Photoredox Catalysis

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Photoredox-Catalyzed Reductive Coupling of Aldehydes, Ketones, and Imines with Visible Light

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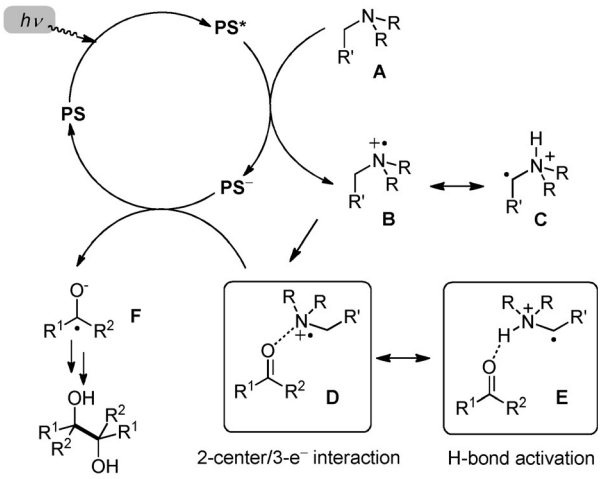
Abstract: *Ketyl radical and amino radical anions, valuable reactive intermediates for C–C bond-forming reactions, are accessible through a C=O/C=NR umpolung. However, their utilization in catalysis remains largely underdeveloped owing to the high reduction potential of carbonyl compounds and imines. In the context of photoredox catalysis, tertiary amines are commonly employed as sacrificial co-reducing agents. Herein, an additional role of the amine is proposed, in which it is essential for the organocatalytic substrate activation. The combination of photoredox catalysis and carbonyl/imine activation enables the reductive coupling of aldehydes, ketones, and imines under mild reaction conditions.*

The development of atom- and step-economical C–C bond-forming reactions is a subject of considerable importance in the field of organic chemistry. In this regard, the discovery of less-conventional intermediates is highly desirable and potentially opens the door for new unexplored reactivities. In the recent past, the arena of photoredox catalysis has gained renewed attention through numerous discoveries of non-classical transformations.[1,2] The reactions are generally classified according to the four different types of operative reactive intermediates: neutral radicals, radical anions, and radical cations, as well as ions resulting from the previous species through further single-electron transfer (SET).[1j] Despite the impressive progress in this field, we realized that the photoredox chemistry of ketyl radicals remains still underdeveloped. While Yoon[3] and Fensterbank[4] have pioneered the concept of the conjugated ketyl system for the reductive cyclization of enones and reductive epoxide/aziridine opening, respectively, methods based on the direct utilization of ketyls are restricted to a handful of reports.[5] In 1983 Pac et al. reported the first photoredox-catalyzed reduction of benzaldehydes to the corresponding alcohols.[5a] The reductive dimerization of benzaldehyde was subsequently described by Yanagida[6] and co-workers employing poly(*p*-phenylene) as an effective photocatalyst. However, these methods are generally limited to few specific aldehydes and, moreover, not applicable to ketones.[7] This deficit is attributed to the large discrepancy in reduction potential between ketones (acetophenone: $E_{1/2}^{red} = -2.48$ V vs. Fc)[8] and established photoredox catalysts, rendering the umpolung to the corresponding ketyl radical anion strongly endergonic. To overcome this barrier, nature, in part, takes advantage of two-center/three-electron bonding.[9,10] In contrast to a stepwise mechanism, wherein an electron and proton are transferred sequentially, the formation of energetic intermediates is avoided, resulting in a lower activation barrier. Owing to the low oxidation potential, tertiary amines **A** are commonly employed as cost-efficient reductive quenchers in photoredox chemistry, being further converted to the amino radical cation **B** (Scheme 1).[11] Based on



Scheme 1. Postulated catalytic cycle for the photoredox-catalyzed pinacol coupling of aldehydes and ketones.

literature reports, we assumed that an attractive interaction between the Lewis acidic species **B** and the weakly basic C=O bond[10] in terms of a two-center/three-electron bond (**D**) would render the activation process less endergonic. Alternatively, the α-ammonium radical **C**, resulting from **B** via a [1,2]-H shift, could engage in the C=O activation as a hydrogen-bond donor.[12] If such a scenario is feasible, a dual role of amines in photoredox catalysis could be established, namely, in substrate activation in addition to serving as a simple sacrificial electron/hydrogen donor.

