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Visible Light Photoredox-Catalyzed Multicomponent Reactions

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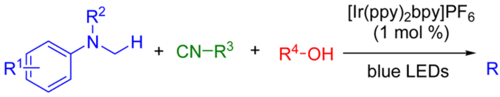
ABSTRACT



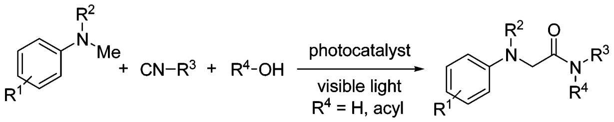
Oxidative three-component reactions for the direct synthesis of α-amino amides and imides from tertiary amines have been developed. These reactions involve the functionalization of C(sp^3)−H bonds adjacent to nitrogen atoms *via* mild aerobic oxidation using visible light photoredox catalysis. The protocols are applicable to a wide range of amines and isocyanides, as well as water and carboxylic acids, providing straightforward access to a variety of highly functionalized α-amino amides and imides.

The Ugi multicomponent reaction[1] has been intensively studied over the past decades and has found wide application in the synthesis of α-amino amides which are important in organic synthesis. One of the main benefits of this procedure is the possibility to prepare large compound libraries through one-pot multicomponent reactions. α-Amino amides are found in a wide range of natural products and pharmaceuticals[2] and have been used as intermediates for the synthesis of different heterocycles.[3] In terms of step and atom economy and with regard to green and mild methodologies to access α-amino amides, the development of Ugi-type reactions represents an important field. While the typical Ugi reaction involves the reaction of an imine, generated in situ from an aldehyde and a primary amine, with an isocyanide and a carboxylic acid, it was Zhu[4a] and Che[4b] who developed an elegant oxidative multicomponent reaction using secondary amines in which the imine is formed via a dehydrogenative pathway.

Furthermore, Ye[5] and co-workers reported the oxidative Ugi-type reaction with tertiary amines by applying copper catalysis in combination with TBHP as oxidant to activate C(sp^3)−H bonds adjacent to nitrogen.

Recently, visible-light-mediated photoredox catalysis[6] has become very attractive in organic synthesis and catalysis. Typically, readily available and easy to handle catalysts are applied in combination with visible light to conduct a variety of organic transformations.[7]

Scheme 1. Photoredox-Catalyzed Oxidative Ugi-Type Multicomponent Reactions



In this regard, the oxidative C−H functionalization of C(sp^3)−H bonds adjacent to nitrogen atoms using photocatalysis has attracted attention.[8−10] Given our interest in visible-light-mediated processes, we envisioned the possibility of synthesizing α-amino amides starting from tertiary amines and employing a visible light photoredox catalysis protocol (Scheme 1).

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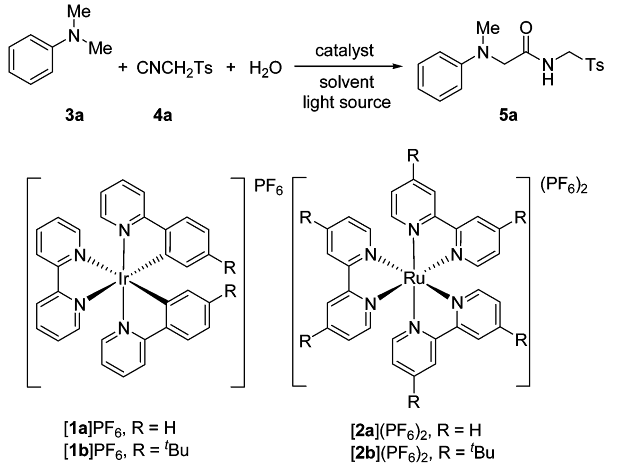
Herein, we present an oxidative photoredox-catalyzed three-component reaction employing tertiary amines, isocyanides, and carboxylic acids or water.

Initially, the reaction between *N*,*N*-dimethylaniline (**3a**), *p*-toluenesulfonylmethyl isocyanide (**4a**), and H_2O was chosen as a model reaction for the optimization of the multicomponent reaction (Table 1). To our delight, by using an iridium [**1a**](PF_6) photoredox catalyst in CH_3CN, we were able to isolate the desired α-amino amide **5a** in 53% yield (Table 1, entry 1). Next, we studied the reactivity in different solvents (Table 1, entries 1−5), and we observed that protic (MeOH) and apolar (toluene) solvents gave poor yields and required longer reaction times. In order to improve the yield of the product, we tested different photoredox catalysts (Table 1, entries 1, 6−8).

