Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 1598

www.rsc.org/obc

PAPER

Asymmetric hydrogenation of α- or β-acyloxy α,β-unsaturated phosphonates catalyzed by a Rh(I) complex of monodentate phosphoramidite†‡

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Received 1st November 2011, Accepted 18th November 2011
DOI: 10.1039/c1ob06835k

The Rh(I) complex of a monodentate phosphoramidite bearing a primary amine moiety (DpenPhos) has been disclosed to be highly efficient for the asymmetric hydrogenation of a variety of α- or β-acyloxy α,β-unsaturated phosphonates, providing the corresponding biologically important chiral α- or β-hydroxy phosphonic acid derivatives with excellent enantioselectivities (90–>99% ee).

Chiral α- or β-hydroxy phosphonic acids are widely used as key building blocks in pharmaceutical chemistry owing to their potential biological activity.[1] Intense efforts have been made in their asymmetric synthesis based on chiral auxiliary strategies in early works.[2] In contrast, more and more reports of enantioselective synthesis *via* asymmetric catalysis have emerged in recent years, which holds the potential of providing optically active products with high efficiency.[2a] Although a plethora of reports have appeared on the synthesis of α-hydroxy phosphonates, including asymmetric reduction of α-carbonyl phosphonates,[3] oxidation of vinyl phosphonates,[4] hydrophosphonylation (Pudovik reaction),[5] and others,[6] metal complex catalyzed asymmetric hydrogenation (AH) has received more and more attention due to its ideal atom efficiency, high activity, clean process and easy manipulation. Since the first report on the Rh(I)-catalyzed asymmetric hydrogenation of α-acyloxy α,β-unsaturated phosphonates by Burk using privileged diphosphine ligands, such as DuPhos or BPE,[7] various bidentate diphosphine ligands [8–12] have been disclosed to be effective for the hydrogenation of this type of substrate. On the other hand, the conceptually analogous AH of β-substituted β-acyloxy α,β-unsaturated phosphonate derivatives for the preparation of chiral β-hydroxyphosphonates has been less explored, albeit that a leading work by Pizzano uses phosphine-phosphite hybrid ligands.[13] With the rapid development of monophosphine ligands for their ready availability and excellent stereocontrol in asymmetric catalysis,[14] there has been no report on the AH of this type of substrate with Rh(I) complexes of monophosphine ligands to the best of our knowledge. Herein, we present a highly efficient AH of various α- or β-acyloxy unsaturated phosphonates using Rh(I) complexes of monodentate phosphoramidite ligands.

We have previously demonstrated that chiral monodentate phosphoramidite DpenPhos ligands are highly efficient in Rh(I)-catalyzed AH of various α,β-unsaturated carboxylates and α- or β-enamido phosphonates, affording the corresponding optically active acid derivatives with excellent ee values.[15] It was disclosed that the presence of a P–N–H moiety in the relevant phosphoramidite ligand is critically important for the high activity of Rh(I) catalyzed asymmetric hydrogenation, which may provide a suitable platform for extending their application in the catalytic asymmetric hydrogenation of challenging substrates.[15b,c] With this concept in mind, we investigated the ligand effect in the Rh(I)-catalyzed asymmetric hydrogenation of (*E*)-1-(dimethoxyphosphoryl)-2-phenylvinyl benzoate (**1a**) in the present work. The monodentate phosphoramidite ligands **L1**,[16] MonoPhos,[17] and **L3**,[15a] were first examined for the catalysis. No reaction occurred under the experimental conditions shown in Table 1 (entries 1–3), even though these ligands were known to be efficient in the Rh(I) catalyzed hydrogenation of several benchmark unsaturated substrates. Gratifyingly, **L2**/Rh(I) complex catalyzed the reaction smoothly, giving the desired product with 79% ee in full conversion of substrate (entry 4), which stimulated us to use Dpen-derived ligand **L4** to further improve the enantioselectivity of the reaction. Excellent ee (98%) and catalytic activity were obtained by using **L4**/Rh(I) complex (entry 5), again indicating the critical importance of P–N–H moiety in the ligands for the catalysis.[15b,c,18] The ee of the product was further increased to 99% with the decrease of hydrogen pressure to 1 atm (entry 7). This is the first time the asymmetric hydrogenation of this kind of substrate has been realized at ambient pressure with such a high enantioselectivity.

