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# Directed Ni-Catalyzed Reductive Arylation of Aliphatic C−H Bonds

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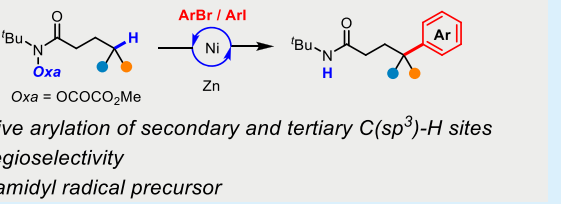
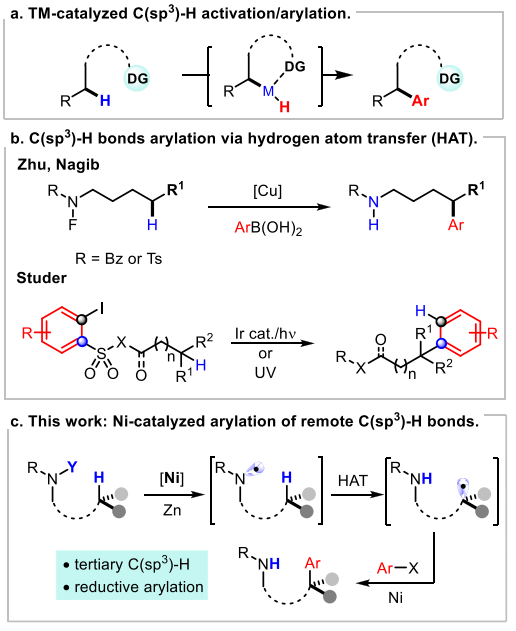
**ABSTRACT:** Herein, we describe the nickel-catalyzed reductive arylation of remote C($sp^3$)−H bonds with aryl electrophiles. The reaction targets secondary and tertiary C($sp^3$)−H bonds to deliver all-carbon quaternary centers. The success of this method relies on a novel amidyl radical precursor that tolerates reducing conditions, namely *O*-oxalate hydroxamic acid esters.






Selective C−H functionalization represents an attractive approach to rapidly increase structural complexity and streamline synthesis.[1] Over the past two decades, efforts to develop practical methods for selective C−H functionalization have led to novel reactivities, new mechanistic paradigms, and synthetically useful protocols.[2] In this area, the transition-metal-catalyzed directed arylation of C−H bonds represents an important protocol for the efficient construction of C−C bonds.[3] The selective arylation of C−H bonds can significantly simplify synthetic routes to construct C−C($sp^2$) bonds by avoiding the use of prefunctionalized starting materials (Scheme 1a). Despite the tremendous progress in the arylation of C($sp^2$)−H bonds,[4] the site-selective arylation of unactivated C($sp^3$)−H bonds remains underdeveloped.[5] Moreover, the additional problems associated with tertiary C($sp^3$)−H bonds, namely steric hindrance and $\beta$-hydride elimination, have severely impeded the development of the transition-metal-catalyzed arylation of tertiary C−H sites.

**Scheme 1. Arylation of C($sp^3$)−H Bonds**




Complementary to transition metal-catalyzed C($sp^3$)−H activation/arylation, another powerful approach is the arylation of carbon-based radicals generated by hydrogen atom transfer (HAT).[6] In that regard, the recently reported copper-catalyzed Suzuki−Miyaura arylation of benzylic and secondary C($sp^3$)−H bonds, reported by Zhu and Nagib,[7] represent creative approaches to this important problem (Scheme 1b).[8] Studer and co-workers recently developed a reaction for the arylation of C($sp^3$)−H bonds that uses the combined processes of 1,*n*-HAT and aryl migration (Scheme 1b).[9] Despite these seminal advances,[10] a general protocol targeting tertiary C−H bonds remains elusive.

Recently, a series of nickel-catalyzed arylation reactions that used prefunctionalized tertiary substrates were reported, offering a variety of approaches for the construction of all-carbon quaternary centers.[11] While powerful for the formation of quaternary centers, the use of tertiary C−H bonds as substrates in nickel-catalyzed arylation remains an unsolved problem.[12] Here, we propose combining 1,5-HAT[13] with nickel-catalyzed reductive coupling[14] to enable the selective arylation of remote tertiary C($sp^3$)−H bonds (Scheme 1c). We envisioned two major obstacles to accomplishing this goal: the choice of amidyl-radical precursor[15] and the combination of producing an amidyl radical and the arylation of a tertiary carbon radical[11a−e] in Ni catalysis. The generation of an amidyl radical through single-electron transfer (SET) from Ni and

