Catalysis Science & Technology

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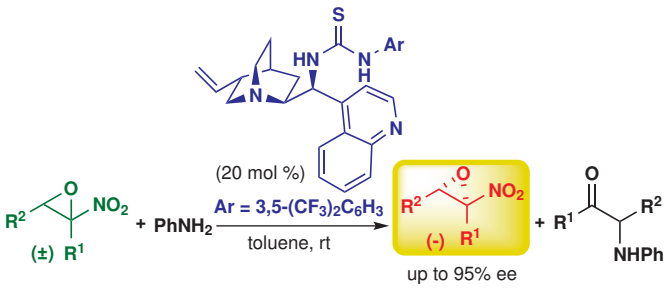

The first enantioselective synthesis of β-aryl-substituted α-nitroepoxides has been developed and their potential as valuable intermediates demonstrated.

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Catalytic enantioselective synthesis of α-nitroepoxides via aminolytic kinetic resolution

Cite this: DOI: 10.1039/xoxxoooooox

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Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

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The first enantioselective synthesis of β-aryl-substituted α-nitroepoxides, exploiting an organocatalyzed aminolytic kinetic resolution (AKR), has been developed. Ring-opening reaction of racemic α-nitroepoxides with aniline in the presence of a readily available *Cinchona* alkaloid-derived thiourea affords unreacted epoxides in up to 95% ee.

The importance of optically active epoxides is widely recognised by their presence as structural motives in several natural products and mostly as highly versatile intermediates, frequently involved in total synthesis.[1] Indeed, a great variety of functionalised products is achievable via regio- and stereoselective opening of the oxirane ring.[2]

The asymmetric epoxidation of alkenes is the most appealing and straightforward approach to prepare epoxides.[3] Amongst the several methodologies developed so far, a steadily growing number of efficient asymmetric nucleophilic epoxidation reactions have been reported for differently substituted enones[4] and enals.[5] In contrast, according to the paucity of examples illustrated in the literature,[6] the asymmetric epoxidation of nitroalkenes, a class of popular electron-poor alkenes,[7] appears to be a challenging process.

Racemic α-nitroepoxides, readily available by epoxidation of the corresponding nitroalkenes with H_2O_2/NaOH system, are synthetically useful compounds, due to the fact that they undergo complete regioselective ring-opening reactions at the β-position by a variety of nucleophiles, to give α-substituted carbonyl compounds,[8] functionalised α-aminoacids,[6a,b] and heterocycles[9] (Figure 1).

Chiral non racemic amines have been recently employed in the ring-opening reaction of racemic α-nitroepoxides to afford, after reduction of imine intermediate, vicinal diamines in stereoselective fashion (Figure 1).[10] Hence, the development of processes to access enantioenriched α-nitroepoxides is of great importance, especially in view of the totally unexplored potential of this class of epoxides in asymmetric synthesis.

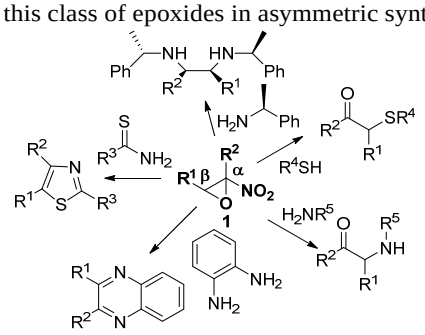


Figure 1 Ring-opening reactions of α-nitroepoxides.

The kinetic resolution of racemic compounds represents a highly valuable strategy and sometimes the unique tool in the synthesis of a chiral non racemic compound.[11] Specifically, since the seminal work by Jacobsen and co-authors, the hydrolytic kinetic resolution (HKR) of terminal epoxides catalysed by a salen-Co-(III)-based complex[12] became widely applied also at an industrial scale,[11b,d,13] as powerful and exclusive approach for the preparation of these challenging compounds in excellent enantioselectivity. In the area of organocatalysis, hydrogen-bonding donors such as hexafluoro-2-propanol,[14] achiral thioureas[15] and ureas[16] have been shown to assist the regioselective ring-opening reaction of epoxides to give differently 1,2-functionalized alcohols. Very recently, a few examples on the desymmetrization of *meso*-epoxides catalyzed by chiral phosphoric acids[17] or sulphonamides[18] have been reported.

