Enantioselective Chlorination

Highly Enantioselective Direct Organocatalytic α-Chlorination of Ketones**

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The stereoselective formation of carbon–halogen bonds is an important challenge in organic synthesis that has recently received considerable attention[1] due to the usefulness of the products as versatile synthetic intermediates.[2] Furthermore, halides are often introduced into pharmaceutical compounds to decrease the rate of metabolic degradation without affecting the pharmacological effects.[3] Until recently, enantioselective halogenation reactions have been limited to particular systems such as 1,3-dicarbonyl compounds using Lewis acid[4] or cinchona alkaloid catalysts.[5] The first catalytic highly enantioselective α-chlorination and α-bromination reactions of carbonyl compounds were reported by Lectka et al. with perhaloquinone-derived halogenation reagents and a cinchona alkaloid catalyst in a tandem halogenation/esterification of acid chlorides.[6] Very recently, these procedures were complemented by the α-chlorination of aldehydes with low-molecular-weight organocatalysts, a method reported by MacMillan et al. and us independently.[7] This novel reaction also complements previous proline-catalyzed α-amination and α-oxidation reactions of aldehydes[8] and ketones,[9] and it was demonstrated that the α-chloroaldehydes could be transformed into optically active epoxides, non-proteinogenic amino acids, α-chloro ester derivatives, α-chloro alcohols and α-amino alcohols.[7b] In this communication we present the development of the first organocatalytic asymmetric α-chlorination of ketones using *N*-chlorosuccinimide (NCS) as an inexpensive chlorine source, yielding optically active α-chloroketones in good yields and excellent enantioselectivities.

We initiated our studies of the α-chlorination reaction by screening a number of known and novel organocatalysts for the α-chlorination of cyclohexanone **1a** by NCS [Eq. (1)] and some representative results are shown in Table 1.

(*S*)-Proline (**3a**) catalyzed the formation of α-chlorocyclohexanone (**2a**) in good yields, but unfortunately **2a** was formed as a racemate (entry 1). In contrast to this result, (*S*)-prolinamide (**3b**), an excellent catalyst for the α-chlorination of aldehydes,[7b] afforded **2a** with up to 81% *ee*; however, the yield of **2a** was moderate (40%, entry 2). Several other organocatalysts **3c–i** were employed for the α-chlorination reaction (entries 3–11), and it is notable that **3e**, which is an excellent catalyst for the α-chlorination of aldehydes, did not catalyze the α-chlorination of ketones (entry 5). Interestingly, the spiro derivative **3h** provided **2a** with 88% *ee* but in low yield (17%, entry 10).[10] We envisioned that the sterically less demanding catalyst 4,5-diphenylimidazolidine[11] **3i** (4,5-DPI) could improve the reaction rate, and to our delight we obtained **2a** in 65% yield and 97% *ee* (entry 11).

The moderate yields of α-chlorocyclohexanone (**2a**) obtained (entries 2 and 11) led us to investigate the reaction course by ^{1}H NMR studies of the reaction mixture. We discovered that the conversion into **2a** accounted for only approximately 60% of the NCS consumed, as significant amounts of polychlorinated cyclohexanones were also obtained. Furthermore, it was observed that chlorination of the catalyst also occurred to some degree, another factor responsible for the moderate yields. The detection of the polychlorinated species led us to investigate the dichlorination of cyclohexanone. Therefore, we studied the chlorination reaction of racemic α-chlorocyclohexanone (*rac*-**2a**) with NCS catalyzed by 10 mol% 4,5-DPI·AcOH salt (vide infra). Interestingly, catalyst **3i**·AcOH, was found to catalyze not only the chlorination of *rac*-**2a** but also a kinetic chiral resolution of *rac*-**2a** [Eq. (2)].

