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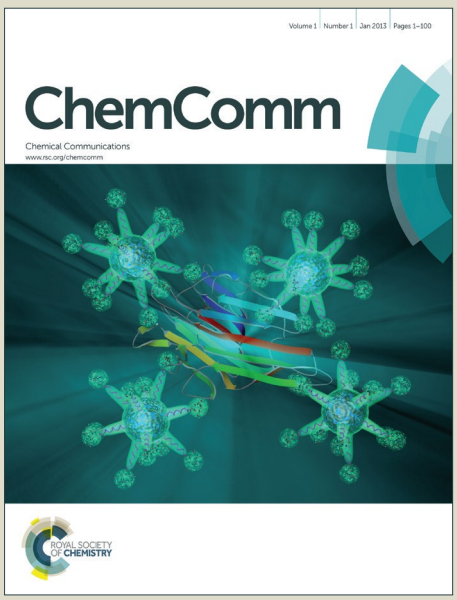

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Photoredox Catalyzed Radical-Radical Coupling Reaction: Facile Access to Multi-Substitued Nitrogen Heterocycles

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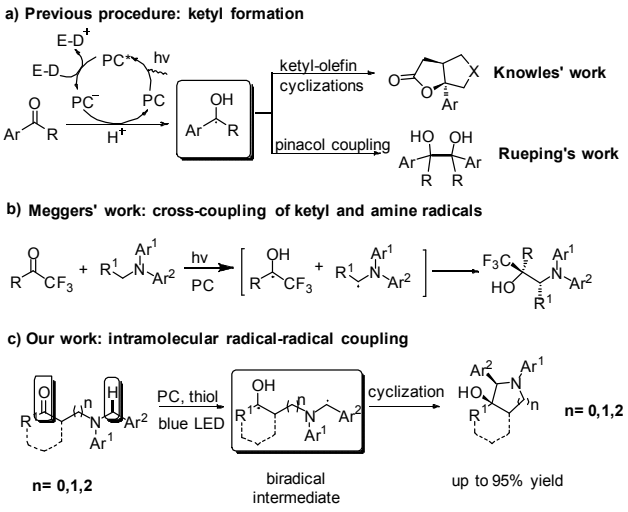
Weipeng Li,[a] Yingqian Duan,[a] Muliang Zhang,[a] Jian Cheng [a] and Chengjian Zhu*[ab]

Visible light induced photoredox catalysis is an efficient method for radical activation. Herein, we report a photoredox catalyzed intramolecular radical-radical coupling reaction that proceeds through biradical intermediate. This protocol represents a new synthetic route to construct multi-substituted *N*-heterocycles. Four, five and six-mumber *N*-heterocyclic structures with a quaternary carbon center are accessible under mild conditions.

The nitrogen heterocycles, as basic alkaloid scaffolds, appear in numerous bioactive products, pharmaceuticals, and agrochemicals.[1] As a result, the synthesis and functionalization of *N*-heterocycles have attracted a long-lasting interest in synthetic field.[2] In the past years, a couple of strategies have been developed for the synthesis of *N*-heterocycles including piperidines, pyrrolidines, azetidines, and indoles.[3] Despite the great achievements in this area, an efficient method for the construction of multi-substituted *N*-heterocycles with quaternary carbon centre from simple substrates is still desirable. Herein, we present a new way to synthesize four, five and six-membered aminated heterocyclic structures via visible-light-induced photoredox catalysis.

