Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX–XXX

pubs.acs.org/OrgLett

Reductive Cross-Coupling of Aldehydes and Imines Mediated by Visible Light Photoredox Catalysis

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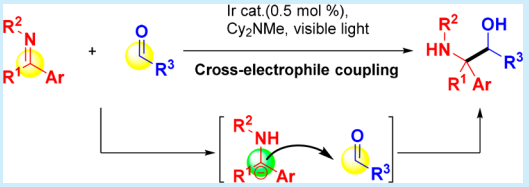
Supporting Information

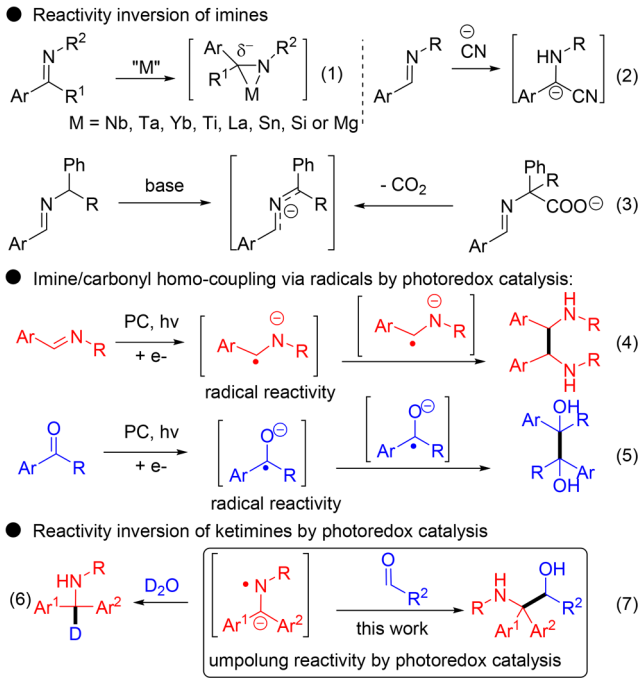
ABSTRACT: Under photoredox catalysis conditions, the conventional electrophilic reactivity of ketimines is inverted to generate nucleophilic species. As a result, chemoselective cross-electrophile couplings between aldehydes and ketimines are achieved via umpolung reactivity of ketimines to furnish amino alcohols (44 examples with good to excellent yields). To illustrate the utility of the amino alcohol products, 1,2-dihydroindol-3-one-based fluorophores are easily synthesized using the coupling products. Finally, a plausible reaction pathway is discussed.



Imines are commonly used as electrophiles in coupling with nucleophilic partners to construct bioactive nitrogen-containing compounds. Coupling of imines with electrophiles (e.g., carbonyls), however, is challenging because it requires reactivity inversion of the imine.[1] It has been shown that the C═N double bond of imines reacts with metals and metalloids (e.g., niobium, tantalum, ytterbium, titanium, lanthanum, tin, silicon, and magnesium, among others) to generate metallaziridines or carbon−metal bonds, which are nucleophilic at carbon (Scheme 1, eq 1).[2] These species react with aldehydes to afford amino alcohols. Addition of cyanides into the C═N double bond of imines is another method to invert the imine reactivity. The nitrile moiety facilitates the generation of a carbanionic species (Scheme 1, eq 2) that readily reacts with aldimines to ultimately generate diimines.[3] A recent strategy involves conversion of the *N*-diarylmethyl imines into 2-azaallyl anions by base-promoted deprotonation[4] or decarboxylation (Scheme 1, eq 3).[5] These 2-azaallyl anion intermediates are nucleophilic and have inspired many useful imine transformations.[5a,b,6]

Over the past decade photoredox catalysis has emerged as a powerful tool to initiate the radical reactivity of C═X double bonds (X = NR or O).[7] For instance, imines accept an electron during the photoredox catalytic cycle, generating reactive radical anion intermediates exhibiting C-centered radical reactivity. Such species undergo homocoupling to yield ethylene diamine derivatives (Scheme 1, eq 4).[8] Similarly, homocoupling of carbonyls via radical pathways has been demonstrated in the synthesis of pinacol coupling products (Scheme 1, eq 5).[8a,b] Reports on nucleophilic reactivity of imines mediated by photoredox catalysis, however, are scarce.[9] Our team[10] and Polyzos'group[7n] recently disclosed that α,α-diarylketimines can be reduced to the corresponding amines under photocatalytic conditions with sacrificial amines.[7o] In our work, water acted as the proton source (or D_2O, Scheme 1, eq 6), supporting the proposed carbanionic nature of the intermediate.[10] This photocatalytic umpolung imine reactivity was subsequently used by Yu and co-workers.[11]

