophiles.

Time-course analysis and mechanistic features of reaction condition A. The reductive coupling of 2-chloropyridine (**1a**) and ethyl 4-bromobenzoate (**2b**) was used to probe the reaction time course of XEC under condition A (**Figure 4A**). Organometallic intermediates were probed by quenching reaction aliquots with iodine, an established protocol that converts arylzinc and arylnickel species into aryl iodides.[41,45] Specifically, 2-pyridyl–NiX or –ZnX species are converted into 2-iodopyridine (**1a–I**), and Ar–NiX or –ZnX (Ar = *p*-CO_2Et-C_6H_4) species are converted into ethyl 4-iodobenzoate (**2b–I**). These aryl iodides (**1a–I** and **2b–I**) and other catalytic reaction products (**3ab**, **1aa**, **2bb**) were analyzed and quantified by ^{1}H NMR spectroscopy at each time point.

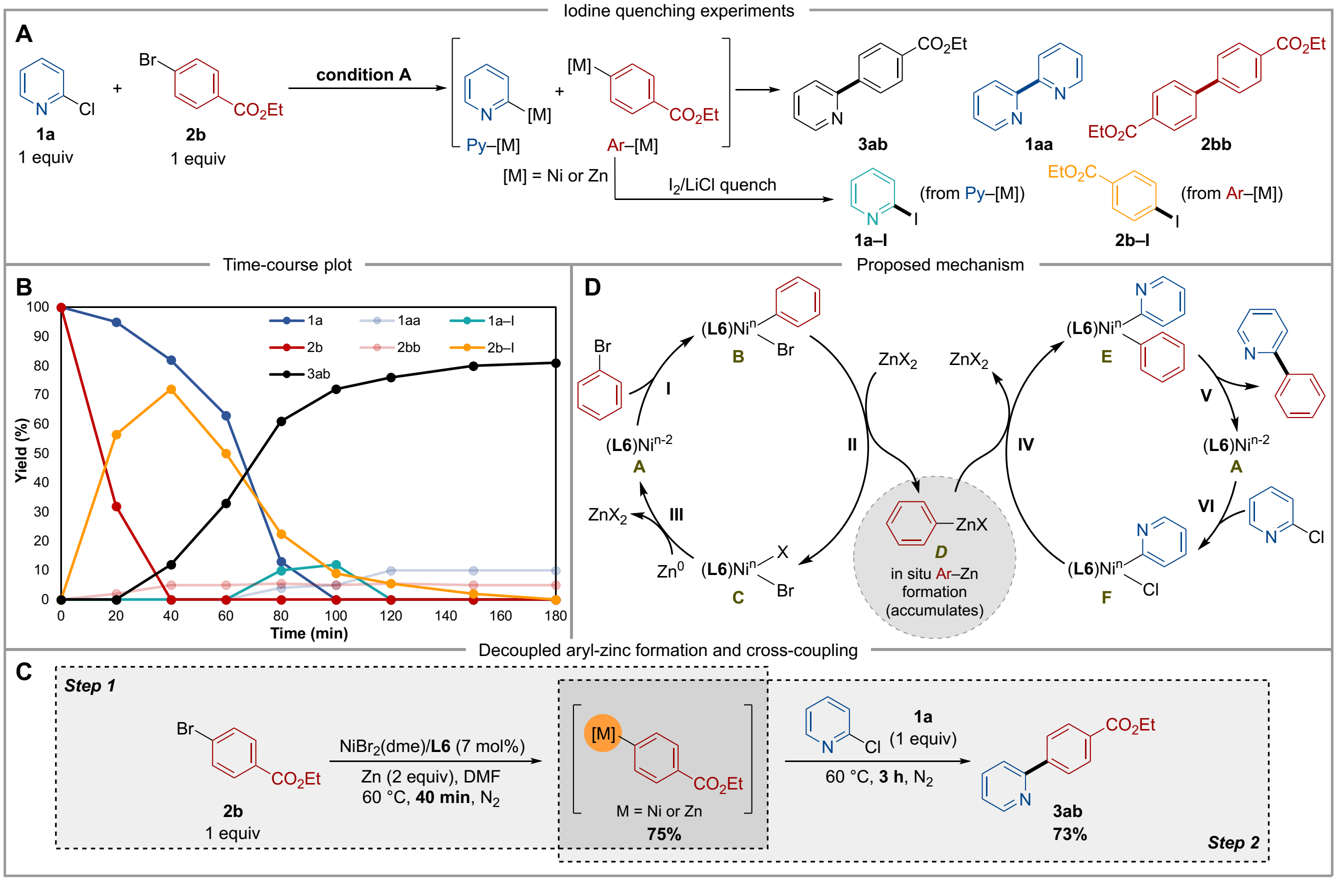


Figure 4. Mechanistic studies on reaction condition A. Iodine quenching experiments (A), time-course plot (B), stepwise reactions (C), and proposed mechanism (D) for XEC of **1a** with **2b** under condition A. See Section 6 of the Supporting Information for experimental details. Yields were determined by ^{1}H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. Yields of homo-coupled dimers are reported on a molar basis, i.e., the maximal theoretical yield is 50%.

The time-course data in **Figure 4B** reveal rapid formation of **2b–I** during the first 40 min of the reaction, along with fast depletion of the aryl bromide (**2b**). Small quantities of the aryl dimer (**2bb**) are also detected during this period. In contrast, substrate **1a** is consumed only slowly and **1a–I** is not observed at early stages of the reaction. The cross-coupled product (**3ab**) begins forming slowing at 20 min and then accelerates after 40 min, as **2b–I** reaches a maximum concentration. Formation of **3ab** ceases upon depletion of **2b–I** and **1a**, reaching a final yield of 81%. The two homo-coupled dimers (**1aa**, **2bb**) form in <10% yields.

The nickel catalyst is present only in 7 mol% with respect to the substrate, so the build-up of **2b–I** to 72% is attributed to formation of a **2b**-derived arylzinc species in situ. To probe this hypothesis, **2b** was subjected to the same reaction conditions in the absence of **1a** and quenched with iodine, resulting in a 75% yield of **2b–I**. The arylzinc species appears to be relatively stable, as the quantity of **2b–I** decreased by only 10% when the product mixture was allowed to sit for 2 h (Figure S8A). A similar test of **1a** in the absence of **2b** led to no evidence for pyridylzinc species (via formation of **1a-I**). This mixture instead generated significant quantities of the homo-coupled dimer **1aa** (69% yield, Figure S8B). No direct reaction of Zn with **2b** (or **1a**) was observed in the absence of the Ni catalyst (Table S3).

