Organocatalytic asymmetric α-bromination of aldehydes and ketones†

Søren Bertelsen, Nis Halland, Stephan Bachmann, Mauro Marigo, Alan Braunton and Karl Anker Jørgensen*

Received (in Cambridge, UK) 1st July 2005, Accepted 26th July 2005
First published as an Advance Article on the web 30th August 2005
DOI: 10.1039/b509366j

The first organocatalytic enantioselective α-bromination of aldehydes and ketones is presented; a C_2-symmetric diphenylpyrrolidine catalyst afforded the α-brominated aldehydes in good yields and up to 96% ee, while ketones were α-brominated by a C_2-symmetric imidazolidine in up to 94% ee; furthermore, the organocatalytic enantioselective α-iodination of aldehydes is also demonstrated to proceed with up to 89% ee.

The transformation of C–H into C–X (X = F, Cl, Br, I) bonds with stereochemical control of the chiral carbon center formed is an important challenge in organic and medicinal chemistry.[1]

In recent years a number of enantioselective halogenation reactions have been developed using chiral Lewis acids and organic compounds[2] as the catalysts. For the chiral Lewis acid-catalyzed reactions the substrates are mainly β-keto esters and phosphonates using electrophilic halogenation reagents and enantioselective α-fluorination, α-chlorination and α-brominations have been successfully developed.[3] A chiral phase-transfer catalyst derived from a cinchona alkaloid has also been shown to be effective for the α-fluorination of β-keto esters giving the corresponding optically active α-fluorinated compounds with up to 69% ee.[4]

Optically active α-chloro- and α-bromoesters have been obtained from ketenes which are formed *in situ* from acetyl chlorides and base, followed by treatment with an electrophilic chlorine or bromine source, in the presence of a cinchona alkaloid acting as a chiral nucleophilic catalyst.[5]

Recently, the organocatalytic enantioselective α-chlorination and α-fluorination of aldehydes, and α-chlorination of ketones were described. Two papers independently presented the α-chlorination of aldehydes. MacMillan *et al.* used a chiral imidazolidinone as the catalyst and hexachloro-cyclohexadienone as the chlorine source leading to the α-chlorinated aldehydes in high yield and enantioselectivity (92–95% ee).[6] Our approach was based on NCS as the chlorinating reagent and L-proline amide or C_2-symmetric diphenylpyrrolidine as the catalysts. The latter afforded the highest enantiomeric excess of the α-chlorinated aldehydes (94–97% ee) in high yields.[7] For the direct α-chlorination of ketones, a simple extension of the related aldehyde transformation was not possible. Neither proline, nor the optimal catalysts for the chlorination of aldehydes promoted this reaction efficiently.[8] A thorough screening of a number of organocatalysts led to the use of a C_2-symmetric imidazolidine as the catalyst of choice.

Danish National Research Foundation: Center for Catalysis, Department of Chemistry, Aarhus University, Aarhus C, DK-8000, Denmark. E-mail: kaj@chem.au.dk; Fax: 45 8619 6199; Tel: 45 8942 3910

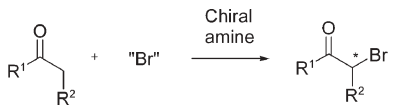
† Electronic supplementary information (ESI) available: Full experimental details. See http://dx.doi.org/10.1039/b509366j

Four papers were very recently published within a few weeks presenting the organocatalytic enantioselective α-fluorination of carbonyl compounds.[9] In the paper by Enders *et al.*,[9a] L-proline and derivatives were shown to catalyze the α-fluorination of *e.g.* hexanal and cyclohexanone in moderate to good yields and up to 36% ee using Selectfluor as the fluorinating agent. We have developed a highly enantioselective α-fluorination of aldehydes employing NFSI as the fluorine source and only 1 mol% of a silyl-protected proline-derived catalyst.[9b] This system led to the formation of stereogenic C–F centers with up to 97% ee. Barbas *et al.*[9c] and MacMillan *et al.*[9d] have employed an imidazolidinone catalyst and NFSI, and obtained α-fluorinated aldehydes with high optical purity. However, high catalyst loadings (20–100 mol%) were employed.

