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Communication

Triple Radical Sorting: Aryl-Alkylation of Alkenes

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ABSTRACT: The cross-coupling of aryl bromides with alkenes can provide access to diverse combinatorial chemical space. Two-component couplings between these partners are well-known, but three-component aryl-functionalizations of unactivated alkenes remain underdeveloped. In particular, the aryl-alkylation of unactivated alkenes would allow for rapid construction of molecular complexity and the expedient exploration of a pharmaceutically relevant and C(sp^3)-rich structural landscape. Herein, we report a general approach toward the aryl-alkylation of alkenes through a triple radical sorting mechanism. Over the course of the reaction, a high energy aryl radical, a primary radical, and a hindered alkyl radical are simultaneously formed. Through mediation by a nickel-based catalyst, the three radicals are sorted into productive bond-forming pathways toward the efficient aryl-alkylation of alkenes. A wide range of electronically and sterically differentiated alkenes and aryl radical precursors can be used to access complex scaffolds. This method was further applied to the synthesis of highly substituted semisaturated fused heterocycles.

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A drug candidate's degree of saturation has been linked to clinical success, as sp^3 carbons can impart enhanced solubility, decreased melting points, and lower off-target promiscuity.[1,2] However, most approved drugs contain few C(sp^3) centers, in part due to the relative dearth of methods for the cross-coupling of C(sp^2)−C(sp^3) and C(sp^3)−C(sp^3) substrates,[3,4] particularly compared to the abundance of C(sp^2)−C(sp^2) cross-coupling platforms. Recent advances in base-metal catalysis,[5,6] metallaphotoredox catalysis,[7,8] and electrochemistry[9,10] have expanded the scope of C(sp^3)-based cross-couplings; however, new methods to accelerate the synthesis of C(sp^3)-rich scaffolds remain of high interest to synthetic chemists. One approach to this challenge is the development of new cross-coupling strategies capable of engaging C(sp^3)-rich native functional handles.[11]

Alkenes are particularly attractive coupling handles, as they possess high structural diversity and are easily accessible as feedstock chemicals. Traditionally, alkenes have been coupled with aryl halides through the venerable Heck or reductive Heck reactions to form single C−C bonds.[12,13] A notable advantage of alkenes, however, is the fact that they possess two potential sites of functionalization that could be harnessed for the rapid buildup of molecular complexity. Recently introduced radical-based strategies have expanded the scope of aryl-alkene coupling and have permitted aryl-heteroatom difunctionalization of alkenes[14−21] (Figure 1a). To date, however, methods that capitalize on the susceptibility of alkenes to difunctionalization as a means to achieve simultaneous formation of multiple C−C bonds remain underdeveloped. Furthermore, few examples of the aryl-alkylation of unactivated alkenes are known. The Nevado lab has reported an elegant approach toward the aryl-alkylation of alkenes, in which a tertiary radical adds into an unactivated alkene, and the nascent secondary radical undergoes nickel-catalyzed arylation.[22,23] To the best of our knowledge, however, aryl-alkylation of unactivated alkenes with the opposite regioselectivity—wherein the alkyl adds to the more hindered position—remains unknown.

One approach to achieving aryl-alkylation of unactivated alkenes would involve simultaneously generating both an aryl radical and an alkyl radical in the presence of the alkene. Ideally, the aryl radical would first add into the alkene, and the resulting radical intermediate would undergo recombination with the alkyl radical species (Figure 1a). Such an approach would avoid the limitations of traditional transition metal mechanisms that particularly arise in the context of hindered radicals, such as premature cross-coupling and competitive β-hydride elimination.[24,25] Typically, free radical pathways suffer from uncontrolled radical recombination and disproportionation,[26] but our laboratory recently introduced the concept of "radical sorting," which overcomes these issues through a nickel-catalyzed bimolecular homolytic substitution (S_H2) step capable of distinguishing between hindered radicals and primary radicals en route to selective C(sp^3)−C(sp^3) cross-couplings.[27−32] This general concept has been expanded from two-component cross-coupling reactions to a three-component alkene dialkylation, in which an electrophilic alkyl radical, primary alkyl radical, and hindered alkyl radical are generated in situ and efficiently sorted.[33,34] We wondered if a similar paradigm could be applied to the sorting of an aryl radical, primary alkyl radical and hindered radical to achieve selective alkene aryl-alkylation. We envisioned simultaneously generating a primary radical and an aryl radical in solution. In the key radical sorting step, the Ni-based S_H2 catalyst would preferentially bind the less sterically encumbered primary

