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Modular reductive radical-polar crossover-based acyl migration reactions of *N*-vinylimides with alkyl, silyl, and acyl radicals†

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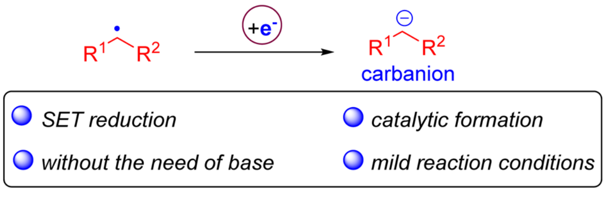
Herein, novel SET reduction-based N → C acyl migration protocols for the preparation of functionalized α-amino ketones were successfully developed. In addition to alkyl and silyl radicals, acyl radicals derived from dihydroquinazolinones or acyl oxime acetates could react with enamides to give various 1,4-diketones. These photocatalytic radical addition/acyl migration cascade reactions feature broad substrate scope, good functional group compatibility, and mild reaction conditions.

Due to the remarkable progress of photoredox catalysis, the generation of radicals under mild and environmentally benign reaction conditions has become especially facile. In addition to the facile formation of radicals, their reduction or oxidation could proceed efficiently *via* the single-electron-transfer (SET) pathway. Consequently, a range of radical-polar crossover (RPC) process-based transformations enabled by photoredox catalysis has been designed and realized.[1] Recently, we employed a SET reduction-based formation of carbanion as a key strategy (Scheme 1), and a number of interesting and useful reactions were developed.[2] Impressively, the SET reduction-based generation of carbanions could proceed efficiently under base-free conditions. Owing to the facile generation of radicals from various radical precursors, the SET reduction of radicals is a complementary and reliable approach to the well-documented formation of carbanions or their analogues *via* a two-electron pathway. Moreover, with the proper combination of photocatalyst and radical precursors, many reductive RPC processes do not require exogenous reductants because the photoexcited photocatalyst and the reduced photocatalyst could serve as the oxidant and reductant, respectively, in the same catalytic cycle.

Realizing this interesting and useful characteristic of photocatalysis, many efficient and robust transformations bearing a reductive RPC process have been developed and employed.[3] Due to its good sustainability and efficiency, synthetic chemists will undoubtedly be interested to uncover more novel methods using redox-neutral photocatalyzed reductive RPC process as the key strategy.

More than 20 years ago, Hamada and co-workers demonstrated a base-mediated N → C acyl migration reaction producing α-amino ketones.[4] According to their proposed mechanism, a base-generated carbanion neighboring the imide nitrogen was the key intermediate for this migration reaction. Recently, we realized the cyclopropanation of enamides with a halomethyl radical *via* an RPC process.[2c] Inspired by the formation of α-nitrogen carbanions from the corresponding radicals *via* SET reduction,[2c,d] redox-neutral photocatalyzed N → C acyl migration reactions were successfully developed *via* the reactions of *N*-vinylimides with alkylsilicates.[5] Owing to the low, relatively uniform redox potentials, the bis-catecholatosilicates were attractive radical precursors for the formation of nonstabilized primary alkyl radicals, which could be involved in the expected migration reactions. However, because of the limited availability of organofunctional trialkoxysilanes, silicates are not a suitable choice for secondary and tertiary C-centered radicals as well as acyl radicals. In light of the importance of α-amino ketones serving as expedient precursors for β-aminoalcohols, which are useful for the preparation of pharmaceuticals and chiral auxiliaries, a modular approach to α-amino ketones *via* the N → C acyl migration



Scheme 1 SET reduction-based formation of carbanion.

