Oxidative Cross Dehydrogenative Coupling of *N*-Heterocycles with Aldehydes through C(*sp³*)–H Functionalization

Mo Chen, Austin M. Ventura, Soumik Das, Paul M. Zimmerman,* John Montgomery*

Department of Chemistry, University of Michigan, Ann Arbor, MI 48109-1055, USA

Abstract

Existing methodologies for metal-catalyzed cross-couplings typically rely on pre-installation of reactive functional groups on both reaction partners. In contrast, C–H functionalization approaches offer promise in simplification of the requisite substrates, however, challenges from low reactivity and similar reactivity of various C–H bonds introduce considerable complexity. Herein, the oxidative cross dehydrogenative coupling of α-amino C(*sp³*)–H bonds and aldehydes to produce ketone derivatives is described using an unusual reaction medium that incorporates the simultaneous use of di-*tert*-butyl peroxide as an oxidant and zinc metal as a reductant. The method proceeds with a broad substrate scope, representing an attractive approach for accessing α-amino ketones through the formal acylation of unactivated C–H bonds in *N*-heterocycles. A combination of experimental investigation and computational modelling provides evidence for a mechanistic pathway involving cross-selective nickel-mediated cross-coupling of α-amino radicals and acyl radicals.

Traditional approaches to cross-couplings utilize complementary functional groups on both reaction partners to enable the assembly of a desired C–C bond.[1] In contrast, C–H activation methods enable simplification of the approach by allowing one of the two substrates to lack a pre-installed functional group,[2] thus streamlining the construction of target molecules.[3] Cross-couplings that accomplish C–C couplings through site-selective C–H activation on *both* substrates, however, are quite rare, while offering considerable advantages in the simplicity of the substrates used. Oxidative dehydrogenative cross-couplings of this type, however, are especially challenging given the low reactivity of C–H bonds and their abundance in complex structures. Furthermore, achieving site-selectivity and suppressing homocoupling of either substrate presents additional hurdles for efficiency, particularly when the bond strengths and the chemical environments of the two C–H motifs are similar.[4]
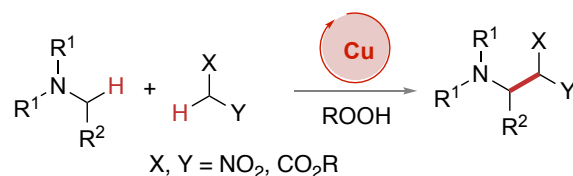
In the realm of cross-couplings that involve a single functionalized reaction partner, key contributions have come from many investigators across a range of reactions and catalyst types (**Scheme 1A**). As representatives examples, contributions from Doyle and MacMillan disclosed metallaphotoredox-catalyzed C−H arylations, where the C(sp^3)–H bonds in dimethylaniline were converted into organic radicals that undergo cross-couplings with aryl halides.[5] The Doyle group has further developed the direct functionalization of C(sp^3)–H bonds of *N*-aryl amines by acyl electrophiles under metallaphotoredox conditions.[6] Following these reports, the fields of photoredox catalysis and hydrogen atom transfer (HAT) have experienced rapid growth with broad scope being demonstrated in α-amino C(sp^3)–H functionalization with different coupling partners, including halides,[7] activated acids,[8] acrylates[9], azoliums,[10] amides.[11] Of these and related reports, work from Doyle,[6] Scheidt,[10] Hong,[11] Huo,[8] Xu,[12] Ohmiya,[13] and Chi[14] describe acylation processes using an array of electrophile classes. Among various HAT agents explored, peroxide oxidants have been demonstrated by Lei as effective in nickel-catalyzed C−H activation processes of heterocyclic C(sp^3)–H bonds.[15] Recent work from Stahl illustrating C−H methylation processes via cross-selective radical-radical couplings relying on methyl radical extrusion[16] and from Gong demonstrating the co-utilization of a peroxide oxidant with a zinc reductant[17] provide important examples of peroxide-mediated processes with nickel involving free radicals generated by HAT processes.

