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In-Situ Bromination Enables Formal Cross-Electrophile Coupling of Alcohols with Aryl and Alkenyl Halides

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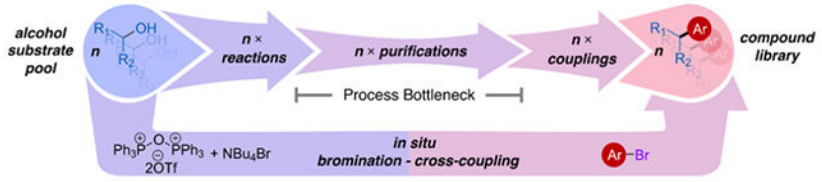
Abstract

Although alcohols are one of the largest pools of alkyl substrates, approaches to utilize them in cross-coupling and cross-electrophile coupling are limited. We report the use of 1° and 2° alcohols in cross-electrophile coupling with aryl and vinyl halides to form C(sp^3)–C(sp^2) bonds in a one-pot strategy utilizing a very fast (<1 min) bromination. The reaction's simple benchtop setup and broad scope (42 examples, 56% ± 15% ave yield) facilitates use at all scales. The potential in parallel synthesis applications was demonstrated by successfully coupling all combinations of 8 alcohols with 12 aryl cores in a 96-well plate.

Graphical Abstract



Cross-coupling reactions to form C(sp^3)–C(sp^2) bonds are increasingly important for the synthesis of structurally diverse molecules in medicinal chemistry[1] and natural product synthesis.[2] In medicinal chemistry, small-scale high-throughput experimentation is now routine to allow rapid synthesis of focused libraries to explore structure-activity relationships (SAR) and optimize lead compounds while preserving valuable material.[3] In these studies, the size of the substrate pool is crucial and even one-step activation approaches that require intermediate isolation or purification can be limiting (Figure 1a). Alcohols have long been the primary source of alkyl diversity in cross-coupling via their conversion to alkyl halides, sulfonate esters,[4] and (more recently) other redox-activated derivatives.[5]

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Supporting Information.

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additional tables of optimization data, experimental procedures, and characterization data for all isolated compounds (PDF)

Conversion of alcohols to halides and pseudohalides represents the most-used functional group interconversion in medicinal chemistry,[1a, 6] however such reactions require additional time and resources for each synthesis and purification, imposing an inherent bottleneck in the conversion of alcohols to libraries of pharmaceutical compounds (Figure 1b). General one-pot activation/coupling strategies compatible with high-throughput experimentation (HTE) approaches[7] have been elusive and largely limited to activated alcohols.[8]

A direct, yet under-explored, approach would be the in-situ conversion of alcohols to alkyl bromides in tandem with cross-electrophile coupling (XEC).[9,10] While building upon established chemistry, this approach presents several challenges. First, the activating agent must be selective for the target alcohol over other Lewis-basic functionalities (e.g., amides, ketones) and not directly react with other components of the reaction (catalyst, reductant, solvent). Second, the co-products of this activation (e.g., phosphine oxide, acid) must be tolerated by the coupling reaction. Finally, the reaction must be fast and high yielding to avoid the need for multiple manipulations of each reaction (Figure 1b and 1c).

We have found that employing oxophilic P(V) reagents, especially Hendrickson's POP reagent ($[(Ph_3P)_2O](OTf)_2$),[11] for one-pot alcohol activation is compatible with XEC conditions, procedurally simple, general, fast, and well-suited to μmol-scale HTE format (Figure 1c). Concurrent with these studies, two other exciting advances towards this goal have appeared that utilize paired electrolysis[9] and metallaphotoredox catalysis.[12] While all three approaches are impressively general, our approach appears better suited to parallel synthesis,[13,14] does not require excess of either coupling partner to achieve selective cross-coupling, and requires no specialized electrochemical or photochemical equipment for preparative or HTE applications.

Keys to the success of this approach are: 1) the discovery of a fast, homogeneous bromination system, POP/TBAB (Bu_4NBr) in MeCN, that is compatible with reductive coupling conditions; and 2) the development of a new ligand, 4,4′-di-*tert*-butyl-6-*N*-cyanocarboxamidine-2,2-bipyridine (t-^{Bu}BpyCam^{CN} or **L1**) that, alone or in combination with dtbbpy,[15] provides high yields of product. Because the new catalyst mixture works well in acetonitrile, problematic amide solvents can be avoided[16] and the bromination can occur concurrent with the cross-electrophile coupling (Table 1).

