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Photoredox Catalysis

Visible-Light Photoredox-Catalyzed Giese Reaction: Decarboxylative Addition of Amino Acid Derived α-Amino Radicals to Electron-Deficient Olefins

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Abstract: A tin- and halide-free, visible-light photoredox-catalyzed Giese reaction was developed. Primary and secondary α-amino radicals were generated readily from amino acids in the presence of catalytic amounts of an iridium photocatalyst. The reactivity of the α-amino radicals has been evaluated for the functionalization of a variety of activated olefins.

Since its discovery in the 1980s, the reductive addition of radicals to electron-deficient olefins, also known as the Giese reaction, has found tremendous applications in the synthesis of key structures and total synthesis.[1] Although the original conditions require the use of stoichiometric amounts of trialkyl tin reagents, the overwhelming interest in this reaction led to the rapid development of more practical and safer additives. First, the use of catalytic amounts of tin reagents combined with borohydride, silane, or thiol additives was reported, and later the potential of silanes and organoboranes alone to promote and propagate radical reactions was demonstrated.[2] Reactions making use of indium, samarium, chromium, nickel, and zinc salts as additives were also developed.[3] However, a drawback is the need for iodine- or bromine-containing starting materials, which are converted into radicals by direct reduction or by halide abstraction. After addition, the resulting radical is either reduced and protonated, or abstracts directly a hydrogen atom to give the hydrofunctionalized product. Thus, this reaction manifold is not redox-neutral and generates stoichiometric amounts of halogen-containing wastes. As a sustainable alternative to the reduction of halogen-containing derivatives, the oxidation of aliphatic carboxylic acids has attracted growing attention in the past years.[4] In this context, a catalytic variant of the Giese reaction is possible, as the process is redox-neutral: after oxidation of the carboxylic acid, decarboxylation occurs to provide the carbon-centered radical. This radical adds onto the olefin and the resulting intermediate can be reduced and protonated, thus regenerating the catalyst. UV-light irradiation in the presence of sensitizers was reported to efficiently promote such Giese-type reactions,[5,6] however it was only very recently that this general type of reaction was successfully performed using visible light in combination with organic dyes or metal-based photocatalysts.[7]

With these considerations in mind, we became interested in developing a method for the generation of α-amino radicals for secondary amines in an easy and efficient manner and apply them as nucleophiles in Giese-type transformations. If successful, these reactions would allow access to a wide range of valuable compounds including natural product derivatives. For this purpose, we turned our attention to glycine derivatives as precursors for α-amino radicals, as these have relatively low oxidation potentials (*N*-phenylglycine: $E_{Ox} = 0.42$ V vs.SCE).[8] In this context, we predicted that the classical and easy to access Ir^{III} photocatalyst $Ir(ppy)_2(dtbbpy)PF_6$ (**1a**) should be able to furnish our desired radical intermediate, as, despite its simplicity, it is a relatively good oxidant ($E_{1/2}^{Red}$ $Ir^{III}*/Ir^{II} = 0.66$ V vs. SCE in acetonitrile).[9]

Following our interest in oxidative and radical photoredox catalysis,[10,11] we report here the successful validation of this challenging task using a visible-light photocatalyst for the reductive radical addition of primary and secondary α-amino radicals to various olefins. To evaluate this transformation, we first turned our attention to the reaction of *N*-phenylglycine (**2a**) with 2-cyclohexen-1-one (**3a**) as a model substrate using $Ir(ppy)_2(dtbbpy)PF_6$ (**1a**) as photocatalyst.