Methods that utilize cross dehydrogenative couplings (CDCs) through C−H functionalization on two different unfunctionalized reaction partners are highly desirable but quite rare.[18] Extensive work from Li has examined cross hydrogenative couplings using copper catalysis (**Scheme 1B**),[19] while fundamental studies from Fagnou illustrated biaryl synthesis through palladium-catalyzed cross-couplings of two arenes with cross selectivity arising from electronic differences in the two arene substrates.[20] C−H activations in CDCs typically operate via different modes, with one of the two substrates bearing acidic protons that enables the formation of a reactive species through acid-base chemistry, while the other substrate undergoes HAT-mediated C−H cleavage.[21]
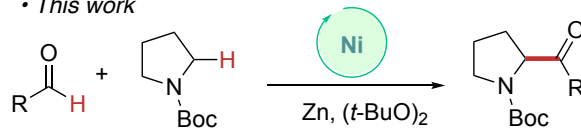
A. C-X / C-H Coupling

Y = N, O, aryl R^2 = aryl, alkyl, acyl
R$_1$ = aryl, alkyl R^{2}X = peroxide for methylation
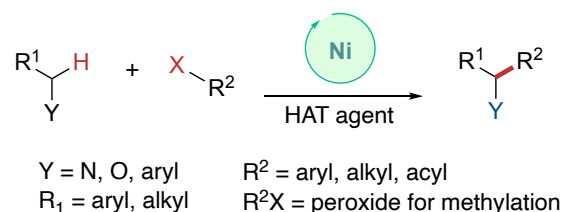
B. C-H / C-H Dehydrogenative Coupling

X, Y = NO$_2$, CO$_2$R

C. Ni-catalyzed C-H / C-H Dehydrogenative Coupling

• *This work*

Scheme 1. Strategies in C(sp^3)–H functionalization

Based on the above advances, we envisioned that the versatile chemistry of nickel in mediating radical-based cross-coupling processes could potentially be paired with HAT chemistry to enable C−H activation methods on two different substrates, thus avoiding functional groups pre-installation. A strategy of this type could potentially allow two different C−H activation processes to simultaneously operate even when the two substrates possess C−H bonds that are not easily distinguished by acidity or bond strength.[22] Towards the goal of developing a nickel-catalyzed direct oxidative dehydrogenative coupling process, we set out to examine the coupling of aldehydes with *N*-heterocycles (**Scheme 1C**), with these studies being motivated by our long-standing interest in the development of nickel-catalyzed additions to aldehydes utilizing unconventional nucleophiles.[23] Herein, we describe the formation of unsymmetrical ketones through the direct acylation of α-amino C(sp^3)–H bonds with aldehydes in a nickel-catalyzed process utilizing peroxide oxidant as the source of the HAT agent.

We began our experimental optimization with the coupling between benzaldehyde (**1a**) and *N*-Boc pyrrolidine (**2a**), where control experiments confirmed the necessity of catalyst, oxidant, and reductant (**Table 1, entry 2**). Ligand screening revealed that *N*-donor types together with Ni(II) pre-catalysts generally resulted in enhanced reactivities compared with NHC and phosphine ligands with Ni(COD)$_2$, though further modification of the bis(pyrazole) pyridine (bpp) scaffold

failed to improve the yield (see supporting information **S1**). The thermal-activation was found to be unique with the combination of Zn and di-*tert*-butyl peroxide (DTBP), as using either metallaphotoredox or different reductants did not yield the desired product (**entry 5**). Different peroxides have also been tested under this dehydrogenative coupling manifold, and DTBP, a stable organic peroxide, performed the best (see supporting information **S3**). The use of silyl chlorides only yielded the silylated pinacol-coupled byproducts (**entry 6**).[24] whereas 2.0 equiv. of water resulted in product **3a** in an improved 62% isolated yield (**entry 7**). Conducting the reaction in darkness resulted in a similar yield, excluded the possibility of photo-activation (**entry 8**). Investigations also indicated that possible oxidative degradation of *N*-Boc pyrrolidine (**2a**) had minor influences on the reaction outcomes (see supporting information for details). Further examination of reaction temperature, concentration and time led to optimal conditions for exploring the reaction scope.

