Nickel-Catalyzed *ipso/ortho* Difunctionalization of Aryl Bromides with Alkynes and Alkyl Bromides *via* a Vinyl-to-Aryl 1,4-Hydride Shift

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Supporting Information Placeholder

ABSTRACT: Polysubstituted arenes are ubiquitous structures in a myriad of medicinal agents and complex molecules. Herein, we report a new catalytic blueprint that merges the modularity of nickel catalysis for bond-formation with the ability to enable a rather elusive 1,4-hydride shift at arene sp^2 C–H sites, thus allowing to access *ipso/ortho* difunctionalized arenes from readily available aryl halides under mild conditions and exquisite selectivity profile.

Polysubstituted arenes are commonly encountered in pharmaceuticals, functional materials and agrochemicals.[1] Conventional routes for their synthesis include nucleophilic aromatic substitution of biased, electron-poor arenes or cross-coupling reactions of aryl (pseudo)halides that results in bond-formation at the *ipso* position via formal group interconversion (Figure 1, *path a*).[2] Over the past two decades, the Pd-catalyzed Catellani-type reaction has expanded the toolbox of our synthetic arsenal[3] when utilizing aryl halide counterparts, offering a complementary selectivity profile that allows to incorporate functional groups at both *ipso* and *ortho* positions (Figure 1, *path b*). However, these reactions require non-negligible amounts of norbornene and mainly restricted to *ortho*-substituted haloarenes to avoid the formation of di-*ortho*-functionalized byproducts,[3f] thus limiting the application profile of these rather appealing endeavors. Consequently, chemists have been challenged to design new catalytic technologies that might streamline the formation of polysubstituted arenes with improved modularity, generality and complementary selectivity profile beyond the realm of noble metal catalysis.[4]

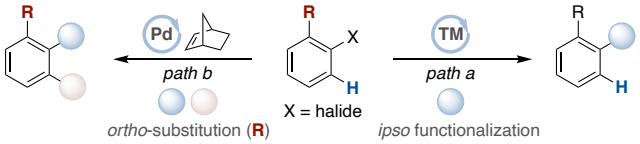


Figure 1. State-of-the-art cross-coupling of aryl halides.

In recent years, nickel catalysis has offered new vistas for forging C–C and C–heteroatom bonds, enabling transformations that are otherwise difficult to reach for other metal catalysts in the d^{10} series.[5] Among these, particularly attractive is the ability to promote a formal translocation of the nickel catalyst throughout the alkyl side chain via a series of formal 1,2-hydride shifts, thus establishing a rationale to functionalize previously unfunctionalized sp^3 C–H reaction sites (Figure 2, *top left*).[6,7] In contrast, the ability to promote a nickel migration at arene sp^2 C–H sites has received much less attention, with remarkable exceptions such as an elegant work by Johnson using aryne complexes,[8a] thus constituting a desirable scenario for chemical invention (*top right*).[8-14] In line with this notion, our group has recently described the ability of nickel catalysts to enable a 1,4-metal shift along a sp^2 backbone as a vehicle to promote a formal reductive sp^2 C–H carboxylation with CO_2 as coupling partner,[15] thus suggesting that the implementation of *de novo* cross-electrophile reactions[16] via 1,4-Ni shift with electrophiles other than CO_2 might not be a chimera. Challenged by this perception, we recently questioned whether we could design a reversible 1,4-Ni migration as a new catalytic blueprint to promote multicomponent cross-electrophile couplings en route to densely functionalized polyfunctionalized arenes. Herein, we report the successful realization of this goal, culminating in the development of a tandem nickel-catalyzed *ipso/ortho* difunctionalization of readily available aryl bromides with unactivated alkyl halides and alkyne congeners (Figure 2, *bottom*). The protocol is distinguished by its simplicity and broad substrate scope – including challenging substrate

combinations –, offering a complementary new platform for preparing polyfunctionalized arenes from simple precursors with exquisite control of the selectivity profile at both sp^2 C–halide and sp^2 C–H sites.

