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Dual C–H Functionalization of N-Aryl Tetrahydroisoquinolines: Highly Diastereoselective Synthesis of Dibenzo[*a,f*]quinolizines via Visible-Light Induced Oxidation and Inverse Electron-Demand Aza-Diels–Alder Reaction
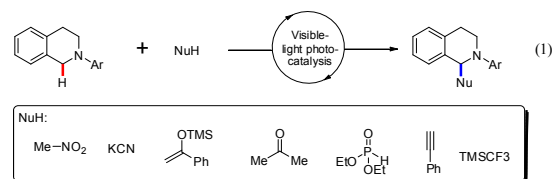
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Described herein is the first example of application of iminium intermediate generated by visible-light photocatalyzed oxidation in an inverse electron-demand aza-Diels–Alder reaction. This dual functionalization of both C(sp^3)–H and C(sp^2)–H bond of N-aryl tetrahydroisoquinolines represents a valuable example to access polycycles with high diastereoselectivity.

The direct functionalization of C–H bonds is one of the most straightforward, economic and efficient strategies toward forming new bonds (such as C–C, C–O and C–N) and for the construction of complex molecules from commercially available hydrocarbons.[1] The majority of the C–H functionalization reactions are based on oxidation catalysed by transition-metals such as palladium, rhodium, or ruthenium.[2] In recent years, the increasingly growing field of visible-light photoredox catalysis offers a powerful platform for the design or development of new chemical transformations.[3] As an electron donor or an electron acceptor upon the irradiation of low-energy visible-light, photoredox catalysts have enabled the construction of a series of useful molecular architectures under mild conditions, especially the functionalization of C–H bonds, which was previously thought to be unreachable via conventional processes. Notably, MacMillan and co-workers have emerged visible-light photoredox catalysis with organocatalysis or transition-metal catalysis to develop numerous efficient methods for the direct functionalization of various C(sp^3)–H bonds[4]. On the other hand, the visible-light photocatalysed oxidation of C–H bonds, another facile strategy of C–H functionalization, especially when the C–H bonds are adjacent to nitrogen, has also been widely used for the synthesis of various complex heterocyclic compounds and even some natural products[5]. Tetrahydroisoquinoline (THIQ) is one of the most useful starting materials for the synthesis of

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† *Electronic Supplementary Information (ESI) available: Experimental procedures and spectra of all new compounds. CCDC 1415206. See DOI: 10.1039/x0xx00000x.*

Previous work: C-H functionalization of THIQs via visible-light photocatalysis

This work: Dual C-H functionalization of THIQs via visible-light photocatalysis
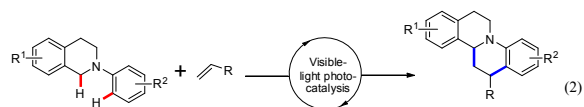
Scheme 1. C–H functionalization by the visible-light photocatalysed oxidation

heterocyclic scaffolds and bioactive compounds.[6] As described in Scheme 1, Equation (1), the reported examples of visible-light photocatalysed oxidative C–H functionalization of THIQs have been mainly focused on the nucleophilic addition of iminium intermediate.[7] Therefore, the application of iminium intermediate in other new type of reactions such as cycloadditions will make an important complementation to this research field and is highly desirable.

Based on our ongoing research program of C–H functionalization[8] and constructing diverse scaffolds and complex molecules[9], considering that iminium ions can be readily generated with visible-light induced oxidation, we propose an inverse electron-demand aza-Diels–Alder (IEDDA) reaction, which involves an electron-rich dienophile and a N-aryl iminium ion, to achieve the dual C–H functionalization of N-aryl tetrahydroisoquinolines using visible-light photocatalysis strategy, as described in Scheme 1, Equation (2). The IEDDA reaction is one of the most powerful methods for the construction of various heterocyclic compounds[10], which has been utilized in different catalytic reactions such as Lewis acid catalysis[11], phosphoric acid catalysis[12] and organocatalysis[13], etc. Herein we use the IEDDA reaction to synthesize the dibenzo[*a,f*]quinolizidine ring system which is one of the seven theoretically possible dibenzoquinolizidines

