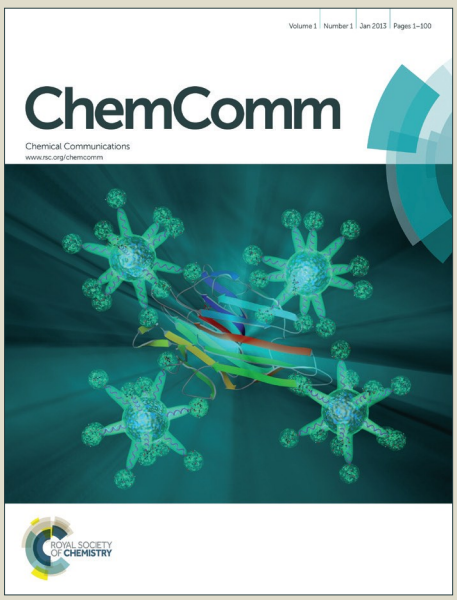
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: W. Song, Y. Zhao, J. C. Lynch, H. Kim and W. Tang, *Chem. Commun.*, 2015, DOI: 10.1039/C5CC07787G.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

View Article Online
DOI: 10.1039/C5CC07787G

Journal Name

COMMUNICATION

Divergent De Novo Synthesis of All Eight Stereoisomers of 2,3,6-Trideoxyhexopyranosides and Their Oligomers

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Wangze Song,[a] Yu Zhao,*[a,b] John C. Lynch,[a] Hyunjin Kim,[a] and Weiping Tang*[a,c]

All eight possible stereoisomers of 2,3,6-trideoxyhexopyranosides are prepared systematically from furan derivatives by a sequence of Achmatowicz rearrangement, Pd-catalysed glycosidation, and chiral catalyst-controlled tandem reductions. This sequence provides access to all possible stereoisomers of naturally occurring rhodinopyranosides, amicetopyranosides, disaccharide narbosine B, and other unnatural oligomeric 2,3,6-trideoxyhexopyranosides. It comprises a unique and systematic strategy for the de novo synthesis of deoxysugars.

Carbohydrates play an important role in many biological processes.[1] Being able to access any stereoisomers systematically will greatly facilitate not only the study of the biological functions of carbohydrates but also the development of carbohydrate analogues as novel therapeutic agents. We herein report a divergent de novo synthetic strategy that allows us to access any possible mono- and oligomeric 2,3,6-trideoxyhexopyranosides at will.[2]

Deoxyhexopyranosides[3] such as rhodinose and amicetose (Figure 1) were found in numerous bioactive natural products.[4-8] Two isomeric disaccharides, **5** and **6**, were isolated from FH-S 1577 strain of Streptomyces from India and named as narbosine B.[9] Congeners of narbosine B such as narbosine D **7** showed distinct antiviral activity.[9] As to oligosaccharides, there are 4096 possible stereoisomers for the tetrameric 2,3,6-trideoxyhexopyranoside **8**, even though 2,3,6-trideoxyhexopyranose is one of the simplest hexoses.

Among various strategies developed for de novo synthesis of carbohydrates[11,12] and *O*-glycosidation,[13] particularly Pd-catalysed Tsuji-Trost allylic alkylation[14] employed by several research groups,[14-18] we are attracted by O'Doherty's de novo synthetic strategy because of its predictability, efficiency, and versatility associated with the resulting enone functional group.[12, 20] The power of this glycosidation method was elegantly demonstrated in the synthesis of several complex oligosaccharides recently.[21]