Driven by our long-standing interest in asymmetric synthesis of epoxides[19] and inspired by these reports, we envisaged that an aminolytic kinetic resolution catalyzed by chiral bifunctional

organic promoters such as a thiourea amine could be a successful strategy to obtain enantioenriched α-nitroepoxides (Figure 2).

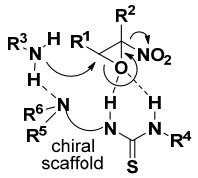
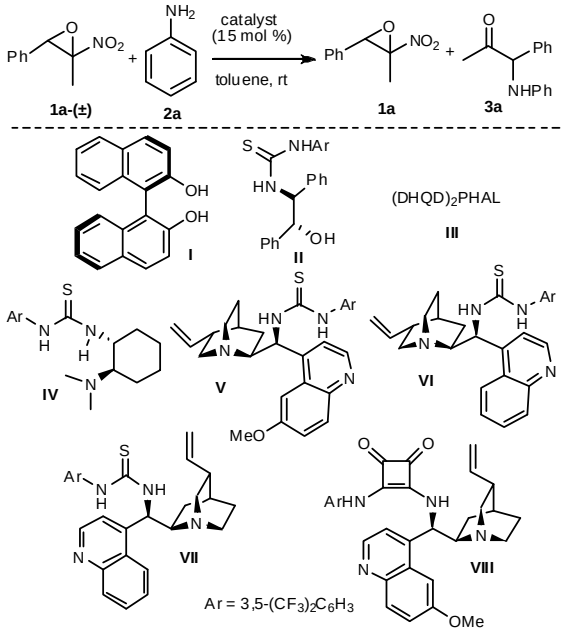


Figure 2 Proposed activation model in the AKR of α-nitroepoxide catalyzed by an amino thiourea.

Activation of the reagents through general acid-base catalysis provided by the bifunctional organocatalyst would have likely given rise to the preferential opening of one enantiomer of the α-nitroepoxide in a highly regioselective manner.

Table 1 Screening of catalysts in model AKR reaction[a]



Entry	Catalyst	Time (h)	**3a** (%)[b]	Yield **1a**(%)[c]	ee **1a** (%)[d]
1	**I**	48	12	nd	nd
2	**II**	48	24	68	2
3	**III**	48	21	74	6
4	**IV**	65	40	50	-23
5	**V**	69	37	51	-11
6	**VI**	48	33	63	-30
7	**VII**	48	40	47	28
8	**VIII**	48	35	59	6

[a] All reactions were carried out using **1a-(±)** (0.15 mmol), **2a** (0.18 mmol), catalyst (15 mol %) in toluene (1.5 mL). [b] Determined by ^{1}H NMR analysis. [c] Isolated yield. [d] Determined by chiral HPLC analysis. Negative ee indicates the formation of the opposite enantiomer.

Herein, we illustrate the first synthesis of enantiomerically enriched aromatic α-nitroepoxides. The kinetic resolution of racemic α-nitroepoxides proceeds via a highly regioselective ring-opening reaction with aniline organocatalysed by a *Cinchona* alkaloid-derived thiourea.

We commenced our study reacting *trans*-2-methyl-2-nitro-3-phenyloxirane **1a-(±)** and aniline[20] in the presence of 15 mol % of chiral H-bonding donors as (*R*)-BINOL **I**[21] and easily accessible amino alcohol derived thiourea **II**[22] at room temperature in toluene (Table 1). In the presence of catalyst **I**, the conversion to the expected ketone **3a** was poor after 48 h (entry 1), whereas in the presence of the thiourea alcohol **II** a slight improvement of the conversion was observed although the epoxide was isolated almost as racemic compound (entry 2). A similar outcome was observed when using the Brønsted base catalyst **III** (entry 3). We were pleased to observe that Takemoto's catalyst **IV** provided the unreacted epoxide in 50% yield and 23% ee (entry 4). This result showed the requirement of a bifunctional organocatalyst for the reaction to proceed in a more effective way, likely via a cooperative activation of reagents as suggested in Figure 2. Among the *Cinchona* alkaloid derived-thioureas, a significant improvement was achieved when using catalyst **VI**, since the epoxide was isolated in 63% yield and 30% ee (entry 6). Compound **VII**, the *pseudo*-enantiomer of **VI**, catalysed the process less effectively (entry 7). Finally, amine-squaramide **VIII** afforded a similar result as the one achieved with *pseudo*-enantiomeric amine thiourea **V** (entry 8). Catalyst **VI** was selected for further optimization of the AKR of epoxide **1a-(±)** (Table 2).

