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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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Abstract

Cross-coupling reactions are some of the most widely utilized methods for C-C bond formation; however, the requirement for pre-activated 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 pre-activation. 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 by-product. 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 pre-activated starting materials.[1] Although these reactions find broad use in organic synthesis, the pre-activation of each substrate generally requires at least one chemical manipulation to prepare and stoichiometric quantities of metal salts are often generated as by-products. 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 to develop methods that do not rely on any prior activation, and take direct advantage of the inherent reactivity of the C-H bond.[4,5] Among these reports, few methods have been shown to selectively activate a prochiral sp^3 C-H bond, offering access to a chiral non-racemic coupling.[6] Of particular note is the ability of a catalyst to activate the α-sp^3 C-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

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ASSOCIATED CONTENT

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

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 pre-activation of the substrate is required and 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 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 the union of chiral N-heterocyclic carbene catalysis of aldehydes with visible light photoredox catalysis of tertiary amines could be achieved, resulting in a direct asymmetric α-acylation of tertiary amines.[1415] 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.

We initially proposed that irradiation of $[Ru(bpy)_3]^{2+}$ with blue light would populate the $*[Ru(bpy)_3]^{2+}$ excited state and in the presence of a suitable oxidative quencher the powerful oxidant $[Ru(bpy)_3]^{3+}$ (1.29 V vs. SCE) should be generated.[16] Single electron oxidation of a tertiary amine, followed by hydrogen atom abstraction would result in formation of an iminium ion **I** returning $[Ru(bpy)_3]^{2+}$ to the catalytic cycle. Interaction of an NHC with an aldehyde generates the nucleophilic Breslow intermediate **II**, which can intercept the 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 onset that oxidation of the Breslow intermediate **III** or NHC **V** by $[Ru(bpy)_3]^{3+}$ could result in unproductive pathways (formation of carboxylic acid or catalyst death) due to the similar redox potential of this catalyst scaffold and a tertiary amine. Furthermore, the more electrophilic iminium ion could react preferentially with the carbene catalyst generating an aza-Breslow intermediate. Our group has recently disclosed a study of aza-Breslow intermediates derived from iminium salts, which has 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 active catalyst can re-enter the catalytic cycle.

We began our investigation by evaluating the addition of butanal **1** to N-phenyl-tetrahydroisoquinoline **2**. After careful manipulation of reaction conditions, we were pleased to find that the desired reactivity could be realized using $[Ru(bpy)_3]Cl_2$ as photocatalyst in the presence of *m*-dinitrobenzene (*m*-DNB), and a chiral NHC under irradiation with blue light. Our amino-indanol 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 provides optimum yield and high enantioselectivity (92% ee) of α-aminoketone **3**.

During our initial studies we found the addition of weak organic oxidants essential to achieving high catalytic efficiency in this process. In the absence of *m*-DNB only 13% yield of the desired product was obtained under otherwise identical conditions (Table 1, entry 4).

Although optimal results are achieved using a stoichiometric quantity of *m*-DNB, comparable results are obtained with substoichiometric amounts. Furthermore, no detectable reduction products of *m*-DNB 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] lead to complete consumption of the amine but provide none of the desired product presumably due to oxidative decomposition of the NHC catalyst; thus, judicious choice of the co-oxidant is crucial. Use of a household 15W fluorescent light bulb as the light source produces moderate yield (63%) of the desired product (Table 1, entry 6), while rigorous exclusion of light results 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 absence of $[Ru(bpy)_3]Cl_2$, a much slower background reaction is observed (32%). In this case, *m*-DNB may be functioning as a weak sensitizer.[21,22]

During our initial screening of conditions with catalyst **4e** we achieved full conversion of the amine (>95%) using acetonitrile as the reaction solvent (Table 1, Entry 7), but only obtained poor yields of the desired product (12%). Under these conditions, aza-Breslow intermediate **5**, derived from trapping of active catalyst **4e** with the *in situ* generated iminium ion, precipitates from the reaction medium (Figure 2). The low yield in this case is attributed to the poor solubility of this intermediate in acetonitrile, effectively removing it from the catalytic cycle. In order to test the catalytic relevance of this intermediate, **5** was re-subjected to the original reaction conditions, providing 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, are likely responsible for catalyst turnover.

