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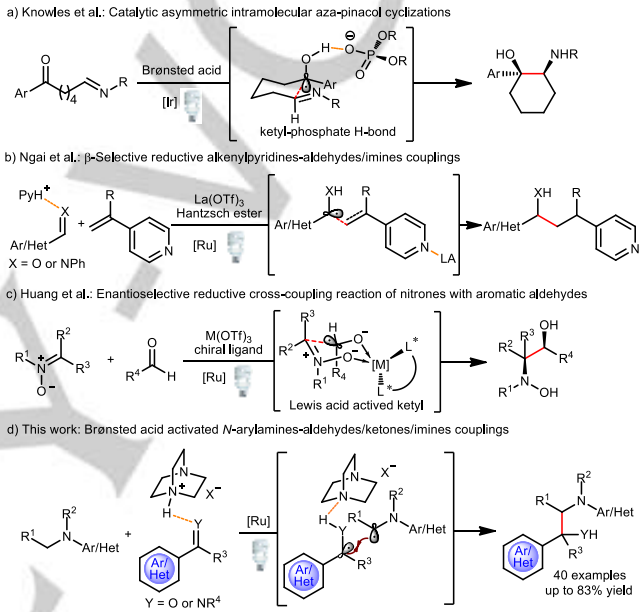
N-Arylamines Coupled with Aldehydes, Ketones, and Imines via Photocatalytic Proton-Coupled Electron Transfer

Qing Xia[a], Hao Tian[a], Jianyang Dong[a], Yi Qu[a], Lili Li[a], Hongjian Song[a], Yuxiu Liu[a], Qingmin Wang[a][b]*

Dedication ((optional))

Abstract: Herein, we report a photoredox-catalyzed umpolung strategy for coupling reactions between aldehydes, ketones, imines and *N*-Arylamines. These reactions proceed by a Brønsted acid-activated proton-coupled electron transfer pathway, and the protocol was used to synthesize broad scope of 1,2-amino alcohols and vicinal diamines, both of which are common motifs in biologically active natural products, pharmaceutically active molecules and ligands.

Carbonyl (C=O) and iminyl (C=N) groups, which are strongly polarized, are valuable synthons for the construction of β-functionalized alcohols and amines by means of reactions with nucleophiles.[1] When reductive umpolung strategies are employed, reactions of carbonyl and iminyl groups can produce ketyl/α-amino radicals, which are versatile synthetic intermediates in numerous important bond-forming and bond-breaking processes.[2] However, the strongly negative reduction potentials of aldehydes ($E_{1/2}^{red}$ = −1.93 V vs. SCE for benzaldehyde),[3] ketones ($E_{1/2}^{red}$ = −2.11 V vs. SCE for acetophenone),[3] and imines ($E_{1/2}^{red}$ = −1.91 V vs. SCE for *N*-benzylideneaniline),[3] as well as the need to use toxic and air- and moisture-sensitive reducing agents greatly restricts the practical utility of umpolung strategies.[4] Recently, photoredox-catalyzed proton-coupled electron transfers (PCETs), in which a proton transfer occurs in concert with an electron transfer, were successfully used to facilitate the formation of ketyl/α-amino radicals by lowering the energy barrier to single-electron transfer.[5] For example, Knowles et al. adopted a concerted PCET strategy for ketyl formation, successfully using dual Brønsted acid/photoredox catalysis for a highly enantioselective intramolecular aza-pinacol coupling reaction (Scheme 1a).[6] In 2017, Ngai et al. harnessed an elegant dual-catalyst system (comprising a Lewis acid and a transition-metal photosensitizer) under visiblelight irradiation to accomplish β-selective additions of ketyl or α-amino radicals to Lewis acid-activated alkenylpyridines (Scheme 1b).[7] Recently, Huang et al. employed a synergistic catalysis of Ru-photocatalyst and chiral *N*,*N*′-dioxide ligand-coordinated rare earth ion to realize enantioselective reductive cross-coupling reaction of nitrones with aromatic ketyl radicals (Scheme 1c).[8]