Table 2 . Optimization of the reaction conditions[a]

Entry	RNH_2	Solvent	**3** (%)[b]	Yield **1a**(%)[c]	ee **1a** (%)[d]
1	1-naphthyl	toluene	34(**b**)	64	24
2	2-naphthyl	toluene	32(**c**)	61	20
3	4-$MeOC_6H_4$	toluene	38(**d**)	47	40
4	benzyl	toluene	nd	34	6
5	Ph	$CHCl_3$	30(**a**)	65	18
6	Ph	*t*BuOMe	52(**a**)	43	22
7	Ph	*p*-xylene	36(**a**)	59	30
8[e]	Ph	toluene	65(**a**)	28	59
9[f]	Ph	toluene	55(**a**)	38	50
10[g]	Ph	toluene	70(**a**)	28	72
11[h]	Ph	toluene	35(**a**)	62	-

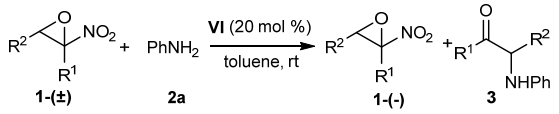
All reactions were carried out using **1a-(±)** (0.15 mmol), **2** (0.18 mmol), **VI** (15 mol %) solvent (1.5 mL) for 48-113 h. [b] Determined by ^{1}H NMR analysis. [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] Reaction carried out with 20 mol% of **VI**, 1.5 equiv of aniline at $C_{\mathbf{1a}}$ (0.2 M). [f] Reaction carried out with 20 mol% of **VI**, 3.0 equiv of aniline at $C_{\mathbf{1a}}$ (0.05 M). [g] Reaction carried out with 20 mol% of **VI**, 3.0 equiv of aniline at $C_{\mathbf{1a}}$ (0.1 M). [h] Reaction carried out without catalyst, with 3.0 equiv of aniline at $C_{\mathbf{1a}}$ (0.1 M).

Sterically demanding 1-, 2-naphthyl amines and 4-methoxy aniline, when reacting with epoxide **1a-(±)**, proved to be inferior reagents compared to aniline (entries 1-3). More nucleophilic benzyl amine reacted faster and less selectively (entry 4).[23] A solvent screening, on model reaction with aniline, confirmed non polar aromatic solvents as the most suitable (entries 5-7). The reaction was further optimized in toluene varying reagents ratio and concentration. In order to increase the conversion to ketone, the reactions were carried out using

20 mol% of catalyst **VI**, increasing the equivalents of aniline at different concentrations (entries 8-10). The best result was achieved using 3 equivalents of aniline working at C 0.1 M, since the epoxide was isolated in 28% yield and 72% ee (entry 10). Finally, a control experiment, performed without the organocatalyst, showed that the background epoxide ring-opening reaction is not a negligible process (entry 11).

Under the optimized conditions a variety of α-nitroepoxides was reacted to study the scope and limitation of the process (Table 3).