that are ubiquitous in biologically active natural products and drugs.[14] Compared with single C-H functionalization, there are more challenges in the dual C-H functionalization of N-Aryl tetrahydroisoquinolines. Seidel[15] and co-workers have recently reported an elegant method to rapidly obtain polycyclic amines by employing the copper-catalysed oxidative Povarov reactions of various N-aryl amines. However, how to obtain a high diastereoselectivity still remains a challenge in this reaction. Noteworthily, there is no example of using iminium intermediate generated by visible-light photocatalysis in cycloaddition reactions. To this end, we reported herein the first application of iminium intermediate involving visible-light in an inverse electron-demand aza-Diels–Alder reaction for the synthesis of quinolizine alkaloids with excellent diastereoselectivity.

To test our hypothesis, the N-phenyl 1,2,3,4-tetrahydroisoquinoline(**1a**) and N-vinyl-pyrrolidin-2-one(**2a**) were chosen as model substrates for optimization of the reaction parameters. Unfortunately, the proposed reaction between **1a** and **2a** did not occur in the presence of [Ru(bpy)$_3$Cl$_2$] (1 mol%), BrCCl$_3$ (3.0 equiv.) and K$_3$PO$_4$ (1.2 equiv.) in degassed MeCN under irradiation by a 3W blue LED for 6h. However, when substrate **1a** in degassed MeCN was irradiated by a 3W blue LED in the presence of [Ru(bpy)$_3$Cl$_2$] and BrCCl$_3$ for 6h, and then substrate **2a** and K$_3$PO$_4$ were added to the mixture which was stirred in dark for 16h, to our delight, the expected product was obtained in 83% yield

with >20:1 diastereoselectivity (Table 1, entry 1). In order to evaluate the factors influencing the reaction, some control experiments were carried out. As expected, the visible-light and oxidant were indispensable for this transformation (Table 1, entries 2, 3). Interestingly, we obtained the product with 42% yield while Ru(bpy)$_3$Cl$_2$ was absent in reaction mixture, which was contributed to forming the EDA complex between **1a** and BrCCl$_3$.[17b] However, compared with standard conditions(Table 1, entry 1), both of the photosensitizer and base were required for improved product yields (Table 1, entries 4, 5). According to the literature[17a], CCl$_4$ is also a good oxidant for visible-light photocatalysis, nevertheless, only 8% of product was isolated from the reaction system when CCl$_4$ was used to replace BrCCl$_3$ (Table 1, entry 6). The yield of **3a** was also reduced when the mole ratio of **2a/1a** was lowered to 1.2 equiv. (Table 1, entry 7).

In an attempt to improve the reaction efficiency, both pure and mixed solvents were tested in the reaction, the results showed that acetonitrile was still the best solvent compared with DCM, THF, toluene, DMSO and even acetonitrile/H$_2$O (1:1) (Table 1, entries 8-12). Surprisingly, the basicity of additives had a dramatic effect on the yield and therefore Cs$_2$CO$_3$ was selected as the optimal additive (entries 13-16).

With the reaction conditions optimized, we then evaluated the substrate scope of this reaction. As demonstrated in table 2, a series of tetrahydroisoquinolines with substituents on the N-Aryl ring were smoothly converted into the corresponding dibenzo[*a,f*]quinolizine derivates **3** in good yields (up to 90%)

