Enantioselective Conjugate Additions of α-Amino Radicals via Cooperative Photoredox and Lewis Acid Catalysis

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S *Supporting Information*

ABSTRACT: We report the highly enantioselective addition of photogenerated α-amino radicals to Michael acceptors. This method features a dual-catalyst protocol that combines transition metal photoredox catalysis with chiral Lewis acid catalysis. The combination of these two powerful modes of catalysis provides an effective, general strategy to generate and control the reactivity of photogenerated reactive intermediates.

While photochemistry has long been appreciated as a powerful tool in organic synthesis,[1] stereocontrol in photochemical reactions remains a significant challenge with few general solutions.[2] A number of novel dual catalytic systems have recently been developed to address this long-standing problem. The combination of transition metal photoredox catalysts with chiral amine,[3] carbene,[4] and Brønsted acid organocatalysts[5] has enabled a number of highly enantioselective photoinduced reactions. We recently reported the first method combining photoredox and chiral Lewis acid catalysis in the context of an asymmetric [2 + 2] photocycloaddition.[6] Compared to organocatalysts, chiral Lewis acids possess a greater diversity of structures known to provide effective enantiodifferentiating environments for a wide range of mechanistically distinct organic reactions.[7] We wondered if the ability to combine organic chemists' detailed understanding of asymmetric Lewis acid catalysis with the emerging versatility of photoredox activation might provide a robust approach to controlling stereochemistry in photocatalytic reactions. Herein, we report our application of the principle of cooperative Lewis acid–photoredox catalysis to highly enantioselective reactions of α-amino radicals (Scheme 1).

Our group has an established interest in the chemistry of α-amino radicals.[8] Pioneering studies by Mariano[9] and Pandey[10] demonstrated that the photosensitized oxidation of amines, α-amino acids, and α-silylamines offers the most straightforward method for the production of these highly nucleophilic,

functionalized radical intermediates. More recently, several groups have shown that transition metal photoredox sensitizers can be used to produce α-amino radicals under visible light irradiation.[11] Although the utility of these amine-functionalized radical species in the synthesis of complex alkaloids has long been appreciated,[12] methods to control the enantioselectivity of their addition reactions are extremely rare. To the best of our knowledge, the only prior example of an asymmetric reaction in this class is a single, elegant addition reaction reported by Bach in which a chiral hydrogen-bonding photosensitizer catalyzes the intramolecular conjugate addition of a photogenerated α-amino radical to a quinolone scaffold.[13] A more general method to control the stereochemistry of such additions, particularly in an intermolecular context, is an unrealized goal with great synthetic potential.

We recently reported the photocatalytic functionalization of *N*-aryl tetrahydroisoquinolines via an α-amino radical intermediate.[8] This study provided two important observations that informed the design of our exploratory investigations. First, we found that the conjugate addition of the α-amino radicals to Michael acceptors was catalyzed by Brønsted acids. If chiral Lewis acids could have a similar effect, they might also control the stereochemistry of these additions.[14] Indeed, Sibi, Porter, and others have established that chiral Lewis acids can dictate the enantioselectivity of radical conjugate additions,[15] although these investigations have been limited to simple, unfunctionalized alkyl radicals. Second, we found that the rate-limiting step was a chain-propagating H atom abstraction process that was only efficient with *N*-aryl tetrahydroisoquinoline substrates with especially activated α-amino C–H bonds. We wondered if this narrow restriction on viable substrates could be overcome by an alternative method for generating the α-amino radical. In particular, we were inspired by Mariano's insight that α-silyl amines undergo facile oxidative fragmentation and generate α-amino radicals several orders of magnitude more efficiently than their nonsilylated analogues.[9e]

Thus, the optimization of the enantioselective α-amino radical addition began with an exploration of the reaction between α-silylmethyl aniline **1** and crotonyl oxazolidinone **2a** (Table 1). Irradiation with a household 23 W fluorescent light bulb in the presence of 2 mol % Ru(bpy)$_3$Cl$_2$ resulted in the slow formation of the expected radical conjugate addition product **3a** in 28% yield after 18 h (entry 1). In accord with our initial hypotheses, Sc(III)-pybox complexes provided both a significant increase in the rate of the reaction and modest enantioselectivity (entries 2–

