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Enantioselective Decarboxylative α-Alkynylation of β-Ketocarbonyls via a Catalytic α-Imino Radical Intermediate

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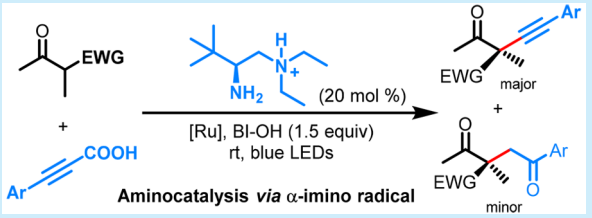
Supporting Information

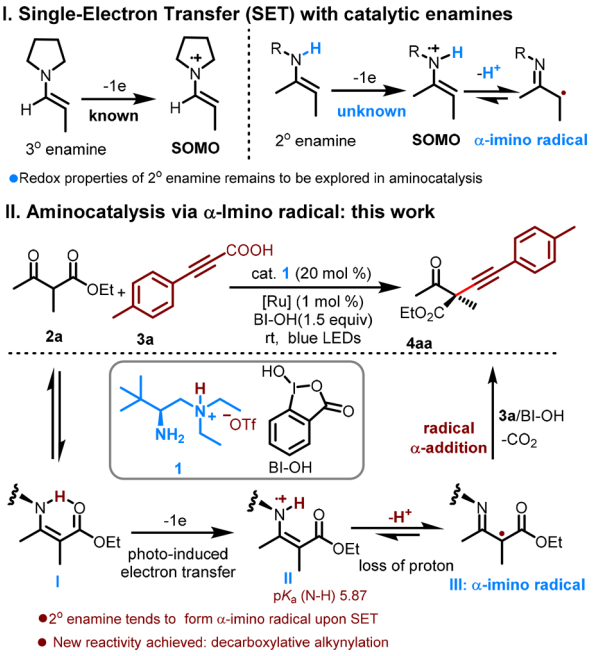
ABSTRACT: A distinctive aminocatalysis via α-imino radical is reported on the basis of SET oxidation of a secondary enamine. The combination of chiral primary amine catalysis and visible-light photoredox catalysis enables the enantioselective decarboxylative coupling of propiolic acid and β-ketocarbonyls to afford alkynylation adducts with high enantioselectivity. Mechanism studies indicate the reaction proceeds via an α-imino radical addition.



Beyond its nucleophilic feature,[1] enamine is also rich in redox properties and can be readily oxidized toa radical cation upon single-electron transfer.[2] The resulting radical cation could couple with nucleophiles, setting the basis for SOMO catalysis in the context of modern enamine chemistry as pioneered by MacMillan and co-workers.[3] Most of the SOMO catalyses are based on tertiary enamines derived from chiral secondary amine catalysts. On the other hand, SOMO-type catalysis with a secondary enamine, derived from the equally prevalent chiral primary amine catalysts,[4] have surprisingly remained underdeveloped. Unlike tertiary enamine, secondary enamine may easily lose an N−H proton after SET oxidation to form an α-imino radical (Scheme 1) as it is known that SET could dramatically activate the N−H bond (e.g., aniline pK_a 30.6, vs $C_6H_5NH_2^{+\bullet}$ pK_a 6.5[5]). A neutral α-imino radical,[6] in a close resemblance to its α-carbonyl counterpart, is less electrophilic compared with the parent radical cation, which would contribute to broadening the scope of SOMO catalysis.

We have tried to substantiate α-imino radical catalysis on the basis of enamine catalysis of β-ketocarbonyls by chiral primary amines.[4a] The oxidation potential of enamine ester (Scheme 1, II) was determined to be 1.13 V versus Ag/AgCl in CH_3CN,[7] and selective SET with the in situ generated enamine ester is plausible with most chemical or photo-redox processes. DFT calculation gave a pK_a (N−H) of 5.87 for the radical cation **II**,[8] indicating a facile proton transfer favoring the generation of α-imino radical **III**. Efforts were then devoted to search for a feasible and chemoselective oxidative system. In this context, a photoredox catalytic system involving $Ru(bpy)_3Cl_2$ and hypervalent iodine reagent (BI-OH), initially utilized by Chen,[9] was identified as the optimal oxidative reagent. The joint force of our chiral primary amine with the photoredox system enabled radical α-addition to propiolic acids via imino radical species, leading to an unprecedented decarboxylative α-alkynylation and alkylation reaction. Although enantioselective α-alkynylation of β-ketocarbonyls has been reported previously,[10] the substrates were limited to cyclic β-ketocarbonyls with bulky ester groups.