A significant practical advantage of our approach is the use of a POP/TBAB reagent solution in MeCN, which can be easily handled outside of a glovebox and facilitates parallel reaction assembly. While amide solvents appeared better at solubilizing this reagent and are established for cross-electrophile coupling, we obtained low yields in DMA (Table 1, entry 15) and POP reagents have been reported to be reactive with amides.[17] The tetrabutylammonium cation is critical for the solubility of the POP reagent in acetonitrile as other cations resulted in slurries that would be impractical on small scale (see Supplementary Table S3). The solution is stable for months when stored in a septum vial in a desiccator without any decrease in reactivity (entry 8). Compared to triphenylphosphine dibromide (the intermediate invoked in the paired electrolysis report[9]), we found bromination with POP/TBAB faster (complete in 5 min at rt). *This allowed us to run reactions without any monitoring of the bromination*.

Control reactions showed that each component of the system is necessary for high yields (Table 1, entry 2–5). Triphenylphosphine dibromide and $[(Me_3P)_2O](OTf)_2$/TBAB were both reasonable alternatives to POP (Table 1, entries 6 and 7). Triphenylphosphine dibromide proved useful with substrates prone to elimination,[18] (**3ah**, Scheme 1) and $(Me_3P)_2O](OTf)_2$ could be useful on larger scale because $Me_3P{=}O$ is water soluble. While a variety of non-nucleophilic organic bases were effective, Barton's base ($(Me_2N)_2C{=}N(t\text{-Bu})$) was superior (entries 1, 9, Supplementary Table S2). The reactions worked best with an excess of Mn (entries 1, 12–13),[19] but could be run at lower temperature and without a glovebox, if needed (entries 14, 8).

Informed by our previous studies on carboxamidine ligands[20] and mixed-ligand systems,[15] we found that a new mixed-ligand system with $^{t\text{-Bu}}$BpyCam^{CN} (**L1**)[21] and dtbbpy provided enhanced selectivity for the cross-coupled product in comparison to a single ligand system (Table 1, entry 9–10 and Supporting Information Table S1). Examination of our results with single ligands showed that **L1** and dtbbpy had complementary reactivity: dtbbpy-ligated Ni primarily consumed the aryl bromide, whereas **L1**-ligated Ni favored alkyl bromide consumption. The synergistic effect of both catalysts[22] enabled the development of a general, tunable reaction system (*vide infra*, Scheme 2*)*, even in a non-amide solvent.[23]

These new conditions enable a simple, one-pot reaction for the cross-coupling of alcohols with aryl bromides by stepwise addition of reagents. The alcohol is combined with the POP/TBAB solution and Barton's base for about 1 min before being combined with the catalyst, aryl bromide, and Mn.

This system proved effective for the coupling of a wide array of 1° and 2° unactivated alcohols with aryl, heteroaryl, and vinyl bromides (Scheme 1).[24] The one-pot bromination/cross-coupling reaction has a wide functional group tolerance for both aryl and alkyl coupling partners. Aryl substrates bearing esters (**3h, 3i, 3n, 3t**), ethers (**3c, 3g**, **3k**), ketones (**3m, 3s**), carbamates (**3b**), chloride (**3l**), and heteroarenes (**3b-f**) were compatible under these conditions. Sterically hindered aryl substrates bearing *ortho* substituents such as in 2-naphthalene, methoxy, and isopropyl could also be coupled (**3j, 3k, 3an**). Because the alcohol activation is usually complete before aryl bromide is added, the development of reactions that tolerate free alcohols on the aryl bromide is feasible: in the coupling of **3q** the less reactive alcohol is coupled over the benzylic alcohol, albeit in only 34% yield (unoptimized). Future improvements will enable telescoped three-component reactions and sequential cross-couplings.

While the optimized two-ligand system worked best for electron-rich aryl halides, more reactive C(sp^2) electrophiles, such as 2-bromopyridines (**3e**, **3x**, **3y**, **3ab**, **3ad**, **3ae**, **3af**, **3ai**, **3ao**), aryl bromides with strong electron withdrawing groups in the para position (**3t**, **3u**), and alkenyl electrophiles (**3z**, **3aa**, **3ak**) performed best using only **L1** (10 mol%) with no dtbbpy. Furthermore, the ratio of **L1** to dtbbpy can be adjusted to improve yields: the coupling between primary alcohol **1b** and methyl 3-bromobenzoate **2i** afforded the product **3i** in 72% yield with 75:25 **L1**/dtbbpy compared to 62% using a 1:1 ligand ratio.

