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Communication

Direct Enantioselective C(sp^3)–H Acylation for the Synthesis of α-Amino Ketones

Xiaomin Shu,[†] Leitao Huan,[†] Qian Huang, and Haohua Huo*

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ABSTRACT: A direct enantioselective acylation of α-amino C(sp^3)–H bonds with carboxylic acids has been achieved via the merger of transition metal and photoredox catalysis. This straightforward protocol enables cross-coupling of a wide range of carboxylic acids, one class of feedstock chemicals, with readily available *N*-alkyl benzamides to produce highly valuable α-amino ketones in high enantioselectivities under mild conditions. The synthetic utility of this method is further demonstrated by gram scale synthesis and application to late-stage functionalization. This method provides an unprecedented solution to address the challenging stereocontrol in metallaphotoredox catalysis and C(sp^3)–H functionalization. Mechanistic studies suggest the α-C(sp^3)–H bond of the benzamide coupling partner is cleavage by photocatalytically generated bromine radicals to form α-amino alkyl radicals, which subsequently engages in nickel-catalyzed asymmetric acylation.

Chiral α-amino ketone is a privileged motif found in many important pharmaceutically active agents (Figure 1a).[1] Despite its importance in medical science, the development of direct yet robust strategies for the enantioselective synthesis of this pharmacophore remains an important challenge in organic synthesis.[2] Limited successful examples generally rely on asymmetric electrophilic or nucleophilic amination of carbonyl compounds (Figure 1b). However, asymmetric electrophilic α-amination of ketone enolates (top of Figure 1b) often suffers from mixed enolate formation for dialkyl ketones and requires specific nitrogen electrophiles (e.g., azodicarboxylates) to deliver products that necessitates additional transformation to deliver synthetic useful compounds.[3] Recently, several elegant approaches for nucleophilic α-amination have been described by employing free amines as the nitrogen source (bottom of Figure 1b).[2] These methods require additional steps to prepare α-functionalized carbonyl compounds such as α-bromo cyclic ketones, α-diazo ketones, and α-carbonyl sulfonium ylides.

As an alternative to α-amination processes, asymmetric acylation of α-amino C(sp^3)–H bonds provides straightforward and modular access to α-amino ketones via C–C bond construction.[4] Whereas transition-metal-catalyzed enantioselective C(sp^3)–H functionalization is a persistent challenge in asymmetric catalysis,[5,6] there is a growing need for the development of new C–H bond activation and late-stage functionalization reactions that proceed with nontraditional disconnections.[7]

In recent years, transition metal and photoredox dual catalysis, particularly photoredox nickel catalysis, has emerged as a powerful tool to construct chemical bonds that are difficult to form via traditional two-electron pathways.[8] For examples, nickel-mediated photoredox catalysis has enabled the direct C(sp^3)–H functionalization of both feedstock hydrocarbons and complex molecules by leveraging nickel's unique ability in alkyl fragment couplings.[9] In these photochemical methods,[10] the C–H cleavage proceeds through the single electron transfer (SET) or hydrogen atom abstraction (HAT) process, which overcomes the limitations often associated with classic C–H activation, including the requirements for coordinating directing groups and high reaction temperatures. Although substantial efforts have been devoted to the realm of metallaphotoredox catalysis, enantioselective metallaphotoredox catalysis remains underexplored,[11] especially for C(sp^3)–H functionalization.[12] Herein, we report an unprecedented metallaphotoredox-mediated enantioselective C(sp^3)–H acylation reaction for the synthesis of highly valuable and enantienriched α-amino ketones from readily available materials (Figure 1c). We envision that a photocatalyst-induced hydrogen atom abstraction (HAT) of an α-amino C(sp^3)–H bond would produce a prochiral α-amino radical. Meanwhile, a chiral nickel catalyst could engage sequentially with the acyl electrophiles formed in situ from carboxylic acids and α-amino radicals through oxidative addition and radical capture. The resulting diorganonickel adduct would undergo reductive elimination to produce enantioenriched α-amino ketones.

