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Distinctive Reactivity of *N*-benzylidene-[1,1'-biphenyl]-2-amines under Photoredox Catalysis

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Abstract

A simple photocatalytic method was developed for the synthesis of unsymmetrical 1,2-diamines by the unprecedented reductive coupling of *N*-benzylidene-[1,1'-biphenyl]-2-amines with an aliphatic amine. The presence of phenyl substituent in the aniline moiety of the substrate was critical for the reactivity. The reaction proceeded via radical-radical cross-coupling of α-amino radicals generated by proton-coupled single-electron transfer in the presence of an Ir-photocatalyst. On the other hand, symmetrical 1,2-diamines were selectively produced from the same starting materials by judicious choice of the reaction conditions, showcasing the distinct reactivity of *N*-benzylidene-[1,1'-biphenyl]-2-amines. The developed method can be employed for the synthesis of various bulky vicinal diamines, which are potential ligands in stereoselective synthesis.

Keywords

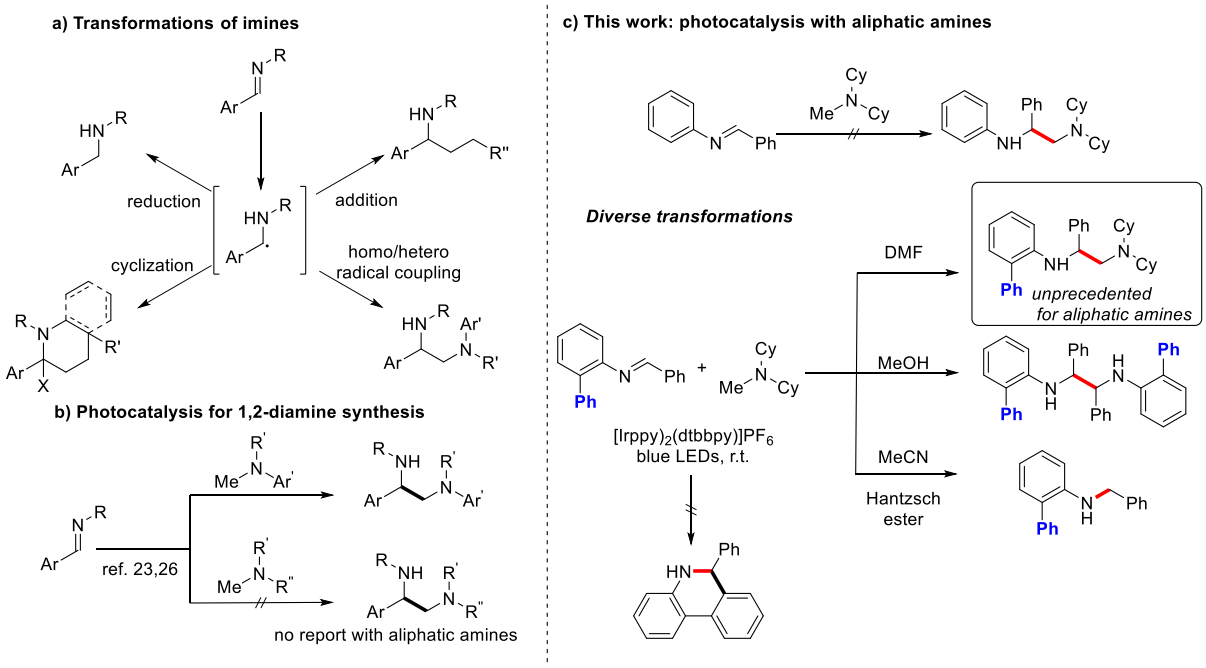
photocatalysis; imine; 1,2-diamine; visible light; diversity

Introduction

The selective formation of distinct valuable compounds from the same starting material is a highly attractive divergent approach, though it represents significant synthetic challenges. Recent advances in visible-light photocatalysis, mediated by visible-light-absorbing photosensitizers, have allowed ready access to complex molecules in a controlled manner, where subtle differences in the reaction conditions opened up distinct reaction pathways.[1-5]