Scheme 1. Ketyl Radical Generation and Follow-up Chemistry

1,2-Amino alcohols and vicinal diamines represent one of the most significant synthetic building blocks and key subunits of bioactive natural products, pharmaceutically active molecules, chiral auxiliaries and ligands.[9] In seeking to develop more efficient and straightforward protocols for the construction of diverse 1,2-amino alcohols and vicinal diamines under mild conditions using readily available starting materials, we hypothesized that the introduction of proton shuttle,[10] might mediate proton transfer from *N*-arylamines to aldehydes, ketones, or imines. Acceleration of one-electron reduction by the proton shuttle might make aldehydes, ketones, and imines attractive candidates for PCET activation, thus presenting an opportunity to develop catalytic ketyl and α-amino radical chemistries that employ comparatively mild outer-sphere reductants in combination with a proton donor catalyst.[6a] Herein, we report the realization of this hypothesis in the form of intermolecular radical coupling reactions of ketyl and α-amino radicals under Brønsted acid-activated condition. This mild, broad-scope method can be expected to be valuable for the synthesis of 1,2-amino alcohols and vicinal diamines.

We began by focusing on the reaction between *N*-phenyl-tetrahydroisoquinoline (**1a**) and *p*-(trifluoromethyl)benzaldehyde (**2**) (Table 1). The successful implementation of oxidized base radical cation activated the aldehyde or imine by the PCET

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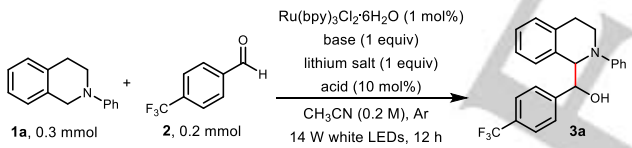
mechanism urged us firstly investigate the base additive in the reaction condition.[5h, 11] In the presence of base 1,4-diaza[2.2.2]bicyclooctane (DABCO) and photoredox catalyst $Ru(bpy)_3Cl_2{\cdot}6H_2O$, irradiation of a CH_3CN solution of the two substrates under Ar with 14 W white LEDs as a light source gave 1,2-amino alcohol **3a** in 43% yield as a 1.4:1 mixture of diastereomers (entry 1). Extensive screening of alternative bases did not improve the yield (entries 2 and 3; see also the Supporting Information). Previous reports of visible-light induced ketyl radical formation reactions are enhanced by the addition of acids,[11b, 12] which were consistent with this reaction when catalytic amount of oxalic acid was added (entry 4, 63% yield). Futhermore, to suppress the possible formation of undesired diol,[12b] and coordinate α-amino radical and ketyl radical cross-coupling by Li^+,[13] we added a lithium salt ($LiBF_4$, 1 equiv) to the reaction mixture and found that the yield improved to 72% (entry 5, 70% isolated yield). In the absence of DABCO and acid, a sharply decrease in efficiency was found (entry 6), indicated that the lithium salt serves as a Lewis acid to induce Lewis acid-activated single electron transfer (SET) process to afford corresponding ketyl radical is impossible.[14] Remarkably, we did not observe any of the product **3a** under the acid conditions without DABCO and lithium salt (entry 7). Replaced DABCO with DABCO conjugate acid (DABCO-oxalic acid) also lowered the reaction efficiency (entry 8). Control experiments demonstrated the critical roles of the photocatalyst, light, and an Ar atmosphere; none of the desired product was detected in the absence of any of these components (entries 9–11).

Table 1. Optimization Studies[a]

