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Enantioselective Direct α-Amination of Aldehydes via a Photoredox Mechanism: A Strategy for Asymmetric Amine Fragment Coupling

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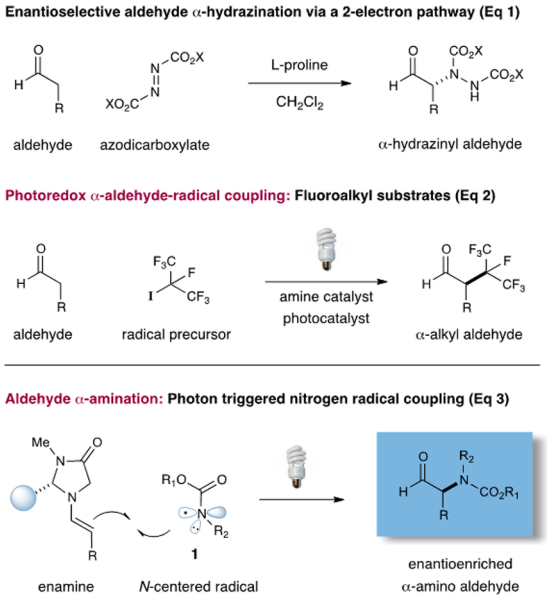
Supporting Information

ABSTRACT: The direct, asymmetric α-amination of aldehydes has been accomplished via a combination of photoredox and organocatalysis. Photon-generated N-centered radicals undergo enantioselective α-addition to catalytically formed chiral enamines to directly produce stable α-amino aldehyde adducts bearing synthetically useful amine substitution patterns. Incorporation of a photolabile group on the amine precursor obviates the need to employ a photoredox catalyst in this transformation. Importantly, this photoinduced transformation allows direct and enantioselective access to α-amino aldehyde products that do not require postreaction manipulation.

A central goal in organic synthesis is the development of methods to enantioselectively build C−N bonds within complex molecular structures. In particular, aldehydes, acids, and alcohols bearing α-amine substitution are widely distributed among pharmaceutically active compounds, and their broad representation has prompted the invention of a number of catalysis strategies for stereogenic nitrogen installation.[1,2] In this context, α-amino aldehydes represent a valuable structural motif, mainly because of their capacity to serve as versatile synthetic handles en route to a diverse range of complex N-containing synthons.[3] However, the development of robust methods for the asymmetric α-amination of aldehydes has been complicated by the requirement for electrophilic sources of nitrogen along with the need to circumvent postreaction racemization with relatively acid- or base-sensitive products. As a consequence, traditional α-carbonyl amination reactions often involve π-electrophile addition pathways that culminate in the installation of hydrazinyl or oxyamino substituents,[4] a class of N-stereogenicity that must be chemically modified (e.g., N−N or N−O reduction) prior to synthetic elaboration (eq 1). In 2008, our lab introduced a versatile platform for catalytic activation that we termed photoredox organocatalysis. In a common embodiment, electron-rich chiral enamines, derived from the condensation of aldehydes and secondary amine catalysts, undergo rapid and enantioselective coupling with electrophilic radical systems (e.g., $CF_3^{\bullet}$, $ArCH_2^{\bullet}$, etc.; eq 2).[5] Here we demonstrate that this "borrowed electron" catalysis strategy can be readily translated to the enantioselective α-amination of aldehydes using N-centered radicals (eq 3). As a critical design element, this open-shell coupling mechanism allows for the direct generation of broadly diverse α-amino aldehyde products that do not require postreaction manipulation yet are stable to racemization.



Design plan. A detailed catalytic cycle for our proposed asymmetric aldehyde amination is presented in Scheme 1. We postulated that an electrophilic N-based radical **1** might be generated under mild conditions from an amine substrate **3** bearing a photolabile leaving group. While recent literature suggests that N-centered radicals might be formed using photoredox-active metal complexes,[6] we envisioned that direct access to such open-shell reaction partners might be best accomplished using a traceless activation handle such as the dinitrophenylsulfonyloxy (ODNs) group (a subunit that can be chemoselectively triggered using a simple household lightbulb). From the outset, it seemed plausible that an electrophilic nitrogen radical such as **1** would rapidly undergo coupling with a transiently generated π-rich enamine **2** (derived from the condensation of an imidazolidinone catalyst with the aldehyde coupling partner). Oxidation of the resulting three-π-electron α-amino radical species **4** would then occur via single-electron transfer (SET) to a second equivalent of the photoexcited amine reagent **3***, a critical propagation step that would deliver iminium ion **5** and simultaneously release the next round of the nitrogen radical coupling partner.[7] Hydrolysis of **5** would then reconstitute the imidazolidinone catalyst and at the same time deliver the enantioenriched α-amino aldehyde product. Notably, despite growing interest in N-centered radicals as a source of