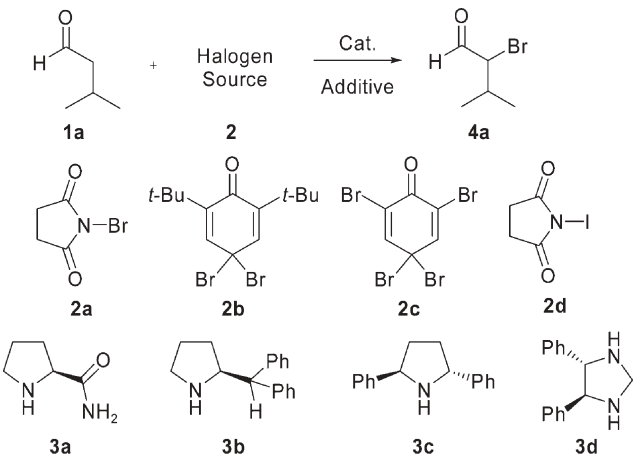
In this communication the first organocatalytic enantioselective α-bromination of aldehydes and ketones is presented (Scheme 1).

We initially screened several bromine sources **2a–c** for the α-bromination of 3-methyl butanal **1a** in the presence of various chiral amines as catalysts (Scheme 2).

We started our investigations using the reaction conditions successfully applied to the α-chlorination of aldehydes with NBS (**2a**) as the bromine source.[7] However, these conditions were found to be unsuitable, giving low conversion and enantioselectivity (8% yield and 19% ee). Further studies indicated that this might be due



Scheme 1 Organocatalytic α-bromination of aldehydes and ketones.



Scheme 2 Bromination reagents and catalysts screened during the optimization.

Table 1 Catalytic enantioselective α-bromination of 3-methyl butanal under various reaction conditions

Entry	Cat	Halogen source	Solvent	Additive (mol%)	Conversion[a] (%)	ee[b] (%)
1	**3a**	**2a**	CH_2Cl_2 : pentane 1 : 3		91	−49
2	**3b**	**2a**	CH_2Cl_2 : pentane 1 : 3	$PhCO_2H$ (20)	100	58
3	**3b**	**2a**	CH_2Cl_2 : pentane 1 : 3		24	11
4	**3c**	**2a**	CH_2Cl_2 : pentane 1 : 3	$PhCO_2H$ (20)	95	45
5	**3c**	**2b**	CH_2Cl_2 : pentane 1 : 3	$PhCO_2H$ (20)	71	97
6[c]	**3c**	**2b**	CH_2Cl_2 : pentane 1 : 3	$PhCO_2H$ (10)	60	97
7	**3c**	**2c**	CH_2Cl_2 : pentane 1 : 3	$PhCO_2H$ (20)	81	86
8	**3c**	**2b**	PhMe	$PhCO_2H$ (20), H_2O (200)	40	94
9	**3c**	**2b**	Pentane	$PhCO_2H$ (20), H_2O (200)	46	93
10	**3c**	**2b**	MeCN	$PhCO_2H$ (20), H_2O (200)	100	83
11	**3c**	**2b**	CH_2Cl_2 : pentane 1 : 1	$PhCO_2H$ (20), H_2O (200)	90	96

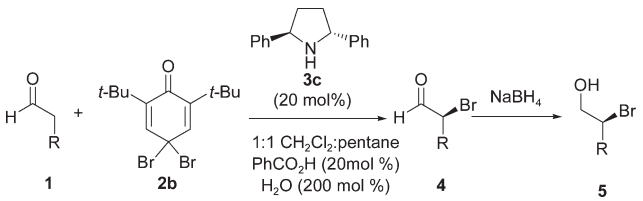
[a] Conversion after 60 min measured by ^1H NMR spectroscopy of the crude reaction mixture and confirmed by GC. [b] ee of 2-bromo-3-methyl butanal determined by CSP-GC. [c] 10 mol% catalyst used compared to 20 mol% in the other experiments.

