ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Open Access Article. Published on 23 December 2016. Downloaded on 4/4/2026 11:16:27 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

Cite this: *Chem. Commun.*, 2017, 53, 1156

Received 8th December 2016,
Accepted 23rd December 2016

DOI: 10.1039/c6cc09774j

www.rsc.org/chemcomm

Cooperative Lewis acid–onium salt catalysis as tool for the desymmetrization of *meso*-epoxides†

Florian Broghammer, Daniel Brodbeck, Thorsten Junge and René Peters*

Epoxide desymmetrizations by bromide are very rare despite the large synthetic potential of chiral bromohydrins. Herein we present a new concept for epoxide desymmetrizations in which a bifunctional Lewis acid/ammonium salt catalyst allows for efficient enantioselective epoxide ring openings by Br^-. With acetylbromide as a Br^- source bromohydrin esters are formed.

Desymmetrizations of *meso*-epoxides *via* nucleophilic ring opening reactions provide an attractive synthetic tool towards enantiopure β-functionalized alcohols possessing two adjacent stereocenters.[1] Different methods for O,[2] N,[3] and Cl[4] centred nucleophiles are established. In comparison, the use of bromide and iodide has been described in a single study so far. Nugent (*DuPont*) reported in 1998 that a chiral zirconium complex is capable of catalyzing the asymmetric ring opening of primarily cycloolefin derived epoxides using a combination of $TMSN_3$ and an excess allyl iodide or bromide.[5]‡ A common feature of this and many other epoxide desymmetrizations[1] is the simultaneous silyl protective group installation on the generated alcohol functions. The direct installation of alternative protecting group types is much more unusual.[6]

In this communication we report the development of an enantioselective method to form *O*-acetyl protected bromohydrins starting from achiral epoxides and acetylbromide. The use of an ester protecting group is synthetically appealing, because it might be later readily removed by mild enzymatic or chemical protocols.[6,7] Bromohydrin esters are interesting building blocks which allow for a range of chemical manipulations. In this context the ester group does not only serve as protective group, but has also been further functionalized as a part of the targeted skeleton.[8]

Ether cleavages[9] including those of epoxides by acylhalides[10] are assumed to usually proceed *via* *O*-acylation of the ethers followed by a nucleophilic halide attack. For the present study we strived for a different scenario: a chiral Lewis acid should trigger an enantioselective nucleophilic attack at the epoxide by Br^- which is directed by an onium moiety connected to the ligand (Fig. 1, right). The generated metal alcoholate might then be acylated by acetylbromide to release the product and regenerate the catalytically active Lewis acid and Br^-.

For epoxide desymmetrizations cooperative bimetallic catalysis has been successfully employed as dual activation strategy[1,11] (Fig. 1, left).[3–5,12] The here reported approach is conceptually different as it capitalizes on the cooperation of an aprotic onium salt ion pair with a Lewis acid. Delivering an anionic nucleophile *via* an aprotic ion pair was expected to offer a reactivity advantage, because metal coordination of a nucleophile is likely to considerably decrease its electron density.[13] Our research group has previously introduced the concept of cooperative intramolecular Lewis acid/aprotic onium salt catalysis to asymmetric synthesis.[14,15] In these earlier studies a halide counterion was an active part of the catalyst. In the present case it is also a part of the final product and thus needs to be regenerated to enable catalytic turnover.

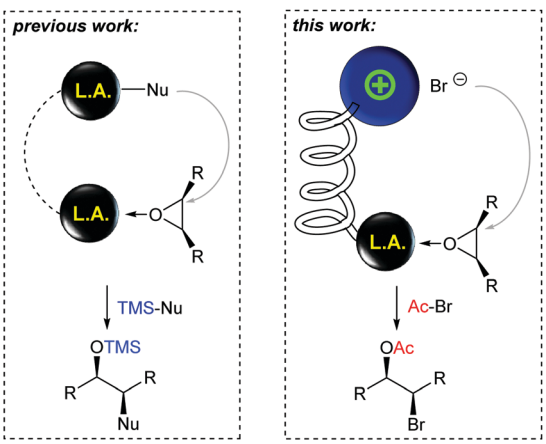


Fig. 1 Desymmetrization of *meso*-epoxides by cooperative catalysis.