Upon evaluating different reaction conditions, we found that when equimolar amounts of **2a** and **3a** were irradiated with blue LEDs in methanol (0.3 M) in the presence of a catalytic amount of lithium carbonate (20 mol%) and 1 mol% of photocatalyst, the desired product **4a** was obtained in 84% yield (Table 1, entry 1). The reaction occurred in an efficient manner and with a complete selectivity for the 3-position of **3a**. Examination of different reaction parameters showed no impact on the reactivity in the case of dilution (0.1 M, entry 2), but the yield dropped to only 56% at a concentration of 1 M (entry 3). The catalyst loading was also evaluated, however when using 0.5 mol% of **1a**, the reaction did not reach completion and the product was obtained with a yield of 55% only (entry 4). Appling white light resulted in a yield of 64% for the desired product (entry 5). We also noticed the crucial role of Li_2CO_3, as

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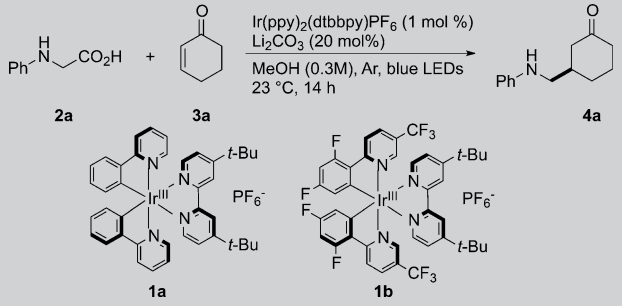
Table 1. Evaluation of the reaction parameters.[a]



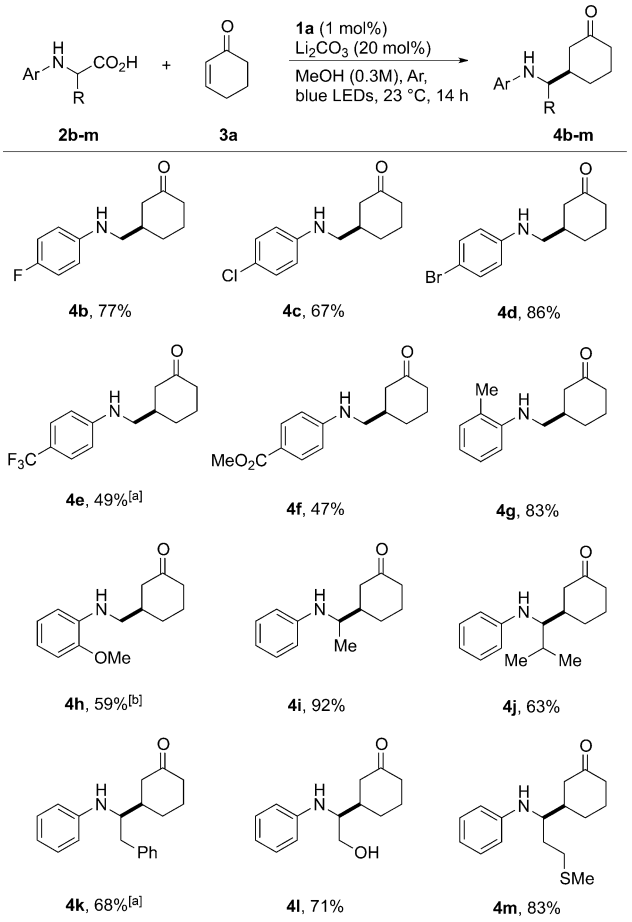
Entry	Modification from standard conditions	Yield [%][b]
1	none	84
2	0.1 M	83
3	1 M	56
4	0.5 mol% of photocatalyst	55
5	11 W White light bulb	64
6	without Li_2CO_3	26
7	in the dark	0
8	without photocatalyst	0
9	under air atmosphere	0

[a] Reactions performed using *N*-phenylglycine **2a** (0.3 mmol, 1 equiv), 2-cyclohexen-1-one **3a** (0.3 mmol, 1 equiv), Li_2CO_3 (20 mol%), Ir(ppy)$_2$(dtbbpy)PF_6 **1a** (1 mol%) in degassed MeOH (1 mL) under argon and blue LEDs (11 W rubber strip) for 14 h. [b] Yield after purification.

only 26% yield was obtained in its absence (entry 6). Finally, we confirmed that no reactivity was observed in the dark, in the absence of photocatalyst, or under an air atmosphere (entries 7–9). Additionally, using *N*-methylaniline as substrate gave no conversion, confirming the importance of the decarboxylation event for the generation of the α-amino radical.