We next explored the scope of the alcohol coupling partner. Our attention was focused on alcohol substrates for which the corresponding alkyl bromide was either not commercially available or is an order of magnitude more expensive per mole (Supporting Information Table S3). A wide variety of primary and secondary alcohols[25] could be coupled with aryl, heteroaryl, and vinyl substrates to give a structurally diverse set of products. Finally, we could scale the reaction of **3al** from 0.25 mmol to 3.6 mmol scale using standard glassware with about the same yield (from 70% to 67% yield).

More hindered alcohols and those with β-heteroatoms reacted more slowly and were prone to form elimination products, consistent with literature reports on the POP reagent.[18] A preliminary workaround is the use of Ph_3PBr_2 instead of POP/TBAB, which enabled coupling with serine to form heteroaryl phenylalanine derivative **3ah** with useful stereoretention (93% *cee*).

As noted above, the ability to directly use alcohols in cross-electrophile coupling reactions without extra steps will be of particular advantage in the generation of small libraries in medicinal chemistry.[1,20c] To explore this application, we coupled all combinations of 12 aryl halide cores with 8 alcohols on 10 μmol scale in a 96 well plate using three ligand regimes (dtbbpy only, 1:1 dtbbpy/**L1**, and **L1** only). All reagents except Mn were dosed using liquid handling and standard multichannel pipettes. We used the AbbVie Mn@Chembead approach[20c] to dose the Mn using a calibrated scoop, and a shaker/heater was used in place of a tumble stirrer. These results show that 1:1 dtbbpy/**L1** is the most general set of conditions (product observed in 95/96 cases, 99% hit rate), but that **L1** alone can improve yields for some combinations: **E10** had no detected product with **L1**/dtbbpy but product was detected with **L1** alone. When combined, the two catalyst combinations, dtbbpy/**L1** and **L1**, provided product in all 96 combinations. Screening at this scale requires minimal material investment per 96-well plate – 0.96 mmol of each coupling partner and 0.05 mmol each of **L1 (**16 mg**)** and dtbbpy (13 mg).

Mechanistically, the bromination and cross-electrophile coupling reactions are expected to proceed by their established mechanisms.[26] The bromination reaction is quantitative in about 5 min at rt (monitored by GC). Nickel-mediated cross-electrophile coupling then occurs between the alkyl bromide and the aryl electrophile. Our data show that (**L1**)Ni is capable of activating both substrates, but it appears to form too much alkyl radical, leading to alkyl dimerization. On the other hand, (dtbbpy)Ni is a less-effective catalyst for alkyl radical generation under these conditions but readily consumes ArBr, leading to poor selectivity for cross-product. We hypothesize that, in the dual-catalyst system, the (dtbbpy)Ni catalyst forms cross-product by capturing the excess alkyl radical produced by (**L1**)Ni.[27] This system can be rationally adjusted to improve yields. For example, reactions that consume aryl bromide too fast benefit from increasing the ratio of **L1** to dtbbpy (**3i** in Scheme 1).

The synthetic utility of this approach is exemplified by the fact that 37 out of the 41 products in Scheme 1 are new compounds, despite being simple derivatives of commercial materials. This advance, in tandem with related advances from MacMillan[5] and Li,[9] may lead to alcohols supplanting alkyl halides in the synthesis of Csp^3–Csp^2 bonds. Further, these reactions set the stage for selective deoxygenation of more complex polyols, such as