Visible-light-induced photocatalysis has proven to be one of the most effective methods for radical activation,[4] a large number of radical reactions have been realized via visible light irradiation.[5] Ketyl is valuable synthetic radical in organic synthesis.[6] However, the unfavorable activation barrier during ketyl formation severely prevented their wider application. Recently, the groups of Knowles [7] and Rueping [8] reported efficient protocols to access ketyls under mild conditions by visible light photoredox catalysis. In their work, a



Scheme 1. Photoredox catalysed ketyl formation reaction.

sacrificial electron-donor reagent was needed to initiate catalytic cycle (Scheme 1-a). Meggers and co-workers also introduced a visible-light-driven asymmetric intermolecular ketyl/α-amine radical coupling reaction between one electron-acceptor (E-A) and one electron-donor (E-D) which avoids the use of an extra sacrificial electron-donor (Scheme 1-b). However, only electron-deficient trifluoromethyl ketones are suitable substrates. Inspired by our recent success in visible light photoredox catalysis,[10] we assumed that a substrate bearing both ketone as electron-acceptor and tertiary amine as electron-donor[11] would generate an active biradical intermediate which undergo radical- radical cyclization under visible light photoredox catalysis (Scheme 1-c).

In order to demonstrate our hypothesis mentioned above, we synthesized compound **1a** as a model substrate. However, visible light irradiation of substrate **1a** in MeCN solution containing 1 mol% $Ir(ppy)_2(dtbbpy)PF_6$ led to no conversion (Table 1, entry 1). Addition of protonic acid $(PhO)_2PO_2H$ was also ineffective (Table 1, entry 2). To our surprise, when thioacetic acid (CH_3COSH) was employed,

[a] State Key Laboratory of Coordination Chemistry, School of Chemistry and Chemical Engineering, Nanjing University Nanjing 210093 (P. R. China) E-mail: cjzhu@nju.edu.cn.
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Insti- Institute of Organic Chemistry, Shanghai 200032 (P. R. China).

† Footnotes relating to the title and/or authors should appear here.
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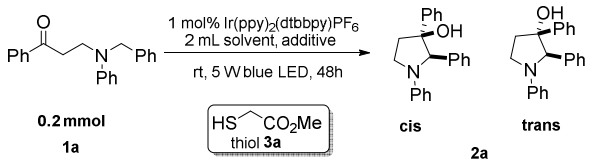
36% yield of pyrrolidine product was obtained with 2.5:1 mixture of diastereomers (Table 1, entry 3). While MacMillan and co-workers

Table 1. Optimization studies [a]