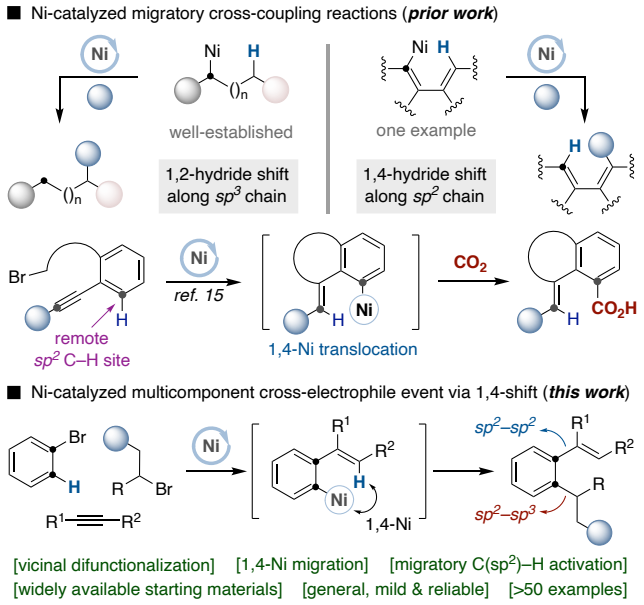


Figure 2. Ni-catalyzed migratory cross-coupling reactions.

The design principle of our Ni-catalyzed *ipso/ortho* difunctionalization is outlined in Figure 3. We hypothesized that a suitable $\mathbf{L_n}$Ni(0) catalyst might trigger an oxidative addition at the sp^2 C–Br site followed by a *syn*-migratory insertion into an alkyne, thus generating an alkenylnickel(II) species (**III**). This intermediate (**III**) could undergo reversible *E/Z* isomerization to generate a mixture of *E/Z* isomers (**III** and **III'**). Subsequently, reversible 1,4-Ni migration might translocate the metal center at the arene backbone (**IV**), thus setting the stage for a rapid recombination with an open-shell intermediate generated upon single-electron transfer (SET) to an alkyl halide (**V**). Reductive elimination of **VI** would then deliver the targeted difunctionalized framework (**4**) and a Ni(I) intermediate (**VII**) that would ultimately recover the propagating $\mathbf{L_n}$Ni(0) species upon SET with an alkyl halide (**3**) and Mn as terminal reductant.

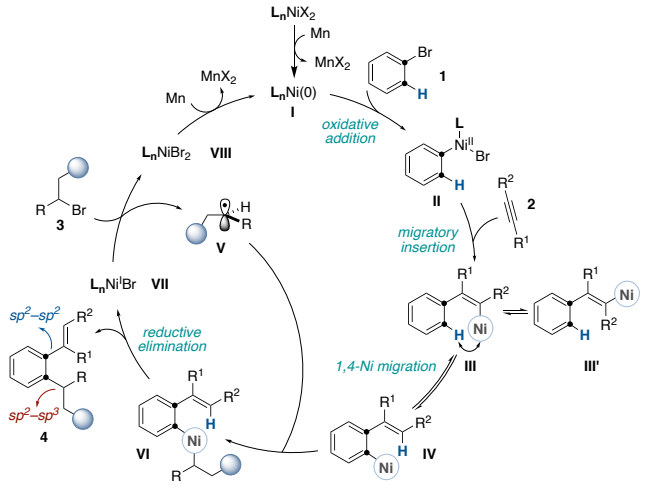
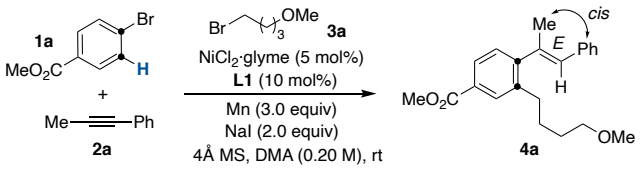


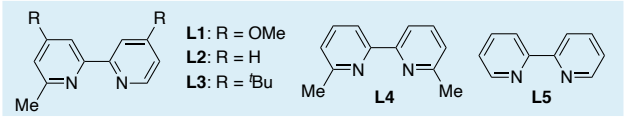
Figure 3. Proposed Mechanistic Pathway.