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Scheme 1. Proposed Mechanism for Aldehyde α-Amination

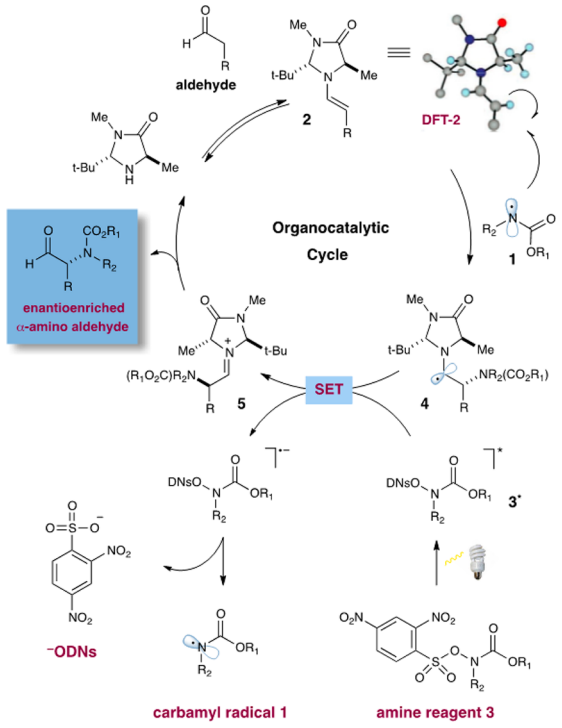
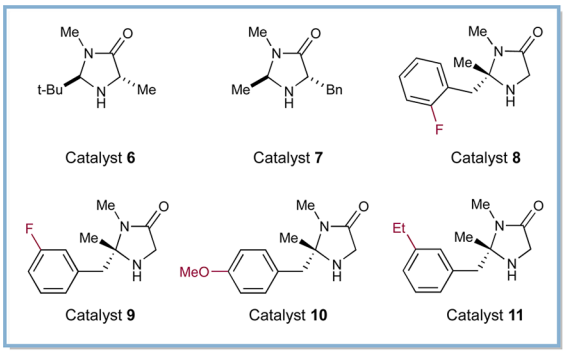
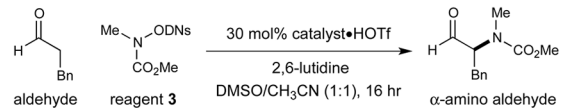


Table 1. Initial Studies toward α-Amination of Aldehydes





entry	catalyst	temp (°C)	light source[a]	yield (%)[b]	ee (%)[c]
1	**6**	rt	26 W CFL	30	91
2	**6**	rt	none	0	--
3[d]	**6**	rt	26 W CFL	0	--
4[e]	**6**	rt	LZC (300 nm)	38	90
5	**7**	rt	26 W CFL	40	75
6	**6**	−15	26 W CFL	47	92
7	**7**	−15	26 W CFL	65	78
8	**8**	−15	26 W CFL	82	88
9	**9**	−15	26 W CFL	77	86
10	**10**	−15	26 W CFL	72	86
11	**11**	**−15**	**26 W CFL**	**76**	**91**

[a]CFL = compact fluorescent light. [b]Obtained by ^{1}H NMR analysis using methyl benzoate as an internal standard. [c]Determined by chiral HPLC analysis of the corresponding alcohol. [d]Without 2,6-lutidine. [e]Carried out in a photobox equipped with 10 × Luzchem LZC-UVB.

electrophilic nitrogen,[8] few intermolecular amine coupling processes have been reported,[9] and indeed, no enantioselective applications have been described to date.

Our evaluation of the proposed aldehyde−amine coupling began with exposure of 3-phenylpropionaldehyde to a series of chiral amine catalysts and a large collection of N-based coupling partners (Table 1). We were delighted to find that carbamate **3** incorporating a photolabile ODNs residue is competent to produce the requisite heteroatom-centered radical upon exposure to household light in the presence of catalyst **6** (30% yield, 91% ee; entry 1).[10] Presumably, photonic excitation of amine **3** yields **3***, which readily undergoes single-electron reduction and mesolysis of the weak N−O bond to yield the desired amine-centered radical and ODNs anion. Initial experiments using catalyst **6** confirmed that the reaction does indeed require the use of light (entry 2 vs 1) and that a continuous source of photons is required for reaction propagation.[11] Moreover, the use of a monochromatic light source tuned to 300 nm (λ_{max} = 292 nm for **3**)[10] resulted in increased conversion and efficiency (38% yield, 90% ee, 6 h; entry 4).[12] These experiments provide additional evidence for the participation of **3*** in the photoredox process as described in Scheme 1.

