A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201710523
Angew. Chem. 10.1002/ange.201710523

Link to VoR: http://dx.doi.org/10.1002/anie.201710523
http://dx.doi.org/10.1002/ange.201710523

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10.1002/anie.201710523

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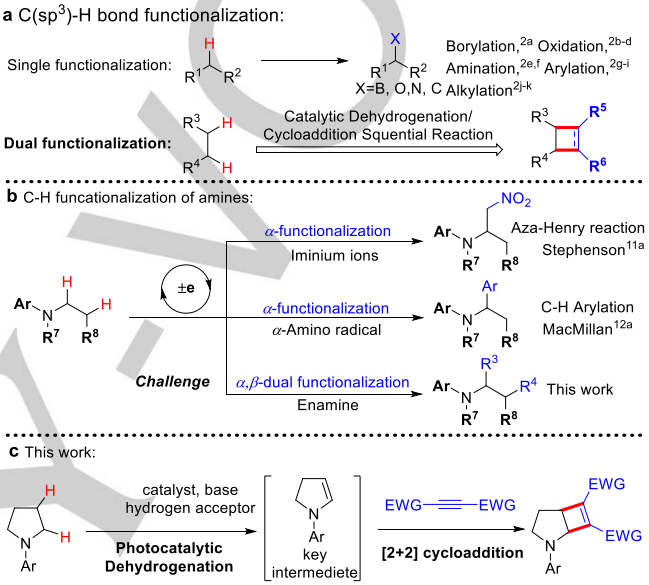
Dual C(sp^3)-H Bond Functionalization of N-Heterocycles *via* Visible-Light Photocatalyzed Dehydrogenation/[2+2] Cycloaddition Sequential Reaction

Guo-Qiang Xu,[a][b] Ji-Tao Xu,[a] Zhi-Tao Feng,[a] Hui Liang,[a] Zhu-Yin Wang,[a] Yong Qin [b] and Peng-Fei Xu*[a]

Abstract: Here we describe a mild method to achieve dual C(sp^3)-H bond functionalization of saturated nitrogen-containing heterocycles *via* a sequential visible-light photocatalyzed dehydrogenation/[2+2] cycloaddition procedure. As a complementary approach to the well-established iminium ion and *Ũ*-amino radical intermediates, the elusive cyclic enamine intermediates are effectively generated *via* photoredox catalysis under mild conditions, which are efficiently captured by acetylene ester to form a wide array of bicyclic amino acid derivatives and realize 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 recent developments[2] of direct transformations of ubiquitous C(sp^3)-H bonds, including borylation, oxidation, amination, arylation and alkylation, have attracted lots of attention. However, the vast majority of examples have been focused on the single C(sp^3)-H bond functionalization, and dual C(sp^3)-H bond functionalization in a single step is still unkown. Encouraged by our previous work which realized the dual functionalization of both C(*sp*^{3})ï H and C(*sp*^{2})ï H bonds *via* visible-light induced oxidation and aza-Dielsï Alder reaction,[3] we planned to explore the feasibility of dual C(sp^3)-H bond functionalization. The catalytic dehydrogenation process[4] has provided a new method for activing 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] In addition, [2+2] cycloaddition is one of the most powerful and widely applied transformations in organic chemistry,[6] which plays a remarkable role in building strained and unusual molecular architectures that cannot be accessed through other pathways.[7] Recently, Zhou and his co-workers developed a unprecedented catalytic enantioselective Heck annulation of propargylic acetates and cycloalkenes to obtain highly strained, fused cyclobutenes.[8] Based on all these factors, we decided to tackle the aforementioned difficulty by merging catalytic dehydrogenation with [2+2] cycloaddition into a sequential process (**Scheme 1a**).