Table 1: Optimization of the reaction conditions[a]
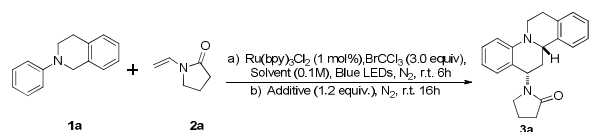
entry	solvent	additive	yield (%)[b]	d.r.[c]
1	MeCN	K$_3$PO$_4$	83	>20:1
2[d]	MeCN	K$_3$PO$_4$	0	/
3[e]	MeCN	K$_3$PO$_4$	0	/
4[f]	MeCN	K$_3$PO$_4$	42	>20:1
5	MeCN	/	30	>20:1
6[g]	MeCN	K$_3$PO$_4$	8	/
7[h]	MeCN	K$_3$PO$_4$	53	>20:1
8	Toluene	K$_3$PO$_4$	28	>20:1
9	DCM	K$_3$PO$_4$	50	>20:1
10	THF	K$_3$PO$_4$	63	>20:1
11	DMSO	K$_3$PO$_4$	80	>20:1
12	MeCN/H$_2$O	K$_3$PO$_4$	66	>20:1
13	MeCN	K$_2$HPO$_4$	45	>20:1
14	MeCN	KH$_2$PO$_4$	22	>20:1
15	MeCN	Cs$_2$CO$_3$	86	>20:1
16	MeCN	NaOAc	45	>20:1

[a] Unless otherwise noted, the reaction was carried out with **1a** (0.2 mmol), BrCCl$_3$ (0.6 mmol) and Ru(bpy)$_3$Cl$_2$ (0.002 mmol) in MeCN (2 mL) at room temperature. After full conversion of **1a** as monitored by TLC, **2a** (1.0 mmol) and Cs$_2$CO$_3$ (0.24 mmol) was added to the mixture and the reaction was stirred in dark under N$_2$ atmosphere at room temperature. [b] Isolated yield. [c] Determined by 1H NMR. [d] No Blue LEDs. [e] No BrCCl$_3$. [f] No Ru(bpy)$_3$Cl$_2$. [g] CCl$_4$ instead of BrCCl$_3$. [h] **2a** was 1.2 equiv.

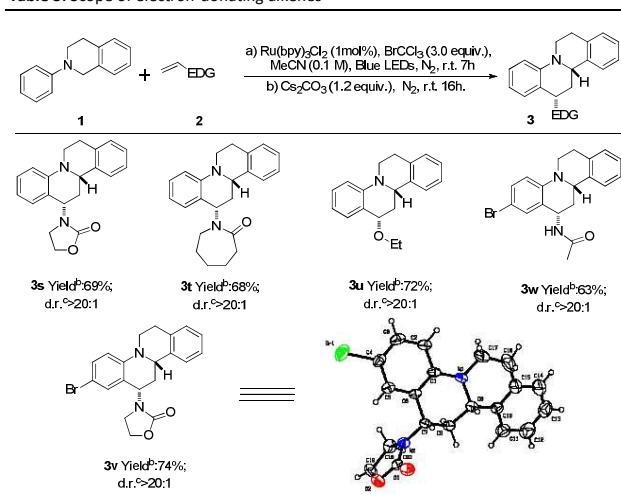**Table 2:** Substrate scope of N-Aryl tetrahydroisoquinolines[a]
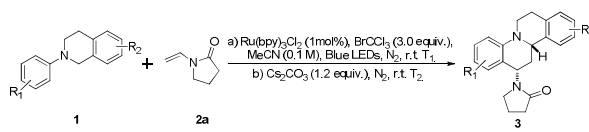
entry	R^1	R^2	T$_1$(h)	T$_2$(h)	yield(%)[b]	d.r.[c]
1	H	H	6	16	86(**3a**)	>20:1
2	4-F	H	11	16	82(**3b**)	>20:1
3	4-Cl	H	7	16	88(**3c**)	>20:1
4	4-Br	H	23	16	90(**3d**)	>20:1
5	4-CF$_3$	H	22	24	86(**3e**)	>20:1
6	4-Ac	H	8	16	72(**3f**)	>20:1
7	4-CO$_2$^{i}Pr	H	13	34	82(**3g**)	>20:1
8	3-Cl	H	10	16	45(**3h**)	>20:1
9	4-MeO	H	6	16	66(**3i**)	>20:1
10	4-Me	H	6	16	64(**3j**)	>20:1
11	3-MeO	H	6	16	11(**3k**)	>20:1
12	H	5-F	36	16	60(**3l**)	>20:1
13	H	6-F	36	16	50(**3m**)	>20:1
14	H	7-F	36	16	56(**3n**)	>20:1
15	H	6-Cl	8	16	85(**3o**)	>20:1
16	H	5-Cl	11	16	80(**3p**)	>20:1
17	H	6-Br	6	16	73(**3q**)	>20:1
18	H	6,7-diMeO	8	16	34(**3r**)	>20:1