Our investigations began by studying the reaction of methyl 4-bromobenzoate (**1a**) with 1-phenyl-1-propyne (**2a**) and 1-bromo-4-methoxybutane (**3a**). After some experimentation, we found that a combination of $NiCl_2$·glyme, **L1**, Mn as reductant in DMA at rt delivered **4a** in 74% isolated yield with excellent *E/Z* ratio (96:4) and regioselectivity pattern (96:4) (Table 1, entry 1).[17] In line with our expectations, the nature of the ligand backbone was critical for success, with ligands possessing a single substituent at C6 on the 2,2'-bipyridine core providing the best results.[18] Specifically, similar yields were found for **L2** or **L3** (entries 2 and 3) whereas not even traces of **4a** were found in the crude mixtures when utilizing a Ni/**L4** or Ni/**L5** regime instead (entries 4 and 5), thus showing the subtleties of our ligand motif. Interestingly, a deleterious effect on reactivity was found when employing Zn as reductant or in the absence of either NaI or 4Å MS (entries 5–7). As illustrated in entries 8–11, iodide additives, nickel catalysts and solvents other than NaI, $NiCl_2$·glyme and DMA did not improve further the results.[19] Unfortunately, the utilization of methyl 4-chlorobenzoate (**1a-Cl**) as substrate failed to provide the targeted **4a** (entry 12).

Table 1. Optimization of the Reaction Conditions



entry	deviation from standard conditions	yield **4a** (%)[a]	*E/Z*[b]	rr[c]
1	***none***	***79 (74)***[c]	***96:4***	***96:4***
2	**L2** instead of **L1**	56	86:14	>99:1
3	**L3** instead of **L1**	64	93:7	>99:1
4	**L4** or **L5** instead of **L1**	<1	–	–
5	Zn instead of Mn	14	77:23	>99:1
6	w/o 4Å MS	67	92:8	95:5
7	w/o NaI	21	92:8	>99:1
8	KI instead of NaI	69	92:8	96:4
9	$Ni(cod)_2$ instead of $NiCl_2$·glyme	78	95:5	95:5
10	DMF instead of DMA	59	91:9	90:10
11	THF or MeCN instead of DMA	<1	–	–
12	ArCl instead of **1a**	<1	–	–