In considering the limitations associated with the photoredox-catalyzed pinacol coupling, and in order to probe our hypothesis, we selected the photoreduction of benzaldehyde as our initial subject of investigation.[13] Generally, this transformation allows direct access to diols, which are important structural motifs in natural products,[14] pharmacologically active compounds, ligands, and auxiliaries.[15] Unfortunately, due to the reductive nature, classical protocols operate with the usage of more than stoichiometric amounts

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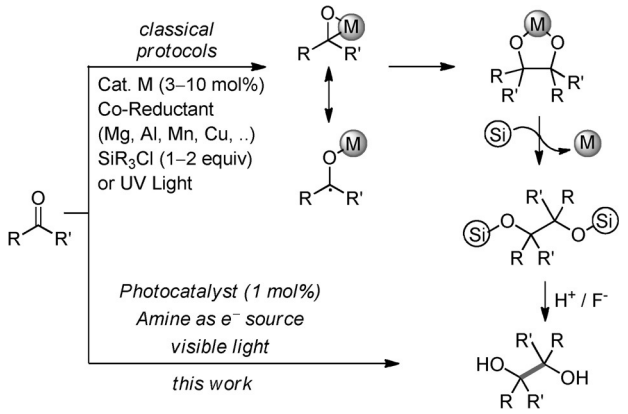


Scheme 2. Divergent strategies for the reductive dimerization of aldehydes and ketones.

of co-reducing metals (Mg, Zn, Al, Me, Te, Cu, etc.) and high catalyst loadings (Scheme 2, top). Furthermore, in order to prevent catalyst inhibition through the coordinating diol, the presence of an alkylsilane protecting group is required. At this stage, the development of a general and protecting-group-free catalyzed pinacol coupling would be attractive from the viewpoint of time, cost, and practical aspects (Scheme 2, bottom).

Preliminary experiments focused on the pinacol coupling of benzaldehyde ($E_{1/2}^{red} = -2.11$ V vs. Fc)[16] in the presence of tri-*n*-butylamine, employing different photocatalysts **2a**–**e**. Selected results are summarized in Table 1. We identified catalyst **2a** as the most effective for this transformation, providing the desired product **3a** in 66% yield (determined by NMR analysis), while the competing reduction to benzyl alcohol **4a** could be virtually prevented (Table 1, entry 1). Further improvement was achieved by switching the solvent from MeCN to DMF, which allowed us to isolate product **3a** in 69% yield (Table 1, entry 8). We validated the reproducibility of the reaction and also carried out control experiments (Table 1, entries 11–14). Indeed, we proved the necessity of the interplay between light, amine, catalyst, and oxygen exclusion.

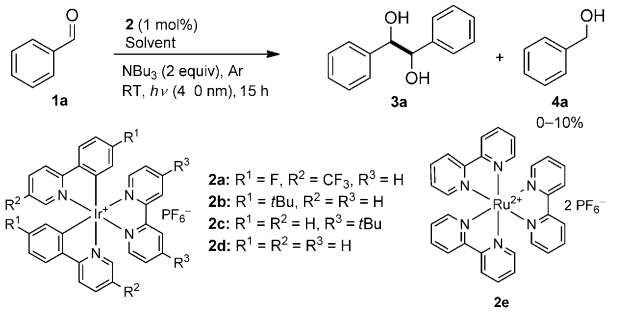
Having established the optimized reaction conditions, we next investigated the scope and limitations of this protocol. To our delight, a broad range of diols with electron-withdrawing (Table 2, **3d**–**h**) and electron-donating substituents (Table 2, **3b, 3c**) as well as steric influence in the *ortho* position (**3j**) were obtained in good yields. Minor limitations were observed for the halogen-substituted substrates **1g** and **1h** due to a competing reductive dehalogenation, which could be slowed down to some extent by using a lower amount of tri-*n*-butylamine. Satisfyingly, heteroaromatic aldehyde **1k** was found to be compatible as well, although it gave only moderate yield.