With the optimal conditions in hand, we started to explore the scope and limitations of the reaction with regard to amino acid partners (Scheme 1). Pleasingly, a very good reactivity was observed for *para*-halogenated anilines (**2b–d**) and no dehalogenation was thereby noticed (**4b–d**). Highly electron-withdrawing groups were also tolerated but led to a moderate reactivity (**4e**, **4f**). Interestingly, poor reactivity was observed with electron-donating groups in the *para* position, but the products could be obtained in good yields when these groups were placed in the *ortho* positions (**4g**, **4h**). In addition, we applied this reaction to natural amino acids with success (see the Supporting Information). *N*-phenylalanine led to the desired product in very high yields (**4i**), whereas more bulky amino acids gave moderate to good yields (**4j**, **4k**). We also observed a good functional group tolerance with the presence of a free OH group for the serine-derived substrate (**4l**), or the methylthiolated residual chain of the methionine-derived substrate (**4m**).

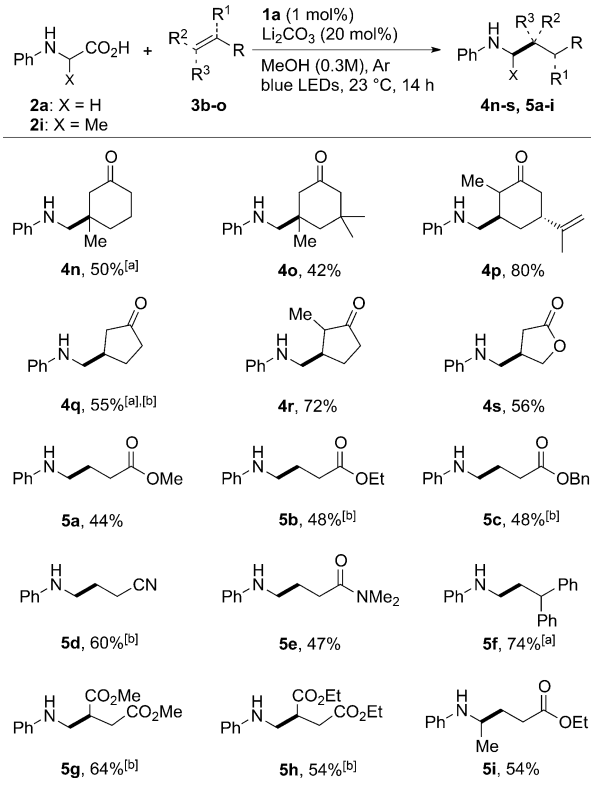
Next, our attention focused on establishing the reactivity pattern with respect to the olefin partner (Scheme 2). First, we were interested in evaluating the reactivity for the formation of a quaternary center and we successfully obtained the desired product **4n** of the addition of α-amino radical onto 3-methyl-2-cyclohexenone, although with a moderate yield of 50%. In addition, we looked at the possibility of derivatization



Scheme 1. Evaluation of *N*-aryl amino acids. Reaction conditions: *N*-aryl amino acids **2b–m** (0.3 mmol, 1 equiv), 2-cyclohexen-1-one **3a** (0.3 mmol, 1 equiv), Li_2CO_3 (20 mol%), Ir(ppy)$_2$(dtbbpy)PF_6 **1a** (1 mol%) in degassed MeOH (1 mL) under argon and blue LEDs (11 W rubber strip) for 14 h, yields after purification. [a] The reaction was performed with 2 equiv of amino acid for 18 h. [b] Reaction was performed for 18 h.

of natural products, which was relatively efficient for isophorone (**4o**) and very good for (*R*)-(−)-carvone (**4p**), although the product was obtained as a mixture of diastereomers. We also looked at other cyclic acceptors with five-membered rings. We observed a limited reactivity of 2-cyclopenten-1-one, whereas the presence of a methyl group in the 2-position restored good yields (**4r**), as it supposedly disfavored the unselective polymerization and cycloaddition pathways.