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (mol %)	solvent	light source	yield (%)[b]
1	[**1a**]PF_6 (1)	CH_3CN	11 W lamp	53
2	[**1a**]PF_6 (1)	CH_2Cl_2	11 W lamp	42
3[c]	[**1a**]PF_6 (1)	toluene	11 W lamp	27
4[c]	[**1a**]PF_6 (1)	THF	11 W lamp	46
5[c]	[**1a**]PF_6 (1)	MeOH	11 W lamp	24
6	[**1b**]PF_6 (1)	CH_3CN	11 W lamp	52
7[c]	[**2a**]$(PF_6)_2$ (1)	CH_3CN	11 W lamp	44
8[c]	[**2b**]$(PF_6)_2$ (1)	CH_3CN	11 W lamp	45
9[d]	[**1a**]PF_6 (1)	CH_3CN	11 W lamp	52
10[e]	[**1a**]PF_6 (1)	CH_3CN	11 W lamp	58
11	[**1a**]PF_6 (1)	CH_3CN	green LEDs	41
12	[**1a**]PF_6 (2)	CH_3CN	11 W lamp	66
13	[**1a**]PF_6 (1)	CH_3CN	blue LEDs	75
14	[**1a**]PF_6 (2)	CH_3CN	blue LEDs	62
15[f]	[**1a**]PF_6 (1)	CH_3CN	blue LEDs	55
16[g]		CH_3CN	blue LEDs	

[a] Reactions were performed with *N*,*N*-dimethylaniline **3a** (0.15 mmol), **4a** (0.15 mmol), H_2O (10 equiv), and catalyst in 1 mL of solvent for 2 days at room temperature. [b] Yield after column chromatography. [c] The reaction time was 3 days. [d] 1.5 equiv of **3a** was used. [e] 1.5 equiv of **4a** was used. [f] 2.0 equiv of **3a** was used. [g] Traces of product were observed after 4 days.

In general, the iridium catalysts showed better reactivity compared to ruthenium catalysts. Subsequently, we examined different light sources and catalyst loadings as well as substrate ratios. The best result was obtained with catalyst

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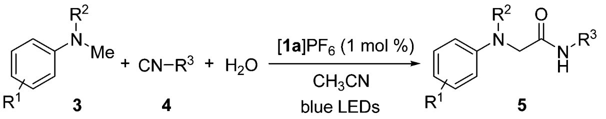
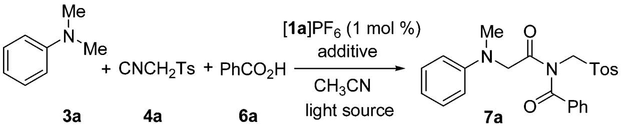
Table 2. Substrate Scope for the Multicomponent Reaction[a]



entry	3	R^1	R^2	4	R^3	5	yield (%)[b]
1	**3a**	H	Me	**4a**	CH_2Ts	**5a**	75
2[c]	**3b**	4-Me	Me	**4a**	CH_2Ts	**5b**	65
3	**3c**	3-Me	Me	**4a**	CH_2Ts	**5c**	70
4[c]	**3d**	3,5-Me_2	Me	**4a**	CH_2Ts	**5d**	65
5	**3e**	4-Cl	Me	**4a**	CH_2Ts	**5e**	60
6	**3f**	4-Br	Me	**4a**	CH_2Ts	**5f**	65
7	**3g**	3-Br	Me	**4a**	CH_2Ts	**5g**	52
8	**3h**	H	Et	**4a**	CH_2Ts	**5h**	48
9	**3a**	H	Me	**4b**	Bu	**5i**	47
10	**3a**	H	Me	**4c**	cyclohexyl	**5j**	45
11	**3a**	H	Me	**4d**	CH_2CO_2Me	**5k**	45
12[c]	**3a**	H	Me	**4e**	CH_2Ph	**5l**	72

[a] Reactions were performed with amine **3** (0.15 mmol), isocyanide **4** (0.225 mmol), H_2O (10 equiv), and [**1a**]PF_6 (1 mol %) in 1 mL of CH_3CN for 2 days at room temperature. [b] Yield after column chromatography. [c] 2.0 equiv of **3** was used.