Having outlined the scope for aldehydes, we next applied our system to ketones without further optimization (Table 3). We were pleased to find that benzophenone (**5a**) ($E_{1/2}^{red} = -1.87$ V vs. SCE)[17] and its derivatives (**5b**–**e**) react to give the corresponding diols **6a**–**e** in good to high yields. Surprisingly, the more challenging acetophenone derivatives were found to provide the desired diols in good yields, although electron-rich substituents were not tolerated in this case. Products derived from acetophenone (**5g**) ($E_{1/2}^{red} = -2.48$ V vs. Fc)[8] and 2-acetylnaphthalene (**5i**) were formed in satisfactory yield, while in case of the electron-deficient ketone **5j** high yield could be achieved. Substitution in α-position was tolerated as well (**5f**, **5h**), and in addition, our methodology could be applied to aliphatic ketones (**5k**, **5l**). Interestingly, 2,2,2-trifluoroacetophenone ($E_{1/2}^{red} = -1.77$ V vs. Fc) was identified to be an unsuitable substrate; it was reduced to the corresponding alcohol.

Taking into account the reduction potential of the employed photocatalyst **2a** ($E_{1/2}^{red} = -1.69$ V vs. Fc) and substrates, the method presented here raises the question of the driving force of the reaction. Illustratively, the single-electron reduction of acetophenone to the corresponding ketyl radical anion is significantly endergonic ($\Delta G^0 = -zF\Delta E = +18.0$ kcal mol^{-1}). Thus, we assumed a direct reduction to the ketyl radical **F**, wherein the C=O activation proceeds via a two-center/three-electron interaction (**D**) or through H-bonding (**E**) initiated by the α-ammonium radical **C**.

As both pathways are feasible, we studied the pinacol coupling of acetophenone with a catalytic amount of Brønsted acid and inorganic base, respectively. Notably, the

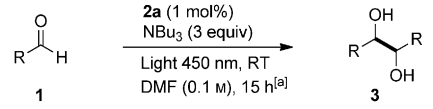
Table 1: Photoredox-catalyzed pinacol coupling of benzaldehyde: optimization studies.[a]



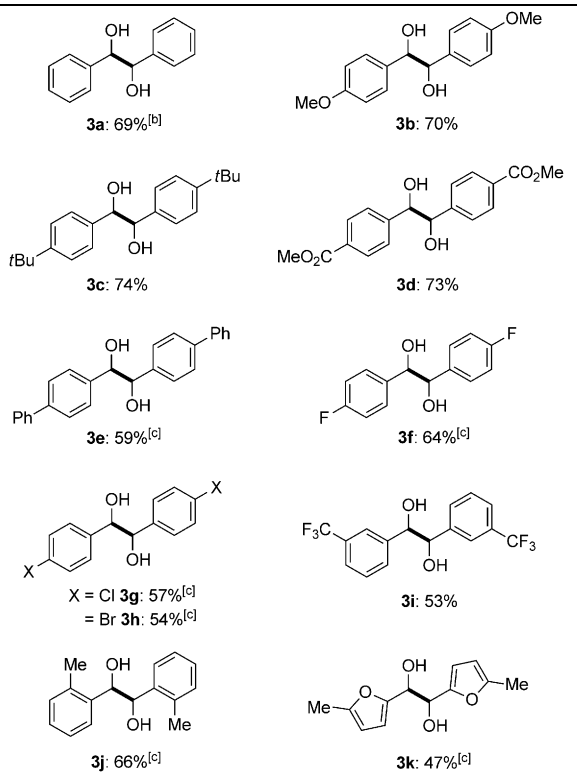
Entry	Photocatalyst	Solvent[b]	Yield [%][c]
1	**2a**	MeCN	66
2	**2b**	MeCN	< 5
3	**2c**	MeCN	44
4	**2d**	MeCN	< 5
5	**2e**	MeCN	n.r.
6	**2a**	EtOH	48
7	**2a**	DMSO	52
8	**2a**	DMF	73 (69)[d]
9	**2a**	THF	61
10	**2a**	DCM	< 5
11[e]	**2a**	DMF	n.r.
12[f]	**2a**	DMF	n.r.
13[g]	**2a**	DMF	n.r.
14[h]	–	DMF	n.r.

[a] Reaction conditions: **1a** (0.15 mmol), NBu_3 (0.3 mmol), **2a**–**e** (1 mol%), room temperature, solvent (2 mL), 11 W LED (450 nm), 15 h. [b] Degassed solvents [c] Yields determined by NMR analysis; 1,3-veratrol as internal standard; n.r. = no reaction. [d] Averaged yield of isolated product from two independent runs. [e] Without light. [f] Reaction under air. [g] Without NBu_3. [h] Without photocatalyst.

