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β-Selective Reductive Coupling of Alkenylpyridines with Aldehydes and Imines via Synergistic Lewis Acid/Photoredox Catalysis

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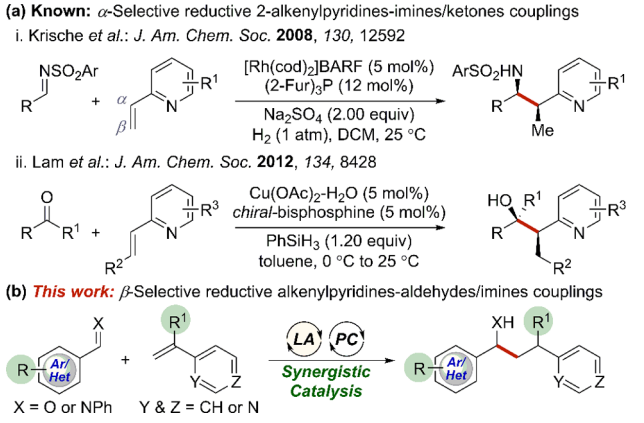
Supporting Information

ABSTRACT: Umpolung (polarity reversal) strategies of aldehydes and imines have dramatically expanded the scope of carbonyl and iminyl chemistry by facilitating reactions with non-nucleophilic reagents. Herein, we report the first visible light photoredox-catalyzed β-selective reductive coupling of alkenylpyridines with carbonyl or iminyl derivatives with the aid of a Lewis acid co-catalyst. Our process tolerates complex molecular scaffolds (e.g., sugar, natural product, and peptide derivatives) and is applicable to the preparation of compounds containing a broad range of heterocyclic moieties. Mechanistic investigations indicate that the key step involves single-electron-transfer reduction of aldehydes or imines followed by the addition of resulting ketyl or α-aminoalkyl radicals to Lewis acid-activated alkenylpyridines.

Pyridines are important substructures of natural products,[1] pharmaceuticals,[2] agrochemicals,[3] functional materials,[4] and ligands in catalysis.[5] They are often recognized as "privileged" scaffolds in medicinal chemistry for discovery and optimization of new synthetic drug molecules. Currently, over 100 marketed pharmaceuticals, including drugs such as Nexium (anti-acid) and Imatinib (anti-cancer), bear at least one pyridine ring.[6] Due to the prevalence of pyridines in medicinal chemistry, there is a high demand for novel synthetic methodologies that enable an access to new molecular architectures containing this important pharmacophore.

Alkenylpyridines are versatile synthetic intermediates that have been used in the synthesis of more complex molecules with pyridine subunits.[7] Due to their electrophilic nature, the reductive coupling of alkenylpyridines with another electrophile is rare.[8] Pioneering studies by Krische and co-workers in 2008 resulted in the first catalytic reductive coupling of 2-vinylpyridines to imines (Scheme 1a).[8a] After that seminal report, Lam et al. developed an elegant copper-catalyzed enantioselective reductive coupling of alkenylpyridines with ketones[8b] and imines (Scheme 1a).[8c] These protocols offer a useful tool for reductive C−C coupling at the α-position of the vinyl or alkenyl moiety. However, a general reaction for β-selective reductive coupling of alkenylpyridines with carbonyl/iminyl derivatives has yet to be achieved. The successful development of such a reaction would provide access to a complementary scope of synthetically useful products.

Scheme 1. Catalytic Transformations of Alkenylpyridines



We postulated that intervention of a reductive Umpolung step involving ketyl/α-aminoalkyl radicals would provide a powerful strategy to access previously unattainable pyridine-containing structures and enhanced flexibility to the design of new synthetic targets. Nevertheless, a widespread application of ketyl radicals in synthesis has been hindered by the highly negative reduction potential of aldehydes ($E_{1/2}^{red}$ = −1.93 V vs SCE for benzaldehyde),[9] and the requirement of employing toxic, air- and moisture-sensitive reducing agents and harsh reaction conditions to access the ketyl radical intermediate.[10] Recently, however, visible light photoredox catalysis has emerged as an efficient way to generate ketyl[11] and α-aminoalkyl radicals from the corresponding aldehydes and imines under mild reaction conditions.[11k,12] Nonetheless, photocatalytic intermolecular ketyl-olefin reductive coupling reactions are very rare.[11l] Herein we report the first β-selective intermolecular reductive coupling reaction between alkenylpyridines and carbonyl or iminyl derivatives enabled by a synergistic Lewis acid/photoredox catalytic system (Scheme 1b).