Table 3 . AKR of α-nitro epoxides with aniline catalysed by **VI**[a]



1-(±) 2a 1-(-) 3

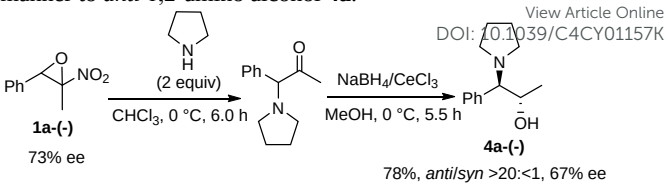
Entry	R^1	R^2	**3**(%)[b]	Yield **1a**(%)[b]	ee **1a** (%)[c]
1	Me	Ph	65	28 (**a**)	72
2	Me	4-MeC_6H_4	79	17 (**e**)	84
3	Me	4-ClC_6H_4	67	29 (**f**)	86
4	Me	4-$CF_3C_6H_4$	48	36 (**g**)	77
5	Me	2-naphthyl	72	26 (**h**)	95
6	Et	Ph	59	21 (**i**)	92
7	Et	3-MeC_6H_4	66	31 (**j**)	92
8	Et	4-BrC_6H_4	64	33 (**k**)	90
9	Et	3,4-$Cl_2C_6H_3$	47	35 (**l**)	61
10	Me	$Ph(CH_2)_2$	28	35 (**m**)	16

[a] All reactions were carried out using **1-(±)** (0.2 mmol), **2a** (0.6 mmol), **VI** (20 mol %), toluene (2.0 mL) for 84-158 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Electron-donating and withdrawing groups are tolerated in the aromatic ring of compounds **1** and unreacted epoxides were recovered in satisfactory yield and good to high enantioselectivity (entries 1-9). The present system appears to be unsuitable for the kinetic resolution of aliphatic α-nitroepoxides. The ring-opening reaction of α-nitroepoxide **1m** proceeded at lower rate and unreacted epoxide was recovered in 35% yield and 16% ee (entry 10).[23] The ee values of α-amino ketones **3** were not determined as they are supposed to be nearly racemic compounds on the basis of the following considerations: i) the estimated stereoselectivity factors of the AKR illustrated in Table 3 are moderate ($3< S <7$)[24] and low ee values[25] are expected for the α-amino ketone products **3**;[11a,b] ii) enantiomerically enriched α-amino ketones were reported to be sensitive compounds suffering partial racemization under basic conditions.[26]

Jackson's[6a,b] and Aggarwal's[27] groups demonstrated that ring-opening reactions of diastereoisomerically pure arylthio nitrooxirane or spirocyclic bis-sulfinyl oxiranes with amines proceeded stereospecifically with inversion of configuration to give enantioenriched α-amino thioesters and amides, respectively.

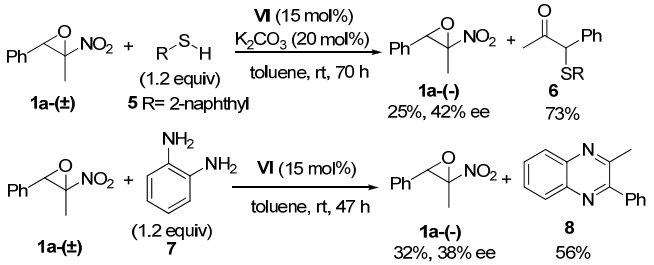
In order to determine either the absolute configuration of optically enriched epoxides and to show the utility of these compounds in asymmetric synthesis, we set up a one-pot two-step diastereoselective route to produce 1,2-amino alcohols (Scheme 1). Enantiomerically enriched **1a-(-)**, treated with pyrrolidine at 0 °C, afforded the corresponding α-amino ketone, which was in situ reduced in fairly good overall yield and highly diastereoselective manner to *anti* 1,2-amino alcohol **4a**.[28]



1a-(-) 73% ee **4a-(-)** 78%, *anti*/*syn* >20:<1, 67% ee

Scheme 1 One-pot stereoselective ring-opening/reduction sequence to *anti*-1,2-amino alcohol **4a**.

Pleasingly, a slight erosion of the enantioselectivity was observed,[26,29] as assessed by chiral HPLC analysis on 1-phenyl-1-(pyrrolidin-1-yl)propan-2-ol **4a**, whose absolute configuration was determined to be (1*R*,2*S*) by comparison of the optical rotation to literature reported data.[30] Consequently, absolute configuration of 2-methyl-2-nitro-3-phenyloxirane **1a-(-)** was assigned to be (2*R*,3*S*). Finally, other nucleophiles such as thiols and 1,2-diamines are applicable and pharmaceutically important targets such as quinoxalines[31] are accessible exploiting the organocatalysed kinetic resolution of α-nitroepoxides (Scheme 2).