Similar time-course analysis was conducted for the reaction of **1a** and **2b** with a catalyst using tpy (**L5**), rather than **L6**, as the ligand. Slower consumption of **2b** and less build-up of the arylzinc intermediate is evident with **L5**/NiBr$_2$ (Figure S9). While the mechanistic origin of this difference between **L5** and **L6** is not well understood, this observation implies that steric and/or electronic effects of the bromo substituents on tpy lead to increased rates of Ni-catalyzed conversion of **2b** into an arylzinc intermediate.

A further test of the **L6**/NiBr$_2$-catalyzed reaction was conducted by stirring substrate **2b** under condition A for 40 min in the absence of **1a**. Analysis of an aliquot of this solution using the iodine quench revealed the formation of **2b–I** in 75% yield (**Figure 4C**, step 1). Then, one equivalent of **1a** was added to the reaction mixture, and the solution was stirred for an additional 3 h. The 73% yield of the cross-coupled product **3ab** obtained from this stepwise sequence (**Figure 4C**, step 2) indicates that the second Negishi-like coupling step is very efficient.

The formation of an arylzinc intermediate from **2b** is consistent with previous observations that arylzinc species can be formed from aryl halides under reductive conditions with a different Ni/tpy catalyst.[46] This precedent and the data summarized above support a mechanism for nickel-catalyzed heteroaryl-aryl coupling under condition A that is outlined in **Figure 4D**. A reduced nickel catalyst **A** undergoes oxidative addition of aryl bromide to form an aryl-nickel intermediate **B**, followed by transmetallation to ZnX$_2$ salts derived from the reductant to form arylzinc species **D** and nickel salt **C**. The arylzinc species accumulate in the reaction mixture before they undergo transmetallation to a pyridyl-nickel species **F**, arising from oxidative addition of 2-chloropyridine to **A**. The resultant nickel complex **E** reductively eliminates to form the cross-coupled product and regenerates the low-valent nickel catalyst **A**. This decoupled sequence enables differentiation between the two coupling partners, which leads to high XEC yields and cross-selectivity.