Imines are versatile substrates that can be converted into various azo-compounds, depending upon the reaction conditions.[6-9] In particular, the reactivities of *N*-benzylidenes have been extensively explored under visible-light photocatalysis.[10-16] *N*-benzylidenes can undergo facile single-electron reduction to generate α-amino radical intermediates, which can participate in diverse processes depending upon the nature of the substrates and the reaction conditions (Scheme 1a). Various amine systems are generated from such intermediates via a wide range of processes, including hydrogen atom abstraction,[17,18] addition to unsaturated compounds,[19-21] radical-radical coupling,[22-30] and cyclization[31-33] reactions. Among these diverse applications, the Rueping group has reported excellent examples of reductive umpolung homocoupling of imines and hetero-coupling with α-amino radicals for the synthesis of symmetrical and unsymmetrical vicinal diamines (Scheme 1b).[23,26]

Notably, 1,2-diamines have widespread applications as core structures in a variety of natural products, pharmaceuticals, and agrochemicals,[34-38] and are valuable ligands[39, 40] in stereoselective organic synthesis. Despite the availability of a plethora of synthetic methods for 1,2-diamines,[41-45] the reported photocatalytic synthetic methods are mainly limited to aniline-based substrates and do not encompass aliphatic amines.



Scheme 1: Photocatalytic transformations of imines.

We planned the synthesis 1,2-diamine compounds having aliphatic amine moiety by intermolecular coupling of *N*-benzylidines with aliphatic amines which not only act as coupling partner but also as electron donor in photoredox cycle, the results of which we report herein. We began with the reaction of the simple *N*-benzylideneaniline. However, this substrate did not furnish the desired products under several different

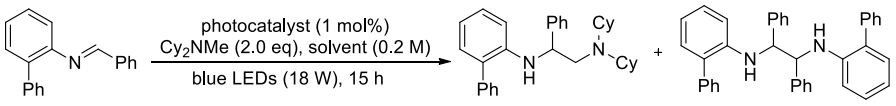
photocatalysis conditions, including those reported by Rueping. We hypothesized that the structural modification of the substrate might affect its reactivity, and to our delight, the introduction of an ortho-phenyl moiety on the *N*-benzylideneaniline provided the desired 1,2-amine product, wherein the *N*,*N*-dicyclohexylmethylamine (Cy_2NMe) acted as both the coupling partner and an electron donor in the photoredox cycle (Scheme 1c). It is likely that the presence of the additional phenyl group in the substrate stabilizes the α-amino radical intermediate, and modulates its reactivity.[46,47] In addition to the cross-coupled 1,2-diamines, we envisioned the generation of other valuable structural motifs via careful control of the reaction conditions for the reaction of the biphenyl imine derivative, *N*-benzylidene-[1,1'-biphenyl]-2-amine.

Results and Discussion

With the initial results in hand, we attempted the optimization of reaction conditions to improve the yield of the 1,2-diamine product (Table 1). Among the series of photocatalysts tested, ranging from the Ru/Ir polypyridyl complexes to organic dyes, the $[Ir(dtbbpy)ppy)_2]PF_6$ photocatalyst was found to be the best and afforded **2a** in 60% yield, along with 11% of the homo-coupled product **3a** (entries 1-9). The amount of Cy_2NMe was critical for achieving selectivity, and less than two equivalents of Cy_2NMe gave greater amounts of the homo-coupled product **3a** (entry 10). Control experiments showed that the photocatalyst, amine base, and light source are integral aspects of the reaction (entries 11-13). DMF was found to be the best solvent and yielded **2a** selectively (entries 15-22). On the other hand, the homo-coupled **3a** was selectively obtained in protic solvents (entries 19 and 22), and in particular, CH_3OH showed good reactivity and formed **3a** in 75% yield. Unexpectedly, the cyclized product with the

tethered phenyl ring proposed in Scheme 1c was not generated under any of the photocatalytic conditions evaluated.

Table 1: Reaction optimization.[a,b]