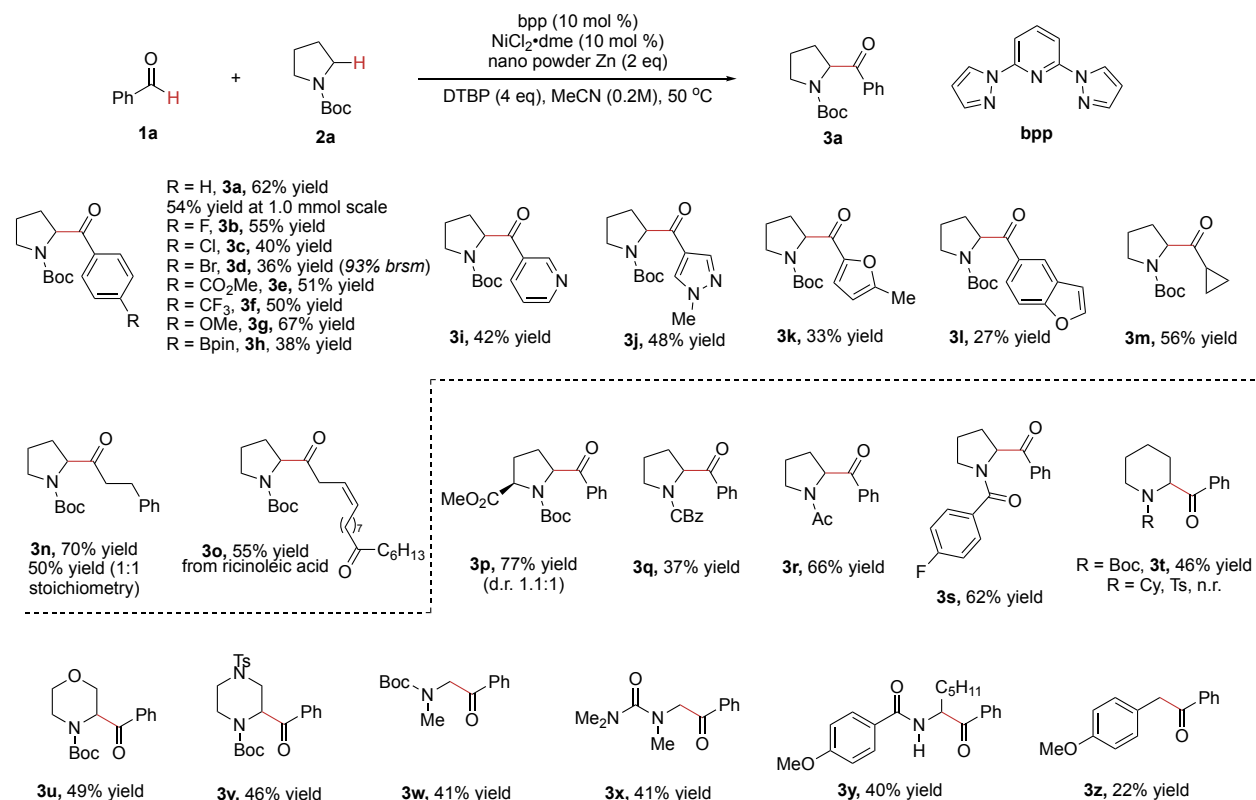**Table 1**. Nickel-catalyzed *N*-heterocycle aldehyde coupling optimization[a]
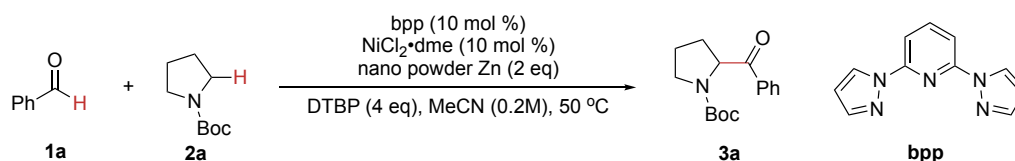
Entry	Deviation from standard condition	% yield
1	No	50
2	Absence of Ni or bpp or Zn or DTBP	<5
3	Ni(COD)$_2$ instead of NiCl$_2$•dme	0
4	Other N-donor, PR$_3$, NHC ligands	0-40
5	[Ir], blue LED instead of Zn	0
6	With 1 eq TESCl	0
7	With 2 eq water	67 (62)
8	In dark	64[b]

[a] The reaction was performed with **1a** (0.1 mmol, 1.0 eq), **2a** (0.24 mmol, 2.4 eq), bpp (0.01 mmol, 0.1 eq), NiCl$_2$•dme (0.01 mmol, 0.1 eq), nano powder Zn (0.2 mmol, 2.0 eq), and DTBP (0.4 mmol, 4 eq) in MeCN (0.5 mL, 0.2 M) at 50 °C for 16h. Yield was determined by ^{1}H NMR using CH$_2$Br$_2$ as an internal standard. [b] 2 eq H$_2$O was used as an additive.