1a-(±) **5** R= 2-naphthyl **1a-(-)** 25%, 42% ee **6** 73%

1a-(±) **7** **1a-(-)** 32%, 38% ee **8** 56%

Scheme 2 Kinetic resolution of epoxide **1a-(±)** with thiol **5** and diamine **7**.

Conclusions

In conclusion, we developed the first enantioselective synthesis of β-aryl-substituted α-nitroepoxides taking advantage of an aminolytic kinetic resolution with aniline catalysed by an easily accessible *Cinchona* alkaloid-derived thiourea. The epoxides are recovered in acceptable yield and good to high enantioselectivity. Enantioenriched α-nitroepoxides can serve as synthetically useful intermediates, as demonstrated in the one-pot stereoselective approach to highly valuable *anti*-1,2-amino alcohols.[32] Despite improvements are required for the present AKR to be of practical value, this work highlights the great potential of bifunctional organocatalysts in epoxides ring-opening reactions. Efforts to improve and expand the scope of the organocatalytic kinetic resolution of racemic epoxides are currently underway.

Acknowledgements

This work was supported financially by MIUR. We thank Dr. P. Iannece for assistance with MS spectra and elemental analyses. A.L. thanks the European COST Action CM0905-Organocatalysis.

Notes and references

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Electronic Supplementary Information (ESI) available: NMR spectra and HPLC traces for all the new compounds. See DOI: 10.1039/c000000x/

1 For selected reviews, see: (a) J. Marco-Contelles, M. T. Molina and S. Anjum, *Chem. Rev.*, 2004, **104**, 2857; (b) K. Miyashita and T. Imanishi, *Chem. Rev.*, 2005, **105**, 4515; (c) Z.-L. Zhou, Y.-X. Yang, J. Ding, Y.-C. Li and Z.-H. Miao, *Nat. Prod. Rep.*, 2012, **29**, 457.

2 For reviews, see: (a) C. Lauret, *Tetrahedron: Asymmetry*, 2001, **12**, 2359; (b) *Aziridines and Epoxides in Organic Synthesis* (Ed. A. K. Yudin), Wiley-VCH: Weinheim, 2006; (c) G. S. Singh, K. Mollet, M. D'hooghe and N. De Kimpe, *Chem. Rev.*, 2013, **113**, 1441.

3 For general reviews, see: (a) T. Katsuki in *Comprehensive Asymmetric Catalysis*, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 621; (b) E. M. McGarrigle and D. G. Gilheany, *Chem. Rev.*, 2005, **105**, 1563; (c) Q.-H. Xia, H.-Q. Ge, C.-P. Ye, Z.-M. Liu and K.-X. Su, *Chem. Rev.*, 2005, **105**, 1603; (d) Y. Zhu, Q. Wang, R. G. Cornwall and Y. Shi, *Chem. Rev.*, 2014, **144**, 8199.

4 For selected examples, see: (a) D. Enders, J. Zhu and G. Raabe, *Angew. Chem. Int. Ed.*, 1996, **35**, 1725; (b) M. Bougauchi, S. Watanabe, T. Arai, H. Sasai and M. Shibasaki, *J. Am. Chem. Soc.*, 1997, **119**, 2329; (c) B. Lygo and P. G. Wainwright, *Tetrahedron Lett.*, 1998, **39**, 1599; (d) T. Ooi, D. Ohara, M. Tamura and K. Maruoka, *J. Am. Chem. Soc.*, 2004, **126**, 6844; (f) R. W. Flood, T. P. Geller, S. A. Petty, S. M. Roberts, J. Skidmore and M. Volk, *Org. Lett.*, 2001, **3**, 683; (g) X. Lu, Y. Liu, B. Sun, B. Cindric and L. Deng, *J. Am. Chem. Soc.*, 2008, **130**, 8134; (h) X. Wang, C. M. Reisinger and B. List, *J. Am. Chem.* Soc., 2008, **130**, 6070.

