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Direct Organocatalytic Asymmetric α-Chlorination of Aldehydes

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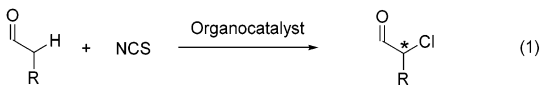
An important goal for asymmetric catalysis is the development of new reactions affording optically active building blocks using simple and easily available starting materials and catalysts.[1] Optically active halogen-containing compounds are especially attractive due to their high value as synthetic intermediates. Despite intensive research efforts over the past few years, examples of highly enantioselective halogenation reactions are unfortunately scarce and often limited to 1,3-dicarbonyl compounds or multistep procedures requiring expensive reagents.[2] Here we wish to report the first catalytic enantioselective α-chlorination of aldehydes to provide highly attractive α-chloro aldehydes in excellent yields and enantioselectivities using inexpensive *N*-chlorosuccinimide (NCS) as the chlorine source (eq 1). This novel reaction is based on organocatalysis and clearly complements the recently developed highly enantioselective proline-catalyzed α-amination and α-oxidation reactions.[3]



(1)

Optimization of the reaction conditions for the organocatalytic enantioselective α-chlorination reaction of 3-methylbutanal **1a** with different catalysts and solvents (eq 2) gave the results shown in Table 1. The chiral amines **3a**−**j** catalyze the direct enantioselective α-chlorination of **1a** in various yields and enantioselectivities. L-Proline **3a**, which has been found very useful in a variety of other direct α-addition reactions of aldehydes,[4] afforded full conversion; however, 2-chloro-3-methylbutanal **2a** was obtained with only 23−25% ee (Table 1, entries 1,2). Use of 2-methyl-L-proline **3b** and L-proline amide **3c** catalysts in 1,2-dichloroethane (DCE) as the solvent afforded a significant improvement in the ee, and **2a** was obtained in 60 and 78% ee, respectively (entries 3,4). Both the yield and optical purity of the α-chlorinated product are dependent on the solvent (entries 4−8), and e.g. in DMSO the product racemizes during the reaction. (2*R*,5*R*)-Diphenylpyrrolidine **3i** turned out to be the most promising catalyst as full conversion was obtained after only 1 h reaction time and **2a** was formed in 94% ee (entries 14−16). It should be noted that in all cases the reaction was found to proceed cleanly at ambient temperature and only the formation of homo-aldol product was observed with some solvents and catalysts.

Other commercially available chlorination reagents have been employed: *N*-chlorophthalimide afforded 76 and 93% ee using **3c** and **3i**, respectively, in DCE, but yields were generally lower due to slow reaction rates. Under similar conditions 1,3-dichloro-5,5-dimethylhydantoin afforded 75% ee using **3i** as the catalyst in CH_2Cl_2. Generally, NCS was found to be superior to the other chlorine sources in terms of yield and was therefore used for subsequent reactions.

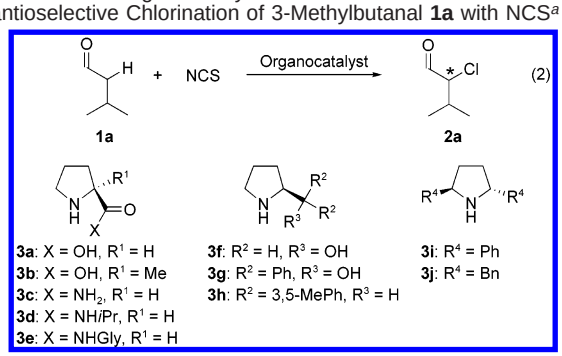
To demonstrate the scope of the reaction we subjected a series of aldehydes to the chlorination conditions using **3c** and **3i** as the catalysts, and to our delight we found that excellent yields and enantioselectivities were obtained (Table 2). Generally, **3c** catalyzes the direct enantioselective α-chlorination of the aliphatic aldehydes **1a**−**e** in excellent yields (Table 2, entries 1−5) with enantioselectivities ranging from 70% ee for 2-chloro-1-octanal **2e** (entry 5) to 95% ee for 2-chloro-3,3-dimethylbutanal **2d** (entry 4). For aldehyde **1f**, the reaction also proceeds in excellent yield and with good ee (entry 6), while slightly lower yields were obtained in the reactions of **1g** and **1h** (entries 7,8).

The use of the C_2-symmetric organocatalyst **3i** leads to a significant improvement in the ee of the α-chlorination reaction (Table 2). For the simple aliphatic aldehydes **1a**,**c**,**e**,**f** nearly quantitative yields of the optically active α-chlorinated aldehydes were obtained in ≥94% ee (entries 2,3,5,6).

Furthermore, the other aldehydes studied, with the exception of **1d**, proceeded also in very high yields and enantioselectivities (entries 6−8).

