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Synergistic Combination of Visible-Light Photo-Catalytic Electron and Energy Transfer Facilitating Multicomponent Synthesis of β-Functionalized α,α-Diarylethylamines

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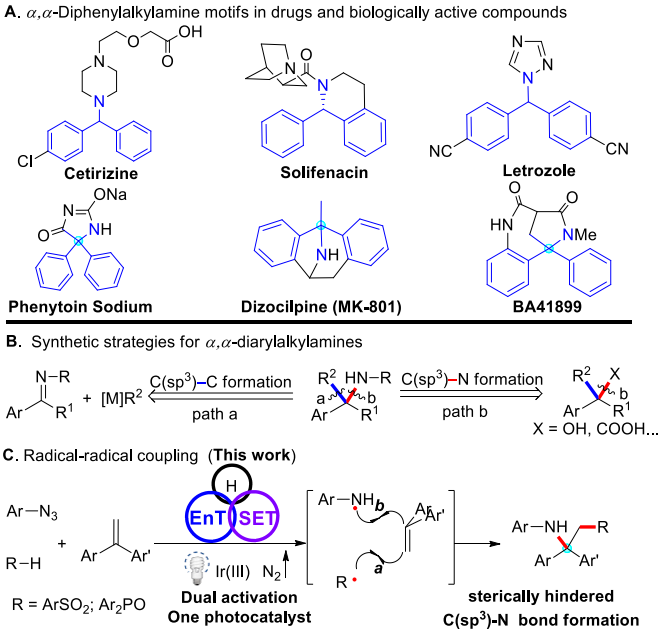
A synthetic strategy with the visible-light photo-catalytic synergistic combination of electron and energy transfer processes has been developed. The mild reaction conditions allow the radical-radical cross-coupling phenomenone for the multicomponent synthesis of *β*-arylsulfonyl(diarylphosphinoyl)-*α,α*-diarylethyl-amines from readily available arylsulfinic acids (diarylphosphine oxides), 1,1-diarylethylenes and arylazides.

Photo-catalysis induced by visible light is an important tool to access chemistry in which reactive intermediates often cannot be generated readily in the absence of photo-chemical strategies.[1] Because such catalysis supports novel chemical transformations, it has received much attention recently.[2] Photo-catalysts are known to be excited by absorption of visible light and the excited forms can be used to activate organic substrates through different pathways, such as single electron transfer (SET), energy transfer (EnT) and atom transfer. A strategy enabling the combination of photo-catalysis with other types of catalysis has emerged. In such reactions, a photo-catalyst activates an organic substrate while the second, nonphoto-chemical catalyst activates another substrate and/or intermediates, leading to various chemical transformations that are otherwise either unexpected or difficult.[3] Inspired by such cooperative strategy and recent relevant examples[4] and considering the fact that many photo-redox catalysts are also powerful photosensitizers,[5] a synthetic method dependent on the synergistic combination of visible-light photo-catalytic SET and EnT processes is a new reaction paradigm which is interesting to explore.



Scheme 1 Synergistic combination of electron and energy transfer processes in the synthesis of tertiary *α,α*- diarylalkylamines

Diphenylmethylamine derivatives are a class of hydrophobic and polar molecules present in marketed drugs such as Cetirizine, Solifenacin and Letrozole (Scheme 1A, top). However, their counterparts such as *α,α*-diarylalkylamines (alkyl ≠ methyl) have been explored less, although this structural moiety is found in for example, the anti-epileptic drug Phenytoin Sodium, the *N*-methyl-*D*-aspartate antagonist Dizocilpine,[6] and the calcium sensitizing agent BA41899[7] (Scheme 1A, bottom). The synthesis of such compounds are mostly based on the direct 1,2-addition of organometallic nucleophiles to ketoimines which involves the construction of C(sp³)–C bonds (Path a, Scheme 1B).[8] The low reactivity of ketoimines and high reactivity of organometallic nucleophiles however, make it difficult to construct the appropriate scaffold and this results in a relative scarcity of the available drugs or drug candidates with this scaffold. Direct construction of a C(sp³)–N bond is a simple and feasible strategy for the

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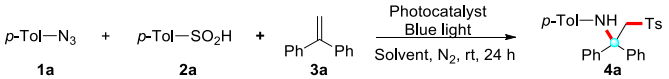
construction of α,α-diarylalkylamines, but it is hindered by the challenging synthesis of the necessary starting materials (Path b, Scheme 1B). Radical-radical cross-coupling reactions have an activation energy close to zero and have emerged as a powerful tool in the construction of new chemical bonds.[9] Herein, we report a new strategy enabling such multicomponent synthesis of α,α-diarylalkylamines, wherein a visible-light photocatalytic SET and EnT process are combined to facilitate the desired outcome. This enables the construction of sterically hindered C(sp^3)–N bonds through a radical-radical cross-coupling process (Scheme 1C). The major challenge in such a reaction is the difficulty in controlling the regio- and chemo-selectivity in the presence of multiple active species.

