

Cite this: *Chem. Commun.*, 2019, 55, 7077Received 14th April 2019,
Accepted 22nd May 2019

DOI: 10.1039/c9cc02900a

rsc.li/chemcomm

Enantioselective reduction of *N*-alkyl ketimines with frustrated Lewis pair catalysis using chiral borenium ions†

Dan M. Mercea,^a Michael G. Howlett,^a Adam D. Piascik,^a Daniel J. Scott,^a Alan Steven,^b Andrew E. Ashley^a and Matthew J. Fuchter^{a*}

Enantioselective reduction of ketimines was demonstrated using chiral *N*-heterocyclic carbene (NHC)-stabilised borenium ions in frustrated Lewis pair catalysis. High levels of enantioselectivity were achieved for substrates featuring secondary *N*-alkyl substituents. Comparative reactivity and mechanistic studies identify key determinants required to achieve useful enantioselectivity and represent a step forward in the further development of enantioselective FLP methodologies.

The concept of 'frustration' continues to be useful in the development of transition metal free Lewis acid/base pairs with fascinating reactivity.¹ Pioneered by Stephan and co-workers,² 'frustration' is often seen as a result of steric demands and this view currently serves as the dominant design principle.³ The frustrated Lewis pair (FLP) formalism not only applies to the discovery of new reactions, but also to rationalise chemistry that pre-dates the coining of the term, a notable example being Piers-type hydrosilylation.⁴ FLPs have now been exploited in both stoichiometric and catalytic manifolds, in applications as diverse as polar hydrogenation (of imines,^{5a} carbonyls,^{5b} alkenes and alkynes^{5c}), C–H bond activation,^{5d} and polymer chemistry.^{5e} Key to this work is the reduction of substrates using H₂ and hydrosilanes, a topic that has been extensively reviewed by Oestreich *et al.*⁶

Despite many impressive developments in FLP chemistry and catalysis, enantioselective FLP-catalysed reduction is still significantly limited (Fig. 1). Chiral borane FLPs were pioneered by Klankermayer and co-workers,^{7a} followed by ferrocene-derived boranes^{7b} and *ansa*-ammonium borates^{7c} from other groups. However, many of these catalysts showed limited enantioselectivity.

The most successful scaffold for chiral borane FLP catalysts to date is the binaphthyl core. Binaphthyl-derived, C₆F₅-substituted boranes were first investigated by Piers and co-workers as catalysts for the asymmetric allylstannation of aromatic aldehydes^{7d} followed by reports of chiral borepine catalysts (Oestreich, **1a**)^{7e} and acyclic designs (Repo and Du; **1b**)^{7f} and **1c**,^{7g} respectively). Beside this scaffold, a novel bicyclic bis-borane has also been reported recently by Peng, Wang *et al.*, for *N*-aryl ketimine reduction.^{7h} It is notable amongst these examples that, with the exception of FLP **1b**,^{7f} asymmetric ketimine reduction is limited to substrates with an *N*-aryl group. Herein we report a method to use a chiral borenium catalyst in the FLP reduction of *N*-alkyl ketimines, which gives good to high enantioselectivity for secondary alkyl ketimine substrates. We compare hydrosilylation and hydrogenation pathways, which give important insight into the factors that underpin good enantioselectivity. We believe these results will



Fig. 1 Examples of chiral FLP Lewis acid catalyst used in FLP reductions.

^a Department of Chemistry, Imperial College London, Molecular Sciences Research Hub, White City Campus, Wood Lane, London, W12 0BZ, UK.
E-mail: m.fuchter@imperial.ac.uk

^b AstraZeneca PT&D, Charter Way, Macclesfield, SK10 2NA, UK

† Electronic supplementary information (ESI) available: Experimental and crystallographic details. Data files are openly available (DOI: 10.14469/hpc/5645). CCDC 1902956. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc02900a

further contribute to the development of FLP catalysts for highly enantioselective reduction methodologies.