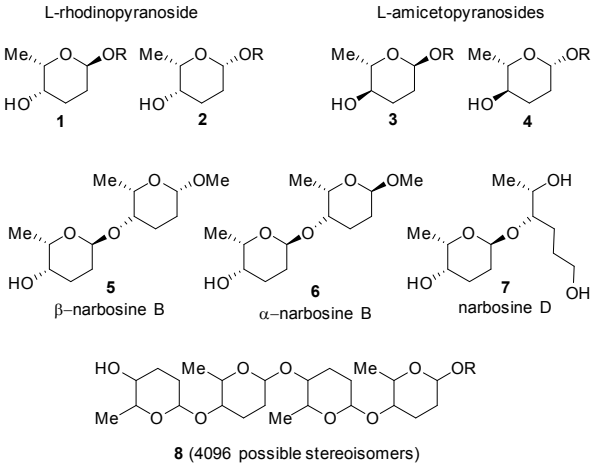


Figure 1. Natural and Unnatural 2,3,6-Trideoxyhexopyranosides

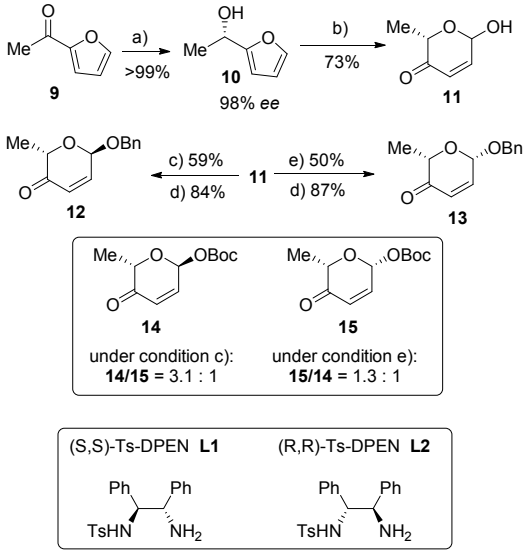
Dihydropyranones **12** and **13** were prepared as the precursors of monomeric 2,3,6-trideoxy hexopyranosides according to the strategy developed by O'Doherty (Scheme 1).[17] Alcohol **10** was obtained in nearly quantitative yield and 98% *ee* according to known protocols.[22] Achmatowicz rearrangement converts furan **10** to dihydropyranone **11**.[23] Following O'Doherty's methods,[24] benzyl glycosides **12** and **13** are prepared efficiently from the corresponding carbonates via Pd-π-allyl intermediates. Carbonate intermediates **14** was isolated in 59% yield under condition c, while carbonate intermediate **15** was isolated in 50% yield under condition e.[24] The enantiomers of **12** and **13** were synthesized similarly by using (R,R)-ligand **L2**.

Previously, the enantiomer of α-L-amicetopyranoside **16** (Scheme 2) was prepared from **ent-12** by a two-step sequence including a highly diastereoselective reduction of the ketone by $NaBH_4$ at -78 °C and a diimide reduction of the alkene.[25] The diastereoselectivity for the reduction of enone **ent-13** to the corresponding allylic alcohols was about 1.5:1 under the condition of Luche reduction.[26] To the best our knowledge, there is no direct one-step method that can provide access to 2,3,6-

[a] School of Pharmacy, University of Wisconsin-Madison, Madison, WI 53705-2222, USA, E-mail: wtang@pharmacy.wisc.edu.
[b] Institute of Nautical Medicine, Nantong University, Nantong, Jiangsu Province, 226001, China. E-mail: zhaoyoo@163.com.
[c] Department of Chemistry, University of Wisconsin-Madison, WI 53706, USA.
Electronic Supplementary Information (ESI) available: [^{1}H NMR, ^{13}C NMR, IR, HRMS]. See DOI: 10.1039/x0xx00000x

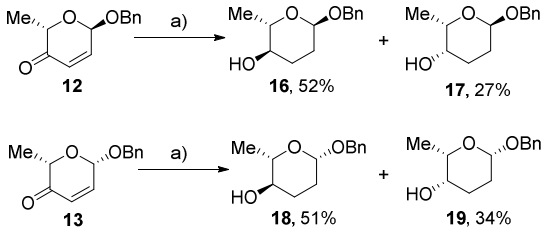
View Article Online
DOI: 10.1039/C5CC07787G

trideoxyhexopyranosides **16** to **19** from enones **12** or **13** stereoselectively. We envisioned that a chiral catalyst-controlled tandem reduction could provide divergent products with high predictability.[27] To achieve high stereoselectivity for each product, low intrinsic diastereoselectivity is highly desirable.[28] Given the high efficiency and selectivity of Rh^{III}-catalysed transfer hydrogenation of ketone **9**, we investigated the reduction of enones **12** and **13** using achiral ligands. Both ketone and alkene groups were reduced and the diastereomeric ratios were less than 2:1 for the two pairs of alcohol products (Scheme 2).