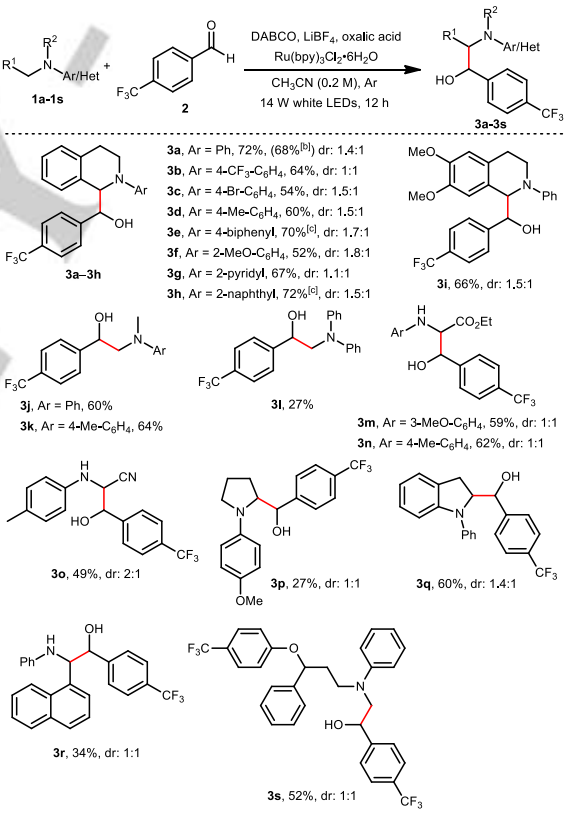


entry	base	acid	lithium salt	yield(%)[b]
1	DABCO	-	-	43
2	quinuclidine	-	-	40
3	Hantzsch ester	-	-	33
4	DABCO	oxalic acid	-	63
5	DABCO	oxalic acid	$LiBF_4$	72 (70)
6	-	-	$LiBF_4$	trace
7	-	oxalic acid	-	0
8	DABCO-oxalic acid	-	$LiBF_4$	25
9[c]	DABCO	$LiBF_4$	$LiBF_4$	0
10[d]	DABCO	$LiBF_4$	$LiBF_4$	0
11[e]	DABCO	$LiBF_4$	$LiBF_4$	0

[a]Reaction conditions, unless otherwise stated: **1a** (0.3 mmol), **2** (0.2 mmol), photocatalyst (1 mol%), base (1 equiv), lithium salt (1 equiv), and acid (10 mol%) in CH_3CN (1 mL) were irradiated with 14 W white LEDs at rt for 12 h under Ar. See Supporting Information for the details of the optimization studies. [b]Yields were determined by ^{19}F NMR analysis of the crude reaction mixture with trifluoroanisole as an internal standard. The value in parentheses is an isolated yield. [c]Without photocatalyst. [d]Without light. [e]Under air atmosphere. Abbreviations: DABCO, 1,4-diaza[2.2.2]bicyclooctane.

With the optimal conditions for this radical-radical coupling protocol in hand (Table 1, entry 5), we sought to determine the substrate scope with respect to the *N*-arylamines (Table 2). *N*-Aryl and *N*-heteroaryl tetrahydroisoquinolines bearing substituents with varying electronic properties smoothly furnished the desired products in 52–72% yields (**3a**–**3i**). *N*,*N*-Dimethylanilines (**3j** and **3k**) were amenable to the reaction, whereas a low yield of **3l** was observed with *N*-methyldiphenylamine as a substrate. *N*-Phenyl-substituted five-membered-ring substrates readily afforded the corresponding 1,2-amino alcohols (**3p** and **3q**) in moderate yields. We also evaluated some secondary amines. Reactions of arylglycine ester substrates, as well as a substrate in which the ethyl ester was replaced with a cyano group, gave moderate yields of the corresponding products (**3m**–**3o**, 49–62%). *N*-(Naphthalen-1-ylmethyl)aniline also tolerated the reaction conditions, affording 1,2-amino alcohol **3r** in 34% yield. Finally, we used this reaction system for late-stage functionalization of a derivative of the antidepressant agent fluoxetine,[15] obtaining **3s** in good yield.