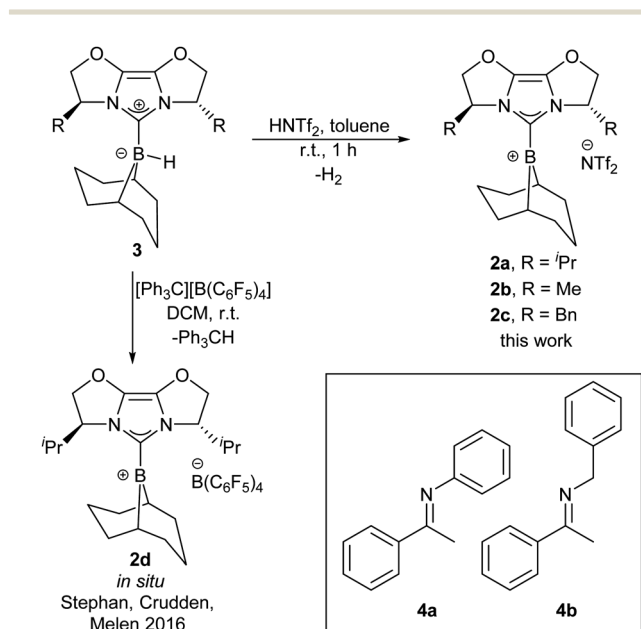
One of the key issues with the prior designs for chiral borane FLP catalysts is the challenging synthesis required to assemble the Lewis acid. We considered chiral NHC-stabilised borenium ions to hold promise as alternative asymmetric FLP catalysts, given their effectiveness in FLP-catalysed reduction chemistry,^{8a} and potential modularity: a large variety of chiral NHCs are available.^{9a} We chose to initially survey chiral NHCs of the IBiox class^{9b} for generating our borenium catalysts (**2a–c**, Scheme 1) given our previous work on such NHCs,^{9c} and the fact that the corresponding borohydride **3a** has been shown to act as a stoichiometric enantioselective reducing agent towards ketones.^{10a} During the early phases of our project, Stephan, Crudden, Melen and co-workers reported the attempted asymmetric reduction of ketimines using borenium **2d** as part of a large screening effort of chiral borenium FLP catalysts.^{8b} Catalyst **2d** hydrogenated *N*-phenyl ketimine **4a** with poor selectivity (56:44 e.r.), and showed no activity towards *N*-benzyl ketimine **4b**, even under 102 atm H₂ pressure (298 K, CH₂Cl₂).^{8b} Given this outcome, we sought to further understand how the reducing agent, catalyst components (NHC, borenium counterion, *etc.*) and ketimine substrate could be developed to enable good reactivity and enantioselectivity.

Borenium catalyst **2a** was prepared from hydride **3a** by treatment with HNTf₂ in 73% yield on gram scale.^{10b} ‡ The borenium ion nature of **2a** was confirmed by ¹¹B NMR spectroscopy ($\delta = 73$ ppm (br), CD₂Cl₂), DOSY NMR studies ($D_c/D_a = 1.06$),^{10b,11} and X-ray crystallography on the isolated species (see ESI†). Compound **2a** displayed good solubility in halogenated solvents: chloroform, dichloromethane, and 1,2-difluorobenzene (1,2-DFB). A Gutmann–Beckett measurement,¹² which provides a measure of Lewis acidity in terms of an acceptor number (AN), revealed **2a** to be a weaker Lewis acid (AN = 70.7) than the

common FLP borane B(C₆F₅)₃ (AN = 78.1¹³). We additionally synthesised borenium catalysts **2b** and **2c** which vary in steric bulk of the chiral NHC (Scheme 1) and investigated counterions more coordinating than NTf₂. However, a preliminary assessment of NHC–borenium ions with OTf, OMs, or OTs counterions revealed that such complexes are unable to cleave H₂ in combination with ketimine substrates (Fig. S13, ESI†), due to coordination of the counterion of the borenium (see ESI†).