With the leading results in hand, we investigated the adaptability of the catalytic system by further extending the substrate scope. The hydrogenation was carried out in CH_2Cl_2 at 1 atm of H_2 with 1 mol% of catalyst. As shown in Table 2, Rh/(*S*,*S*)-**L4** catalyst turns out to be quite general for the catalysis and works very well (>99% conversion in 1 h) for a wide range of

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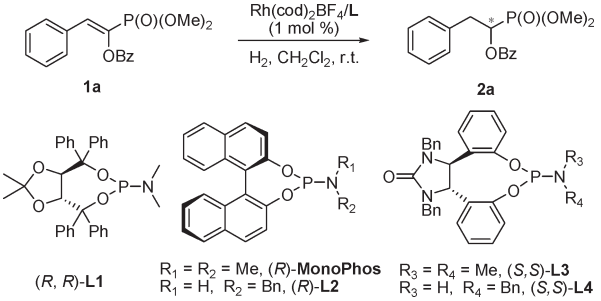
†Dedicated to Professor Christian Bruneau on the occasion of his 60th birthday.

‡Electronic supplementary information (ESI) available: Experimental details and characterization data for all new compounds. See DOI: 10.1039/c1ob06835k

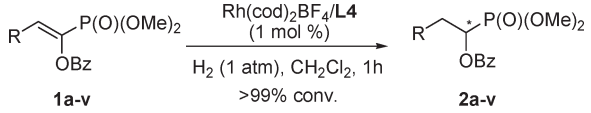
Table 1 AH of α-benzoloxy α,β-unsaturated phosphonate (**1a**) with Rh(I) complexes of various monodentate phosphoramidite ligands[a]



Entry	Ligand	P_{H_2} (atm)	Conv. (%)[b]	Ee (%)[c]
1	**L1**	20	—	—
2	MonoPhos	20	—	—
3	**L3**	20	—	—
4	**L2**	20	>99	79
5	**L4**	20	>99	98
6	**L4**	5	>99	98
7	**L4**	1	>99	>99
8	**L2**	1	31	26

[a] Unless otherwise specified, all reactions were carried out with 0.25 mmol of substrate in 2.5 mL of CH_2Cl_2 for 16 h, in the presence of 1 mol% of catalyst prepared from $[Rh(cod)_2]BF_4$ and 2 equiv of ligand. [b] Determined by ^{31}P NMR analysis. [c] The ee values were determined by chiral HPLC.

Table 2 Rh(I)/(*S*,*S*)-**L4** catalyzed AH of α-acyloxy β-substituted α,β-unsaturated phosphonic acid dimethyl esters[a]



Entry	R in substrate	Ee (%)[b]
1	C_6H_5 (**1a**)	99(*S*)
2	4-FC_6H_4 (**1b**)	>99(+)
3	4-ClC_6H_4 (**1c**)	99(+)
4	4-BrC_6H_4 (**1d**)	98(+)
5	4-$MeOC_6H_4$ (**1e**)	98(*S*)
6	4-$O_2NC_6H_4$ (**1f**)	98(+)
7	2-ClC_6H_4 (**1g**)	97(+)
8	2-BrC_6H_4 (**1h**)	98(+)
9	2-$MeOC_6H_4$ (**1i**)	>99(+)
10	3,4-$(MeO)_2C_6H_3$(**1j**)	>99(+)
11	3,4-$Cl_2C_6H_3$ (**1k**)	>99(+)
12	3,4-$(AcO)_2C_6H_3$ (**1l**)	98(+)
13	Benzo[*d*][1,3]dioxol-5-yl (**1m**)	98(+)
14	Naphtha-1-yl (**1n**)	98(+)
15	Thien-2-yl (**1o**)	90(+)
16	H (**1p**)	>99(*S*)
17	Me (**1q**)	>99(*S*)
18	MeO (**1r**)	>99(*S*)
19	EtO (**1s**)	>99(+)
20	*i*PrO (**1t**)	>99(+)
21	BnO (**1u**)	98(+)
22	C_6H_5 (**1v**)[c]	96(+)
23[d]	MeO (**1r**)	>99(*S*)

