Published in final edited form as:
Chem Sci. 2014 January ; 5(1): . doi:10.1039/C3SC52265B.

Photoredox Activation and Anion Binding Catalysis in the Dual Catalytic Enantioselective Synthesis of β-Amino Esters

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Abstract

The enantioselective oxidative C-H functionalization of tetrahydroisoquinoline derivatives is achieved through the merger of photoredox and asymmetric anion-binding catalysis. This combination of two distinct catalysis concepts introduces a potentially general approach to asymmetric transformations in oxidative photocatalysis.

Introduction

Photoredox catalysis has emerged recently as a powerful tool for organic synthesis.[1] Irradiation of photoactive catalysts with visible light can be parlayed to the practical generation of synthetically useful high-energy organic intermediates such as free radicals[2] and radical anions and cations.[3,4] Successful efforts to induce enantioselective catalytic control in such photocatalyzed processes have relied thus far on covalent organocatalysis: photoredox aminocatalysis as introduced by MacMillan,[2a,5] and the combination of photoredox catalysis with N-heterocyclic carbene catalysis as developed by Rovis.[6,7]The main text of the article should appear here.

Since many reactions initiated by visible light photocatalysis involve the reductive generation of halide anions, [8] we considered whether the use of chiral anion-binding catalysts[9] in combination with photocatalysis would provide opportunities for new types of enantioselective transformations[10,11] In one specific embodiment of this idea, we envisioned that iminium ion equivalents generated under mild conditions from tertiary amines by photocatalyzed oxidation[12] might be trapped in stereoselective nucleophilic addition reactions under the influence of a chiral H-bond donor catalyst (Figure 1). We describe here the successful development of a dual catalyst strategy for the enantioselective oxidative alkylation of tetrahydroisoquinolines with silyl ketene acetals.

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†Electronic Supplementary Information (ESI) available: Detailed experimental procedures and spectroscopic data of all new compounds. See DOI: 10.1039/b000000x/

‡Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

We chose to evaluate the proposed dual catalytic reaction design in enantioselective oxidative Mannich reactions to access tetrahydroisoquinoline derived β-amino esters such as **3a** (Table 1).[13,14] In this context, we reported recently a photocatalytic method for the oxidative generation of iminium ion precursors from simple *N*-aryltetrahydroisoquinolines such as **1a** using bromotrichloromethane as the stoichiometric oxidant.[15,16,17] Coupling this protocol to an enantioselective thiourea-catalyzed addition of enolate equivalents such as silyl ketene acetal **2** would require identification of the appropriate photoredox and chiral thiourea catalysts, as well as reaction conditions suitable for both transformations.

Results and Discussion

In initial experiments, the proper choice of solvent systems was revealed as a key challenge. In relatively polar media (CH_3CN, CH_2Cl_2, DMF), with CCl_4 as the stoichiometric oxidant, the oxidative photocatalytic Mannich reaction of *N*-phenyltetrahydroisoquinoline (**1a**) and silyl ketene acetal **2** afforded **3a** cleanly in the presence of chiral thiourea catalysts, but always in racemic form. In contrast, unreacted tetrahydroisoquinoline **1a** could be recovered from attempted oxidations in non-polar solvents such as MTBE, which are optimal for attaining high enantioselectivity in anion-binding thiourea catalysis. The failure of the photoredox reaction under these conditions could be ascribed simply to the lack of solubility of the photocatalyst, even when relatively non-polar complexes such as $Ru(bpy)_3(PF_6)_2$ were employed. Ultimately, the enantioselective oxidative Mannich reaction could be achieved by performing the photocatalytic oxidation in CH_3CN and switching solvents to MTBE for the thiourea-catalyzed alkylation reaction. In this manner, full conversion of **1a** to the corresponding iminium ion in CH_3CN was observed after irradiation with blue LEDs for 16 hours using 2 equiv of CCl_4, and tetrahydroisoquinoline **3a** was obtained in 50% ee upon alkylation with **2** in the presence of chiral thiourea **5a** at −78 °C.