Scheme 1. Dual C(sp^3)-H functionalization strategy

In recent years, visible-light photoredox catalysis[9] as 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 had been effectively generated by photoredox catalysis and successfully applied to various α-functionalization of amines,[13] enamines as promising intermediates for α,β-functionalization of amines are rarely reported (**Scheme 1b**). Besides the general difficulties associated with C(sp^3)-H functionalization (e.g., high bond energy and similar reactivities), it faces greater challenges to realize dual C-H functionalization of saturated N-heterocycles: (1) how to generate sufficient reactive cyclic enamine intermediate and avoid forming more stable heterocyclic aromatics[14], and (2) the well-established α-functionalization[13] of iminium ions[11] and α-amino radicals[12] will strongly compete with this process. Herein, we describe a mild method to generate the highly reactive cyclic enamine intermediate *via* a visible-light photocatalytic dehydrogenation process, and then realize dual C(sp^3)-H bond functionalization through coupling with the traditional [2+2] cycloaddition, thus to furnish a variety of highly strained bicyclic amino acid derivatives which are rather elusive to obtain *via* other methods (**Scheme 1c**).

We initiated this novel sequential reaction with N-phenylpyrrolidine **1a** and dimethyl acetylene dicarboxylate (DMAD, **2a**), along with a variety of photocatalysts, inorganic bases, hydrogen acceptors and light sources. To our delight, it

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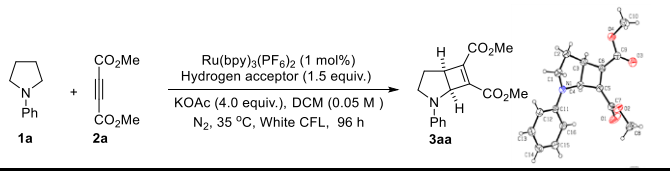
10.1002/anie.201710523

was found that the desired [2+2] cycloaddition product **3aa** was produced in a yield of 70% when $Ru(bpy)_3(PF_6)_2$, nitrobenzene and KOAc were used in the presence of a 23-W fluorescent light bulb after 96 h photolysis at 35 °C (entry 1 of Table 1). To improve this result, several nitrobenzene derivatives were evaluated (entries 2-4 of Table 1) and it turned out that the electron-withdrawing substituents on the benzene ring of nitrobenzene gave better results, and the highest reaction efficiency was observed when pentafluoronitrobenzene (PFNB) was used in this system, furnishing 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 (entries 5, 6 of Table 1), and both of the photocatalyst and the inorganic base were necessary to improve the reaction efficiency (entries 7, 8 of Table 1). Finally, the relative configuration of product **3aa** was determined by the single-crystal X-ray diffraction, which showed that **3aa** was a *syn*-configuration product.

Table 1. Optimization of the reaction conditions[a]

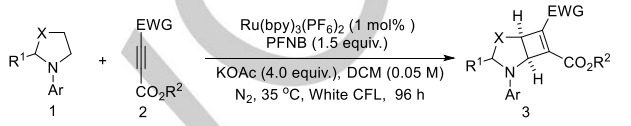


Entry	Hydrogen acceptor	Yield (%) [b]	d.r.[c]
1	nitrobenzene	70	>20:1
2	1-methoxy-4-nitrobenzene	42	>20:1
3	1-chloro-4-nitrobenzene	77	>20:1
4	PFNB	99	>20:1
Entry	Change from entry 4	Yield (%)	
5	No light	0	/
6	No PFNB	0	/
7	No $Ru(bpy)_3(PF_6)_2$	24	>20:1
8	No KOAc	21	>20:1