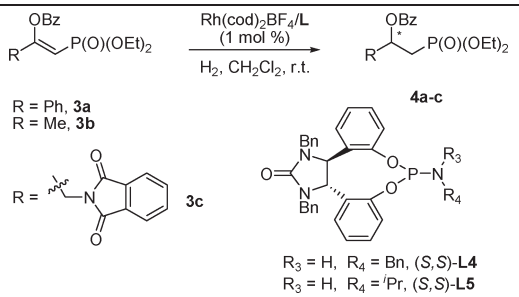
[a] Unless otherwise specified, all reactions were carried out under 1 atm of hydrogen pressure with 0.25 mmol of substrate in 2.5 mL of CH_2Cl_2 in the presence of 1 mol% of catalyst generated *in situ* from $[Rh(cod)_2]BF_4$ and 2 equiv of the ligand. [b] Determined by chiral HPLC. The absolute configuration was determined by comparison of the specific rotation with the literature value.[10] [c] Benzoyl group (Bz) is replaced with acetyl (Ac) in this substrate. [d] S/C = 500, 40 atm H_2, rt, 16 h.

α-acyloxy β-substituted α,β-unsaturated phosphonic acid dimethyl esters with various substitution patterns and electronic properties. All substrates with *para*- or *meta*- substituted phenyl rings either having an electron-donating or electron-withdrawing substituent (**1a–1i**) afforded complete conversion (>99%) and uniformly high enantioselectivities (97–99% ee), showing that the electronic properties of the substrates have a negligible effect on the enantioselectivity of the reaction (Table 2, entries 1–9). The hydrogenation of the substrates (**1j–m**) having two electron-donating or electron-withdrawing substituents at both the *para*- and the *meta*- positions also achieved excellent enantiomeric excesses in the corresponding products (entries 10–13). The hydrogenation of 1-naphthyl or 2-thienyl substituted substrates (**1n–o**) afforded the corresponding hydrogenation products (**2n–o**) with 98% and 90% ee, respectively (entries 14–15), indicating a slight negative impact of the 2-thienyl group on the enantioselectivity of the catalysis, probably due to the competing coordination of the 2-thienyl moiety in the substrate **1o**. The hydrogenation of β-H, β-alkyl, or β-alkoxy substituted α-acyloxy α,β-unsaturated phosphonic acid dimethyl esters (**1p–1u**) proceeded smoothly with excellent enantiocontrol of the catalysis (>98% ee) and complete conversion of the substrates (entries 16–21). The enantioselectivity decreased slightly in the hydrogenation of the phosphonate **1v** with an acetoxy group in comparison with that obtained in the hydrogenation of **1a** having benzoyloxy group (entries 22 *vs.* 1), showing the favorable impact of the bulky chelating unit in the substrates. The efficiency of the catalytic system was also studied at a lower catalyst loading (0.2 mol%, entry 23), the yield and enantioselectivity of **2r** remained unchanged although higher hydrogen pressure (40 atm) and longer reaction time were needed to realize the complete conversion of substrate.

We then decided to apply the present methodology to the hydrogenation of β-acyloxy β-substituted α,β-unsaturated phosphonates for the synthesis of optically active β-hydroxy phosphonic acid derivatives, one type of key building block for potential drug candidates.[19] As can be seen from Table 3, the substrates (**3a–c**) examined here were hydrogenated with good to full conversion of starting material and excellent enantioselectivity (entries 1–3), providing an efficient approach to the optically active β-hydroxy phosphonic acid derivatives (**4a–c**). The hydrogenation of γ-phthalimide substituted substrate **3c** proceeded with a slight decrease of catalytic activity and enantioselectivity in comparison with those of β-phenyl (**3a**) or β-methyl (**3b**) substituted α,β-unsaturated phosphonates.

In conclusion, the Rh(I) complex of a monodentate phosphoramidite bearing a primary amine moiety (DpenPhos) has been disclosed to be highly efficient for the asymmetric hydrogenation of a variety of α- or β-acyloxy α,β-unsaturated phosphonates, providing a convenient methodology for access to the corresponding optically active α- or β-hydroxy phosphonic acid derivatives with biological importance. This methodology represents the first use of monodentate chiral phosphine ligands in the Rh(I)-catalyzed asymmetric hydrogenation of α- or

Table 3 Asymmetric hydrogenation of β-acyloxy β-substituted α,β-unsaturated phosphonic acid diethyl esters[a]



Entry	Substrate	Ligand	P_{H_2} (atm)	T (h)	Conv. (%)[b]	Ee (%)[c]
1	**3a**	**L4**	20	16	>99	95(+)
2	**3b**	**L5**	10	16	>99	96(−)
3	**3c**	**L5**	50	24	86	93(+)

[a] Unless otherwise specified, all reactions were carried out with 0.25 mmol of substrate in 2.5 mL of CH_2Cl_2 in the presence of 1 mol% of catalyst generated *in situ* from $[Rh(cod)_2]BF_4$ and 2 equiv of the ligand. [b] Determined by ^{31}P NMR analysis. [c] Determined by chiral HPLC.