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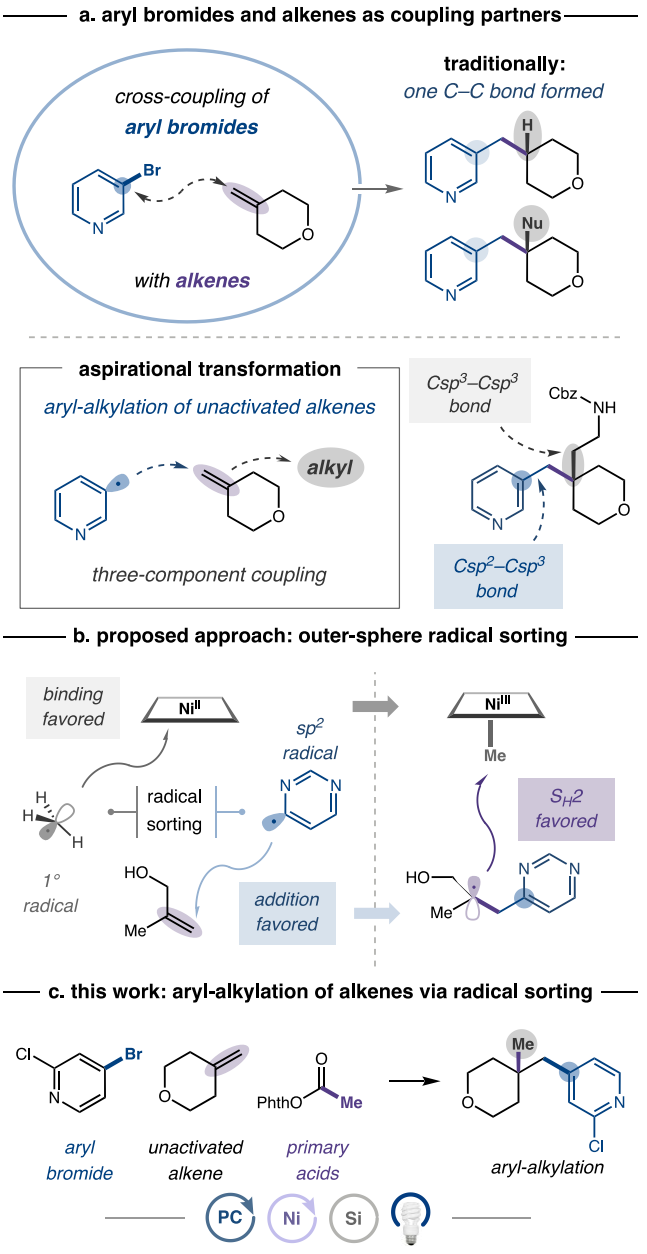

Figure 1. Aryl-alkylation of unactivated alkenes.

alkyl radical (Figure 1b). The aryl radical would remain in solution, where it would preferentially add into an unactivated alkene, generating a hindered radical species, which would engage in S_H2 reaction with the Ni(III)-alkyl complex. Success of the envisioned reaction would be predicated on several factors. First, the S_H2 catalyst must preferentially bind a primary alkyl radical (primary alkyl−H bond dissociation energy (BDE): 100−105 kcal/mol)[35] in favor of a higher energy aryl radical (aryl−H BDE: ∼ 110 kcal/mol),[35] while the aryl radical must add into an unactivated alkene to form a hindered radical. Subsequently, the hindered radical must preferentially engage in an S_H2 reaction with the primary alkyl-metal complex over the reactive aryl radical. Additionally, the S_H2 catalyst of choice should not be capable of undergoing oxidative addition to prevent degradation of the aryl radical precursor. Herein, we report the aryl-alkylation of alkenes via a triple radical sorting mechanism that effectively distinguishes between aryl radicals, primary alkyl radicals, and hindered radicals resulting from addition into unactivated alkenes.