Table 2: Photoredox-catalyzed pinacol coupling of aldehydes.[a]

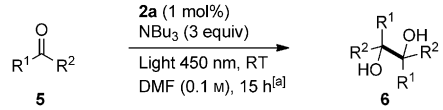


1 → 3

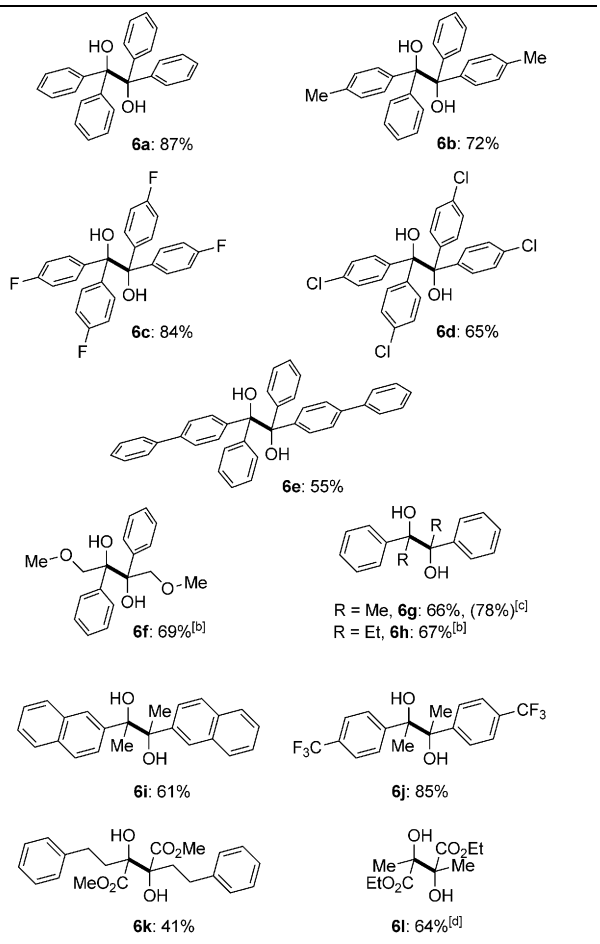


[a] Reaction conditions: aldehyde (0.2 mmol), NBu_3 (0.6 mmol), **2a** (1 mol%), degassed DMF (2.0 mL), room temperature, argon, light (450 nm), 15 h. Yields of isolated products, d.r.: 1.2:1 to 1.4:1; [b] Average yield of two independent runs, NBu_3 (0.4 mmol). [c] Aldehyde (0.4 mmol), NBu_3 (0.6 mmol).

Table 3: Photoredox-catalyzed pinacol coupling of ketones.[a]



5 → 6

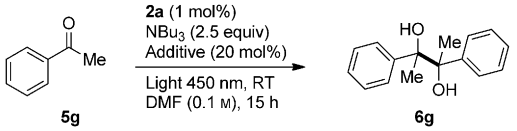


[a] Reaction conditions: ketone (0.2 mmol), NBu_3 (0.6 mmol), **2a** (1 mol%), degassed DMF (2.0 mL), RT, argon, light (450 nm), 15 h; yields of isolated products, d.r.: 1.1:1 to 1.5:1. [b] Ketone (0.5 mmol), NBu_3 (1.5 mmol). [c] With oxalic acid (20 mol%). [d] Ketone (0.6 mmol), NBu_3 (1.8 mmol).

presence of 20 mol% K_2CO_3 or K_3PO_4 completely suppressed the reaction (Table 4, entries 2 and 3). This observation suggests the essential role of the Brønsted acidic α-ammonium radical **C** in the C=O activation event. On the other hand, the intentional increase of the ammonium salt concentration by addition of oxalic acid or diphenyl phosphoric acid enhanced the yield significantly (Table 4, entries 4 and 5). These results indicate a proton-coupled electron transfer (PCET) in the elementary activation step.

While our protecting-group-free method proved to be compatible with a broad range of aldehydes and ketones under mild reaction condition and low catalyst loading (1 mol%), we questioned whether imines might be suitable candidates for our reductive coupling. This scenario would provide symmetric diamines, which are valuable synthetic building blocks. Since the reductive dimerization of imines with catalytic amounts of metals is scarcely described, the development of a photoredox-catalyzed pinacol coupling of imines with visible light attracted our attention. To our delight, we were able to isolate the desired diamine under the reaction conditions described above. Further evaluation of photosensitizers, light sources, solvents, amines, and

Table 4: Photoredox-catalyzed pinacol coupling of acetophenone: additive effects.[a]



5g → 6g

Entry	Additive	Yield [%][b]
1	–	66
2	K_2CO_3	0
3	K_3PO_4	0
4	oxalic acid	78
5	$(PhO)_2P(O)OH$	71

[a] Reaction conditions: acetophenone (0.2 mmol), NBu_3 (0.5 mmol), additive (20 mol%), **2a** (1 mol%), RT, argon, degassed DMF (2 mL), 11 W LED (450 nm), 15 h. [b] Yields of isolated products.