Our investigation began with optimizing reaction conditions for the cross-coupling of commercially available butyric acid and *N*-pentyl benzamide (Figure 2).[13] We chose dimethyl dicarbonate (DMDC) as the activator to convert butyric acid to a mixed anhydride in situ. This elegant acid activation strategy has been previously employed in ketone synthesis.[14] Notably, commercially available, bench-stable carboxylic acids

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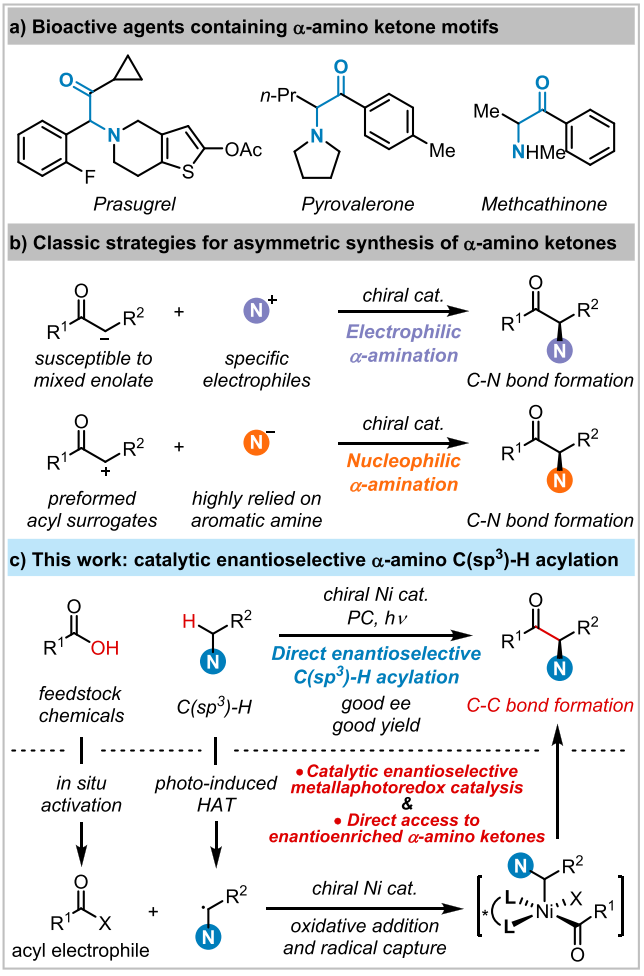
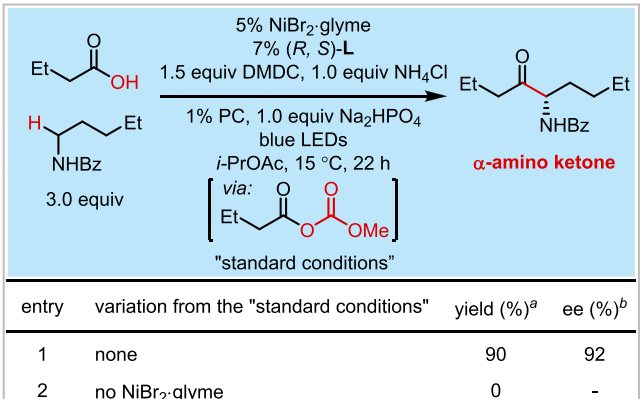


Figure 1. Bioactive α-amino ketone motifs and approaches for their asymmetric synthesis. (a) Examples of pharmaceutically active agents possessing α-amino ketone motifs. (b) Classic approaches for the asymmetric synthesis. (c) This study.



entry	variation from the "standard conditions"	yield (%)[a]	ee (%)[b]
1	none	90	92
2	no $NiBr_2$·glyme	0	-
3	no (*S, R*)-**L**	0	-
4	no PC, or no light	0	-
5	no NH_4Cl	77	92
6	under air in a capped vial	77	92
7	25 °C, instead of 15 °C	89	91
8	Boc_2O, instead of DMDC	20	86
9	EA, instead of *i*-PrOAc	75	87
10	dioxane, instead of *i*-PrOAc	72	90
11	**L1**, instead of (*R, S*)-**L**	89	–13
12	**L2**, instead of (*R, S*)-**L**	79	–23

PC = $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$. DMDC = Dimethyl dicarbonate.
[a] Determined through GC analysis. [b] Determined through HPLC analysis.