We next evaluated amine catalysts of varying steric demand, with the supposition that higher enamine content[13] and increased exposure of the reactive π system would facilitate the critical radical addition step. Indeed, experiments performed in the presence of imidazolidinone catalyst **7**, a system that generally provides higher enamine content, exhibited improved overall efficiency (40% yield; entry 5), albeit with lower levels of stereocontrol (75% ee). Next, the effect of temperature on this α-amination protocol was evaluated. A significant improvement in the reaction yield was observed at subambient temperatures (47 vs 30%; entry 6 vs 1), presumably because of the capacity to circumvent deleterious reduction of the carbamyl radical, a pathway that would consume the amine reagent without productive C−N bond formation.[14] Finally, during the course of our optimization studies, we determined that the aminal C2 position on the imidazolidinone framework was susceptible to H-atom abstraction by the N-centered radical, leading to diminished reaction efficiency. This catalyst decomposition pathway was suppressed via the design of a novel organocatalyst framework wherein the C2 position incorporates a fully substituted carbon stereocenter (catalysts **8**−**11**; entries 8−11).[15] In particular, the use of imidazolidinone **11** provided the desired α-amino aldehyde adduct with optimal levels of efficiency and enantiocontrol (76% yield, 91% ee; entry 11).

It is notable that amine catalyst **11** was identified as the optimal organocatalyst for this transformation, as it has not previously been utilized in enamine- or iminium-based transformations. The high levels of enantiocontrol observed in this study can be rationalized on the basis of enamine olefin geometry and π-facial selectivity. More specifically, density functional theory (DFT) studies[16] of the corresponding enamine intermediate DFT-**12** (Figure 1) revealed that the *E* configuration of the four-π-electron olefin system is preferred, as it positions the electron-rich reaction site away from the fully substituted carbon center on the imidazolidinone framework. This preferred enamine geometry along with the *m*-ethyl arene orientation (as shown) was further confirmed by 2D nuclear Overhauser effect spectroscopy (NOESY) NMR studies.[17]

Reaction scope. With our optimal conditions in hand, we examined the scope of this new enantioselective C−N bond-forming protocol. This radical-based coupling is compatible with

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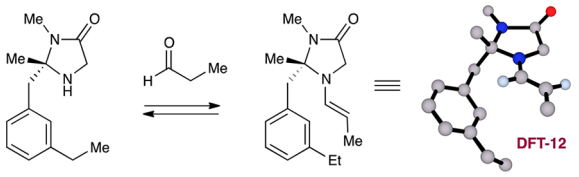
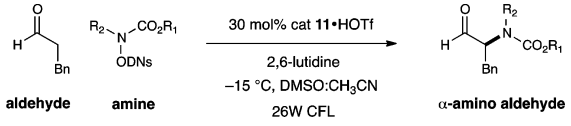


Figure 1. DFT structure of the catalyst-derived enamine (DFT-**12**).

a variety of amine reaction partners adorned with an array of alkyl motifs and carbamate protecting groups (71–79% yield, 86–94% ee; Table 2). It is important to note that many of these novel amine reagents are readily accessed in two steps from *N*-methyl hydroxylamine and are uniformly bench-stable, crystalline solids.[18] Moreover, the bisprotected *N*-Moc-*N*-MOM amine reagent can be effectively used for α-amination of aldehydes with excellent enantiocontrol (75% yield, 94% ee; entry 6). This specific example represents an important expansion of the scope of this method, offering a means to access orthogonally N,N-protected α-amino aldehydes enantioselectively.

We next sought to establish the scope of the aldehyde coupling partner in this transformation (Table 3). We were pleased to find that these mild redox conditions accommodate a wide range of substituents on the aldehyde component, including ethers, amines, alkenes, and aromatic rings (71–79% yield, 88–91% ee; entries 2–6). Moreover, excellent levels of enantiocontrol were achieved with sterically demanding formyl substrates (67–72% yield, 91–94% ee; entries 7 and 8). It should be noted that α-dialkyl aldehyde systems are not useful substrates in this transformation, as the imidazolidinone family of catalysts do not readily condense with α-branched aldehydes. This is an important catalyst design feature as it prevents postreaction racemization with the products generated in Tables 2 and 3.

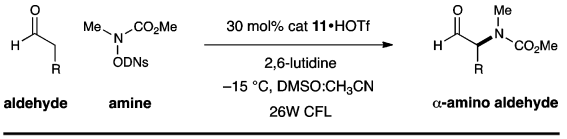
Table 2. Enantioselective α-Amination: Amine Scope



1	79% yield[a]	92% ee[b]	5	71% yield[a]	89% ee[b]
2	77% yield[a]	89% ee[b]	6	75% yield[a]	94% ee[b]
3	75% yield[a]	90% ee[b]	7	73% yield[a]	89% ee[b]
4	76% yield[a]	90% ee[b]	8	71% yield[a]	86% ee[b]

[a]Stereochemistry assigned by chemical correlation or by analogy. [b]Determined by chiral HPLC analysis of the corresponding alcohol.