Scheme 1. Reactivity of Imines under Various Conditions



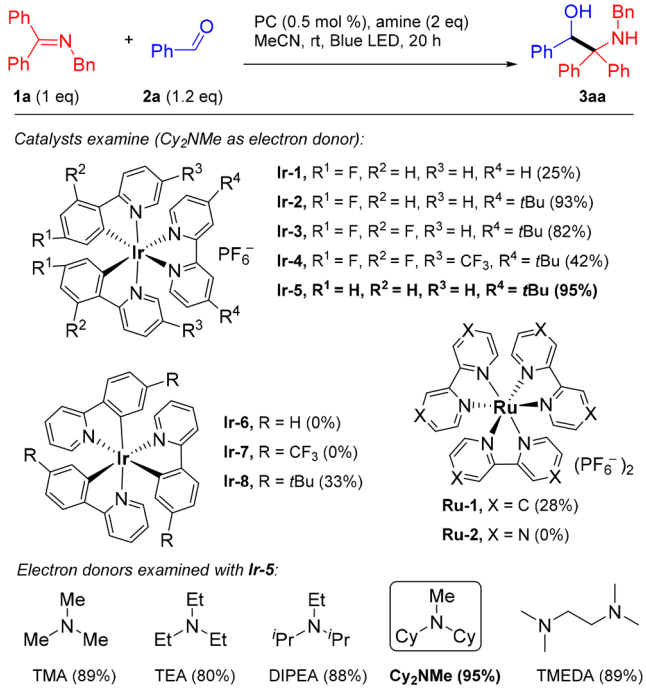
Received: October 23, 2018

DOI: 10.1021/acs.orglett.8b03394
Org. Lett. XXXX, XXX, XXX–XXX

These unusual results inspired us to explore the nucleophilic reactivity of these intermediates toward other electrophiles.[12] Compared to the reduction reaction, which generates C−H bonds (Scheme 1, eq 6), the formation of C−C bonds is more attractive for the introduction of complexity and the construction of functional molecules. Efficient cross-electrophile coupling reactions between imines and aldehydes by photoredox catalysis, however, are still challenging. This is likely due to the prevailing radical coupling mechanisms, necessitating the generation of two different types of radical intermediates under the same conditions and their highly chemoselective coupling. Herein, we report a novel and efficient cross-electrophile coupling of ketimines with aldehydes mediated by photoredox catalysis using visible light (Scheme 1, eq 7).

We initiated our study with cross-electrophile coupling between benzophenone imine (**1a**, 1.0 equiv) and benzaldehyde (**2a**, 1.2 equiv) in acetonitrile, with Cy_2NMe as the sacrificial electron donor and $[Ir(4'\text{-F-ppy})_2bpy]PF_6$ (**Ir-1**) as the photoredox catalyst (Scheme 2). To our delight, under

Scheme 2. Examination of Photoredox Catalysts and Sacrificial Electron Donors for the Cross-Electrophile Coupling Reaction