2,6-Dichlorocyclohexanone **2aa** was obtained in 27% yield and 87% *ee* after 20 h, and for the remaining mono-

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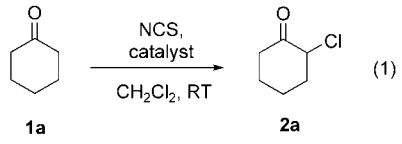
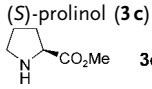
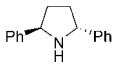
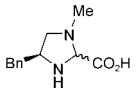
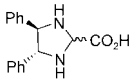
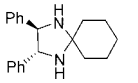
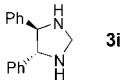
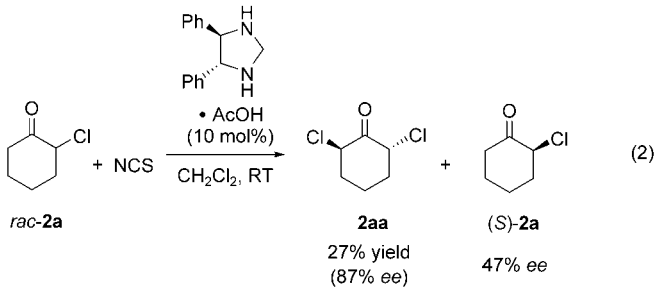


1a 2a (1)

Table 1: Screening of catalysts **3** (10–20 mol%) for the enantioselective α-chlorination of cyclohexanone (**1a**).[a]

Entry	Catalyst		*t* [h]	Yield [%][b]	*ee* [%][c]
1	(*S*)-proline (**3a**)		24	65[f]	0
2[d]	(*S*)-prolinamide (**3b**)		24	40[e]	81
3	(*S*)-prolinol (**3c**)		24	5[f]	45
4		**3d**	24	20[f]	20
5		**3e**	24	<5[f]	–
6		**3f**	0.75	12[f]	23
7			72	58	0
8		**3g**	0.75	10[f]	62
9			72	34	39
10		**3h**	22	17[f]	88
11[d]		**3i**	20	65[e]	97

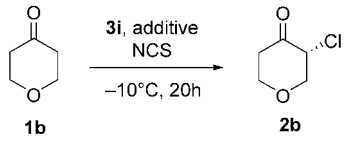
[a] Procedure: To a mixture of **1a** (1.25–2.5 mmol) and catalyst in CH_2Cl_2 was added NCS (0.5 mmol), and the reaction mixture was stirred at ambient temperature for the time indicated. [b] Conversion of cyclohexanone determined by GC and based on NCS as the limiting reagent. [c] Enantiomeric excess determined by CSP-GC. [d] Reaction performed at −24 °C. [e] Moderate yield due to formation of polychlorinated products (see text). [f] Moderate yield due to low conversion.



rac-**2a** **2aa** 27% yield (87% *ee*) (*S*)-**2a** 47% *ee* (2)

chloro compound **2a**, 47% *ee* of (*S*)-**2a** was found indicating that (2*R*)-chlorocyclohexanone is converted to (*R*,*R*)-2,6-dichlorocyclohexanone (**2aa**). The fact that (2*R*)-chlorocyclohexanone, the major enantiomer obtained in the α-chlorination of cyclohexanone catalyzed by **3i**·AcOH, is the more reactive enantiomer in the second chlorination step shows that the asymmetric induction for the first chlorination step is even better than observed. This also explains the slight decrease in optical purity observed after extended reaction times, as well as the formation of polychlorinated ketones. Similar observations were made for the tetrahydropyran-4-one (**1b**, vide infra).

We next turned our attention to the use of other ketones and discovered that, for example, tetrahydropyran-4-one (**1b**), was much less reactive than cyclohexanone (**1a**) as only a low yield of α-chlorotetrahydropyran-4-one (**2b**) was obtained [Eq. (3)] (Table 2, entry 1).