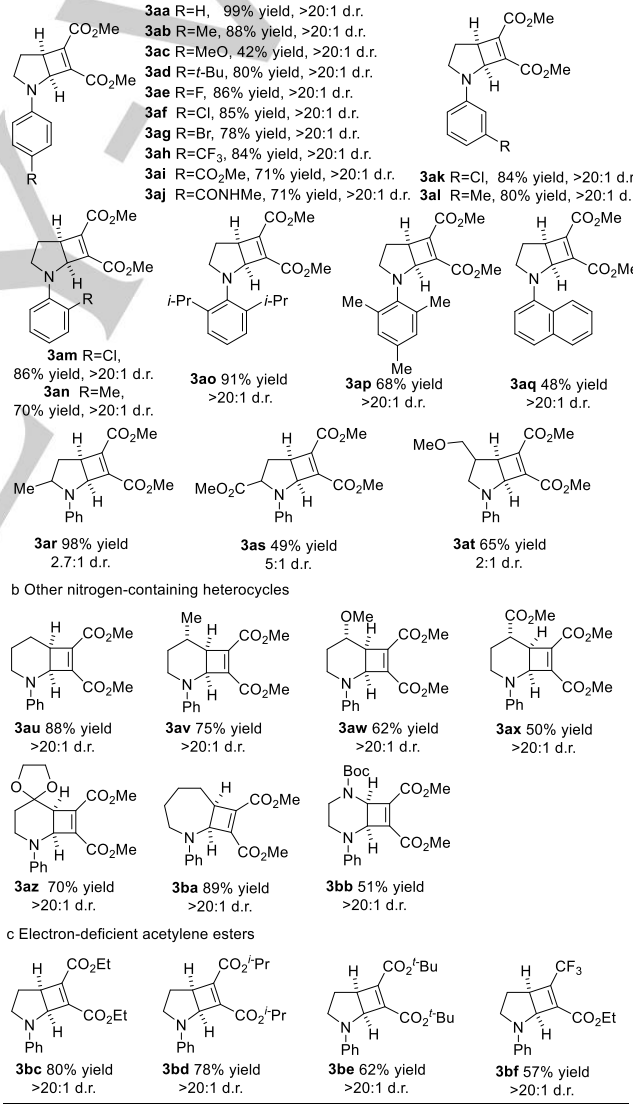
[a]Conditions: Reactions performed with **1a** (0.1 mmol), **2a** (0.3 mmol), photocatalyst (1 mol%), hydrogen acceptor (1.5 equiv.) and KOAc (4.0 equiv.) in DCM (2 mL) at 35 °C under nitrogen atmosphere for 96 h. [b]Isolated yield. [C]Determined by ^{1}H NMR. PFNB: pentafluoronitrobenzene.

Having identified the optimal conditions for this dehydrogenation/[2+2] cycloaddition reaction, the scope of N-phenylpyrrolidine derivatives as the cycloaddition partner was then examined. As shown in Table 2, this sequential transformation had high diastereoselectivity, which was demonstrated by the fact that only *syn*-diastereoisomers were produced as the major products due to the high diastereoselectivity of the [2+2] cycloaddition process. A range of N-arylpyrrolidines bearing electron-donating or electron-withdrawing substituents on the *para*-position of the benzene ring were suitable substrates (**3abī 3ag**). Some valuable functional groups most commonly found in drug molecules were also compatible with this system, including trifluoromethyl, ester, and amido groups (**3ah**, **3ai**, **3aj**). Both electron-rich and electron-deficient substituents at the *ortho*- and *meta*-sites of the phenyl ring were well tolerated (**3ak-3ap**). Besides a variety of phenyl substituents, other aromatic group substituted substrates, such as N-naphthylpyrrolidine, also successfully delivered the desired product **3aq** in good yield. Moreover, the electronic nature of the substituents on the pyrrolidine ring played a critical role in the efficiency of this cycloaddition reaction, which was consistent with the observation that product **3ar** bearing an electron-rich methyl group was obtained in 98% yield while **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-Boc pyrrolidine, N-phenylpyrrolidin-2-one, didn't furnish the corresponding product under the standard conditions.