to the increased reactivity of NBS **2a** compared to that of NCS, and hence the temperature was lowered to −24 °C which gave 91% conversion of 3-methyl butanal **1a** affording 2-bromo-3-methyl butanal **4a** in 49% ee (Table 1, entry 1). A further increase in enantioselectivity was observed when 2-benzhydryl-pyrrolidine **3b** was applied as the catalyst and when 20 mol% benzoic acid was added to the reaction mixture full conversion was observed within 1 h (entry 2). Interestingly, both the yield and enantioselectivity were significantly lower in the absence of an acid additive (entry 3). Compound **3c**, a highly efficient catalyst for the enantioselective α-chlorination of aldehydes, gave good conversion when NBS **2a** was employed as the bromine source (entry 4). However, application of the easily synthesized, air-stable 4,4-dibromo-2,6-di-*tert*-butyl-cyclohexa-2,5-dienone[10] **2b** improved the enantioselectivity and **2b** was found to be an excellent reagent compared to the other bromine sources (entries 4, 5, 7). The reaction conditions were optimized using (2*R*,5*R*)-diphenylpyrrolidine **3c** as catalyst and **2b** as bromine source and the yield was found to be strongly solvent dependent (entries 8–11). We were pleased to find high enantioselectivity and conversion in a 1 : 1 mixture of CH_2Cl_2 and pentane (entry 11). Furthermore, this mixture prevented racemization of the optically active product, since the enantiomeric excess of **4a** was unaltered after 2 days. It is notable that the catalysts **3b** and **3c** gave the opposite enantiomer of **4a**, compared to L-proline amide **3a**.

After optimizing the reaction conditions we expanded the scope of the reaction by α-brominating different aldehydes (Scheme 3 and Table 2).

The enantioselective α-bromination proceeded well for aldehydes **1a–g** with isolated yields of the α-bromo alcohols **5a–g** in the range of 72–95% in 2 steps (Table 2). Furthermore, good to excellent enantioselectivity, in the range 68–96% ee, were observed for linear, branched, cyclic and unsaturated aldehydes (entries 1–7). The absolute configuration of the chiral carbon center formed has been assigned to be (*S*) by comparison of the optical rotation of bromoalcohol **5f** with literature values,[11] when using the (2*R*,5*R*)-diphenylpyrrolidine **3c** as catalyst. This is the same absolute configuration found in the α-chlorination of aldehydes using NCS and the same catalyst.[7]

The reaction condition for the organocatalytic α-bromination of aldehydes have been applied to the enantioselective α-iodination of aldehydes as well. According to our knowledge, there is no procedure for the direct α-iodination of aldehydes. Iodination of aldehydes such as 3-methyl butanal **1a** with NIS **2d** and **3e** as the

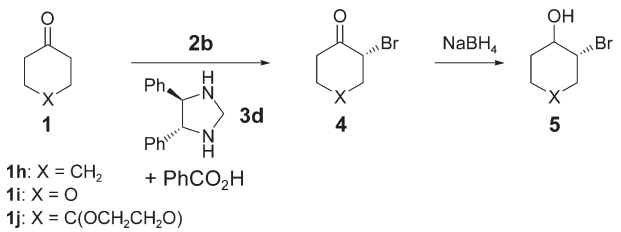


Scheme 3 Organocatalytic α-bromination of aldehydes.

Table 2 Enantioselective α-bromination of aldehydes

Entry	R	Isolated yield (%)[a]	ee[b] (%)
1[c]	*i*-Pr–**1a**	87–**5a**	96
2[c]	*t*-Bu–**1b**	94–**5b**	89
3	Et–**1c**	72–**5c**	77
4	*n*-Pr–**1d**	82–**5d**	85
5	*n*-Hex–**1e**	95–**5e**	68
6	Cyclohexyl–**1f**	92–**5f**	73(*S*)
7	Allyl–**1g**	74–**5g**	76

[a] Isolated yield of the corresponding alcohol after $NaBH_4$ reduction. [b] ee determined of the α-bromo aldehydes by CSP-GC. [c] −24 °C, 1.3 equiv. of **2c**.



