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Communication

A General, Multimetallic Cross-Ullmann Biheteroaryl Synthesis from Heteroaryl Halides and Heteroaryl Triflates

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ABSTRACT: Despite their importance to medicine and materials science, the synthesis of biheteroaryls by cross-coupling remains challenging. We describe here a new, general approach to biheteroaryls: the Ni- and Pd-catalyzed multimetallic cross-Ullmann coupling of heteroaryl halides with triflates. An array of 5-membered, 6-membered, and fused heteroaryl bromides and chlorides, as well as aryl triflates derived from heterocyclic phenols, proved to be viable substrates in this reaction (62 examples, 63 ± 17% average yield). The generality of this approach to biheteroaryls was further demonstrated in 96-well plate format at 10 μmol scale. An array of 96 possible products provided >90% hit rate under a single set of conditions. Further, low-yielding combinations could be rapidly optimized with a single "Toolbox Plate" of ligands, additives, and reductants.

Biheteroaryls are commonly found in drugs, electronic materials, ligands, and natural products,[1] but their synthesis remains a challenge.[2] As all-carbon aromatics are more widely available and have a more discrete range of reactivity than their heteroaryl analogues, strategies toward biheteroaryl synthesis have had to balance substrate availability and stability with reaction generality (Scheme 1). For example, cross-coupling approaches[3] are the most general, but can be limited by the poor availability[4,5] and instability[6] of heteroaryl nucleophile equivalents. C−H arylation[7] and cross-dehydrogenative coupling[8] approaches overcome substrate availability problems, but C−H bond selectivity and generality among the broad reactivity of heteroaryls can be challenging. Recently, sulfur[9,10] and phosphorus[11] chemistry has been developed that allows access to challenging biheteroaryls, but these new approaches share some of the availability and regiocontrol limitations of cross-coupling and C−H functionalization. *Given the wide availability[4] of heteroaromatic bromides, chlorides, and phenols (10−1000 times more than HetAr-[M]), a cross-Ullmann approach would be a powerful addition to biheteroaryl synthesis.*

Cross-Ullmann biaryl syntheses can be divided into two categories: 1-pot, 2-step reactions (*e.g.*, borylation of one HetAr-X followed by coupling with a second HetAr-X) and reductive single-step reactions. While both approaches have had success with biaryl[12,13] and heteroaryl−aryl[14,15] cross-coupling reactions, neither approach has been widely tested against biheteroaryls.[16,17] Indeed, the wide range of reactivities (that present a challenge for selectivity) and the potential for biheteroaryls to coordinate strongly to the catalyst[18] (inhibiting turnover and lowering selectivity) could limit cross-Ullmann biheteroaryl synthesis to a narrow range of coupling partners.[19] Our approach was to use our increasing understanding of Ni and Pd multimetallic cross-Ullmann chemistry[20] to design a comprehensive solution to the synthesis of biheteroaryls from heteroaryl halides and heteroaryl triflates (Scheme 1). Our results, described here provide a general set of conditions effective for a broad array of combinations and the tools necessary to optimize low-yielding reactions.

The initial reaction optimization[20a] using 6-methylpyridin-3-yl triflate (**1a**) and 3-bromopyridine (**2a**) as starting materials (Table 1 and Table S6 in Supporting Information) revealed that nonsymmetric biheteroaryl **3a** could be formed in 50% yield in the presence of 5 mol % $NiBr_2$(dme)/**N1** and 5 mol % $PdCl_2$/**P1** as catalysts, 2 equiv of Zn as reductant, and 2 equiv of KF as additive in DMF at 60 °C (Table 1, entry 1). A series of control reactions confirmed the necessity of metal catalysts, reductant, and salt additive.[20,21] Replacement of the highly hygroscopic[22] KF additive with KBr did not lead to any decrease in yield of **3a** (entry 2). Further screening of the amine ligands on nickel showed that, while dtbbpy (**N1**) remained the most promising for the model substrate pair, 1,10-phenanthroline (**N2**) and substituted terpyridine ligands (**N3** and **N4**) were also relatively effective (entries 3−5). An evaluation of phosphine ligands indicated that product **3a** could be obtained in satisfactory yields when **P2** and **P3** were used (entries 6 and 7), although **P1** was still preferred when the amount of **2a** was increased to 1.5 equiv (73 vs 70%, entries 2 and 6). Finally, the use of rigorously anhydrous KBr (stored in a N_2 filled glovebox) further improved the yield of **3a** to 79% (Table 1, entry 8).