N-protecting groups, allowed us to identify acetonitrile and catalyst **2a** as crucial factors for obtaining satisfying reactivity.

In terms of protecting groups, the choice of a cleavable benzyl group, which permits smooth access to the free diamines, seemed reasonable for us. Regarding the substrate scope, the reductive dimerization of imines is applicable to substrates having various electron-donating and -withdrawing groups in *ortho*, *para*, and *meta* position of the aryl moiety (**7a**–**m**), delivering the corresponding diamines **8a**–**m** in good yields (Table 5). In addition, the compatibility of a pyridine moiety, which is known to be a potential radical acceptor, with our method was confirmed, as indicated by the conversion of **7l** to the diamine **8l**.

In conclusion, we have developed a simple method for the umpolung of carbonyl derivatives to the corresponding ketyl radicals. Their synthetic utility was demonstrated by the reductive dimerization of aldehydes and ketones under mild reaction conditions, with broad functional-group tolerance and without additives. In addition, for the first time, we succeeded in generating amino radical anions with small amounts of a photocatalyst (1 mol%) and visible light, and these intermediates were applied to the synthesis of valuable diamines. The simple generation of ketyl radicals from aldehydes and ketones, as well as amino radical anions opens up new avenues for further transformations in which such highly reactive intermediates can be used. For the first time, we also describe a dual role of the amine, which is typically used as a sacrificial electron donor. In our developed protocols, it acts not only as an electron donor but also serves to activate the substrates. Additional studies on the detailed reaction mechanism and expansion of the substrate scope are currently underway.

Keywords: diamines · photosensitizers · pinacol coupling · proton-coupled electron transfer · radical anions

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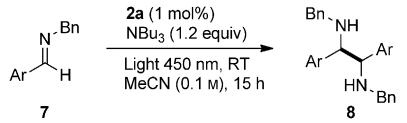
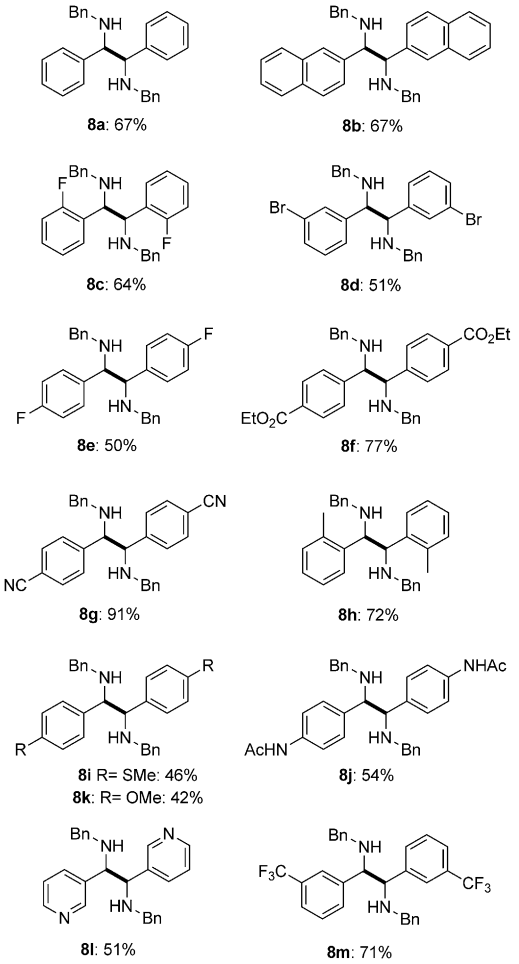
Table 5: Photoredox-catalyzed imino-pinacol coupling.[a]





[a] Reaction conditions: imine (0.25 mmol), NBu_3 (0.3 mmol), **2a** (1 mol%), acetonitrile (1.5 mL), RT, argon, light (450 nm), 15 h. Yields of isolated products, d.r.: 1.7:1 to 100:1.

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