A proposed mechanism for the alkene aryl-alkylation is outlined in Figure 2. First, blue light excites the iridium

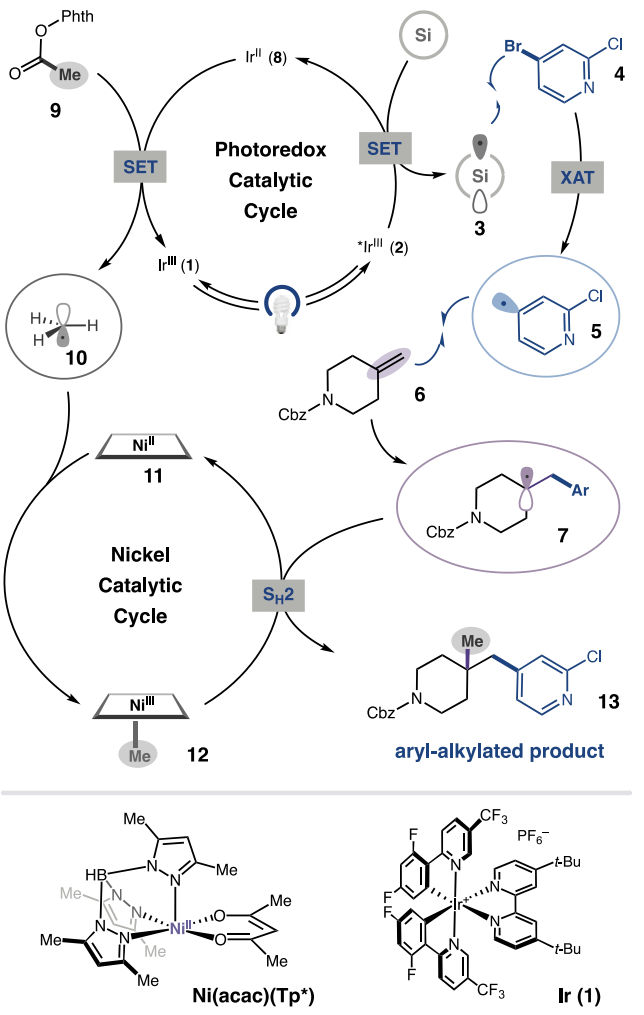

Figure 2. Proposed mechanism of alkene aryl-alkylation. Si = Adamantylaminosupersilane.

photocatalyst (**1**) to access a long-lived, triplet excited state (**2**) ($E_{1/2}^{red}$ [$*Ir^{III}/Ir^{II}$] = +1.21 V vs saturated calomel electrode (SCE) in MeCN).[36] The excited photocatalyst is reductively quenched by Adamantylaminosupersilane (Admn silane) (E_{pa} = +0.86 V vs SCE in DMA/*tert*-amyl alcohol), which undergoes rapid aza-Brook rearrangement to generate a silyl radical (**3**).[37] This radical species performs a halogen atom transfer (XAT) with aryl bromide **4** to form an aryl radical (**5**),[38] which then adds into an unactivated alkene (**6**) to give a hindered alkyl radical (**7**) (see SI Table S15 for preliminary mechanistic experiments that support a radical mechanism). To close the photoredox catalytic cycle, Ir^{II} (**8**) reduces a redox-active ester (RAE, **9**), which, upon decarboxylation, results in a primary alkyl radical (**10**). This species is captured by the S_H2 radical-sorting catalyst (**11**). Finally, the hindered alkyl radical (**7**) performs an S_H2 reaction with alkyl metal complex (**12**) to give the desired aryl-alkylated product (**13**).

We were pleased to observe that under optimized conditions (see SI for details), aryl-alkylation proceeded efficiently across a wide range of alkenes (Table 1). Terminal alkenes with

