JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
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Asymmetric α-Photoalkylation of β-Ketocarbonyls by Primary Amine Catalysis: Facile Access to Acyclic All-Carbon Quaternary Stereocenters

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Supporting Information

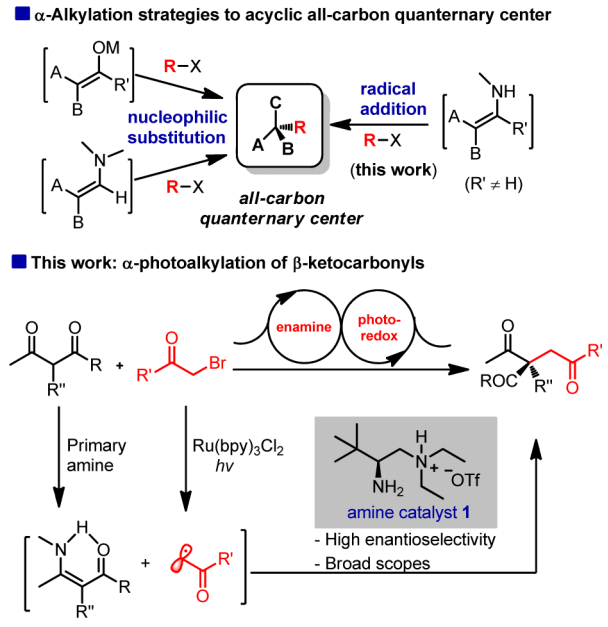
ABSTRACT: We describe the direct construction of all-carbon quaternary stereocenters via α-photoalkylation of β-ketocarbonyls with high efficacy and enantioselectivities by merging photoredox catalysis and primary amine catalysis. The open-shell photoradical approach enables asymmetric α-alkylations that are difficult under thermal conditions.

Asymmetric α-alkylation of carbonyl compounds is one of the fundamental C−C bond formation reactions in forging a carbon stereogenic center.[1] In particular, this reaction has evolved as a viable strategy for the construction of acyclic all-carbon quaternary stereocenters, a significant challenge in asymmetric catalysis and synthesis despite of the tremendous advances in this field. Major progresses along this line have been mainly achieved in the alkylation of stereodefined trisubstituted enolates.[2,3] The enolate approach is limited by the difficulties in accessing geometrically pure enolate intermediates, either preformed[2] or *in situ* generated.[3] Another elegant strategy is the enamine-based alkylations, but the reaction so far is limited to aldehydes.[4] A common feature of these previous successes, either enolate or enamine-based, is the couple of electron-rich intermediates and electrophiles (e.g., alkyl halides) in a typical two-electron HOMO−LUMO coupling manner (Scheme 1). In this context, we sought to approach the construction of acyclic all-carbon quaternary stereocenters using an open-shell radical substitution strategy by invoking the synergy of photochemical process and organocatalysis (Scheme 1).

Recently, enantioselective photochemistry has demonstrated enormously potential in asymmetric catalysis by the judicious combinations with organocatalysts such as hydrogen-bonding catalysts[5] and chiral aminocatalysts.[6,7] In the latter cases, combining enamine-based catalytic cycle with photochemically induced process has enabled asymmetric radical α-alkylation of aldehydes and cyclic ketones. For example, seminal work by MacMillan led to effective asymmetric α-alkylation of aldehydes by merging photoredox catalysts such as $Ru(bpy)_3^{2+}$ and enamine catalysis.[6a,b] The same reaction also proceeded in the absence of photocatalysts through the photon-absorbing chiral electron donor−acceptor (EDA) complex by switching to a different aminocatalyst.[7a] This catalytic principle has been extended to α-alkylation of cyclic ketones but with limited scopes and efficacy.[7b] Despite of these advances, α-photoalkylation of carbonyls remains underdeveloped particularly regarding the creation of full-carbon quaternary centers. Herein, we report the successful application of photoredox/enamine combined catalysis in α-alkylation of β-ketocarbonyls, forging an all-carbon quaternary stereocenter with high enantioselectivity (Scheme 1).