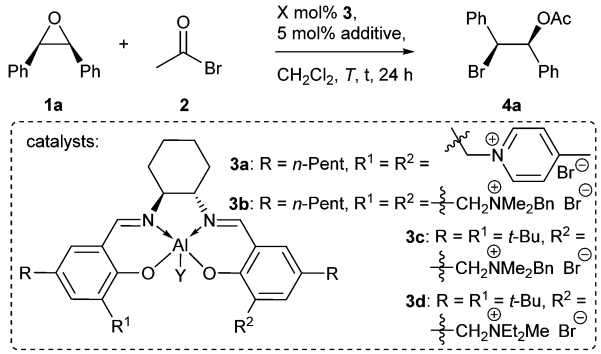
Universität Stuttgart, Institut für Organische Chemie, Pfaffenwaldring 55, 70569 Stuttgart, Germany. E-mail: rene.peters@oc.uni-stuttgart.de

† Electronic supplementary information (ESI) available: Experimental procedures and characterization data of new compounds. See DOI: 10.1039/c6cc09774j

This journal is © The Royal Society of Chemistry 2017

Open Access Article. Published on 23 December 2016. Downloaded on 4/4/2026 11:16:27 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

Table 1 Optimization of the title reaction



No.	3 (X)	Y	Additive	T [°C]	Yield[a] [%]	dr[b]	er[c] [%]
1	**3a** (10)	Me	—	−20	>99	37 : 1	64.5 : 35.5
2	**3b** (10)	Me	—	−20	>99	29 : 1	80.5 : 19.5
3	**3c** (10)	Me	—	−20	>99	10 : 1	85 : 15
4	**3c** (10)	Me	HOAc	−20	99	14 : 1	89 : 11
5	**3c** (5)	Cl	HOAc	−20	99	14 : 1	89.5 : 10.5
6[d]	**3c** (5)	Cl	HOAc	−40 → RT	>99	33 : 1	91.5 : 8.5
7[d]	**3d** (5)	Cl	HOAc	−40 → RT	99	31 : 1	92 : 8

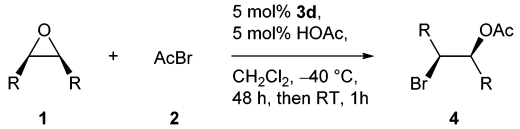
[a] Yield determined by ^{1}H-NMR of the crude product using an internal standard. [b] Diastereomeric ratio determined by ^{1}H-NMR of the crude product. [c] Enantiomeric ratio of determined by HPLC. [d] t = 48 h.

At the outset of the present investigation the reaction of stilbene oxide **1a** and AcBr **2** was examined (Table 1). The Al-salen/bispyridinium complex **3a** was initially chosen, because it provided the highest stereoselectivities for the asymmetric synthesis of *trans*-configured β-lactones.[14c] Gratifyingly, the envisioned reaction proceeded in quantitative yield at −20 °C, albeit with low enantioselectivity (entry 1).

During the subsequent optimization it was found that quaternary ammonium residues like in **3b** allowed for a better enantiotopos differentiation than pyridinium moieties (entry 2). Another improvement was made by the use of catalysts equipped with only one ammonium residue like in **3c** (entry 3) and further by using acetic acid as a catalytic additive (entry 4). With Me and Cl substituents Y bound to the Al center nearly identical results were obtained (entries 4 and 5). Since the Al–Cl containing catalysts are more robust, they were preferentially used in this study. A decrease in the reaction temperature to −40 °C resulted in further improvements in stereoselectivity (entry 6). The best enantioselectivity was obtained with catalyst **3d** possessing a diethylmethylammonium bromide moiety (entry 7).

The optimized reaction conditions were applied to aromatic *meso*-epoxides with different substitution patterns (Table 2). Although some product was always lost upon chromatographic purification as a result of the high reactivity of the benzylic bromides **4** (compare Table 1/entry 7 to Table 2/entry 1), the yields of isolated products were high for all examples (82–92%). Regarding the diastereomeric ratios there is a tendency. Whereas electron donors like methyl groups caused somewhat lower diastereomeric ratios (entries 2 and 3), electron withdrawing substituents led to diastereomerically pure products. This might be due to a lower tendency for a competing S_N1-pathway in the latter case. The highest enantioselectivities were noticed for a CF_3