With appropriate chiral NHC–borenium catalysts **2** in hand, we surveyed the enantioselective hydrosilylation of *N*-aryl ketimine **4a** and *N*-alkyl ketimines **4b** and **4c** (Table 1). Good to excellent reactivity was observed using PhMe₂SiH and a catalyst loading of 4 mol%, which is comparable to other studies (Fig. 1). Substrate **4a** was reduced with low enantioselectivity and a slight preference for the *R* product enantiomer (Table 1, entries 1 and 4). The use of a bulkier hydrosilane (entries 5 and 10) led to a reduced reaction rate with similar enantioselectivity. More promising results were obtained however when the substrate was changed to an *N*-alkyl derivative. Although *N*-benzyl substrate **4b** exhibited excellent reactivity in toluene (entry 6), only low enantioselectivity was observed. Interestingly, the major enantiomer obtained (*S*) was of opposite configuration to that obtained for substrate **4a**. While toluene *versus* 1,2-DFB gave comparable results for **4a**, 1,2-DFB gave an increased enantioselectivity (e.r. 81:19, *S*:*R*, entry 7) in the reduction of **4b**. Increasing the bulk of the *N*-alkyl substituent further improved enantioselectivity. Notably, *N*-cyclohexyl substrate **4c** gave a high enantioselectivity (e.r. 90:10, *S*:*R*, entry 9) comparable with other leading chiral borane FLP catalysts (Fig. 1). Similar enantioselectivity was observed for catalysts **2a–c**.

Given these promising results, substrate scope was further explored in the enantioselective hydrosilylation of *N*-alkyl



Scheme 1 Catalyst synthesis and literature model substrates (Tf = SO₂CF₃).

Table 1 Hydrosilylation development

Entry	Cat.	Subst.	Solvent	Conv. (time)	e.r. (<i>R</i> : <i>S</i>) ^a
1 ^b	2a	4a	Toluene	98% (44 h)	65:35
2	2b^c	4a	Toluene	71% (24 h)	57:43
3	2c^c	4a	Toluene	100% (24 h)	64.5:35.5
4	2a	4a	1,2-DFB	100% (19 h)	57:43
5 ^d	2a	4a	1,2-DFB	89% (286 h)	59:41
6	2a	4b	Toluene	100% (6 h)	38.5:61.5
7	2a	4b	1,2-DFB	100% (34 h)	19:81
8	2a	4c	Toluene	53% (74 h)	21:79
9	2a	4c	1,2-DFB	100% (145 h)	10:90
10 ^d	2a	4c	1,2-DFB	68% (316 h)	10:90

Reactions were carried out on 0.375 mmol scale (0.63 M), conversion to amine product(s) assessed by NMR; unless otherwise stated the hydrosilane used was PhMe₂SiH; products **5** were obtained following workup with MeOH and chromatography. ^a Determined by chiral HPLC, the *N*-acetylated derivative of **5c** was used; enantiomers assigned by comparison of optical rotation values with the literature. ^b Reaction carried out with stirring on double the scale. ^c Catalyst formed *in situ* from the corresponding borohydride and HNTf₂. ^d Hydrosilane used was Ph₂MeSiH.

Table 2 Hydrosilylation substrate scope



Entry	Subst.	Ar	R'	R	Conv. (%)	Yield (%)	e.r. (S:R) ^a
1 ^b	4c	Ph	H	c-Hex	100	91 ^f	90:10
2	4d	Ph	H	i-Pr	91	47	90:10
3	4e	Ph	H	c-Pent	100	71	90:10
4 ^{c,d}	4f	2-Np	H	c-Hex	77	75	93:7
5 ^{c,e}	4b	Ph	H	Bn	97	~100	82:18
6	4g	Ph	H	Bu	100	79	79:21
7	4h	Ph	H	CHPh ₂	0	—	—
8	4i	Ph	Me	c-Hex	61	62	64:36 ^g

Reactions were carried out on 0.375 mmol scale (0.63 M), conversion to amine product(s) assessed by NMR; unless otherwise stated solvent was 1,2-DFB, and the reaction time was 34 h; products **5** were obtained following workup with MeOH and chromatography. ^a Determined using chiral HPLC following acetylation; enantiomers assigned by comparison of optical rotation values with the literature. ^b 145 h. ^c Reaction solvent was DCM. ^d 31 h. ^e 2 h. ^f ~11% (PhMe₂Si)₂O impurity. ^g Enantiomers not assigned.

