Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: V. R. Gandi, B. N. D. Doan, S. Kasinathan and R. W. Bates, *Org. Biomol. Chem.*, 2019, DOI: 10.1039/C9OB00003H.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C9OB00003H

Organic and Biomolecular Chemistry

ARTICLE

Stereocontrol in the synthesis of cyclic amino acids: a new ligand for directed hydrogenation through hydrogen bonding

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

Vasudeva Rao Gandi,[a] Bao Nguyen Do Doan,[a,b] Sivarajan Kasinathan,[a] Roderick W. Bates[a]*

A system for the directed hydrogenation of nitrogen heterocycles in described in which hydrogen is delivered cis to a hydroxymethyl group by a rhodium catalyst with a simple phosphine ligand. The chemistry is applied to synthesis of the hygric acid moiety of lincomycin and the pipecolic acid moiety of Argatroban. A series of control experiments indicate that the stereoselectivity is a result of a combination of both coordination and hydrogen bonding.

Introduction

The stereocontrolled synthesis of substituted cyclic amino acids is an important topic, as these moieties occur in a variety of natural and unnatural molecules of significance (Figure 1). For instance, an *n*-propyl substituted hygric acid **1** is present in the antibiotic lincomycin **2**.[1] Methyl substituted hygric acid moieties have also been found in other natural products, such as the cavinafungins, the griselimycins and the malacidins.[2] An *N*-methyl substituted pipecolic acid **3** is present in the anti-thrombotic drug, argatroban **4**.[3,4] The corresponding *N*-methylated amino acid is present in the cytostatic agents, the tubulysins.[5]

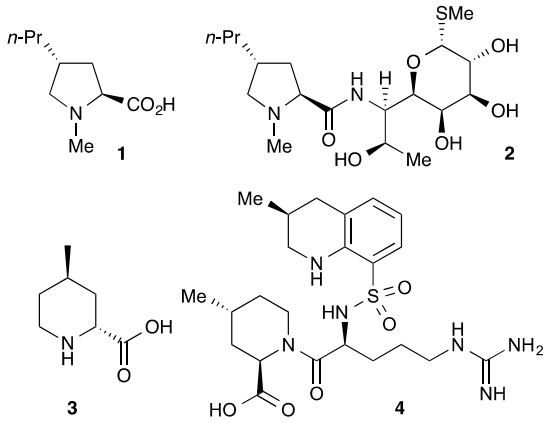


Figure 1. Lincomycin and Argatroban.

In both cases, the substituent is *trans* to the carboxylic acid group. A possible method for achieving the stereocontrolled synthesis is, therefore, by directed hydrogenation of an unsaturated heterocycle (Figure 2).

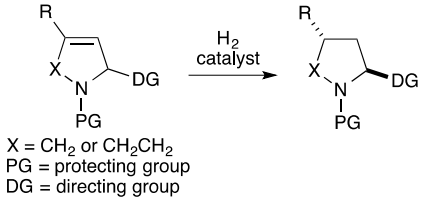


Figure 2. Retrosynthesis through directed hydrogenation.

Directed hydrogenation, the stereochemical direction of catalytic hydrogenation by interaction between a polar atom and the catalyst, has been shown to be a useful method for stereocontrol in organic synthesis.[6] Following an early observation concerning palladium on carbon,[7] the method was refined and made general by Evans[8] and by Crabtree.[9] Their methods have remained "state of the art" in the meantime. Our approach to cyclic amino acids outlined above would complement those of Goodman[10] (*exo*-cyclic alkenes) and Hulme[11] (4,5-unsaturation in five membered rings) and should be applicable to the synthesis of further novel cyclic amino acids and related compounds.

The Crabtree and Evans methods rely upon coordination of a polar group, such as an alcohol, to a cationic rhodium or iridium atom, further stabilised by other ligands. We were interested in how substituents on the ligand might interact with the substrate to achieve the same directing effect. Thus, a ligand-substrate interaction might be able to enhance the substrate-metal interaction of the Evans and Crabtree systems and provide an alternative catalytic system to the heterocycles of interest.