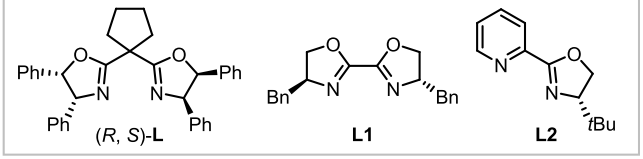


Figure 2. Effect of reaction parameters for photocatalytic enantioselective acylation.

can offer practical advantages over other acyl surrogates such as chemically sensitive anhydrides, acyl halides, preformed thioesters and amides.[15] After extensive investigation (also see Supporting Information), it was revealed that a chiral nickel/(bis-oxazoline) catalyst and a known Ir-photocatalyst could accomplish the desired acylation to deliver the aminoketone product in 90% yield and 92% ee (entry 1). Control experiments showed that nickel, chiral ligand, photocatalyst, and light are essential for product formation (entries 2–4). The reaction run under air in a closed vial or without NH_4Cl afforded unaltered enantioselectivity, albeit with slightly reduced yield (entries 5 and 6). Raising the reaction temperature to room temperature had almost no effect on the acylation reaction (entry 7). While Boc_2O was less effective than DMDC (entry 8), the use of EA or dioxane as solvent led to a comparable outcome (entries 9 and 10). Two other commercially available chiral ligands **L1** and **L2** can deliver the product in good yield but with poor asymmetric induction (entries 11 and 12).

With the optimized reaction conditions in hand, we investigated the scope of direct cross-coupling of carboxylic acids and *N*-alkyl benzamides (Figure 3). Carboxylic acids with different steric properties were suitable acyl donors (**1**–**8**). Remarkably, good yields and enantioselectivities were obtained when the carboxylic acid was functionalized with a variety of functional groups, including a phenyl group, a trifluoromethyl group, a nitrile, an ester, an alkyl chloride, an alkyl bromide, and a thiophene (**9**–**15**). Our protocol allowed for the coupling of not only alkyl carboxylic acids but also aromatic carboxylic acids with diverse electronic properties (**16**–**21**), complementing existing methods for asymmetric synthesis of α-amnio ketones based on organocatalytic α-amination reactions.[2,3]

The acylation reaction tolerated benzamides bearing alkyl groups with different steric properties (**22**–**26**). Various functional groups, such as an ester, an alkyl chloride, an alkyl bromide, an alkyl ether, a silyl ether, and an acetate, were well compatible (**27**–**32**). The alkyl halides provided versatile synthetic handles for further functionalization. The R substituent at the nitrogen protected group could be varied as well (**33**–**37**).

The exceptionally mild conditions and fairly broad functional group tolerance of our method prompted us to apply it to late-stage functionalization of natural products and drug molecules. Indeed, the present method could be used to produce an array of chiral α-amino ketones containing a pharmacophore or bioactive fragments in good stereoselectivities (**38**–**49**).

To further demonstrate the synthetic utility of the present method, a gram-scale synthesis of **20** was performed with

