Organocatalysis

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Enantioselective Linchpin Catalysis by SOMO Catalysis: An Approach to the Asymmetric α-Chlorination of Aldehydes and Terminal Epoxide Formation**

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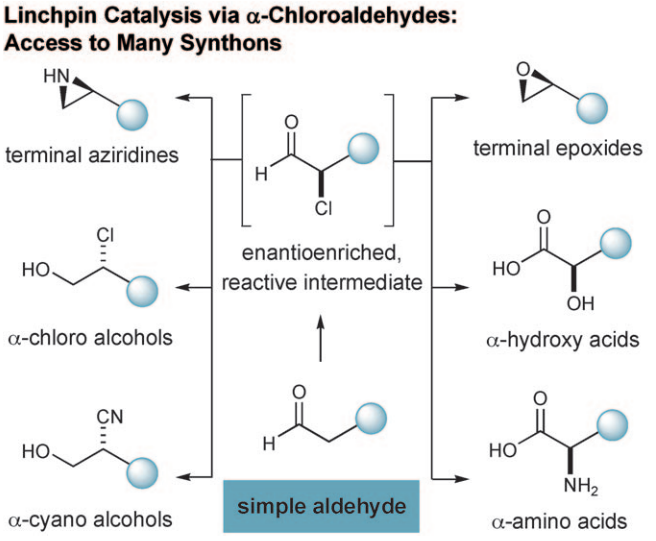
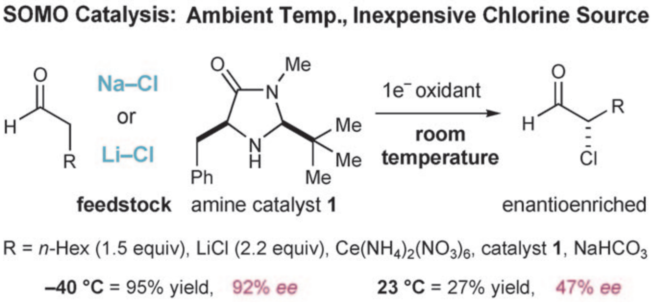
Over the last 40 years, research strategies in the field of asymmetric catalysis have been founded upon the direct production of enantioenriched synthons which typically exist within a unique structural class (e.g. epoxide, aziridine, 1,2-diol, amino acid, etc.).[1] Whereas the collective value of these individual transformations is beyond measure, it is intriguing to consider that such synthon-specific studies do not often provide generic lessons that can be translated into other reaction classes (e.g. epoxidation catalysts are not employed in amino acid synthesis). Recently, we became interested in the concept of "linchpin" catalysis (Scheme 1), an alternative strategy for reaction design wherein the key induction step does not lead to a unique end-point, but instead, to an enantioenriched reactive intermediate that can be rapidly converted (in situ) into a broad range of valuable structural motifs.[2] As one example, we hypothesized that simple aldehydes might be readily transformed into a variety of fundamental organic building blocks including epoxides,[3a,b] aziridines,[3b] or α-amino acids[3c] by the asymmetric production and in situ derivation of α-formyl chlorides, a versatile sp^3-carbon electrophile.[4–6] Towards this goal, we report a new mechanistic approach to the enantioselective α-chlorination of aldehydes using organo-SOMO catalysis (SOMO = singly occupied molecular orbital),[7] a novel transformation that employs LiCl as a chlorine source and a simple amine catalyst. As a first example of our linchpin catalysis strategy, we document a pragmatic and inexpensive protocol for the in situ conversion of aldehydes into enantioenriched terminal epoxides, a motif that remains elusive to direct catalysis technologies.[8,9]



Scheme 1. Linchpin catalysis using α-chloroaldehydes to access many synthons.

From the outset, we realized that the success of our multisynthon strategy would require the development of a linchpin formyl/chlorination reaction which is highly selective at room temperature yet inexpensive, nontoxic, and operationally trivial to perform.[10] Whereas studies from the group of Jørgensen and our own group have shown that such α-halocarbonyl products can be furnished by enamine catalysis,[11] we recognized that organo-SOMO activation of aldehydes using a chiral amine catalyst might allow low-molecular weight, feedstock reagents such as LiCl or NaCl to be used as suitable chlorine sources (Scheme 2).[7a,12] The proof of principle experiments with octanal, catalyst **1**, and LiCl demonstrated the feasibility of this approach, albeit using a Ce(IV) oxidant and cryogenic conditions (Scheme 2). Moreover, we found that the same protocol performed at 23 °C resulted in a dramatic drop in enantioselectivity, which was not within the expected Boltzman distribution. Indeed, subsequent control experiments revealed that the enantioin-



Scheme 2. SOMO catalysis at ambient temperature and using inexpensive chlorine sources.