The transformation tolerated different electronic environments on benzaldehydes, while electron withdrawing groups generally led to lower yields (**Table 2**). Functional groups that were facile for activation with nickel catalysis under reductive conditions underwent chemoselective C–H functionalization, enabling orthogonal functionalization at a later stage (**3c, 3d, 3h**). Of note, by analyzing crude reaction profiles, remainders of mass balances were largely unreacted starting

materials (**1** and **2**), and good mass recovery was demonstrated with the synthesis of **3d** (93% *brsm*). The synthetic utility was illustrated with a 1.0 mmol scale synthesis of **3a** in 54% isolated yield. Heteroaryl aldehydes were also compatible with this dehydrogenative coupling (**3i-3l**), and though electron-rich heterocycles gave lower yields, the absence of Minisici-type byproducts and clean reaction profile is worth highlighting. Further expanding the scope with aliphatic aldehydes, both cyclopropane carboxaldehyde and hydrocinnamaldehyde smoothly yielded the ketone products **3m** and **3n**, the former with the ring intact, and latter could be carried out with a 1:1 ratio of aldehyde and pyrrolidine. We envisioned that the potential of switching either coupling partner as the limiting reagent would facilitate late-stage applications in a complex setting. Along this line, an aldehyde derived from ricinoleic acid was well tolerated, leading to the formation of the desired coupling product **3o** with a 41% yield.

A broad scope of amine coupling partners has also been developed. A proline derivative was successfully converted to the corresponding acylated product **3p** in 77% yield. Different protecting groups were well tolerated, including CBz, Ac, and Bz (**3q-r**). Piperidine, one of the most prevalent motifs of pharmaceutical ingredient cores,[25] was successfully applied to the dehydrogenative coupling, together with a regioselective C–H functionalization using Boc-morpholine to afford products **3t** and **3u**. Orthogonal functionalization of multiple heteroatoms of similar reactivity has been long sought after in organic synthesis,[3c] and we took advantage of Ts as a deactivating group to enable a regioselective activation of the C–H bond proximal to the Boc-protected nitrogen of piperazine (**3v**). Such substrate-controlled regioselectivity has also been observed by Nicewicz and co-workers.[9,26] The desired acylation was also observed in acyclic systems, with simple building blocks including carbamate and urea derivatives of dimethylamine (**3w** and **3x**). Benzamides, which have been studied extensively under metallaphotoredox C–H functionalization regimes, also underwent the acylation reaction to afford **3y** in modest yield, providing orthogonal functionalization strategies to secondary amides. Benzylic C–H bonds were also successful candidates for aldehyde coupling and the desired product **3z** was obtained without condition optimization, indicating a potentially broader scope beyond protected amines.

**Table 2**. Nickel-catalyzed *N*-heterocycle aldehyde coupling scope[a]

R = H, **3a**, 62% yield
54% yield at 1.0 mmol scale
R = F, **3b**, 55% yield
R = Cl, **3c**, 40% yield
R = Br, **3d**, 36% yield (*93% brsm*)
R = CO$_2$Me, **3e**, 51% yield
R = CF$_3$, **3f**, 50% yield
R = OMe, **3g**, 67% yield
R = Bpin, **3h**, 38% yield

3i, 42% yield

3j, 48% yield

3k, 33% yield

3l, 27% yield

3m, 56% yield

3n, 70% yield
50% yield (1:1 stoichiometry)

3o, 55% yield
from ricinoleic acid

3p, 77% yield
(d.r. 1.1:1)

3q, 37% yield

3r, 66% yield

3s, 62% yield

R = Boc, **3t**, 46% yield
R = Cy, Ts, n.r.

3u, 49% yield

3v, 46% yield

3w, 41% yield

3x, 41% yield

3y, 40% yield

3z, 22% yield

[a] The reaction was performed with aldehydes (0.2 mmol, 1.0 eq), amines (0.48 mmol, 2.4 eq), bpp (0.02 mmol, 0.1 eq), NiCl$_2$•dme (0.02 mmol, 0.1 eq), nano powder Zn (0.4 mmol, 2.0 eq) and DTBP (0.8 mmol, 4 eq) in MeCN (1.0 mL, 0.2 M) at 50 °C for 16h. Yields were reported as isolated products. [b] The reaction was performed at 0.1 mmol scale.