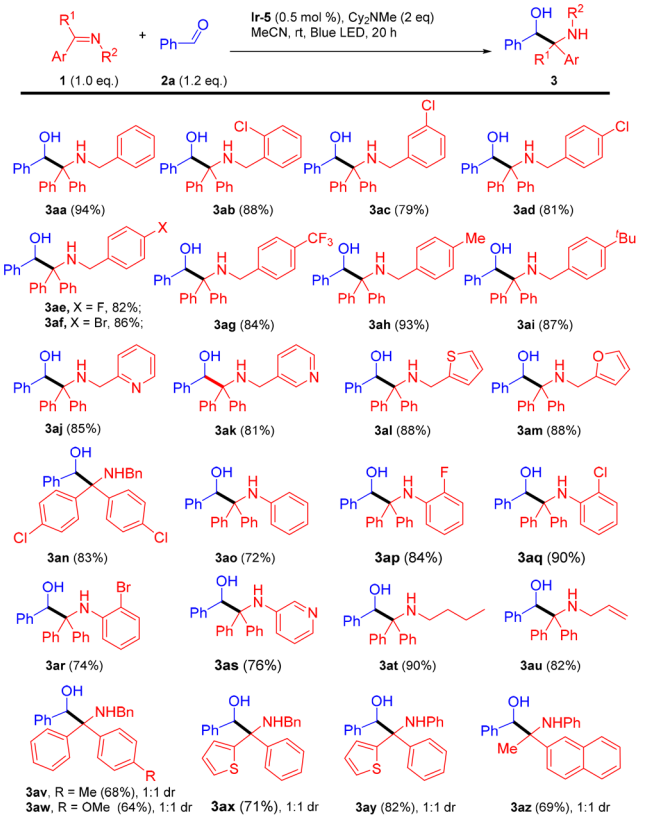


blue LED light irradiation, the desired β-amino alcohol product **3aa** was obtained in 25% assay yield [AY, determined by 1H NMR, see Supporting Information (SI) for details]. Interestingly, modification of the bipyridine ligand of the iridium catalyst with *tert*-butyl groups at the 4,4′-positions dramatically improved the AY (93%, **Ir-2**). Further introduction of fluorine atoms (**Ir-3**) or trifluoromethyl groups (**Ir-4**) into the catalyst, however, decreased the AY to 82% and 42%, respectively. We next tested $[Ir(ppy)_2(4,4'\text{-}t\text{Bu-bpy})]PF_6$ (**Ir-5**), which contains no fluorine but maintains the *tert*-butyl groups on the bipyridine ligand. Excellent AY (95%) was obtained with catalyst **Ir-5**. The commonly used photoredox catalysts *fac*-$Ir(ppy)_3$ (**Ir-6**) and its analogues (**Ir-7** and **Ir-8**), $[Ru(bpy)_3](PF_6)_2$ (**Ru-1**), and $[Ru(bpz)_3](PF_6)_2$ (**Ru-2**) were examined, but led to decreased AY or no observed product.

Sacrificial amines were next examined. Interestingly, all the amines tested were effective reductants and promoted the cross-electrophile coupling reaction (TMA, TEA, DIPEA, and TMEDA, 80−89% AY), with Cy_2NMe being optimal (95% AY).

Encouraged by the excellent reactivity under the optimized conditions, we next aimed to explore the scope of the cross-electrophile coupling reaction (Scheme 3). The isolated yield

Scheme 3. Cross-Electrophile Couplings between Benzaldehyde and Ketimines



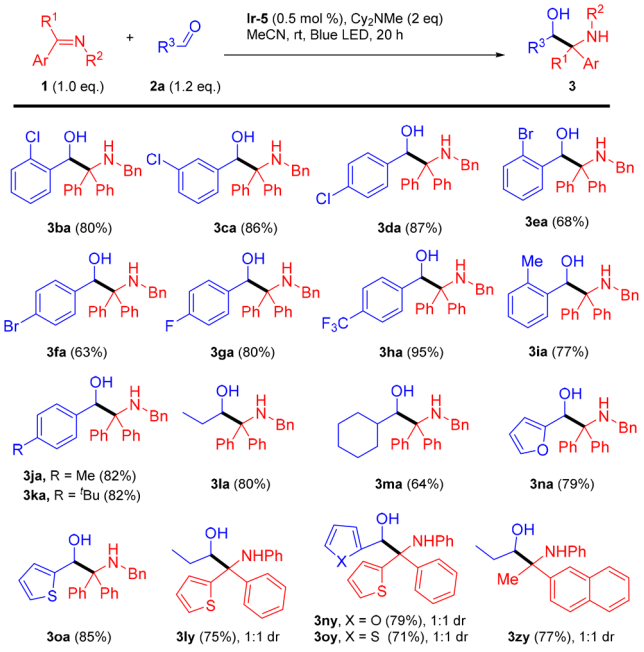
from coupling **1a** with benzaldehyde was 94% (**3aa**). Replacing the benzylic aryl of the ketimine **1a** with differentially substituted aryls did not significantly affect the reactivity (**3ab**−**3ai**, 79−93% yields). Ketimines with heterocyclic substituents, *N*-(2-pyridylmethyl), *N*-(3-pyridylmethyl), *N*-(2-thiophenylmethyl), and *N*-(2-furanylmethyl)ketimines, reacted smoothly with benzaldehyde to afford the corresponding products (**3aj**−**3am**, 81−88% yields). The 4,4′-dichlorobenzophenone ketimine was also tested, giving the desired product **3an** in 83% yield. The current photoredox catalyzed reaction conditions were effective with cross-electrophile coupling reactions between benzaldehyde and *N*-phenyl ketimine or its halogen-substituted analogues (**3ao**−**3ar**, 72−90%). Heterocyclic *N*-(3-pyridyl)ketimine was coupled with benzaldehyde in 76% yield (**3as**). Reaction of *N*-*n*-butyl ketimine afforded the product in 90% yield (**3at**), and the *N*-allyl ketimine provided the product in 82% yield (**3au**). 4-Methyl and 4-methoxy benzophenone ketimines coupled with **2a** smoothly (**3av**, 68%; **3aw**, 64%). Reactions with 2-thiophenyl ketimines yielded the desired products in good yields (**3ax**, 71%; **3ay**,