1a **2a** **3a**

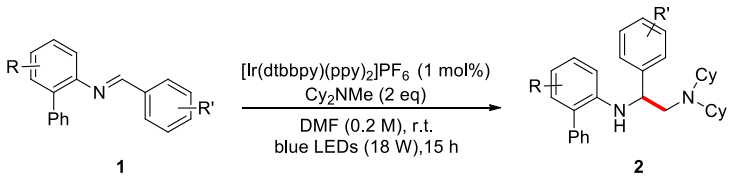
Entry	Photocatalyst	Variations	Solvent	Yield (%)[b]	
				2a	3a
1	$[Ru(bpy)_3]Cl_2.6H_2O$	-	CH_3CN	12	0
2	$[Ru(bpz)_3][PF_6]_2$	-	CH_3CN	0	0
3	$Ir(dFppy)_3$	-	CH_3CN	0	0
4	$Ir(ppy)_3$	-	CH_3CN	3	25
5	$(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$	-	CH_3CN	38	5
6	**$[Ir(dtbbpy)(ppy)_2]PF_6$**	**-**	**CH_3CN**	**60**	**11**
7	TTPP	-	CH_3CN	0	0
8	Crystal Violet	-	CH_3CN	0	0
9	Eosin-Y	-	CH_3CN	38	0
10	$[Ir(dtbbpy)(ppy)_2]PF_6$	Cy_2NMe (1.0 eq)	CH_3CN	14	55
11	$[Ir(dtbbpy)(ppy)_2]PF_6$	no Cy_2NMe	CH_3CN	0	trace
12	No catalyst	-	CH_3CN	0	0
13	$[Ir(dtbbpy)(ppy)_2]PF_6$	no light	CH_3CN	0	0
14	$[Ir(dtbbpy)(ppy)_2]PF_6$	-	DCM	0	16
15	**$[Ir(dtbbpy)(ppy)_2]PF_6$**	**-**	**DMF**	**72**	**7**
16	$[Ir(dtbbpy)(ppy)_2]PF_6$	-	DCE	22	11
17	$[Ir(dtbbpy)(ppy)_2]PF_6$	-	DMSO	37	6
18	$[Ir(dtbbpy)(ppy)_2]PF_6$	-	dioxane	50	13
19	$[Ir(dtbbpy)(ppy)_2]PF_6$	-	TFE	0	20
20	$[Ir(dtbbpy)(ppy)_2]PF_6$	-	Acetone	22	trace
21	$[Ir(dtbbpy)(ppy)_2]PF_6$	-	EtOAc	36	8
22	**$[Ir(dtbbpy)(ppy)_2]PF_6$**	**-**	**CH_3OH**	**4**	**75**

[a]Reaction conditions: **1a** (0.1 mmol), under argon atmosphere; [b]Yields were determined by ^{1}HNMR spectroscopy using 1,3,5-trimethoxy benzene as the internal standard

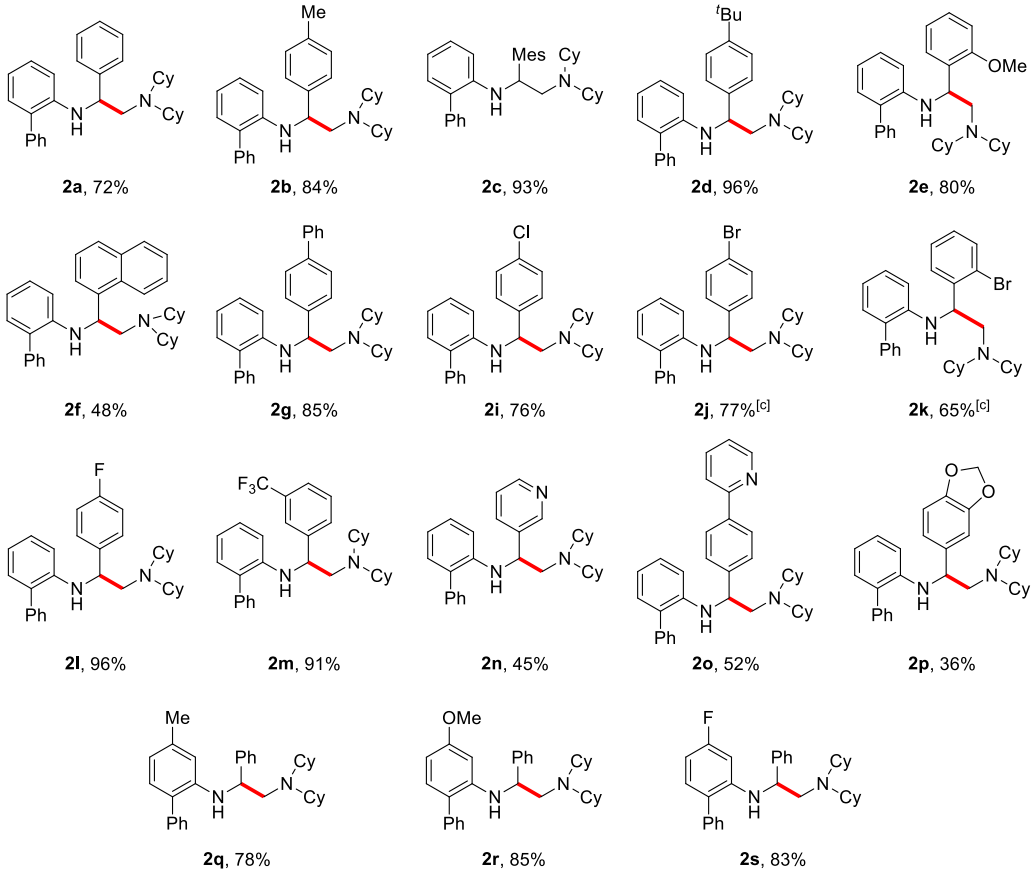
With the optimized conditions in hand, the generality of the transformations was investigated using a wide variety of phenyl-substituted *N*-benzylideneaniline derivatives (Table 2). First, the C-C bond cross-coupling process with Cy_2NMe was explored with variations of the benzylidine moiety. Reactions with both electron-donating (**2b**-**2e**) and electron-withdrawing substituents (**2i**-**2m**) proceeded well. Several functional groups, such as benzylic (**2b**, **2c**), ether (**2e**), halogens (chloro-**2i**, fluoro-**2l**),[48-50] the medicinally important CF_3-group (**2m)**, and acetal (**2p)** were