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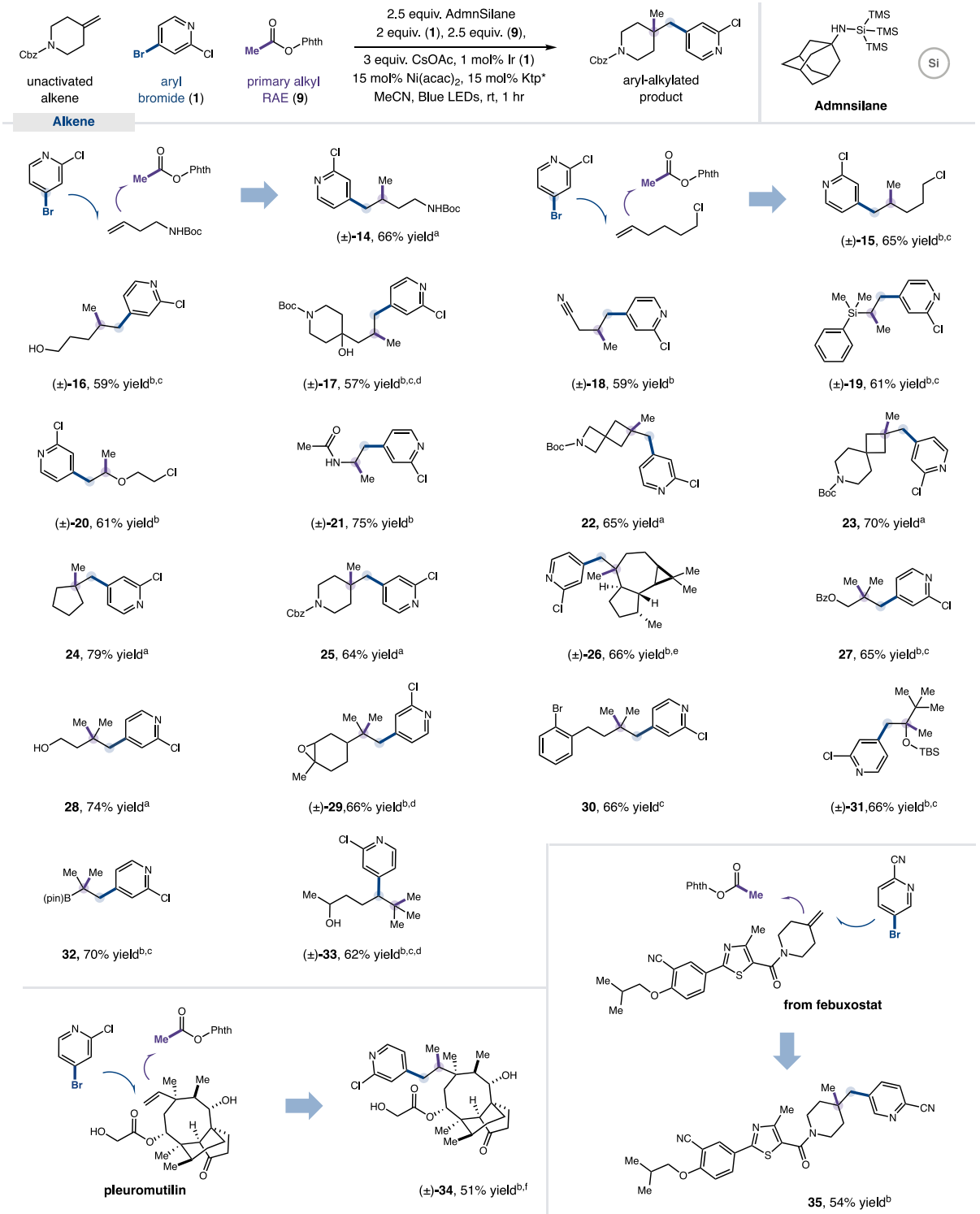
Table 1. Alkene Scope



[a]Alkene (1 equiv), aryl bromide (2 equiv), Me-RAE (2.5 equiv), AdmnSi (2.5 equiv), Cs(OAc) (2.5 equiv), $Ni(acac)_2$ (15 mol %), KTp* (15 mol %), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1 mol %), MeCN (0.1 M), integrated photoreactor (450 nm, M2 plate, 100% light intensity), 1 h. [b]Alkene (3 equiv), aryl bromide (1 equiv), Me-RAE (2 equiv), AdmnSi (2 equiv), Cs(OAc) (2 equiv), $Ni(acac)_2$ (15 mol %), KTp* (15 mol %), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2 mol %), water (250 ul), MeCN (0.1 M), integrated photoreactor (450 nm, M2 plate, 100% light intensity), 1 h. Run at 0.5 mmol scale and all yields are isolated unless otherwise specified. [c]See SI for experimental details. [d]1:1 d.r. [e]1.6:1 d.r. unassigned. [f]2.5:1 d.r. unassigned.