Our studies capitalized on our recent finding that chiral primary amine catalyst (e.g., **1**, Scheme 1) was a viable catalyst for enamine-based transformation of β-ketocarbonyls.[8] In further exploration of this catalysis, it was realized the asymmetric alkylation of β-ketocarbonyls remained a challenging issue in an acyclic setting in asymmetric catalysis. In this context, we were inspired by the early successes in photoredox catalysis and the merging of our primary amine catalysis with photoredox catalysis for a radical addition alkylation was hence pursued. Besides the issue on stereocontrol, another easily conceived pitfall was the

Scheme 1

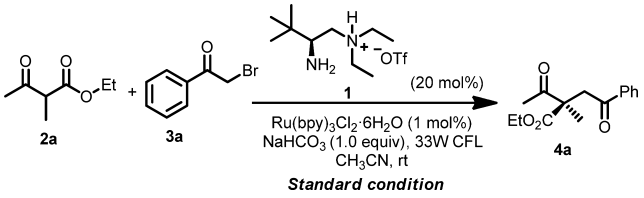


Received: August 26, 2014
Published: September 17, 2014

dx.doi.org/10.1021/ja508605a | J. Am. Chem. Soc. 2014, 136, 14642−14645

stability and compatibility of diamine catalyst **1** under photoredox conditions in the presence of electrophilic alkyl halides.[9] To our delight, the simple chiral primary amine catalyst **1** could promote the α-alkylation smoothly under photoredox conditions (Table 1).

Table 1. Screening and optimization[a]



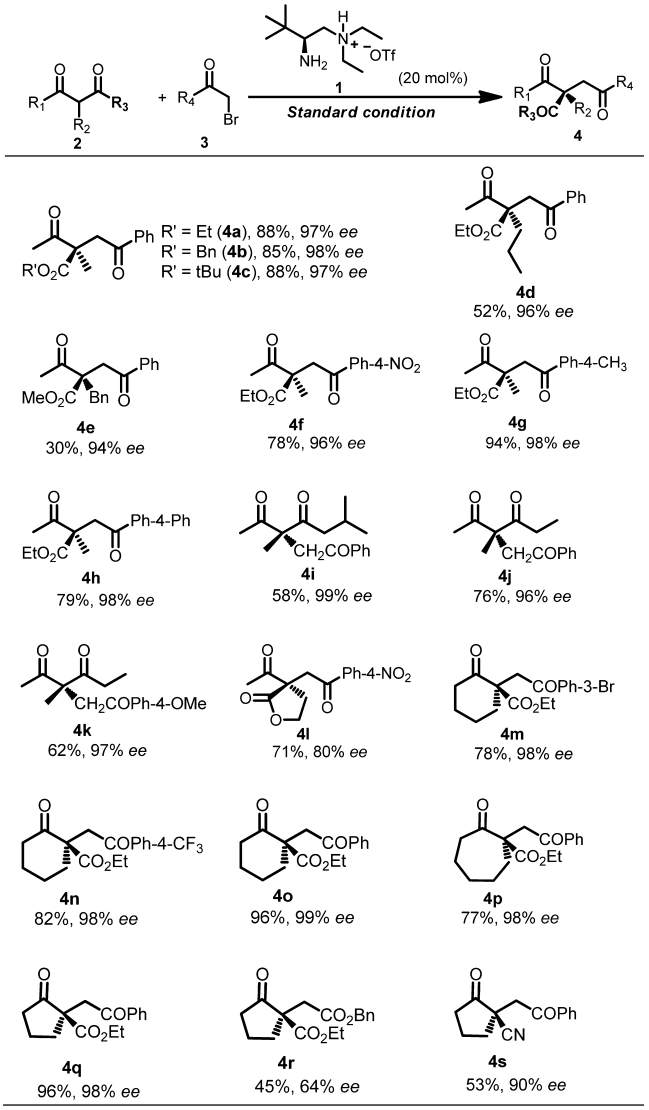
entry	variation from standard conditions	yield (%)[b]	ee (%)[c]
1	none	88	97
2	blue LEDs instead of CFL	88	97
3	no light	no reaction	
4	no $Ru(bpy)_3Cl_2·6H_2O$	24	96
5	eosin Y instead of [Ru]	27	98
6	**2a**:**3a** = 2:1	66	96
7	**2a**:**3a** = 1:2	52	96
8	addition of CF_3COOH (20 mol %)	32	97
10	Na_2HPO_4 instead of $NaHCO_3$	36	98
11	lutidine instead of $NaHCO_3$	43	97
12	Et_3N instead of $NaHCO_3$	no reaction	

[a]Reactions were performed at room temperature in 0.5 mL CH_3CN, with **2a** (0.4 mmol), **3a** (0.1 mmol), **1** (20 mol %), $NaHCO_3$ (1 equiv), 33 W CFL, and $Ru(bpy)_3Cl_2·6H_2O$ (1 mol %) under argon, 48 h. [b]Yield of isolated product. [c]Determined by HPLC analysis.

