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Catalytic Asymmetric α-Acylation of Tertiary Amines Mediated by a Dual Catalysis Mode: N-Heterocyclic Carbene and Photoredox Catalysis

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Supporting Information

ABSTRACT: Cross-coupling reactions are among the most widely utilized methods for C−C bond formation; however, the requirement of preactivated starting materials still presents a major limitation. Methods that take direct advantage of the inherent reactivity of the C−H bond offer an efficient alternative to these methods, negating the requirement for substrate preactivation. In this process, two chemically distinct activation events culminate in the formation of the desired C−C bond with loss of H_2 as the only byproduct. Herein we report the catalytic asymmetric α-acylation of tertiary amines with aldehydes facilitated by the combination of chiral N-heterocyclic carbene catalysis and photoredox catalysis.

The efficient and selective construction of C−C bonds has been a long-standing challenge in organic synthesis. Traditionally, the formation of C−C bonds has relied primarily on preactivated starting materials.[1] Although these reactions find broad use in organic synthesis, the preactivation of each substrate generally requires at least one chemical manipulation to prepare, and stoichiometric quantities of metal salts are often generated as byproducts. For this reason, the area of transition-metal-catalyzed C−H activation has emerged as one of the fastest growing fields in organic chemistry.[2,3] The impact that C−H activation has had on chemical synthesis goes without saying; however, these methods still rely heavily on partial functionalization of one partner to generate the C−C bond.

Recently, considerable effort has been invested in the development of methods that do not rely on any prior activation but instead take direct advantage of the inherent reactivity of the C−H bond.[4,5] Among these reports, few methods have been shown to activate a prochiral sp^3 C−H bond selectively, offering access to chiral nonracemic coupling.[6] Of particular note is the ability of a catalyst to activate the α-C(sp^3)−H bond of a tertiary amine, which is capable of forming a new C−C bond in the presence of a suitable nucleophile.[7] Forming this new C−C bond asymmetrically has been challenging, and only recently has a highly enantioselective method been developed.[8]

An emerging strategy for the activation of C−H bonds is by single electron transfer (SET) processes. The ability of light to induce these types of chemical transformations has been known since the early 20th century.[9] Photoredox catalysis, which takes advantage of the unique photophysical properties of organic molecules and organometallic complexes, has been used for decades, but only recently have chemists taken advantage of these properties to solve long-standing problems in organic synthesis.[10] We were particularly interested in the use of visible-light photoredox catalysis to generate highly reactive iminium ions from tertiary amines, which may be trapped with a variety of nucleophiles, a formal C−H activation, and potential generation of a new C−C bond.[11,12] The use of visible-light photoredox catalysis to generate these reactive species is attractive in the sense that no preactivation of the substrate is required and the reaction conditions are mild, thereby allowing for potential compatibility between multiple catalytic pathways.

The generation of acyl anion or homoenolate equivalents from aldehydes represents a powerful strategy in N-heterocyclic carbene (NHC) catalysis, wherein an aldehyde is converted to a nucleophilic species under very mild conditions. These species have been demonstrated to be competent nucleophiles in a plethora of reactions.[13] We envisioned that the union of chiral NHC catalysis of aldehydes with visible-light photoredox catalysis of tertiary amines could be achieved (Figure 1),

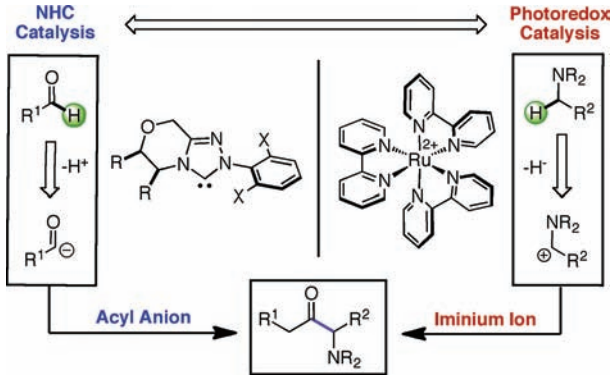

Figure 1. Proposed dual catalysis mode.

resulting in a direct asymmetric α-acylation of tertiary amines.[14,15] The anticipated coupling reaction would rely on two chemically distinct activation pathways, forming a C−C bond stereoselectively while producing H_2 (in the form of H_2O in the presence of a weak oxidant) as the only byproduct. The biological relevance of these products as well as the synthetic utility of the derived 1,2-aminoalcohols makes this a desirable transformation.