Furanone also underwent the transformation in moderate yield (**4s**). Regarding the use of acyclic substrates, although these initially reacted poorly, addition of two equivalents of water provided good yields in most of the cases. Using this strategy, we observed moderate to good reactivity of *N*-phenylglycine **2a** with mono-substituted olefins such as acrylates (**3h–j**), acrylonitrile (**3k**) or *N*,*N*-dimethylacrylamide (**3l**). The reaction with 1,1-diphenylethylene led to a good reactivity after 24 h (74% yield, **5f**), whereas only 58% yield was obtained under the standard conditions. Substrates derived from maleic and fumaric acids participated successfully in the reaction when two equivalents of water were added. Finally, we showed that other amino acid-derived substrates exhibit simi-

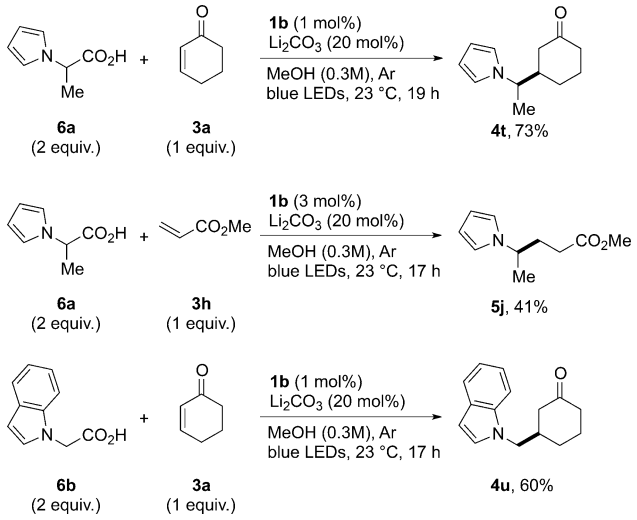


Scheme 2. Evaluation of radical acceptors. Reaction conditions: *N*-phenylglycine **2a** (0.3 mmol, 1 equiv), olefins **3b**–**l** (0.3 mmol, 1 equiv), Li_2CO_3 (20 mol%), $Ir(ppy)_2(dtbbpy)PF_6$ **1a** (1 mol%) in degassed MeOH (1 mL) under argon and blue LEDs (11 W rubber strip) for 14 h, yields after purification. [a] 24 h reaction. [b] With 2 equiv H_2O.

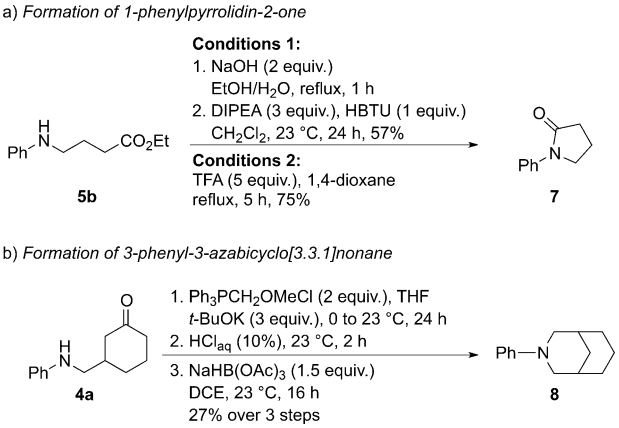
lar reactivity to the one observed with *N*-phenylglycine **2a**, as the addition of *N*-phenylalanine **2i** to ethyl acrylate proceeded in comparable yield (**5i**).