Organic azide is an efficient and convenient amino source due to the advantages of easy preparation, non-oxidative conditions, and clean reactions with N_2 as the only by-product.[10] Activation of organic azides by visible-light photo-catalysis has recently received some attention.[11,12] A visible-light photocatalyst can oxidize arylsulfinic acids to arylsulfonyl radicals,[13] and this results in the formation of arylsulfones, structural moieties common in bioactive compounds.[14] The sulfone unit is useful in various chemical transformations.[15] Inspired by our own research work on C–H amination using different azides,[16] we tested a suitable photo-catalyst to activate both azides and arylsulfinic acids in presence of olefins, eventually producing compounds which are otherwise difficult to construct. We began by reacting phenyl azide **1a** and phenylsulfinic acid **2a** with 1,1-diphenylethylene **3a** under photo-redox catalysis conditions (Table 1). The reaction provided the expected product **4a** in 41% yield (entry 1). Different solvents and photo-catalysts were investigated, and DMF or DMSO as the solvent and Ir(mppy)$_3$ as the catalyst were found optimal (entries 2-9). Fine-tuning the amount of Ir(mppy)$_3$ to 1.5 mol% reduces the efficiency (entry 10). Use of an additional inorganic base such as $NaHCO_3$ does not significantly influence the reaction (entry 11). In the absence of visible light, Ir(mppy)$_3$ or an N_2 atmosphere, the reaction fails to proceed (entries 12-14).

Table 1 Optimization of the Reaction Conditions[a]



1a 2a 3a 4a

entry	PC (mol%)	solvent	yield (%)[b]
1	Ir(mppy)$_3$ (2.5 mol%)	THF	41
2	Ir(mppy)$_3$ (2.5 mol%)	DCE	15
3	Ir(mppy)$_3$ (2.5 mol%)	CH_3CN	47
4	**Ir(mppy)$_3$ (2.5 mol%)**	**DMSO**	**88**
5	**Ir(mppy)$_3$ (2.5 mol%)**	**DMF**	**88**
6	Ir(ppy)$_3$ (2.5 mol%)	DMF	49
7	Ir(dtbby)(ppy)$_2$PF$_6$ (2.5 mol%)	DMF	2
8	Ru(bpy)$_3$(PF$_6$)$_2$ (2.5 mol%)	DMF	17
9	EosinY (2.5 mol%)	DMF	trace
10	Ir(mppy)$_3$ (1.5 mol%)	DMF	72
11[c]	Ir(mppy)$_3$ (2.5 mol%)	DMF	70
12	—	DMF	N.D.
13[d]	Ir(mppy)$_3$ (2.5 mol%)	DMF	N.D.
14[e]	Ir(mppy)$_3$ (2.5 mol%)	DMF	N.D.

[a] Conditions: **1a** (0.12 mmol), **2a** (0.10 mmol), **3a** (0.20 mmol), photocatalyst (Pc) (1.5/2.5 mol%), solvent (1.0 mL), blue light (λmax = 470nm), nitrogen, rt, 24 h. [b] All yields were assessed by crude ^{1}H NMR spectroscopy using dibromomethane as an internal standard. [c] Additional $NaHCO_3$ (2.0 equiv). [d] No light. [e] In the air.

Table 2. β-Arylsulfonyl-α,α-diarylethylamines[a]

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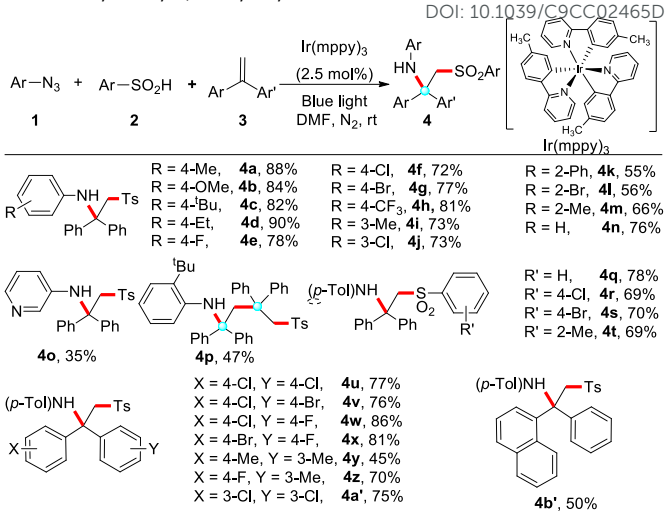
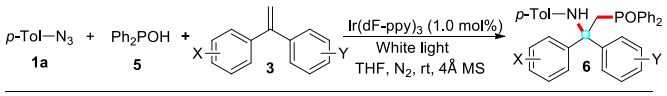