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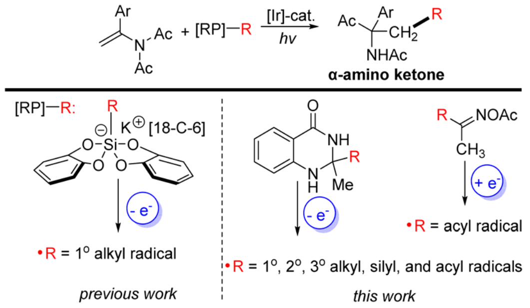
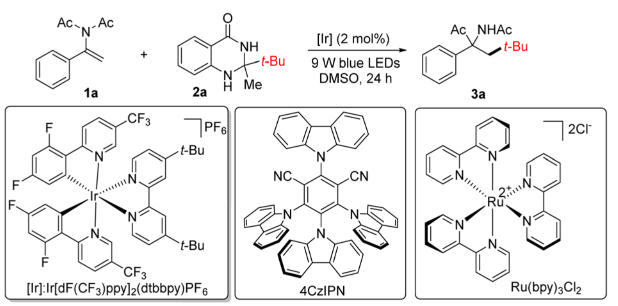


Scheme 2 Generation of α-amino ketone bearing a quaternary carbon center *via* acyl migration reaction.

reaction would be highly desirable (Scheme 2). Herein, with reductive RPC as the strategy, a modular access to functionalized α-amino ketones was generally developed *via* reactions of *N*-vinylimides with various radicals derived from dihydroquinazolinones (DHQs)[6] or acyl oxime acetates.[7] The decisive advantage of such a photo-driven strategy was the facile generation of α-imidocarbanion in the absence of a base and exogenous reductant under mild reaction conditions. Moreover, our method could significantly extend the applications of DHQs and acyl oxime acetates as radical precursors.

Our initial study of acyl migration reaction commenced with the reaction of *N*-acetyl-*N*-(1-phenylethenyl)acetamide **1a** with pinacolone-derived dihydroquinazolinone **2a** and the results are listed in Table 1. A simple survey of experimental parameters led us to identify the optimal reaction conditions (2 mol% Ir $[dF(CF_3)ppy]_2(dtbbpy)PF_6$, 9 W blue LEDs irradiation, DMSO, rt, 24 h) (entry 1). As for the photocatalyst, the organic photocatalyst 4CzIPN proved ineffective for this transformation (entry 2). The reaction also gave a low yield using $Ru(bpy)_3Cl_2$ as the photocatalyst (entry 3). The subsequent screening of solvents indicated that both DMA and CH_3CN are suitable solvents for this reaction (entries 4 and 5). Moreover, the lack of either [Ir] or light suggested the indispensable role of each in the desired reactivity (entries 6 and 7).

Table 1 Reaction optimization[a,b]



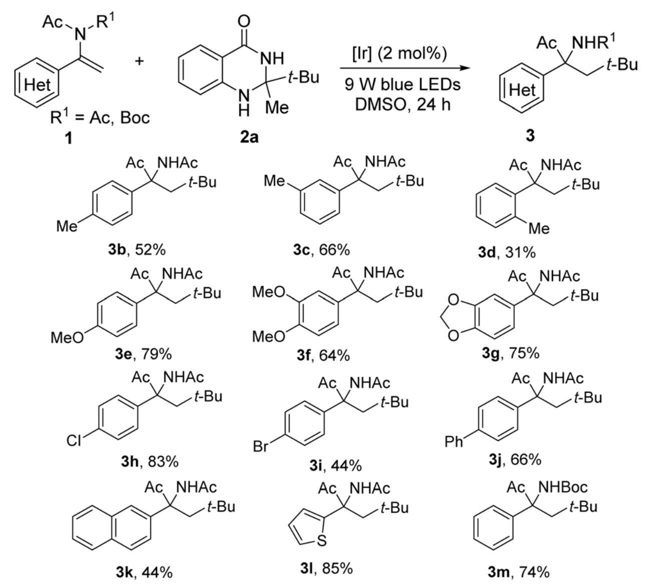
Entry	Deviation from standard conditions	Yield of **3a** (%)
1	None	76
2	4CzIPN instead of [Ir]	20
3	$Ru(bpy)_3Cl_2$ instead of [Ir]	22
4	DMA instead of DMSO	66
5	CH_3CN instead of DMSO	70
6[c]	Without photocatalyst	ND
7[cd]	Without light	ND

[a] Standard reaction conditions: a reaction mixture of **1a** (0.2 mmol), **2a** (0.4 mmol), [Ir] (2 mol%), and DMSO (6.0 mL) was irradiated with 9 W blue LEDs for 24 h at room temperature (r.t.) (cooling with a fan). [b] Yield of the isolated product **3a**. [c] NMR analysis of crude reaction mixture. [d] The reaction was run in the dark. ND = not detected.