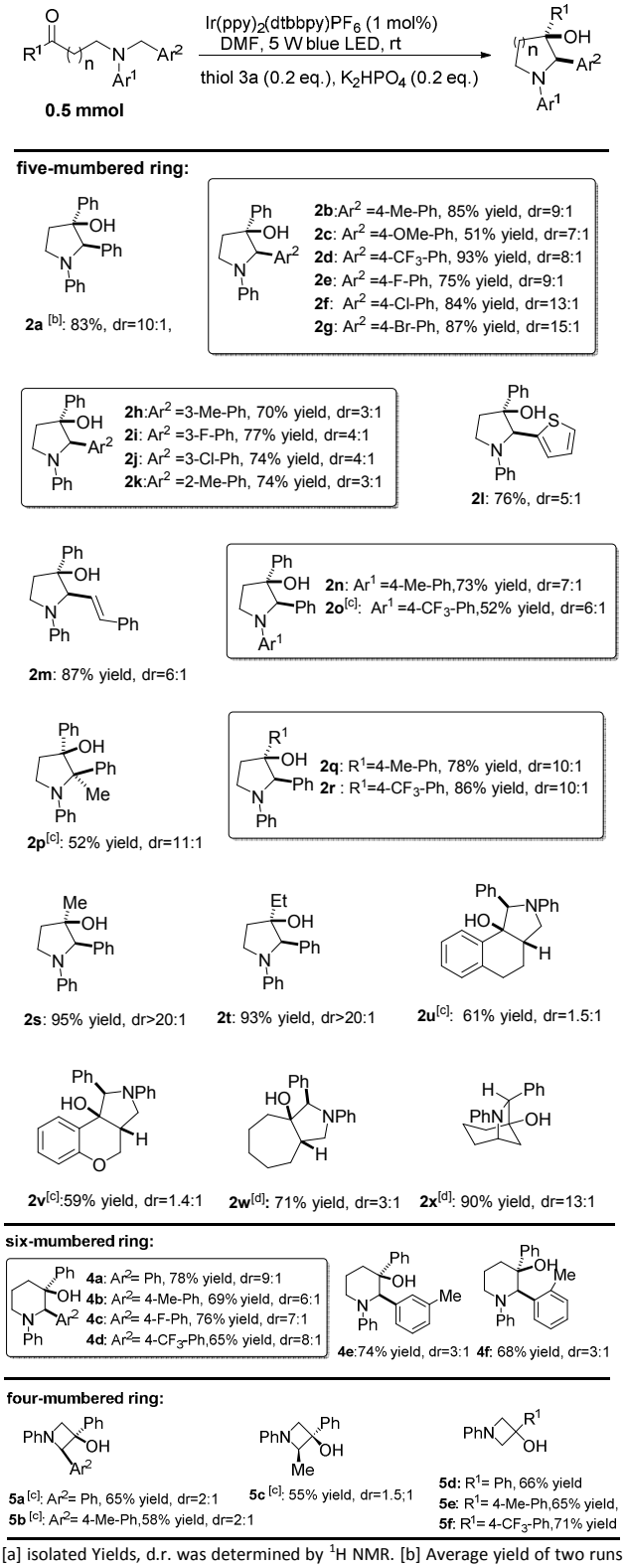


Entry	Solvent	Additive[b]	Yield/%	cis:trans [c]
1	CH_3CN		0	-
2	CH_3CN	$(PhO)_2PO_2H$	trace	-
3	CH_3CN	CH_3COSH	36	2.5:1
4	CH_3CN	Thiol **3a**, K_2HPO_4	66	2:1
5	DCM	Thiol **3a**, K_2HPO_4	64	1.5:1
6	THF	Thiol **3a**, K_2HPO_4	36	2.3:1
7	**DMF**	**Thiol 3a, K_2HPO_4**	**82**	**12:1**
8	DMSO	Thiol **3a**, K_2HPO_4	73	14:1
9	DMF	Thiol **3a**, K_3PO_4	7	ND
10	DMF	Thiol **3a**, KH_2PO_4	70	12:1
11	DMF	Thiol **3a**, K_2CO_3	13	ND
12	DMF	Thiol **3a**, $KHCO_3$	64	12:1
13	DMF	K_2HPO_4	0	-
14	DMF	Thiol **3a**	trace	-
15[d]	DMF	Thiol **3a**, K_2HPO_4	0	-
16 [e]	DMF	Thiol **3a**, K_2HPO_4	0	-

[a] Optimization reactions performed on 0.2 mmol scale with anhydrous solvent under Argon atmosphere. Isolated yield. [b] All additives were used in 0.2 eq. [c] Determined by ^{1}HNMR. [d] No catalyst. [e] No light. ND = not determined.

have pioneered the strategy for thiol activation of C-H bonds via photoredox catalysis.[12] We guessed that the electrophilic R-S$^{\cdot}$ radical generated from MeCOSH may have an acceleration effect on the reaction by abstraction of H$^{\cdot}$ from substrate **1a**. Based on this hypothesis and after screening several similar conditions (see more details in Table 1 in *ESI*), the combination of methyl thioglycolate (thiol **3a**) and K_2HPO_4 was adopted. In survey of various solvents, it was found that polar solvents provided better results. With DMF as reaction medium, the desired *N*-heterocycle **2a** was obtained in 82% yield with high level of diastereoselectivity (Table 1, entries 4-8). Bases have a great influence on reaction yield (Table 1, entries 9-12). Among the bases screened, K_2HPO_4 proved to be the best choice (see more details in Table 1 in SI). Control experiments indicated the necessary of photocatalyst, thiol, light, and base, no desired product was detected in absence of any elements mentioned above (Table 1, entries 13-16).