a) $[Cp^*RhCl_2]_2$ (0.05 mol%), (S,S)-Ts-DPEN **L1** (0.12 mol%), HCO_2Na, 40 °C; b) NBS, NaOAc, $NaHCO_3$; c) Boc_2O, DMAP, -78°C; d) $Pd_2(dba)_3$ (0.5 mol%), PPh_3 (2 mol%), BnOH; e) Boc_2O, NaOAc, 80°C.

Scheme 1. Preparation of Precursors of Monomeric Hexopyranosides by O'Doherty's De Novo Synthetic Strategy



a) $[Cp^*RhCl_2]_2$ (0.5 mol%), $TsNHCH_2CH_2NH_2$ **L3** (1.2 mol%), HCO_2Na, 40 °C;

Scheme 2. Reduction of Enone Using Achiral Ligand

When we switched to chiral ligands, we were pleased to find that a single stereoisomer was observed for products **16**, **17**, **18**, and **19** depending on the choice of substrate and chiral ligand (Table 1). Similarly, products **ent-16**, **ent-17**, **ent-18**, and **ent-19** were prepared selectively from **ent-12** and **ent-13**. In all cases, the (S,S)-ligand always yielded hydroxyl groups with S-configuration, while the (R,R)-ligand afforded R-configured secondary alcohols. The stereochemistry of the product is completely controlled by the chiral catalyst regardless the absolute or relative stereochemistry of the enone precursors.

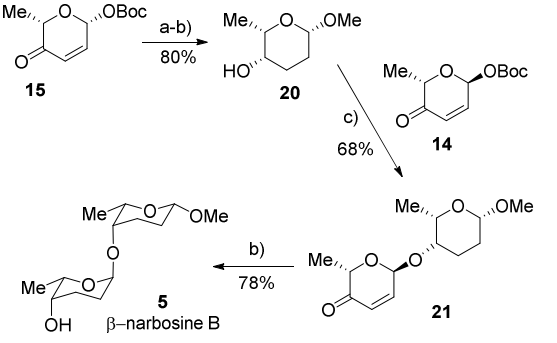
Table 1. Preparation of All Eight Stereoisomers of 2,3,6-Trideoxyhexopyranosides by Chiral Catalyst-Controlled Reduction[a]

Substrate	Product	Ligand	Yield (%)[b]
12	**16**	**L2**	89
12	**17**	**L1**	86
13	**18**	**L2**	71
13	**19**	**L1**	73
ent-12	**ent-17**	**L2**	79
ent-12	**ent-16**	**L1**	84
ent-13	**ent-19**	**L2**	79
ent-13	**ent-18**	**L1**	83

[a.] Conditions: $[Cp^*RhCl_2]_2$ (0.5 mol%), ligand (1.2 mol%), HCO_2Na, 40 °C; [b.] Isolated yield, dr > 20:1.

We further examined the scope of this chiral catalyst-controlled divergent synthesis in more complex settings (Schemes 3 and 4). Naturally occurring disaccharides β-narbosine B **5** was synthesized for the first time from building blocks **15** and **14** derived from Achmatowicz rearrangement product **11** (Scheme 3). Natural product α-narbosine B **6** was prepared similarly. The spectral data and optical rotation of our synthetic **6** are in accordance with those reported by Trost.[10] The (S,S)- ligand (**L1**) was employed to install all the hydroxyl groups with (S)-configuration in intermediates and products **5**/**6**.

