Photoredox Catalysis

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Dual C(sp^3)–H Bond Functionalization of N-Heterocycles through Sequential Visible-Light Photocatalyzed Dehydrogenation/[2+2] Cycloaddition Reactions

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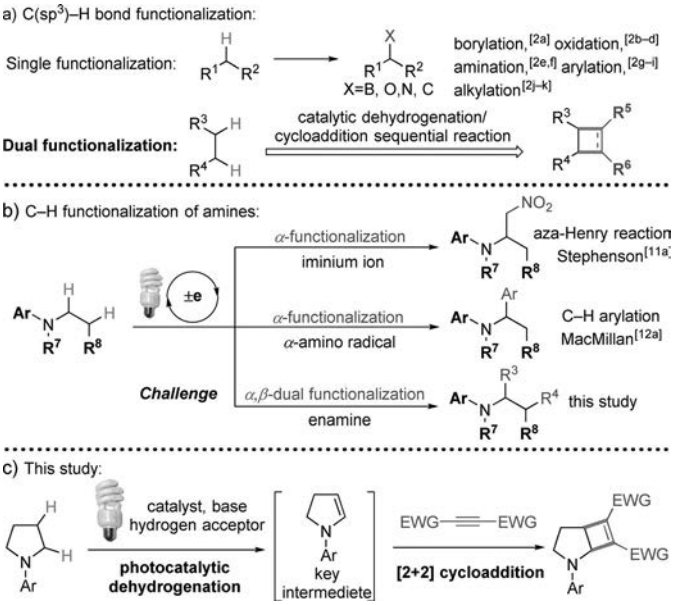
Abstract: *Herein we describe a mild method for the dual C(sp^3)–H bond functionalization of saturated nitrogen-containing heterocycles through a sequential visible-light photocatalyzed dehydrogenation/[2+2] cycloaddition procedure. As a complementary approach to the well-established use of iminium ion and α-amino radical intermediates, the elusive cyclic enamine intermediates were effectively generated by photoredox catalysis under mild conditions and efficiently captured by acetylene esters to form a wide array of bicyclic amino acid derivatives, thus enabling the simultaneous functionalization of two vicinal C(sp^3)–H bonds.*

The direct functionalization of C–H bonds is one of the most challenging yet highly desirable goals in modern organic synthesis,[1] and developments[2] in direct transformations of ubiquitous C(sp^3)–H bonds, including borylation, oxidation, amination, arylation, and alkylation, have attracted much attention. However, the vast majority of examples have focused on the functionalization of a single C(sp^3)–H bond, and dual C(sp^3)–H bond functionalization in a single step is still unknown. Encouraged by our previous study, in which we realized the dual functionalization of both a C(sp^3)–H and a C(sp^2)–H bond through visible-light induced oxidation and an aza-Diels–Alder reaction,[3] we planned to explore the feasibility of dual C(sp^3)–H bond functionalization. Catalytic dehydrogenation[4] has provided a new method for activating two C(sp^3)–H bonds, since the reactive alkene intermediate generated by this process could be utilized in a secondary reaction to forge new carbon frameworks.[5] [2+2] cycloaddition is one of the most powerful and widely applied transformations in organic chemistry[6] and plays a remarkable role in building strained and unusual molecular architectures that cannot be accessed through other pathways.[7] Recently, Zhou and co-workers developed an unprecedented catalytic enantioselective Heck annulation of propargylic acetates and cycloalkenes to obtain highly strained, fused cyclobutenes.[8] On the basis of all these factors, we decided to tackle the aforementioned difficulty by merging catalytic dehydrogenation with [2+2] cycloaddition in a sequential process (Scheme 1 a).



Scheme 1. Dual C(sp^3)–H functionalization strategy. EWG = electron-withdrawing group.

In recent years, visible-light photoredox catalysis,[9] another powerful technology in organic synthesis, has had a profound impact on the C–H functionalization of saturated N-heterocycles, which represent a privileged motif in pharmaceuticals and natural products.[10] Although a variety of synthetically useful iminium ion[11] and α-amino radical[12] intermediates have been effectively generated by photoredox catalysis and successfully applied to various α-functionalization reactions of amines,[13] enamines as promising intermediates for α,β-functionalization of amines are rarely reported (Scheme 1 b). Besides the general difficulties associated with C(sp^3)–H functionalization (e.g., high bond energy and similar reactivities), it faces greater challenges in the context of the dual C–H functionalization of saturated N-heterocycles: 1) the need to generate sufficient amounts of the reactive cyclic enamine intermediate and avoid the formation