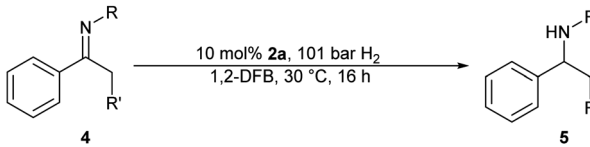
ketimines using **2a** (Table 2). Catalyst **2a** showed comparably high enantioselectivity (e.r. 90:10–93:7) in the reduction of a range of bulky secondary *N*-alkyl ketimines (Table 2, entries 1–4). Although primary *N*-alkyl substituents gave slightly lower selectivity (Table 2, entries 5 and 6), we highlight that the enantioselectivity observed (e.r. 79:21–82:18, entries 5 and 6) is comparable to the only other example of FLP asymmetric reduction of *N*-alkyl ketimines.^{7f} While a bulky substituent on the nitrogen atom improves enantioselectivity, excessive bulk prevents reaction (Table 2, entry 7). Extending the aliphatic chain that derives from the ketone component of the ketimine (substrate **4i**) also leads to a reduction in enantioselectivity.

Given the competency of catalyst **2a** for the asymmetric hydrosilylation of *N*-alkyl ketimines, we additionally assessed the potential to use H₂ as the reductant. Increasing the catalyst loading to 10 mol% allowed for a range of substrates to be hydrogenated (Table 3). Similarly to hydrosilylation, the reduction of secondary *N*-alkyl ketimines derived from acetophenone (**4c,e**) gave good reactivity and enantioselectivity (e.r. 90:10, Table 3 entries 1 and 2).

Lowering the pressure to 10 bar H₂ dramatically reduced the reaction rate. In agreement with the results of Stephan, Crudden, Melen and co-workers,^{8b} hydrogenation of substrate **4a** occurred with much lower enantioselectivity (e.r. 59:41, entry 3). Consistent with our results for hydrosilylation, substrate **4i** only gave moderate enantioselectivity (e.r. 65:35, entry 4). Changing the steric bulk of the nitrogen substituent to be either larger (entry 5) or smaller (entries 6 and 7) resulted in a substantial drop in product yield.

It is notable that the enantioselectivity observed for substrates **4a** and **4c** is analogous, regardless of whether a hydrosilane or H₂ was used. Oestreich and co-workers have previously shown that borane-promoted imine reduction using

Table 3 Hydrogenation substrate scope



Entry	Subst.	R'	R	Conv. (%)	Yield (%)	e.r. (S:R) ^a
1	4e	H	c-Pent	100	67	90:10
2 ^{b,c}	4c	H	c-Hex	99	66	89:11
3 ^d	4a	H	Ph	100	91	41:59
4	4i	Me	c-Hex	67	36	65:35 ^e
5	4h	H	CHPh ₂	0	—	—
6	4b	H	Bn	8	—	—
7	4g	H	Bu	11	—	—

Reactions carried out on a 0.375 mmol scale (0.63 M) using SPR (screening pressure reactor) equipment, conversion to amine product assessed by NMR. ^a Determined using chiral HPLC following acetylation; enantiomers assigned by comparison of optical rotation values with the literature. ^b At 10 bar H₂, NMR tube (re-pressurised after 192 h); 97%, 212 h, e.r. 90:10. ^c For the reaction carried out in DCM an e.r. value of 91:9 was obtained. ^d 4 mol% **2a**, 90 bar H₂, 24 h. ^e Enantiomers not assigned.