The direct catalytic enantioselective halogenation reaction is not only restricted to chlorination reactions, and preliminary investiga-

Table 1. Screening of Catalysts and Solvents for the Direct Enantioselective Chlorination of 3-Methylbutanal **1a** with NCS[a]



entry	catalyst (mol %)	solvent	time (h)	conv.[b] (%)	ee[c] (%)
1	**3a** (20)	$CHCl_3$	1.0	>95	23
2	**3a** (20)	CH_2Cl_2	1.0	>95	25
3	**3b** (20)	DCE	5.0	76	60
4	**3c** (20)	DCE	3.0	>95	78
5	**3c** (20)	DMSO	1.0	<5	<5
6	**3c** (20)	EtOH	1.0	<5	28
7	**3c** (20)	THF	1.0	23	30
8	**3c** (10)	CH_2Cl_2	1.0	>95	82
9	**3d** (20)	DCE	0.5	>95	54
10	**3e** (20)	DCE	1.0	33	81
11	**3f** (20)	DCE	1.0	34	77
12	**3g** (20)	DCE	1.0	15	85
13	**3h** (20)	DCE	0.5	92	64
14	**3i** (20)	DCE	0.5	>95	94
15	**3i** (10)	DCE	1.0	>95	94
16	**3i** (5)	DCE	1.0	77	94
17	**3j** (20)	DCE	1.0	<10	78

[a] Reaction conditions: NCS (2.0 equiv) was added to a mixture of aldehyde at ambient temperature. [b] Measured by ^{1}H NMR of the crude reaction mixture and confirmed by GC, due to the high volatility of the products. [c] ee determined by CSP-GC.

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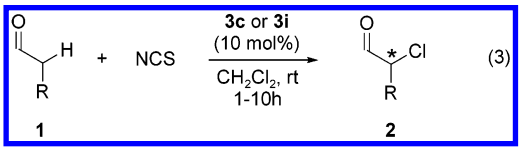
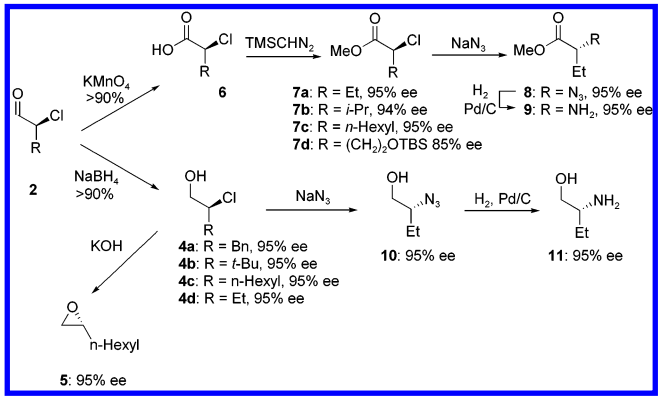
Table 2. Direct Organocatalytic Enantioselective α-Chlorination of Aldehydes Catalyzed by **3c** and **3i**[a]



		catalyst **3c**		catalyst **3i**	
entry	aldehyde	yield[b] (%)	ee (%)	yield[b] (%)	ee (%)
1	Me − **1b**	**2b** − 99	75[c] (*R*)[h]	−	−
2	Et − **1c**	**2c** − 99	80[d] (*R*)[j]	**2c** − 90	97[d] (*S*)[j]
3	*i*-Pr − **1a**	**2a** − 95	87[d] (*R*)[h]	**2a** − 90	94[d] (*S*)
4	*t*-Bu − **1d**	**2d** − 93[g]	95[d] (*R*)[i]	**2d** − 30[f]	94[d] (*S*)
5	*n*-Hexyl − **1e**	**2e** − 95	70[c] (*R*)[k]	**2e** − 99	95[c]
6	Allyl − **1f**	**2f** − 90	74[d]	**2f** − 90	95[d]
7	CH_2Ph − **1g**	**2g** − 99	78[e]	**2g** − 82	95[e]
8	$(CH_2)_2OTBS$ − **1h**	**2h** − 92	86	**2h** − 95[g]	81

[a] Reaction conditions: NCS (1.3 equiv.) was added to a mixture of aldehyde and catalyst at 0 °C and the reaction mixture was allowed to warm to ambient temperature. [b] Measured by ^1H NMR and confirmed by GC due to the high volatility of the products. [c] ee determined by CSP-GC after oxidation and esterification to the corresponding methyl ester. [d] ee determined by CSP-GC. [e] ee determined by CSP-HPLC after reduction to the corresponding alcohol. [f] Due to homo-aldol product formation. [g] Reaction conducted at −24 °C for 20 h to avoid homo-aldol condensation. [h] Absolute configuration determined by comparison of the optical rotation with literature values. [i] Absolute configuration determined by X-ray crystallography after reduction to the corresponding alcohol. [j] Absolute configuration determined by comparison of optical rotation with literature values after transformation to amino ester **9**. [k] Absolute configuration determined by comparison of optical rotation with literature values after transformation to epoxide **5**.