Table 2 Investigation of substituent effects



No.	4	R	Conversion[a] [%]	Yield[b] [%]	dr[c]	er[d] [%]
1	**4a**	Ph	>99	88	31 : 1	92 : 8
2	**4b**	4-Me-C_6H_4	>99	88	22 : 1	91 : 9
3	**4c**	3-Me-C_6H_4	>99	85	25 : 1	91 : 9
4	**4d**	4-F-C_6H_4	>99	91	50 : 1	95 : 5
5	**4e**	3-F-C_6H_4	>99	92	>50 : 1	94 : 6
6	**4f**	4-F_3C-C_6H_4	>99	89	>50 : 1	95.5 : 4.5
7	**4g**	3-F_3C-C_6H_4	>99	82	>50 : 1	88 : 12
8	**4h**	3-Cl-C_6H_4	>99	89	>50 : 1	90.5 : 9.5
9	**4i**	3-MeO-C_6H_4	>99	85	>50 : 1	91 : 9

[a] Conversion of **1** determined by ^{1}H-NMR of the crude product. [b] Yield of isolated **4** after column chromatography. [c] Diastereomeric ratio determined by ^{1}H-NMR of the crude product. [d] Enantiomeric ratio determined by HPLC.

and fluoro substituted substrates (entries 4–6), although in these cases the reactions were found to be a little slower. Good results were also attained with chloro (entry 8) and methoxy (entry 9) substituents on the aromatic residues R.

The scope is complementary to Nugent's Zr-catalyzed reaction which was not described for substrates with aromatic residues.[5] In contrast, our method provided lower enantioselectivity for aliphatic substrates, while reactivity was comparable (*e.g.*, with cyclohexenoxide 99% yield under standard conditions, dr > 50 : 1, nearly racemic product; for R = CH_2OBn: 80% yield after 72 h, dr > 50 : 1, ee = 40%).

A reaction monitoring was conducted by ^{1}H-NMR (Fig. 2) which shows that in the preferred pathway the acylated product **4a** is not directly formed from the expected alkoxide intermediate **II** generated in the ring opening step (Scheme 1). Instead alcohol **5** is first released. Fig. 2 shows that the reaction reaches 92% conversion after 24 h. Additional reaction time is mainly needed for acylation of the alcohol intermediate. Conversion of **1a** is practically complete after 48 h (99%). To form the ester product in a quantitative yield it is then necessary to warm the reaction mixture to room temperature to ensure that unreacted OH groups (8% after 48 h) are acylated.

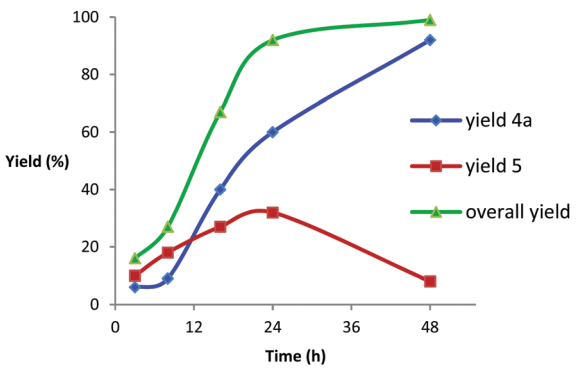
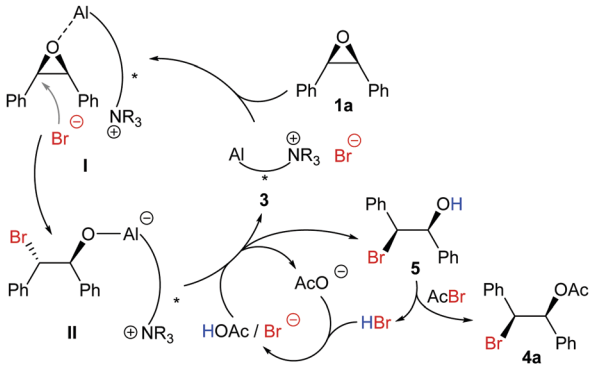


Fig. 2 ^{1}H-NMR monitoring of the reaction described in Table 1/entry 7.

Open Access Article. Published on 23 December 2016. Downloaded on 4/4/2026 11:16:27 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

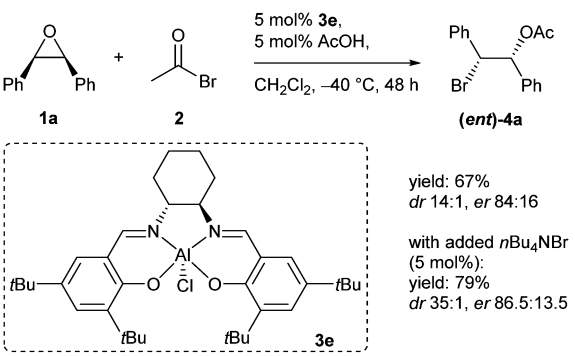


Scheme 1 Mechanistic proposal.