tolerated under the mild reaction conditions. The pattern of the substitutions on the aryl groups, such as ortho (**2c**, **2e**, **2k**), meta (**2m**, **2p**), and para (**2b**-**2d**, **2g**, **2i**, **2l**, **2o**, **2p**), did not have any significant impact on the reaction outcome. The heteroaryl ring-bearing substrates (**2n** and **2o**) also underwent the transformation and furnished the valuable vicinal diamine products.

Table 2: Substrate scope for radical cross-coupling.[a,b]



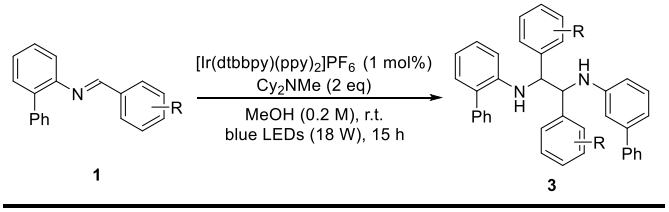
1 **2**

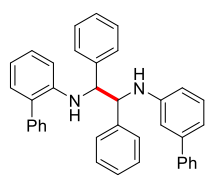


[a]Reaction conditions: **1** (0.3 mmol), under argon atmosphere; [b]Isolated yields; [c]Debrominated product was also detected and yield represents the mixture of bromo and debrominated products

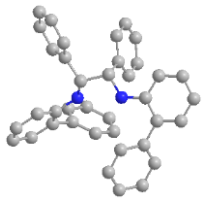
The modifications on the aniline moiety were also suitable, and substrates with both electron-donating (**2q** and **2r**) and electron-withdrawing (**2s**) substituents underwent the cross-coupling with excellent reactivities. We also tried the transformation with aliphatic amines other than Cy_2NMe, such as TMEDA, TEA, and DIPEA. However, these reactions proceeded with poor chemoselectivity and resulted in the formation of mixtures of several types of amine compounds.

Table 3: Substrate scope for homo-coupling.[a,b]

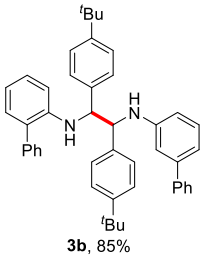




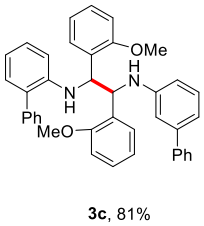
3a, 75%



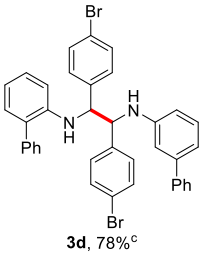
X-ray structure of **3a**



3b, 85%



3c, 81%



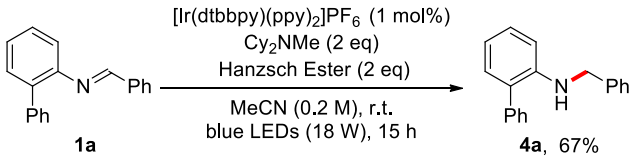
3d, 78%[c]