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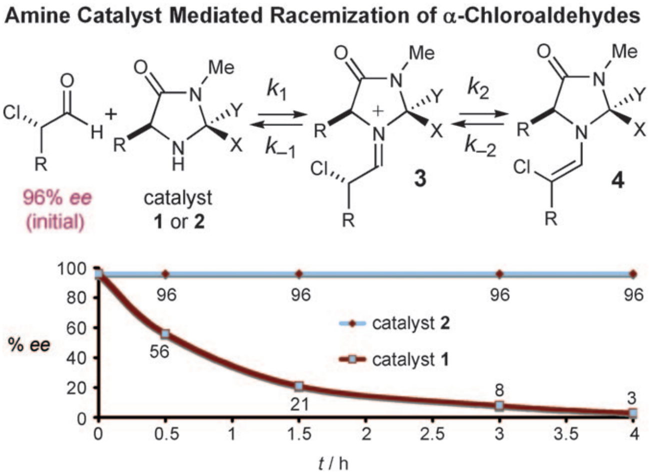
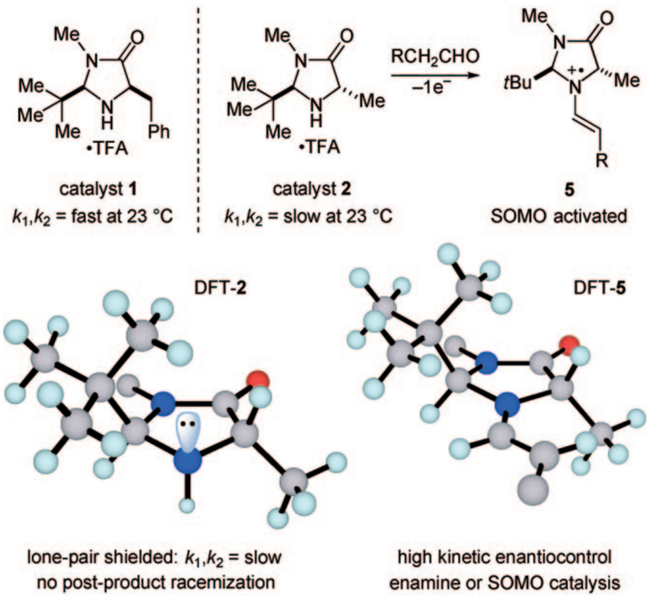
tegrity of the product is rapidly compromised by catalyst **1** at room temperature, presumably through an iminium–enamine equilibration mechanism (Scheme 3). On this basis we recognized that our linchpin strategy would require the de novo design of a 23 °C enamine SOMO catalyst which 1) could provide high levels of kinetic enantiocontrol in the C−Cl bond-forming event yet 2) be inert to enamine formation with the α-chloro product, thereby avoiding a post-product racemization pathway. On the basis of DFT calculations, we proposed that the imidazolidinone catalyst **2**[13] should selectively form the SOMO-activated radical cation **5** (DFT-**5**) which projects the 3π-electron system away from the bulky *tert*-butyl group, whereas the carbon-centered radical atom will selectively populate an *E* configuration to minimize nonbonding interactions with the imidazolidinone ring (Scheme 4).[14] In this topography, the methyl group on the catalyst system will effectively shield the *Re* face of the radical cation, leaving the *Si* face exposed for enantioselective chlorination. With respect to post-reaction racemization, we anticipated that catalyst **2** would exist in a ground state (DFT-**2**) wherein the nitrogen lone pair of electrons is eclipsed by the adjacent *tert*-butyl substituent, a structural feature that will impede the rate of iminium formation (k_1) with the α-chloro product (and thereafter enamine formation k_2). Indeed, control experiments revealed that 2-chlorooctanal does not undergo an erosion of optical purity when exposed to catalyst **2** for 6 hours at 23 °C (Scheme 3).[15]



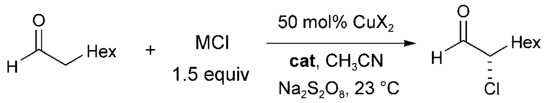
Scheme 3. Amine catalyst mediated racemization of α-chloroaldehydes. The data was recorded for the reaction run at 23 °C in acetone.



Scheme 4. Comparison of catalysts **1** and **2** in the SOMO catalysis.