Table 2. Substrate scope [a]



[a] isolated Yields, d.r. was determined by ^{1}H NMR. [b] Average yield of two runs (81% and 85%). [c] thiol (0.25 mmol), K_2HPO_4 (0.25 mmol). [d] relative configuration was determined by NOE.

With the optimized conditions in hand, we next engaged to

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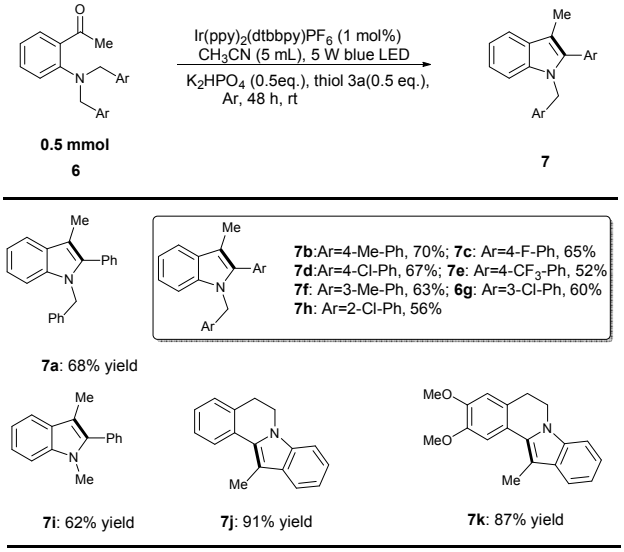
define the substrate generality of this protocol. When the reaction was performed on 0.5 mmol scale, model substrate **1a** provided cyclized product in an undiminished yield (83%) as a 10:1 mixture of diastereomers (Table 2, **2a**). We then investigated a variety of Ar^2 groups. Both electron-rich and electron-poor substrates functioned well in this process (Table 2, **2b-2k**). Substrates with strong electron-withdrawing group (CF_3) on the benzene ring (Table 2, **2d**) resulted in high yield (93%) but in slow conversion. It was found that the position of substituents have great impact on the diastereomeric ratio. *Meta*-substituted and *orth*-substitued analogues led to poor diastereoselectivity (Table 2, **2h-2k**). Heteroarene structures are prevalence in bioactive molecules, so heteroaromatic substrate (Table 2, **2l**) was tested too, and 76% yield of product was obtained. Conjugated substrate was also suitable for this system which could offer 2-vinyl substituted *N*-heterocycle in 76% yield (Table 2, **2m**). The effect of Ar^1 groups were examined too, all underwent reaction to provide desired products in moderate to good yields (Table 2, **2n-2o**). The two aromatic groups (Ar^1 and Ar^2) are necessary to the successful of this transformation, while replacing of either Ar^1 or Ar^2 by aliphatic groups lead to no conversion (see details in *ESI Table 2*). Notably, α-alkyl branched substrate was successfully cyclized to provide product containing two continuous quaternary carbons in 52% yield with good diastereoselectivity (Table 2, **2p**). Aliphatic ketones **1s** and **1t** were also tolerable substrates (Table 2, **2s** and **2t**), furnishing cyclization in good results with high level diastereoselectivity (dr>20:1). Multi-substituted pyrrolidine fused to 6-, 7- membered rings were readily accessible *via* this protocol (Table 2, **2u-2w**). The bridged bicyclic structure was also prepared in 90% yield which further demonstrated the generality of this method in constructing *N*-heterocycle compounds (Table 2, **2x**). Next, we explored the possibility of expanding this protocol to synthesize *N*-heterocycles of different sizes. At first, we employed our protocol to synthesize piperidine scaffold. The corresponding piperdines could be isolated in good yields (Table 2, **4a**-**4f**). Then, we questioned if it is possible to obtain azetine with high ring strain. To our delight, the cyclization procedure proceeded well to provide multi-substituted azetidines in moderate yields (Table 2, **5a**-**5b**). It was needed to mention that substrates with *N*-Me or *N*-Et substitution also could smoothly furnish the cyclization reactions (Table 2, **5a**-**5f**). Gram-scale experiments were also performed to test the potential application of this method in organic synthesis (see results in *ESI*, page of 6).