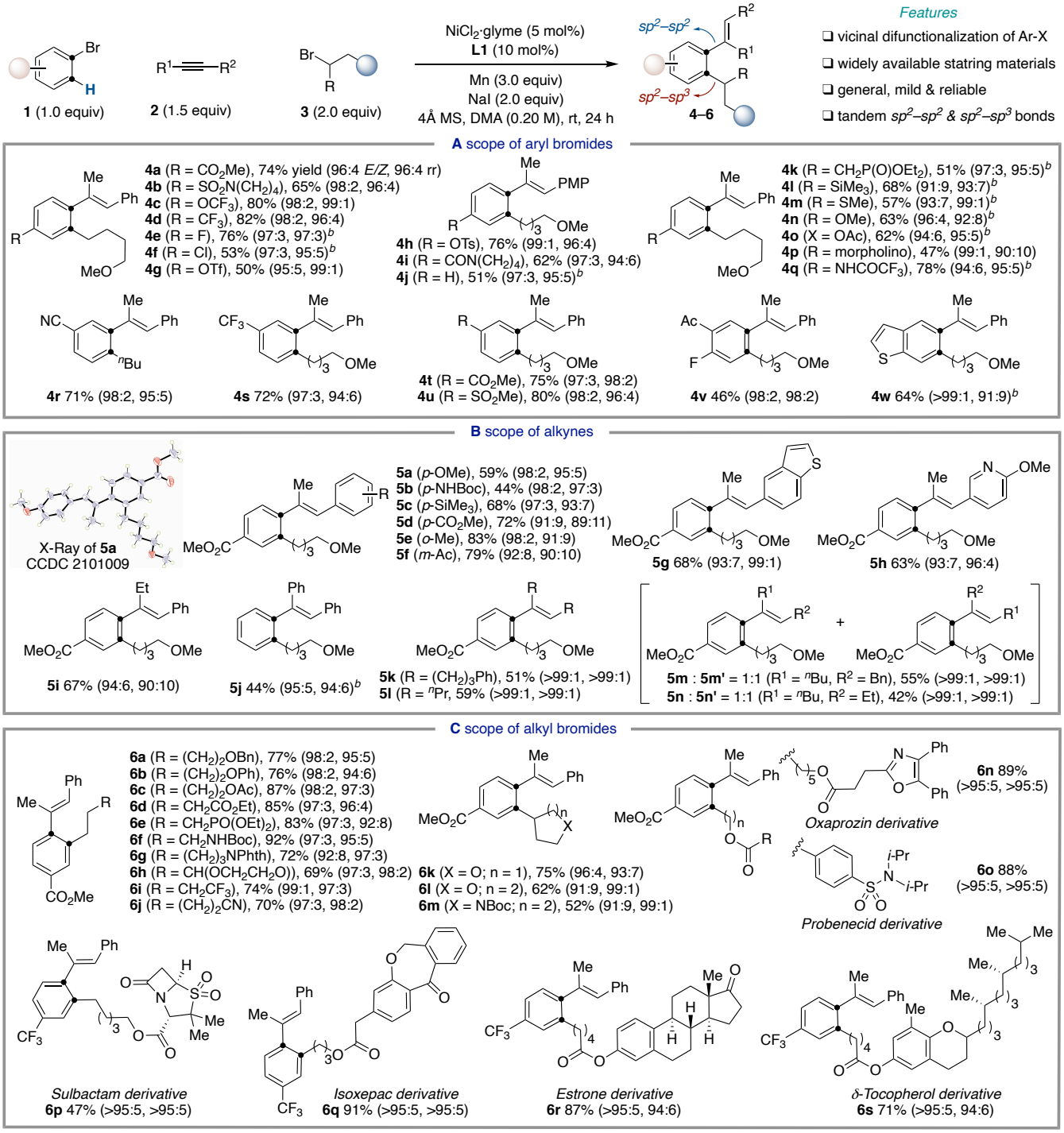


[a]**1a** (0.20 mmol), **2a** (0.30 mmol), **3a** (0.40 mmol), $NiCl_2$·glyme (5 mol%), **L1** (10 mol%), Mn (0.60 mmol), NaI (0.40 mmol), 4Å molecular sieves (40 mg), DMA (0.20 M) at rt for 24 h. Yields were determined by GC using *n*-dodecane as internal standard. [b]The ratio of (*E*)-**4a**/(*Z*)-**4a**, determined by GC and compared with standard *E/Z* isomers of **4a**, see SI for details. [c]rr, regioisomeric ratio, representing the ratio of **4a** with the sum of all other observed *ipso*-coupling isomers, as determined by GC and GC-MS analysis and compared with standard *ipso*-coupling isomers, see SI for details. [c]Isolated yield, average of two independent runs.

With these results in hand, we next turned our attention to exploring the preparative scope of our *ipso/ortho*-functionalization of aryl bromides via 1,4-nickel shift. As evident from the results compiled in Table 2A, our protocol was found to be applicable across a wide number of aryl bromides, alkyl bromides and alkyne counterparts. In addition, good yields were