The proposed SOMO α-formyl chlorination was first examined at room temperature using octanal and LiCl, with imidazolidinone catalysts **1** and **2**, and a series of stoichiometric oxidants (not shown).[16] As revealed in Table 1, excellent levels of reaction efficiency and enantiocontrol (Table 1, entry 1) were accomplished using catalyst **2** in the presence of an oxidant combination consisting of sodium persulfate and catalytic copper(II) trifluoroacetate [Cu(TFA)$_2$] in CH$_3$CN.[17] As expected, post-product racemization was only observed when the same protocol was employed with catalyst **1** (Table 1, entry 2). We have found that both LiCl and NaCl can be used successfully in this reaction, an important consideration given the low molecular weight and cost of both halide sources (Table 1, entries 1 and 4).[10] Moreover, CuCl$_2$ can be used as both a stoichiometric oxidant and a halide source in the presence of lithium trifluoroacetate (Table 1, entry 3). The effect of the catalyst loading on reaction efficiency was also evaluated. Whereas 20 mol % of imidazolidinone **2** was routinely employed in this investigation, it appears that catalyst loadings as low as 1 mol % provide useful levels of enantioselectivity (Table 1, compare entries 1 and 6). Lastly, higher levels of enantiocontrol are observed when the transformation is performed at 10 °C in the presence of 2.2 equivalents of H$_2$O (Table 1, entry 7). The superior levels of induction and efficiency exhibited by amine salt **2** in CH$_3$CN at 10 °C to afford (*S*)-2-chlorooctanal in 97 % *ee* and 94 % conversion prompted us to select these catalytic conditions for additional exploration.

Table 1: Effect of the oxidant, halide source, and catalyst loading on the reaction.



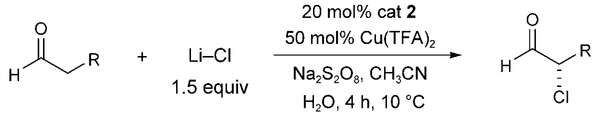
Entry[a]	Catalyst	CuX$_2$	MCl	*t* [h]	Conv. [%][a]	*ee* [%][b]
1	**2** (20 mol %)	Cu(TFA)$_2$	LiCl	4	91	94
2	**1** (20 mol %)	Cu(TFA)$_2$	LiCl	4	92	10
3	**2** (20 mol %)	CuCl$_2$[c]	LiTFA	4	94	89
4	**2** (20 mol %)	Cu(TFA)$_2$	NaCl	4	82	91
5	**2** (5 mol %)	Cu(TFA)$_2$	LiCl	5	88	94
6	**2** (1 mol %)	Cu(TFA)$_2$	LiCl	5	67	95
7[d]	**2** (20 mol %)	Cu(TFA)$_2$	LiCl	4 (10 °C)	94	97

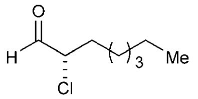
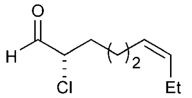
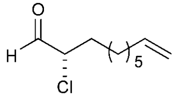
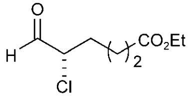
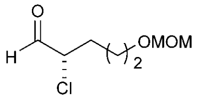
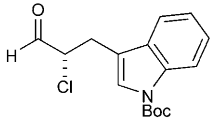
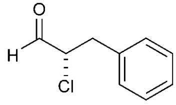
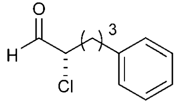
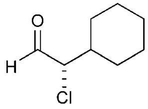
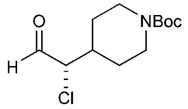
[a] Conversion determined by GLC analysis using an internal standard. [b] Enantiomeric excess determined by chiral GLC analysis. [c] Using stoichiometric CuCl$_2$. [d] Using 2.2 equivalents of H$_2$O as an additive.

We next examined the scope of the aldehyde component in this enantioselective α-chlorination protocol. As highlighted in Table 2, a wide range of functional groups, including olefins, esters, amines, carbamates, and aryl rings can be readily tolerated on the aldehydic substrate (Table 2, entries 2–4 and 6–8). Moreover, considerable variation in the steric demand of the aldehyde component (Table 2, entries 1, 7, and 9) is possible without loss in efficiency or enantiocontrol (≥ 89 % yield, 95–96 % *ee*). These mild catalytic conditions are also tolerant of both oxidation and acid-sensitive functionalities such as indoles and acetals, respectively (Table 2, entries 5 and 6). Notably, a catalyst exposure study has revealed that product racemization is not observed over the indicated reaction time (4 h) for any case shown in Table 2. These results serve to illustrate the remarkable capacity of amine catalyst **2** to successfully differentiate between the aldehyde α-methylene substrates and the α-chloroaldehyde products.