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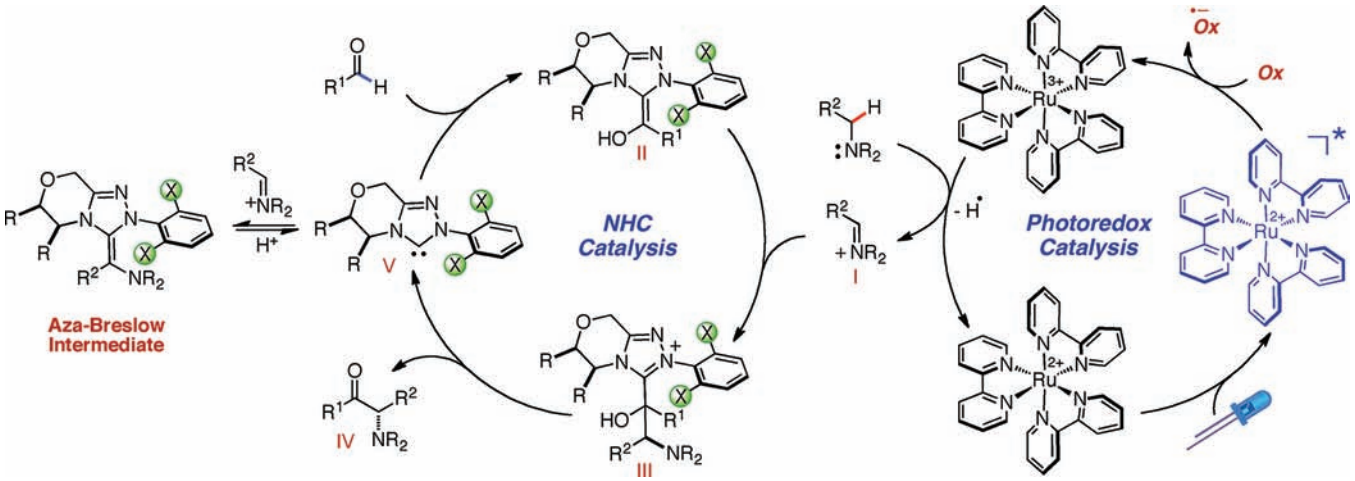
Scheme 1. Proposed Catalytic Cycles



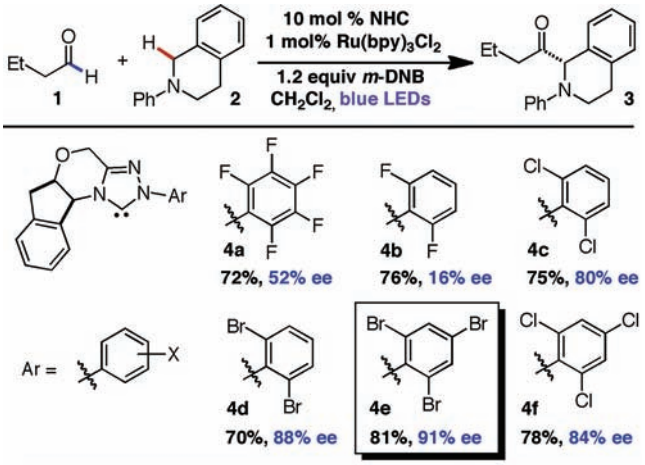
We initially proposed that irradiation of $[Ru(bpy)_3]^{2+}$ with blue light would populate the $*[Ru(bpy)_3]^{2+}$ excited state, from which the powerful oxidant $[Ru(bpy)_3]^{3+}$ (1.29 V vs SCE) should be generated in the presence of a suitable oxidative quencher (Scheme 1).[16] Single-electron oxidation of a tertiary amine followed by hydrogen atom abstraction would then result in the formation of iminium ion **I**, returning $[Ru(bpy)_3]^{2+}$ to the catalytic cycle. Interaction of an NHC with an aldehyde would generate the nucleophilic Breslow intermediate **II**, which could then intercept iminium ion **I**, forging a new C–C bond. Elimination of the NHC from **III** would provide the α-amino ketone **IV** and allow the NHC **V** to re-enter the catalytic cycle.

We realized at the outset that oxidation of the Breslow intermediate **II** or NHC **V** by $[Ru(bpy)_3]^{3+}$ could result in unproductive pathways (formation of carboxylic acid or catalyst death) because of the similar redox potentials of this catalyst scaffold and tertiary amines. Furthermore, the more electrophilic iminium ion could react preferentially with the carbene catalyst, generating an aza-Breslow intermediate. A study of aza-Breslow intermediates derived from iminium salts that was recently disclosed by our group provided evidence that these intermediates are stable resting states for the catalyst.[17] In the presence of a weak acid, this process is reversible, and the active catalyst can re-enter the catalytic cycle.