those recently reported by Diao[5c] and MacMillan,[12] and improved activating agents tuned to cover an even wider range of alcohols. Indeed, while this work was in review, Gong and Ma reported on another approach to in situ bromination/cross-electrophile coupling that is capable of selectively monofunctionalizing diols![10c]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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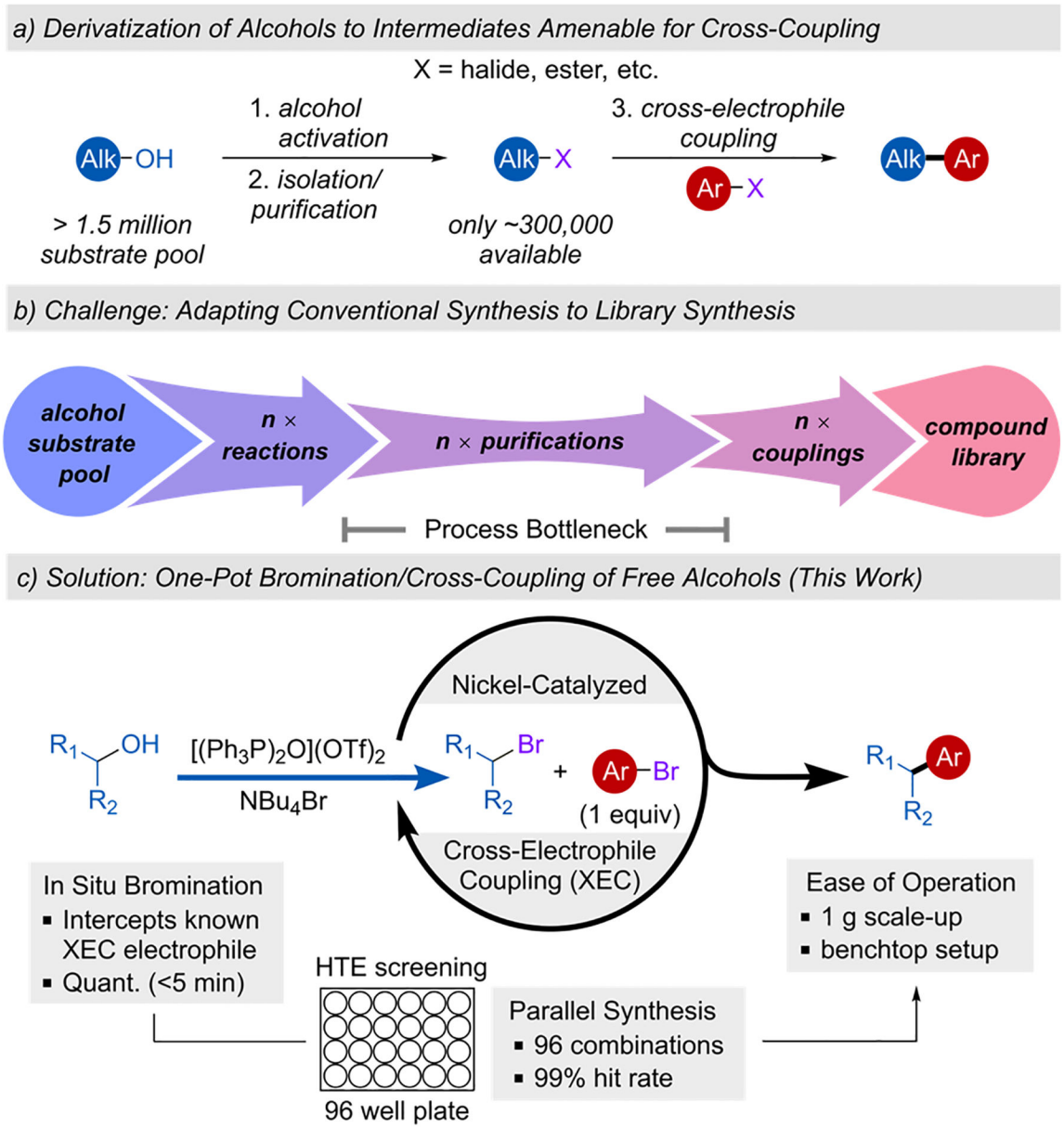
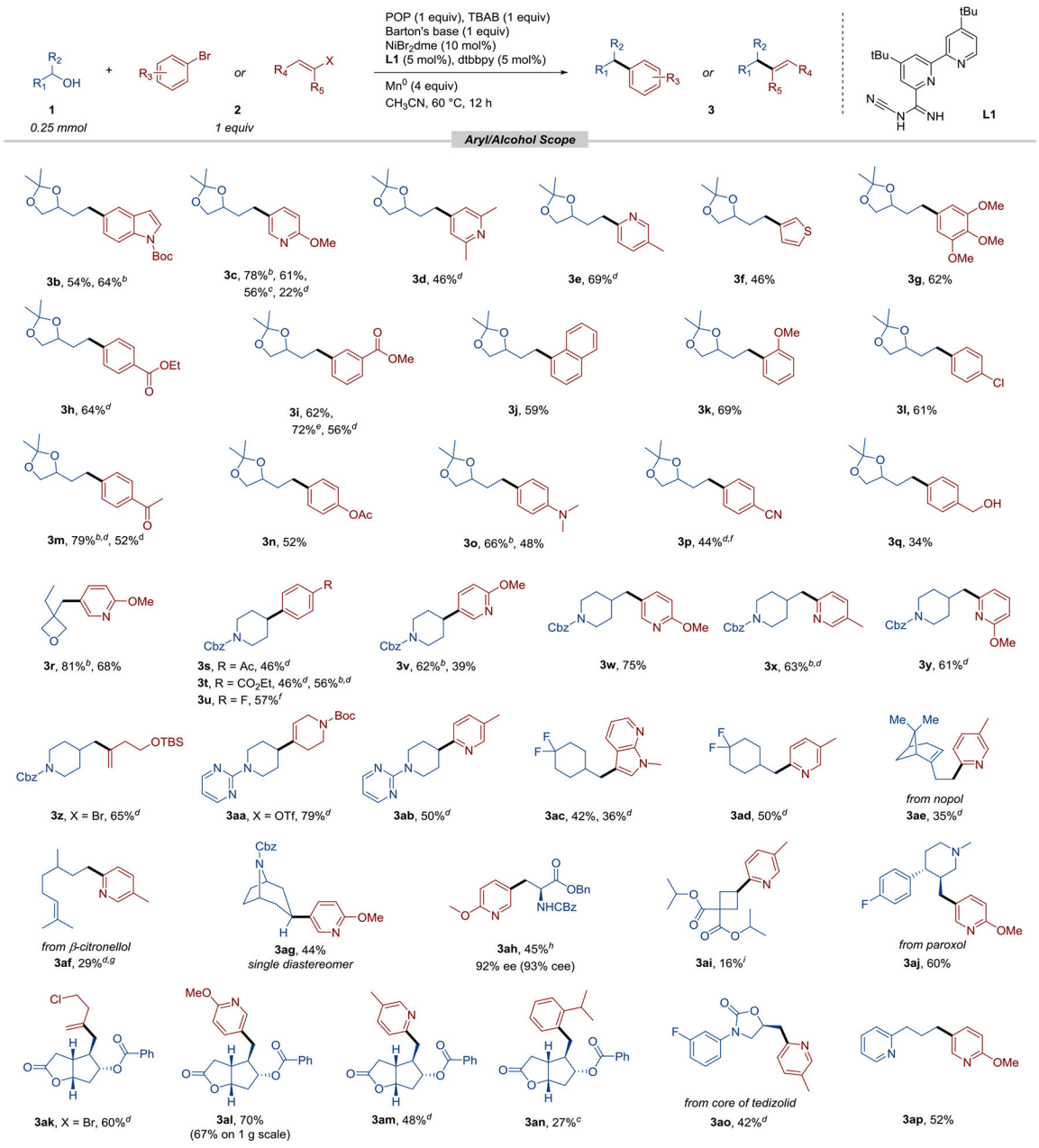