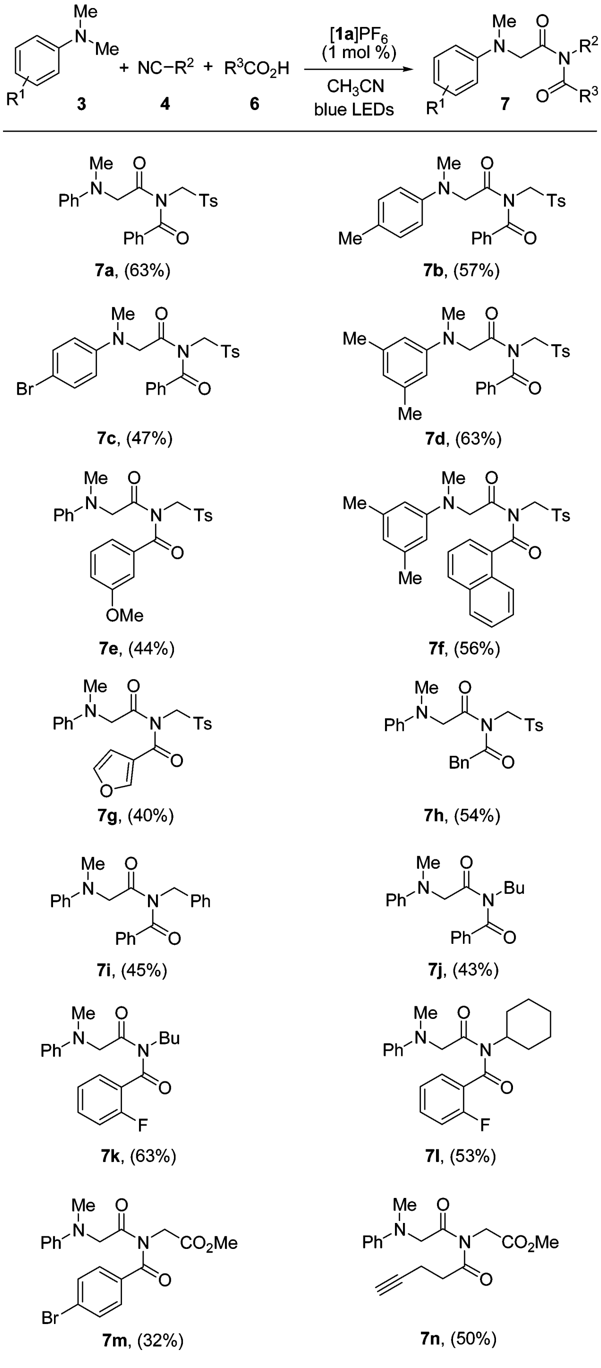
Table 3. Optimization of the Reaction Conditions[a]



entry	additive	light source	yield (%)[b]
1		11 W lamp	41
2		blue LEDs	32
3	100 mg Na_2SO_4	11 W lamp	34
4	100 mg 4 Å	11 W lamp	40
5	100 mg 3 Å	11 W lamp	48
6[c]	150 mg 3 Å	11 W lamp	55
7[c]	150 mg 3 Å	blue LEDs	60
8[c,d]	150 mg 3 Å	blue LEDs	63

[a] Reactions were performed with *N*,*N*-dimethylaniline **3a** (0.15 mmol), **4a** (0.15 mmol), **6a** (0.15 mmol), and [**1a**]PF_6 (1 mol %) in 1 mL of CH_3CN for 2 days at room temperature. [b] Yield after column chromatography. [c] 2.0 equiv of **3a**, 1.0 equiv of **4a**, and 1.5 equiv of **6a** were used. [d] Dry CH_3CN was used as solvent.

Scheme 2. Substrate Scope for Multicomponent Reaction[a]



[a] Reactions were performed with amine **3** (0.3 mmol), isocyanide **4** (0.15 mmol), acid **6** (0.225 mmol), 150 mg 3 Å, and [**1a**]PF_6 (1 mol %) in 1 mL of CH_3CN at room temperature.

1a in acetonitrile and blue LEDs (Table 1, entry 13), and the product was isolated in 75% yield. In the absence of light, only traces of product were obtained after prolonged reaction time.

With the optimized conditions in hand, we explored the scope of the reaction with different amines **3**, isocyanides **4**, and water (Table 2).