An array of 6-membered, 5-membered, and fused heteroaryl bromides were next evaluated as substrates under these optimal conditions (Scheme 2).[23] In addition to 3-pyridyl bromides, a 2-pyridyl bromide (**3k**) and a substituted 4-pyridyl bromide (**3l**) could both be coupled with 3-pyridyl triflates

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Scheme 1. Approaches to Access Nonsymmetric Biheteroaryls by Merging Heteroarene Feedstocks

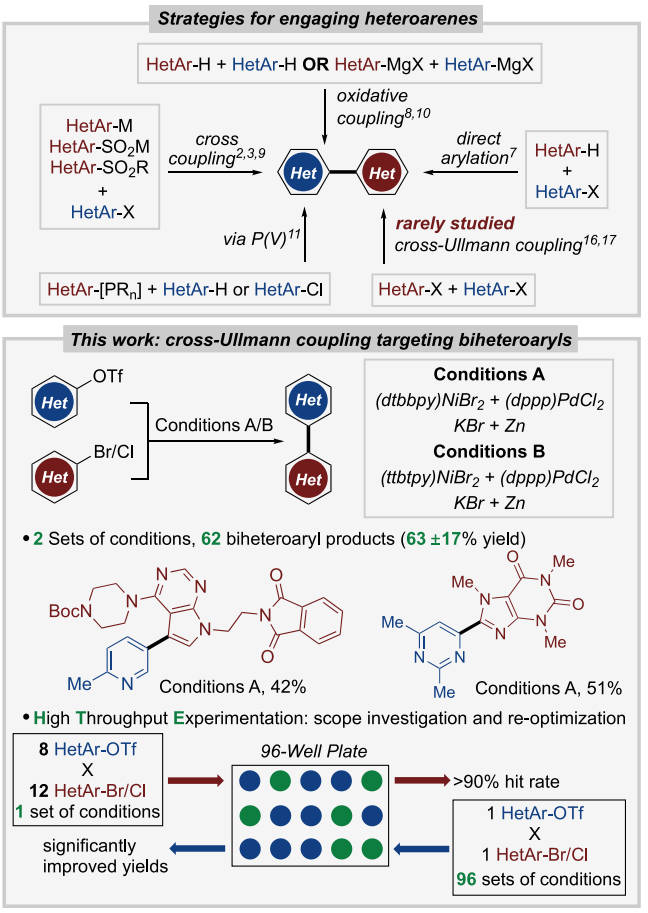
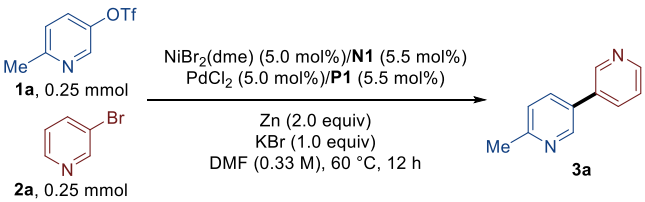
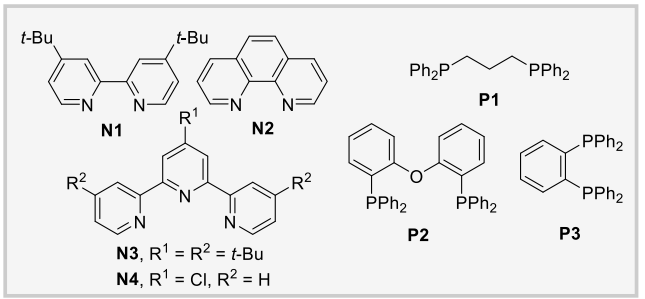