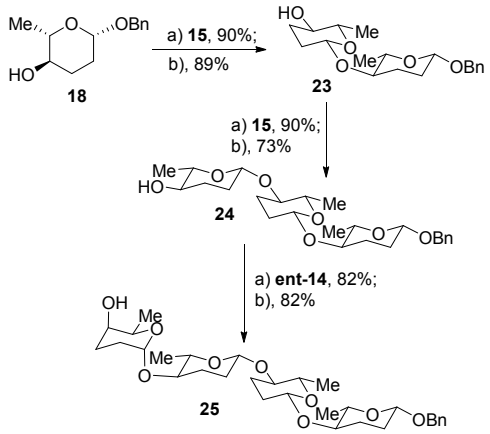
Disaccharide **23**, trisaccharide **24**, and tetrasaccharide **25** were synthesized efficiently and stereoselectively from α-L-amicetopyranoside **18** in a few steps (Scheme 4). The (R,R)-ligand (**L2**) was employed to install all the hydroxyl groups with R-configuration in these oligosaccharides. The high fidelity of Pd-catalysed glycosidation and chiral catalyst-controlled reduction allows the preparation of any one of the 4096 possible stereoisomeric tetrasaccharides, which complements to the approach developed by Rhee recently.[19]



a) $Pd_2(dba)_3$ (0.5 mol%), PPh_3 (2 mol%), MeOH;
b) $[Cp^*RhCl_2]_2$ (0.5 mol%), (S,S)-Ts-DPEN **L1** (1.2 mol%), HCO_2Na, 40 °C;
c) $Pd_2(dba)_3$ (2.5 mol%), PPh_3 (10 mol%).

Scheme 3. Preparation of Naturally Occurring Disaccharides Narbosine B

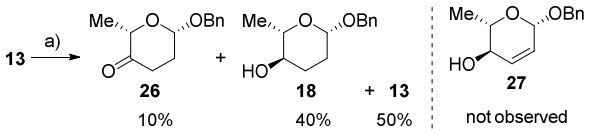
View Article Online
DOI: 10.1039/C5CC07787G



a) $Pd_2(dba)_3$ (2.5 mol%), PPh_3 (10 mol%);
b) $[Cp^*RhCl_2]_2$ (0.5 mol%), (R,R)-Ts-DPEN **L2** (1.2 mol%), HCO_2Na, 40 °C.

Scheme 4. Preparation of Tetrasaccharide by the Sequence of Pd-Catalysed Allylic Alkylation and Chiral Catalyst-Controlled Reduction

To understand the mechanism of the tandem reduction in more details, we studied the distribution of products using limited amount of sodium formate reducing agent (Scheme 5). A mixture of ketone **26**, alcohol **18**, and starting material **13** was obtained in 10%, 40%, and 50% yields, respectively, based on NMR of the crude product. No allylic alcohol **27** was observed by NMR. This suggests that the 1,4-reduction is much faster than the 1,2-reduction of enone **13**. The ratio of **26**/**18** also indicates that the reduction of ketone **26** is faster than the 1,4-reduction of enone **13**.



a) $[Cp^*RhCl_2]_2$ (0.5 mol%), (R,R)-Ts-DPEN **L2** (1.2 mol%), HCO_2Na (1 equiv).

Scheme 5. Reduction with Limited Amount of Reducing Agent

In summary, we realized a divergent synthesis of all eight stereoisomers 2,3,6-trideoxyhexopyranosides. The sequence of Pd-catalysed glycosidation and chiral catalyst-controlled tandem reduction can lead to a systematic de novo synthesis of all stereoisomers of any oligomeric 2,3,6-trideoxyhexopyranosides. We expect that the chiral catalyst-directed divergent synthesis strategy can be extended to the divergent synthesis of other oligosaccharides and their analogues.