hydrosilanes can occur *via* hydride addition to silyl-iminium **6** and proto-iminium **7** intermediates; the latter also involves the formation of silyl-enamine intermediate **8** (Fig. 2).¹⁴ Monitoring the hydrosilylation of substrate **4c** using **2a** by NMR indicated a comparable mechanism to be operative here (see ESI,† Fig. S6, S7 and S11). Given the operation of both reduction pathways, and the comparison with hydrogenation – where polar reduction can only occur *via* a proto-iminium **7** intermediate – it would appear that the nature of the imine activating group (*SiR₃ or *H) has little or no effect on enantioselectivity. Furthermore, it suggests that improvements in enantioselectivity are due to better substrate/catalyst matching and not due to a potential change in mechanism between hydrogenation and hydrosilylation. The successful enantioselective reduction using catalyst **2a** appears to be mostly a result of the presence of a bulky alkyl substituent on the nitrogen atom of the ketimine.

In conclusion, we have explored the use of chiral IBiox NHC-stabilised borenium scaffolds for the enantioselective

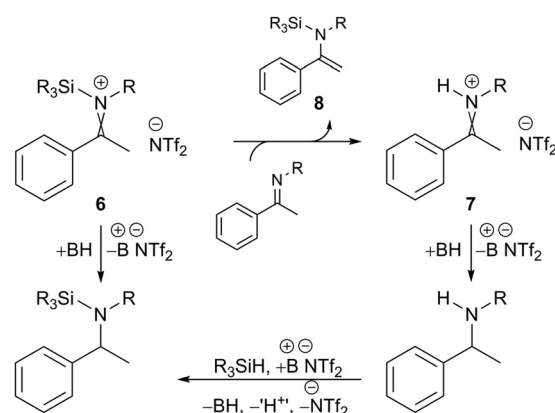


Fig. 2 Lewis acid catalysed hydrosilylation using a borenium cation. For a full mechanism see ref. 14 and Fig. S8 (ESI†).

hydrosilylation and hydrogenation of ketimine substrates. In contrast with prior results of borenium-mediated FLP reductions,^{8b} we have discovered that optimisation of the reaction conditions allowed synthetically useful levels of enantioselectivity to be achieved for a range of substrates. The best results were obtained for substrates featuring secondary *N*-alkyl substituents; substrates that are poorly explored in prior enantioselective FLP reductions. For such substrates, the level of enantioselectivity obtained is competitive with other chiral borane catalysts (Fig. 1) and comparable for both hydrosilylation and hydrogenation, with higher reactivity observed for the former. In future work, we believe that further optimization of chiral NHC–borenium catalysts may be possible to build upon the results described herein. For example, in preliminary work we have investigated the potential to use a borenium catalyst with the very weakly coordinating counterion $\{\text{Al}[\text{O}(\text{CF}_3)_3]_4\}$,¹⁵ given the need for a non-coordinating counterion for effective catalysis (*vide supra*). We observed slightly improved enantioselectivity (*e.g.* product **5c**, *e.r.* = 90:10 NTf₂ counterion, 95:5 $\{\text{Al}[\text{O}(\text{CF}_3)_3]_4\}$ counterion see ESI,† Table S12). We believe our results pave the way for future developments in enantioselective asymmetric reductions using FLP catalysts.

We wish to thank the EPSRC and AstraZeneca for PhD funding (CASE studentship to DMM). MJF would like to thank the EPSRC for an Established Career Fellowship (EP/R00188X/1). AEA would like to thank the Royal Society for a University Research Fellowship (UF/160395). We would also like to thank Kevin Leslie and Fiona Bell (AstraZeneca) for technical support.

Conflicts of interest

There are no conflicts to declare.