Having established the optimal conditions (entry 1, Table 1), we next set out to investigate the scope with respect to the *N*-vinylimides **1** using dihydroquinazolinone derivative **2a** as the radical precursor. As shown in Table 2, *N*-vinylimides **1** having *para*-, *meta*-, or *ortho*-substituents were all eligible to forge the desired α-amino ketones **3b–3d** in 31–66% yields. Clearly, steric variance on the phenyl ring had an influence on the reaction efficiency. Not surprisingly, substrates bearing a methoxy or methylenedioxy group on the phenyl ring were well tolerated, giving the corresponding products **3e–3g** in good yields (64–79%). Moreover, enamides containing electron-withdrawing groups (–Cl and –Br) reacted smoothly to give the expected products **3h** and **3i** in 83% and 44% yields, respectively. In addition to the smooth reactions of monoaryl-substituted radical acceptors, enamides with biphenyl and naphthyl substituents could be efficiently transformed into the expected products **3j** and **3k** with good results. Interestingly, after the aryl substituent of enamides was replaced with a thiophene group, the yield of product **3l** was 85%. Besides *N*-Boc-*N*-(1-phenylvinyl)acetamide **1m** proved to be a viable substrate, giving **3m** in 74% yield.

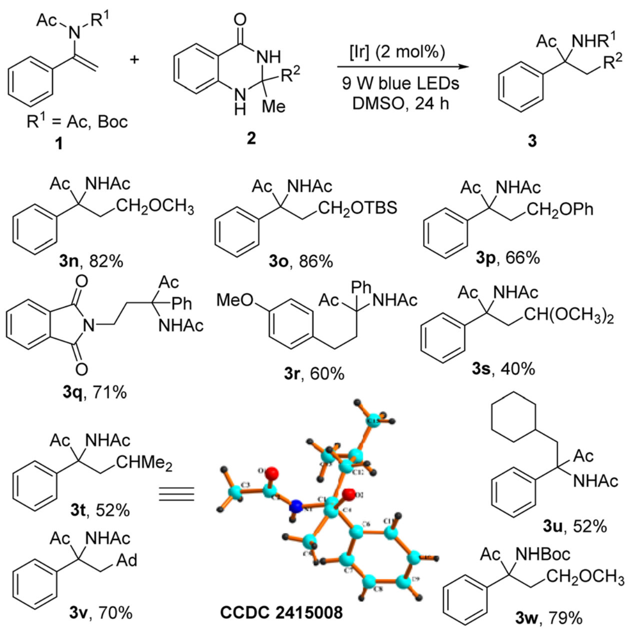
After demonstrating the scope of *N*-vinylimides, we next set out to investigate the generality of DHQs using *N*-acyl-protected enamide **1a** as the model radical acceptor. As listed in Table 3,

Table 2 Substrate scope of *N*-vinylimides **1** [a]

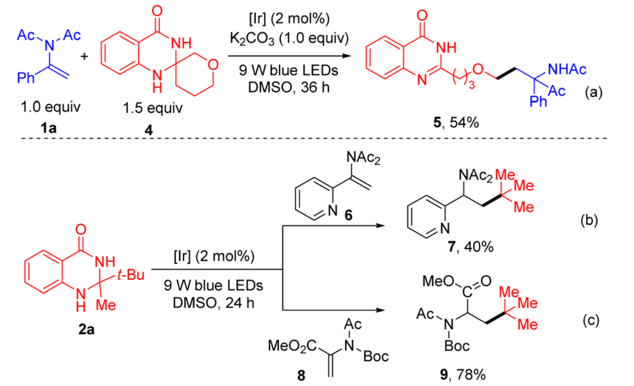


[a] Reaction conditions: see entry 1, Table 1. Isolated yields.

Table 3 Scope of dihydroquinazolinones **2** [a]



[a] Reaction conditions: see entry 1, Table 1. Isolated yields.