Table 1. Optimization of Model Reaction[a]





entry	variations from above conditions	3a (%)
1	KF (2.0 equiv) as additive	50
2	none	50 (73[b])
3	**N2** instead of **N1**	40
4	**N3** instead of **N1**	43
5	**N4** instead of **N1**	42
6	**P2** instead of **P1**	52 (70[b])
7	**P3** instead of **P1**	45
8	rigorously anhydrous KBr	79[b] (81[c])

[a]Reactions on a 0.25 mmol scale in 0.75 mL of DMF. Calibrated GC yield. KBr was stored in air unless otherwise noted. See Supporting Information, Table S6 for additional selectivity data. [b]1.5 equiv of **2a** was used. [c]^{1}H NMR yield.

successfully, affording the biheteroaryls in 58% and 83% yield. These conditions were also effective for a variety of 5-membered heteroaryl bromides (**3m**–**3w**), including a number that are much more electron-rich than pyridines (**3m**–**3o**, **3r**–**3w**), and a diverse array of fused ring heterocycles (**3x**–**3aj**). In all except three cases,[24] lower yields were due to formation of side products (homodimers and HetAr–H) or challenges in isolation.[25] In three of the lower-yielding cases, higher yields could be obtained with further optimization (see Figure 1).

Although heteroaryl chlorides are the most widely available heteroaryl electrophile,[4] their low reactivity can present challenges to selectivity in cross-electrophile coupling.[20c] Our standard conditions (**A**) allow the coupling of a variety of heteroaryl chlorides, ranging from those activated toward oxidative addition (**3al**–**3ao**) to deactivated (**3ap**–**3ar**). The wider availability of aryl chlorides provides unique coupling partners, such as precursors to drug molecules imiquimod[26] and pazopanib[27] (**3as** and **3at**).[28,29] Finally, 2,3′-bipyridine **3ao** was scaled 10-fold, from 0.5 to 5 mmol, with comparable yields (71% to 63%).

These general conditions tolerate a variety of electrophilic functional groups that could be challenging for other methods. For example, ketones, esters, and aldehydes could react with Grignard reagents, but are unreactive under these conditions (**3g**, **3h**, **3p**, **3q**, **3an**, **3ao**). A wide variety of protecting groups are tolerated, including acid-sensitive protecting groups (**3m**, **3s**, **3t**, **3x**, **3ah**) and even an allyl group is tolerated (**3ag**). Finally, some steric hindrance is tolerated (**3e**, **3o**, **3u**, **3w**, **3x-aa**, **3ac**, **3ae**).

While electron-neutral and electron-rich pyridyl and pyrimidyl bromides proved to be viable substrates (**3a**–**3e**), we found that couplings with electron-poor heteroaryl bromides (**3f**–**3j**) led to low yields due to rapid homocoupling. Re-examination of the other effective ligands in Table 1 led to a new set of conditions (**B**) utilizing ttbtpy (**N3**) instead of dtbbpy (**N1**) that suppressed competitive homocoupling and delivered the products **3f**–**3j** in 50–75% yields.[30]

The scope of heteroaryl triflates was also found to be broad (Scheme 3). In addition to the pyridyl triflates substituted with electron donating groups used in Scheme 2, pyridyl triflates with electron-neutral (–H, **3au**) or -deficient (–CO_2Me, **3aw**) substituents could be coupled, as could more electron-rich benzothiazole (**3ax**).

More importantly, these conditions can be used to synthesize challenging chelating biheteroaryls with varying electronic and steric properties (**3aac**–**3aai**) that could be useful in medicinal chemistry or as nonsymmetric bidentate ligands.[31] While these products should be competitive ligands for both Ni and Pd, reactions were complete by 24 h.[32] Notably, products **3aae** and **3aai** feature biheteroaryl cores that have not been previously reported.[33] Finally, the conditions could be extended to a nonaromatic vinyl triflate (**3aaj**).