Scheme 1. Synthetic Transformations of α-Chloro Aldehydes



tions of the bromination of 3,3-dimethylbutanal **1d** with NBS using **3i** as the catalyst afforded the corresponding optically active α-bromo aldehyde in up to 80% ee. Under similar conditions the α-iodination of 3-methylbutanal **1a** using NIS proceeded in quantitative yields and up to 24% ee. Furthermore, we have also found that ketones can be α-chlorinated using NCS with, for example, cyclohexanone affording α-chlorocyclohexanone with up to 76% ee.

This novel enantioselective organocatalytic α-chlorination reaction of aldehydes giving optically active α-chloro aldehydes provides highly versatile chiral building blocks for a variety of different synthetic transformations leading to optically active compounds. Scheme 1 outlines several examples: Direct reduction of the 2-chloro aldehydes **2** with $NaBH_4$ affords the corresponding 2-chloro alcohols **4** in >90% yield without any decrease in optical purity.

Furthermore, the 2-chloro alcohol **4c** can be transformed into the optically active terminal epoxide **5** by treatment with KOH.[5] The versatile 2-chloro aldehydes **2** were also easily transformed into α-chloro acids **6** after a brief (1−10 min) $KMnO_4$ oxidation in high yields (>90%). It was demonstrated that the oxidation proceeded completely without loss of optical purity by converting the α-chloro acids **6** into α-chloro methyl esters **7** with $TMSCHN_2$ and checking the optical purity by CSP-GC.

The α-chloro ester **7** was also transformed into the corresponding azide **8** by treatment with NaN_3 in DMF at 60 °C, without loss of ee as demonstrated for 2-chloro butanoic acid methyl ester **7a**. Hydrogenolysis of the azide with H_2 (atm) and Pd/C catalyst afforded the nonproteinogenic (*R*)-2-aminobutanoic acid methyl ester **9** in high yields and enantioselectivity. A similar azide substitution−hydrogenolysis sequence was performed on the 2-chloro alcohol **4d** to afford optically active 2-amino butanol **11**, the key intermediate in the synthesis of tuberculostatic ethambutol.[6]

These synthetic transformations show the potential of this novel organocatalytic direct enantioselective α-chlorination of aldehydes as the products obtained are highly versatile chiral building blocks. Today, many of these compounds are obtained by kinetic resolution, and the present approach affords an attractive alternative to this procedure.[6]

In summary, we have developed an organocatalytic α-chlorination of aldehydes affording optically active α-chloro aldehydes in excellent yields and enantioselectivities. We are currently investigating the extension of these new findings to a general halogenation reaction of ketones, as well as to bromination and iodination of aldehydes. These results and investigations concerning the mechanism will be reported shortly.

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Supporting Information Available: Complete experimental procedures and characterization of novel compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org

References

(1) See e.g.: *Comprehensive Asymmetric Catalysis;* Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999.

(2) For recent examples of catalytic enantioselective electrophilic chlorination and bromination reactions see, e.g.: (a) Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531. (b) Hintermann, L.; Togni, A. *Helv. Chim. Acta* **2000**, *83*, 2425. (c) Marigo, M.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Eur. J.* **2004**, *10*, in press. For recent examples of catalytic enantioselective electrophilic fluorination reactions see, e.g.: (d) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359. (e) Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni A. *Org. Lett.* **2002**, *41*, 979. (f) Hamashima Y.; Yagi, K. Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530. (g) Kim, D. Y.; Park. E. J. *Org. Lett.* **2002**, *5*, 1709.

(3) For α-amination reactions, see: (a) Bøgevig, A.; Juhl. K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790. (b) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (c) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254. (d) Duthaler, R. O. *Angew. Chem., Int. Ed.* **2003**, *42*, 975. (e) Vogt, H.; Vanderheiden, S.; Bräse, S. *Chem. Commun*. **2003**, 2448. For α-oxidation reactions, see: (f) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247. (g) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (h) Bøgevig, A.; Sundéen, H.; Córdova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109. (i) Hayashi, M.; Yamaguchi, J.; Sumaiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112.

(4) See, e.g.: (a) List, B. *Tetrahedron* **2002,** *58*, 5573. (b) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450. (c) Notz, W.; Tanaka, F.; Watanabe, S.-I.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III. *J. Org. Chem*. **2003**, 9624.

(5) Koppenhoefer, B.; Weber, R.; Schurig, V. *Synthesis* **1982**, 316.

(6) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kesseler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788.

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