In the model reaction between acetoacetate **2a** and phenacyl bromide **3a**, the combined catalysis of **1** and $Ru(bpy)_3Cl_2$ gave the desired alkylation adduct **4a** in 88% yield and 97% ee under the optimized condition (Table 1, entry 1). No reaction occurred in the absence of light irradiation (Table 1, entry 3). The use of blue LED instead of CFL gave the similar result (Table 1, entry 2). These results verified light responsive nature of the reaction. In addition, the use of organic dye photocatalyst such as eosin Y was less effective than $Ru(bpy)_3Cl_2$ complex, affording a lower yield (entry 5). Interestingly, the reaction also proceeded in the absence of any photocatalyst (under visible light), furnishing the expected adduct with high enantioselectivity, albeit in much lower yield (entry 4). This observation is suggestive of the existence of a photoresponsive EDA mechanism recently disclosed by Melchiorre.[7a] However, this process might not be a major productive pathway as the reaction was rather low yielding without photocatalyst. The reaction has also been further optimized in terms of acidic additives and molar ratio of starting materials as well as different bases (entries 6−12). It was found a larger ratio of **2a**/**3a** led to higher yield of the alkylation adduct **4a** (entries 6−7), likely via enhanced enamine formation. Our previously identified weak acidic effect seemed to not work for the reaction[10] and no much improvement was observed when weak acid such as TFA was added (entry 8). In particular, we found the use of inorganic base $NaHCO_3$ to trap the *in situ* liberated HBr was critical for high productivity (Table 1, entries 10−12). The use of other bases, either inorganic or organic, gave inferior results or totally inhibited the reaction (Table 1, entry 12).

With the optimized conditions in hand, we first examined the scope of acyclic ketoesters as radical acceptors. As shown in Table 2, acyclic acetoacetates bearing either sterically bulky *tert*-butyl or benzyl ester group could be equally applied to afford the

Table 2. Scope of β-Ketocarbonyls and α-Bromocarbonyls[a]



[a]All reactions were performed at room temperature in 0.5 mL CH_3CN, with **2** (0.4 mmol), **3** (0.1 mmol), **1** (20 mol %), $NaHCO_3$ (1 equiv), 33 W CFL, and $Ru(bpy)_3Cl_2·6H_2O$ (1 mol %) under argon, 48−72h. Yield of isolated product. Determined by HPLC analysis.

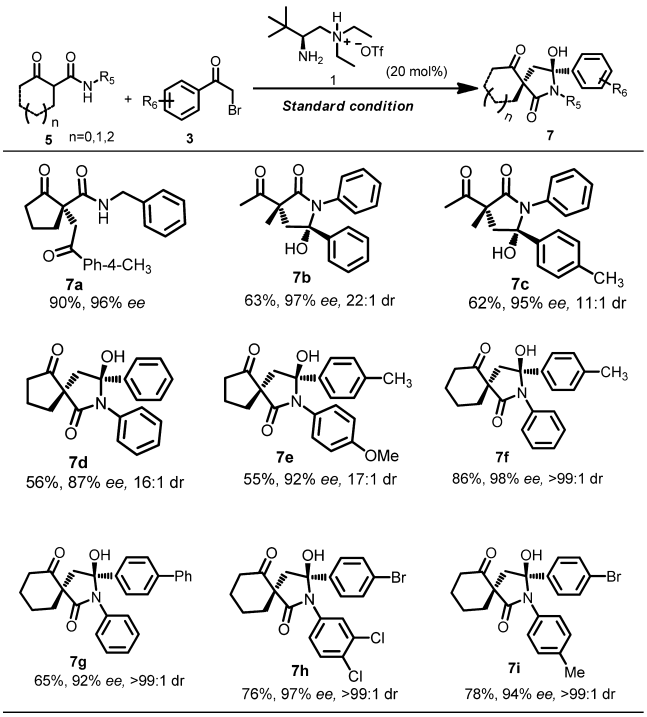
desired adducts with all-carbon quaternary stereocenter in high yields and excellent enantioselectivities (Table 2, **4a**−**c**). The reaction also tolerated a range of substituents on R_2 position (**4d**,**e**). Most delightfully, aliphatic 1,3-diketones, for which an asymmetric alkylation reaction remains elusive so far, reacted smoothly to give the desired adducts in good yields and high ee (**4i**−**k**). The current catalysis worked extremely well with cyclic β-ketoesters to deliver the alkylation adducts with high yields and excellent enantioselectivities (**4m**−**r**), even for enol-ketoesters (>85% enol for **2l**). The relatively unstable α-acetybutyrolactone was also amenable to the mild photoredox/organocatalysis conditions, showing slightly reduced enantioselectivity (**4l**). Moreover, β-ketonitrile could be accommodated to furnish the desired adduct with good enantioselectivity (**4s**), and competitive oligomerization of the cyano group was observed in this case.