[a] Conditions: **1** (0.12 mmol), **2** (0.10 mmol), **3** (0.20 mmol), Ir(mppy)$_3$ (2.5 mol%), DMF (1.0 mL), blue light (λmax = 470nm), N_2, rt, 24 h. Isolated yield.

With the optimal reaction conditions available, the scope and generality of this reaction were explored (Table 2). Electron-rich or electron-deficient substituents in the *p*-position of the arylazide do not influence the reaction (**4a-h**) and reactions with *m*-substituted arylazides proceed well (**4i-j**). Sterically hindered *o*-substituted arylazides deliver the desired products in good yield (**4k-m**). Unsubstituted phenyl azide works well (**4n**) and a heterocyclic 3-pyridyl counterpart can serve as a reaction partner giving the target product (**4o**). When *o*-tert-butylphenylazide (**1p**) was used, compound **4p** with two tertiary carbons was obtained in moderate yield. This unexpected result could be due to the presence of the bulky *t*-butyl and sulfonyl groups obstructing nearby positions and therefore allowing flexible radical walking into a different 1,1-diphenylethylene. Phenylsulfinic acids bearing electron-rich (4-Me, **4a**), electron-neutral (H, **4q**), electron-deficient (4-Cl, **4r**; 4-Br, **4s**) or sterically hindered (2-Me, **4t**) groups at different positions on the phenyl ring are tolerated well (69-78% yield). Finally, the feasibility of different substituted 1,1-diarylethylenes (**3**) was explored. When the substituent groups are in the *p*-position of the phenyl ring, the reaction achieves good yields with symmetrical (**4u**) or asymmetric olefins (**4v-4x**). Substrates with substituents at different positions in the phenyl ring are also well tolerated (**4y-4a'**). A moderate yield was obtained for 1,1-(1-naphthyl)phenylethylene (**4b'**).

Organophosphorus compounds have broad applications in agro-chemicals, drugs and drug candidates[17] and their derivative α,β-amino-phosphinoyl compounds attributes special biological activities.[18] Therefore, we began to explore

Table 3. β-Diarylphosphonyl-α,α-diarylethylamines[a]