To gain additional information on the applicability of these conditions to medicinal chemistry, we adapted our chemistry to a standard high-throughput experimentation (HTE) setup. Modern medicinal chemistry often utilizes HTE to facilitate the synthesis of collections of molecules for biological

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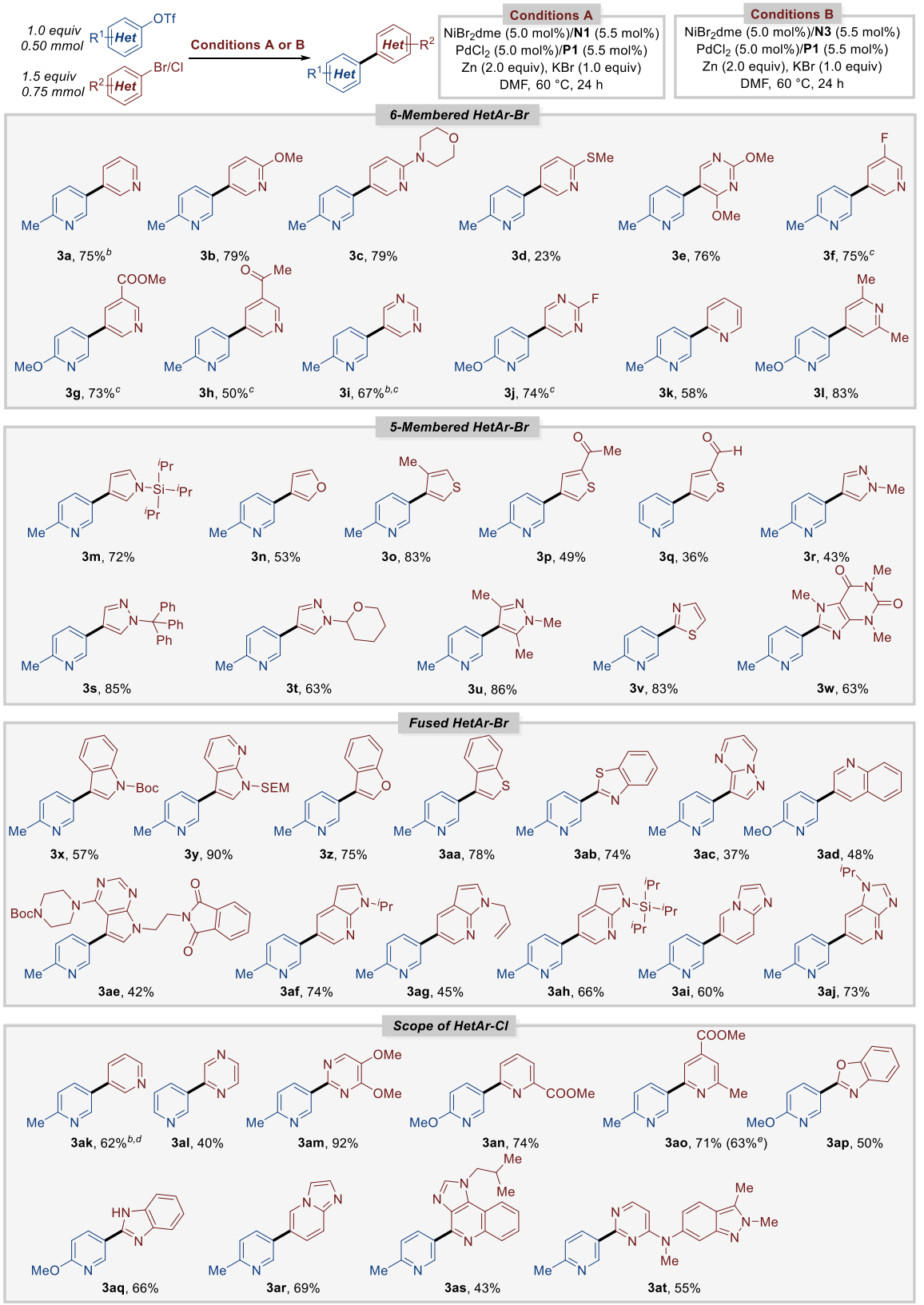
Scheme 2. Scope of Heteroaryl Bromides and Chlorides Coupled with Heteroaryl Triflates[a]



[a]Isolated yields of reactions on a 0.5 mmol scale. Reactions were conducted under conditions A unless otherwise noted. [b]NMR yield of a mixture of product and side products, see Supporting Information for details. [c]Reactions were conducted under conditions B. [d]Reaction temperature was 80 °C. [e]Isolated yield of a 5.0 mmol scale reaction.