Our initial investigation focused on the reaction between 4-fluorobenzaldehyde **1a** and 4-vinylpyridine **2a** (Table 1). We observed that Lewis acid plays a critical role in achieving the desired reactivity. When a solution of **1a** and **2a** in MeCN was irradiated with blue LED light employing $Ru(bpy)_3(PF_6)_2$ as a photoredox catalyst and Hantzsch ester (HEH) as a stoichiometric reductant, no desired product (**3a**) was formed in the

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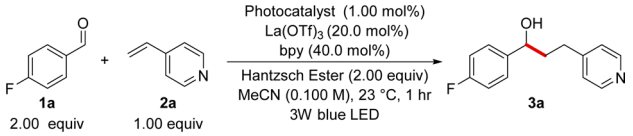
Table 1. Selected Optimization Experiments



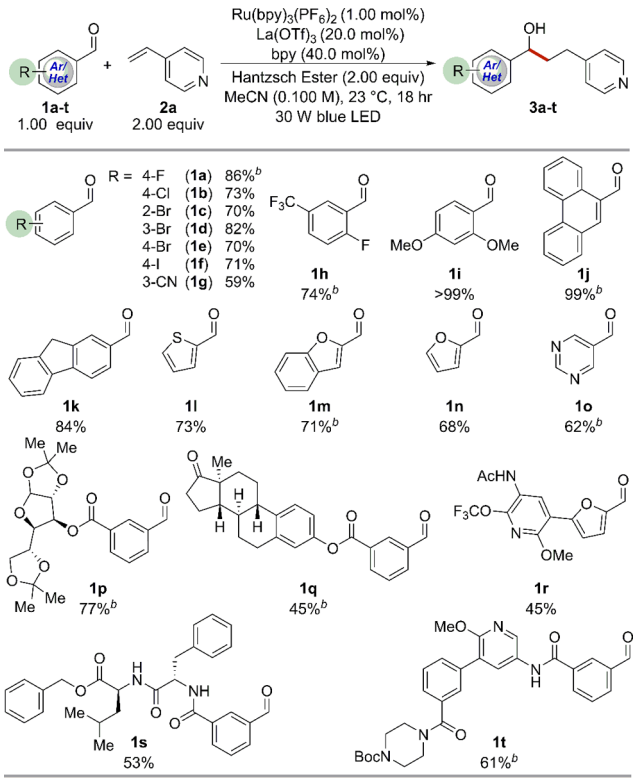
entry	photocatalyst (1.00 mol%)	Lewis acid (20.0 mol%)	reductant (2.00 equiv)	yield [%][a]
1	$Ru(bpy)_3(PF_6)_2$	–	HEH	0
2	$Ru(bpy)_3(PF_6)_2$	$Yb(OTf)_3$	HEH	18
3	$Ru(bpy)_3(PF_6)_2$	$Gd(OTf)_3$	HEH	85
4	$Ru(bpy)_3(PF_6)_2$	$La(OTf)_3$	HEH	>99
5	$Ir(ppy)_3$	$La(OTf)_3$	HEH	>99
6	Rho 6G	$La(OTf)_3$	HEH	47
7	–	$La(OTf)_3$	HEH	16
8	$Ru(bpy)_3(PF_6)_2$	$La(OTf)_3$	DIPEA	0
9	$Ru(bpy)_3(PF_6)_2$	$La(OTf)_3$	BNAH	0
10	$Ru(bpy)_3(PF_6)_2$	$La(OTf)_3$	HEH	78[b]
11	$Ru(bpy)_3(PF_6)_2$	$La(OTf)_3$	HEH	0[c]
12	$Ru(bpy)_3(PF_6)_2$	$La(OTf)_3$	HEH	0[d]

[a]Yields were determined by ^{19}F NMR using 3-fluoronitrobenzene as the internal standard unless otherwise specified. [b]Without bipyridine. [c]Without light. [d]Under oxygen atmosphere.