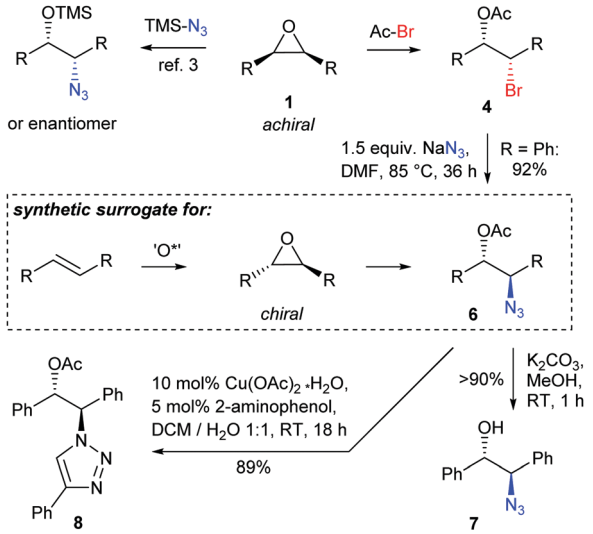
We propose a major mechanistic pathway, in which the epoxide is activated by coordination to the catalyst (**I**, Scheme 1). Br^- is delivered as nucleophile by the internal ammonium moiety in **I** providing Al alkoxide **II**. For protonation of **II** HOAc may act as a proton source, but also HBr, which is present in acetylbromide as an impurity and difficult to remove. HBr is also released during the acylation step and could serve to regenerate HOAc plus a bromide anion for the next turnover.

A number of experiments were also performed with Jacobsen's Al salen catalyst **3e**[16] as control system (Scheme 2).§ By optimizing the reaction conditions, an er of 84 : 16 could be achieved with this catalyst. Comparison of **3e** with the bifunctional catalyst **3d** by kinetic monitoring (see ESI†) showed that the latter is considerably more active. Moreover, addition of nBu$_4$NBr had a beneficial effect on both reactivity and enantioselectivity using **3e** (Scheme 2) thus supporting a cooperative mechanism. Dual activation by Lewis acid catalysts like **3e** and onium salts might therefore also allow for useful catalyst systems in the future. Nevertheless, yield and enantioselectivity were significantly lower than with bifunctional **3d**. Since **3d** is readily prepared in high yields over 3 steps starting from commercial 1,2-diaminocyclohexane (see ESI†), its use is also operationally similarly appealing.

Like the *meso*-epoxides the bromohydrin esters **4** serve as alkylating agents, yet provide access to the complementary set of product diastereomers compared to the direct use of *meso*-epoxides. The reported products thus represent synthetic equivalents for enantioenriched *trans*-epoxides (Scheme 3) for which only few protocols have been developed.[5,17]



Scheme 2 Control experiments.



Scheme 3 Examples for derivatizations.

To showcase the value of the acetyl protected bromohydrins, **4a** was treated with NaN_3 under S_N2 conditions providing azide **6** by smooth inversion of the configuration at the reacting C-atom. As all known desymmetrizations using $TMSN_3$ have a limitation for alkyl substituted epoxides,[3] the here reported method is also complementary in that aspect to the existing methods. As expected, deprotection of the acetyl group was readily achieved under mild conditions. The acetyl group should also be interesting for mild enzymatic deprotections allowing for the formation of almost enantiopure products often being required for pharmaceutical applications. The absolute configuration of **4a** could be assigned by the optical rotation of literature known derivative **7**.[18] Azide **6** was also applied to a click reaction to form a (1*R*,2*S*)-configured 2-(triazol-1-yl)ethyl acetate **8**, a motif which might, *e.g.*, be of potential pharmacological interest.

A catalyst concept is described for the desymmetrization of epoxides which exploits the cooperation of a Lewis acid and an aprotic onium salt moiety within a bifunctional chiral catalyst framework. This catalyst type allowed for the development of a reaction in which achiral epoxides react with AcBr to deliver enantioenriched acetyl protected bromohydrins. The title reaction was shown to proceed *via* the intermediate formation of the bromohydrin which is then acylated. Preliminary studies show that the combination of a Lewis acid catalyst plus a cooperating external ammonium salt cocatalyst is also an attractive option for future developments.