Results and Discussion

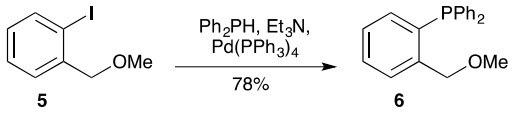
Development of the method

[a] Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371.
[b] Singapore University of Technology and Design, 8 Somapah Road, Singapore 487372.

† Electronic Supplementary Information (ESI) available: Experimental procedures and ^{1}H and $^{13}C\{1H\}$ NMR spectra for compounds **6**, **9a**, **9b**, **9c**, **10a**, **10b**, **10c**, **10e**, **10f**, **10g**, 11a, **12**, **13**, **14**, **15**, **17**, **18**, **19**, **1** and **3**. X-ray structures and other data of the *p*-nitrobenzoate esters of compounds **11a** and **19**. Notes for the general hydrogenation procedure. DFT calculation details. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C9OB00003H

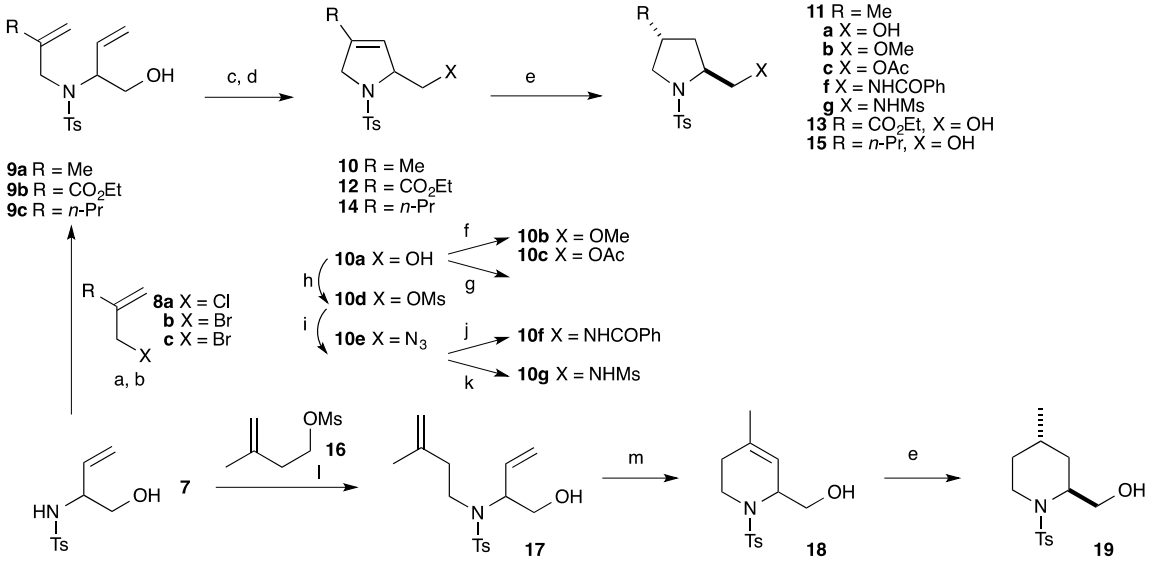
We chose a simple ligand to investigate this idea: ligand **6** which is triphenylphosphine modified by the presence of an *ortho*-methoxymethyl group on one of the rings. Ligand **6** was prepared by a modification of the reported method (Scheme 1).[12] In particular, we found it to be advantageous to employ palladium catalysed coupling of aryl iodide **5** with diphenylphosphine,[13] rather than to employ an organolithium intermediate or a Grignard reagent.



5 6

Scheme 1. Ligand synthesis.