Table 2. Substrate Scope with Respect to the *N*-Arylamines [a]

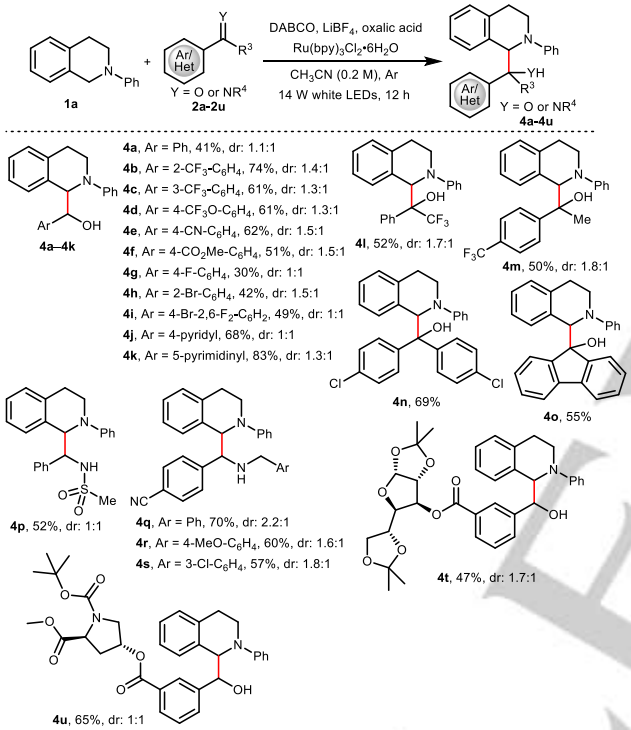


[a]Reaction conditions: Table 1, entry 5. Isolated yields are provided. Diastereomeric ratios (dr) were detected by ^1H NMR. [b]Yield of gram-scale reaction. [c]Dimethylacetamide was used as the solvent.

Next, we focused on evaluating the variety of aldehydes, ketones, and imines that could be used in this protocol (Table 3). Benzaldehydes bearing a wide variety of electron-withdrawing groups smoothly yielded the desired products in 30–74% yields (**4b**–**4i**). Benzaldehyde, which is electroneutral ($E_{1/2}^{red}$ = −1.93 V vs. SCE),[3] provided desired product **4a** in moderate yield.

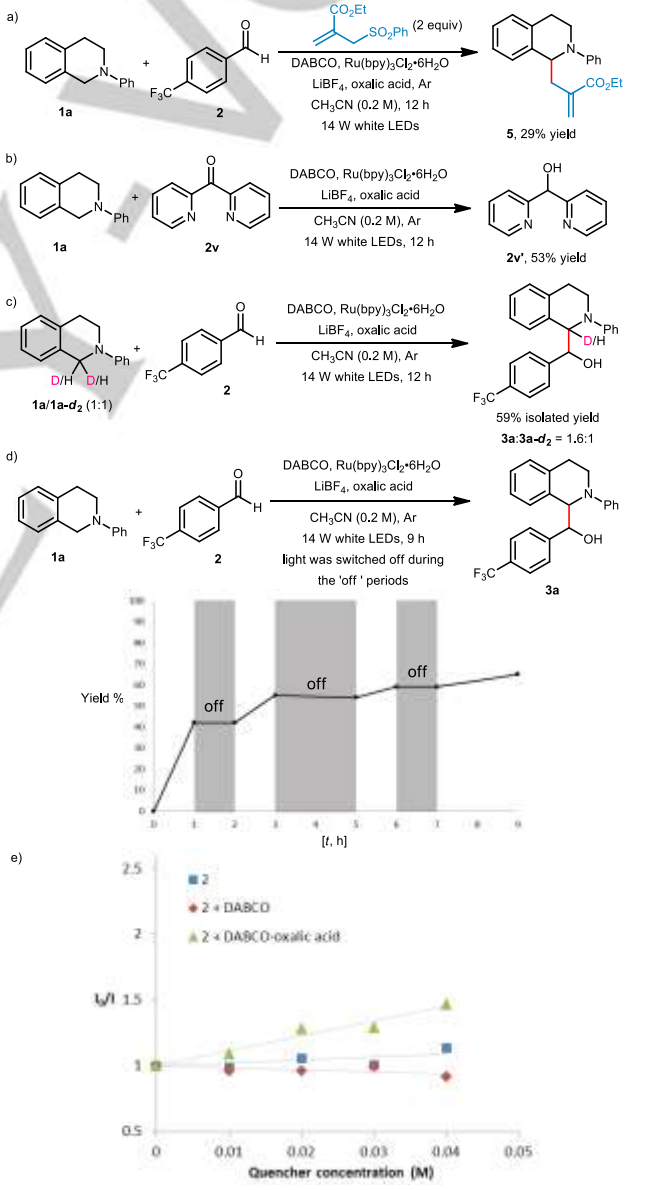
Pyridinecarboxaldehyde and pyrimidinecarbaldehyde were both amenable to the reaction conditions, efficiently affording **4j** and **4k**, respectively. To explore the generality of the reaction further, we tested several more challenging aromatic ketones, which afforded moderate yields of the corresponding products (**4l**–**4o**). We wondered whether an aldimine could be used as a substrate. We were pleased to find that α-amino radicals generated from aldimines could indeed undergo coupling reactions with **1a**, affording **4p**–**4s**. To demonstrate further the synthetic utility of the protocol, we tested several more-complex substrates, including a sugar (diacetone-D-glucose, **4t**)[7] and an amino acid derivative (**4u**). To our delight, they all afforded the desired products in synthetically useful yields.