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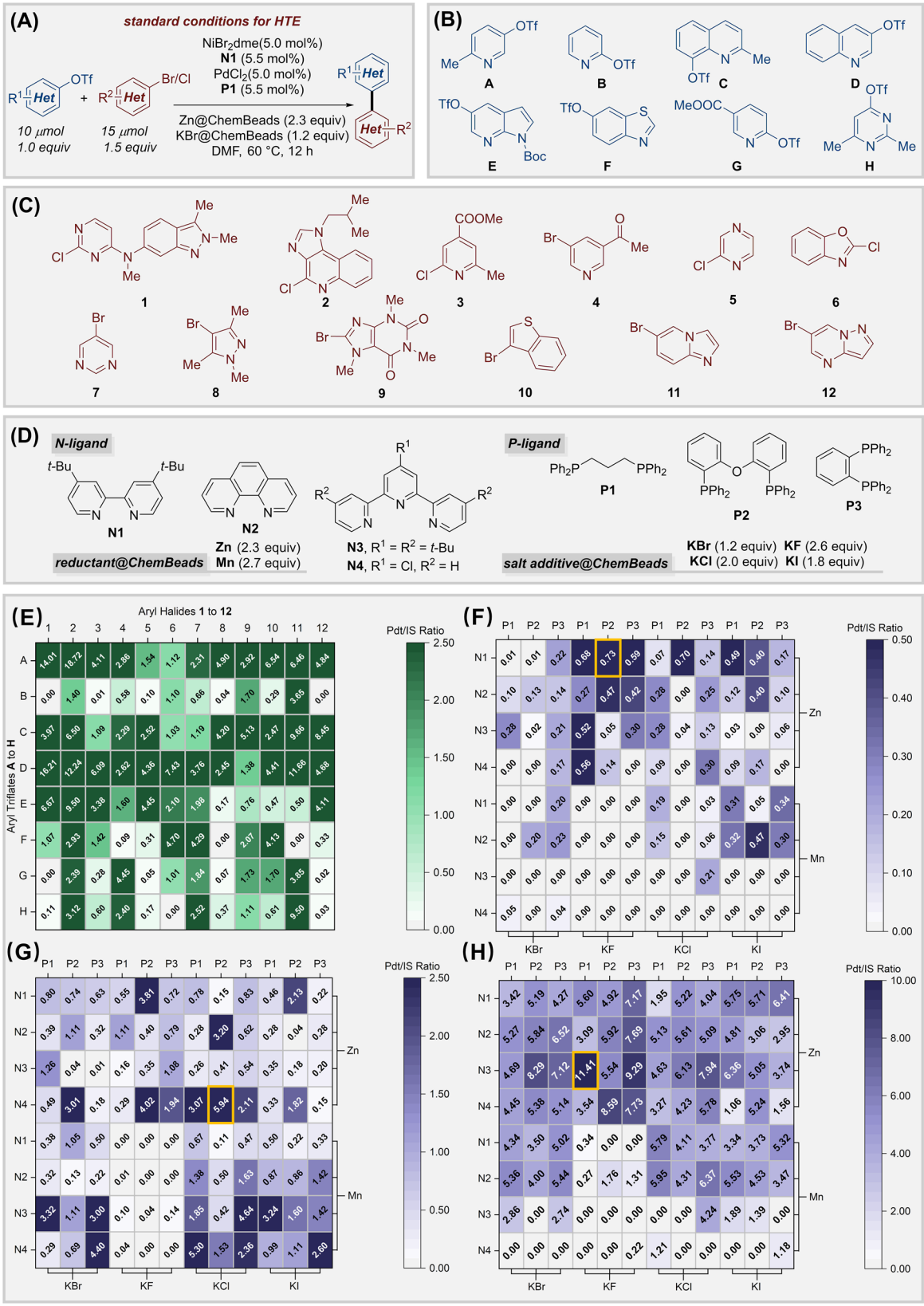