Notes and references

† Previously borenium **2d** was generated *in situ*.^{8b} Lindsay *et al.* treated IMes-9-BBN-H with HOTf and characterised the resulting product without isolation.^{10b}

- 1 F.-G. Fontaine and D. W. Stephan, *Philos. Trans. R. Soc., A*, 2017, **375**, 20170004.
- 2 G. C. Welch, R. R. S. Juan, J. D. Masuda and D. W. Stephan, *Science*, 2006, **314**, 1124–1126.
- 3 D. J. Scott, M. J. Fuchter and A. E. Ashley, *Chem. Soc. Rev.*, 2017, **46**, 5689–5700.
- 4 D. J. Parks and W. E. Piers, *J. Am. Chem. Soc.*, 1996, **118**, 9440–9441; J. M. Blackwell, E. R. Sonmor, T. Scoccitti and W. E. Piers, *Org. Lett.*, 2000, **2**, 3921–3923; D. J. Parks, J. M. Blackwell and W. E. Piers, *J. Org. Chem.*, 2000, **65**, 3090–3098.
- 5 (a) D. W. Stephan, S. Greenberg, T. W. Graham, P. Chase, J. J. Hastie, S. J. Geier, J. M. Farrell, C. C. Brown, Z. M. Heiden, G. C. Welch and M. Ullrich, *Inorg. Chem.*, 2011, **50**, 12338–12348; (b) D. J. Scott, M. J. Fuchter and A. E. Ashley, *J. Am. Chem. Soc.*, 2014, **136**, 15813–15816; T. Mahdi and D. W. Stephan, *J. Am. Chem. Soc.*, 2014, **136**, 15809–15812; T. Mahdi and D. W. Stephan, *Angew. Chem., Int. Ed.*, 2015, **54**, 8511–8514; (c) J. Paradies, *Angew. Chem., Int. Ed.*, 2014, **53**, 3552–3557; (d) M.-A. Legare, M.-A. Courtemanche, E. Rochette and F.-G. Fontaine, *Science*, 2015, **349**, 513–516; J. Légaré Lavergne, A. Jayaraman, L. C. Misal Castro, E. Rochette and F.-G. Fontaine, *J. Am. Chem. Soc.*, 2017, **139**, 14714–14723; K. Chernichenko, M. Lindqvist, B. Kótai, M. Nieger, K. Sorochkina, I. Pápai and T. Repo, *J. Am. Chem. Soc.*, 2016, **138**, 4860–4868; (e) Y. Zhang, G. M. Miyake and E. Y. X. Chen, *Angew. Chem., Int. Ed.*, 2010, **49**, 10158–10162; T. Xu and E. Y.-X. Chen, *J. Am. Chem. Soc.*, 2014, **136**, 1774–1777; Q. Wang, W. Zhao, S. Zhang, J. He, Y. Zhang and E. Y.-X. Chen, *ACS Catal.*, 2018, **8**, 3571–3578.
- 6 M. Oestreich, J. Hermeke and J. Mohr, *Chem. Soc. Rev.*, 2015, **44**, 2202–2220.
- 7 (a) D. Chen and J. Klankermayer, *Chem. Commun.*, 2008, 2130; D. Chen, Y. Wang and J. Klankermayer, *Angew. Chem., Int. Ed.*, 2010, **49**, 9475–9478; D. Chen, V. Leich, F. Pan and J. Klankermayer, *Chem. – Eur. J.*, 2012, **18**, 5184–5187; G. Ghattas, D. Chen, F. Pan and J. Klankermayer, *Dalton Trans.*, 2012, **41**, 9026; (b) X. Wang, G. Kehr, C. G. Daniliuc and G. Erker, *J. Am. Chem. Soc.*, 2014, **136**, 3293–3303; K.-Y. Ye, X. Wang, C. G. Daniliuc, G. Kehr and G. Erker, *Eur. J. Inorg. Chem.*, 2017, 368–371; (c) V. Sumerin, K. Chernichenko, M. Nieger, M. Leskelä, B. Rieger and T. Repo, *Adv. Synth. Catal.*, 2011, **353**, 2093–2110; (d) D. J. Morrison, W. E. Piers and M. Parvez, *Synlett*, 2004, 2429–2433; (e) M. Mewald, R. Fröhlich and M. Oestreich, *Chem. – Eur. J.