This work was financially supported by the Deutsche Forschungsgemeinschaft (DFG, PE 818/3-1) and the Carl-Zeiss-Stiftung (PhD fellowship to DB).

Notes and references

‡ In contrast, the direct use of TMSBr results in a very rapid epoxide ring opening even in the absence of a catalyst thus hampering useful enantioselectivity as our own studies revealed.
§ In no case using bifunctional catalysts **3a–d** or Jacobsen's catalyst **3e** a pinacol type rearrangement product was observed as side product.

 This journal is © The Royal Society of Chemistry 2017

Open Access Article. Published on 23 December 2016. Downloaded on 4/4/2026 11:16:27 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.

1 (*a*) D. M. Hodgson, A. R. Gibbs and G. P. Lee, *Tetrahedron*, 1996, **52**, 14361; (*b*) P. A. Wang, *Beilstein J. Org. Chem.*, 2013, **9**, 1677; (*c*) S. Meninno and A. Lattanzi, *Chem. – Eur. J.*, 2016, **22**, 3632; (*d*) L. P. C. Nielsen and E. N. Jacobsen, in *Aziridines and Epoxides in Organic Synthesis*, ed. A. K. Yudin, Wiley-VCH, Weinheim, 2006, pp. 229–269; (*e*) E. N. Jacobsen, *Acc. Chem. Res.*, 2000, **33**, 421; (*f*) A. Borissov, T. Q. Davies, S. R. Ellis, T. A. Fleming, M. S. W. Richardson and D. J. Dixon, *Chem. Soc. Rev.*, 2016, **45**, 5474.

2 (*a*) E. N. Jacobsen, F. Kakiuchi, R. G. Konsler, J. F. Larrow and M. Tokunaga, *Tetrahedron Lett.*, 1997, **38**, 773; (*b*) T. Iida, N. Yamamoto, S. Matsunaga, H.-G. Woo and M. Shibasaki, *Angew. Chem., Int. Ed.*, 1998, **37**, 2223; (*c*) S. Matsunaga, J. Das, J. Roels, E. M. Vogl, N. Yamamoto, T. Iida, K. Yamaguchi and M. Shibasaki, *J. Am. Chem. Soc.*, 2000, **122**, 2252.

3 (*a*) W. A. Nugent, *J. Am. Chem. Soc.*, 1992, **114**, 2768; (*b*) L. E. Martínez, J. L. Leighton, D. H. Carsten and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1995, **117**, 5897; (*c*) K. B. Hansen, J. L. Leighton and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1996, **118**, 10924; (*d*) B. W. McCleland, W. A. Nugent and M. G. Finn, *J. Org. Chem.*, 1998, **63**, 6656; (*e*) A. Sekine, T. Ohshima and M. Shibasaki, *Tetrahedron*, 2002, **58**, 75; (*f*) J. A. Birrell and E. N. Jacobsen, *Org. Lett.*, 2013, **15**, 2895.

4 (*a*) E. Denmark, P. A. Barsanti, K.-T. Wong and R. A. Stavenger, *J. Org. Chem.*, 1998, **63**, 2428; (*b*) B. Tao, M. M.-C. Lo and G. C. Fu, *J. Am. Chem. Soc.*, 2001, **123**, 353; (*c*) S. E. Denmark, P. A. Barsanti and G. L. Beutner, *Adv. Synth. Catal.*, 2007, **349**, 567; (*d*) E. Gnanamani, N. Someshwar, J. Sanjeevi and C. R. Ramanathan, *Adv. Synth. Catal.*, 2014, **356**, 2219 and cited references; with fluoride: (*e*) J. A. Kalow and A. G. Doyle, *J. Am. Chem. Soc.*, 2011, **133**, 16001.

5 W. A. Nugent, *J. Am. Chem. Soc.*, 1998, **120**, 7139.

6 M. R. Monaco, S. Prévost and B. List, *Angew. Chem., Int. Ed.*, 2014, **53**, 8142.

7 P. G. M. Wuts and T. W. Greene, *Greene's Protective Groups in Organic Synthesis*, Wiley-Interscience, 4th edn, 2006.

8 (*a*) K. G. Watson, Y. M. Fung, M. Gredley, G. J. Bird, W. R. Jackson, H. Gountzos and B. R. Matthews, *J. Chem. Soc., Chem. Commun.*, 1990, 1018; (*b*) H. C. Kolb, Y. L. Bennani and K. B. Sharpless, *Tetrahedron: Asymmetry*, 1993, **4**, 133; (*c*) Y. Iwasaki and T. Yamane, *J. Mol. Catal. B: Enzym.*, 2000, **10**, 129; (*d*) J. Prades, S. S. Funari, P. V. Escriba and F. Barcelo, *J. Lipid Res.*, 2003, **44**, 1720; (*e*) K. Parang, L. I. Wiebe and E. E. Knaus, *Curr. Med. Chem.*, 2000, **7**, 995.