1b **2b** (3)

Table 2: Screening of acid additives for the α-chlorination of tetrahydropyran-4-one (**1b**).[a]

Entry	Add.	Equiv	Solv.	**1b** (equiv)	NCS (equiv)	Yield [%][b]	*ee* [%][c]
1	–	–	CH_2Cl_2	5	1	30	90
2	$PhCO_2H$	0.20	CH_2Cl_2	5	1	53	84
3	$PhCO_2H$	0.20	MeCN	2.5	1	15	97
4	AcOH	0.10	MeCN	2.5	1	19	87
5[d]	CF_3CO_2H	0.10	CH_2Cl_2	5	1	62	68
6	$ClCH_2CO_2H$	0.10	MeCN	2.5	1	50	91
7	2-NO_2-$PhCO_2H$	0.25	MeCN	1	1.5	63	97
8[e]	2-NO_2-$PhCO_2H$	0.25	MeCN	1	2.0	72	98

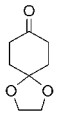
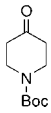
[a] Procedure: To a mixture of **1b** (0.5–2.5 mmol), additive, and **3i** (0.05 mmol) in the indicated solvent (1 mL) at −10 °C was added NCS (0.5–0.6 mmol), and the reaction mixture was stirred for 24 h. [b] Conversion of tetrahydropyran-4-one determined by GC and based on NCS as the limiting reagent. [c] *ee* determined by CSP-GC. [d] Reaction time 4 h. [e] Reaction performed at −24 °C.

This result led us to develop reaction conditions for α-chlorination of less reactive ketones, and it turned out that variation of the solvent, the amount of ketone and NCS, and the addition of acids[12] could influence the outcome of the reaction. Table 2 shows some results for the screening of various acid additives with 4,5-DPI **3i** as the catalyst for the α-chlorination of **1b**.

The use of benzoic acid in combination with 4,5-DPI **3i** increased the reaction rate, and the optically active product **2b** was obtained in 53% yield, a significant improvement over the reaction without additive (Table 2, entries 1 and 2).[13] Various solvents were also screened for the reaction, and it was found that the reaction in MeCN was cleaner and the formation of polychlorinated pyranones was suppressed since only minor amounts were formed as determined by GC-MS and ^{1}H NMR spectroscopy. Furthermore, the optical purity of the α-chloropyranone (**2b**) was better (97% *ee*) than when the reaction was conducted in CH_2Cl_2 (entries 2 and 3). The best results in terms of reactivity and asymmetric induction were obtained with 2-nitrobenzoic acid.[14] The enhanced reactivity allowed us to use NCS in a slight excess, and **2b** was obtained in 63% yield and 97% *ee* (entry 7). This result is particularly remarkable since the reactions of ketones catalyzed by proline derivatives are usually sluggish, and a large excess of ketone is often necessary to obtain high yields. Lowering the reaction temperature to −24 °C improved the yield and enantioselectivity to 72% and 98% *ee*, respectively (entry 8).

The general scope of the organocatalytic enantioselective α-chlorination of various cyclic and acyclic ketones is presented in Table 3. The cyclic ketones **1a–d** were converted into the corresponding α-chloroketones **2a–d** with excellent enantioselectivities (90–98% *ee*) and in good yields even though the ketone is not used in excess (Table 3, entries 1–4). In these reactions, full conversion of the ketone was observed together with the α-chloroketone product and a minor amount of the polychlorinated ketone as a by-product. For the acyclic ketones 3-pentanone (**1e**) and 4-heptanone (**1f**), good enantiomeric excesses of the corresponding α-chloroketones **2e**,**f** were also obtained; however, yields were slightly lower due to their lower reactivity, and an excess of ketone was required.[15] Isolation of the α-chloroketone products from the polychlorinated ketones was found to be difficult on silica and, furthermore, a slight racemization was found to occur.[16] Therefore, α-chloroketone **2a** was converted to lactone **4** by Baeyer–Villiger oxidation, and **2b** to the corresponding chloroalcohol **9** by reduction with $NaBH_4$. α-Chloroketones **2c**,**d** were purified on neutral alumina, and **2e**,**f** were isolated after conversion to the corresponding thiophenyl ketone using thiophenol (see the Supporting Information). It should be noted that α-chloroketones **2c**,**d** racemize during flash chromatography on neutral alumina, and in order to isolate optically active products in situ reduction to the α-chloro alcohols is recommended.