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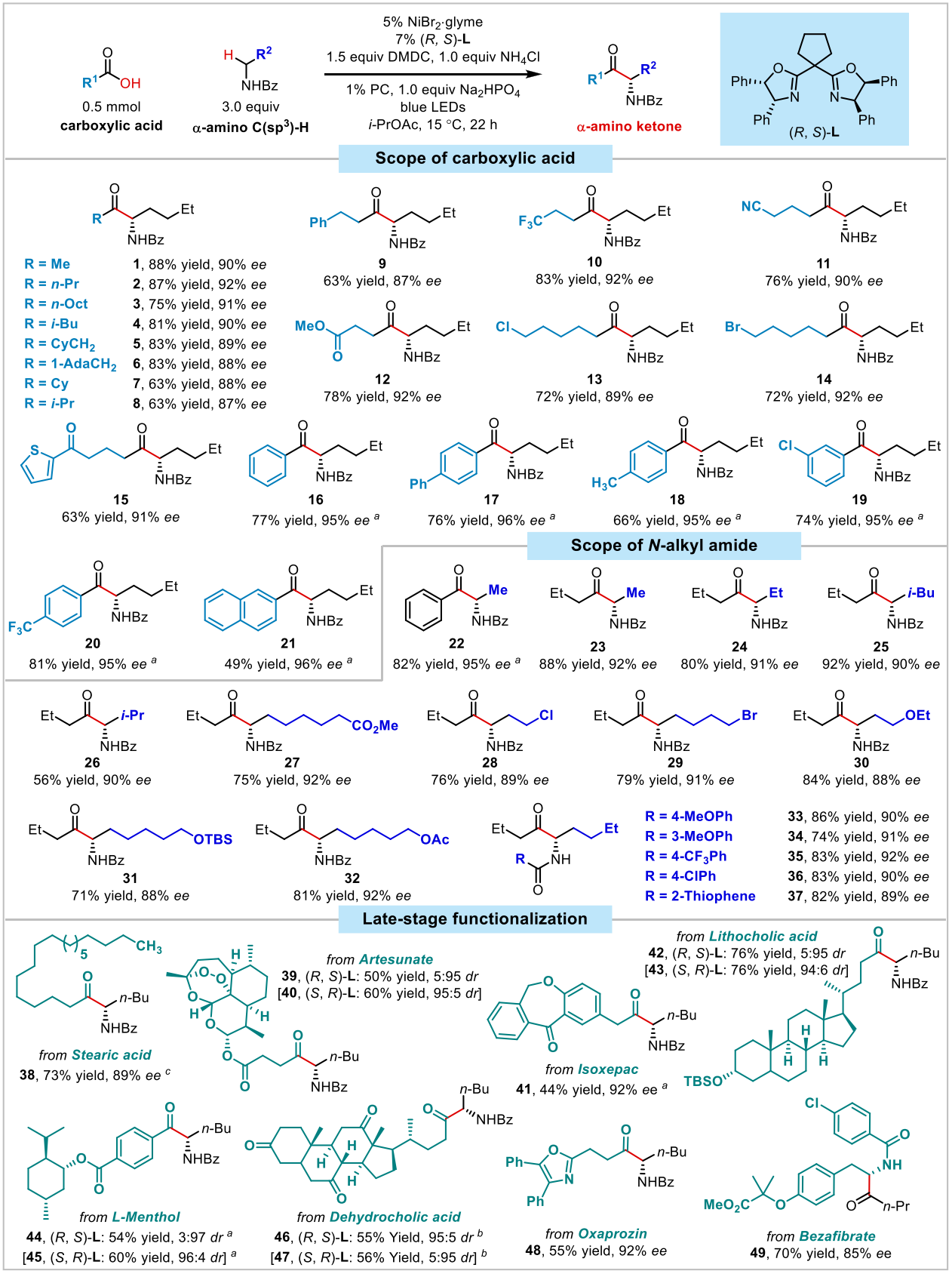

Figure 3. Catalytic enantioselective acylation of α-amino C(sp^3)–H bonds with carboxylic acids. All data represent the average of two experiments. Unless otherwise stated, reactions were conducted on a 0.5 mmol scale under standard conditions. [a]In lieu of the standard conditions, 10% Ni and 13% chiral ligand were used. [b]In lieu of the standard conditions, dioxane was used as solvent. [c]In lieu of the standard conditions, the reaction was conducted at 25 °C.

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excellent ee and synthetically useful yield (Figure 4). This aminoketone product could be directly converted through