Scheme 1. Design Plan for Cooperative Lewis Acid–Photoredox Catalysis of α-Amino Radical Additions
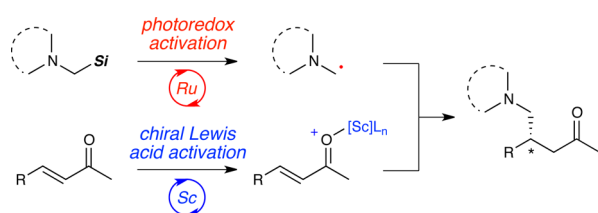
Table 1. Optimization of the Asymmetric α-Amino Radical Addition[a]
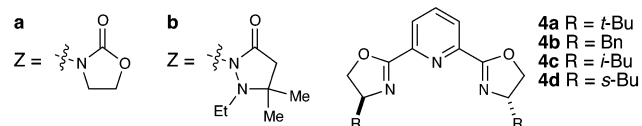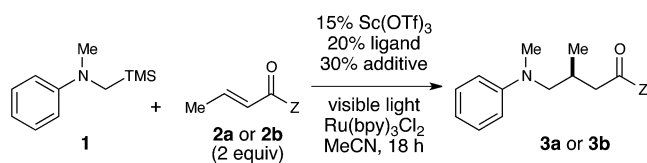
entry	acceptor	ligand	[Ru] mol %	additive	yield (%)[b]	ee (%)[c]
1[d,e]	2a	none	2%	none	28	–
2[d]	2a	tBuPybox (4a)	2%	none	18	49
3[d]	2a	BnPybox (4b)	2%	none	75	27
4[d]	2a	iBuPybox (4c)	2%	none	15	42
5[d]	2a	sBuPybox (4d)	2%	none	70	43
6	2a	sBuPybox (4d)	2%	none	94	50
7	2a	sBuPybox (4d)	5%	none	93	59
8	2a	sBuPybox (4d)	15%	none	97	66
9	2a	sBuPybox (4d)	2%	KCl	74	59
10	2a	sBuPybox (4d)	2%	$Bu_4N^+Cl^-$	91	67
11	2a	sBuPybox (4d)	2%	$Bu_4N^+PF_6^-$	52	43
12	2a	sBuPybox (4d)	2%	$Bu_4N^+ClO_4^-$	40	46
13	2b	sBuPybox (4d)	2%	$Bu_4N^+Cl^-$	80	89
14	2b	iBuPybox (4c)	2%	$Bu_4N^+Cl^-$	**83**	**93**
15[f]	2b	iBuPybox (4c)	2%	$Bu_4N^+Cl^-$	<5	–
16[e]	2b	none	2%	$Bu_4N^+Cl^-$	52	–
17	2b	iBuPybox (4c)	0%	$Bu_4N^+Cl^-$	0	–
18	2b	iBuPybox (4c)	2%	none	91	86

[a]Unless otherwise noted, reactions were conducted at 0.05 M in **1** and irradiated at a distance of 30 cm from a 23 W compact fluorescent light bulb. [b]Yields determined by ^{1}H NMR using an internal standard. [c]Enantiomeric excess determined by chiral SFC analysis. [d]Reaction conducted at 0.25 M in **1**. [e]Reaction conducted without Lewis acid. [f]Reaction conducted with N,N-dimethyl amine in place of silyl amine **1**.

5); the sBuPybox complex gave the optimal combination of yield and ee in this screen. An examination of reaction concentration showed that the rate and ee were improved somewhat at lower concentrations (entry 6). We next made the surprising observation that the concentration of Ru(bpy)₃Cl₂ had an effect on ee (entries 6−8). It seemed unlikely that the photocatalyst itself could be involved in the stereochemistry-determining conjugate addition step. Speculating instead that the chloride counteranion might be responsible for the observed effect on ee, we found that the addition of either KCl or $Bu_4N^+Cl^-$ also improved enantioselectivity, while addition of noncoordinating anions did not (entries 9−12). Finally, inspired by the success of Sibi's chiral relay auxiliary in other enantioselective radical addition processes, we discovered that the use of Michael acceptor **2b** provided substantially higher ee (entry 13). A rescreening of chiral ligands at this point revealed that iBuPybox provided the optimal chiral environment with this acceptor, affording γ-aminocarbonyl adduct **3b** in 93% ee (entry 14). Control experiments verified the necessity of each reaction component (entries 15−18). Two experiments are particularly notable. First, the electrofugal silyl substituent is critical for

successful reaction; N,N-dimethyl aniline produces only a trace of the conjugate addition product (entry 15), consistent with our design strategy. Second, we observed the formation of 52% yield of **3b** after 18 h even in the absence of Lewis acid (entry 16). Thus, the rate acceleration afforded by the Lewis acid catalyst must be large enough to overcome a significant racemic background addition in the absence of Lewis acid catalyst.