relatively low π-nucleophilicity,[39] bearing carbamates, alkyl chlorides, free alcohols, or nitriles, reacted efficiently under our optimized conditions (**14**−**18**, 57−66% yield). Moreover, terminal vinyl silanes, enol ethers, and vinyl amides served as competent partners in the reaction (**19**−**21**, 61−75% yield). Quaternary centers, which are typically challenging to access,[40]

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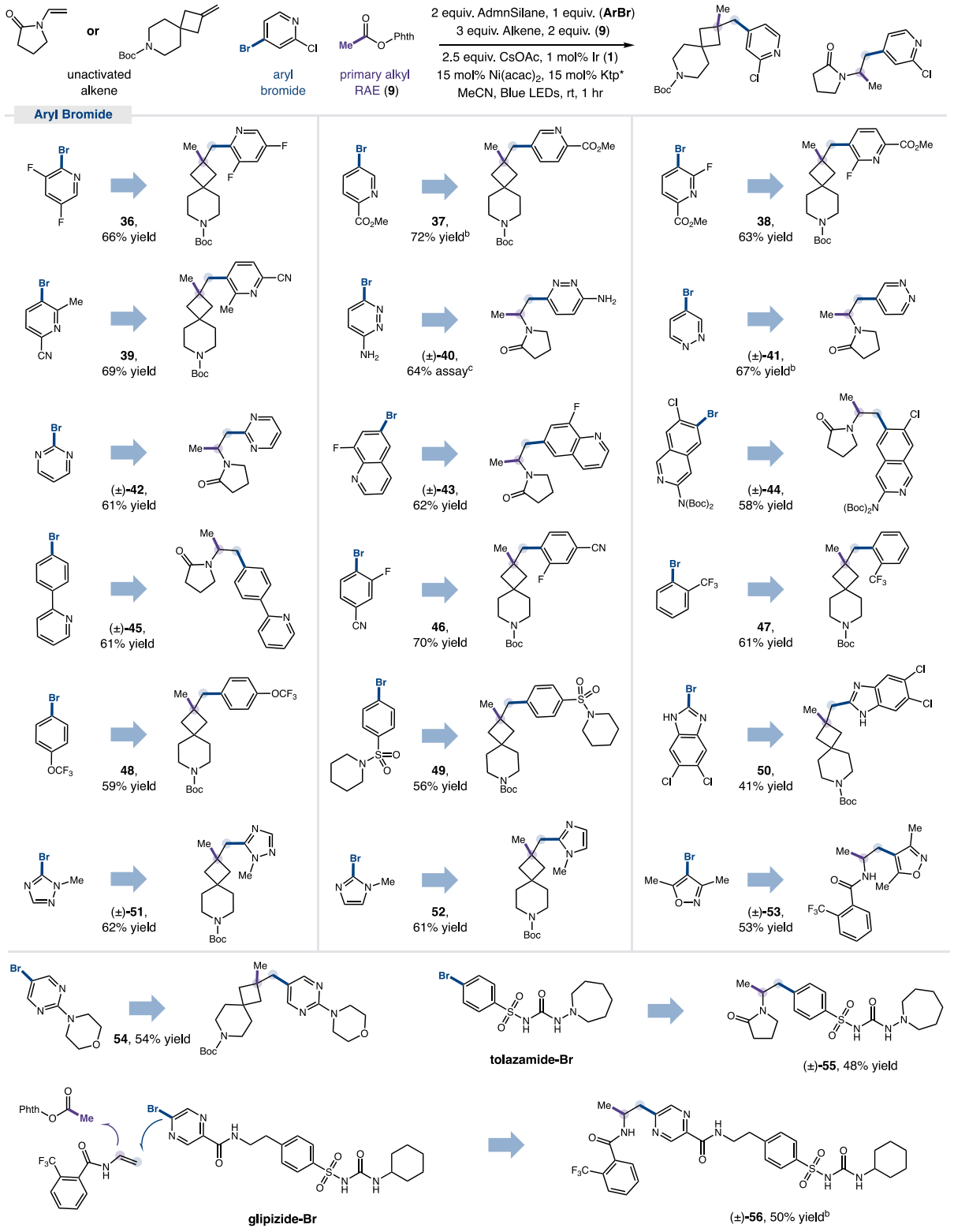
Table 2. Aryl Bromide Scope