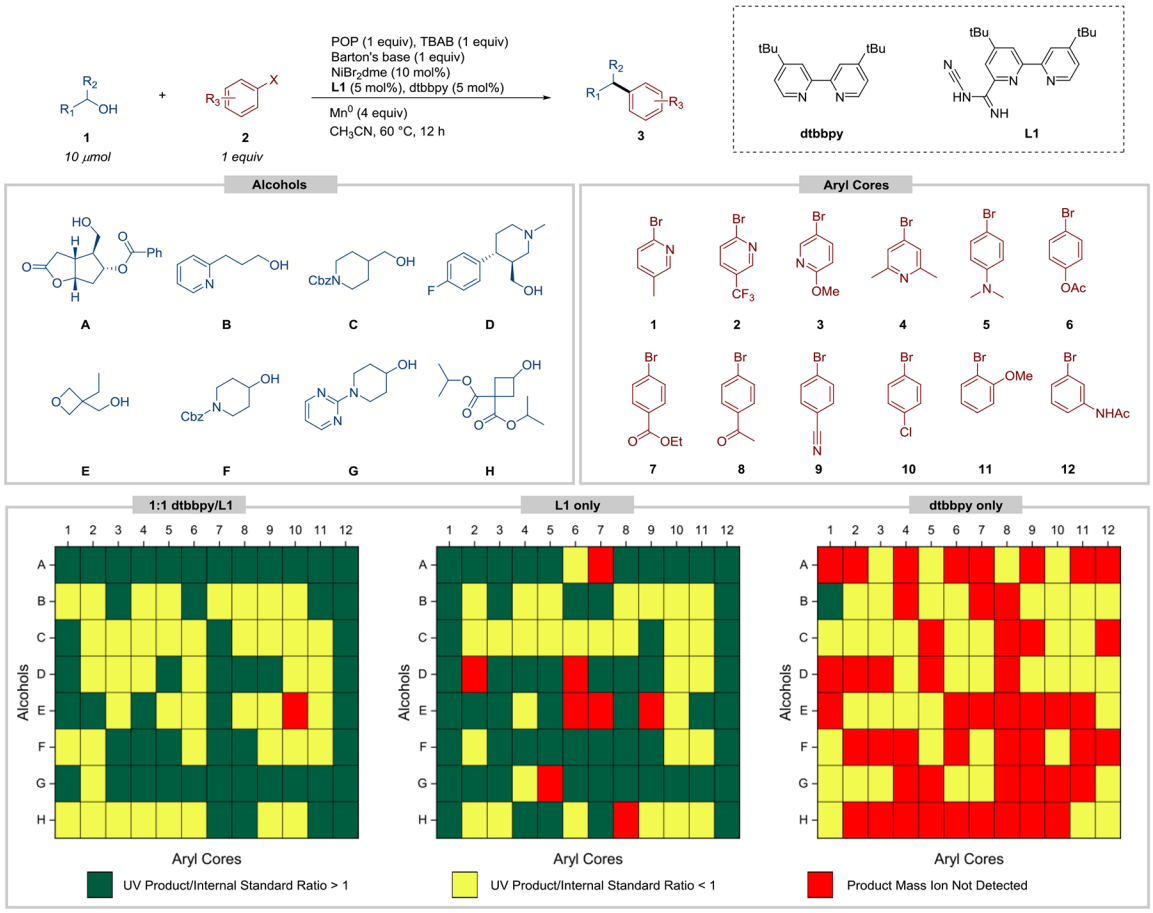
Figure 1.
Cross-Electrophile Coupling of Alcohols with Aryl Bromides Via In-Situ Bromination.