Table 3. Substrate Scope with Respect to Aldehydes, Ketones, and Imines[a]



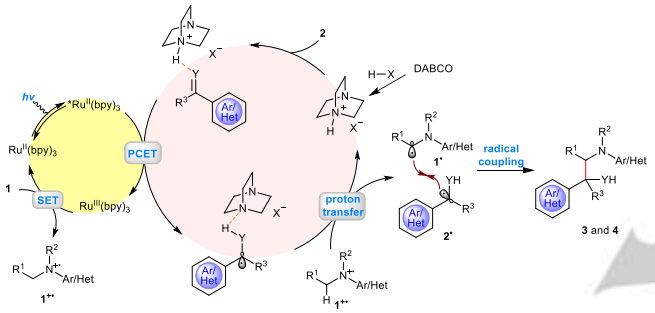
[a]Reaction conditions: Table 1, entry 7. Isolated yields are provided. Diastereomeric ratios (dr) were detected by ^{1}H NMR.

We carried out several reactions designed to provide insight into the reaction mechanism. When the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidinooxy) was present under standard conditions, the reaction was completely inhibited (Supporting Information). A reaction carried out under the standard conditions but with an added allyl sulfone produced radical addition product **5** in 29% yield. This result indicates the involvement of an α-*N*-phenyl-tetrahydroisoquinoline radical (**1a**•, Scheme 2a). When di(pyridin-2-yl)methanone **2v** was inject into the standard condition, reductive product **2v'** was only produced in 53% yield, suggested the existence of ketyl in this reaction (Scheme 2b). A competition experiment involving a 1/1 mixture of **1a** and deuterated substrate **1a-*d*$_2$** revealed a mixed products of **3a** and **3a-*d*$_2$** in 59% yield with a 1.6:1 ratio, indicating that proton transfer may not be the rate-determining step (Scheme 2c). An experiment in which the light source was switched on and off for the reaction of **1a** and **2** was performed, and the results clearly excluded the possibility of a radical chain process in this reaction system (Scheme 2d). Electrochemical analysis demonstrated that $Ru(bpy)_3^{3+}$ ($E_{1/2}^{III/II}$ = +1.29 V vs. SCE), not $*Ru(bpy)_3^{2+}$ ($E_{1/2}^{*II/I}$ = +0.77 V vs. SCE), is able to oxidize **1a** ($E_{1/2}^{red}$ = +0.87 V vs. SCE, Supporting Information). A Stern-Volmer experiment (Scheme 2e) showed no measurable luminescence quenching of $*Ru(bpy)_3^{2+}$ by **2** ($E_{1/2}^{red}$ = −1.93 V vs. SCE) or by **2**/DABCO in MeCN. However, inclusion of DABCO-oxalic acid with **2** resulted in a decrease in the measured fluorescence, thus suggested an oxidative quenching cycle through the PCET mechanism. [6, 16] DABCO radical cation ($DABCO^{+\bullet}$, $E_{1/2}^{red}$ = +0.69 V vs. SCE for DABCO) also cannot be able to oxidize **1a**, therefore excluded the possibility that DABCO act as an electron transfer agent.[12a]