Figure 1. (A) General conditions used for HTE scope investigation (E). (B) Heteroaryl triflates used in HTE scope investigation (E). (C) Heteroaryl halides used in HTE scope investigation (E). (D) Ligands, salt additives, and reductants used in optimization Toolbox Plates (F–H). (E) Heatmap of results of HTE scope (using conditions from A and substrates from B and C). (F) Heatmap of results of product **B3** reoptimization (using toolbox from D). (G) Heatmap of results of product **C6** reoptimization (using toolbox from D). (H) Heatmap of results of product **H2** reoptimization (using toolbox from D).

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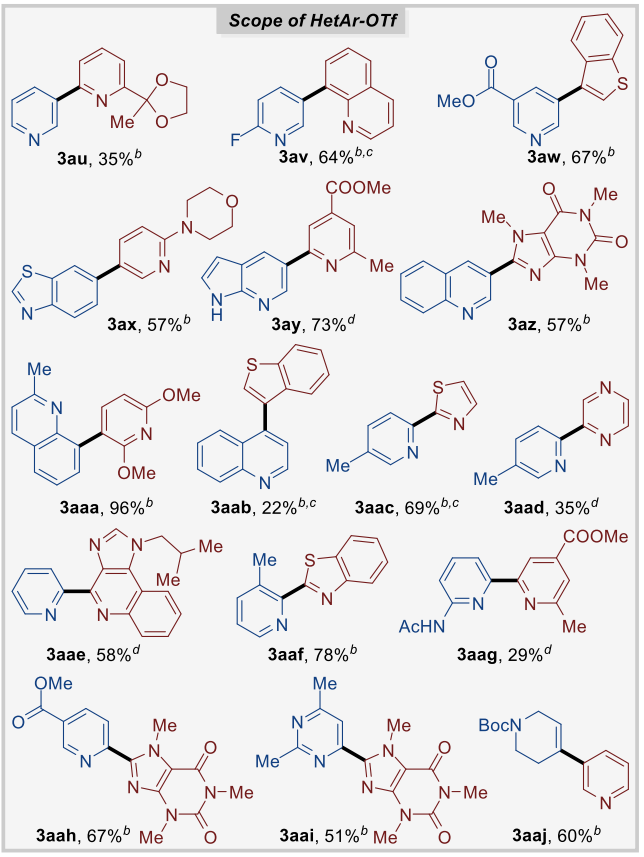
Scheme 3. Scope of Heteroaryl Triflates[a]



[a]Isolated yields from reactions on a 0.5 mmol scale under conditions A. Aryls from triflates are blue and aryls from halides are red. [b]HetAr-X was HetAr-Br. [c]NMR yield of a mixture of product and side products, see Supporting Information for details. [d]HetAr-X was HetAr−Cl.

testing.[34] Generally, μmol scale strikes the right balance between material cost and providing enough material for isolation and characterization (although the actual testing often needs only nanomoles[35] of material). Here, the solid reagent coated glass ChemBeads[36] in combination with our multivariable catalytic system can quickly access arrays of biheteroaryls (Figure 1E) and efficiently improve the yields of target molecules via fast reoptimizations with a "Toolbox Plate" (Figure 1F−H).

Starting with standard conditions on 10 μmol scale (Figure 1A),[37] we evaluated all combinations of eight heteroaryl triflates (Figure 1B, **A**−**H**) and 12 heteroaryl halides (Figure 1C, **1**−**12**) in a 96-well plate. The results are shown in a heatmap based on the product/internal standard ratio (Pdt/IS) (Figure 1E). These ratios are useful for comparing the same coupling under different conditions (as in the optimization plates Figure 1F−H), but the ratios between different pairs of coupling partners are not easily compared with each other. The standard conditions were generally effective, with 94% (90/96) of cross-coupled products observed by UV and MS analysis.