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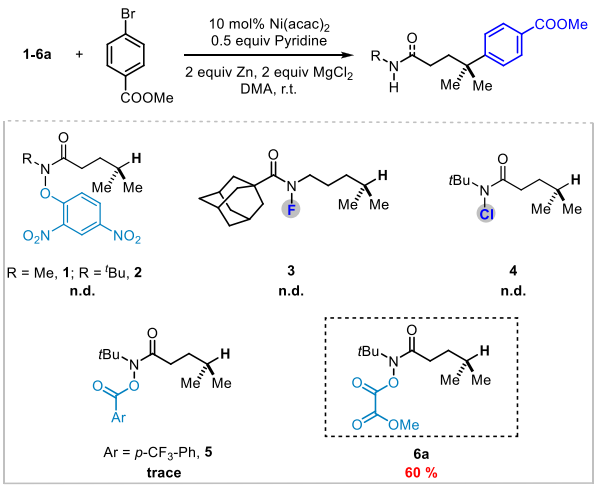
subsequent C($sp^3$)−H arylation may offer a new paradigm for nickel-catalyzed C−H functionalization.[6,16]

With these challenges in mind, we started our investigation with a series of amidyl-radical precursors **1**−**6** and chose $Ni(acac)_2$ as a catalyst with a combination of pyridine, Zn, and $MgCl_2$ in DMA.[11f] The reactions of substrates **1**,[15d] **2**, **3**,[15a,h] and **4**[15b] all failed to produce the desired product. Interestingly, a trace amount of product **7a** was found when **5**[15c] was used as the starting material. When we subjected the *O*-oxalate hydroxamic ester (Oohe) **6a**—a novel structural motif—to the reaction conditions, the remote arylation product **7a** was obtained in a 60% yield (Scheme 2).

**Scheme 2. Evaluation of Amidyl Radical Precursors for the Arylation of Remote C−H Bonds**[a]

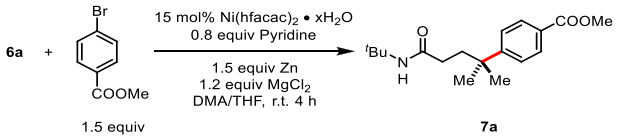



[a]Performed on 0.1 mmol scale a 0.1 M concentration. n.d. = not detected. Yields were determined by $^1$H NMR analysis using 1,3,5-trimethoxybenzene (Ar−H) as the internal standard.

After an extensive examination of the reaction conditions, we identified that the reaction of **6a** with methyl 4-bromobenzoate in the presence of $Ni(hfacac)_2{\cdot}xH_2O$, pyridine, Zn, and $MgCl_2$ provided the arylated product **7a** in a 69% yield (Table 1, entry 1). In the absence of $MgCl_2$, pyridine, or Zn, the reaction did not proceed (Table 1, entries 2−4). Since both $MgCl_2$ and LiCl can be used to activate Zn, we switched $MgCl_2$ to LiCl, but this significantly decreased the yield (Table 1, entry 5).[11b,17] The reaction with 0.4 equiv of pyridine produced **7a** in a moderate 59% yield (Table 1, entry 6). When a series of electronically differentiated pyridine ligands were examined (see the Supporting Information), all were found to be inferior to pyridine. For example, 4-OMe-pyridine provided less than half the yield (28%) relative to pyridine (Table 1, entry 7). Furthermore, the reaction provided no product when 2,6-bipyridine replaced pyridine in the reaction (Table 1, entry 8). The use of Mn or other zero-valent metals as the reductant provided the desired product in low yield (e.g., Table 1, entry 9). The use of other nickel sources, namely $Ni(acac)_2$ and $NiBr_2{\cdot}DME$, also decreased the yield to 50% and 34%, respectively (Table 1, entries 10 and 11). Using DMA instead of the mixed THF/DMA solvent system slightly decreased the yield to 65% (Table 1, entry 12).

With the optimized reaction conditions in hand, we next evaluated a range of substrates with tertiary and secondary C($sp^3$)−H bonds (Table 2). First, a series of electronically

**Table 1. Optimization of Reaction Conditions**[a]




| entry | deviation | yield (%)[b] |
|---|---|---|
| 1 | none | 69 |
| 2 | without $MgCl_2$ | n.d. |
| 3 | without pyridine | n.d. |
| 4 | without Zn | n.d. |
| 5 | LiCl instead of $MgCl_2$ | 30 |
| 6 | 0.4 equiv pyridine | 59 |
| 7 | 4-OMe-Py instead of pyridine | 28 |
| 8 | 15 mol % bpy instead of pyridine | n.d. |
| 9 | Mn instead of Zn | 35 |
| 10 | 10 mol % $Ni(acac)_2$ | 50 |
| 11 | 10 mol % $NiBr_2{\cdot}DME$ | 34 |
| 12 | DMA as the solvent | 65 |