We began our investigation by evaluating the addition of butanal (**1**) to *N*-phenyltetrahydroisoquinoline (**2**) (Table 1). After careful manipulation of the reaction conditions, we were pleased to find that the desired reactivity could be realized using $[Ru(bpy)_3]Cl_2$ as the photocatalyst in the presence of *m*-dinitrobenzene (*m*-DNB) and a chiral NHC under irradiation with blue light. Our aminoindanol-derived catalyst scaffold proved to be optimal for this application; however, low enantioselectivity was initially observed using known catalysts. Exploration of the steric and electronic properties of the NHC through derivatization of the *N*-aryl substituent enabled the discovery of catalyst **4e** containing the 2,4,6-tribromophenyl group. This catalyst combination provided the optimum yield and high enantioselectivity (92% ee) of α-amino ketone **3** (Table 1, entry 2).

During our initial studies, we found the addition of weak organic oxidants to be essential for achieving high catalytic efficiency in this process. In the absence of *m*-DNB, only a 13% yield of the desired product was obtained under otherwise identical conditions (Table 1, entry 4). Although optimal results were achieved using a stoichiometric quantity of *m*-DNB, comparable results were obtained with substoichiometric

Table 1. Catalyst and Reaction Optimization[a]



Entry	dev. from standard conditions	conv %[b]	yield %[c]	ee %[d]
1.	none	>95%	81%	91%
2.	5 mol % NHC	>95%	84%	92%
3.	No $Ru(bpy)_3Cl_2$	47%	32%	90%
4.	No *m*-DNB	46%	13%	88%
5.	No light	19%	5%	90%
6.	15 W fluorescent light	89%	63%	90%
7.	CH_3CN as solvent	>95%	12%	70%
8.	Precatalyst + 10 mol% *i*-Pr_2NEt	>95%	40%	89%
9.	Precatalyst + 10 mol% NaOAc	>95%	57%	84%
10.	Precatalyst w/ no base	>95%	78%	88%
11.	Degassed (Ar)	>95%	75%	87%
12.	Open to air	>95%	46%	92%

[a]Reactions were conducted with 1.5 equiv of **1** and 1.0 equiv of **2** at ambient temperature. [b]Based on consumption of **2** as determined by NMR analysis using an internal standard. [c]Based on NMR analysis using an internal standard. [d]Determined by HPLC using a chiral stationary phase.

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amounts. Furthermore, no detectable products of *m*-DNB reduction could be identified upon completion of the reaction. Nitrobenzenes are known oxidative quenchers of the *$[Ru(bpy)_3]^{2+}$ excited state;[18] thus, the role of *m*-DNB is likely to induce an oxidative quenching cycle of *$[Ru(bpy)_3]^{2+}$ under these conditions, with adventitious oxygen likely being the terminal oxidant.[19] Stronger oxidants such as $BrCCl_3$[20] led to complete consumption of the amine but provided none of the desired product, presumably because of oxidative decomposition of the NHC catalyst; thus, a judicious choice of the co-oxidant is crucial. Use of a household 15 W fluorescent light bulb as the light source produced a moderate yield of the desired product (63%; Table 1, entry 6), while rigorous exclusion of light resulted in <5% product formation, suggesting the participation of the *$[Ru(bpy)_3]^{2+}$ excited state in the catalytic cycle. In the presence of *m*-DNB but the absence of $[Ru(bpy)_3]Cl_2$, a much slower background reaction was observed (32%). In this case, *m*-DNB may function as a weak sensitizer.[21,22]

During our initial screening of conditions with catalyst **4e**, we achieved full conversion of the amine (>95%) but obtained only a poor yield of the desired product (12%) using acetonitrile as the reaction solvent (Table 1, entry 7). Under these conditions, aza-Breslow intermediate **5**, derived from trapping of the active catalyst **4e** with the in situ-generated iminium ion, precipitated from the reaction medium (Figure 2).