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



a Pyrrolidine derivatives

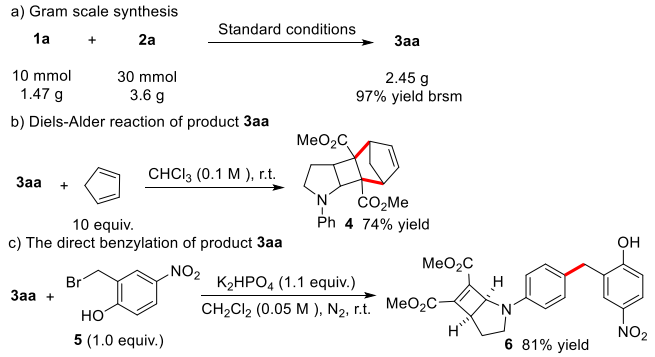


b Other nitrogen-containing heterocycles

c Electron-deficient acetylene esters

The scope of nitrogen-containing heterocycle substrates was further evaluated for this novel protocol. As shown in Table 2b, 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 compound **3av**-**3ax** due to its high stability in this configuration. Furthermore, other nitrogen-containing heterocycles, such as Azepane and Piperazine, were also found to be suitable substrates (**3ba**, **3bb**). Finally, the alkyne components were examined in this cycloaddition protocol in Table 2c. A range of acetylene ester substrates could be smoothly transformed into corresponding products with good yields (**3bcī 3be**). Encouragingly, the unsymmetrically-substituted acetylene ester substrate also furnished the [2+2] cycloaddition product **3bf** in 57% yield.



Scheme 2. Application and transformation of product 3aa.

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

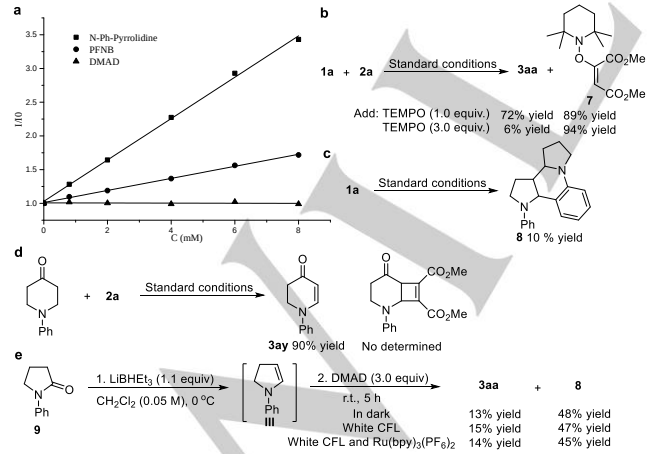


Figure 1. Mechanistic investigations

To further confirm our hypothesis, a series of mechanistic investigations were conducted as shown in Figure 1. First, the quantum yield of the reaction of **1a** and **2a** was determined to be 0.016, which confirmed that the reaction was not a photo-initiated chain process, but a photocatalyzed process. In addition, Stern-Volmer experiments (Figure 1a) illustrated that the luminescence emission of excited-state *Ru(bpy)$_3^{2+}$ was quenched by N-phenylpyrrolidine **1a** more efficiently than pentafluoronitrobenzene (PFNB), which indicated a reduction quenching mechanism. Furthermore, under the standard conditions, when the amount of the radical quencher TEMPO was added from 1.0 equiv. to 3.0 equiv., the yield of product **3aa** was sharply decreased, suggesting that this process involved the 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 1c). Additionally, the fact that the dimerization product **8** was obtained in only 10% isolated yield in absence of DMAD, indicated that both the iminium ions and enamine **III** intermediates existed in this visible-light reaction condition (Figure 1d). Finally, a computational experiment for this [2+2] cycloaddition process provided three possible reaction pathways (see supporting information). The fact that similar yields of product **3aa** were obtained from the alternative transformations under dark conditions or with the irradiations of visible light in Figure 1e supported the conclusion that the [2+2] cycloaddition between the enamine intermediate and DMAD was a thermal reaction (Path I, see Supporting Information).