absence of Lewis acid (entry 1).[13] With a sub-stoichiometric amount of $Yb(OTf)_3$ and bipyridine ligand, **3a** was formed, albeit in low yield (entry 2). The yield of **3a** was drastically improved with $Gd(OTf)_3$ (entry 3), while with $La(OTf)_3$, **3a** was generated quantitatively (entry 4). We also observed that the reaction worked equally well when $Ru(bpy)_3(PF_6)_2$ was substituted with $Ir(ppy)_3$ (entry 5), but the yield was diminished with Rhodamine 6G (entry 6). Interestingly, without any photoredox catalyst, a small amount of **3a** was still observed (entry 7). Presumably, ketyl radicals were formed through direct single electron transfer (SET) between photo-excited Hantzsch ester and aldehydes.[14] Yet, such SET is less efficient than that in the presence of a photoredox catalyst. Notably, the use of Hantzsch ester as a reductant is crucial. When either Hünig's base (entry 8) or 1-benzyl-1,4-dihydronicotinamide (BNAH) (entry 9) was employed as a stoichiometric reductant in place of HEH, no **3a** was obtained. Use of HEH as a reductant is beneficial because the oxidized-Hantzsch ester (Ox-HE) could be readily recycled and converted to HEH through hydrogenation.[15] In the absence of bipyridine, the reaction afforded **3a** in only 78% yield (entry 10), the drop likely attributed to the poor solubility of unligated $La(OTf)_3$ in MeCN. In the control experiments, we found that both light (entry 11) and an oxygen-free atmosphere (entry 12) were necessary for the reaction to proceed.

With the optimized reaction conditions in hand, we then examined the generality of this transformation with respect to the aldehyde component. As shown in Table 2, the coupling reactions of both electron-deficient and electron-rich benzaldehydes proceeded with high efficiency (up to quantitative yield). It is noteworthy that halogen functionalities (**1a**–**1f**, **1h**), in particular Br and I, remain intact after the reaction, providing easy handles for further synthetic elaborations. In addition, the *ortho*-, *meta*-, and *para*-substituents show little influence on the reaction efficiency (**1c**–**1e**). Moreover, the mild reaction conditions are compatible with a wide range of other functional groups including ester (**1p**, **1q**, **1s**), ketone (**1q**), amide (**1r**–**1t**), nitrile (**1g**), ether (**1i**, **1p**, **1r**, **1t**), $-OCF_3$ (**1r**), and $-CF_3$

Table 2. Selected Examples of the Coupling Reaction between Aldehydes and 4-Vinylpyridine[a]



[a]Cited yields are of isolated material following chromatography. [b]Reactions performed with 2 equiv of aldehyde and 1 equiv of 4-vinylpyridine.

(**1h**). Given the importance of heterocyclic structures in the synthesis of biologically important molecules, we were pleased to find that heteroaryl aldehydes (**1l**–**1o**) and aryl aldehydes bearing heteroarene substituents (**1t**) readily participated in the coupling reaction. To further demonstrate the synthetic utility of the reaction, we tested more complex substrates, including sugar (diacetone-D-glucose, **1p**), natural product (estrone, **1q**), and peptide (**1s**) derivatives. To our delight, they all afforded the desired products in synthetically useful yields. Notably, only one diastereomer was obtained in these cases, which indicates that existing chiral centers on aldehydes have a strong influence on the stereochemical outcome of the transformation.

Next, we directed our attention to delineating the scope of alkenylpyridine coupling partners (Table 3). Gratifyingly, 2-vinylpyridine (**4a**), 2-(1-methylalkenyl)pyridine (**4b**), and a range of 2-(1-arylalkenyl)pyridines (**4c**–**4j**) were converted into the corresponding products **5** in good to excellent yields and with modest diastereoselectivities. The reaction tolerated substrates bearing electron-neutral (**4c**), electron-rich (**4d**–**4f**), and electron-poor (**4g**, **4h**) arene rings, as well as heterocyclic structures such as benzofuran (**4i**) and indole (**4j**). The coupling reaction between aldehydes and 2-(1-arylalkenyl)-pyridines described here provides the first general route to compounds **5c**–**5j**, which prior to our studies remained unknown. Our Lewis acid/photoredox catalytic protocol enables a straightforward synthesis of this novel molecular scaffold and its exploration in the context of medicinal chemistry.