We found that aliphatic aldehydes react efficiently, affording the desired α-amino ketones in good yield and high enantioselectivity. α-Branched aldehydes generally lead to loss in reactivity with the exception of cyclopropane carboxaldehyde, which undergoes smooth conversion, albeit with modest enantioselectivity (59%). Additional functionality can also be incorporated into the aldehyde tether without deleterious effect to either efficiency or enantioselectivity, such as thioethers, esters, and protected amines. Derivatives of the N-aryl tetrahydroisoquinoline have also been investigated. Electron-releasing substituents on either the backbone or N-aryl group are well tolerated; however, electron-withdrawing groups lead primarily to products of competing radical dimerization processes.[23]

In conclusion, we have identified a productive dual-catalysis mode, which now enables a catalytic asymmetric α-acylation of tertiary amines. The direct conversion of sp^3 C-H bonds to C-C bonds in a highly enantioselective manner has been a long sought transformation and has received a great amount of attention in the past decade. Utilizing the powerful combination of N-heterocyclic carbene catalysis and visible-light photoredox catalysis, the direct asymmetric functionalization of sp^3 C-H bonds with aldehydes is now accessible. Extension of this methodology to a broad scope of tertiary amines is currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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22. The azolium precatalyst may also be used in the presence of base. In absence of exogenous base, tetrahydroisoquinoline **2** is sufficiently basic to induce formation of the carbene (Table 1, entries 8-10).
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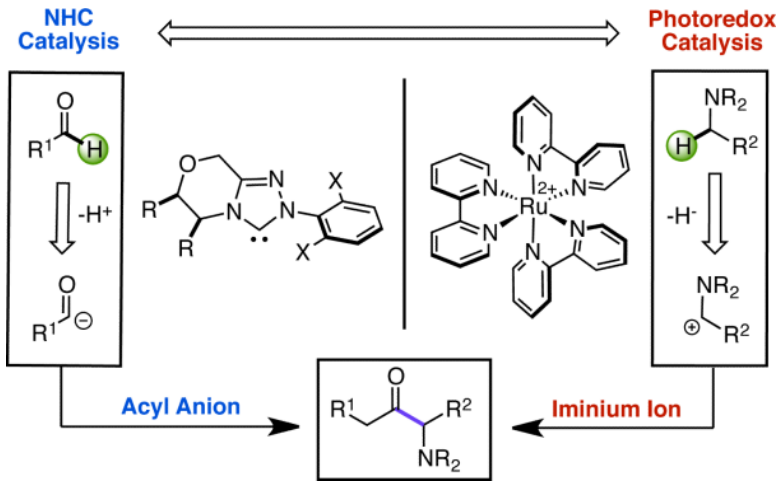
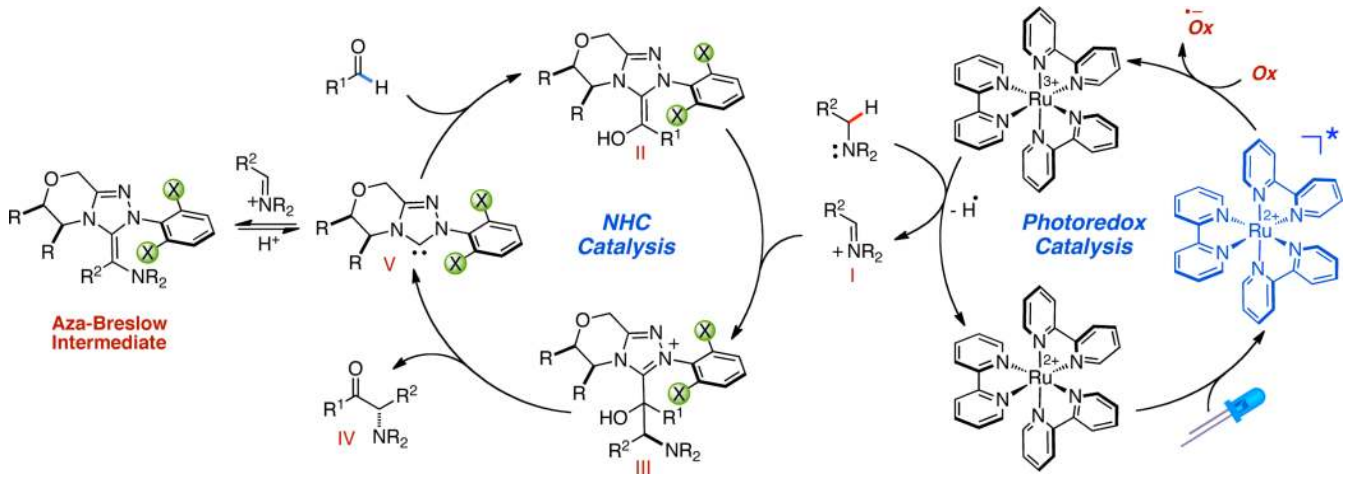