Scheme 1. Enantioselective Aminocatalysis via α-Imino Radical



Our initial investigation was performed with acetoacetate **2a** and propiolic acids **3a** employing the hypervalent iodine photoredox system under blue LED irradiation. Gratifyingly, in the catalysis with our chiral primary amine catalyst **1**/TfOH,

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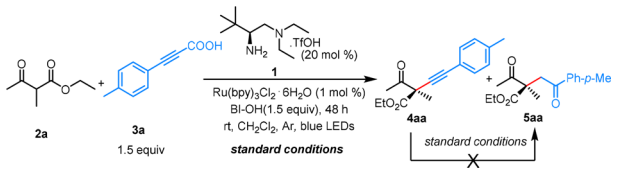
the desired α-alkynylation product **4aa** was obtained in 54% yield and 95% ee under the standard conditions, along with the formation of α-alkylation product **5aa** in 22% yield and 80% ee (Table 1, entry 1). In control experiments, **4aa** could not be converted into **5aa** under the reaction conditions, indicating two coexisting C−C bond formation pathways. Among different photocatalysts (entries 6−8) and hyervalent iodine reagents (entries 9−12) examined, $Ru(bpy)_3Cl_2{\cdot}6H_2O$ and hydroxybenziodoxole (BI-OH) were identified to give the optimal results in terms of both yield and enantioselectivity. In the absence of $Ru(bpy)_3Cl_2{\cdot}6H_2O$, hydroxybenziodoxole (BI-OH), or light, neither **4aa** nor **5aa** was observed (entries 2, 3, and 13). No desired product was obtained in the absence of primary aminocatalyst **1**/TfOH (entry 4), and the reaction was rather poor yielding and virtually racemic if no TfOH was added (entry 5). These results highlight the critical role of the primary amine−TfOH catalyst. Efforts to suppress the formation of alkylation product have been in vain, and two C−C bond formations coexisted with the alkynylation process generally favored (see the Supporting Information for details).

Table 1. Screening and Optimization[a]