Having successfully developed a new room-temperature, α-chlorination reaction, we directed our efforts to exploiting this asymmetric mechanism in our linchpin catalysis strategy. As a first example, we sought to rapidly convert simple aldehydes into enantioenriched terminal epoxides in a one-flask, three-stage operation that would incorporate an α-chlorination/reduction/ring-closure sequence. As a central design criteria, we restricted our studies to reaction conditions that could be telescoped into a single vessel without the need for solvent switching or reagent quenching (i.e. the overall transformation would involve only the sequential addition of reagents over a predetermined time frame). As highlighted in Table 3, we have found that the exposure of a series of aldehydes to our new SOMO-activation, α-chlorination conditions and subsequent in situ treatment with $NaBH_4$ and then KOH shortly thereafter (15 min) allows the formation of a range of terminal epoxides with high levels of reaction efficiency and enantiocontrol. Once again, these mild reaction conditions tolerate electron-rich π systems which are typically prone to oxidation under many epoxidation conditions (Table 3, entry 6). Moreover, acid-sensitive functionalities such as *tert*-butylcarbamates are tolerated with good levels of reaction efficiency and high levels of enantio-

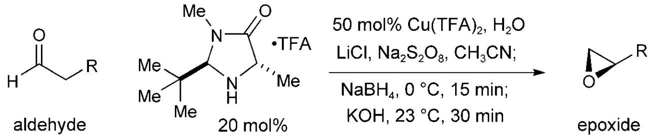
Table 2: Enantioselective α-formyl chlorination: Substrate scope.

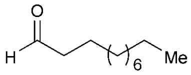
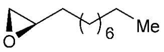
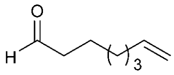
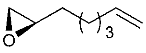
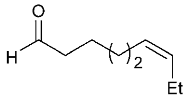
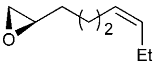
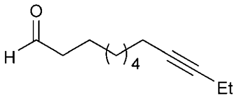
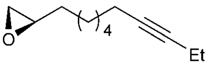
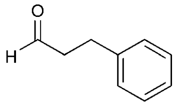
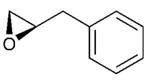
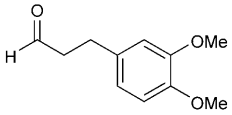
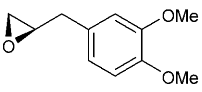
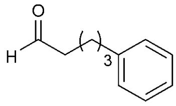
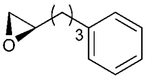
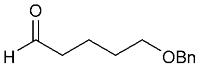
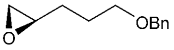
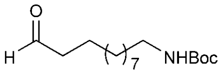
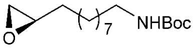
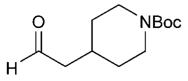
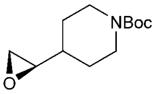


Entry	Product[a,b]	Entry	Product[a,b]
1	 90 % yield, 96 % *ee*	2	 89 % yield, 96 % *ee*
3	 81 % yield, 95 % *ee*	4	 91 % yield, 94 % *ee*
5	 84 % yield, 94 % *ee*	6	 75 % yield, 91 % *ee*
7	 89 % yield, 95 % *ee*	8	 95 % yield, 95 % *ee*
9	 89 % yield, 96 % *ee*	10	 95 % yield, 95 % *ee*

[a] Yield and enantioselectivity obtained after $NaBH_4$ reduction to the corresponding alcohol. [b] Enantiomeric excess determined by SFC analysis. MOM = methoxymethyl ether, Boc = *tert*-butoxycarbonyl.

Table 3: Aldehydes converted into enantioenriched terminal epoxides: Scope.



Entry	Aldehyde	Product	Yield [%]	*ee* [%][a]
1			85	95
2			80	95
3			80	95
4			77	95
5			84	94
6			89	93
7			92	94
8			77	95
9			82	94
10			73	94

[a] Enantiomeric excess determined by HPLC analysis after expoxide opening with 2-naphthyl thiol. TFA = trifluoroacetate, Bn = benzyl.

meric excess (Table 3, entries 9 and 10). Importantly, the enantioselectivities achieved in the α-chlorination step were comprehensively maintained throughout this epoxide formation sequence. Furthermore, this complete aldehyde→terminal epoxide sequence is accomplished in less than five hours, using inexpensive, nontoxic reagents and catalysts, at temperatures between 0 and 23 °C for all of the examples shown in Table 3.

In summary, we report a new SOMO-activated aldehyde α-chlorination reaction which can be exploited as part of a linchpin-catalysis approach to the enantioselective production of terminal epoxides. Application of this strategy to the asymmetric synthesis of aziridines and α-amino acids will be disclosed shortly.

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Keywords: epoxidation · enantioselectivity · asymmetric catalysis · organocatalysis

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[6] While it has been established that aldehydes can be converted into epoxides, α-amino acids etc., over several discrete steps (see references [11a–d]), linchpin catalysis provides a strategy that enables the direct in situ conversion of simple aldehydes into these valuable synthons (in one reaction vessel) without the isolation or purification of the intermediate.

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[15] Similar results were obtained using CH$_3$CN/H$_2$O.

[16] See the Supporting Information for details.

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