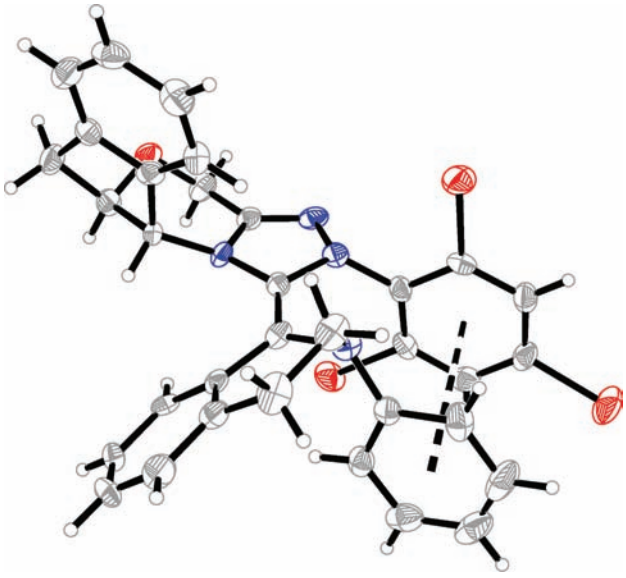
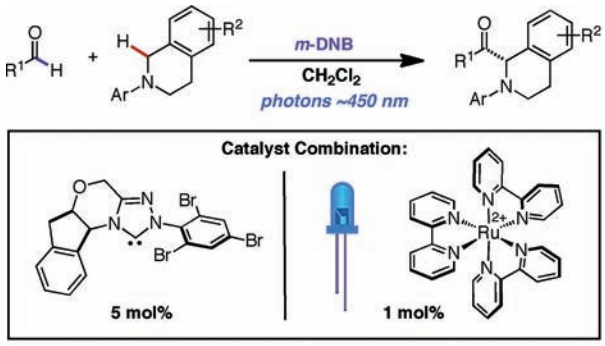


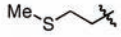
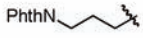
Figure 2. X-ray structure of isolated catalyst resting state **5**. Ellipsoids are drawn at the 75% probability level.

The low yield in this case is attributed to the poor solubility of this intermediate in acetonitrile, effectively removing it from the catalytic cycle. To test the catalytic relevance of this intermediate, **5** was resubjected to the original reaction conditions and provided ketone **3** in 76% yield and 92% ee, similar to that observed using the carbene directly. Catalytic amounts of carboxylic acid impurities, either present or generated under the reaction conditions, were likely responsible for catalyst turnover.

We found that aliphatic aldehydes reacted efficiently, affording the desired α-amino ketones in good yield and high enantioselectivity (Table 2). α-Branched aldehydes generally led to a loss in reactivity, except for cyclopropanecarboxaldehyde, which underwent smooth conversion, albeit with modest enantioselectivity (59%). Additional functionality, such as thioethers, esters, and protected amines, could also be incorporated into the aldehyde tether without a deleterious effect on either the efficiency or enantioselectivity. Derivatives of the *N*-aryltetrahydroisoquinoline were also investigated. Electron-releasing substituents on either the backbone or the *N*-aryl group were well-tolerated; however, electron-withdrawing groups led primarily to products of competing radical dimerization processes.[23]

Table 2. Reaction Scope[a,b]



Entry	R^1	R^2	Ar	yield %[c]	ee %[d]
1	Me	H	Ph	72%	62%
2	Et	H	Ph	67%	91%
3	n-Pr	H	Ph	81%	92%
4		H	Ph	61%	87%
5		H	Ph	91%	92%
6		H	Ph	75%	92%
7		H	Ph	61%	59%
8		H	Ph	79%	88%
9		H	Ph	88%	92%
10	*i*-Pr	H	Ph	<5%	N/A
11	*n*-Pr	H	*p*-tolyl	84%	92%
12	*n*-Pr	H	4-Br-C_6H_4	51%	90%
13	*n*-Pr	H	4-MeO-C_6H_4	54%	91%
14	*n*-Pr	H	4-CF_3-C_6H_4	<5%	N/A
15	*n*-Pr	6,7-MeO	Ph	94%	90%

[a]Reactions were conducted with 1.5 equiv of aldehyde, 1.0 equiv of amine, and 1.2 equiv of *m*-DNB at ambient temperature without exclusion of oxygen. [b]NHCs were generated from the corresponding azolium salts using NaH; see the Supporting Information. [c]Isolated yields after chromatography. [d]Determined by HPLC using a chiral stationary phase. The absolute stereochemistry was determined by X-ray analysis: see the Supporting Information.

In conclusion, we have identified a productive dual-catalysis mode that now enables the catalytic asymmetric α-acylation of tertiary amines. The direct conversion of $C(sp^3)$–H bonds to C–C bonds in a highly enantioselective manner has been a long-sought transformation that has received a great amount of

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attention in the past decade. Through the powerful combination of NHC catalysis and visible-light photoredox catalysis, the direct asymmetric functionalization of C(sp^3)−H bonds with aldehydes is now accessible. The extension of this methodology to a broad scope of tertiary amines is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details, spectroscopic data for all new compounds, and crystallographic data for **5** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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