[a]Performed on 0.1 mmol scale (0.1 mmol **6a**) at 0.1 M concentration. n.d. = not detected. [b]Yields were determined by $^1$H NMR analysis using 1,3,5-trimethoxybenzene (Ar−H) as the internal standard.

differentiated aryl bromides and iodides possessing various common functional groups were tested with the Oohe derivative **6a** as the model substrate (Table 2a). The electron-deficient *para*-substituted aryl bromides worked well in the reaction, giving the corresponding products **7a**−**7e** in moderate to good isolated yields. The coupling with multisubstituted aryl bromides provided the products **7f**−**7h** in moderate yields. Notably, the reaction offers the ability to employ multisubstituted aryl coupling partners, difficult substrates when using the elegant intramolecular aryl migration methodology.[9] For *meta*-trifluoromethyl bromobenzene, the arylation delivered product **7i** in a 62% isolated yield. The reaction was also compatible with other arenes, such as methyl 6-bromo-2-naphthoate (**7j**) and 3-bromopyridine (**7k**). The site-selectivity en route to product **7j** suggests the difference between the reaction and the Minisci-type alkylation of pyridines, which gives the product with C2 or C4 selectivity.[18] In contrast to the use of electron-deficient aryl coupling partners, the use of electron-rich aryl halides presents a greater challenge.[11b−e] In this protocol, the arylation with electron-rich aryl iodides, such as methyl, OAc, OBz-substituted iodobenzene, and *N*-acetyl iodoindole, proceeded smoothly with the use of 3-fluoropyridine as the ligand and the addition of LiCl, providing the products **7l**−**7o**, respetively, in moderate yields. Overall, this scope offers direct access to challenging products.

Next, different structural motifs around the targeted C−H bond were evaluated using electron-deficient aryl bromides (Table 2b). As expected, both sterically hindered and electronically differentiated tertiary C−H bonds could be arylated to produce products **8**−**15** in 40−64% isolated yields. Impressively, even sterically hindered homobenzylic C−H bonds (e.g., **9**), and the tertiary C−H bond of cyclopentene (e.g., **12**) produced products in only slightly lower yields. Moreover, the methodology can target an $\alpha$-methyl-substituted substrate (e.g., **13**) for remote arylation. Substituting the aliphatic backbone with a methyl or phenyl group to produce sterically hindered tertiary C−H bonds as targets led to products **14** and **15** in good yields. The reaction to produce product **14** demonstrates the preference of this reaction to