Scheme 2. Mechanistic Experiments

A proposed mechanism for the transformation reported herein is depicted in Scheme 3. We envisioned a catalytic cycle initiated by in situ generated DABCO conjugate acid ($HDABCO^+X^-$), which to be the Brønsted acid to activated the aldehydes, ketones or imines **2** through hydrogen bond. Concerted PCET would follow, with electron transfer from the photoexcited state $*Ru(bpy)_3^{2+}$ ($E_{1/2}^{*II/III}$ = −0.81 V vs. SCE) occurring concomitantly with proton transfer to the **2** along the hydrogen-bond coordinate to generate a neutral ketyl or α-amino radical intermediate **2**•. The resulting $Ru(bpy)_3^{3+}$ ($E_{1/2}^{III/II}$ = +1.29 V vs. SCE) is able to be reduced by *N*-arylamines **1** by means of SET to afford $Ru(bpy)_3^{2+}$, and radical cation **1**+•. Subsequently, radical intermediate **1**• is produced by means of DABCO-promoted deprotonation, which regenerate the $HDABCO^+X^-$. **2**• rapidly combines with **1**• to furnish the desired 1,2-amino alcohol or vicinal diamines (**3** and **4**). Lastly, irradiation of $Ru(bpy)_3^{2+}$ with visible light would deliver $*Ru(bpy)_3^{2+}$ and close the catalytic cycle.



Scheme 3. Proposed Mechanism

In summary, we have developed a mild and practical protocol for the coupling between a wide variety of aldehydes, ketones, imines, and functionalized amines by photoredox catalysis. Mechanistic studies offer valuable insight into the key step that involves Brønsted acid-activated PCET process to generate ketyl or α-aminoalkyl radicals. It can be expected to facilitate syntheses of 1,2-amino alcohols and vicinal diamines, both of which are common motifs in biologically active natural products, pharmaceutically active molecules and ligands. Studies directed toward the development of an asymmetric version of the reaction are currently underway in our laboratory.

Experimental Section

General Procedure: To a solution of an *N*-arylamine (0.3 mmol, 1.5 equiv) in fresh distilled CH_3CN (1.0 mL, 0.2 M) (dimethylacetamide for **1e** and **1h**) was added $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (1.5 mg, 0.002 mmol, 1 mol%), DABCO (22 mg, 0.2 mmol, 1.0 equiv), $LiBF_4$ (19 mg, 0.2 mmol, 1.0 equiv), oxalic acid (2.0 mg, 0.02 mmol, 10 mol%), and aldehyde, ketone or imine **2,2a**–**2u** (0.2 mmol, 1.0 equiv) in a 8 mL vial. The mixture was bubbled with Ar for 1 min, and the reaction executed under argon atmosphere. The reaction was then stirred and photolyzed with two white LEDs (10 W + 4 W) from opposite sites at distances to the vial of approximately 3 cm. The reaction was monitored by TLC analysis. Afterwards, the mixture was diluted with CH_2Cl_2 and purified by flash chromatography on silica gel to afford target products **3a**–**3s** and **4a**–**4u**.

Acknowledgements

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Keywords: PCET • photoredox catalysis • ketyl radical • α-amino radicals • radical reactions

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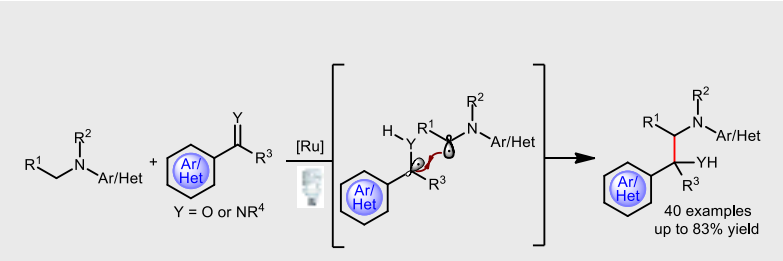

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