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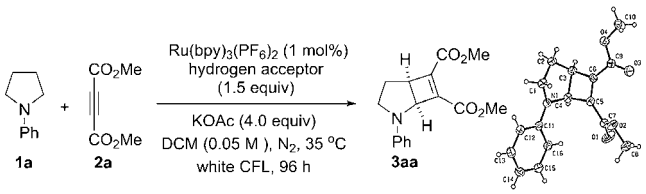
of more stable aromatic heterocycles,[14] and 2) the strong competition of the well-established α-functionalization[13] of iminium ions[11] and α-amino radicals[12] with this process. Herein, we describe a mild method to generate the highly reactive cyclic enamine intermediate by a visible-light photocatalytic dehydrogenation process, and then dual C(sp^3)–H bond functionalization through coupling with traditional [2+2] cycloaddition, to furnish a variety of highly strained bicyclic amino acid derivatives, which are rather difficult to obtain by other methods (Scheme 1c).

We initiated this novel sequential reaction with *N*-phenylpyrrolidine (**1a**) and dimethyl acetylenedicarboxylate (DMAD, **2a**), along with a variety of photocatalysts, inorganic bases, hydrogen acceptors, and light sources. To our delight, it was found that the desired [2+2] cycloaddition product **3aa** was produced in 70% yield when $Ru(bpy)_3(PF_6)_2$, nitrobenzene, and KOAc were used in the presence of a 23 W fluorescent light bulb upon photolysis for 96 h at 35 °C (Table 1, entry 1). To improve this result, we evaluated several nitrobenzene derivatives (Table 1, entries 2–4). It turned out that those with electron-withdrawing substituents on the benzene ring gave better results, and the highest reaction efficiency was observed with pentafluoronitrobenzene (PFNB), which furnished the desired dehydrogenation/[2+2] cycloaddition product in 99% yield. Control experiments demonstrated that both the light and the hydrogen acceptor were indispensable for this transformation (Table 1, entries 5 and 6), and both the photocatalyst and the inorganic base were necessary for an efficient reaction (entries 7 and 8). Finally, the relative configuration of product **3aa** was determined by the single-crystal X-ray diffraction, which showed that **3aa** had the *syn* configuration.[15]

Having identified optimal conditions for this dehydrogenation/[2+2] cycloaddition reaction, we examined the scope of the reaction with respect to the *N*-aryl pyrrolidine cycloaddition partner. The sequential transformation gave the *syn* diastereoisomer as the major product in all cases studied owing to the high diastereoselectivity of the [2+2] cycloaddition process (Table 2). A range of *N*-aryl pyrrolidines bearing electron-donating or electron-withdrawing substituents at the *para* position of the benzene ring were suitable substrates (products **3ab**–**ag**). Some valuable functional groups most commonly found in drug molecules were also compatible with this system, including trifluoromethyl, ester, and amido groups (products **3ah**–**aj**). Both electron-rich and electron-deficient substituents at the *ortho* and *meta* positions of the phenyl ring were well tolerated (**3ak**–**ap**). *N*-Naphthylpyrrolidine was also successfully converted into the

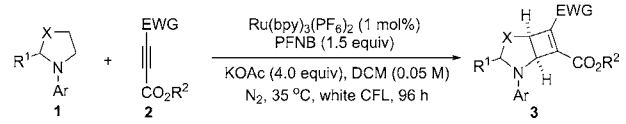
Table 1: Optimization of the reaction conditions.[a]



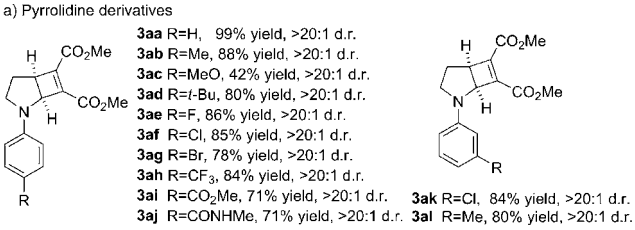
Entry	Hydrogen acceptor	Yield [%][b]	d.r.[c]
1	nitrobenzene	70	>20:1
2	1-methoxy-4-nitrobenzene	42	>20:1
3	1-chloro-4-nitrobenzene	77	>20:1
4	PFNB	99	>20:1
Entry	**Change from entry 4**	**Yield [%][b]**	**d.r.[c]**
5	no light	0	/
6	no PFNB	0	/
7	no $Ru(bpy)_3(PF_6)_2$	24	>20:1
8	no KOAc	21	>20:1

[a] Reactions were performed with **1a** (0.1 mmol), **2a** (0.3 mmol), the photocatalyst (1 mol%), a hydrogen acceptor (1.5 equiv), and KOAc (4.0 equiv) in DCM (2 mL) at 35 °C under a nitrogen atmosphere for 96 h. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR spectroscopy. bpy = 2,2′-bipyridine, DCM = dichloromethane, PFNB = pentafluoronitrobenzene.