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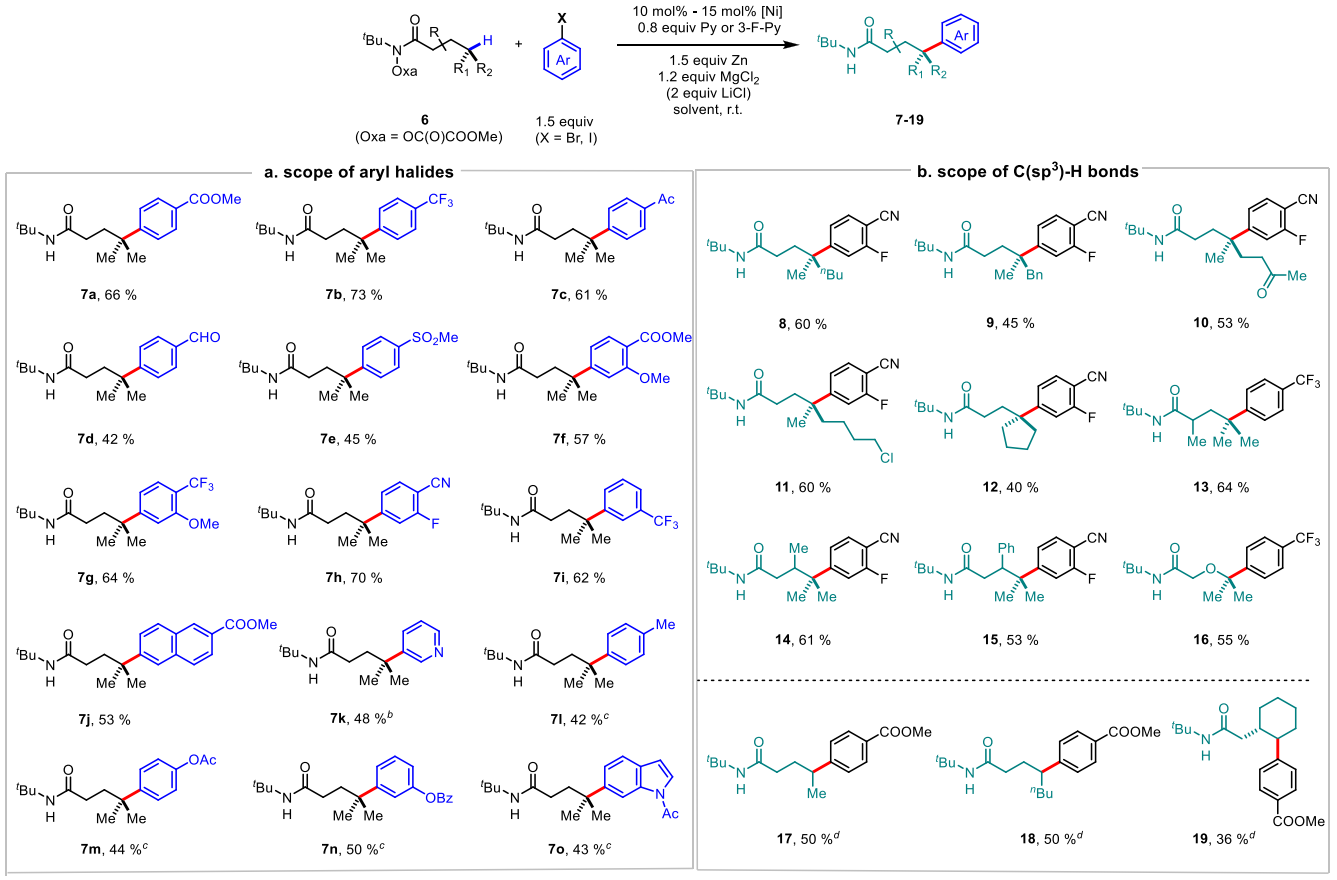
**Table 2. Substrate Scope of C(sp$^3$)−H Arylation**[a]




[a]Performed on 0.2 mmol scale with 15 mol % Ni(hfacac)$_2$·$x$H$_2$O, 0.8 equiv of pyridine, 1.5 equiv of Zn, and 1.2 equiv of MgCl$_2$ in 0.2 M DMA/THF (3:1). The reaction time was 4 h. Isolated yields are shown. [b]Performed with no pyridine, 2 equiv of Zn, and 2 equiv of MgCl$_2$ in 0.13 M DMA/THF (3:1). [c]Performed with 1.5 equiv of ArI, 10 mol % Ni(acac)$_2$, 0.8 equiv of 3-F-pyridine, and 2 equiv of LiCl, in 0.4 M DMA/THF (3:1). [d]Performed with 10 mol % Ni(acac)$_2$ and 15 mol % 4,4-di-*tert*-butylbipyridine (dtbbpy) in 0.1 M THF. The reaction time was 16 h.

select tertiary C−H bonds over primary C−H bonds. Moreover, tertiary ethereal C−H bonds (e.g., **16**) could be successfully arylated. Importantly, the arylation of secondary C(sp$^3$)−H bonds could be achieved by switching the ligand and solvent. With this change, linear substrates produced the arylated products in a 50% yield (**17** and **18**). The reaction of cyclic C(sp$^3$)−H bonds delivered product **19** in a modest yield but with excellent diastereoselectivity. Overall, the reaction demonstrates significant versatility with regard to the steric and electronic environment of the target coupling.

In an effort to better understand the key mechanistic features of the target reaction, some straightforward mechanistic inquiries were performed (Scheme 3). For example, the addition of TEMPO completely inhibited the reaction while leaving significant (>50%) starting material intact (Scheme 3a). Next, when we subjected substrate **6n** to the reaction, the ring-opened product **22** was obtained in a 46% yield, and the direct arylation product **21** was not detected (Scheme 3b). This suggests that a carbon-centered radical is required for the subsequent arylation process. Additionally, competition experiments between our arylation reaction and the Giese reaction[19] were conducted (Scheme 3c). The addition of alkene **23** completely inhibited the arylation process and provided the Giese product **24** in only a 34% yield, thereby suggesting that the Giese reaction of the tertiary carbon radical either effectively outcompetes the desired Ni-catalyzed arylation process or inhibits the catalytic cycle directly. The Giese reaction performed even better when excluding the aryl bromide. Surprisingly, in the absence of the aryl bromide and nickel, the Giese product **24** could also be detected in a 4% yield. This observation suggests that the generation of an amidyl radical could proceed through a single-electron transfer (SET) process from Zn, which is likely slower than that with Ni.