Encouraged by the results of the aldehyde-alkenylpyridine coupling, we tested imines as potential coupling partners in the

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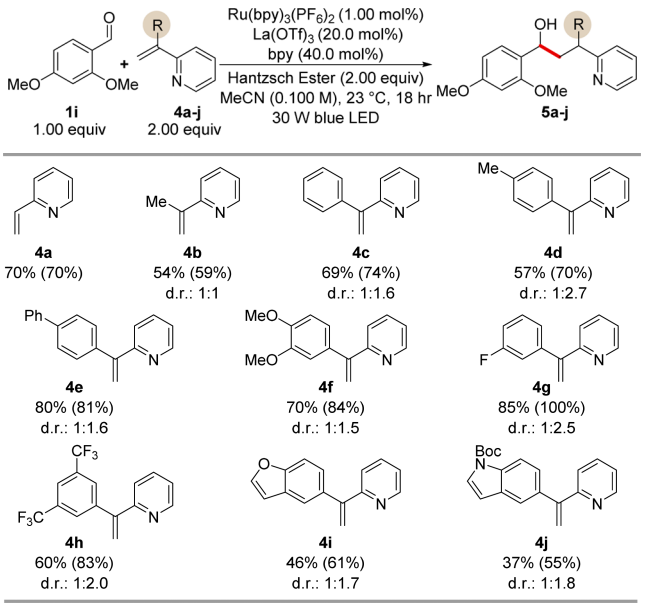
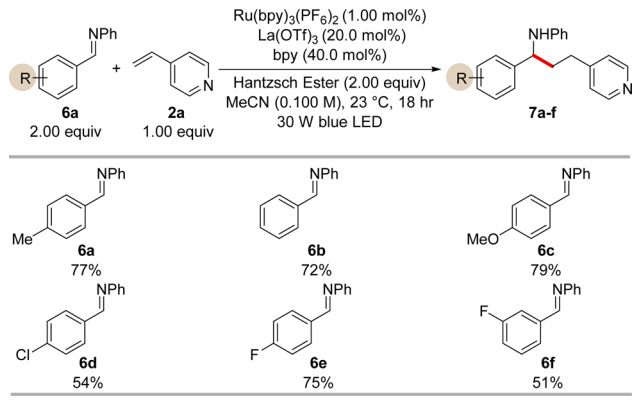
Table 3. Selected Examples of the Coupling Reaction between 2,4-Dimethoxybenzaldehyde and Alkenylpyridines[a]



[a]Cited yields are of isolated material following chromatography. NMR yield in parentheses and d.r. were determined on the crude reaction sample using ^{1}H NMR.

reaction with 4-vinylpyridine (Table 4). Prior to this report, intermolecular reductive imine−olefin coupling reactions under photoredox conditions were rare.[11l,12c] This is unfortunate, considering the great importance of amines in drug design and development. We were pleased to find that α-aminoalkyl radicals generated from aromatic imines upon a SET can indeed undergo the coupling reaction with 4-vinylpyridine. Importantly, the reaction proceeded well regardless of the electronic state of the iminyl aromatic rings.

Table 4. Selected Examples of the Coupling Reaction between Imines and 4-Vinylpyridine[a]



[a]Cited yields are of isolated material following chromatography.

The proposed mechanistic details of our transformation are depicted in Figure 1. Irradiation of $Ru(bpy)_3^{2+}$ with visible light produces a long-lived (1.1 μs)[16] photoexcited state, $*Ru(bpy)_3^{2+}$. A Stern−Volmer experiment showed no measurable luminescence quenching of $*Ru(bpy)_3^{2+}$ ($E_{1/2}^{red}$ = +0.77 V vs SCE)[17] by HEH ($E_{1/2}^{red}$ = +0.887 V vs SCE)[18] in MeCN. In addition, neither benzaldehyde nor 4-vinylpyridine quenches

