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Direct and Enantioselective Organocatalytic α-Chlorination of Aldehydes

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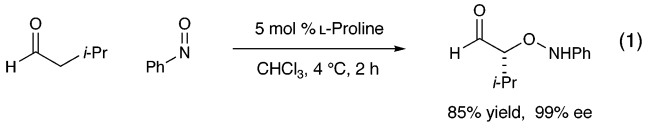
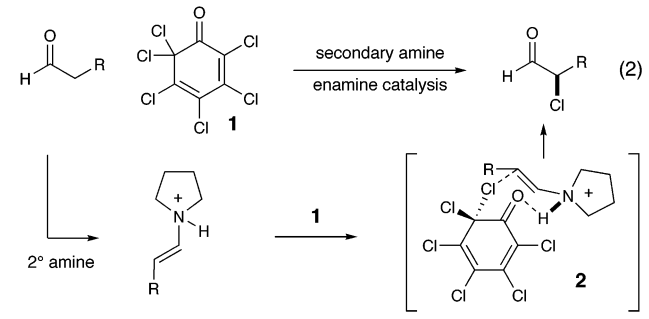
The enantioselective construction of carbon−halogen stereogenicity has become an important objective for practitioners of medicinal chemistry and organic synthesis.[1] Within the realm of drug design, the stereospecific replacement of C−H or C−Me bonds with fluorine or chlorine substituents can often endow metabolic stability without loss in substrate binding affinity.[2] Meanwhile, as a stereodefined electrophile, the α-halocarbonyl substructure represents a versatile linchpin for organic fragment coupling and the stereocontrolled construction of C−C, C−N, C−S, or C−O bonds.[3] As part of a program aimed at developing broadly useful organic catalysts for enantioselective synthesis,[4] we recently reported the proline-catalyzed α-oxidation of aldehydes (eq 1).[5,6] In this Communication, we advance this enamine catalysis concept to describe a highly enantioselective procedure for the α-chlorination of aldehydes. To our knowledge, this study represents the first example of a direct formyl α-chlorination that is accomplished with high levels of asymmetric induction.

Proline Catalyzed Direct α-Oxyamination



85% yield, 99% ee

Organocatalyzed Direct α-Chlorination



In our aldehyde oxidation studies,[5] the enantioselective step was proposed to involve a proton-mediated cyclic transition state that enforces nitrosobenzene activation in the asymmetric environment of a π-rich enamine. Intrigued by the possibility that such a mechanistic scenario might be expanded to encompass electrophilic forms of chlorine, we identified *N*-chlorosuccinimide (NCS) and the perchlorinated quinone **1** as reagents that might engage in an analogous transition state **2** via carbonyl-proton association and concomitant chlorine activation (eq 2). It is important to note that the capacity of quinone **1** to function in enantioselective enolate halogenations has previously been established by the pioneering studies of Leckta and co-workers.[1a,b]

As revealed in Table 1, exposure of octanal to NCS in the presence of L-proline, or imidazolidinone catalysts **3** or **4**, resulted in a facile but nonselective aldehyde chlorination (Table 1, entries 1−3). Changing the electrophilic chlorine source to the Leckta quinone **1** was initially less than fruitful (entries 4, 5, and 7, proline, 2% ee, imidazolidinone **4**, 42% ee). However, a dramatic increase in enantioselectivity was achieved using quinone **1** in the presence of amine catalyst **3** to access (*S*)-2-chlorooctanal in 92% ee (Table 1, entry 6).

A survey of reaction media for this organocatalytic chlorination revealed that a variety of solvents may be employed without significant loss in enantiocontrol (Table 2). Surprisingly, the use of acetone provided optimal selectivity, reaction rate, and chemical yield, without halogenation of the bulk medium (entry 6, 93% conversion, 92% ee). Moreover, product epimerization, formation of α,α-dichlorooctanal, or octanal aldol dimerization were comprehensively suppressed using these conditions. The superior levels of asymmetric induction and efficiency exhibited by amine salt **3** in acetone at −30 °C to afford (*S*)-2-chlorooctanal in 92% ee prompted us to select these catalytic conditions for further exploration.

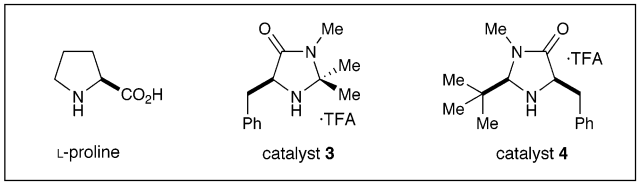
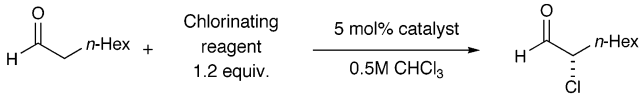


Table 1. Effect of Catalyst and Chlorinating Reagent on α-Chlorination



entry	catalyst	reagent	temp (°C)	time (h)	% conversion[a]	% ee[b]
1	L-proline	NCS	4	6	99	2
2	**3**	NCS	4	6	20	19
3	**4**	NCS	4	6	60	10
4	L-proline	**1**	4	12	44	2
5	L-proline	**1**	−30	30	NR	NA
6	**3**	**1**	−30	8	91	92
7	**4**	**1**	−30	6	78	42

[a] Conversion determined by GLC analysis of product relative to an internal standard (benzyl methyl ether). [b] Enantiomeric excess determined by chiral GLC analysis (Bodman Γ-TA).