Encouraged by these results, we next turned our attention towards the generation of α-amino radicals of unsaturated heterocycles to further expand the scope of our transformation (Scheme 3). However, the alanine-derived pyrrole **6a** did not give the desired radical intermediate using our previous conditions. We rationalized that $Ir(ppy)_2(dtbbpy)PF_6$ (**1a**) might not be oxidizing enough for this substrate, and we thus decided to use the more oxidizing catalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (**1b**; see Table 1) ($E_{1/2}^{Red}$ $Ir^{III}*/Ir^{II} = +1.21$ V vs: SCE in acetonitrile).[11] To our delight, we could achieve the generation of the radical followed by addition to 2-cyclohexen-1-one in good yield (**4t**), or to methyl acrylate in moderate yield (**5j**), forming a product which is an intermediate for the synthesis of monomorine, a Pharaoh's ant pheromone.[12] Thus, our methodology might be applied to the synthesis of various analogues of this natural product using inexpensive natural amino acids as starting materials instead of harder to access γ-lactones. We also could extend this reaction to indole **6b**, which underwent the reaction with 2-cyclohexen-1-one (**3a**) in relatively good yield (**4u**).

Finally, we were interested in taking advantage of our structures for the synthesis of valuable structural motifs. First, we investigated the synthesis of γ-lactam **7** from **5b** (Scheme 4a).



Scheme 3. Evaluation of the reactivity of α-amino radicals derived from *N*-heterocyclic amino acids.



Scheme 4. Synthesis of valuable structural motifs.

We could access the desired product **7** using two different sets of conditions. The first one involved a saponification reaction with sodium hydroxide (2 equiv), followed by a peptide-type coupling using HBTU (*N*,*N*,*N*′,*N*′-tetramethyl-O-(1*H*-benzotriazol-1-yl)uranium hexafluorophosphate, 1 equiv) in the presence of diisopropylethylamine (DIPEA, 3 equiv) in dichloromethane for an overall yield of 57%. Using a complementary approach, we could also directly access the lactam **7** in 75% yield by refluxing the starting material in 1,4-dioxane in the presence of trifluoroacetic acid (5 equiv). We also realized the three-step synthesis of 3-phenyl-3-azabicyclo[3.3.1]nonane (**8**) from **4a** (Scheme 4b). A two-step Wittig homologation of the ketone to the aldehyde was performed by stirring the starting material in THF in the presence of (methoxymethyl)triphenylphosphonium chloride (2 equiv) and potassium *tert*-butoxide (3 equiv), followed by hydrolysis of the enol ether with 10% hydrochloric acid. The crude aldehyde was then directly submitted to the reductive amination step using sodium triacetoxyborohydride (1.5 equiv) to give the desired bicyclic product **8** in 27% yield over three steps after purification. Although this

bicyclic structure is of high importance in drug discovery, as confirmed by its presence in twenty patents,[13] this work describes the first synthesis of an aryl-substituted derivative.

In conclusion, we have successfully developed a tin-free and halide-free Giese reaction by efficiently generating primary and secondary α-amino radicals starting from readily accessible amino acids.[7] The α-amino radicals could be efficiently coupled with various α,β-unsaturated carbonyl compounds to give various cyclic and acyclic γ-amino ketones with different substitution patterns. Furthermore, we were able to demonstrate the possibility to apply this method to *N*-heterocyclic amino acids which allows the access to various biologically active molecules.

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Keywords: amino acid · decarboxylation · heterocycles · photoredox catalysis

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COMMUNICATION

Photoredox Catalysis

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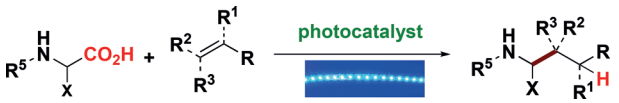
Visible-Light Photoredox-Catalyzed Giese Reaction: Decarboxylative Addition of Amino Acid Derived α-Amino Radicals to Electron-Deficient Olefins



Easy CO_2upling! A tin- and halide-free, visible-light photoredox-catalyzed Giese reaction was developed. Primary and secondary α-amino radicals were generated from amino acids in the presence of catalytic amounts of an iridium photocatalyst and catalytic amounts of base. These radicals added readily onto activated olefins, giving CO_2 as sole by-product.