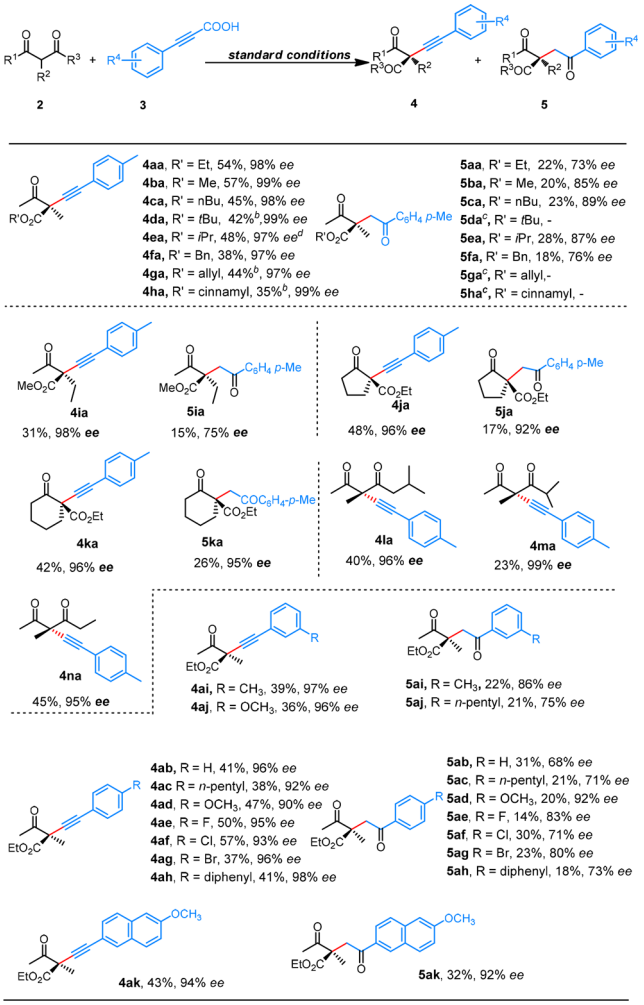


entry	variation from standard conditions	yield (**4aa**/**5aa**)[b] (%)	ee (**4aa**/**5aa**)[c] (%)
1	none	54/22	95/80
2	no $Ru(bpy)_3Cl_2{\cdot}6H_2O$	0	
3	no BI−OH	0	
4	no aminocatalyst	dimer of **2a**	
5	no TfOH	12/4	*rac*/8
6	$Ir(ppy)_3$	20/15	91/63
7	$Ir(ppy)_2(dtbbpy)(PF_6)$	trace	
8	Eosin Y	trace	
9	$PhI(OCOCF_3)$	trace	
10	$PhI(OAc)_2$	mess	
11	BI-OAc	dimer of **2a**	
12	BI-OMe	trace	
13	dark	0	

[a]Reactions were performed at room temperature in 0.5 mL of CH_2Cl_2 with **2a** (0.10 mmol), **3a** (0.15 mmol), hypervalent iodine reagent (0.15 mmol), **1** (20 mol %), and photocatalysts (1 mol %) under Ar with 0.5 W blue LED irradiation for 48 h, unless otherwise noted. [b]Isolated yield. [c]Determined by HPLC analysis.

With the optimized conditions in hand, we first investigated the scope of β-ketocarbonyl compounds (Scheme 2). Acetoacetates with different ester moieties including those with sterically bulky *tert*-butyl ester, benzyl, and allyl ester groups afforded the desired alkynylation adducts in moderate yields with excellent enantioselectivities (**4aa**−**ha**), along with the corresponding minor alkylation products with good enantioselectivities (**5aa**−**ca**, **5ea**−**fa**). Interestingly, when R′ = *t*Bu, allyl, and cinnamyl, the reaction afforded mainly alkynylation products with only trace amounts of alkylation products detected (**5da**, **5ga**, **5ha**). Larger α-substituents on acetoacetates (e.g., R^2 = Et) led to reduced yields, but enantioselectivities were not affected (**4ia**, **5ia**). Cyclic β-ketoesters were also tolerated to give the desired products **4ja**/**5ja** and **4ka**/**5ka** with high enantioselectivities. Notably, acyclic 1,3-diketones are workable substrates with excellent enantioselectivities under the current conditions (**4la**−**na**), and only alkynylation products were isolated with trace alkylation adducts observed.

Scheme 2. Scope of the Asymmetric α-Alkynylation of β-Ketocarbonyls and Propiolic Acids[a,d]



[a]All of the reactions were performed at room temperature in 0.5 mL of CH_2Cl_2 with **2** (0.10 mmol), **3a** (0.15 mmol), BI-OH (0.15 mmol), **1** (20 mol %), and $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (1 mol %) under Ar with 0.5 W blue LED irradiation for 48 h, unless otherwise noted. Yields shown are of isolated products; ee was determined by HPLC (slight peak overlapping was noted for compound **4ma** and **4ah**). [b]Reaction time: 60 h. [c]Trace product; ee values not determined. [d]The ee value was determined after one-step transformation into **5ea**.