Scheme 4 Organocatalytic α-bromination of different ketones.

catalyst, was observed to be a very rapid reaction, with full conversion in only 20 min. For the α-iodination of **1a**, 78% yield and 89% ee of 2-iodo-3-methyl butanal was obtained, while butanal **1c** afforded the corresponding optically active α-iodo aldehyde in 60% ee, however, only 30% yield was obtained.

We have extended the catalytic α-bromination reaction to the α-bromination of ketones (Scheme 3). We were pleased to find that the bromine source 4,4-dibromo-2,6-di-*tert*-butyl-cyclohexa-2,5-dienone **2b** was significantly better compared to the other reagents tested. Furthermore, it was established that the reaction conditions

Table 3 Catalytic enantioselective α-bromination of cyclic ketones catalysed by 4,5-diphenyl-imidazolidine **3d**[a]

Entry	Ketone	Solvent	Temp/°C	Time/h	Conversion[b] (isolated yield (%))	ee[c] (%)
1	**1h**	MeCN	−24	20	66 (58)[d]–**5h**	85
2	**1h**	CH_2Cl_2 : pentane 1 : 3	−24	20	87–**5h**	86
3	**1h**	Et_2O	−30	0.5	16–**5h**	88
4	**1h**	*i*-PrOH	−30	20	63–**5h**	88
5	**1h**	EtOH	−30	20	66–**5h**	94
6	**1h**	*t*-BuOMe	−30	40	90 (81)[d]–**5h**	90
7	**1h**	THF	−30	20	76 (70)[d]–**5h**	91
8	**1i**	THF	−30	20	80[e]–**4i**	89
9	**1j**	THF	−30	40	67[e]–**4j**	73

[a] Reaction conditions: See Supporting Information. [b] Measured by ^{1}H NMR of the crude reaction mixture and confirmed by GC. [c] ee determined of the α-bromo ketones by CSP-GC. [d] Yield of the corresponding *cis*-alcohol after $NaBH_4$ reduction and FC. [e] Yield after FC on Iatrobeads.

previously developed for the organocatalytic asymmetric chlorination of ketones[8] also proved successful for the α-bromination of ketones. Table 3 entries 1–7 show the optimization of the reaction conditions for the α-bromination of cyclohexanone **1h**.

Cyclohexanone **1h**, in the presence of catalyst **3d**, could be brominated in good yield with an enantioselectivity of up to 94% ee under the optimized reaction conditions (Table 3, entry 5). For the two other cyclic ketones (**1i,j**) presented in Table 3, the α-bromination also procceds well and with good enantioselectivity (entries 8, 9). The absolute configuration of the chiral carbon center formed has been assigned by X-ray analysis of compound **4i** to be (*R*) when using the (4*R*,5*R*)-diphenylimidazolidine catalyst. ‡This is the same absolute configuration as observed in the corresponding α-chlorination of ketones using the same catalyst.[8]

In conclusion, we have developed the first organocatalytic enantioselective α-bromination of aldehydes and ketones. For the aldehydes a C_2-symmetric diphenylpyrrolidine catalyst gave the optically active α-brominated aldehydes in moderate to good yields and up to 96% ee, while the ketones were α-brominated by a C_2-symmetric imidazolidine in up to 94% ee. Furthermore, we have also demonstrated the organocatalytic enantioselective α-iodination of aldehydes to proceed with up to 89% ee.

This work was made possible by a grant from The Danish National Research Foundation. We are grateful to Dr. Rita G. Hazell for performing X-ray crystallographic studies.

Notes and references

‡ CCDC 277076. Crystals of **4i**, 3-bromo-tetrahydro-pyran-4-one, $C_5H_7BrO_2$, M = 179.01, are orthorhombic, $P2_12_12_1$, unit cell: a = 4.3135(4), b = 11.327(1), c = 12.558(1) Å, V = 613.57(9) Å^3, Z = 4, μ(Mo-Kα) = 6.602 mm^{-1}. A total of 15870 reflections (2615 independent) were collected at 100 K on an APEX diffractometer with CCD detector. The structure was solved by direct methods and refined by least squares on F to a final R = 0.031, Rw = 0.033, GOF = 0.870 using 2585 reflections with $I > 0.103$ parameters refined. A parameter according to Rogers[12] refined against all positive reflections including 1063 Bijvoet pairs gave the value 1.00(2) establishing the (*R*) configuration at C3. See http://dx.doi.org/10.1039/b509366j for crystallographic data in CIF or other electronic format.