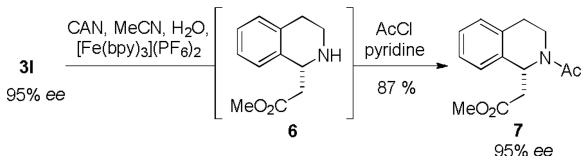
Enantioselective oxidative Mannich reactions of **1a** and silyl ketene acetal **2** were evaluated with a variety of thiourea catalysts (Table 1). Only catalysts bearing both 3,5-bis(trifluoromethyl)aniline and tertiary amide components were found to promote useful reaction rates at −78 °C.[18] Constrained arylpyrrolidine-derived thiourea catalysts of the general structure **5**, which have proven effective in a wide range of enantioselective transformations,[19,20] induced significantly higher ee's than catalysts bearing a less constrained tertiary amide fragment (e.g. **4**). In that context, the relative configuration of the arylpyrrolidine unit relative to the *tert*-leucine component had a significant impact on reaction enantioselectivity (entries 7–8), pointing to the importance of the precise disposition of the aryl group relative to the thiourea anion-binding site. No straightforward correlation between the expanse of the α-aryl substituent on the pyrrolidine and reaction enantioselectivity was observed (Table 1, entries 3–6). In contrast, substitution on the *ortho*-position of the arylpyrrolidine resulted in significant improvements in enantioinduction, although the electronic properties of the substituent had little impact (entries 9–11). Further reaction optimization using catalyst **5c** revealed a significant improvement in enantioselectivity when the reaction was conducted at −60 °C with an initial concentration of 0.05M (entries 5 and 7). After extensive evaluation of different arylpyrrolidine-derived analogs of **5**, thiourea **5g** was identified as an optimal catalyst for the model transformation of **1a** to **3a**.

During the course of the optimization studies outlined above, we observed that the identities of both the photocatalyst counterion and the halogen atom source had significant effects on enantioselectivity in the thiourea-catalyzed silyl ketene acetal addition reaction (Table 2). Consistently lower enantioselectivity was observed when using $BrCCl_3$ as the stoichiometric oxidant compared with CCl_4, a result that is attributable to more favorable interactions of the chloride-bound thiourea catalyst in the enantioselectivity-determining transition

structure.[21] When $Ru(bpy)_3(PF_6)_2$ was used as the photocatalyst in place of $Ru(bpy)_3Cl_2$ together with CCl_4 as the stoichiometric oxidant, highly variable enantioselectivities were obtained (e.g. 61–97% ee with catalyst **5g**). This unpredictable behavior associated with the use of the $Ru(bpy)_3(PF_6)_2$ photocatalyst appears to be tied to the heterogeneous nature of the alkylation reaction mixture. Although only 2 mol % of PF_6^- is present in the reaction medium and the iminium ion intermediate is predominantly associated with chloride (Cl^-/PF_6^- = ca. 51:1), the PF_6^- may impart enhanced solubility properties to the iminium ion, and thereby enable the racemic, background reaction to a greater extent.

With optimized conditions in hand we next explored the substrate scope of the reaction (Figure 2). The time required for full conversion of the *N*-aryltetrahydroisoquinoline derivatives **1** in the oxidation reaction was highly dependent on the electronic nature of the substrate, with electron-rich derivatives being more readily oxidized. To ensure complete conversion to the iminium ion, the amine was treated under the photochemical oxidation conditions for 16 h in all cases. The position of substituents on the *N*-aryl group influenced the enantioselectivity of the oxidative alkylation addition more profoundly than did their electronic properties. Thus, *ortho*-substituted substrates generally provided higher *ee* compared to *para*-substituted analogs (**3l** vs **3b; 3j** vs **3d**). In contrast, reaction enantioselectivities were very sensitive to the electronic nature substituents on the tetrahydroisoquinoline ring, with electron-rich systems generally affording lower ee's and/or yields (e.g. **3e, 3h, 3i**).