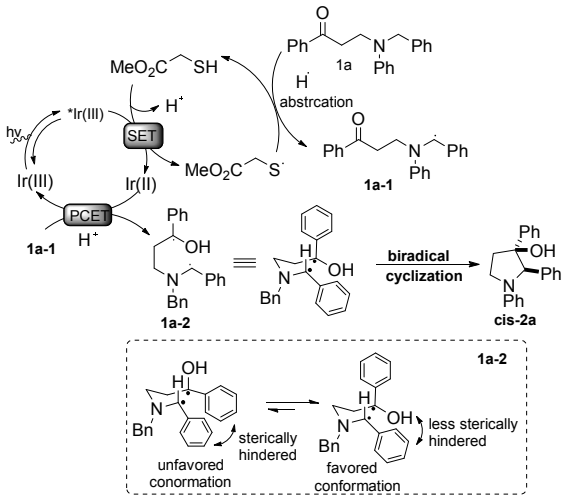
With *N*-substituted amino acetophenone as substrate, we get dehydration products which led to 1, 2, 3,-trisubstituted indoles. In consideration of the widely existence of indole scaffolds in natural products, the generality of this method was then examined (see optimization studies in Table 3 in *ESI*), the results are shown in Table 3. A range of functional groups on the aryl moiety were tolerated very well (Table 3, **7a-7i**). Indolo[2,1-a]isoquinoline structures were also accessible in good yields (Table 3, **7j**-**7k**).

Table 3. Substrates scope of indole formation [a]



[a] Reaction conditions: substrate (0.5 mmol), thiol (0.25 mmol), K_2HPO_4 (0.25 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (0.005 mmol), CH_3CN (5mL) irradiate by 5 W blue LED under argon atmosphere for 48 hours. Yields of isolated products.

Based on our experiment results (see details in *ESI*) and the previous research done in visible light photoredox catalysis,[12] a plausible mechanism is proposed in Scheme 2. Visible light irradiation of Ir^{III} photocatalyst lead to a long-lived photoexcited state $*Ir^{III}$. $*Ir^{III}$ undergoes a single electron transfer (SET) oxidation process with thiol to generate thiyl radical and reduced photocatalyst Ir^{II}. The thiol radical abstracts $H^{\cdot}$ from **1a**, providing α-amino radical **1a-1**. At this juncture, electron transfer to the ketone part of **1a-1** by the Ir^{II} forms biradical intermediate **1a-2** while concomitantly regenerating the Ir^{III}. The active biradical **1a-2** prefers to go through intramolecular coupling in the less hindered conformation, which leads to **cis**-**2a** as the main diastereomer.



Scheme 2. Proposed catalytic cycles for radical-radical coupling.

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Conclusions

In conclusion, we have developed a visible light photoredox catalyzed radical-radical coupling reaction to construct 4-, 5-, and 6-membered *N*-heterocycles. Ketyl and α-amino radical were formed in one catalytic cycle via proton-coupled electron transfer without extra sacrificial electron donor. We anticipate this reaction will prove to be a versatile method for *N*-heterocycles formation and find synthetic utility among orgnic synthesis.

Acknowledgements

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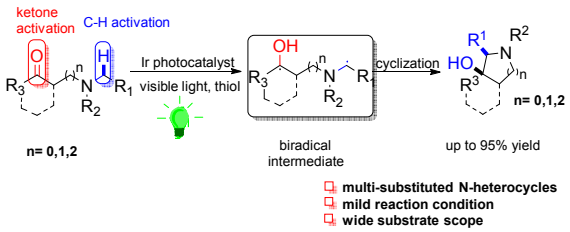

A visible light mediated radical-radical coupling reaction towards valuable nitrogen heterocyle has been developed. Piperidines, pyrrolidine, indoles, and azetidines scafolds were synthesized in good to excellent yields from simple substrates.