5 For selected examples, see: (a) M. Marigo, G. Franzén, T. B. Poulsen, W. Zhuang and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 6964; (b) H. Sundén, I. Ibrahem and A. Córdova, *Tetrahedron Lett.*, 2006, **47**, 99; (c) X. Wang and B. List, *Angew. Chem. Int. Ed.*, 2008, **47**, 1119.

6 For diastereoselective epoxidations, see: (a) R. F. W. Jackson, J. M. Kirk, N. J. Palmer, D. Waterson and M. J. Wythes, *J. Chem. Soc., Chem. Commun.*, 1993, 889; (b) Jackson R. F. W., N. J. Palmer, M. J. Wythes, W. Clegg and M. R. J. Elsegood, *J. Org. Chem.*, 1995, **60**, 6431; (c) L. A. Evans, H. Adams, C. G. Barber, L. Caggiano and R. F. W. Jackson, *Org. Biomol. Chem.*, 2007, 3156; (d) A. Jain, S. Rodríguez, I. López and F. V. González, *Tetrahedron*, 2009, **65**, 8362. For a stoichiometric enantioselective epoxidation of aliphatic *trans*-disubstituted nitroalkenes, see: (e) D. Enders, L. Kramps and J. Zhu, *Tetrahedron: Asymmetry*, 1998, **9**, 3959.

7 For recent reviews, see: (a) D. Roca-Lopez, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero and P. Merino, *Tetrahedron: Asymmetry*, 2010, **21**, 2561; (b) T. Ikariya and I. D. Gridnev, *Chem. Rec.*, 2009, **9**, 106; (c) J. L. Vicario, D. Badía and L. Carrillo, *Synthesis*, 2007, 2065.

8 Y. D. Vankar, K. Shah, A. Bawa and S. P. Singh, *Tetrahedron*, 1991, **47**, 8883.

9 For the synthesis of 1,3-thiazoles, see: (a) H. Newman and R. B. Angier, *Tetrahedron*, 1970, **26**, 825; (b) K. M. Weiß, S.-W. Wei and S. B. Tsogoeva, *Org. Biomol. Chem.*, 2011, **9**, 3457. For the synthesis of quinoxalines, see: (c) M. M. Ibrahim, D. Grau, F. Hampel and S. B. Tsogoeva, *Eur. J. Org. Chem.*, 2014, 1401; (d) A. Vidal-Albalat, S. Rodríguez and F. V. González, *Org. Lett.*, 2014, **16**, 1752.

10 J. Agut, A. Vidal, S. Rodríguez and F. V. González, *J. Org. Chem.*, 2013, **78**, 5717.

11 (a) H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, 1988, **18**, 249; (b) J. M. Keith, J. F. Larrow and E. N. Jacobsen, *Adv. Synth. Catal.*, 2001, **343**, 5.

12 M. Tokunaga, J. F. Larrow, F. Kakiuchi and E. N. Jacobsen, *Science*, 1997, **277**, 936.

13 (a) J. F. Larrow and P. F. Quigley in *Comprehensive Chirality*, (Eds.: E. M. Carreira, H. Yamamoto), Elsevier, Oxford, 2012, pp. 129. For other examples on kinetic resolution of racemic epoxides, see: (b) A. Gayet, S. Betilsson and P. G. Andersson, *Org. Lett.*, 2002, **4**, 3777; (c) G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, P. Melchiorre and L. Sambri, *Org. Lett.*, 2004, **6**, 3973.

14 U. Das, B. Crousse, V. Kesavan, D. Bonnet-Delpon and J.-P. Bégué, *J. Org. Chem.* 2000, **65**, 6749.

15 (a) T. Weil, M. Kotke, C. M. Kleiner and P. R. Schreiner, *Org. Lett.*, 2008, **10**, 1513; (b) S. S. Chimni, N. Bala, V. A. Dixit and P. V. Bharatam, *Tetrahedron*, 2010, **66**, 3042.