Table 3. Enantioselective α-Amination: Aldehyde Scope



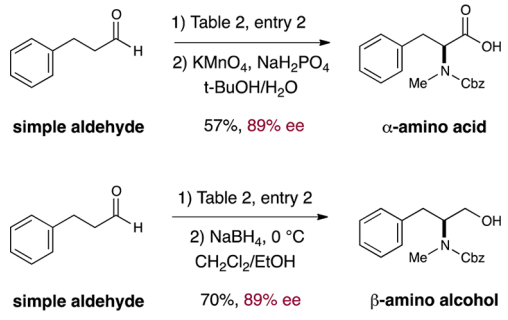
1	71% yield[a]	90% ee[b]	5	71% yield[a]	90% ee[b]
2	73% yield[a]	88% ee[b]	6	79% yield[a]	91% ee[b]
3	77% yield[a]	90% ee[b]	7	72% yield[a]	91% ee[b]
4	76% yield[a]	90% ee[b]	8	67% yield[a]	94% ee[b]

[a]Stereochemistry assigned by chemical correlation or by analogy. [b]Determined by chiral HPLC analysis of the corresponding alcohol or 2-naphthoyl ester.

Moreover, this protocol provides direct asymmetric access to synthetically valuable, configurationally stable α-amino aldehyde adducts that can be readily isolated and purified via column chromatography without further derivatization.

As a further demonstration of the synthetic utility of this method, we illustrate representative procedures for the conversion of these enantioenriched α-amino aldehyde adducts to either β-amino alcohol or α-amino acid motifs (Scheme 2).

Scheme 2. Telescoped Syntheses of β-Amino Alcohols and α-Amino Acids from Hydrocinnamaldehyde



The crude product of the α-amination reaction (Table 2, entry 2) could be directly converted to the corresponding β-amino alcohol in good yield with complete stereofidelity. Alternatively, direct oxidation with buffered $KMnO_4$ afforded the Cbz-protected *N*-methylphenylalanine with useful reaction efficiency and retention of optical purity. We anticipate that this α-amination/aldehyde derivatization strategy will find broad application in the synthetic community as a facile means to obtain rapid access to high-value nonproteogenic α-amino acids and *N*-alkyl-α-amino acids.[19−22]

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In summary, we have developed an organocatalytic photoredox-based approach to the asymmetric α-amination of aldehydes via the direct coupling of functionalized nitrogen and formyl precursors. This operationally facile process provides ready access to complex N-substituted α-amino aldehydes and at the same time offers a useful alternative to standard π-electron addition approaches to carbonyl α-amination. Moreover, to the best of our knowledge, this disclosure marks the first demonstration of the use of N-based radicals as viable reagents in a catalytic enantioselective transformation. We anticipate that this α-amination method will prove widely useful in the synthesis of complex target structures bearing chiral amine fragments.

■ ASSOCIATED CONTENT

Supporting Information

Procedures, spectral data, and complete ref 16. 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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(10) For synthesis details and UV−vis spectra of the amine reagents, see sections XI and XII in the Supporting Information (SI).

(11) The transformation did not undergo propagation upon removal of the light source, implicating a photon-induced electron transfer event. Moreover, generation of the N-centered radical required the presence of the electron-rich enamine (Table 1, entry 3). More specifically, UV−vis analysis of the radical precursor and the catalytically activated enamine (generated separately and concurrently) clearly showed that disproportionation of a charge transfer complex is not the mechanism for carbamyl radical production (Scheme 1). Lastly, we determined that N−O bond homolysis of **3** does not occur in the absence of an SET event.

(12) We chose to optimize this transformation using a household light source in lieu of the slightly more efficient LZC system to allow operational convenience for practitioners of this chemistry.

(13) The enamine concentration during the reaction was evaluated by ^{1}H NMR analysis of the crude reaction mixture performed in CD_3CN/DMSO-d_6.

(14) ^{1}H NMR analysis of the crude reaction mixture showed decreased levels of $MeNHCO_2Me$ (10−15%) for couplings performed at −15 °C. $MeNHCO_2Me$ can be formed from the corresponding radical by either H-atom abstraction from the solvent or SET reduction to the amine anion followed by protonation from the medium.

(15) For the synthesis of **11**, see sections IV and V in the SI.

(16) DFT calculations were performed at the B3LYP/6-31G* level as implemented in Gaussian 03: Frisch, M. J.; et al. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

(17) For NMR studies, see section IX in the SI.

(18) These amine reagents can be stored in the presence of moisture or light at ambient temperatures without decomposition.

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