Figure 1.
Proposed Dual Catalysis Mode



Scheme 1.
Proposed Catalytic Cycles

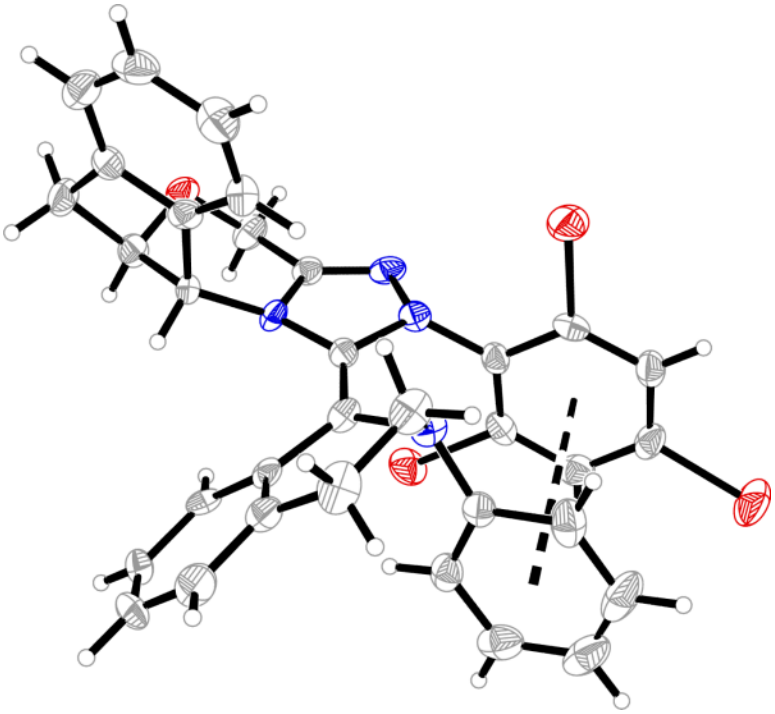
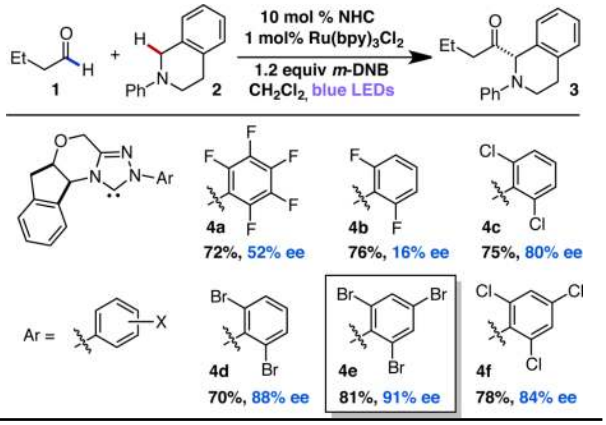


Figure 2. X-Ray Structure of Isolated Catalyst Resting State 5
Ellipsoids drawn at the 75% probability level.

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 atmosphere	>95%	46%	92%

[a]Reactions conducted with 1.5 equiv **1** and 1.0 equiv **2** at ambient temperature.

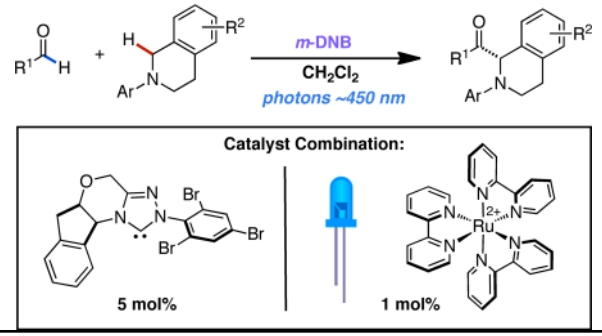
[b]Conversion based on consumption of **2** by NMR using an internal standard.

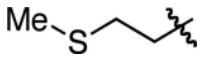
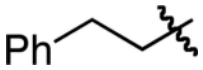
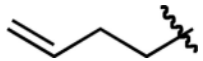
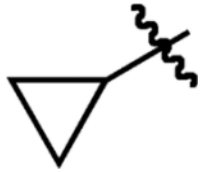
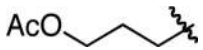
[c]Yield based on NMR yield using an internal standard.

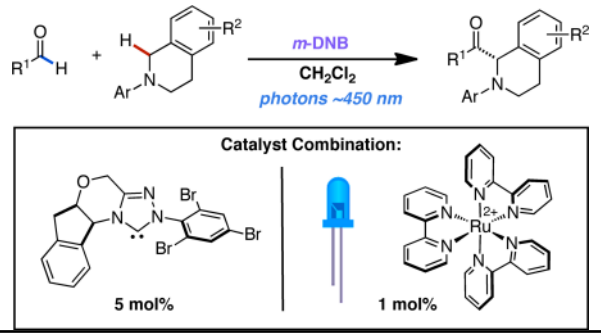
[d]Enantioselectivity determined by HPLC using a chiral stationary phase.

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%



Entry	R^1	R^2	Ar	yield %[c]	ee %[d]
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%

[e]Absolute stereochemistry determined by x-ray analysis: see supporting information.

[a]Reaction conducted with 1.5 equiv aldehyde, 1.0 equiv of amine, and 1.2 equiv of *m*-DNB at ambient temperature without exclusion of oxygen.

[b]NHC generated from the corresponding azolium salt using NaH; see supporting information.

[c]Yield refers to isolated yield after chromatography.

[d]Enantioselectivity determined by HPLC using a chiral stationary phase.