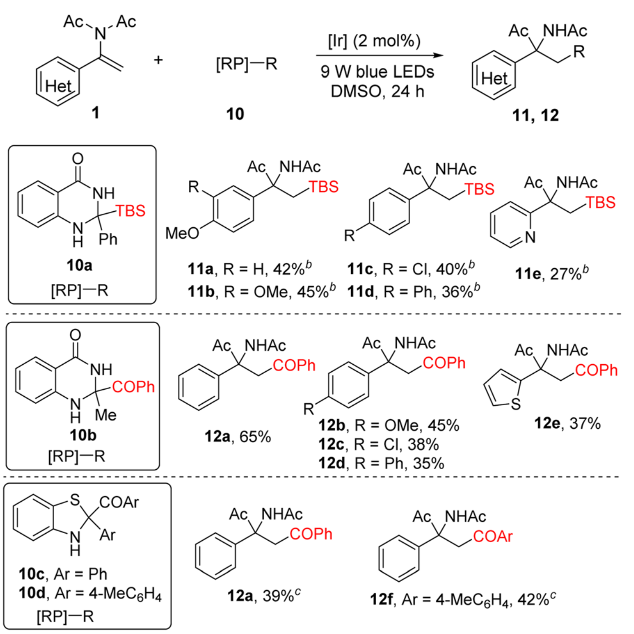
Scheme 3 Acyl migration and Giese-type reactions.

oxygen- or nitrogen-stabilized primary alkyl radicals were all readily accessed by the use of Me-substituted dihydroquinazolinones, giving the products **3n–3q** in 66–86% yields. Interestingly, the products **3o** and **3q** could serve as the precursors of 1,3-aminoalcohol[8] and 1,3-diamine,[9] respectively. Moreover, stable 4-methoxybenzyl radical also gave the corresponding product **3r** in 60% yield. Secondary oxygen-stabilized dimethoxymethyl radical[10] generated from pyruvic aldehyde dimethyl acetal-derived dihydroquinazolinone participated in this transformation, forging **3s** in 40% yield. Both acyclic and cyclic secondary alkyl radicals could react with **1a** efficiently to produce the desired products **3t** and **3u** in good yields. The structure of **3t** was further confirmed by single-crystal X-ray analysis (CCDC 2415008).[11] Dihydroquinazolinone, derived from 1-adamantly methyl ketone, was also effective in delivering the expected **3v** in 70% yield under these redox-neutral conditions. Again, this straightforward acyl migration reaction can be applied to *N*-Boc-*N*-(1-phenylvinyl)acetamide **1m**, producing **3w** in 79% yield.

As an extension, with **1a** as the radical acceptor, spiro dihydroquinazolinone **4** [12] successfully underwent the expected ring-opening/radical addition/acyl migration cascade reaction to give **5** in 54% yield (Scheme 3a). Of note, the acyl migration reaction is highly dependent on the electron properties of radical acceptors.[5] Using enamide-bearing pyridine moiety **6** as the radical acceptor, the Giese-type reaction instead of acyl migration reaction was observed, yielding **7** in 40% yield (Scheme 3b). Similarly, only the Giese-type reaction product **9** was isolated for the reaction of **2a** with *N*-Boc-*N*-acetyldehydroalanine methyl ester **8** (Scheme 3c).

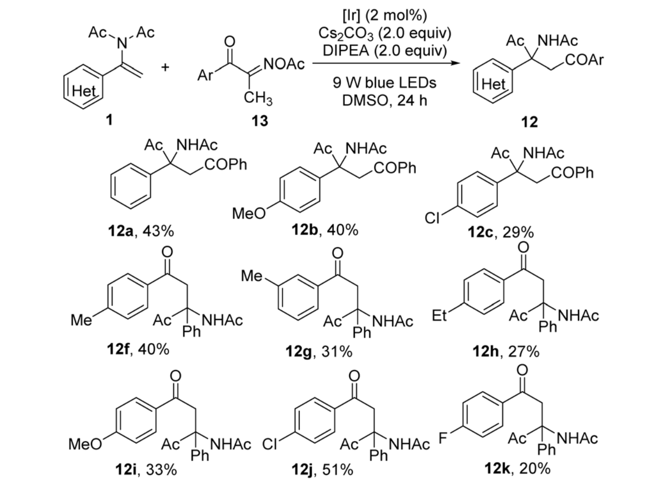
To investigate the generality of this method, we focused on the acyl migration reactions of enamides with silyl and acyl radicals instead of alkyl radicals (Table 4). Interestingly, under the optimized reaction conditions in combination with K_2CO_3 (2.0 equiv.), using 2-silylated dihydroquinazolinone **10a** as the silyl radical precursor,[13] a range of *N*,*N*-diacetylimidostyrenes bearing various functional groups underwent acyl migrations to give **11a–11d** in 36–45% yields. Furthermore, pyridine-containing enamide was also applied, producing **11e** in moderate yields. In addition, the benzoyl radical generated from 2-benzoyl-2-methyl-2,3-dihydroquinazolin-4(1*H*)-one **10b** readily reacted with various *N*-acetyl-*N*-(1-arylvinyl)acetamides **1**, furnishing the expected products **12a–12d** in moderate to good yields ranging from 35 to 65% yields. Moreover, enamide