In general, this new visible-light-mediated catalysis protocol proceeded well, and the corresponding α-amino amides **5** were obtained in good yields. Different *N*,*N*-dimethylanilines bearing electron-donating or electron-withdrawing substituents at the *para* or *meta* position (Table 2, entries 2−7) proved to be good substrates for the reaction, giving the products in good yields.

The methyl group of the *N*-ethyl-*N*-methylaniline **3h** was chemoselectively oxidized, and the corresponding amide **5h** was obtained (Table 2, entry 8). Moreover, different isocyanides reacted with *N*,*N*-dimethylaniline affording the corresponding products with moderate to high yields (Table 2, entries 8−12).

After examining the scope of the three-component reaction with water, we turned our attention to the reaction with carboxylic acids as this would not only lead to the corresponding imides but also demonstrate the generality of the newly developed photoredox catalysis procedure.

Hence, we studied the reaction of *N*,*N*-dimethylaniline, *p*-toluenesulfonylmethyl isocyanide, and benzoic acid using [**1a**]PF_6 as photoredox catalyst under irradiation with 11 W lamp or blue LEDs (Table 3, entries 1 and 2). To our delight, the reaction occurred, affording the α-amino imide **7a** with moderate yield. Evaluation of different additives, such as molecular sieves (Table 3, entries 3−8), had a beneficial effect on the product formation and yield.

After having established the optimal reaction conditions for the three-component reaction with carboxylic acids, we examined the scope of the reaction this time using different amines **3**, isocyanides **4**, and carboxylic acids **6**. Again, a series of highly diverse functionalized α-amino imides **7** were obtained (Scheme 2). Differently substituted *N*,*N*-dimethylanilines **3** as well as aromatic carboxylic acids **6**, including 4-bromo, 3-methoxy, 2-fluorobenzoic acid, 1-naphthoic acid, or 3-furancarboxylic acid, were successfully applied in the oxidative multicomponent reaction. Furthermore, aliphatic carboxylic acids, such as 2-phenylacetic acid or 4-pentynoic acid, reacted smoothly, and the imides were isolated in 50 and 54% yield, respectively. Finally, the reaction was carried out with different isocyanides, resulting in a varied substitution pattern at the imide nitrogen.

A catalytic cycle for the present transformation is proposed in Figure 1. Upon irradiation, Ir^{III+} is excited to Ir^{III+*} and reductively quenched by **3** to produce Ir^{II+} and radical cation **3′** via SET oxidation. In the presence of oxygen, the radical amine cation **B** is converted into iminium intermediate **A**. The subsequent nucleophilic attack of isocyanide **4** results in intermediate **B** (nitrilium ion). This nitrilium ion is trapped by water or carboxylic acid **6**, generating intermediate **C** which rearranges to give the corresponding amide **5** or imide **7**, respectively.

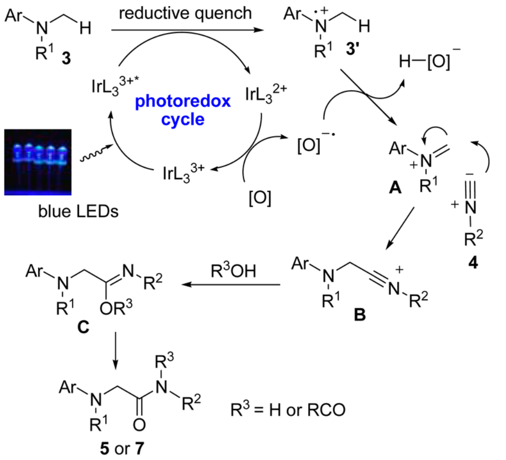


Figure 1. Proposed mechanism for the photoredox-catalyzed multicomponent reaction.

In summary, we have developed an oxidative three-component reaction for the synthesis of valuable α-amino amides and imides from tertiary amines, isocyanides, and water or carboxylic acids using visible light photoredox catalysis. The reaction proceeds smoothly using only 1 mol % of iridium photoredox catalyst and visible light without the need for an additional external oxidant. In general, the catalysis procedure tolerates various functional groups and can be conducted in open reaction vessels in the presence of air and moisture, providing a series of differently substituted products. Further investigations of the aerobic visible light photoredox catalysis to enable multicomponent reactions are currently in progress and will be reported in due course.

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Supporting Information Available. Experimental procedures and full characterization (^1H and ^{13}C NMR data and spectra, MS and IR analyses) for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.