*, 2011, **17**, 9406–9414; M. Mewald and M. Oestreich, *Chem. – Eur. J.*, 2012, **18**, 14079–14084; L. Süsse, J. Hermeke and M. Oestreich, *J. Am. Chem. Soc.*, 2016, **138**, 6940–6943; (f) M. Lindqvist, K. Borre, K. Axenov, B. Kótai, M. Nieger, M. Leskelä, I. Pápai and T. Repo, *J. Am. Chem. Soc.*, 2015, **137**, 4038–4041; (g) Y. Liu and H. Du, *J. Am. Chem. Soc.*, 2013, **135**, 6810–6813; S. Wei and H. Du, *J. Am. Chem. Soc.*, 2014, **136**, 12261–12264; X. Zhu and H. Du, *Org. Biomol. Chem.*, 2015, **13**, 1013–1016; X. Ren, G. Li, S. Wei and H. Du, *Org. Lett.*, 2015, **17**, 990–993; X. Ren and H. Du, *J. Am. Chem. Soc.*, 2016, **138**, 810–813; X. Liu, T. Liu, W. Meng and H. Du, *Org. Biomol. Chem.*, 2018, **16**, 8686–8689; (h) X. Tu, N. Zeng, R. Li, Y. Zhao, D. Xie, Q. Peng and X. Wang, *Angew. Chem., Int. Ed.*, 2018, **57**, 15096–15100.
- 8 (a) J. M. Farrell, J. A. Hatnean and D. W. Stephan, *J. Am. Chem. Soc.*, 2012, **134**, 15728–15731; J. M. Farrell, R. T. Posaratnanathan and D. W. Stephan, *Chem. Sci.*, 2015, **6**, 2010–2015; (b) J. Lam, B. A. R. Günther, J. M. Farrell, P. Eisenberger, B. P. Bestvater, P. D. Newman, R. L. Melen, C. M. Crudden and D. W. Stephan, *Dalton Trans.*, 2016, **45**, 15303–15316.
- 9 (a) M. N. Hopkinson, C. Richter, M. Schedler and F. Glorius, *Nature*, 2014, **510**, 485–496; (b) F. Glorius, G. Altenhoff, R. Goddard and C. Lehmann, *Chem. Commun.*, 2002, 2704–2705; G. Altenhoff, R. Goddard, C. W. Lehmann and F. Glorius, *Angew. Chem., Int. Ed.*, 2003, **42**, 3690–3693; G. Altenhoff, R. Goddard, C. W. Lehmann and F. Glorius, *J. Am. Chem. Soc.*, 2004, **126**, 15195–15201; (c) J.-N. Levy, C. M. Latham, L. Roisin, N. Kandziora, P. Di Fruscia, A. J. P. White, S. Woodward and M. J. Fuchter, *Org. Biomol. Chem.*, 2012, **10**, 512–515.
- 10 (a) D. M. Lindsay and D. McArthur, *Chem. Commun.*, 2010, **46**, 2474; (b) D. McArthur, C. P. Butts and D. M. Lindsay, *Chem. Commun.*, 2011, **47**, 6650.
- 11 M. Valentini, H. Rügger and P. S. Pregosin, *Helv. Chim. Acta*, 2001, **84**, 2833–2853.
- 12 U. Mayer, V. Gutmann and W. Gerger, *Monatsh. Chem.*, 1975, **106**, 1235–1257; M. A. Beckett, G. C. Strickland, J. R. Holland and K. Sukumar Varma, *Polymer*, 1996, **37**, 4629–4631.
- 13 A. E. Ashley, T. J. Herrington, G. G. Wildgoose, H. Zaher, A. L. Thompson, N. H. Rees, T. Krämer and D. O'Hare, *J. Am. Chem. Soc.*, 2011, **133**, 14727–14740.
- 14 J. Hermeke, M. Mewald and M. Oestreich, *J. Am. Chem. Soc.*, 2013, **135**, 17537–17546.
- 15 I. Krossing, *Chem. – Eur. J.*, 2001, **7**, 490–502; S. M. Ivanova, B. G. Nolan, Y. Kobayashi, S. M. Miller, O. P. Anderson and S. H. Strauss, *Chem. – Eur. J.*, 2001, **7**, 503–510.