In order to better establish the synthetic utility of this chiral tetrahydroisoquinoline synthetic methodology, we sought to develop a protocol for *N*-dearylation of the products to provide access to the more useful secondary amine derivatives.[22] Electron-rich anilines have favorable redox properties that render them prone to *N*-aryl bond cleavage under oxidative conditions.[23] Accordingly, compound **3l**, which was generated with nearly perfect enantioselection in the oxidative Mannich reaction, was chosen as a model substrate for dearylation studies. Application of standard oxidative protocols for PMP or PMB removal (CAN, $PhI(TFA)_2$, or DDQ) led to rapid consumption of **3l** but low yields of the desired secondary amine due to product decomposition via over-oxidation. We anticipated that the use of an oxidant more closely matched to the oxidation potential of the substrate would have a better chance of avoiding decomposition of the relatively sensitive secondary amine product. Evaluation of Fe(III)-based oxidants led to the identification of $[Fe(bpy)_3]^{3+}$, formed in situ upon treatment of $[Fe(bpy)_3](PF_6)_2$ with CAN,[24] as a highly effective oxidant for this transformation, leading to clean conversion to the desired amine **6**. Comparison of the optical rotation of **6** with the reported value enabled the assignment of its absolute configuration. Acylation of **6** with acetyl chloride provided **7** (95% ee, 87% yield starting from **3l**) with no significant compromise of enantiomeric purity.



(1)

Conclusions

In summary, we have developed an approach to the oxidative, enantioselective C-H functionalization of tetrahydroisoquinoline derivatives. A mild method for the selective

dearylation of products bearing *N*-*o*-anisyl groups was developed, thereby enabling further derivatization of the tetrahydroisoquinoline scaffold. Further applications of photoredox / chiral anion binding dual catalysis are anticipated and are the subject of current study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support for this research from the NIH-NIGMS (PO1 GM69721 and R01-GM43214) to ENJ and R01-GM096129 to CRJS), the Alfred P. Sloan Foundation, Amgen, Boehringer Ingelheim, Eli Lilly, and Novartis is gratefully acknowledged. GB is grateful to the Spanish Ministry of Education and Science (MEC) for a FPU predoctoral fellowship (AP2009-0950). Postdoctoral support from the Alexander von Humboldt Foundation (Feodor Lynen fellowship to CSS) and the Swedish Research Council (to CJW) is gratefully acknowledged.

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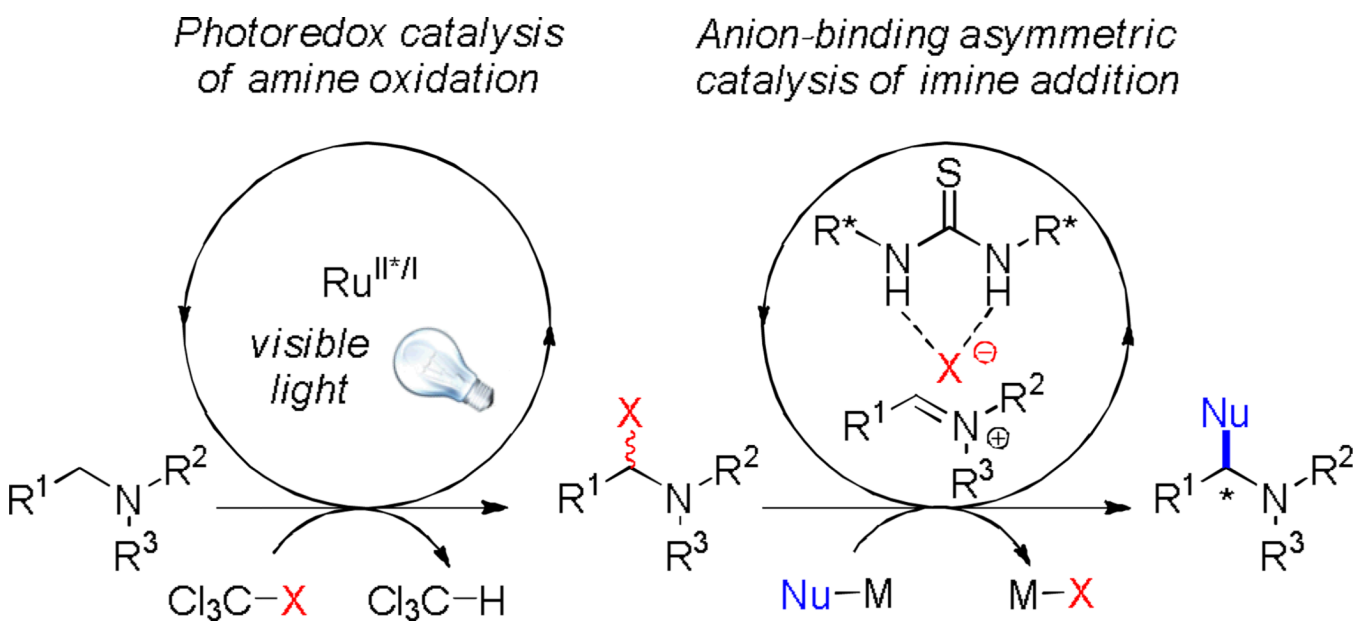