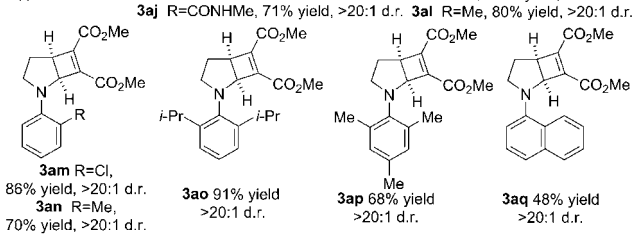
Table 2: Scope of the sequential dehydrogenation/[2+2] cycloaddition reaction.



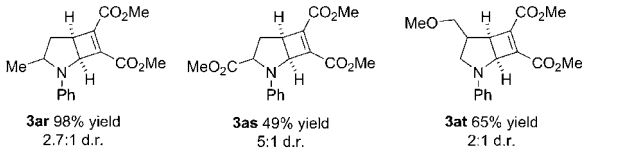
a) Pyrrolidine derivatives



3aa R=H, 99% yield, >20:1 d.r.
3ab R=Me, 88% yield, >20:1 d.r.
3ac R=MeO, 42% yield, >20:1 d.r.
3ad R=*t*-Bu, 80% yield, >20:1 d.r.
3ae R=F, 86% yield, >20:1 d.r.
3af R=Cl, 85% yield, >20:1 d.r.
3ag R=Br, 78% yield, >20:1 d.r.
3ah R=CF_3, 84% yield, >20:1 d.r.
3ai R=CO_2Me, 71% yield, >20:1 d.r.
3aj R=CONHMe, 71% yield, >20:1 d.r.
3ak R=Cl, 84% yield, >20:1 d.r.
3al R=Me, 80% yield, >20:1 d.r.

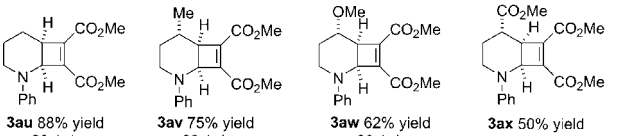


3am R=Cl, 86% yield, >20:1 d.r.
3an R=Me, 70% yield, >20:1 d.r.
3ao 91% yield >20:1 d.r.
3ap 68% yield >20:1 d.r.
3aq 48% yield >20:1 d.r.

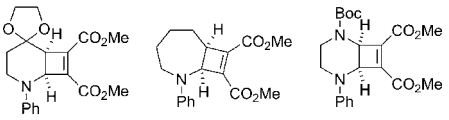


3ar 98% yield 2.7:1 d.r.
3as 49% yield 5:1 d.r.
3at 65% yield 2:1 d.r.

b) Other nitrogen-containing heterocycles

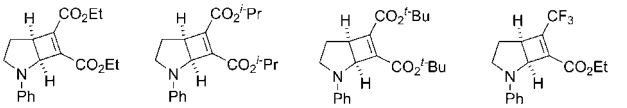


3au 88% yield >20:1 d.r.
3av 75% yield >20:1 d.r.
3aw 62% yield >20:1 d.r.
3ax 50% yield >20:1 d.r.



3az 70% yield >20:1 d.r.
3ba 89% yield >20:1 d.r.
3bb 51% yield >20:1 d.r.

c) Electron-deficient acetylene esters



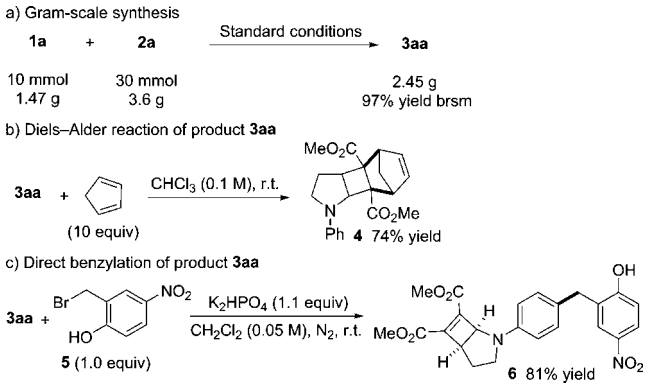
3bc 80% yield >20:1 d.r.
3bd 78% yield >20:1 d.r.
3be 62% yield >20:1 d.r.
3bf 57% yield >20:1 d.r.