We then set out to explore the scope of propiolic acids under the standard conditions. It was observed that a variety of phenylpropiolic acids bearing either electron-donating or electron-withdrawing groups at the *meta* or *para* position of the arene moiety reacted to produce the alkynylation products in moderate yield and excellent enantioselectivities (**4ab**−**ah**). At the same time, the corresponding alkylation products were obtained in low yields and moderate to good enantioselectivities (**5ab**−**ah**). Markedly, 3-(6-methoxynaphthalen-2-yl)prop-2-ynoic acid (**3k**) underwent this transformation with **2a** leading to **4ak** and **5ak** in moderate yields and good

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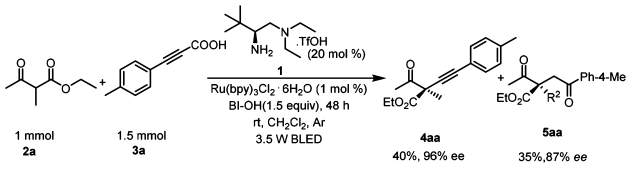
enantioselectivities. Unfortunately, alkylpropiolic acids did not work in the reactions.

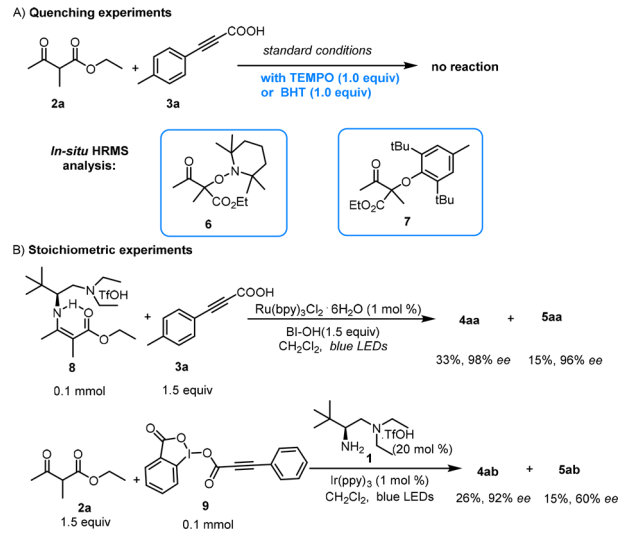
To probe the utility of our method in preparative synthesis, a gram-scale reaction of β-ketoesters **2a** was performed, delivering the product **4aa** and **5aa** with similar yield and enantioselectivity (Scheme 3). It is noted that stronger power blue LEDs are required to allow the reaction to proceed efficiently due to the heterogeneity of the reaction system.

Scheme 3. Gram-Scale Reaction



Alkyl radical was known to undergo α-addition to α,β-unsaturated carboxylic acids, leading to decarboxylative processes.[9b,11] For the current enamine-based process, the exclusive formation of α-addition product, instead of the typical nucleophilic β-addition with enamine, is reminiscent of a radical process. Radical-quenching experiments were then conducted, and the reactions were completely inhibited in the presence of TEMPO or butylated hydroxytoluene (BHT) (Scheme 4, A).

Scheme 4. Control Experiments

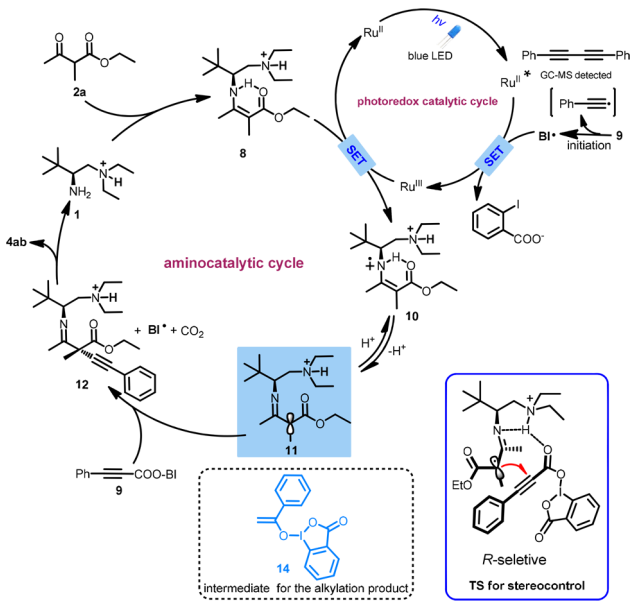


HRMS analysis of the quenched reaction mixture clearly indicated radical-trapped adducts **6** and **7** from TEMPO and BHT, respectively. This observation provided direct support to the radical mechanism. Stoichiometric experiment with preformed enamine **8** led to the desired adducts with consistently high enantioselectivity under otherwise identical conditions, verifying the enamine catalytic nature (Scheme 4, B).