Table 3: Organocatalytic enantioselective α-chlorination of cyclic and acyclic ketones by NCS catalyzed by 10–20 mol% 4,5-DPI **3i**.[a]

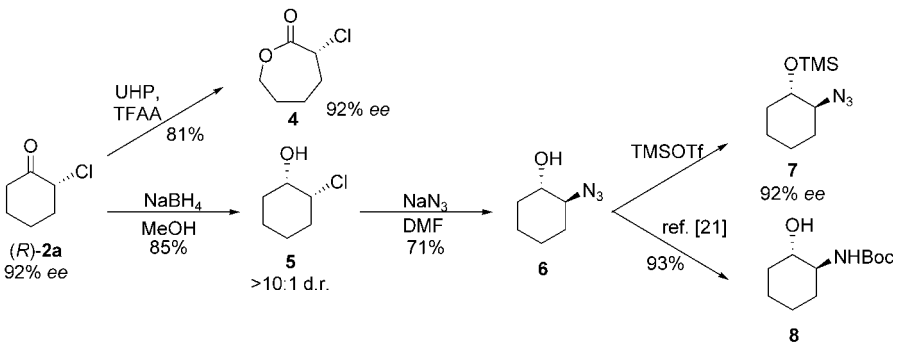
Entry	Ketone	*T* [°C]	Prod.	Yield [%][b]	*ee* [%][c]
1	 **1a**	−24	**2a**	82(54)[f]	97
2[d]	 **1b**	−24	**2b**	72(50)[g]	98
3	 **1c**	−24	**2c**	83(65)	93
4	 **1d**	−24	**2d**	76(63)	93
5[e]	 **1e**	−10	**2e**	62(51)[h]	86
6[e]	 **1f**	−10	**2f**	40(35)[h]	89

[a] Reaction conditions: To a mixture of ketone (0.5 mmol), 4,5-DPI **3i** (0.1 mmol, 20 mol%) and 2-NO_2-$PhCO_2H$ (0.25 mmol, 50 mol%) in MeCN at the indicated temperature was added NCS (1.0 mmol, 2.0 equiv), and the reaction mixture was stirred for 20 h. [b] Determined by ^1H NMR spectroscopy using an internal standard and confirmed by GC analysis. Yields of isolated products are shown in brackets (see the Supporting Information). [c] *ee* determined by CSP-GC. [d] Performed using 10 mol% 4,5-DPI **3i** and 0.25 equiv. 2-NO_2-$PhCO_2H$. [e] Performed using 5 equiv. of ketone. Reaction time 40 h. [f] Isolated after Baeyer–Villiger oxidation to lactone **4**. [g] Isolated after $NaBH_4$ reduction to the corresponding chloroalcohol **9**. [h] Isolated as the corresponding thiophenyl ketone.

An important aspect of the α-chlorination reaction of ketones is that the optically active α-chloroketones obtained provide highly versatile chiral building blocks for a variety of synthetic transformations. In Scheme 1 the transformation of (*R*)-α-chlorocyclohexanone (**2a**) into α-chloro-ε-lactone (**4**) and *cis*-2(*R*)-chlorocyclohexan-1(*S*)-ol (**5**) are shown. Lactone **4** was formed in 81% yield by a regioselective Baeyer–Villiger oxidation using urea hydrogen peroxide (UHP) and trifluoroacetic anhydride (TFAA), without a decrease in optical purity. Furthermore, cyclohexanol **5** was formed in good yield and with a diastereoselectivity of >10:1 by reduction of (*R*)-α-chlorocyclohexanone **2a** using $NaBH_4$ in MeOH (see the Supporting Information).[17]