[a] Unless otherwise noted, the reaction was carried out with **1** (0.2 mmol), BrCCl$_3$ (0.6 mmol) and Ru(bpy)$_3$Cl$_2$ (0.002 mmol) in MeCN (2 mL) at room temperature. After full conversion of **1** as monitored by TLC, **2a** (1.0 mmol) and Cs$_2$CO$_3$ (0.24 mmol) was added to the mixture and the reaction was stirred in dark under N$_2$ atmosphere at room temperature. [b] Isolated yield. [c] Determined by 1H NMR.

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with excellent diastereoselectivities (>20:1, d.r.). It was found that the electron-withdrawing substituents gave better yields (72-90%) (Table 2, entries 2-7) while the electron-donating substituents (**3i** and **3j)** gave lower yields (66%, 64%) (Table 2, entries 9, 10), which could be attributed to the nature of the inverse electron-demand aza-Diels–Alder reaction that involves the interaction between the HOMO of the dienophiles and the LUMO of the aza-dienes. Since the electron-poor substituents had lower LUMO, they were more reactive toward dienophiles. However, both electron-rich substituent **3k** and electron-poor substituent **3h** on the *meta*-position of N-aryl had a distinctly negative influence on the yields. In addition, *ortho*-substituents, including methyl and chloro, on the N-aryl ring did not produce the corresponding products (data not shown), presumably due to the A$_{1,3}$-type strain developed in the transition state of this reaction. Interestingly, the groups on the tetrahydroisoquinoline ring exhibited the similar electronic effect, as demonstrated by the results that the electron-poor substituents on the tetrahydroisoquinoline ring (Table 2, entries 12-17) offered better yields than 9,10-dimethoxy substituent **3r** (Table 2, entry 18). Notably, this reaction always exhibited excellent diastereoselectivity and only one diastereoisomer was formed in the reaction.

In order to explore the generality of this reaction, a wide range of dienophiles were also tested with the results described in table 3. Clearly this reaction could be applicable to various enamides. For instance, products containing oxygen atom (**3s**) or big ring (**3t**) could be smoothly afforded with moderate yields (69%, 68%) and excellent diastereoselectivities (>20:1, dr). Importantly, the general acyclic enol ether and acyclic enamide also readily underwent the title reaction to give the corresponding polycyclic product **3u** and **3w** in good yield (72%, 63%), respectively. Consistent with the former results, with the

Table 3: Scope of electron-donating alkenes[a]

3s Yield[b]:69%; d.r.[c]>20:1

3t Yield[b]:68%; d.r.[c]>20:1

3u Yield[b]:72%; d.r.[c]>20:1

3w Yield[b]:63%; d.r.[c]>20:1

3v Yield[b]:74%; d.r.[c]>20:1

[a] Unless otherwise noted, the reaction was carried out with **1** (0.2mmol), BrCCl$_3$ (0.6 mmol) and Ru(bpy)$_3$Cl$_2$ (0.002 mmol) in the MeCN (2 mL) at room temperature. After full conversion of **1** as monitored by TLC, **2** (1.0 mmol) and Cs$_2$CO$_3$ (0.24 mmol) was added to the mixture and the reaction was stirred in dark under N$_2$ atmosphere at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR.

introduction of a bromine atom on the phenyl ring, the corresponding product **3v** was obtained in higher yield (74%), and the structure of **3v** was determined by X-ray analysis. However, more substituted on alkenes, such as tert-butyl 2,3-dihydro-1H-pyrrole-1-carboxylate, 1-(prop-1-en-2-yl)pyrrolidin-2-one and (E)-1-(prop-1-en-1-yl)pyrrolidin-2-one, were not smoothly transferred into the desired products, presumably due to the steric effect of substrates.