To elucidate a photoredox process, a series of Stern–Volmer fluorescence quenching studies were performed with Ru(bpy)$_3$Cl$_2$. Surprisingly, none of the added species showed a significant quenching effect; only with the preformed propiolate hypervalent iodine **9** was obvious fluorescence quenching observed (see the SI for details). According to recent studies on the Ru/BI-OH photoredox system,[9] propiolate **9**, readily formed in situ under the reaction conditions, may serve as a precursor of BI radical, which participates in the oxidative quenching of photoexcited *Ru(II) species. The determined reduction potential of **9** ($E^{red}_{1/2}$ = 0.20 V vs Ag/AgCl) indicates that both **9** and its homolytic cleavage product BI radical can serve as the oxidant for SET process. Our control experiment with preformed **9** also led to the formation **4ab** and **5ab** in comparable yields and enantioselectivities, thus suggesting the complex **9** might be a key intermediate (Scheme 4, B).

On the basis of the mechanistic investigations above, a plausible mechanism for this photoreaction is proposed (Scheme 5). Photoexcited $[Ru(bpy)_3]^{2+*}$ was oxidatively

Scheme 5. Proposed Catalytic Cycle



quenched by benziodoxole radical (BI·) to $[Ru(bpy)_3]^{3+}$, which oxidizes enamine intermediate **8** to radical cation **10**. This SET process can be reasoned by considering the experimentally determined oxidative potential of **8** ($E^{ox}_{1/2}$ = 1.13 V vs Ag/AgCl, $E_{1/2}^{Ru(III)/(II)}$ = 1.40 V vs Ag/AgCl). α-Imino radical **11**, formed by a facile N–H proton loss process from **10**, undergoes α-addition to **9**, leading to the alkynylation product **4ab** along with the loss of CO_2 and the regeneration of benziodoxole radical. An alternative radical–radical cross-coupling between phenylacetylene radical and **11** can be discounted by the facts that (1) radical–radical cross-coupling is kinetically disfavored and (2) enamine facial selection with a neutral acetylene radical would be notoriously challenging to control. The absolute configuration of the alkynylation product was determined to be *R* by comparison with the known compound.[12] On the basis of our previous studies, an H-bonding transition state involving H-bonding between protonated N–H and propiolate carbonyl was proposed to account for the observed *R* selectivity (Scheme 5). As products **5ab** are not derived from **4ab**, a competing side cycle involved an unavoidable hydration of phenyl propiolic acid with BI-OH, which generates intermediate **14**, was proposed. The interception of **11** by **14** led to the formation of **5ab** (see the SI for a complete cycle).

We have attempted to apply the proposed mechanism to other radical acceptor candidates. Preliminary studies have revealed that alkenyl carboxylic acids such as cinnamic acid **16**

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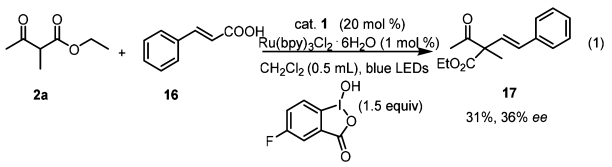
also work to give the decarboxylative adduct **17**, albeit with moderate yield and enantioselectivity (eq1).



In conclusion, we have developed an unprecedented enantioselective direct α-alkynylation of β-ketocarbonyls via visible-light-induced oxidative decarboxylation coupling. The reactions enable the creation of all-carbon stereocenters with excellent enantioselectivities under mild conditions. Mechanism studies formulate a distinctive aminocatalytic mode via an α-imino radical intermediate that facilitates α-radical addition process. Further explorations on α-imino radical chemistry are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02386.

Experimental procedures, characterization data, and ^{1}H NMR and ^{13}C NMR spectra and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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