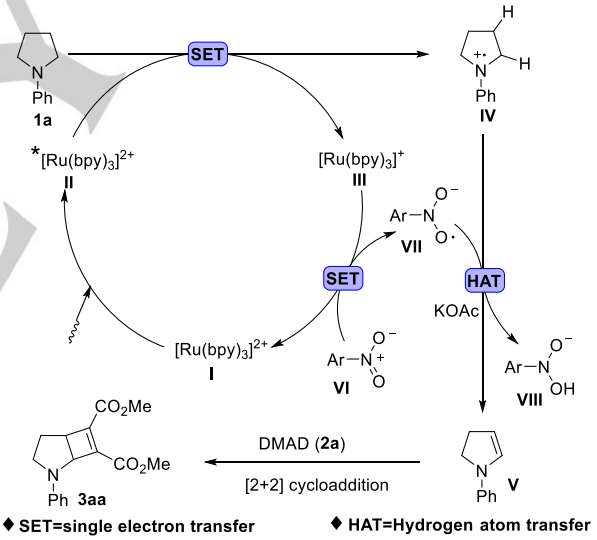


Figure 2. Proposed mechanism

Based on a series of mechanistic experiments, a detailed description of the prospective mechanism for this visible-light photocatalyzed dehydrogenation/ [2+2] cycloaddition sequential reaction is shown in Figure 2. It is well-known that Ru(bpy)$_3^{2+}$ (**I**) has a strong absorption cross section in the visible light range, and the exited state *Ru(bpy)$_3^{2+}$ (**II**) (*Ru^{II}/Ru^{I}= 0.84 V) will be highly populated via accepting a photon from a variety of light sources. Subsequently, this high-energy intermediate (**II**) primarily undergoes a 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 the 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} =ï 1.33 V versus SCE in CH_3CN), commercially available

nitrobenzene (**VI**) (the reductive potential of PFNB is -0.96 V versus SCE in CH_3CN), as an electron and hydrogen acceptor, enables the $Ru(bpy)_3^+$ (**III**) to back to the ground state and produce a high activated nitrobenzene anion radical (**VII**). Under the cooperation between the nitrobenzene anion radical (**VII**) and weak base KOAc, the amine radical cation (**IV**) is effectively transformed into the desired enamine intermediates (**V**). Finally, a thermal [2+2] cycloaddition reaction between the enamine intermediate (**V**) and dimethyl acetylenedicarboxylate (DMAD, **2a**) successfully occurs to deliver dual C-H functionalized product **3aa**.

In summary, we have developed a novel visible-light photocatalyzed dehydrogenation/[2+2] cycloaddition sequential reaction to achieve dual functionalization of two $C(sp^3)$-H bonds. In this transformation, an array of elusive cyclic enamines were formed under mild conditions, which opens a new way for developing further transformations. *In situ* building small strained cyclobutene skeletons on saturated N-heterocycles to furnish a variety of complex bicyclic amino acid derivatives was successfully realized *via* this sequential process.

Acknowledgements

We are grateful to the NSFC (21632003, and 21572087), the key program of Gansu province (17ZD2GC011) and the ñ111ò program from the MOE of P. R. China, and Syngenta Company for financial support.

Keywords: C-H bond functionalization Ådehydrogenation Å[2+2] cycloaddition Åvisible-light photocatalysis

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10.1002/anie.201710523

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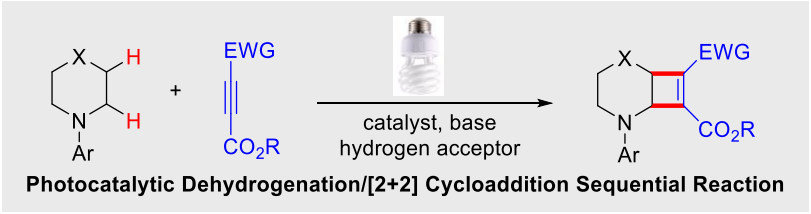

Photocatalytic Dehydrogenation/[2+2] Cycloaddition Sequential Reaction

Here, we describe a novel dual C(sp^3)-H bonds functionalization strategy *via* merging visible-light photocatalyzed dehydrogenation and [2+2] cycloaddition reaction into a sequential process, which provides a valuable method to install a variety of cyclobutene scaffolds onto various saturated nitrogen-containing heterocycles to produce a series of cyclic amino acid derivatives.

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