[a]Alkene (3 equiv), aryl bromide (1 equiv), Me-RAE (2 equiv), AdmnSi (2 equiv), Cs(OAc) (2 equiv), $Ni(acac)_2$ (15 mol %), KTp* (15 mol %), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1 mol %), water (250 μL), MeCN (0.1 M), integrated photoreactor (450 nm, M2 plate, 100% light intensity), 1 h. [b]See SI for experimental details. [c]Assay yield vs 1,3,5-trimethoxybenzene. Run at 0.5 mmol scale, and all yields are isolated unless otherwise specified.

can be generated from the aryl-alkylation of 4, 5, 6, and 7-membered exocyclic alkenes (**22**−**26**, 64−79% yield). Importantly, homolytically labile allylic ester C−H motifs were well-tolerated (**27**, 65% yield), while cyclic 1,1-disubstituted alkenes containing alcohols, epoxides, and less electron-poor aryl bromides were also aryl-alkylated in good

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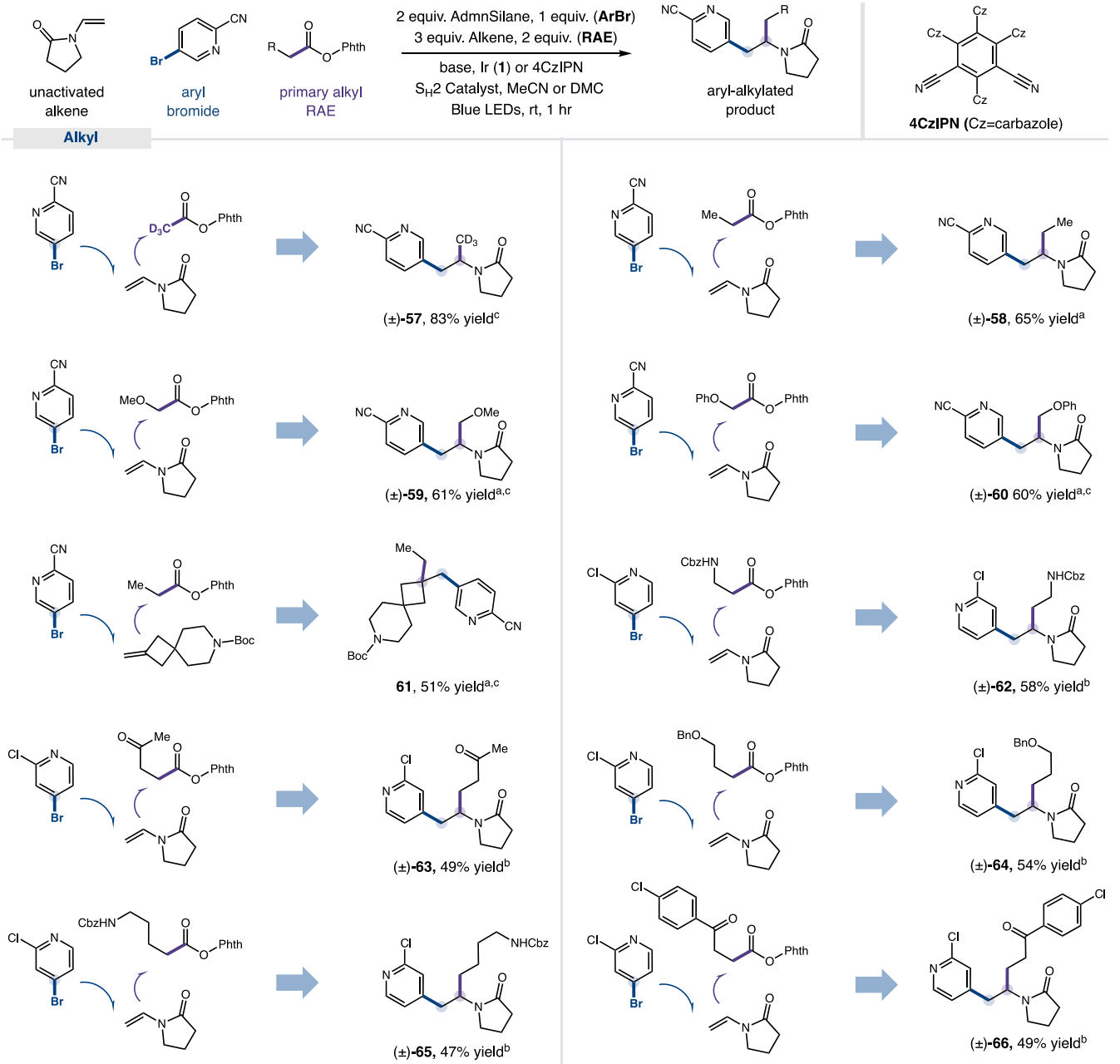
Table 3. Alkyl Scope