Inspired by the complementary reactivity of ttbtpy (**N3**) in couplings involving electron-poor heteroaryl halides (Scheme 2, Conditions B, **3f**−**3j**), we developed a 96-well "Toolbox Plate", which consists of known-useful variations of ligands, additives, and reductants. Such a Toolbox Plate could be useful for improving the yields of target molecules from the initial HTE substrate scope screen. To maximize coverage, we included suboptimal, but promising ligands and additives from our initial optimization (Table 1), including amine ligands for Ni (Figure 1-D, **N1**−**N4**), phosphine ligands for Pd (**P1** to **P3**), salt additives (KBr, KF, KCl, and KI), and reductants (Zn and Mn). Products detected under standard conditions (Figure 1-E) in well **B3** (Pdt/IS = 0.01), **C6** (Pdt/IS = 1.03), and **H2** (Pdt/IS = 3.12) were chosen for reoptimization to represent three scenarios: low, medium, and relatively high initial yields.

When optimized using the Toolbox Plate, a significant increase in Pdt/IS ratios was observed for all these three products (Figure 1F−H). For challenging 2,2′-bipyridine **B3**, replacement of **P1** and KBr in the standard conditions with **P2** and KF was found to boost the Pdt/IS ratio of product **B3** from 0.01 to 0.73. For benzoxazolyl quinoline **C6**, a combination of **N4**, **P2**, KCl, and Zn increased the yield of product **C6** by more than 6-fold. Ligand-like pyrimidinyl imidazoquinoline **H2** benefitted from a combination of **N3**, **P1**, KF, and Zn, which improved the Pdt/IS from 3 to 11. Finally, the syntheses of products **B3**, **C6**, and **H2** under these reoptimized conditions[38] were conducted on a 0.5 mmol scale with 14%[39] (**B3**), 29% (**C6**), and 44% (**H2**) isolated yields, respectively. While further optimization could be conducted, these yields would be sufficient for testing[35] and can be obtained quickly with minimal material (2−4 mg of substrate per reaction).

In conclusion, we have developed a new cross-Ullmann approach that offers a general, reliable, and complementary solution to biheteroaryls. This strategy leverages abundant starting materials (heteroaryl halides and phenols), exhibits good functional group tolerance due to mild reductive conditions and demonstrates outstanding compatibility with a wide array of heterocycles. Indeed, the 62 examples in this manuscript include 38 different biheteroaryl cores. In addition, although the products in this manuscript are low molecular weight and quickly accessed from commercial compounds, 82% are new compounds (51/62). Finally, because these conditions are amenable to HTE format, the rapid synthesis of biheteroaryl collections and optimization of individual couplings can be accomplished quickly and with minimal material cost.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c10907.

Additional tables of optimization data, detailed experimental procedures, characterization of products, and copies of product NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(24) Reactions run with 4-bromo-3,5-dimethylisoxazole, 2-chloro-1-(4-fluorobenzyl)-1*H*-benzo[*d*]imidazole, and 6-bromo-2-methylthiazolo[4,5-*b*]pyridine resulted in no conversion of either starting material. This appears to be a catalyst poisoning effect because adding 4-bromo-3,5-dimethylisoxazole to a productive coupling pair shut down reactivity as well.

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(28) The coupling of 6-methylpyridin-3-yl triflate (**1a**) with 3-pyridyl tosylate under the optimal conditions was also investigated. Because of the slow conversion of 3-pyridyl tosylate, the cross-product **3a** was delivered in only 39% yield, accompanied by almost equal amount (32%) of dimerization product from **1a**. We expect that further optimization could lead to a general cross-coupling reaction. See ref 29.

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(38) In these 0.5 mmol scale reactions, 2.0 equiv of reductant and 1.0 or 2.0 equiv of salt additives were used. See Supporting Information for details.

(39) NMR yield from a mixture of product and side products.

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