β-acyloxy α,β-unsaturated phosphonates, and the results are comparable or even superior to those obtained with Rh(I) complexes of bidentate phosphine ligands. Further research on the application of this type of ligand in the asymmetric catalysis of other type of challenging substrates is undergoing in our laboratory.

Experimental

1. General procedure for hydrogenations under ambient pressure

The chiral monodentate phosphoramidite ligand (5 μmol) and $Rh(cod)_2BF_4$ (2.5 μmol; cod = 1,5-cyclooctadiene) were added to CH_2Cl_2 (1.2 mL) in a Schlenk tube under argon atmosphere. A hydrogen balloon was switched to the Schlenk tube to replace the argon. The mixture was stirred for 10 min and then the substrate **1** (0.25 mmol) in CH_2Cl_2 (1.3 mL) was added. The reaction mixture was stirred for the specified period of time. The hydrogen gas was released and the conversion was determined by ^{31}P NMR or ^{1}H NMR analysis of an aliquot of the mixture. The reaction mixture was filtered through a short pad of silica gel and eluted with EtOAc. The ee of the product was determined by chiral HPLC.

2. General procedure for hydrogenations under pressures higher than 1 atm

The chiral monodentate phosphoramidite ligand (5 μmol) and $Rh(cod)_2BF_4$ (2.5 μmol; cod = 1,5-cyclooctadiene) were dissolved in 2.5 mL of solvent under argon atmosphere in a vial. The vial was transferred into a Parr steel autoclave in a glove box, where the substrate **3** (0.25 mmol) was added into the catalyst solution. The autoclave was sealed and purged three times with hydrogen and finally pressurized to a specified pressure of hydrogen. The reaction mixture was stirred for the specified period of time. The hydrogen gas was released and the conversion was determined by ^{31}P NMR or ^{1}H NMR analysis. The reaction mixture was filtered through a short pad of silica gel and eluted with EtOAc. The ee of the product was determined by chiral HPLC.

Acknowledgements

Financial support from the National Natural Science Foundation of China (Nos. 21172237, 20821002, 21032007), the Major Basic Research Development Program of China (Grant No. 2010CB833300), the Science and Technology Commission of Shanghai Municipality, and the Chinese Academy of Sciences is gratefully acknowledged.