A series of dihydropyrrole substrates were prepared as test substrates for the directed hydrogenation reaction (Scheme 2). For the dihydropyrrole substrates, the *p*-toluene sulfonamide **7** of 2-aminobut-3-en-1-ol was *N*-alkylated with 2-substituted allyl halides **8** in the presence of cesium carbonate to give dienes **9abc**. Cesium carbonate proved to be superior to potassium carbonate in this reaction. Subsequent ring closing metathesis gave the dihydropyrroles **10abc** and **12**. Importantly, hydrogenation of dihydropyrrole **10a** under "traditional" conditions, using Pd/C as the catalyst, gave pyrrolidine **11a** as a mixture of diastereoisomers (table 1, entry 1), underlining the need for directing methodology. After extensive experimentation, we were pleased to find that a system consisting of bis(norbornadiene)rhodium(I) tetrafluoroborate and ligand **6**, was effective giving pyrrolidine **10a** in high yield and high diastereoselectivity (entry 2).[14] An efficient reaction was only achieved when dichloromethane was employed as the solvent. In THF, toluene and dioxane, high diastereoselectivity was observed, but only partial conversion (26-39%). In methanol, complete conversion was achieved, but with low diastereoselectivity (2:1). Pyrrolidine **10a** was shown to be the anticipated *trans* isomer by X-Ray crystallographic analysis of the corresponding *p*-nitrobenzoate.[15] Importantly, the reaction could be run on a gram scale using a slightly increased concentration (0.2 – 0.3 M) with no loss of diastereoselectivity.



Scheme 2. Substrate synthesis and hydrogenation.

Reagents and conditions: (a) R = Me, X = Cl, Cs_2CO_3 (2 eq.), DMF, rt, 96%; (b) R = CO_2Et, X = Br, Cs_2CO_3 (1 eq.), DMF, rt, 46%; (c) R = Me, Grubbs' I, toluene, 70°C, 90%; (d) R = CO_2Et, Grubbs' II, toluene, 70°C, 93%; (e) see table 1; (f) MeI (3 eq.), NaOH (powdered, 2 eq.), *n*-Bu_4NI, toluene, 40° C, 89%; (g) Ac_2O (2 eq.), Et_3N, CH_2Cl_2, 95%; (h) MsCl, Et_3N; (i) NaN_3, DMSO, 60°C, 58% (2 steps); (j) $PhCO_2H$, PPh_3, toluene, reflux, 95%; (k) PPh_3, THF/ H_2O (10:1 v/v) then MsCl, Et_3N, CH_2Cl_2, 63% (two steps) (l) Cs_2CO_3 (2.5 eq.), DMF, 60°C, 91%; (m) Grubbs' I, toluene, 70°C, 89%.

Interestingly, use of chloro(1,5-cyclooctadiene)rhodium(I) dimer resulted in no reaction (entry 3). We believe that the presence of chloride inhibits the reaction by coordinating to the rhodium.[16] Given the success of the reaction, the question arose as to whether the methoxymethyl group had any effect.[17] When ligand **2** was replaced by either triphenylphosphine or tri(*o*-tolyl)phosphine, poor conversion and selectivity was observed (entries 4 and 5), indicating that the methoxy group is, indeed, essential. Additionally, we prepared the methyl ether **10b** and the acetate **10c** to test whether the selectivity arises from just substrate to metal coordination. Both of these functional groups would be expected to have the ability to coordinate, yet, when hydrogenation of these substrates was carried out, poor conversion and selectivity was again observed (entries 6 and 7). It, therefore, seemed likely that the high diastereoselectivity was due to hydrogen bonding[18] between the free alcohol of substrate **10a** and the methoxy group of ligand **6**, as the presence of both of these functional groups is required. We reasoned that an amide would also act as a strong hydrogen bond donor. However, amide substrate **10f**, prepared by Staudinger reaction[19] of azide **10e**, gave disappointing results (entry 8). As this result might also be attributed to the amide moiety acting as a η^3-ligand, we also prepared sulfonamide **10g**, which would also be expected to be an effective hydrogen bond donor. Subjecting this compound to the hydrogenation