Experiments that probe the scope of the aldehyde substrate are summarized in Table 3. Considerable variation in the steric demand of the aldehyde component (entries 1, 3−5, R = *n*-Hex, *Cy*-Hex, adamantyl, Bn) is possible without loss in efficiency or enantiocontrol (71−85% yield, 92−94% ee). Moreover, these mild catalytic conditions are tolerant of acid sensitive functionality such as acetals (Table 3, entry 6). It is important to note that these α-chloroaldehydes are typically configurationally stable to pH neutral silica purification.[7] Indeed, only the α-chlorohydrocinnamaldehyde adduct was found to significantly diminish in optical purity upon isolation (entry 5, crude 92% ee, isolated 80% ee).

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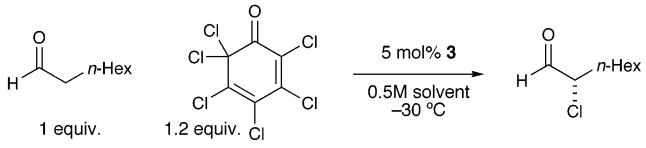
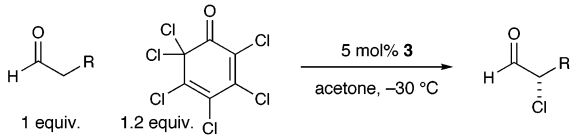
Table 2. Effect of Solvent on Organocatalyzed α-Chlorination

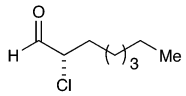
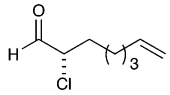
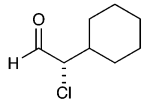
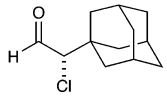
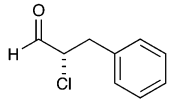
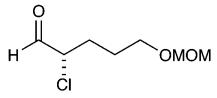
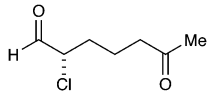


entry	solvent	time (h)	% conversion[a]	% ee[b]
1	EtOAc	12	93	87
2	THF	18	56	89
3	toluene	18	83	89
4	CH_3CN	8	65	92
5	$CHCl_3$	8	91	92
6	acetone	7	93	92

[a] Conversion determined by GLC analysis of product relative to an internal standard (benzyl methyl ether). [b] Enantiomeric excess determined by chiral GLC analysis (Bodman Γ-TA).

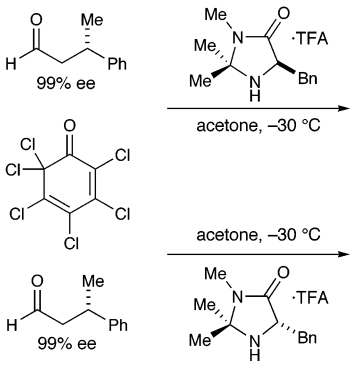
Table 3. Enantioselective α-Chlorination: Substrate Scope



entry	product	time (h)	% ee[a,b] crude	% yield	% ee[a] isolated
1		6	95	71	92
2		8	93	76	92
3		8	94	87	94
4		24	NA	85[c]	95[d]
5		6	92	92[e]	80
6		12	93	94[e]	93
7		12	91	78	87

[a] Enantiomeric excess determined by chiral GLC analysis (Bodman Γ-TA). [b] Determined by analysis of the crude reaction prior to purification. [c] Using 20 mol % catalyst and −40 °C. [d] Enantiomeric excess determined by GLC analysis of the corresponding epoxide generated by $NaBH_4$ reduction and exposure to aqueous KOH. [e] Performed at −40 °C.

We next examined the ability of catalyst **3** to override the inherent bias of resident stereogenicity in the chlorination of enantiopure β-chiral aldehydes. As shown in eqs 3 and 4, exposure of enantiopure (*S*)-3-phenylbutyraldehyde to catalyst antipode (*R*)-**3** results in the diastereoselective production of the anti α,β-disubstituted isomer, while the catalyst antipode (*S*)-**3** affords the corresponding syn adduct with high fidelity. These transformations clearly demonstrate the synthetic advantages of catalyst-enforced induction versus substrate directed stereocontrol.



In summary, we have described the first direct, enantioselective α-chlorination of aldehydes. Importantly, the chlorinated quinone **1** and both enantiomers of catalyst **3** are bench stable and commercially available. Further studies to evaluate the mechanism of this process, expand the scope, and utilize the α-chloroaldehydes via in situ functionalization are now underway. Finally, it should be noted that the imidazolidinone scaffold has revealed itself to be a broadly useful catalyst for enantioselective synthesis within the realms of both iminium activation[4,8] and now enamine catalysis.

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Supporting Information Available: Experimental procedures, structural proofs, and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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