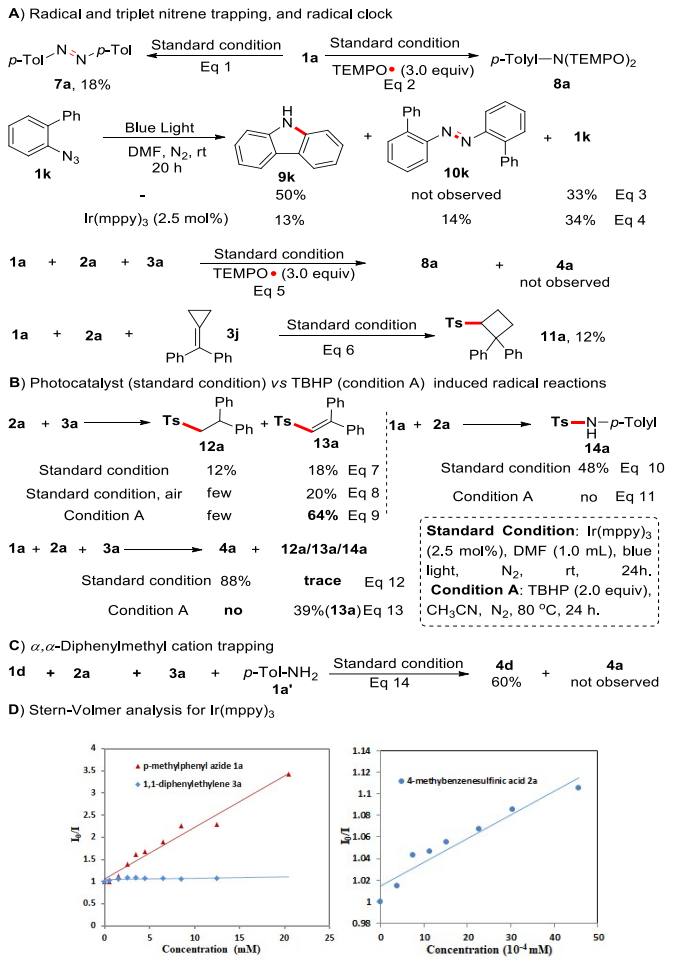


X = H, Y = H, **6a**, 72%
X = 4-F, Y = 4-F, **6b**, 64%
X = 4-Cl, Y = 4-Cl, **6c**, 62%
X = 4-Br, Y = 4-Cl, **6d**, 67%
X = 4-F, Y = 4-Cl, **6e**, 65%
X = 4-F, Y = 4-Br, **6f**, 71%
X = 4-Me, Y = 3-Me, **6g**, 63%
X = 4-F, Y = 3-Cl, **6h**, 53%
X = 4-Me, Y = 2-Me, **6i**, 67%
X = 4-Cl, Y = 2-Cl, **6j**, 60%
X = 2-Me, Y = 2-Me, **6k**, 50%

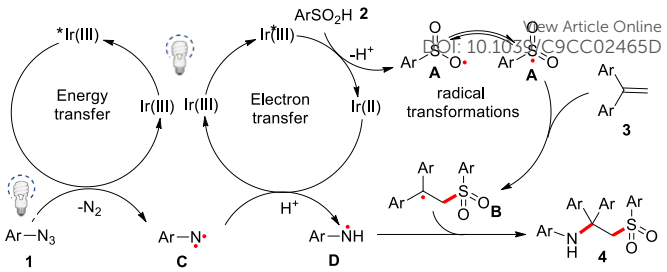
[a] Conditions: **1** (0.25 mmol), **3** (0.20 mmol), **5** (0.10 mmol), Ir(dF-ppy)$_3$ (1.0 mol%), DMF (1.0 mL), 4 Å MS (50 mg/0.1 mmol), white light, N_2, rt, 24 h. Isolated yield.

diarylphosphine oxide (**5**) in place of arylsulfinic acids (**2**) in this reaction. After screening different reaction conditions (see details in Table S1 in SI), the optimized reaction conditions were identified using Ir(dF-ppy)$_3$ as a photocatalyst with white light irradiation. The scope with respect to the olefin (**3**) was evaluated (Table 3). Symmetrical, asymmetric, electronic rich and electronic deficient substrates all worked well, providing the desired *β*-diarylphosphonyl-*α*,*α*-diarylethylamines (**6a**-**6k**) in good yields.

To investigate the mechanism of this reaction, we conducted several control experiments (Scheme 2). The photocatalyst can significantly promote decomposition of **1a**, in which the diazo product (**7a**) was obtained (Eq 1) and product **8a** containing two TEMPO units was achieved in the present of TEMPO (Eq 2). Direct photosis of *o*-phenyl phenylazide (**1k**) is known to promote the formation of a singlet nitrene species *via* an energy transfer process, providing carbazole (**9k**) with 50% yield (Eq 3).[19] While the same reaction was carried in presence of photocatalyst, the diazo compound (**10k**) was obtained and the yield of **9k** was reduced to 13% (Eq 4). When TEMPO was added to the standard reaction, **8a** was observed predominantly over **4a** (Eq 5). These results suggest that activation of azide is



Scheme 2. Mechanistic Studies



Scheme 3. Plausible Reaction Pathway

governed by the photo-catalyst through an EnT process and the triplet nitrene is formed.[19] When methylenecyclopropane (**3j**) was used, a ring opening product (**11a**) was formed (Eq 6), implying $PhSO_2$• radical is generated. When the reaction of **2a** and **3a** was performed (Eqs 7 and 8), the addition products **12a** and **13a** were observed. Compound **13a** is thought to be generated from the *β*-H elimination of the *α*,*α*-diarylalkyl cation, and this implies that the *α*,*α*-diarylalkyl radical intermediate can be oxidized easily. Since the $PhSO_2$• radical can be generated by a radical initiator,[20] TBHP was used to test this feasibility (condition A). In the reaction with TBHP, a small amount of **12a** was formed and **13a** was obtained in 64% yield (Eq 9). While the reaction of **1a** and **2a** produces the coupled product sulfonamide (**14a**) in moderate yield, no **14a** is formed during TBHP-induced radical reaction (Eqs 10 and 11). The multi-component reaction of **1a**, **2a** and **3a** is able to selectively produce **4a**, but no obvious products (**12a**-**14a**) from the coupling of two components are observed (Eq 12). In contrast, the TBHP-induced radical reaction fails to produce **4a** (Eq 13). These results show that the activation of the azide by photocatalyst is necessary for the success of the reaction. With addition of *p*-Tol-NH_2, the reaction still proceeds smoothly without the formation of **4a**, suggesting that *α*,*α*-diphenylalkyl cation intermediate is not involved (Eq 14). Several fluorescence quenching experiments were performed (Scheme 2D and Figure S2 in SI). It was observed that the fluorescence intensity of Ir(mppy)$_3$ decreases with increasing concentration of **1a** or **2a**. A linear relationship between I_0/I and the concentrations of **1a** or **2a** was observed showing that the Ir(mppy)$_3$* is quenched by **1a** or **2a**. The fluorescence intensity of Ir(mppy)$_3$ remains unchanged with increasing concentrations of **3a**.