Table 4 Reactions of **1** with silyl and acyl radicals[a]



[a] Reaction conditions: see entry 1, Table 1. Isolated yields. [b] K_2CO_3 (0.4 mmol) was used. [c] Cs_2CO_3 (0.4 mmol) was used.

Table 5 Preparation of 1,4-diketones[a]



[a] Reaction conditions: a reaction mixture of **1** (0.2 mmol), **13** (0.4 mmol), [Ir] (2 mol%), Cs_2CO_3 (0.4 mmol), DIPEA (0.4 mmol) and DMSO (6.0 mL) was irradiated with 9 W blue LEDs for 24 h at room temperature (rt) (cooling with a fan). Isolated yields.

bearing a heteroaryl unit, thiophene, was tolerated here, affording product **12e** in 37% yield. In addition to employing 2-benzyl-2-phenylbenzothiazoline **10c** as a benzoyl radical source,[14] 4-methyl-subsituted benzoyl radical derived from **10d** also reacted with **1a** to give product **12f** in 42% yield in the presence of a stoichiometric amount of Cs_2CO_3. Of note, compared to the broad substrate scope of 2,2-disubstituted DHQs for the formation of alkyl radicals, the generality of 2-acyl-substituted DHQs and benzothiazolines remains an issue.[15]

Considering the synthetic importance of 1,4-diketones and their unique biological activities,[16] we decided to develop a simple and straightforward method for their access based on the acyl migration of enamides with acyl radicals. Fortunately, with *N*,*N*-diisopropylethylamine (DIPEA) as the reductant and Cs_2CO_3 as the base, we found easily accessible acyl oxime esters could serve as general and efficient acyl radical precursors enabled by photocatalysis (Table 5).[7,17] The *para*-position of *N*,*N*-diacetylimidostyrenes with electron-rich and electron-deficient groups proceeded smoothly, affording 1,4-diketones **12b** and **12c** in moderate yields. In addition to benzoyl radicals, aryl acyl radicals bearing substituents (*p*-Me, *m*-Me, *p*-Et, *p*-OMe, *p*-Cl, *p*-F) on the aromatic ring at different positions or with different electronic properties can uniformly undergo expected cascade reactions, delivering the desired 1,4-diketones (**12f–12k**, 20–51% yields). Note that in contrast to the oxidative generation of acyl radicals from 2-acyl-substituted DHQs, acyl oxime esters serve as precursors of acyl radicals under reductive conditions. In this regard, the current reductive method is complementary to the above-mentioned oxidative SET approaches (see the ESI† for details).[18]

In summary, with reductive RPC as the strategy, we have described a new protocol that enables modular access to functionalized α-amino ketones through photoredox catalysis. Using DHQs or acyl oxime acetates as the radical precursors, a variety of *N*-vinylimides bearing various functional groups could undergo smooth radical addition/acyl migration cascade reactions under mild conditions. Both SET oxidation and photoreduction pathways for the generation of acyl radicals are compatible with the following catalytic cascade reaction for the preparation of 1,4-diketones. Expectedly, the modular preparation of functionalized α-amino ketones bearing quaternary carbon centers would be feasible using radical addition/acyl migration cascade reactions as the strategy under mild reaction conditions.[19]

Data availability

The data supporting this study have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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