We thank University of Wisconsin (UW) for funding. Y. Zhao thanks Jiangsu Overseas Research and Training Program for financial support of the visiting scholar position at UW-Madison. We thank Professor George O'Doherty (Northeastern University) for reading the manuscript and offering insightful comments. This study made use of the Medicinal Chemistry Center at UW-Madison instrumentation, funded by the Wisconsin Alumni Research Foundation (WARF) and the UW School of Pharmacy

Notes and references

1. For selected reviews, see: a) B. Ernst and J. L. Magnani, *Nat. Rev. Drug Discovery*, 2009, **8**, 661; b) P. Stallforth, B. Lepenies, A. Adibekian and P. H. Seeberger, *J. Med. Chem.*, 2009, **52**, 5561; c) J. J. Reina and A. Bernardi, *Mini-Rev. Med. Chem.*, 2012, **12**, 1434; d) C.-H. Wong, *Carbohydrate-based Drug Discovery*, WILEY-VCH Verlag GmbH & Co. KGaA,, Weinheim, 2003.
2. For selected examples of deoxysugar synthesis, see: a) K. C. Nicolaou, T. Ladduwahetty, J. L. Randall and A. Chucholowski, *J. Am. Chem. Soc.*, 1986, **108**, 2466; b) J. Gervay and S. Danishefsky, *J. Org. Chem.*, 1991, **56**, 5448; c) W. R. Roush and X. F. Lin, *J. Am. Chem. Soc.*, 1995, **117**, 2236; d) W. R. Roush, D. P. Sebesta and C. E. Bennett, *Tetrahedron*, 1997, **53**, 8825; e) W. R. Roush, D. P. Sebesta and R. A. James, *Tetrahedron*, 1997, **53**, 8837; f) W. R. Roush and C. E. Bennett, *J. Am. Chem. Soc.*, 1999, **121**, 3541; g) W. R. Roush, B. W. Gung and C. E. Bennett, *Org. Lett.*, 1999, **1**, 891; h) B. Yu and Z. Y. Yang, *Org. Lett.*, 2001, **3**, 377; i) B. Yu and P. Wang, *Org. Lett.*, 2002, **4**, 1919; j) A. F. G. Bongat, M. N. Kamat and A. V. Demchenko, *J. Org. Chem.*, 2007, **72**, 1480; k) E. I. Balmond, D. M. Coe, M. C. Galan and E. M. McGarrigle, *Angew. Chem. Int. Ed.*, 2012, **51**, 9152; l) J. P. Issa, D. Lloyd, E. Steliotes and C. S. Bennett, *Org. Lett.*, 2013, **15**, 4170; m) K. N. Baryal, D. Zhu, X. Li and J. Zhu, *Angew. Chem. Int. Ed.*, 2013, **52**, 8012; n) E. I. Balmond, D. Benito-Alifonso, D. M. Coe, R. W. Alder, E. M. McGarrigle and M. C. Galan, *Angew. Chem. Int. Ed.*, 2014, **53**, 8190; o) J. P. Issa and C. S. Bennett, *J. Am. Chem. Soc.*, 2014, **136**, 5740; p) D. Zhu, K. N. Baryal, S. Adhikari and J. Zhu, *J. Am. Chem. Soc.*, 2014, **136**, 3172; q) M. Kaneko and S. B. Herzon, *Org. Lett.*, 2014, **16**, 2776; r) T. K. Pradhan, C. C. Lin and K. K. T. Mong, *Synlett*, 2013, **24**, 219; s) T. K. Pradhan, C. C. Lin and K.-K. T. Mong, *Org. Lett.*, 2014, **16**, 1474; t) J.-H. Chen, J.-H. Ruei and K.-K. T. Mong, *Eur. J. Org. Chem.*, 2014, 1827.
3. For selected reviews, see: a) A. Kirschning, M. Jesberger and K. U. Schoning, *Synthesis*, 2001, 507; b) W. Chen, G. Zhang, L. Zhu, L. Fang, X. Cao, J. Kedenburg, J. Shen, D. Sun and P. G. Wang, in *Frontiers in Modern Carbohydrate Chemistry*, ed. A. V. Demchenko, 2007, vol. 960, pp. 15; c) R. M. De Lederkremer and C. Marino, in *Advances in Carbohydrate Chemistry and Biochemistry, Vol 61*, ed. D. Horton, 2008, vol. 61, pp. 143; d) A. Borovika and P. Nagorny, *J. Carbohydr. Chem.*, 2012, **31**, 255; e) M. Emmadi and S. S. Kulkarni, *Nat. Prod. Rep.*, 2014, **31**, 870.
4. Y. Hayakawa, T. Iwakiri, K. Imamura, H. Seto and N. Otake, *J. Antibiot.*, 1985, **38**, 960.
5. a) T. Henkel, J. Rohr, J. M. Beale and L. Schwenen, *J. Antibiot.*, 1990, **43**, 492; b) S. Weber, C. Zolke, J. Rohr and J. M. Beale, *J. Org. Chem.*, 1994, **59**, 4211.
6. L. M. Canedo, J. L. F. Puentes, J. P. Baz, X. H. Huang and K. L. Rinehart, *J. Antibiot.*, 2000, **53**, 479.
7. a) S. Kunimoto, T. Someno, Y. Yamazaki, J. Lu, H. Esumi and H. Naganawa, *J. Antibiot.*, 2003, **56**, 1012; b) T. Someno, S. Kunimoto, H. Nakamura, H. Naganawa and D. Ikeda, *J. Antibiot.*, 2005, **58**, 56.
8. A. Luzhetskyy, J. Hoffmann, S. Pelzer, S.-E. Wohlert, A. Vente and A. Bechthold, *Appl. Microbiol. Biotechnol.*, 2008, **80**, 15.