On the basis of these studies, a plausible mechanism is shown in Scheme 4. Both the [Ni$^{I}$] species and Zn[11b] can generate the requisite amidyl radical **25** through single-electron transfer (SET) processes (Scheme 4, path a and path b), but the SET initiated by [Ni$^{I}$] represents the major pathway since the addition of a catalytic amount of nickel improves the Giese reaction. After the formation of amidyl radical **25**, a 1,5-HAT reaction forms tertiary radical **26**, which subsequently reacts with the [Ar−Ni$^{II}$] species[11] to give the final product. MgCl$_2$ plays a dual role of activating Zn[11b,16] and facilitating the generation of amidyl radical **25**. This is accomplished through the chelation of the oxalate hydroxamic acid ester to promote SET.[11b] Additional mechanistic work—ongoing in our laboratory—should provide finer detail to this catalytic cycle.

In summary, we have demonstrated the arylation of remote tertiary and secondary C(sp$^3$)−H bonds through a 1,5-HAT and nickel-catalyzed reductive coupling process. By employing reductive coupling with Ni, the methodology enables the use of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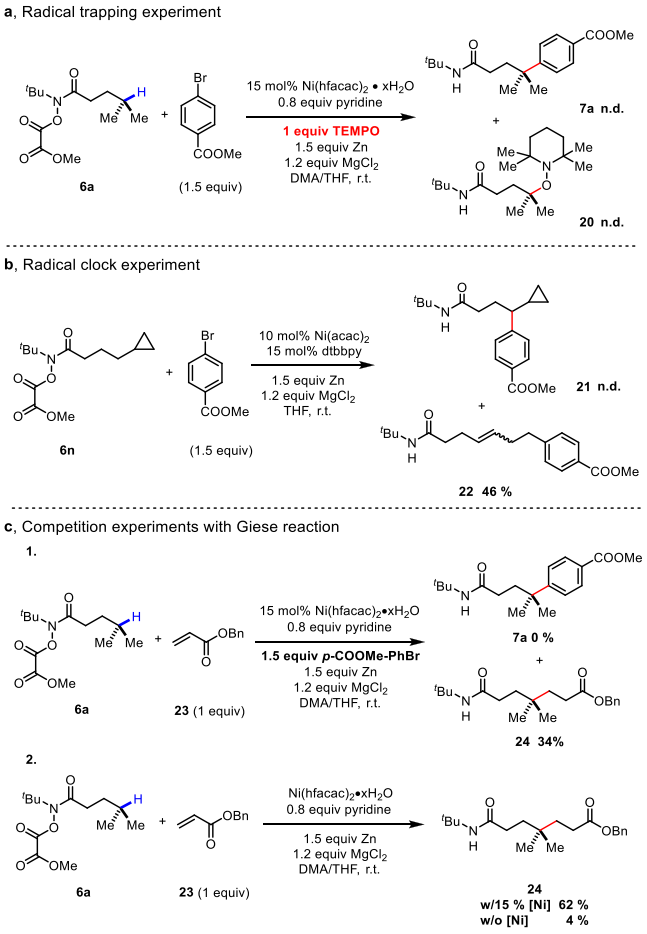
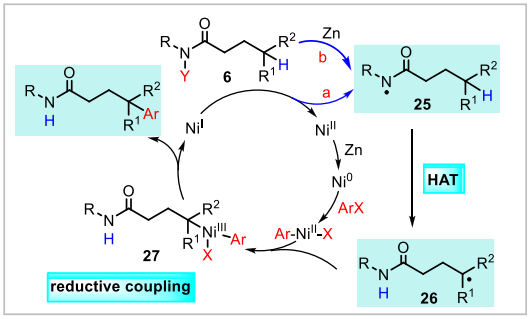
**Scheme 3. Key Mechanistic Studies**




**Scheme 4. Proposed Mechanism**




aryl electrophiles to target difficult-to-access C($sp^3$)−H bonds. Moreover, the reaction represents a direct strategy for the construction of all-carbon quaternary centers from unactivated tertiary C($sp^3$)−H bonds. The reaction proceeds with commercially available reagents and an inexpensive nickel precatalyst under mild conditions, offering practical utility. Finally, the novel substrates, namely *O*-oxalate hydroxamic esters, will be suitable for other valuable HAT-based reactions.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c00447.

Experimental details, compound characterization, and NMR data (PDF)

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### Notes

The authors declare no competing financial interest.

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