Table 2 summarizes the effects of structurally varied α-silylamines under the optimized conditions for enantioselective

Table 2. Reactions of Structurally Varied α-Silylamines with Michael Acceptor 2b[a]

entry	amine	product	time	yield (%)[b]	ee (%)[c]
1	R = H		6 h	87	93
2	R = F		6 h	94	94
3	R = Cl		6 h	96	93
4	R = Br		6 h	90	92
5	R = Me		12 h	79	91
6	R = OMe		12 h	<5	--
7			6 h	85	92
8			6 h	80	96[d,e]
9			12 h	80	90
10			12 h	<5	--
11			12 h	93	91[d,e]
12	R = Bn		6 h	60	94
13	R = i-Pr		12 h	33	95
14	R = Boc		12 h	<5	--

[a]Unless otherwise noted, reactions were conducted using 1.5 equiv of **2**, 2 mol % Ru(bpy)₃Cl₂, 15 mol % Sc(OTf)₃, 20 mol % (S,S)-**4c**, and 30 mol % $Bu_4N^+Cl^-$ in degassed MeCN (0.05 M) and were irradiated using a 23 W compact fluorescent light bulb. [b]Values represent the averaged isolated yields of two reproducible experiments. [c]Enantiomeric excess determined by chiral SFC analysis. [d]Enantiomeric excess of the corresponding alcohol. [e]Reaction conducted using (R,R)-**4c** to facilitate measurement of ee.

conjugate addition. A variety of electron-withdrawing para substituents are easily accommodated on the N-aryl moiety (entries 2−4). Modestly electron-donating substituents slow the rate of the reaction without negatively impacting ee (entry 5). Strongly electron-donating para substituents inhibit reactivity altogether (entry 6), which is consistent with Mariano's

observation that electron-releasing *p*-methoxy groups retard the desilylation of α-silylmethyl anilines by an order of magnitude compared to their unsubstituted analogues.[16] A *meta*-methoxy substituent, however, is well tolerated and provides the desired product in good yield and with excellent enantioselectivity (entry 7). Gratifyingly, substitution in the ortho position is also tolerated (entries 8 and 9). We found that successful Michael reaction required the presence of one *N*-aryl substituent; aliphatic amines undergo protodesilylation without adding to the Michael acceptor (entry 10). However, both *N,N*-diaryl and mixed *N*-alkyl-*N*-aryl α-silylamines participate in this reaction (entries 11 and 12) although sterically bulky α-amino radicals react sluggishly. Unfortunately, substrates bearing *N*-acyl groups were recovered unchanged, consistent with the greater difficulty with which they are oxidized (entry 14).

The generality of the reaction with respect to the Michael acceptor is outlined in Table 3. A variety of aliphatic acceptors

Table 3. Reactions of Structurally Varied Michael Acceptors with α-Silylamine 1[a]

| entry	amine	product	time	yield (%)[b]	ee (%)[c]
1	R = *n*-Pr		6 h	76	93
2	R = *i*-Pr		6 h	71	93
3	R = CH₂OBn		6 h	75	91
4	R = *t*-Bu		12 h	35	96
5	R = H		12 h	74	93
6	R = *p*-Cl		12 h	63	91
7	R = *p*-OMe		12 h	83	94
8	R = *o*-Me		12 h	81	85
9			12 h	83	91

[a]Unless otherwise noted, reactions were conducted using 1.5 equiv of Michael acceptor, 2 mol % Ru(bpy)₃Cl₂, 15 mol % Sc(OTf)₃, 20 mol % (*S,S*)-**4c**, and 30 mol % Bu₄N⁺Cl⁻ in degassed MeCN (0.05 M) and were irradiated using a 23 W compact fluorescent light bulb. [b]Values represent the averaged isolated yields of two reproducible experiments. [c]Enantiomeric excess determined by chiral SFC analysis.

react smoothly and deliver the expected conjugate addition products with high ee (entries 1−4). Aromatic acceptors are also excellent partners for this transformation, and both electron-poor and electron-rich substrates undergo facile Michael addition (entries 5−7). Substitution at the ortho position is well tolerated, with only marginally diminished enantioselectivity (entry 8). A heterocyclic group was also compatible with the reaction conditions (entry 9).