1 For some recent reviews see *e.g.*: (*a*) H. Ibrahim and A. Togni, *Chem. Commun.*, 2004, 1147; (*b*) K. Muniz, *Angew. Chem., Int. Ed.*, 2001, **40**, 1653; (*c*) M. Oestreich, *Angew. Chem., Int. Ed.*, 2005, **44**, 2324; (*d*) S. France, A. Weatherwax and T. Lectka, *Eur. J. Org. Chem.*, 2005, 475.

2 For general reviews on organocatalysis see *e.g.*: (*a*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138; (*b*) J. Seayad and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719; (*c*) A. Berkessel and H. Gröger, *Metal-Free Organic Catalysts in Asymmetric Synthesis*, Wiley-VCH, Weinheim, 2004.

3 See *e.g.*: (*a*) L. Hintermann and A. Togni, *Angew. Chem., Int. Ed.*, 2000, **39**, 4359; (*b*) L. Hintermann and A. Togni, *Helv. Chim. Acta.*, 2000, **83**, 2425; (*c*) H. Ibrahim, F. Kleinbeck and A. Togni, *Helv. Chim. Acta.*, 2004, **87**, 605; (*d*) Y. Hamashima, K. Yaga, H. Takano, L. Tomás and M. Sodeoka, *J. Am. Chem. Soc.*, 2002, **124**, 14530; (*e*) J.-A. Ma and D. Cahard, *Tetrahedron: Asymmetry*, 2004, **15**, 1007; (*f*) M. Marigo, N. Kumaragurubaran and K. A. Jørgensen, *Chem. Eur. J.*, 2004, **10**, 2133; (*g*) L. Bernardi and K. A. Jørgensen, *Chem. Commun.*, 2005, 1324; (*h*) Y. Hamashima, T. Suzuki, Y. Shimura, T. Himizu, N. Umebayashi, T. Tamura, N. Sasamoto and M. Sodeoka, *Tetrahedron Lett.*, 2005, **46**, 1447; (*i*) N. Shibata, J. Kohno, K. Takai, T. Ishimura, S. Nakamura, T. Toru and S. Kanamasa, *Angew. Chem., Int. Ed.*, 2005, **44**, 4204; (*j*) Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura and M. Sodeoka, *J. Am. Chem. Soc.*, 2005, **127**, 10164.

4 D. Y. Kim and E. J. Park, *Org. Lett.*, 2002, **4**, 545.

5 See *e.g.*: (*a*) S. France, A. Weatherwax and T. Lectka, *Eur. J. Org. Chem.*, 2005, 475; (*b*) S. France, H. Wack, A. E. Taggi, A. M. Hafez, T. R. Wagerle, M. H. Shah, C. L. Duisch and T. Lectka, *J. Am. Chem. Soc.*, 2004, **126**, 4245.

6 M. P. Brochu, S. P. Brown and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2004, **126**, 4108.

7 N. Halland, A. Braunton, S. Bachmann, M. Marigo and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2004, **126**, 4790.

8 M. Marigo, S. Bachmann, N. Halland, A. Braunton and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2004, **43**, 5507.

9 (*a*) D. Enders and R. M. Hüttl, *Synlett*, 2005, 991; (*b*) M. Marigo, D. Fielenbach, A. Braunton, A. Kjærsgard and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2005, **44**, 3703; (*c*) D. D. Steiner, N. Mase and C. F. Barbas III, *Angew. Chem., Int. Ed.*, 2005, **44**, 3706; (*d*) T. D. Beeson and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 8826.

10 K. Omura, *J. Org. Chem.*, 1996, **61**, 2006.

11 P. L. Bailey, A. D. Briggs, R. F. W. Jackson and J. Pietrizka, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3359.

12 D. Rogers, *Acta Crystallogr., Sect. A*, 1981, **A37**, 734.