DOI: 10.1039/C9OB00085H

conditions resulted in just 37% conversion with poor diastereoselectivity (entry 9). We therefore concluded that hydrogen bonding is necessary but not sufficient in this system. We propose that the powerful and efficient directing effect observed is due to a cooperative combination of hydrogen bonding and coordination (Figure 3). Of the substituents tested in this position, only the alcohol group is able to provide both effects. It may be noted that high diastereoselectivity may be obtained in the absence of hydrogen bonding (entries 4 and 7). This is likely to be due to simple coordination of the polar group X to the rhodium centre, as in the system of Evans *et al.*[8] In these examples the yield is low. This is presumably due to catalyst decomposition in these examples. Thus, it may be proposed that hydrogen bonding not only enhances the stereoselectivity by strengthening the directing effect, but also enhances the catalytic efficiency by stabilising the intermediates.[20]

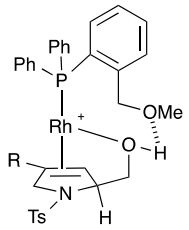
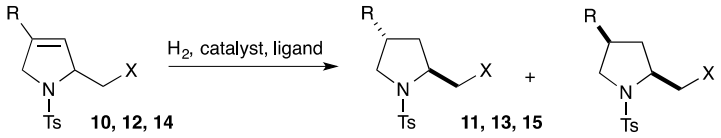


Figure 3. Proposed catalyst substrate interactions.

Table 1. Hydrogenation reactions



entry	substr.	X	R	catalyst(s)[a]	ligand	yield	*trans*:*cis*
1	**10a**	OH	Me	Pd/C[b]	-	99%	1:1
2	**10a**	OH	Me	$(nbd)_2RhBF_4$	**6**	99%	>99:1
3	**10a**	OH	Me	$[Rh(COD)Cl]_2$	**6**	0	-
4	**10a**	OH	Me	$(nbd)_2RhBF_4$	PPh_3	50%[c]	10:1
5	**10a**	OH	Me	$(nbd)_2RhBF_4$	$P(o\text{-}tol)_3$	75%[c]	2.5:1
6	**10b**	OMe	Me	$(nbd)_2RhBF_4$	**6**	53%[c]	1:1
7	**10c**	OAc	Me	$(nbd)_2RhBF_4$	**6**	48%[c]	10:1
8	**10f**	NHCOPh	Me	$(nbd)_2RhBF_4$	**6**	0	-
9	**10g**	NHMs	Me	$(nbd)_2RhBF_4$	**6**	37%[c]	2:1
10	**12**	OH	CO_2Et	$(nbd)_2RhBF_4$	**6**	89%	>99:1
11	**14**	OH	*n*-Pr	$(nbd)_2RhBF_4$	**6**	87%	95:5
12	**18**[d]	OH	Me	$(nbd)_2RhBF_4$	**6**	88%	98:2

a) Rhodium catalysed reactions were carried out in CH_2Cl_2 (0.05 M) at 100 psi H_2 pressure, at room temperature, overnight, using 10 mol% of rhodium complex and 12 mol% of ligand **6**. b) The reaction was carried out with a balloon of H_2 at room temperature. c) Conversion estimated by ^1H NMR. The balance of the material is starting material. d) Six-membered ring substrate: see Scheme 4.