To provide mechanistic insight, experimental and computational studies were performed. A series of radical trapping experiments were carried out to probe the proposed nickel catalyzed radical-radical cross-coupling pathway (*vide infra*). Benzyl acrylate was selected as an electron deficient alkene for the Giese reaction[27] wherein the α-amino radical addition product was isolated in 30% yield (**Scheme 2A**). Swapping the radical scavenger to diphenyl diselenide, which has been used as a trapping agent for acyl radicals,[28] afforded the acyl-selenide product in 15% yield based on GCMS analysis. These experiments indicated that both carbon-centered radicals were involved in the transformation, and the use of TEMPO as an additive completely inhibited the reaction.

To further understand roles that Zn and DTBP played in this transformation, several control experiments were conducted. In the absence of either nickel catalyst or Zn, only trace decomposition of DTBP was observed at 50 °C over 16h. Moreover, we were able to correlate

the stoichiometry of Zn and product yield based on GC analysis, indicating that Zn played a crucial role in the catalytic cycle rather than merely participating in a reductive event during reaction initiation (**Scheme 2B**).[29] Three potential HAT reagents were independently considered: chlorine radicals (via oxidation of chloride from the nickel pre-catalyst); *tert*-butoxy radicals (via decomposition of DTBP); and methyl radicals (via β-scission of *tert*-butoxy radicals).[16] Addition of different tetrabutylammonium halides salts, which has been shown in promoting HAT processes in metallaphotoredox reactions[8a,30] all led to inferior results, suggesting that chlorine radicals may not be the HAT agent in this reaction. (**Scheme 2C**) Moreover, the trace acetone generation in this reaction also excluded the possibility of methyl radicals being the major HAT agent (see supporting information for details). These observations support the notion that *tert*-butoxy radicals are the major HAT agent involved in the catalytic process.
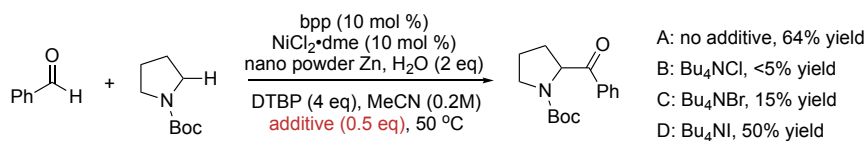
A. Radical Trapping Experiments
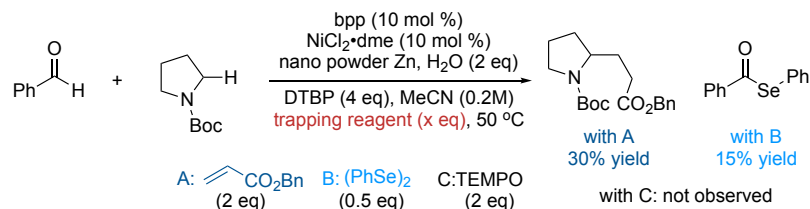

B. Zn Dependent Reactivities
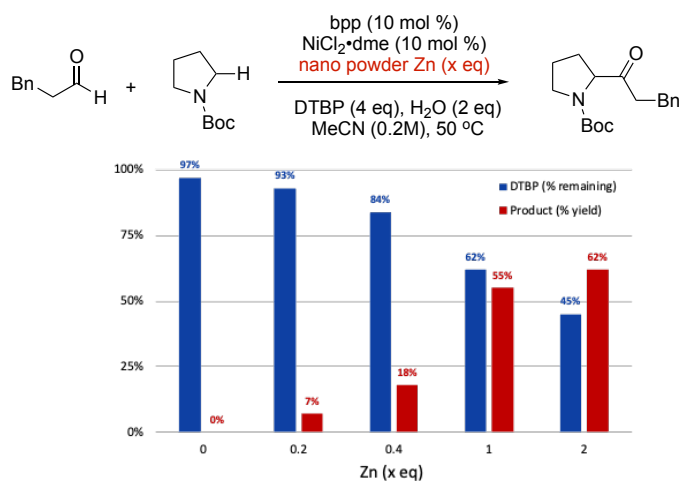
C. Additive Experiments

Scheme 2. Experimental mechanistic investigations.