[a]Alkene (3 equiv), aryl bromide (1 equiv), Alkyl-RAE (2 equiv), AdmnSi (2 equiv), K(OBz) (2 equiv), $Ni(acac)_2$ (25 mol %), KTp (25 mol %), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1 mol %), water (100 μL), MeCN (0.1 M), integrated photoreactor (450 nm, M2 plate, 100% light intensity), 1 h. [b]Alkene (3 equiv), aryl bromide (1 equiv), Alkyl-RAE (2 equiv), AdmnSi (2 equiv), $Cs_2(CO_3)$ (2 equiv), $Ni(TMHD)_2$ (25 mol %), 4CzPN (5 mol %), DMC (0.15 M), integrated photoreactor (450 nm, M2 plate, 50% light intensity), 1 h. [c]See SI for experimental details. Run at 0.5 mmol scale, and all yields are isolated unless otherwise specified.

yields (**28**−**30**, 66−74% yield). Sterically demanding vicinal quaternary centers, such as enol ether (**31**, 66% yield), were readily accessed. Reaction of a vinyl boronic ester results in formation of a tertiary boronic ester that is poised for further functionalization[41] (**32**, 70% yield). Alkenes bearing steric bulk at the site of aryl-radical addition also undergo aryl-alkylation (**33**, 62% yield). Furthermore, we were delighted to observe that this protocol was amenable to complex settings. For example, both the natural product pleuromutilin and a derivative of febuxostat participated in aryl-alkylation in synthetically useful yields (**34** and **35**, 51 and 54% yield, respectively; see SI Table S2 for additional examples and limitations).[42]

We next sought to explore the range of aryl radicals that could be employed in this reaction (Table 2). Pyridyl radicals formed at the 2, 3, and 4-positions were observed to efficiently add into alkenes to generate the desired aryl-alkylated products (**36**−**39**, 63−72% yield). Other heteroaromatics commonly found in pharmaceuticals,[43] such as pyridazines (**40**, **41**), pyrimidines (**42**), quinolines (**43**), and isoquinolines (**44**) were readily incorporated into three-dimensional scaffolds through this method. A wide range of benzenes possessing

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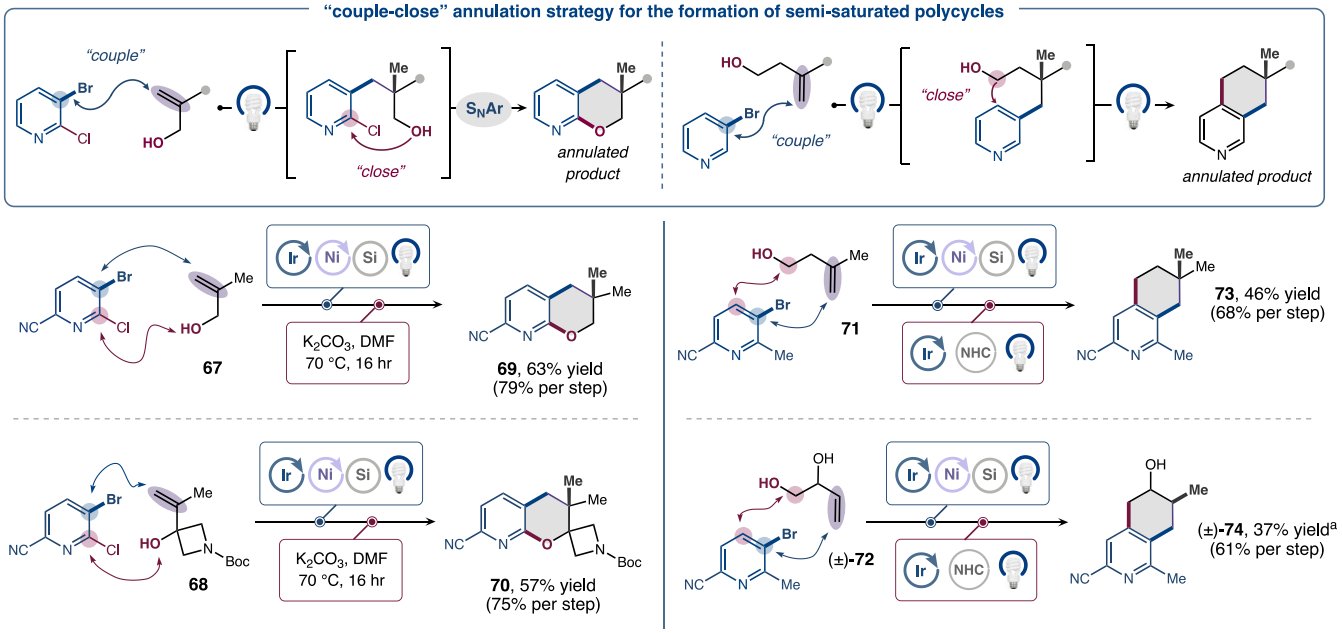
Table 4. Couple-Close Sequence toward Substituted Semi-saturated Heterocycles