To expand the synthetic value of this method, we also investigated conditions for efficient removal of the pyrazolidi-

none auxiliary (Scheme 2). Standard conditions for hydrolysis and reduction of imides proved to be unselective, producing

Scheme 2. Auxiliary Removal
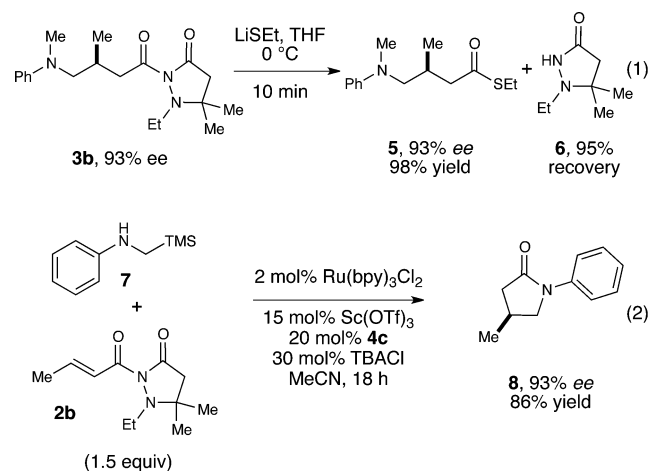
mixtures of acyl cleavage products. However, the auxiliary can be cleanly cleaved upon reaction with ethanethiolate, providing thioester **5** in quantitative yield with no erosion of enantioselectivity (eq 1). Importantly, the auxiliary (**6**) can be recovered in 95% yield after this cleavage step. Auxiliary cleavage can also be induced in an intramolecular fashion by a sufficiently nucleophilic moiety in the product.[17] For example, when secondary aniline **7** is subjected to the optimized conditions, the conjugate addition product undergoes spontaneous intramolecular transacylation in situ to afford pyrrolidinone **8** in very high yield and excellent ee (eq 2).[18]

An intriguing unexpected result for our investigations was the observation that added chloride salts were required for optimal ee.[19] We quickly ruled out the possibility of an electrolyte effect, as addition of other ammonium salts bearing noncoordinating ions had no impact on ee (Table 1, entries 11 and 12). We then examined the influence of chloride on the background and the Lewis-acid-free reaction between **1** and **2b**, and observed no measurable change in the rate of product formation upon the addition of 30 mol % Bu₄N⁺Cl⁻ to a reaction conducted in the absence of Lewis acid. Thus, we conclude that chloride does not have a significant impact on the photooxidation or desilylation steps leading to formation of the key α-amino radical intermediate. Instead, chloride must be interacting intimately with the Lewis acid. One would expect a scandium(III) chloride complex to be a weaker Lewis acid than its triflate analogue; indeed, a (pybox)ScCl₃ complex proved to give rates inferior to those of the optimized triflate catalyst. However, analysis of (pybox)Sc(OTf)₃-catalyzed reactions at incomplete conversions revealed that the addition of exogenous Bu₄N⁺Cl⁻ significantly increased the rate of formation of adduct **3b** under catalytic conditions.

A reasonable interpretation consistent with these results is that chloride is involved in accelerating the turnover of the Lewis acid catalyst.[20] Thus, we do not believe that chloride alters the intrinsic stereoselectivity of the (pybox)Sc(OTf)₃-catalyzed conjugate addition. Rather, the addition of chloride aids the enantioselective Lewis acid-mediated pathway to out-compete a slower but still significant rate of racemic background radical addition. This conclusion highlights an important conceptual distinction between this method and the asymmetric [2 + 2]

cycloaddition recently reported by our laboratory:[6] in this new reaction, the Lewis acid is not directly involved in the photoinduced electron transfer step. Rather, the chiral Lewis acids control the rate and selectivity of a step independent of the photoredox process itself. Thus, this study provides compelling evidence that the combination of photoredox and chiral Lewis acid catalysis might be broadly applicable to the design of enantioselective reactions involving the increasingly wide range of reactive intermediates known to be readily generated via photoredox catalysis.

In summary, we have developed the first highly enantioselective intermolecular reaction of α-amino radicals. This process showcases the ability of chiral Lewis acid catalysts to control the reactivity of these photogenerated nucleophilic intermediates, and we expect that the combination of photoredox and chiral Lewis acid catalysis will provide an approach to control the stereochemistry of a wide variety of photoinitiated organic reactions. Studies to expand this concept to other synthetically useful transformations are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, characterization data for all new compounds, and crystallographic data (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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