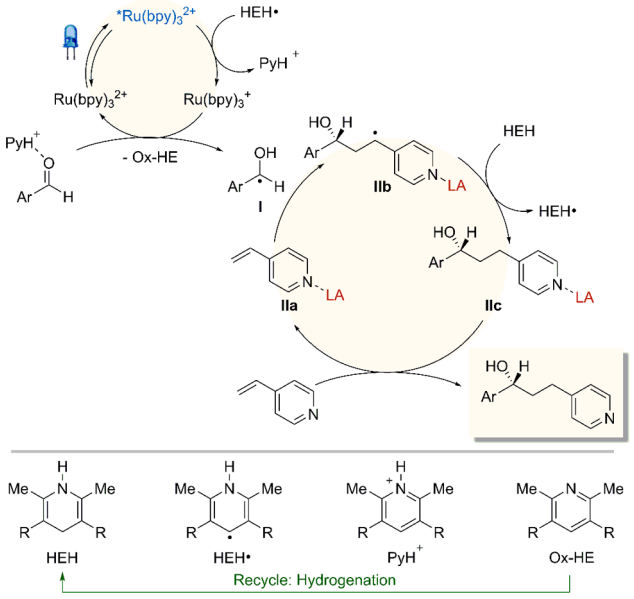


Figure 1. Proposed reaction mechanism.

the excited photocatalyst (both in the absence and presence of Lewis acid). In order to exclude the possibility of excited HEH (*HEH) (λ_{max} = 362 nm in MeCN) being the quencher of $*Ru(bpy)_3^{2+}$, we ran the reaction using a laser line filter (CWL = 488 ± 2 nm, fwhm = 10 ± 2 nm) and obtained the desired product. Based on these observations, we postulated that the excited photocatalyst is likely quenched by the catalytically generated intermediate Hantzsch ester radical (HEH•).[19] Since HEH• is absent at the beginning of the reaction, it is initially generated via an alternative pathway that involves photoexcitation of HEH (*HEH), followed by a SET from *HEH to an aldehyde with a concomitant proton transfer. Reduction of $*Ru(bpy)_3^{2+}$ by HEH• ($E_{1/2}^{red}$ = −0.76 V vs SCE)[18] affords a strongly reducing ruthenium(I) species, $Ru(bpy)_3^{+}$, and pyridinium ion PyH^+. $Ru(bpy)_3^{+}$ ($E_{1/2}^{red}$ = −1.33 V vs SCE)[17] engages in a SET with aldehydes activated by hydrogen bonding with PyH^+ to regenerate the $Ru(bpy)_3^{2+}$ catalyst and afford ketyl radical intermediate **I**. Addition of **I** to Lewis acid-activated 4-vinylpyridine (**IIa**) forms radical **IIb**, which can abstract hydrogen atom directly from HEH, thus generating the Lewis acid-bound product (**IIc**) and another molecule of a reductant (HEH•) capable of reducing $*Ru(bpy)_3^{2+}$. Complex **IIc** undergoes ligand exchange with 4-vinylpyridine to liberate the desired coupling product and complete the catalytic cycle.

In conclusion, we have developed the first photocatalytic reaction for the coupling between alkenylpyridines and carbonyl or iminyl derivatives with a Lewis acid co-catalyst. The unique features of our synergistic catalytic system include the following: (i) mild reaction conditions that tolerate a wide scope of functional groups and complex molecular architectures such as sugar, natural product, and peptide derivatives; (ii) the ability to forge alcohols and amines using a catalytic protocol that couples two bench stable electrophiles, carbonyl/iminyl derivatives and alkenylpyridines, provides an attractive alternative to methods that use stoichiometric amounts of reactive, unstable intermediates; (iii) access to a broad range of "privileged" and novel heterocyclic structures, which could provide a powerful new strategy for the synthesis of versatile small molecules of potential pharmaceutical relevance; (iv) the exclusive β-selectivity of our protocol offers a complementary

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method to the existing α-selective reductive coupling reactions of alkenylpyridines; (v) mechanistic studies offer valuable insight into the key step that involves addition of ketyl or α-aminoalkyl radicals to Lewis acid-activated alkenylpyridines. We anticipate that this reaction will serve as the basis for the development of broadly useful coupling reactions of two electrophiles. Further efforts will be directed toward the development of an asymmetric coupling reaction with the aid of a chiral ligand/Lewis acid system. In addition, we will continue working on new visible light photoredox-catalyzed transformations involving ketyl radical intermediates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b01373.

Experimental details and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(19) See SI for detailed mechanistic studies and discussions.

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