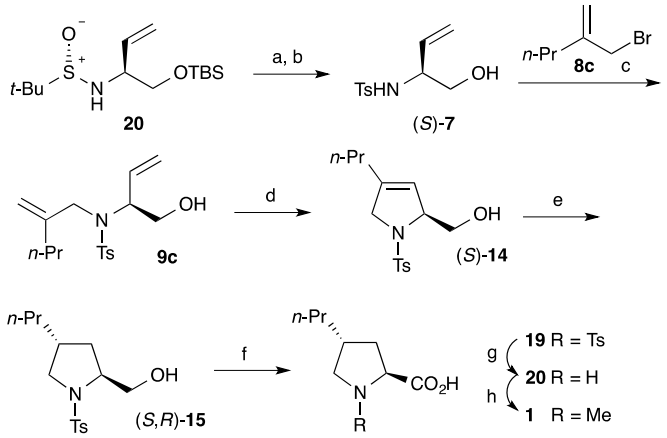
The substrate **12** with an ester substituent was also reduced in high yield and with high diastereoselectivity to give pyrrolidine **13** (entry 10). Similarly, substrate **14** with a larger alkyl substituent was also reduced efficiently (entry 11; see scheme 3). In addition, tetrahydropyridine **18**, prepared analogously from sulfonamide **3**, behaved similarly upon reduction to give piperidine **19** in 88% yield with a d.r. of 98:2 (entry 12). Again, *trans* stereochemistry was demonstrated by X-ray crystallographic analysis of the corresponding *p*-nitrobenzoate.[15]

Application of the Method to Synthesis

The method was then applied to the two amino acid synthetic targets. The antibiotic lincomycin **2** contains *trans*-4-*n*-propylhygric acid **1** ((*2S, 4R*)-*N*-methyl-4-propylproline). With the exception of a single report of a stereo-unselective hydrogenation of the corresponding *exo*-cyclic alkene,[1b] the only reported method for the synthesis of this amino acid, to the best of our knowledge and to our surprise, is by degradation of lincomycin itself![21]

To obtain the absolute stereochemistry, sulfinamide **20** was prepared according to the reported method (Scheme 3).[22] We initially attempted to retain the *t*-butyl based protecting regime, but found a number of problems, beginning with the difficulty of achieving *N*-allylation.[23] The *t*-butylsulfinyl group was, therefore, removed using HCl in dioxane and the nitrogen was reprotected as a toluenesulfonamide, yielding (*S*)-**7**, allowing straightforward completion of the synthesis. Allylic bromide **8c**[24] was prepared from ethyl butyrate using the Kulinkovich reaction[25] and then used to alkylate the nitrogen of sulfonamide (*S*)-**7** under the conditions that we had already developed in the racemic series. Ring closing metathesis gave the dihydropyrrole (*S*)-**14** which was subjected to our

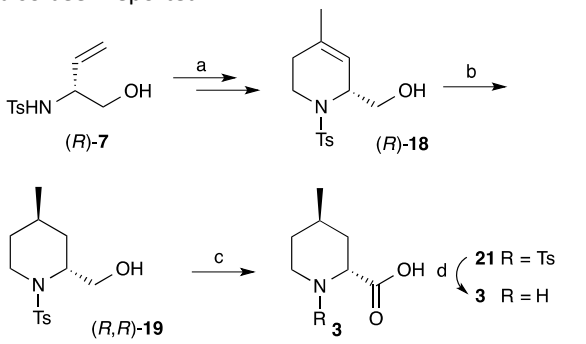
hydrogenation conditions (entry 12). In this way, the pyrrolidine (*S*,*R*)-**15** was obtained in high yield and with high diastereoselectivity. The synthesis was continued by oxidation of the alcohol to the carboxylic acid **19** using *in situ* generated ruthenium tetroxide under Sharpless conditions.[26] *N*-Detosylation was carried out using sodium naphthalenide[27] as use of neither magnesium nor calcium in methanol was effective. The synthesis was completed by reductive *N*-methylation of amine **20**,[1b,28] to give hygric acid **1**, which was purified by ion exchange chromatography. The observed data for the synthetic material was found to be in good agreement with that reported.[1b, 21]



Scheme 3. Lincomycin amino acid synthesis.