Fig. 1.
Merger of photoredox and anion-binding catalysis in oxidative enatioselective C-H functionalization of amines

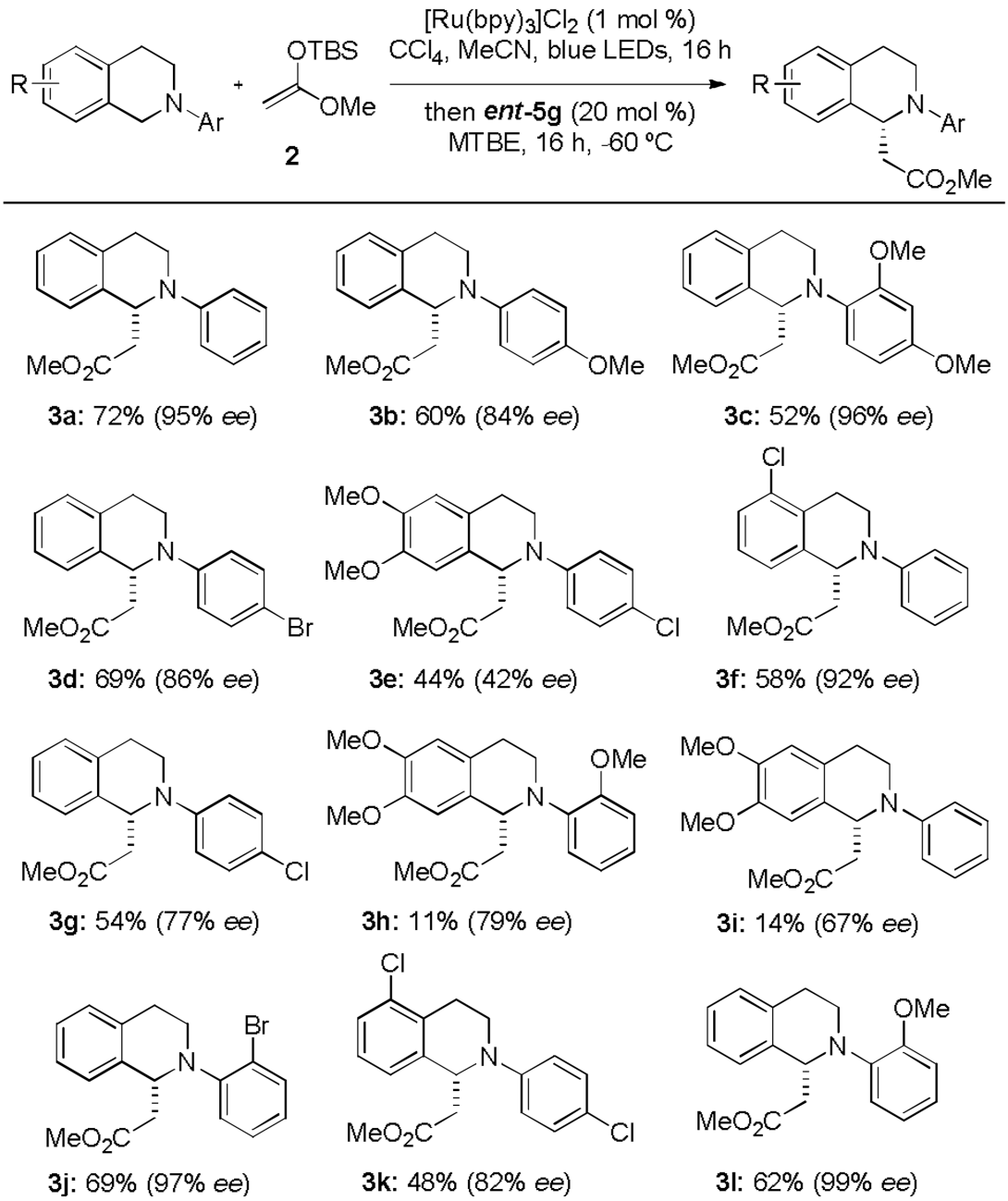
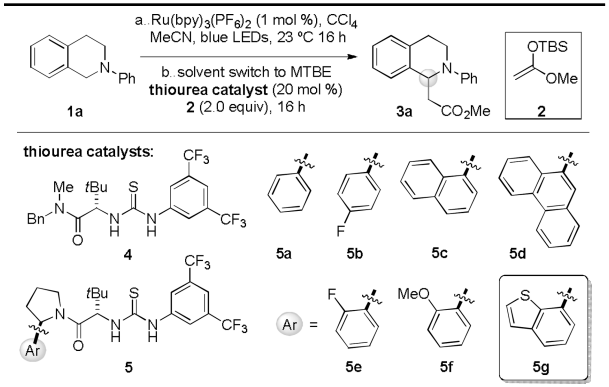