The absolute configuration of the α-chloroketones was determined to be (*R*) by transformation of **5** into *trans*-2(*S*)-azidochlorocyclohexan-1(*S*)-ol (**6**) by treatment with NaN_3 in DMF, and comparison of the optical rotation with literature values (Scheme 1).[18] After TMS protection of **6** to obtain **7**, the enantiomeric excess was determined by GC using a chiral stationary phase and it was found that the optical purity had not decreased during the transformations. Furthermore, the elution order of the enantiomers confirmed the assignment of the absolute configuration.[19] Azide **6** can also be transformed easily into the highly useful protected amino alcohol **8** in 93% yield by a simple hydrogenolysis/protection procedure.[20]

In summary, we have developed the first catalytic asymmetric α-chlorination of ketones affording optically active α-chloroketones. The reaction proceeds in moderate to high yields and excellent enantioselectivities using inexpensive NCS as the chlorine source. Furthermore, we have developed a novel organocatalytic system comprising an easily available imidazolidine catalyst and a carboxylic acid and demonstrated the synthetic usefulness of the α-chloroketones formed in the catalytic reaction.



Scheme 1. Synthetic transformations of (*R*)-α-chlorocyclohexanone **2a**.

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[1] For reviews on enantioselective halogenation reactions see, for example, a) H. Ibrahim, A. Togni, *Chem. Commun.* **2004**, 1147; b) K. Muñiz, *Angew. Chem.* **2001**, *113*, 1701; *Angew. Chem. Int. Ed.* **2001**, *40*, 1653.

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[8] α-Amination of aldehydes: a) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang, K. A. Jørgensen, *Angew. Chem.* **2002**, *114*, 1868; *Angew. Chem. Int. Ed.* **2002**, *41*, 1790; b) B. List, *J. Am. Chem. Soc.* **2002**, *124*, 5656; c) H. Vogt, S. Vanderheiden, S. Bräse, *Chem. Commun.* **2003**, 2448; α-oxidation of aldehydes: d) G. Zhong, *Angew. Chem.* **2003**, *115*, 4379; *Angew. Chem. Int. Ed.* **2003**, *42*, 4247; e) S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808.

[9] α-Amination of ketones: a) N. Kumaragurubaran, K. Juhl. W. Zhuang, A. Bøgevig, K. A. Jørgensen, *J. Am. Chem. Soc.* **2002**, *124*, 6254; α-oxidation of ketones: b) A. Bøgevig, H. Sundéen, A. Córdova, *Angew. Chem.* **2004**, *116*, 1129; *Angew. Chem. Int. Ed.* **2004**, *43*, 1109; c) M. Hayashi, J. Yamaguchi, T. Sumaiya, M. Shoji, *Angew. Chem.* **2004**, *116*, 1132; *Angew. Chem. Int. Ed.* **2004**, *43*, 1112.

[10] The catalytic properties of these compounds were found during ^{1}H NMR investigations of the mechanism of the α-chlorination of cyclohexanone by NCS catalyzed by (1*R*,2*R*)-diphenylethylenediamine. These investigations showed that the active catalyst was the condensation product between (1*R*,2*R*)-diphenylethylenediamine and cyclohexanone (**3h**) and not (1*R*,2*R*)-diphenylethylenediamine.

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[13] We believe that acid additives promote enamine formation and suppress chlorination of the catalyst.

[14] 2-Nitrobenzoic acid (20 mol%) led to less than 1% conversion after 18 h in the absence of 4,5-DPI **3i** in a 1:1 mixture of cyclohexanone and NCS at ambient temperature.

[15] Less than 1% conversion of **1e** and **1f** was observed in the absence of 2-nitrobenzoic acid.

[16] No racemization was found to occur during filtration through a short silica plug.

[17] In order to obtain high diastereoselectivities, dry MeOH, careful temperature control, and slow addition of $NaBH_4$ were required.

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