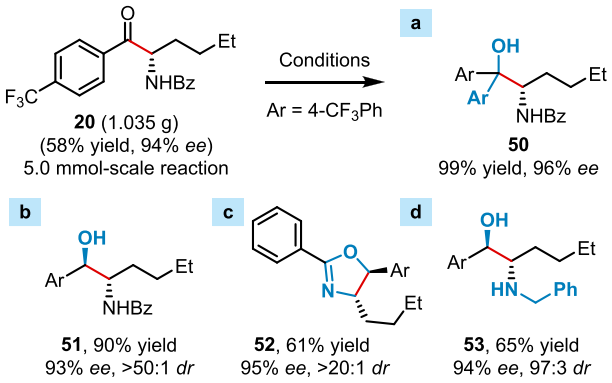
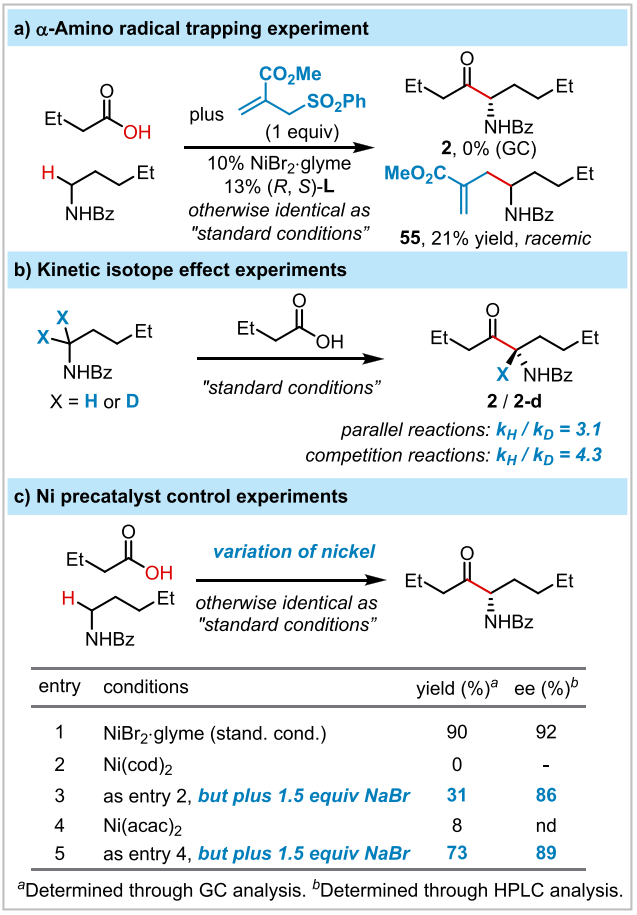


Figure 4. Gram-scale reaction and synthetic transformations. All data represent the average of two experiments. Reaction conditions: (a) 4-CF_3PhMgBr, THF; (b) Cp_2ZrHCl (1.2 equiv), THF; (c) DIAD, Ph_3P, DCM; (d) Cp_2ZrHCl (4.0 equiv), THF.

single-step reactions into other useful enantioenriched building blocks, such as β-amino tertiary alcohol **50**, β-amino secondary alcohol **51**, chiral oxazoline ligand framework **52**,[16] and β-benzyl amine **53**.

To provide some insights into the reaction mechanism, preliminary studies were conducted (Figure 5). Addition of 1 equiv of allylic sulfone to the model reaction led to a racemic adduct **55** in 21% yield without formation of α-amino ketone product (Figure 5a). This observation suggested that the reaction may involve formation of α-amino radicals. Furthermore, a primary kinetic isotope effect (KIE) was obtained by parallel (KIE = 3.1) and competition reactions (KIE = 4.3), which indicated that C−H cleavage has a significant contribution to the rate-determining step (Figure 5b). The use of the nickel precatalyst free of bromide led to less than 10% product formation (Figure 5c, entries 2 and 4). Interestingly, the product formation could be restored by addition of NaBr (Figure 5c, entries 3 and 5), alluding to the crucial role of the bromide anion in the coupling reaction. It has been reported that photocatalytic oxidation of bromide anion, a dissociable ligand on nickel, could generate bromine radicals for hydrogen atom abstraction from C(sp^3)−H bonds.[17]