desired product **3aq** in good yield. The electronic nature of the substituents on the pyrrolidine ring played a critical role in the efficiency of this cycloaddition reaction: Product **3ar** bearing an electron-rich methyl group was obtained in 98% yield, whereas **3as** and **3at** with electron-withdrawing substituents were only produced in moderate yields (49 and 65%, respectively). Unfortunately, other pyrrolidine derivatives, such as *N*-methylpyrrolidine, *N*-(*tert*-butoxycarbonyl)pyrrolidine, and *N*-phenylpyrrolidin-2-one, did not furnish the corresponding product under the standard conditions.

The scope of the reaction with respect to the nitrogen-containing heterocyclic substrate was further evaluated. A range of *N*-phenylpiperidine derivatives smoothly delivered the corresponding [2+2] cycloaddition products in moderate to excellent yields, and only one diastereoisomer was obtained for compounds **3av–ax** owing to the high stability of this configuration (Table 2b). Furthermore, azepane and piperazine derivatives were found to be suitable substrates (products **3ba**, **3bb**). Finally, the alkyne component was examined in this cycloaddition protocol (Table 2c). A range of acetylene ester substrates could be smoothly transformed into the corresponding products **3bc–be** in good yields. Encouragingly, an unsymmetrically substituted acetylene ester substrate also furnished the [2+2] cycloaddition product **3bf** in 57% yield.

To demonstrate the applicability of this photocatalytic method in organic synthesis, we carried out the reaction on a 10 mmol scale under the irradiation of four 23 W fluorescent light bulbs. The cycloaddition product **3aa** was obtained in 97% yield (based on the recovered starting material) after two experiments (Scheme 2a). Furthermore, it was found that this versatile scaffold could be used to construct more complex polycyclic compounds through a Diels–Alder reaction (Scheme 2b). Under mild conditions, this scaffold was subjected to C(sp^2)–H benzylation to install a valuable 2-hydroxy-5-nitrobenzyl moiety (Scheme 2c).

To further confirm our hypothesis, we conducted a series of mechanistic investigations (Figure 1). First, the quantum



Scheme 2. Application and transformation of product **3aa**.

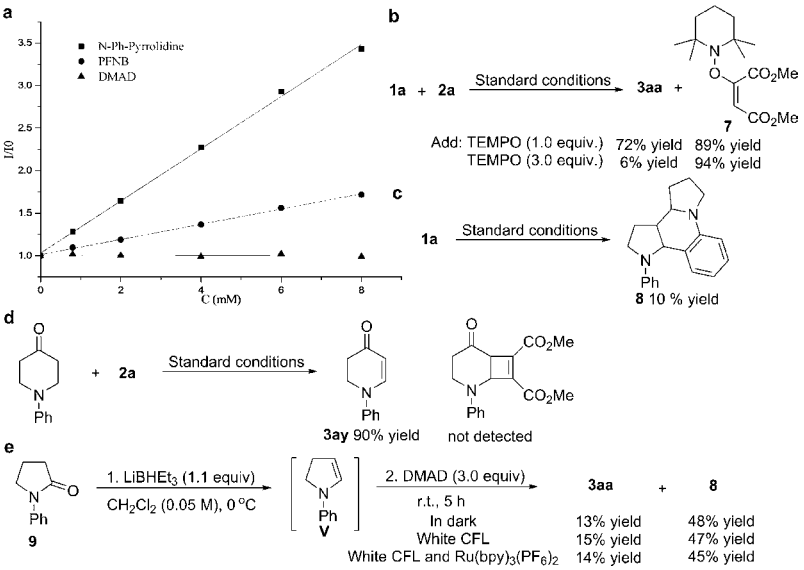


Figure 1. Mechanistic investigations.