See SI for experimental details. Run at 0.5 mmol scale and all yields are isolated unless otherwise specified. [a]2:1 d.r. unassigned.

diverse electronic and steric properties also served as viable substrates (**45**–**49**, 56–70% yield). Moreover, electron-rich 5-membered ring heterocyclic bromides were competent aryl radical precursors, forming the desired product in good yields (**50**–**53**, 41–62% yield). Finally, a series of complex aryl bromides, including heteroaryl amine (**54**) and bromides derived from tolazamide (**55**) and glipizide (**56**) were found to be competent reaction partners (see SI Table S1 for 34 additional examples).

We next evaluated the scope of the primary alkyl radical coupling partner (Table 3). Unsurprisingly, a deuterated methyl group could be efficiently incorporated into complex scaffolds under standard conditions (**57**, 83% yield). We were pleased to observe that ethyl, α-methoxy, and α-phenoxy radicals served as competent primary radical partners for both terminal and 1,1-disubstituted alkenes (**58**–**61**, 51–65% yield). Moreover, longer chain primary radicals containing carbamates, ketones, and ethers were well-tolerated under the reaction conditions (**62**–**66**, 47–58% yield).

Our laboratory recently introduced a "couple-close" strategy that deploys a C(sp^2)–C(sp^3) coupling–annulation sequence to rapidly build semisaturated fused polycycles in a modular fashion.[44] As an extension of our aryl-alkylation method, we envisioned a similar couple-close protocol in which three bonds would be formed in two steps to generate highly substituted semisaturated fused heterocycles. As outlined in Table 4, the sequence would entail coupling an aryl bromide with the olefin of an allylic or homoallylic alcohol. Subsequent S_NAr or deoxygenative Minisci reaction would serve to close the ring and form the annulated product. This general strategy proved effective: allylic alcohols (**67**, **68**) and pyridyl bromides were coupled under our standard reaction conditions, and the resulting intermediates were directly subjected to S_NAr without further purification, to afford the substituted semisaturated heterocycles with high efficiency (**69** and **70**, 63 and 57% yield, respectively). Similarly, homoallylic alcohols (**71**, **72**) were coupled with a pyridyl bromide using the aryl-alkylation protocol. Upon purification, the intermediates were subjected to deoxygenative Minisci conditions to yield semisaturated heterocycles (**73** and **74**, 46 and 37% yield, respectively).

In summary, we describe a triple radical sorting strategy for the direct aryl-alkylation of unactivated alkenes. A wide range of alkenes, aryl-bromides, and primary alkyl radicals were found to serve as competent partners, permitting the synthesis of a diverse scope of C(sp^3)-rich molecules. Notably, complex aryl-bromides and alkenes react efficiently, suggesting that the protocol may be applicable to late-stage settings. Additionally, a couple-close protocol was demonstrated which permits the formation of highly substituted semisaturated heterocycles through either a S_NAr or Minisci reaction. We envision that the modular, three-component nature of this reaction, along with the broad substrate scope, should offer accelerated access to pharmaceutically relevant C(sp^3)-rich chemical space.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c05744.

Additional experimental details, optimization, additional substrate tables, characterization, and spectra (PDF)

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Notes

The authors declare the following competing financial interest(s): D.W.C.M. declares a competing financial interest with respect to the integrated photoreactor.

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