Reagents and conditions: (a) MeOH, AcCl, dioxane; (b) TsCl, Et_3N, CH_2Cl_2, 68% (2 steps); (c) **8c**, Cs_2CO_3, DMF, 95%; (d) Grubbs' II, toluene, 70°C, 90%; (e) see table 1, entry 12; (f) $RuCl_3$ (10 mol%), $NaIO_4$ (6 eq.), $CHCl_3/CH_3CN/H_2O$ (2:2:3); (g) Na•$C_{10}H_8$, THF, -40°C, then HCl; (h) aq. HCHO, H_2 (75 psi), Pd/C, 52% (3 steps).

Amino acid **3**, a moiety present in Argatroban **4**, was originally prepared by a process involving the separation of all four stereoisomers.[3] A diastereoselective synthesis of racemic **3** has been reported.[29] Some asymmetric syntheses involving alkene hydrogenations with moderate to good stereoselectivity have also been reported.[30]



Scheme 4. Synthesis of *trans*-4-methylpipecolic acid.

Reagents and conditions: (a) see scheme 2 (b) see table 1, entry 12; (c) $RuCl_3$ (10 mol%), $NaIO_4$ (6 eq.), $CHCl_3/CH_3CN/H_2O$ (2:2:3); (d) Na•$C_{10}H_8$, THF, -40°C, then HCl, 68% (two steps).

Thus, alcohol (*R*)-**7** was converted to alkene (*R*)-**18** by the method described above (see Scheme 2) and reduced with excellent diastereoselectivity to (*R*)-**19** (Scheme 4). This material was then converted into amino acid **3**, isolated as its hydrochloride salt, by oxidation to carboxylic acid **21** with RuO_4[26] and deprotection with sodium naphthalenide.[27] After purification by ion exchange chromatography, the desired compound **3** was obtained in 68% yield over two steps. Again, the observed data for the synthetic material was found to be in good agreement with that reported.[5,29]

Conclusions

Syntheses of the hygric acid moiety of lincomycin and the pipecolic acid moiety of Argatroban have been completed, employing a novel catalyst system for control of the relative stereochemistry of the substituents. The method promises to be applicable to further targets. Hydrogen bonding is proposed as a key factor in the catalytic directed hydrogenation. Famously invoked as the cause of a directing effect by Henbest,[16] hydrogen bonding much more often considered in organocatalysis[31] than transition metal catalysis. There is only a modest number of examples in which hydrogen bonding is proposed as the cause of regiochemical or stereochemical direction.[32] It is, therefore, an example of a non-covalent interaction[33] that has under-exploited potential in catalyst design.

Experimental

General procedure for the directed hydrogenation.

A solution of bis(norbornadiene)rhodium(I) tetrafluoroborate (10 mol%) in CH_2Cl_2 was added to a solution of ligand **6** (12 mol%) in CH_2Cl_2 in a Fischer – Porter tube. The solution was stirred for 30 min at room temperature under nitrogen. The hydrogenation substrate (1.0 eq) in CH_2Cl_2 was then added dropwise to the solution. The tube was charged with H_2 to 100 psi and stirred for 16-60 h at room temperature. The final concentration of the substrate is ca 0.05 – 0.2 M A higher concentration may be used for larger scale reactions. The mixture was filtered through a short pad of Celite and concentrated. The residue was purified by flash chromatography, eluting with 20-30% EtOAc/Hexane to give the hydrogenated product.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Agency for Science Technology and Research (A-Star) (PSF grant number 1321202095) and Nanyang Technological University for financial support of this work. We thank Dr Richmond Lee (Singapore University of Technology & Design) for helpful discussions & resources for DFT calculations.

View Article Online
DOI: 10.1039/C9OB00005H

Notes and references

1 (a) G. Slomp, F. A. MacKellar, *J. Am. Chem. Soc.* **1967**, *89*, 2454-2459; (b) B. J. Magerlein, R. D. Birkenmeyer, R. R. Herr, F. Kagan, *J. Am. Chem. Soc.* **1967**, *89*, 2459-2464.