View Article Online
DOI: 10.1039/C5CC07787G

9. T. Henkel, S. Breidingmack, A. Zeeck, S. Grabley, P. E. Hammann, K. Hutter, G. Till, R. Thiericke and J. Wink, *Liebigs Ann. Chem.*, 1991, 575.
10. B. M. Trost and Y. H. Rhee, *J. Am. Chem. Soc.*, 2002, **124**, 2528.
11. For selected examples on de novo synthesis of carbohydrates, see: a) S. Y. Ko, A. W. M. Lee, S. Masamune, L. A. Reed, K. B. Sharpless and F. J. Walker, *Science*, 1983, **220**, 949; b) M. Takeuchi, T. Taniguchi and K. Ogasawara, *Synthesis*, 1999, 341; c) J. M. Harris, M. D. Keranen and G. A. O'Doherty, *J. Org. Chem.*, 1999, **64**, 2982; d) J. M. Harris, M. D. Keranen, H. Nguyen, V. G. Young and G. A. O'Doherty, *Carbohydr. Res.*, 2000, **328**, 17; e) A. B. Northrup and D. W. C. MacMillan, *Science*, 2004, **305**, 1752; f) M. M. Ahmed, B. P. Berry, T. J. Hunter, D. J. Tomcik and G. A. O'Doherty, *Org. Lett.*, 2005, **7**, 745; g) D. Enders and C. Grondal, *Angew. Chem. Int. Ed.*, 2005, **44**, 1210; h) D. J. Covell, N. A. Vermeulen, N. A. Labenz and M. C. White, *Angew. Chem. Int. Ed.*, 2006, **45**, 8217; i) S. B. Han, J. R. Kong and M. J. Krische, *Org. Lett.*, 2008, **10**, 4133.
12. For recent reviews on de novo synthesis of carbohydrates, see: a) A. Z. Aljahdali, P. Shi, Y. Zhong and G. A. O'Doherty, in *Advances in Carbohydrate Chemistry and Biochemistry, Vol 69*, ed. D. Horton, 2013, vol. 69, pp. 55; b) M. F. Cuccarese, J. J. Li and G. A. O'Doherty, in *Modern Synthetic Methods in Carbohydrate Chemistry: From Monosaccharides to Complex Glycoconjugates*, eds. D. B. Werz and S. Vidal, 2014 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2014, ch. 1, pp. 1.
13. For selected reviews, see: a) A. V. Demchenko, *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, 2008; b) X. Zhu and R. R. Schmidt, *Angew. Chem. Int. Ed.*, 2009, **48**, 1900; c) X. Li and J. Zhu, *J. Carbohydr. Chem.*, 2012, **31**, 284; d) M. J. McKay and H. M. Nguyen, *Acs Catalysis*, 2012, **2**, 1563; e) D. B. Werz and S. Vidal, *Modern Synthetic Methods in Carbohydrate Chemistry: From Monosaccharides to Complex Glycoconjugates*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2014; f) T. Nokami, *J. Synth. Org. Chem. Jpn.*, 2014, **72**, 797.