yield of the reaction of **1a** and **2a** was determined to be 0.0002, which confirmed that the reaction was not a photoinitiated chain process, but a photocatalyzed process. Stern–Volmer experiments (Figure 1a) showed that the luminescence emission of excited-state $*Ru(bpy)_3^{2+}$ was quenched by *N*-phenylpyrrolidine (**1a**) more efficiently than by pentafluoronitrobenzene (PFNB), which indicated a reduction quenching mechanism. Furthermore, under the standard conditions, when the radical quencher TEMPO was added and the amount was increased from 1.0 to 3.0 equivalents, the yield of product **3aa** sharply decreased, thus suggesting that this reaction involved a single-electron-transfer process (Figure 1b). Moreover, the dehydrogenation product **3ay** was obtained in 90% yield, which strongly demonstrated the high efficiency of this process (Figure 1d). Additionally, the fact that the dimerization product **8** was isolated in only 10% yield in the absence of DMAD (Figure 1c) indicated that both iminium ions and enamine intermediates **V** existed under these visible-light reaction conditions. Finally, a computational experiment for this [2+2] cycloaddition process provided three possible reaction pathways (see the Supporting Information). The fact that product **3aa** was obtained in similar yields in the dark and under irradiation with visible light (Figure 1e) supported the conclusion that the [2+2] cycloaddition between the enamine intermediate and DMAD was a thermal reaction (see the Supporting Information).

On the basis of a series of mechanistic experiments, we propose the mechanism shown in Figure 2 for this sequential visible-light photocatalyzed dehydrogenation/[2+2] cycloaddition reaction. It is well-known that $[Ru(bpy)_3]^{2+}$ (**I**) has a strong absorption cross-section in the visible range, and the exited state $*[Ru(bpy)_3]^{2+}$ (**II**) ($*Ru^{II}/Ru^{I} = 0.84$ V) will be highly populated through the acceptance of a photon from a variety of light sources. Subsequently, this high-energy intermediate **II** primarily undergoes single-electron transfer (SET) with the amine substrate **1a** ($E_{ox} = 0.74$ V versus SCE in CH_3CN) to initiate the first catalytic cycle and provide

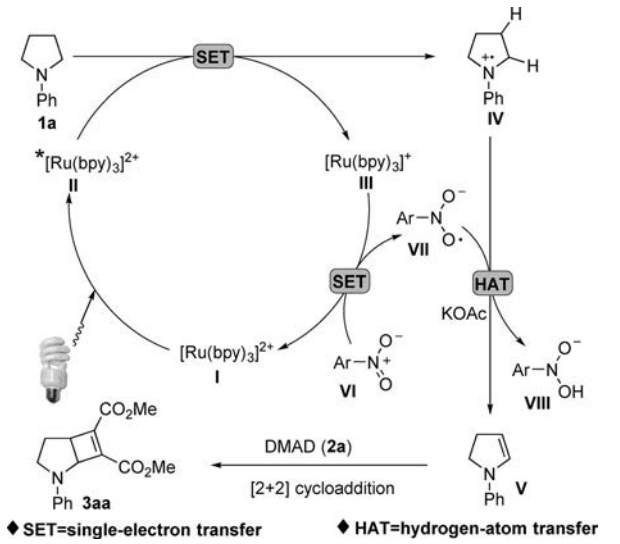


Figure 2. Proposed mechanism.

highly reducing $[Ru(bpy)_3]^+$ (**III**) and the amine radical cation **IV**. Given that $[Ru(bpy)_3]^+$ (**III**) has been shown to be a potent reductant ($Ru^{II}/Ru^{I} = -1.33$ V versus SCE in CH_3CN), a commercially available nitrobenzene **VI** (the reductive potential of PFNB is −0.96 V versus SCE in CH_3CN) serves as an electron and hydrogen acceptor to return $[Ru(bpy)_3]^+$ (**III**) to the ground state and produce a highly activated nitrobenzene anion radical **VII**. By cooperation between the nitrobenzene anion radical **VII** and the weak base KOAc, the amine radical cation **IV** is effectively transformed into the desired enamine intermediate **V**. Finally, a thermal [2+2] cycloaddition reaction between the enamine intermediate **V** and dimethyl acetylenedicarboxylate (DMAD, **2a**) successfully occurs to deliver the dual C–H functionalized product **3aa**.

In summary, we have developed a novel visible-light photocatalyzed dehydrogenation/[2+2] cycloaddition sequence for the dual functionalization of two $C(sp^3)$–H bonds. In this transformation, an array of elusive cyclic enamines were formed under mild conditions. Small strained cyclobutene skeletons attached to saturated N-heterocycles were successfully constructed in situ to furnish a variety of complex bicyclic amino acid derivatives through this sequential process.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H functionalization · [2+2] cycloaddition · dehydrogenation · synthetic methods · visible-light photocatalysis

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[15] CCDC 1568396 (**3aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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