On the basis of these observations and information in the literatures,[10,11,21] a plausible reaction mechanism is proposed in Scheme 3. Visible-light induces $[Ir(mppy)_3]^{3+}$ to produce $[Ir(mppy)_3]^{3+*}$ through energy transfer. Subsequently, **2** and $[Ir(mppy)_3]^{3+*}$ participate in a SET process to obtain the valence-lower $[Ir(mppy)_3]^{2+}$ and arylsulfonyl radical (**A**) accompanied by proton dissociation. **A** is then captured by **3** to form the *α*,*α*-diarylalkyl radical (**B**) as a persistent radical. At the same time, $[Ir(mppy)_3]^{3+*}$ transfers energy to **1** resulting in loss of N_2 and the formation of triplet nitrene (**C**). After undergoing a SET process and protonation, **C** is converted to a nitrogen radical (**D**) as a transient radical which is then coupled with the persistent radical **B** to give the product (**4**).

Conclusions

In summary, we have achieved a synthetic strategy involving a synergistic combination of SET and EnT processes using a single photocatalyst. This enables the multicomponent synthesis of *α,α*-diarylalkylamine scaffolds. Using $Ir(mppy)_3$ as photo-redox catalyst and photosensitizer, the readily available arylsulfinic acid or diphenylphosphine oxide, 1,1-diarylethylenes and arylazides were easily converted to *β*-arylsulfonyl(diarylphosphinoyl)-*α,α*-diarylethylamines. The sulfonyl and phosphinoyl groups present in the *β*-position of desired amines can be potentially useful and transferable, and this may enhance the utility of this reaction. Mechanistic studies showed that arylsulfinic acid undergoes a SET process and deprotonation to form $ArSO_2$• which adds to 1,1-diarylethylene to form an *α,α*-diarylalkyl radical as a persistent radical. Simultaneously, the azide goes through an EnT process, a SET process and protonation with visible-light photocatalysis to produce a transient nitrogen radical. The cross-coupling of the *α,α*-diarylalkyl radical and this nitrogen radical is crucial to the construction of sterically hindered $C(sp^3)$-N bonds which are difficult to prepare with ionic chemistry. Further investigation of the reaction mechanism and applications of this newly discovered reaction are currently in progress.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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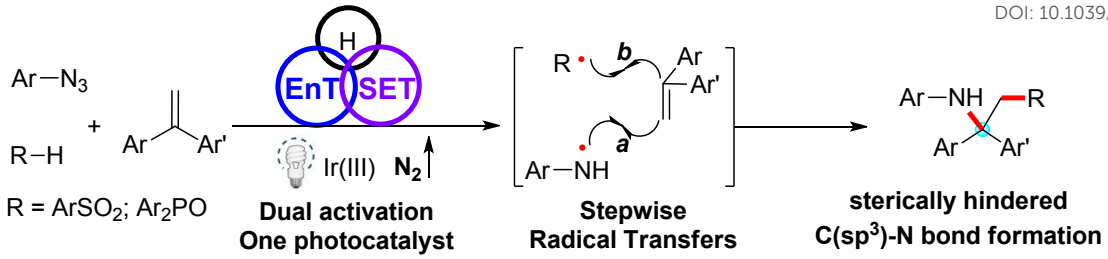

- Readily available
- Mild and no-oxidative
- Multicomponent synthsis
- Functional group tolerance
- Biologically active skeleton
- High chemo- and regio-selectivity

A synthetic strategy which takes advantage of the synergistic combination of electron and energy transfer processes using only one photocatalyst has been developed for the multicomponent synthesis of the *α*,*α*-diarylalkylamine skeleton, providing a simplified and feasible synthetic method for the direct construction of sterically hindered C(sp^3)-N bonds.