obtained regardless of whether electron-poor or electron-rich bromoarenes were utilized as coupling partners. In general, migration occurs to the less-sterically hindered *ortho*-position (**4r**–**4w**). A wide variety of functional groups such as esters (**4a**, **4o**, **4t**), amides (**4i**, **4q**), sulfonamides (**4b**), phosphonates (**4k**), amines (**4p**), nitriles (**4r**), sulfones (**4u**) or ketones (**4v**) were perfectly accommodated. Moreover, the presence of groups amenable for Ni-catalyzed reactions such as aryl fluorides (**4e**, **4m**), aryl chlorides (**4f**), aryl triflates (**4g**) or aryl tosylates (**4h**) did not interfere with productive formation of the difunctionalized arene, thus leaving ample room for further functionalization via conventional cross-coupling protocols.[5] As shown in Table 2B, our platform could be applied for a wide number of alkynes end-capped with either aromatic or aliphatic backbone. It is worth noting, however, that alkynes bearing electron-donating arene substituents resulted in better regioselectivity profiles (**5a**–**5c** *vs* **5d**, **5f**). Importantly, X-ray crystallographic analysis of **5a** univocally revealed the structure of the difunctionalized arene with an *E*-configured olefin. Notably, alkynes bearing *ortho*-substituted arenes (**5e**), or heterocyclic motifs (**5g**, **5h**) posed no problems. Interestingly, the reaction could be extended to either symmetrical diarylated or dialkylated alkynes,[20] invariably obtaining **5j**–**5l** in good yields and regioselectivities. Unsymmetrically substituted dialkyl alkynes led to regioisomeric mixtures due to the difficulty of controlling migratory insertion of arylnickel(II) species into alkyne (**5m/5m'** and **5n/5n'**). Similarly, our reaction was equally applicable across a number of differently substituted unactivated alkyl bromides (Table 2C). Indeed, similar results were found for both primary (**6a**–**6j**) and secondary alkyl bromides (**6k**–**6m**); note, however, that a slight erosion in regioselectivity was observed for the latter. The chemoselectivity of the reaction was further illustrated by the compatibility with esters (**6c**, **6d**, **6n**–**6s**), phosphonates (**6e**), carbamates (**6f**, **6m**), amides (**6g**, **6p**), acetals (**6h**), nitriles (**6j**), sulfonamides (**6o**), ketones (**6q**, **6r**) or sulfones (**6p**), among others. The prospective potential of our methodology was further illustrated by the successful preparation of **6n**–**6s**, thus showing the suitability of our method to be applied in advanced intermediates derived from Oxaprozin (**6n**), Probenecid (**6o**), Sulbactam (**6p**), Isoxepac (**6q**), Estrone (**6r**) and δ-Tocopherol (**6s**).

Table 2. Scope of Ni-Catalyzed Three-Component Migratory C(sp^2)–H Alkylation of Aryl Bromides[a]



[a]As Table 1 (entry 1). Isolated yields, average of two independent runs; *E/Z* corresponds to the *E/Z* isomeric ratio, rr corresponds to the regioisomeric ratio, representing the ratio of the depicted product with the sum of all other observed *ipso*-isomers, as determined by GC, GC-MS analysis and ^{1}H NMR of the crude mixture, see SI for details. [b]$NiBr_2$·diglyme (5 mol%), **L3** (10 mol%), Mn (2.0 equiv), NaI (1.0 equiv), $MgCl_2$ (50 mol%), NMP (0.20 M), rt, 48 h.

The synthetic utility of our protocol is further highlighted in Figure 4. As shown, the pending alkenyl group could be utilized as a handle for subsequent manipulation; specifically, Ru-catalyzed oxidative cleavage enabled the synthesis of **7a** whereas a Pd-catalyzed hydrogenation resulted in **7b**, thus indirectly serving as a manifold to incorporate two sp^2–sp^3 linkages via formal vicinal difunctionalization of a simple and commercially available aryl halide.