Fig. 3.
Substrate scope

Table 1

Thiourea catalyst optimization



entry	thiourea catalyst	T (°C)[a]	[1a]^o (M)	yield[%][b]	ee[%][c]
1	-	−78	0.1	0	N/A
2	**4**	−78	0.1	75	10
3	**5a**	−78	0.1	68	50
4	**5b**	−78	0.1	63	20
5	**5c**	−78	0.1	57	80
6	**5d**	−78	0.1	63	29
7	**5c**	−60	0.05	37	93
8	*epi*-**5c** [d]	−60	0.05	68	44
9	**5e**	−60	0.05	63	87
10	**5f**	−60	0.05	63	85
11	*ent*-**5g**	−60	0.05	72	−97

[a] Reaction temperature for the alkylation step in MTBE.

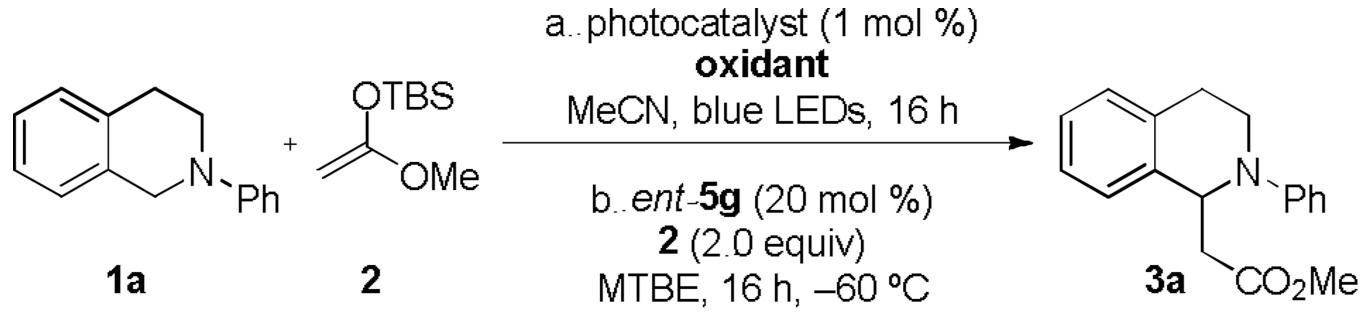
[b] Yields determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture relative to 2,5-dimethylfuran as the internal standard.

[c] Determined by HPLC on commercial chiral columns.

[d] Pyrrolodine configuration is (*R*), *tert*-leucine configuration is (*S*).

Table 2

Counterion effects



$[Ru(bpy)_3^{2+}]2Y^-$

$Y = Cl^-$ or PF_6^-

Y^-	oxidant	yield (%)	ee (%)[a]
Cl^-	$BrCCl_3$	65[b]	79
PF_6^-	CCl_4	80-95[c]	61-97[d]
Cl^-	CCl_4	69-72[b]	95-97[d]

[a] Determined by HPLC on commercial chiral columns.

[b] Isolated yield after purification by chromatography on silica gel.

[c] Determined by ^1H NMR spectroscopic analysis of the crude reaction mixture relative to 2,5-dimethylfuran as the internal standard.

[d] Range of enantiomeric excess achieved over >10 runs.