Time-course analysis and mechanistic features of reaction condition B. We next sought to gain insights into the XEC mechanism associated with condition B, using **1c** and **2a** as coupling partners. The use of TDAE as the reductant, rather than Zn, excludes the possibility of arylzinc formation under these conditions. The contributions of NaI and FeBr$_2$ to the

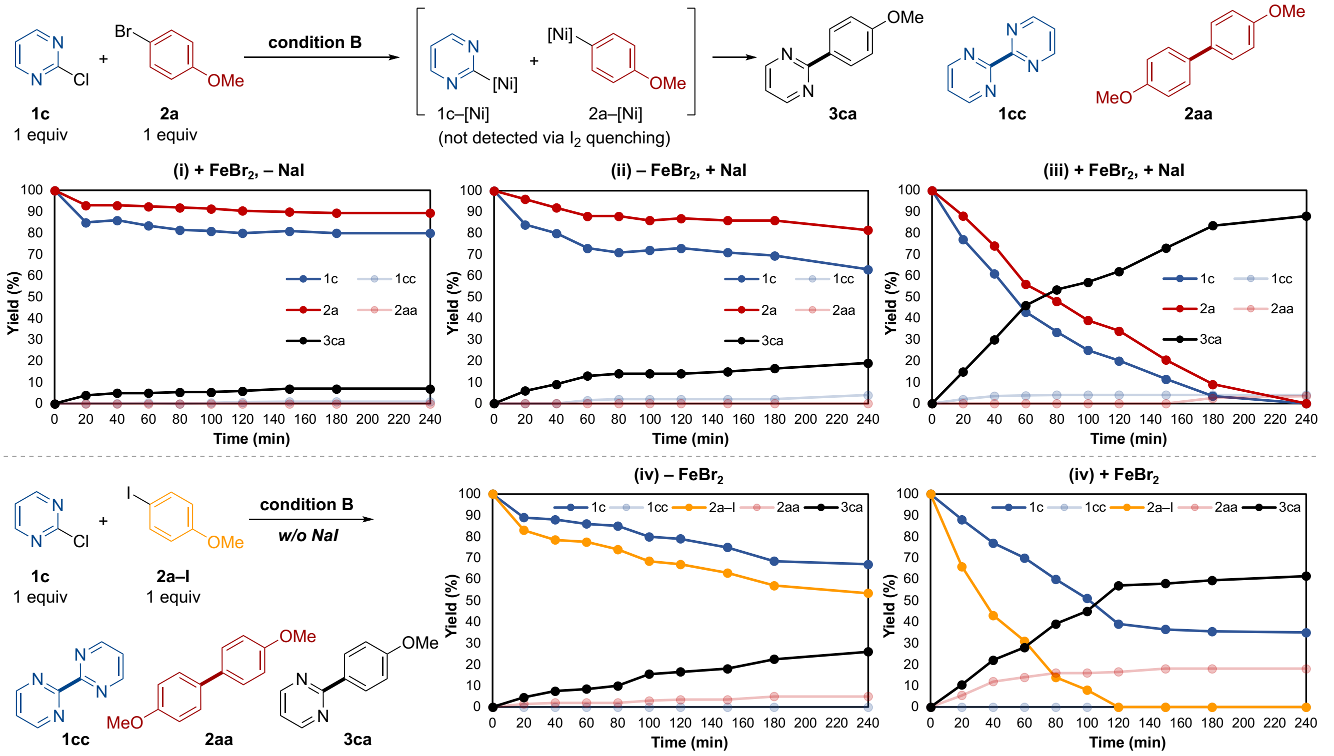


Figure 5. Time-course experiments for XEC of **1c** with **2a** or **2a–I** under condition B. See Section 6 of the Supporting Information for experimental details. Yields were determined by ^{1}H NMR spectroscopy of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. Yields of homo-coupled dimers are reported on a molar basis, i.e., the maximal theoretical yield is 50%.

reaction were probed through time-course experiments of the reaction in the absence and presence of these additives. The data show that both substrates exhibit minimal reactivity when either of the two additives is excluded from the reaction mixture (**Figures 5-i** and **5-ii**). In the presence of both NaI and $FeBr_2$, the consumption of two coupling partners proceeds at a similar rate, leading to steady formation of the cross-coupled product (**3ca**) with minimal formation of two homo-coupled byproducts **1cc** and **2aa** (**Figure 5-iii**). In all three experiments, **1c** appears to react slightly more quickly than that of **2a**, and more **1cc** is observed than **2aa**.