According to our mechanistic studies (also see Supporting Information) and literature precedent,[17] a possible mechanism is proposed (Figure 6). The reaction is initiated by oxidative addition of Ni(0) intermediate **I** to acyl electrophile formed in situ to provide Ni(II) intermediate **II**. Concurrently, an oxidatively generated bromine radical ($E_{1/2}$[Ir(III*/II)] = + 1.21 V vs SCE in CH_3CN; for bromide: $E_{1/2}^{ox}$ = + 0.80 V vs SCE in DME)[17a] abstracts the hydrogen atom from α-amino C−H bond to afford a stabilized α-amino radical, which is readily intercepted by intermediate **II**. The resultant Ni(III) intermediate **III** undergoes reductive elimination to generate the final coupling product and Ni(I) intermediate **IV**.[18] The subsequent single electron transfer (SET) reduction of intermediate **IV** by reduced photocatalyst regenerates the Ni(0) intermediate **I** and closes the catalytic cycle ($E_{1/2}^{red}$ [Ir(II/III)] = − 1.37 V vs SCE in CH_3CN). This proposal involving a key HAT process is consistent with our mechanistic observations. The moderate bond dissociation energy of HBr



entry	conditions	yield (%)[a]	ee (%)[b]
1	$NiBr_2$·glyme (stand. cond.)	90	92
2	$Ni(cod)_2$	0	-
3	as entry 2, ***but plus 1.5 equiv NaBr***	**31**	**86**
4	$Ni(acac)_2$	8	nd
5	as entry 4, ***but plus 1.5 equiv NaBr***	**73**	**89**

[a]Determined through GC analysis. [b]Determined through HPLC analysis.

Figure 5. Preliminary mechanistic studies. (a) α-Amino alkyl radical trapping experiment. (b) Kinetic isotope effect experiments. (c) Ni-precatalyst control experiments.

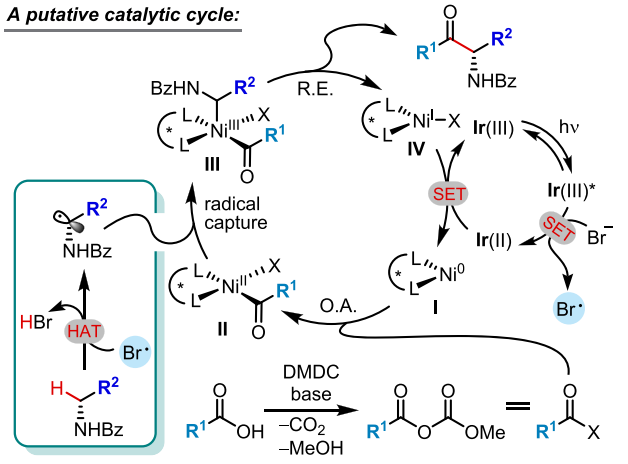


Figure 6. Putative catalytic cycle. R. E. = reductive elimination, O. A. = oxidative addition.

(BDE = 88 kcal/mol) ensures broad functional group tolerance of this protocol.[19]

In summary, a metallaphotoredox-mediated enantioselective C(sp^3)−H acylation reaction has been developed. This robust method employs abundant, air-stable carboxylic acids and readily available *N*-alkyl benzamides as coupling partners, boasts a fairly broad substrate scope and excellent functional group tolerance, and provides straightforward access to

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important enantiomeric α-amino ketones. The development of other classes of enantioselective radical C(sp^3)−H functionalization reactions is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c10471.

Crystallographic data for (*S*)-**19** (CIF)
Crystallographic data for (*S*)-**29** (CIF)
Experimental procedures, compound characterization data, NMR spectra, HPLC traces, crystallographic data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Haohua Huo − *State Key Laboratory of Physical Chemistry of Solid Surfaces, Key Laboratory of Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, P. R. China;* orcid.org/0000-0003-1785-4128; Email: hhuo@xmu.edu.cn

Authors

Xiaomin Shu − *State Key Laboratory of Physical Chemistry of Solid Surfaces, Key Laboratory of Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, P. R. China*

Leitao Huan − *State Key Laboratory of Physical Chemistry of Solid Surfaces, Key Laboratory of Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, P. R. China*

Qian Huang − *State Key Laboratory of Physical Chemistry of Solid Surfaces, Key Laboratory of Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c10471

Author Contributions

†X.S. and L.H. contributed equally.

Notes

The authors declare no competing financial interest.

Crystallographic data for (*S*)-**19** and (*S*)-**29** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 2032048 and 2032050, respectively.

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