Based on the above reaction results and literatures[16], a plausible mechanism for the reaction is proposed in Scheme 2. Amino radical cation **I** is formed by reductive quenching of the excited state of [Ru^{II}] by **1a**, and the powerful reducing agent [Ru^I] ([Ru^{II}]/[Ru^I]=-1.33 V vs. SCE in MeCN) is produced at the same time. Catalyst turnover may be accomplished by the reduction of BrCCl$_3$ to afford the trichloromethyl radical, which may abstract a hydrogen atom from the amino radical cation to form the desired iminium ion, **II** (path A).[16a] However, according to the experiment result (table1, entry 4) and the report of Zeitler[16b], there is another possible pathway which would involve EDA complexes that are in terms of amine substrates and BrCCl$_3$ and do not involve photocatalyst, whose excitation facilitates charge transfer to generate both the amino radical cation and an instable BrCCl$_3$ radical anion. Upon the irradiation with visible light, the EDA complex smoothly generates an amino radical cation and a trichloromethyl radical, and then the trichloromethyl radical abstracts a hydrogen atom from the amino radical cation to generate the desired iminium ion, **II (**path B**).** According to the report of Seidel[15], the iminium ion **II** and **2a** may be via a Povarov reaction approach to form the polycyclic amines, which maybe show that the electron-donating substituents on the N-Aryl tetrahydroisoquinolines give better yields than the electron-withdrawing substituents. However, we have an opposite results that the electron-withdrawing substituents give better yields (Table 2, entries 2-7, 12-17) while the electron-donating substituents give lower yields (Table 2, entries 9, 10, 18). In addition, the iminium ion is trapped by HRMS ([C$_{13}$H$_{14}$N$_1$]$^+$ calcd.208.1121, found 208.1118). Therefore, we are inclined to agree that the iminium ion **II** and **2a** form the endo-intermediate **III** through an inverse electron-demand aza-Diels–Alder reaction, and that approach is more helpful to understanding the high diastereoselectivity of this reaction. Finally, the endo-intermediate **III** is deprotonated by base to afford the desired product **3a**.
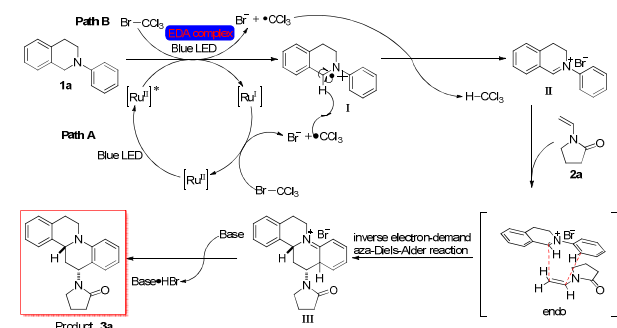
Scheme 2. Plausible reaction mechanism

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In summary, we have developed the first example of an inverse electron-demand aza-Diels–Alder reaction employing iminium intermediate generated by visible-light photocatalyzed oxidation. This reaction synchronously proceeds to achieve the functionalization of both a C(sp^3)–H and a C(sp^2)–H bond. By using this method, perfect diastereocontrol was achieved in the synthesis of dibenzo[a,f]quinolizines. As a result, this work makes a significant complementation to this research field which generally applied iminium intermediate described herein in nucleophilic addition reactions.

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