[a]Reaction conditions **1** (0.3 mmol) under argon atmosphere; [b]isolated yield; [c]Debrominated product was also detected and yield represents the mixture of bromo and debrominated products

Next, the homo-coupling reactions of substituted (*E*)-*N*-benzylidene-[1,1'-biphenyl]-2-amines were studied in CH_3OH (Table 3).[51-56] It is noteworthy that the resulting symmetrical 1,2-amine compounds are potential ligands for a variety of organic transformations. The dimerization reactions proceeded well, regardless of the

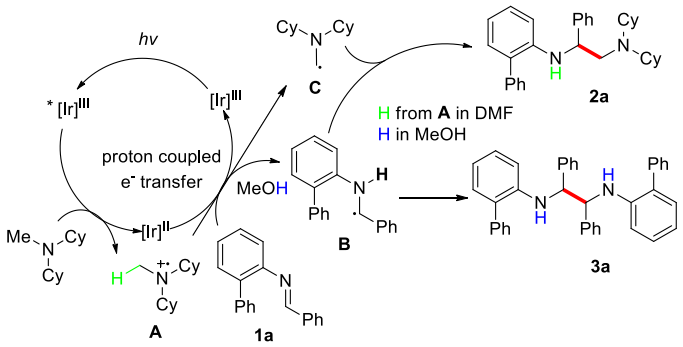
electron-density or position of the substituent on the benzylidene moiety. The structure of the homo-coupled 1,2-diamine product **3a** was unambiguously confirmed using X-ray crystallography.[57]

To further extend the diversity of reactivity of the imines in this process, we also attempted the use of a reducing agent in the reaction of **1a**. Pleasingly, the reaction of **1a** with 2 equivalents of the Hantzsch ester in MeCN produced the reduced amine product **4a** in 67% yield (Scheme 2).[17, 18, 58-61]



Scheme 2: Reduction of imine **1a** to amine **4a**.

Based on the observations and previous reports, a plausible reaction mechanism was proposed for the developed transformation, as shown in Scheme 3. Upon visible-light irradiation, the excited photocatalyst $[Ir^{III}]^*$ is formed, and is reductively quenched by single electron transfer from Cy_2NMe, resulting in the generation of the highly reducing $[Ir^{II}]$ and the radical cation **A**. The formation of **2a** might be attributed to the proton-coupled electron transfer[62-66] from $[Ir^{II}]$ to imine **1a**, where the radical cation **A** donates a proton to **1a** to form the α-amino radical intermediates **B** and **C**, which underwent cross-coupling to give the desired unsymmetrical vicinal diamine **2a**. On the other hand, in CH_3OH, **1a** preferentially abstracts a proton from CH_3OH, than from **A**, which in turn prevents the generation of the α-amino radical **C** from Cy_2NMe, resulting in the homocoupling of **B** to selectively form the symmetrical diamine product **3a**.



Scheme 3: Proposed mechanism.

Conclusion

We developed a divergent synthetic approach for the valuable 1,2-diamine motifs from *N*-benzylidene-[1,1'-biphenyl]-2-amines, by slight alterations to the reaction conditions. The in-situ generated α-amino radical intermediates successfully underwent cross- and homo-coupling to yield the unsymmetrical and symmetrical 1,2-amines, respectively. It is notable that the presence of phenyl substituent at the aniline moiety was critical in the hetero-coupling with aliphatic amines. Furthermore, the reduced amine product was also obtained by employing the Hantzsch ester as an additive. The developed method can be employed for the synthesis of bulky vicinal diamines with potential applications as ligands for stereoselective synthesis.

Acknowledgement

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Experimental

An oven-dried resealable tube, equipped with a magnetic stir bar, was charged with the *N*-benzylidene-[1,1'-biphenyl]-2-amines (0.3 mmol), $[Ir(dtbbpy)(ppy)_2]PF_6$ (0.003 mmol), and Cy_2NMe (0.6 mmol). The reaction mixture was purged with argon for 20 min. Then, degassed DMF or MeOH was added to the reaction mixture under inert conditions. The reaction mixture was stirred at ambient temperature for 15 h under visible-light irradiation with blue LEDs (18 W). The progress of the reaction was monitored by using TLC. Upon reaction completion, the crude product was diluted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated on a rotary evaporator. The desired vicinal diamine products were purified by silica-gel column chromatography using hexane/EtOAc as the eluent.

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