9 R. L. Burwell, Jr., *Chem. Rev.*, 1954, **54**, 615.

10 Examples: (*a*) H. Kotsuki, Y. Ichikawa and H. Nishizawa, *Chem. Lett.*, 1988, 673; (*b*) T. Oriyama, A. Ishiwata, Y. Hori, T. Yatabe, N. Hasumi and G. Koga, *Synlett*, 1995, 1004; (*c*) D. J. Goldsmith, E. Kennedy and R. G. Campbell, *J. Org. Chem.*, 1975, **40**, 3571; (*d*) K. Nakano, S. Kodama, Y. Permana and K. Nozaki, *Chem. Commun.*, 2009, 6970; (*e*) G. Aghapour and R. Hatefipour, *Synth. Commun.*, 2013, **43**, 1030.

11 *Cooperative Catalysis – Designing Efficient Catalysts for Synthesis*, ed. R. Peters, Wiley-VCH, Weinheim, 2015.

12 (*a*) T. Iida, N. Yamamoto, H. Sasai and M. Shibasaki, *J. Am. Chem. Soc.*, 1997, **119**, 4783; (*b*) S. Matsunaga, J. Das, J. Roels, E. M. Vogl, N. Yamamoto, T. Iida, K. Yamaguchi and M. Shibasaki, *J. Am. Chem. Soc.*, 2000, **122**, 2252.

13 Selected reviews on asymmetric onium salt catalysis: (*a*) S. Shirakawa and K. Maruoka, *Angew. Chem., Int. Ed.*, 2013, **52**, 4312; (*b*) K. Maruoka, *Org. Process Res. Dev.*, 2008, **12**, 679.

14 (*a*) T. Kull and R. Peters, *Angew. Chem., Int. Ed.*, 2008, **47**, 5461; (*b*) T. Kull, J. Cabrera and R. Peters, *Chem. – Eur. J.*, 2010, **16**, 9132; (*c*) P. Meier, F. Broghammer, K. Latendorf, G. Rauhut and R. Peters, *Molecules*, 2012, **17**, 7121; (*d*) M. Mechler and R. Peters, *Angew. Chem., Int. Ed.*, 2015, **54**, 10303.

15 The concept is also useful in macromolecular chemistry. See, *e.g.*: (*a*) M. Winnacker, S. Vagin and B. Rieger, Cooperative Catalysis in Polymerization Reactions, in *Cooperative Catalysis – Designing Efficient Catalysts for Synthesis*, ed. R. Peters, Wiley-VCH, Weinheim, 2015; (*b*) T. Ema, Y. Miyazaki, J. Shimonishi, C. Maeda and J.-y. Hasegawa, *J. Am. Chem. Soc.*, 2014, **136**, 15270; (*c*) W.-M. Ren, Y. Liu and X.-B. Lu, *J. Org. Chem.*, 2014, **79**, 9771; (*d*) D. J. Darensbourg, W.-C. Chung and S. J. Wilson, *ACS Catal.*, 2013, **3**, 3050; it has also been recently used by other groups for small molecules: (*e*) D. Tian, B. Liu, Q. Gan, H. Li and D. J. Darensbourg, *ACS Catal.*, 2012, **2**, 2029; (*f*) K. Ohmatsu, S. Kawai, N. Imagawa and T. Ooi, *ACS Catal.*, 2014, **4**, 4304.

16 M. S. Sigman and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1998, **120**, 5315.

17 (*a*) S. Chang, J. M. Galvin and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1996, **116**, 6937; (*b*) V. K. Aggarwal, E. Alonso, G. Hynd, K. M. Lydon, M. J. Palmer, M. Porcelloni and J. R. Studley, *Angew. Chem., Int. Ed.*, 2001, **40**, 1430.

18 (*a*) P. Lupattelli, C. Bonini, L. Caruso and A. Gambacorta, *J. Org. Chem.*, 2003, **68**, 3360; (*b*) B. B. Lohray and J. R. Ahuja, *J. Chem. Soc., Chem. Commun.*, 1991, 95.