14. For selected reviews, see: a) J. Tsuji, *Acc. Chem. Res.*, 1969, **2**, 144; b) B. M. Trost, *Acc. Chem. Res.*, 1980, **13**, 385; c) J. Tsuji, *Tetrahedron*, 1986, **42**, 4361; d) J. Tsuji and I. Minami, *Acc. Chem. Res.*, 1987, **20**, 140; e) B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921.
15. a) H. Kim and C. Lee, *Org. Lett.*, 2002, **4**, 4369; b) H. Kim, H. Men and C. Lee, *J. Am. Chem. Soc.*, 2004, **126**, 1336.
16. A. C. Comely, R. Eelkema, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2003, **125**, 8714.
17. a) R. S. Babu and G. A. O'Doherty, *J. Am. Chem. Soc.*, 2003, **125**, 12406; b) R. S. Babu, M. Zhou and G. A. O'Doherty, *J. Am. Chem. Soc.*, 2004, **126**, 3428.
18. a) S. Xiang, Z. Lu, J. He, K. L. M. Hoang, J. Zeng and X.-W. Liu, *Chem. Eur. J.*, 2013, **19**, 14047; b) S. Xiang, J. He, Y. J. Tan and X.-W. Liu, *J. Org. Chem.*, 2014, **79**, 11473; c) S. Xiang, K. L. M. Hoang, J. He, Y. J. Tan and X.-W. Liu, *Angew. Chem. Int. Ed.*, 2015, **54**, 604.
19. W. Lim, J. Kim and Y. H. Rhee, *J. Am. Chem. Soc.*, 2014, **136**, 13618.
20. N. L. Holder, *Chem. Rev.*, 1982, **82**, 287.
21. R. S. Babu, Q. Chen, S.-W. Kang, M. Zhou and G. A. O'Doherty, *J. Am. Chem. Soc.*, 2012, **134**, 11952.
22. a) X. Wu, X. Li, A. Zanotti-Gerosa, A. Pettman, J. Liu, A. J. Mills and J. Xiao, *Chem. Eur. J.*, 2008, **14**, 2209; b) M. P. Croatt and E. M. Carreira, *Org. Lett.*, 2011, **13**, 1390.
23. O. Achmatowicz, P. Bukowski, B. Szechner, Z. Zwierzch and A. Zamojski, *Tetrahedron*, 1971, **27**, 1973.
24. M. Zhou and G. A. O'Doherty, *Org. Lett.*, 2006, **8**, 4339.
25. M. Shan, Y. Xing and G. A. O'Doherty, *J. Org. Chem.*, 2009, **74**, 5961.
26. M. Zhou and G. A. O'Doherty, *J. Org. Chem.*, 2007, **72**, 2485.
27. For selected examples of chiral catalyst controlled divergent synthesis, see: a) N. Minami, S. S. Ko and Y. Kishi, *J. Am. Chem. Soc.*, 1982, **104**, 1109; b) S. Kobayashi, A. Ohtsubo and T. Mukaiyama, *Chem. Lett.*, 1991, DOI: 10.1246/cl.1991.831, 831; c) M. P. Doyle, A. V. Kalinin and D. G. Ene, *J. Am. Chem. Soc.*, 1996, **118**, 8837. Also see referenece 11.
28. For a recent example of enantio- and diastereodivergent catalysis, see: S. Krautwald, D. Sarlah, M. A. Schafroth and E. M. Carreira, *Science*, 2013, **340**, 1065.