With these experimental observations in hand, a plausible Ni^I/Ni^{III} redox cycle is proposed as an operative pathway for catalytic conversion (**Scheme 3**). Quantum chemical simulations (see supporting information) revealed a feasible pathway to convert the precatalyst to the $Ni^I(O^tBu)(bpp)$ species (**A**). A *tert*-butoxy radical from the decomposition of DTBP allows **A** to transform to a thermodynamically stable $Ni^{II}(O^tBu)_2(bpp)$ intermediate **B**. Potentially, Zn-based reduction of intermediate **B** back to species **A** could effectively serve as a redox-buffering process, leading to further consumption of DTBP. Detailed recent studies from Sevov describe electrocatalytic studies of a nickel bpp catalyst system including related one-electron redox conversions.[31] The reversible **B** to **A** interconversion increases the concentration of *tert*-butoxy radicals to enable productive catalysis. For the productive pathway, **B** can undergo radical addition with either **1R** or **2R** generated from off-cycle HAT processes governed by *tert*-butoxy radicals. The addition with acyl radical **1R** was found to be favorable by 13.8 kcal/mol compared to the alternative α-amino radical (**2R**) addition, largely due to steric interactions with radical **2R** in complex **B** (see supporting information **Figure S1**). Such energetic differences give rise to the high cross selectivity, as the trapping of **B** with **1R** lowers the concentration of acyl radical in solution,[32] kinetically prohibiting the addition of second equivalent of **1R**. A similar phenomenon has also been observed by MacMillan and co-workers in their radical sorting pathway.[8b,33] Following the formation of intermediate **C**, another Zn-based reduction could transform the Ni^{III} species to a Ni^{II} intermediate **D**, which could undergo subsequent α-amino radical (**2R**) addition. The resulting Ni^{III} hetero-adduct **E** undergoes reductive elimination to produce the desired cross-coupled product, while regenerating the nickel complex **A**. A complete energy profile for this catalytic cycle is presented in the supporting information.
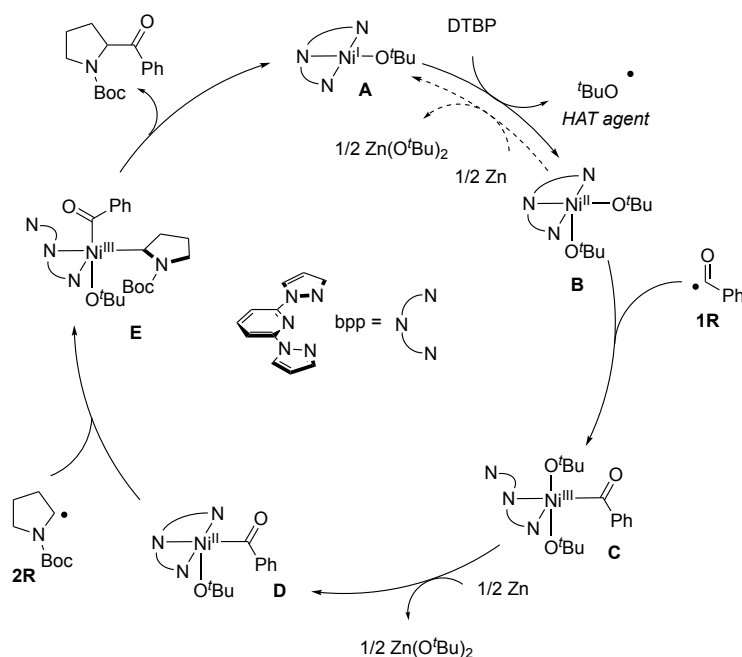
Scheme 3. Proposed catalytic mechanism involving a Ni^I/Ni^{III} redox cycle, based on experimental and computational investigations.

In summary, we report a method for nickel-catalyzed *N*-heterocycle C(sp^3)–H functionalization using aldehydes as coupling reagents. We have demonstrated a highly cross-selective dehydrogenative coupling with a broad scope of aldehydes and *N*-heterocycles. An unusual combination of peroxide and zinc metal has been shown to be crucial for reaction success, with mechanistic investigations supporting the formation of radicals from both substrates generated from *t*-butoxy radical as the hydrogen atom transfer (HAT) agent. This method offers a strategy for exploring chemical space via a late-stage C(sp^3)–H acylation approach. Further mechanistic study and investigation of the factors giving rise to the high cross-selectivity are currently underway.

Author Information

Mo Chen: 0000-0002-4421-4073

Austin M. Ventura: 0000-0001-8958-2497

Soumik Das: 0000-0002-1951-1906

Paul M. Zimmerman: 0000-0002-7444-1314

paulzim@umich.edu

John Montgomery: 0000-0002-2229-0585

jmontg@umich.edu

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