DOI: 10.1021/acs.orglett.8b03394
Org. Lett. XXXX, XXX, XXX−XXX

82%). The alkyl ketimine derived from 2-naphthylmethyl ketone reacted with benzaldehyde to give the coupling product **3az** in 69% yield. Throughout these studies, the use of unsymmetrical benzophenone imines resulted in formation of diastereomers (~1:1 dr).

The aldehyde scope was examined next (Scheme 4). Halogen substituted benzaldehydes coupled with ketimine **1a**

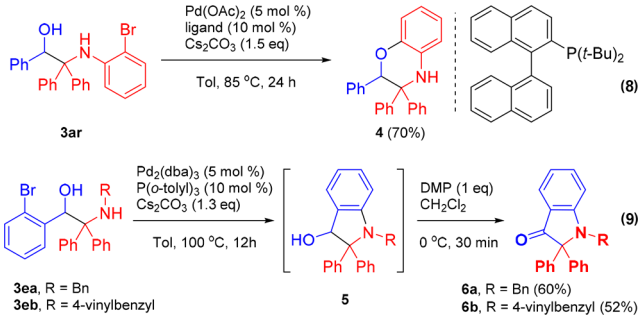
Scheme 4. Cross-Electrophile Couplings between Aldehydes and Ketimines



smoothly in good yields (**3ba**–**3ga**, 63–87% yields). Benzaldehydes with electron-withdrawing 4-CF_3 or electron-donating 2-methyl, 4-methyl, or 4-*tert*-butyl groups reacted with imines **1** effectively, affording the desired products in high yields (**3ha**–**3ka**, 77–95% yields). Alkyl aldehydes, such as *n*-propanal and cyclohexanal, were also readily coupled with imine **1a** under the optimal conditions (**3la**, 80%; **3ma**, 64%). Heterocyclic substrates 2-furanyl aldehyde and 2-thiophenyl aldehyde furnished the desired products in high yields (**3la**, 79%; **3ma**, 85%). The coupling between 2-thiophenyl ketimine **1y** with *n*-propanal, 2-furanyl aldehyde, or 2-thiophenyl aldehyde afforded the corresponding products (**3ly**, 75%; **3ny**, 79%; **3oy**, 71%). To our delight, *n*-propanal also coupled with the 2-naphthylmethyl ketimine under the optimal conditions to give the desired product (**3zy**, 77% yield).

We next set out to demonstrate the utility of the products prepared above. One-step conversion of **3ar** into benzomorpholines, which are core structures of potentially bioactive compounds,[13] was achieved in 70% yield via a *O*-arylation reaction (Scheme 5, eq 8). A second application of our products was realized by conversion to fluorescent organic molecules, which play important roles in biological studies (biomolecule labeling, living system imaging, activity probing, etc.).[14] Cyclization of **3ea** by Buchwald–Hartwig amination, followed by Dess-Martin periodinane (DMP) oxidation, yielded 1,2-dihydroindol-3-one type fluorophores (Scheme 5, eq 9).[15] Fluorophore **6a** was synthesized in 60% overall yield. Its vinyl-functionalized analogue **6b**, which is capable of labeling biomolecules-containing free thiol groups via the