dx.doi.org/10.1021/ja508605a | J. Am. Chem. Soc. 2014, 136, 14642−14645

We have also explored the scope of α-bromocarbonyl alkylation agents. A broad array of phenacyl bromide, including electron-deficient and electron-donating group on aryl, could participate in the photoredox alkylation of β-ketoesters smoothly (**4f**−**h**, **4k**−**n**). To our delight, benzyl bromoacetate ($BrCH_2CO_2Bn$) was also applicable, furnishing the desired product in reduced, but decent yield and enantioselectivity (**4r**), likely a result of the lower electron-withdrawing property of ester moiety compared with keto moiety, hence weakening the H-bonding between its carbonyl and protonated tertiary amine in catalyst **1**. Electron-deficient benzyl bromide such as 2, 4-dinitrobenzyl bromide has also been attempted in the reaction, showing unfortunately rather poor reactivity (<10% yield).

To further explore the synthetic utility of the current α-photoalkylation reaction, β-ketoamides with a free N−H bond have also been examined as radical acceptors under the mild photoredox condition. Free amides are challenging substrates in asymmetric alkylation chemistry due to the competitive N-alkylation by-pathway. Delightfully, β-ketoamides worked very well in the reactions to give cleanly C-alkylation products. As shown in Table 3, *N*-benzyl β-ketoamide reacted to furnish the

Table 3. Scope of β-Ketoamides in α-Alkylation Reaction[a]

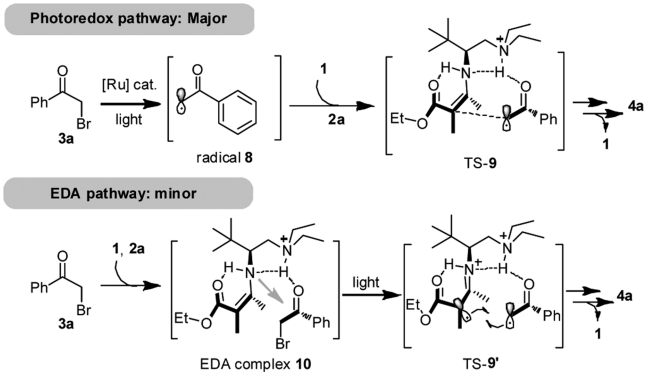


[a]All reactions were performed at room temperature in 0.5 mL CH_3CN, with **2** (0.4 mmol), **3** (0.1 mmol), **1** (20 mol %), $NaHCO_3$ (1 equiv), 33 W CFL, and $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (1 mol %) under argon, 48−72 h (TLC analysis). Yield of isolated product. Determined by HPLC analysis.

expected C-alkylation adduct in 90% yield with 96% ee (Table 3, **7a**). Intriguingly, intramolecular ketalization occurred spontaneously in the cases with *N*-aryl amides. Spiro-γ-lactams containing two nonadjacent quaternary stereocenters were obtained as single diastereoisomers with high enantioselectivities (**7b**−**i**, 55−86% yield, 88−98% ee). This class of spiro-γ-lactams has recently been found to have promising pharmaceutical profiles,[11] and their asymmetric synthesis has not been achieved so far. The reason for high chiral induction in the ketalization step might origin from H-bonding to phenacyl-carbonyl as well as π−π interaction between the two aromatic rings; to note that the same reaction with *N*-benzyl amide gave no ketalization product at all (**7a**, Table 3).