Scheme 1.

Alcohol and Aryl Halide Scope for the Bromination/Cross-Electrophile Coupling Reaction.[a]

[a]Isolated yields after purification. Alcohol **1**, POP/TBAB solution, and base were mixed for 1 min before being combined with the rest of the reagents. [b]1.5 Equiv of alcohol, POP, TBAB, and Barton's base used. [c]Only dtbbpy (10 mol%) was used. [d]Only **L1** (10 mol%) was used. [e](1:3) dtbbpy:**L1** used. [f]Yield adjusted to account for <5% of inseparable impurity. [g]Alcohol **1** mixed with base before addition of POP/TBAB solution. [h]1.25 equiv of PPh_3Br_2, and DIPEA used. [i]Product appears to decompose on silica gel.



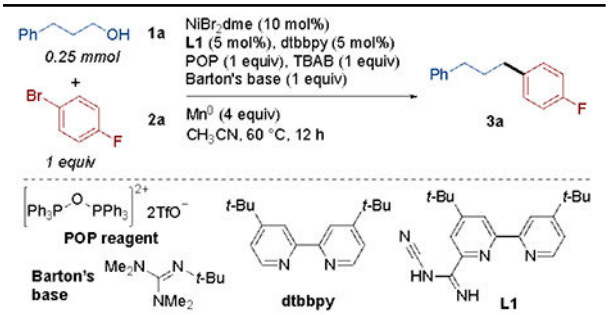
Scheme 2.

Coupling of Alcohols with Aryl Halides on 10 μmol Scale in 96-Well Plate Format.[a]

[a]Reactions run at 10 μmol scale. Assay yields are raw product/Internal standard (UV) ratios vs. 1,3,5-trimethoxybenzene.

Table 1.

Optimization and Control Studies.[a]



entry	deviations from above conditions	3a[b] (%)
1	none	89 (79)
2	no POP/TBAB[c]	0
3	no TBAB	28
4	no base	41
5	no ligand	2
6	PPh_3Br_2 in place of POP/TBAB	43
7	$[(Me_3P)_2O](OTf)_2$ in place of POP	62
8	benchtop assembly[d]	89
9	DIPEA instead of Barton's base	57
10	only dtbbpy (10 mol %) as ligand	34
11	only **L1** (10 mol %) as ligand	23
12	4 equiv of Zn instead of Mn	58
13	2 equiv of Mn	82
14	rt instead of 60 °C	75
15	DMA instead of CH_3CN	4

[a] Reactions run at a 0.25 mmol scale. The alcohol was mixed with POP/TBAB solution (30 s) and base (30 s) before being combined with the rest of the reagents.

[b] Corrected GC yields. Isolated yields shown in parentheses.

[c] TBAB = tetrabutylammonium bromide.

[d] Reaction run with POP/TBAB solution stored in a desiccator for 2 months.