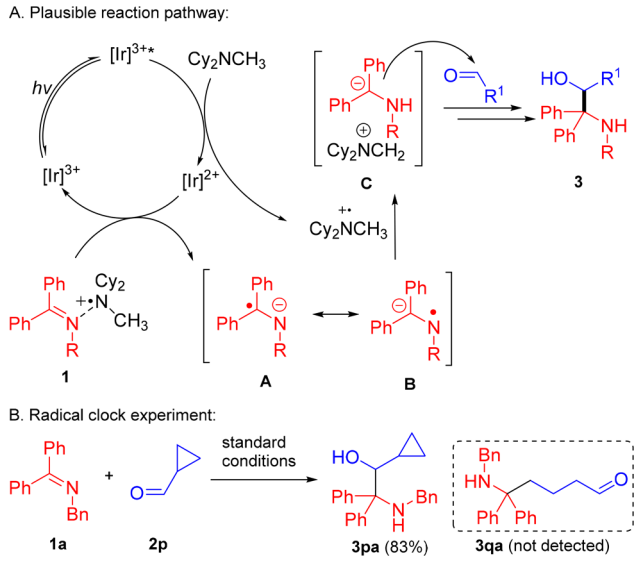
Scheme 5. Transformations of Representative Products



thiol–ene click reaction,[16] was obtained in 52% yield. It is noteworthy that the product structure can be easily fine-tuned using our cross-electrophile coupling method, making it possible to adjust the fluorophore spectra, as well as to anchor different functional groups for diverse applications.

To rationalize the observed reactivity, we postulate that the catalyst is irradiated by visible light to its excited state $[Ir]^{3+*}$, which is reduced by Cy_2NMe to generate $[Ir]^{2+}$ and the amine radical cation, $[Cy_2NMe]^{+\bullet}$. Ketimine **1** is activated by the amine radical cation, $[Cy_2NMe]^{+\bullet}$, to form a 2-center-3-electron interaction.[8a,17] This complex is then reduced by one electron from $[Ir]^{2+}$ and forms the radical anion intermediate **A**/**B**.[18] Due to the high reactivity of the *N*-centered radical, **B** is quickly quenched by HAT from $[Cy_2NMe]^{+}$ to give the intermediate carbanion **C** and the iminium ion. Carbanion **C** attacks the aldehyde via nucleophilic addition, ultimately affording the *β*-amino alcohol product (Scheme 6A). The

Scheme 6. Plausible Reaction Pathway



postulated ketimine activation pathway is based on the umpolung reactivity of diarylketimines under photoredox catalysis observed by us[10] and Polyzos[7n] and under electrochemical conditions by Reed.[18a] Indeed, our previous computational calculation on the spin density of the radical anion intermediate supported that **B** is more favorable than **A** since the nitrogen atom carries more radical character than the carbon atom (see SI).[18b] However, a radical coupling mechanism involving both aldehyde and ketimine reductions is also possible based on the previously reported pinacol

DOI: 10.1021/acs.orglett.8b03394
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couplings and the imine dimerizations (Scheme 1, eqs 4 and 5). Therefore, a radical clock experiment using cyclopropanecarboxaldehyde (**2p**) was conducted. Exposure of cyclopropanecarboxaldehyde to the standard photocatalytic coupling reaction conditions led to formation of cyclopropane-containing **3pa** in 83% isolated yield. No ring-opened products, e.g. **3qa**, were observed by ^{1}H NMR spectroscopy, indicating that the diradical coupling pathway is unlikely (Scheme 6B).

In summary, reductive coupling of imines with aldehydes by stoichiometric metal complexes is a synthetically valuable transformation. To avoid the use of highly reactive metal-based reagents, and circumvent generation of copious waste products, we have demonstrated the photoredox catalyzed cross-electrophile coupling of ketimines and aldehydes. Such reactions generally proceed via radical−radical coupling mechanisms. In contrast, we have demonstrated cross-electrophile coupling transformations via the nucleophilic addition pathway with photoredox catalysis. The advantages of the nucleophilic addition are exemplified with the cross-electrophile couplings between ketimines and aldehydes, which are difficult to achieve via radical−radical coupling pathways due to challenges associated with the generation of two different radical species and their chemoselective coupling. We have also demonstrated that the amino alcohol products prepared herein are easily converted into biological fluorescent probes or biologically active compounds by palladium catalyzed coupling reactions. Other transformations exploiting the novel umpolung reactivity of imines are currently underway in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03394.

Procedures, characterization data, and spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

X.F. thanks the Young Scientists Fund of the National Natural Science Foundation of China (21708020) and the Natural Science Foundation of Jiangsu Provence (BK20170969) for financial support. P.J.W. is grateful to the NSF (CHE-1464744) for support.

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DOI: 10.1021/acs.orglett.8b03394
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