The time-course data show that both $FeBr_2$ and NaI are needed to support effective reactivity. A similar beneficial effect of $FeBr_2$ was observed by Gosmini and coworkers when studying analogous reactions under electrochemical conditions.[27] They proposed that $FeBr_2$ serves as a Lewis acid in the reaction to prevent poisoning of the Ni catalyst through heterocycle coordination. To gain further insight into the role of $FeBr_2$ under condition B, a collection of Lewis acids was tested in the XEC of **1c** with **2a** (Table S7). The results show that the product yield with $MgBr_2$ (87%) is nearly as high as that with $FeBr_2$ (91%). While we cannot exclude a redox role of $FeBr_2$ (see Section 6.5 of the Supporting Information for cyclic voltammetry data), the similar outcomes with $MgBr_2$ and $FeBr_2$ are most consistent with a Lewis acid effect. The beneficial effect of NaI could be attributed to its ability to activate the aryl bromide substrate through Ni-catalyzed halide exchange, as has been observed by others.[47,48] Although the iodide analog of **2a** (i.e., **2a–I)** is not observed during the reaction, it could form transiently and undergo rapid reaction. To probe this hypothesis, we conducted two additional time-course experiments using 4-iodoanisole (**2a–I**) instead of **2a** and NaI (**Figures 5-iv** and **5-v**). Aryl iodide **2a–I** is consumed faster than the heteroaryl chloride **1c** in the absence and presence of $FeBr_2$, contrasting the relative rates observed between aryl bromide **2a** and **1c**.[49] Slow reactivity is again observed with both substrates in the absence of $FeBr_2$ (**Figure 5-iv**). Efficient conversion of **2a–I** is observed in the presence of $FeBr_2$, affording a 62% yield of the cross-coupled product **3ca** and 16% yield of the homo-coupled dimer **2aa** (accounting for 32% of **2a–I**) (**Figure 5-v**). These results indicate that **2a–I** is too reactive to achieve high cross-selectivity. On the other hand, in situ formation of a transient aryl iodide in the presence of NaI could support the requisite balance in reactivity between the two coupling partners. NaI could also contribute to the XEC outcome in other ways, for example, undergoing halide exchange at Ni and altering the redox potential or influencing the kinetics of individual reaction steps in the coupling reaction.[50,51]

The current data, together with previous literature reports,[22,33] are consistent with a sequential oxidative addition mechanism for the XEC under condition B, wherein low-valent nickel-halide species and (hetero)aryl-nickel species undergo selective oxidative addition of one of the two coupling partners. Other possible pathways, such as reductive transmetallation between two nickel species,[52] are also possible, however.

Conclusion

The results outlined above introduce two highly effective Ni-only catalyst systems to support XEC that accesses heteroaryl-aryl structures. Both reaction conditions (A and B) enable XEC with a 1:1 ratio of heteroaryl chloride and aryl bromide substrates, and they exhibit high cross-selectivity, good functional group tolerance, and compatibility with multiple different aromatic heterocycles. The reactions show complementary reactivity, and mechanistic studies provide evidence for different XEC pathways for the reactions under conditions A and B. XEC condition A uses a sterically hindered terpyridine ligand on the Ni catalyst, which promotes in situ formation of aryl-zinc species that undergo subsequent coupling with the heteroaryl electrophile. XEC condition B leverages synergistic contributions of $FeBr_2$ and NaI additive to match the relative reactivity of the two coupling partners and achieve high cross-selectivity. Together, these methods achieve general XEC reactivity and provide access to an unprecedented scope of nitrogen-containing biaryls.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Additional tables of optimization data, mechanistic studies, CV studies, detailed experimental procedures, characterization of products, copies of NMR spectra (PDF).

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All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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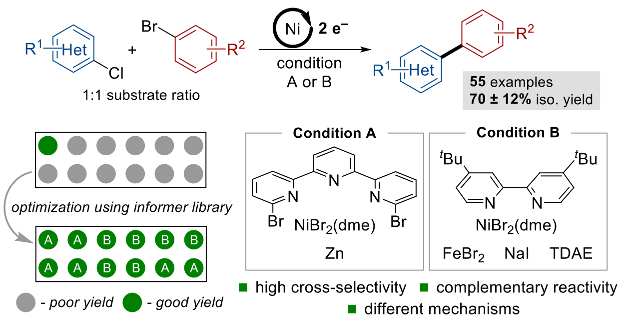
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55 examples
70 ± 12% iso. yield
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A A B B B B
A A B B A A
- poor yield
- good yield
Condition A
N N N Br Br
NiBr2(dme)
Zn
Condition B
tBu tBu N N
NiBr2(dme)
FeBr2 NaI TDAE
high cross-selectivity
complementary reactivity
different mechanisms