Notes and references

1 (*a*) D. V. Patel, K. Riellygauvin and D. E. Ryono, *Tetrahedron Lett.*, 1990, **31**, 5587; (*b*) D. V. Patel, K. Riellygauvin and D. E. Ryono, *Tetrahedron Lett.*, 1990, **31**, 5591.
2 For reviews, see: (*a*) O. I. Kolodiazhnyi, *Tetrahedron: Asymmetry*, 2005, **16**, 3295; (*b*) S. Sobhani and Z. Tashrifi, *Tetrahedron*, 2010, **66**, 1429; (*c*) P. Merino, E. Marqués-López and R. P. Herrera, *Adv. Synth. Catal.*, 2008, **350**, 1195.
3 (*a*) T. Gajda, *Tetrahedron: Asymmetry*, 1994, **5**, 1965; (*b*) C. Meier and W. H. G. Laux, *Tetrahedron*, 1996, **52**, 589; (*c*) N. S. Goulioukina, G. N. Bondarenko, A. V. Bogdanov, K. N. Gavrilov and I. P. Beletskaya, *Eur. J. Org. Chem.*, 2009, 510; (*d*) M. Kitamura, M. Tokunaga, T. Pham, W. D. Lubell and R. Noyori, *Tetrahedron Lett.*, 1995, **36**, 5769; (*e*) I. Gautier, V. RatovelomananaVidal, P. Savignac and J. P. Genêt, *Tetrahedron Lett.*, 1996, **37**, 7721; (*f*) V. V. Nesterov and O. I. Kolodiazhnyi, *Tetrahedron*, 2007, **63**, 6720.
4 (*a*) T. Yokomatsu, Y. Yoshida, K. Suemune, T. Yamagishi and S. Shibuya, *Tetrahedron: Asymmetry*, 1995, **6**, 365; (*b*) T. Yokomatsu, T. Yamagishi, T. Sada, K. Suemune and S. Shibuya, *Tetrahedron*, 1998, **54**, 781.
5 (*a*) H. Wynberg and A. Smaardijk, *Tetrahedron Lett.*, 1983, **24**, 5899; (*b*) A. A. Smaardijk, S. Noorda, F. Vanbolhuis and H. Wynberg, *Tetrahedron Lett.*, 1985, **26**, 493; (*c*) T. Yokomatsu, T. Yamagishi and S. Shibuya, *Tetrahedron: Asymmetry*, 1993, **4**, 1779; (*d*) T. Yokomatsu, T. Yamagishi and S. Shibuya, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1527; (*e*) M. D. Groaning, B. J. Rowe and C. D. Spilling, *Tetrahedron Lett.*, 1998, **39**, 5485; (*f*) H. Sasai, M. Bougauchi, T. Arai and M. Shibasaki, *Tetrahedron Lett.*, 1997, **38**, 2717; (*g*) T. Arai, M. Bougauchi, H. Sasai and M. Shibasaki, *J. Org. Chem.*, 1996, **61**, 2926; (*h*) J. P. Duxbury, A. Cawley, M. Thornton-Pett, L. Wantz, J. N. D. Warne, R. Greatrex, D. Brown and T. P. Kee, *Tetrahedron Lett.*, 1999, **40**, 4403; (*i*) B. Saito, H. Egami and T. Katsuki, *J. Am. Chem. Soc.*, 2007, **129**, 1978; (*j*) B. Saito and T. Katsuki, *Angew. Chem., Int. Ed.*, 2005, **44**, 4600; (*k*) J. P. Abell and H. Yamamoto, *J. Am. Chem. Soc.*, 2008, **130**, 10521; (*l*) S. H. Gou, X. Zhou, J. Wang, X. H. Liu and X. M. Feng, *Tetrahedron*, 2008, **64**, 2864; (*m*) X. Zhou, X. H. Liu, X. Yang, D. J. Shang, J. G. Xin and X. M. Feng, *Angew. Chem.,Int. Ed.*, 2008, **47**, 392; (*n*) X. Zhou, Y. L. Liu, L. Chang, J. N. Zhao, D. J. Shang, X. H. Liu, L. L. Lin and X. M. Feng, *Adv. Synth. Catal.*, 2009, **351**, 2567; (*o*) D. Uraguchi, T. Ito and T. Ooi, *J. Am. Chem. Soc.*, 2009, **131**, 3836; (*p*) D. Uraguchi, T. Ito, S. Nakamura and T. Ooi, *Chem. Sci.*, 2010, **1**, 488; (*q*) K. Suyama, Y. Sakai, K. Matsumoto, B. Saito and T. Katsuki, *Angew. Chem., Int. Ed.*, 2010, **49**, 797; (*r*) F. Yang, D. B. Zhao, J. B. Lan, P. H. Xi, L. Yang, S. H. Xiang and J. S. You, *Angew. Chem., Int. Ed.*, 2008, **47**, 5646.
6 (*a*) V. D. Pawar, S. Bettigeri, S. S. Weng, J. Q. Kao and C. T. Chen, *J. Am. Chem. Soc.*, 2006, **128**, 6308; (*b*) S. F. Zhu, W. Q. Chen, Q. Q. Zhang, H. X. Mao and Q. L. Zhou, *Synlett*, 2011, 919; (*c*) J. L. Huang, J. Wang, X. H. Chen, Y. H. Wen, X. H. Liu and X. M. Feng, *Adv. Synth. Catal.*, 2008, **350**, 287; (*d*) R. Dodda and C. G. Zhao, *Org. Lett.*, 2006, **8**, 4911; (*e*) S. Samanta and C. G. Zhao, *J. Am. Chem. Soc.*, 2006, **128**, 7442.
7 M. J. Burk, T. A. Stammers and J. A. Straub,, *Org. Lett.*, 1999, **1**, 387.

8 (*a*) I. D. Gridnev, N. Higashi and T. Imamoto, *J. Am. Chem. Soc.*, 2001, **123**, 4631; (*b*) I. D. Gridnev, M. Yasutake, T. Imamoto and I. P. Beletskaya, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5385; (*c*) I. D. Gridnev and T. Imamoto, *Chem. Commun.*, 2009, 7447.