16 (a) E. M. Fleming, C. Quigley, I. Rozas and S. J. Connon, *J. Org. Chem.*, 2008, **73**, 948; (b) J. Park, K. Lang, K. A. Abboud and S. Hong, *Chem. Eur. J.*, 2011, **17**, 2236.

17 (a) Z. Wang, W. K. Law and J. Sun, *Org. Lett.*, 2013, **15**, 5964; (b) M. R. Monaco, S. Prévost and B. List, *Angew. Chem., Int. Ed.*, 2014, **53**, 8142.

18 M. Kumar, R. I. Kureshy, S. Saravanan, S. Verma, A. Jakhar, N. H. Khan, S. H. R. Abdi and H. C. Bajaj, *Org. Lett.*, 2014, **16**, 2798.

19 (a) A. Lattanzi, P. Iannece, A. Vicinanza and A. Scettri, *Chem. Commun.*, 2003, 1440; (b) A. Lattanzi, *Org. Lett.*, 2005, **7**, 2579; (c) C. De Fusco, C. Tedesco and A. Lattanzi, *J. Org. Chem.*, 2011, **76**, 676; (d) A. Russo, G. Galdi, G. Croce and A. Lattanzi, *Chem. Eur. J.*, 2012, **18**, 6152.

20 An excess of aniline (1.2 equiv) was added to neutralize nitrous acid formed as by-product.

21 Y. N. Belokon, V. I. Maleev, M. A. Moskalenko, Yu. V. Samoilichenko, A. S. Peregudov and A. T. Tsaloev, *Russ. Chem. Bull. Int. Ed.*, 2013, **62**, 1371.

22 A. Lattanzi, *Synlett*, 2007, 2106.

23 Other unidentified products were observed in the crude reaction mixture.

24 First order kinetics was assumed for the calculation of the stereoselectivity factors,[11a] which are underestimated because partially affected by contribution of the background ring-opening reaction.

25 As an example, α-amino ketone **3a**, reported in entry 1 of Table 3, was recovered with 16% ee.

26 (a) B. Tiwari, J. Zhang and Y. R. Chi, *Angew. Chem. Int. Ed.*, 2012, **51**, 1911; (b) C. Kison, N. Meyer and T. Opatz, *Angew. Chem. Int. Ed.*, 2005, **44**, 5662.

27 V. K. Aggarwal, J. K. Barrell, J. M. Worrall and R. Alexander, *J. Org. Chem.*, 1998, **63**, 7128.

28 For diastereoselective reduction of α-amino ketones to 1,2-amino alcohols, see: (a) J.-P. Bégué, D. Bonnet-Delpon and N. Fischer-Durand, *Tetrahedron: Asymmetry*, 1994, **5**, 1099; (b) A.

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DOI: 10.1039/C4CY01157K

Abouabdellah, J.-P. Bégué, D. Bonnet-Delpon, A. Kornilov, I. Rodrigues and C. Richard, *J. Org. Chem.*, 1998, **63**, 6529.

29 The ring-opening/reduction sequence was not optimized.

30 J.-H. Xie, S. Liu, W.-L. Kong, W.-J. Bai, X.-C. Wang, L.-X. Wang and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2009, **131**, 4222.

31 For selected examples, see: (a) S. T. Hazeldine, L. Polin, J. Kushner, J. Paluch, K. White, M. Edelstein, E. Palomino, T. H. Corbett and J. P. Horwitz, *J. Med. Chem.*, 2001, **44**, 1758; (b) D. Kong, E. J. Park, A. G. Stephen, M. Calvani, J. H. Cardellina, A. Monks, R. J. Fisher, R. H. Shoemaker and G. Melillo, *Cancer Res.*, 2005, **65**, 9047.

32 For reviews on enantiomerically enriched 1,2-amino alcohols, see: (a) F. D. Klingler, *Acc. Chem. Res.*, 2007, **40**, 1367; (b) J. C. Moore, D. J. Pollard, B. Kosjek and P. N. Devin, *Acc. Chem. Res.*, 2007, **40**, 1412.