Based on the known precedence as well as our own experimental observations, we believe the current reaction proceeds with photoredox catalysis as the major productive pathway, and an EDA reaction pathway may also coexist but should be minor in this case (Scheme 2). Both processes are

Scheme 2



light-responsive involving phenacyl radical addition as the key C−C forming step, the thermal S_N1- or S_N2-type substitution can be excluded as no reactions were observed in the absence of light with/without photocatalyst.

The absolute configuration of the newly formed all-carbon quaternary stereocenter was determined to be *R* by analogue with the crystal structure of **7h** (Figure 1). Accordingly, a

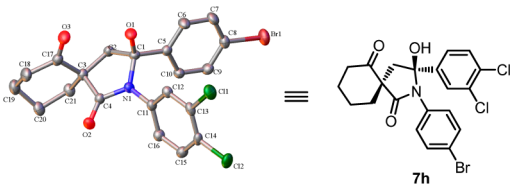


Figure 1. X-ray crystal structure of **7h**.

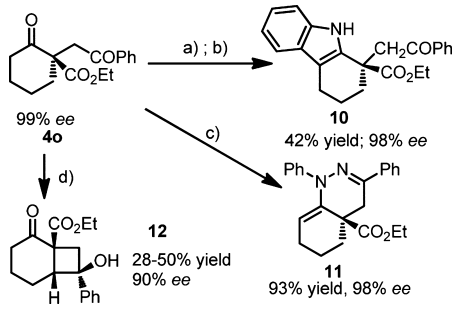
transition state involving *Re*-facial attack of phenacyl radical **8** to enamine was proposed to account for the stereoinduction. In the TS (**TS9** or **TS9′**), H-bonding between protonated tertiary amine and keto moiety of **8** would guide the approach of the radical species.[12] The critical role of H-bonding network was quite evident, leading to poor outcome if weakened (Table 2, **4l** and **4r**). In addition, the observation of low productivity of benzyl bromide, for which H-bonding is not possible, seems also consistent with the H-bonding TS; to note that electron-deficient benzyl bromide was equally active like phenacyl bromide in previous photoalkylation reactions where steric mode was implied.[6,7]

Last, the synthetic utility of the 1,4-dicarbonyl compounds was demonstrated, and in this regard we mainly focused on synthetic transformation of the keto moieties. When treated with phenylhydrazine, adduct **4o** underwent cyclocondensation to form indole derivative **10** or dihyropyridazine **11** under different acidic conditions. Both of these compounds are of privileged structural motif in pharmaceuticals.[13] The Norrish Type II photoreaction of **4o** could also proceed to furnish cyclobutane **12**

dx.doi.org/10.1021/ja508605a | J. Am. Chem. Soc. 2014, 136, 14642−14645

bearing two nonconsecutive quaternary centers with high diastereoselectivity and enantioselectivity (Scheme 3).[14]

Scheme 3. Synthetic Transformations[a]



[a](a) $PhNHNH_2$, AcOH, EtOH, rt, 2 h; (b) TFA, CH_2Cl_2, rt, 4 h; (c) $PhNHNH_2$, TFA, CH_2Cl_2, rt, 3 h; (d) benzene (0.05 mol dm^{-3}), 500 W high-pressure mercury lamp, 8 h.

In summary, we have developed an enantioselective α-photoalkylation of β-ketocarbonyls by merging photoredox catalysis with chiral primary amine catalysis. The reactions enable the creation of all-carbon stereocenters with excellent enantioselectivities and encompass a broad range of substrates including the elusive 1,3-diketones and β-keto amides for the first time in an asymmetric alkylation reaction.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization of new compounds, and CIF data of **7h**. 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.

■ ACKNOWLEDGMENTS

The project was supported by Ministry of Science and Technology (2012CB821600), the Natural Science Foundation of China (NSFC 21390400, 21202171, and 21025208), and the Chinese Academy of Sciences. S.L. is supported by National Program for Support of Top-notch Young Professionals.

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