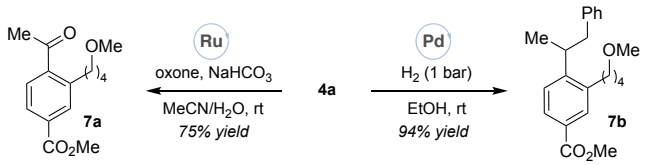
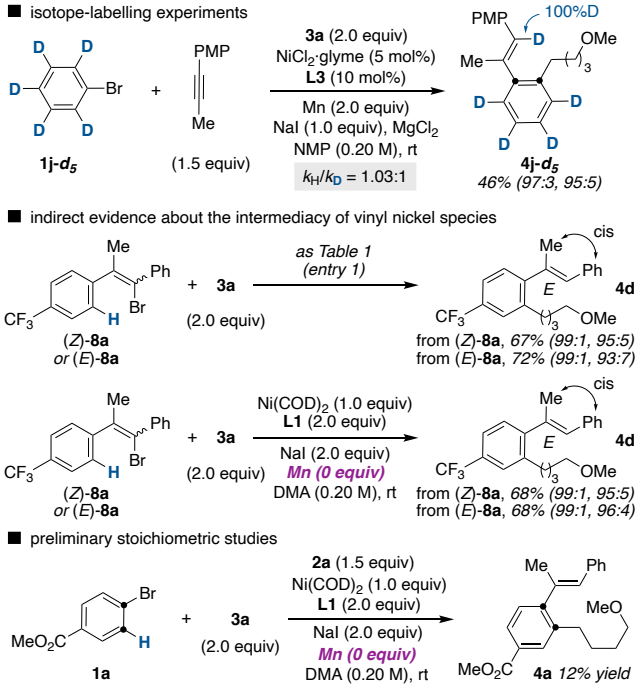


Figure 4. Synthetic utility. Synthesis of **7a**: $RuCl_3$ (3.5 mol%), oxone (2.0 equiv), $NaHCO_3$ (6.2 equiv), MeCN:H_2O (1.5:1, 0.04

M), rt, 2 h; Synthesis of **7b**: $Pd(OH)_2/C$ (10 mol%), H_2 (1 bar), EtOH (0.20 M), rt, 12 h.

Next, we turned our attention to gaining some insight into the 1,4-Ni migration event via isotope-labelling (Scheme 1). Specifically, exclusive deuterium incorporation was found at the alkenyl site upon reaction of **1j-*d*$_5$** with **3a** and **2b** under our optimized reaction conditions (Scheme 1, top), thus indirectly confirming that 1,4-shift occurs prior to alkylation at the *sp*^{2} C–H site. Interestingly, no significant intermolecular kinetic isotope effect was observed by comparing the initial rates of **1j** and **1j-*d*$_5$**. This is in contrast with our recently developed carboxylation event,[15] tacitly suggesting that 1,4-Ni migration might not be involved in the rate-limiting step of the reaction.[21] According to the rationale depicted in Figure 3, the targeted alkylation could also be initiated upon oxidative addition of an alkenyl bromide to Ni(0)L_n en route to **III**. This notion gained credence by observing the formation of **4d** regardless of whether (*Z*)-**8a** or (*E*)-**8a** were utilized as counterparts (Scheme 1, middle). This result is particularly noteworthy, as it suggests a fast and reversible *E*/*Z*-isomerization of alkenylnickel(II) species prior to 1,4-Ni migration.[22] While unravelling the mechanistic underpinnings of our protocol should await further investigations, it is worth noting that exposure of **1a** with **2a** and **3a** to stoichiometric amounts of Ni/**L1** delivered **4a**, albeit in 12% yield (Scheme 1, bottom). Although care should be taken when generalizing these results,[23] at present we support a mechanistic scenario consisting of a 1,4-shift triggered by in situ generated alkenyl nickel(II) intermediates of type **III** (Figure 3).

Scheme 1. Preliminary Mechanistic Studies.



In summary, we have developed a *de novo* platform that streamlines the preparation of vicinal difunctionalized arenes from simple aryl halides by harnessing the potential of Ni catalysts to trigger unconventional 1,4-shifts at previously unfunctionalized *sp*^{2} C–H linkages. This method is characterized by its broad substrate scope and mild conditions, offering a complementary technique to enable formal cross-electrophile regimes at non-polarized *sp*^{2} C–H sites. The development of a catalytic asymmetric version of this transformation with secondary alkyl bromides is currently underway.

ASSOCIATED CONTENT

Experimental procedures, characterization data for all compounds, and crystallographic data of **5a** (CIF). This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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