9 (*a*) M. Rubio, A. Suárez, E. Álvarez and A. Pizzano, *Chem. Commun.*, 2005, 628; (*b*) M. Rubio, S. Vargas, A. Suárez, E. Álvarez and A. Pizzano, *Chem.–Eur. J.*, 2007, **13**, 1821.

10 (*a*) D. Y. Wang, X. P. Hu, J. D. Huang, J. Deng, S. B. Yu, Z. C. Duan, X. F. Xu and Z. Zheng, *Angew. Chem., Int. Ed.*, 2007, **46**, 7810; (*b*) D. Y. Wang, J. D. Huang, X. P. Hu, J. Deng, S. B. Yu, Z. C. Duan and Z. Zheng, *J. Org. Chem.*, 2008, **73**, 2011; (*c*) M. Qiu, X. P. Hu, J. D. Huang, D. Y. Wang, J. Deng, S. B. Yu, Z. C. Duan and Z. Zheng, *Adv. Synth. Catal.*, 2008, **350**, 2683.

11 J. Wassenaar and J. N. H. Reek, *J. Org. Chem.*, 2009, **74**, 8403.

12 H. Fernández-Pérez, S. M. A. Donald, I. J. Munslow, J. Benet-Buchholz, F. Maseras and A. Vidal-Ferran, *Chem.–Eur. J.*, 2010, **16**, 6495.

13 S. Vargas, A. Suárez, E. Álvarez and A. Pizzano, *Chem.–Eur. J.*, 2008, **14**, 9856.

14 (*a*) M. van den Berg, B. L. Feringa and A. J. Minnaard, in *Handbook of Homogeneous Hydrogenation*, ed. J. G. de Vries, C. J. Elsevier, Wiley-VCH, Weinheim, 2007, Vol. 2, p995; (*b*) G. Shang, W. Li and X. Zhang, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, Wiley, Hoboken, 3rd edn., 2010. p343; (*c*) A. J. Minnaard, B. L. Feringa, L. Lefort and J. G. de Vries, *Acc. Chem. Res.*, 2007, **40**, 1267; (*d*) J. H. Xie and Q. L. Zhou, *Acc. Chem. Res.*, 2008, **41**, 581; (*e*) L. Eberhardt, D. Armspach, J. Harrowfield and D. Matt, *Chem. Soc. Rev.*, 2008, **37**, 839.

15 (*a*) Y. Liu and K. Ding, *J. Am. Chem. Soc.*, 2005, **127**, 10488; (*b*) Y. Liu, C. A. Sandoval, Y. Yamaguchi, X. Zhang, Z. Wang, K. Kato and K. Ding, *J. Am. Chem. Soc.*, 2006, **128**, 14212; (*c*) J. Zhang, Y. Li and Z. Wang, K. Ding, *Angew. Chem., Int. Ed.*, 2011, **50**, 11743.

16 (*a*) E. Keller, J. Maurer, R. Naasz, T. Schader, A. Meetsma and B. L. Feringa, *Tetrahedron: Asymmetry*, 1998, **9**, 2409; (*b*) A. Alexakis, J. Vastra, J. Burton, C. Benhaim and P. Mangeney, *Tetrahedron Lett.*, 1998, **39**, 7869.

17 (*a*) R. Hulst, N. K. de Vries and B. L. Feringa, *Tetrahedron: Asymmetry*, 1994, **5**, 699; (*b*) M. van den Berg, A. J. Minnaard, E. Schudde, A A. H. M. de Vries, J. G. de Vries and B. L. Feringa, *J. Am. Chem. Soc.*, 2000, **122**, 11539.

18 For an excellent review, see: J. Meeuwissen and J. N. H. Reek, *Nat. Chem.*, 2010, **2**, 615.

19 (*a*) P. Cui, J. L. Tomsig, W. F. McCalmont, S. Lee, C. J. Becker, K. R. Lynch and T. L. Macdonald, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1634; (*b*) J. F. Dellaria, R. G. Maki, H. H. Stein, J. Cohen, D. Whittern, K. Marsh, D. J. Hoffman, J. J. Plattner and T. J. Perun, *J. Med. Chem.*, 1990, **33**, 534; (*c*) A. E. Wróblewski and A. Halajewska-Wosik, *Tetrahedron: Asymmetry*, 2004, **15**, 3201.