2 (a) the cavinafungins: F. J. Ortíz-Lopez, M. C. Monteiro, V. González-Meneńdez, J. R. Tormo, O. Genilloud, G. F. Bills, F. Vicente, C. Zhang, T. Roemer, S. B. Singh, F. Reyes, *J. Nat. Prod.* **2015**, *78*, 468-475; (b) the griselimycins: P. Lukat, Y. Katsuyama, S. Wenzel, T. Binz, C. König, W. Blankenfeldt, M. Brönstrup, R.Müller, *Chem. Sci.* **2017**, *8*, 7521-7527; and (c) the malacidins: B. M. Hover, S.-H. Kim, M. Katz, Z. Charlop-Powers, J. G. Owen, M. A. Ternei, J. Maniko, A. B. Estrela, H. Molina, S. Park, D. S. Perlin, S. F. Brady, *Nat. Microbio.* **2018**, *3*, 415-422.

3 S. Okamoto, A. Hijikata, R. Kikumoto, S. Tonomura, H. Hara, K. Ninomiya, *Biochem. Biophys. Res. Comm.* **1981**, *101*, 440-446.

4 For a review of methods for the synthesis of pipecolic acid derivatives, see A. A. Cant, A. Sutherland, *Synthesis* **2012**, *44*, 1935-1950.

5 (a) F. Sasse, H. Steinmetz, J. Heil, G. Höfle, Reichenbach, *J. Antibiotics* **2000**, *53*, 879-885; (b) Y. Chai, D. Pistorius, A. Ullrich, K. J. Weissman, U. Kazmaier, R. Müller, *Chem. & Biol.* **2010**, *17*, 296-309; (c) J. S. Parker, M. McCormick, D. W. Anderson, B. A. Maltman, L. Gingipalli, D. Toader, *Org. Process Res. Dev.* **2017**, *21*, 1602-1609.

6 For a review of directing effects, see (a) A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307-1370, and for directed hydrogenation, see (b) J. M. Brown, *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190. For a review of diastereoselective hydrogenation of heterocycles, see M. Besson, C. Pinel, *Top. Catal.* **2003**, *25*, 43-61.

7 H. W. Thompson, *J. Org. Chem.* **1971**, *36*, 2577-2581.

8 D. A. Evans, M. M. Morrissey, *J. Am. Chem. Soc.* **1984**, *106*, 3866-3868.

9 R.H. Crabtree, M.W. Davis, *J. Org. Chem.,* **1986**, *51*, 2655–2661.

10 J. Del Valle, M. Goodman, *J. Org. Chem.* **2003**, *68*, 3923-3931.

11 H. J. Johnston, F. S. McWhinnie, F. Landi, A. N. Hulme, *Org. Lett.* **2014**, *16*, 4778-4781.

12 D. K. Dutta, B. Deb, G. Hua, J. D. Woolins, *J. Mol. Cat. A* **2012**, *7*, 353-354.

13 (a) F. Zhang, L. Wang, S.-H. Chang, K.-L. Huang, Y. Chi, W.-Y. Hung, C.-M. Chen, G.-H. Lee, P.-T. Chou, *Dalton Trans.* **2013**, *42*, 7111. For a review, see (b) F. M. J. Tappe, V. T. Trepohl, M. Oestreich, *Synthesis* **2010**, 3037-3062.

14 Our original concept was to employ a La^{3+} ion as a hard Lewis acid to bridge the two oxygen functional groups, but the presence of La^{3+} proved superfluous.

15 Details of all X-ray structure determinations have been deposited with the Cambridge Crystallographic Data Centre and may be obtained at http://www.ccdc.cam.ac.uk; CCDC deposition numbers: *p*-nitrobenzoate of **11a**: 1563706; of **19**: 1563707.

16 Confirmation of this idea was obtained by carrying out the hydrogenation reaction using a catalyst derived from a combination of $[(COD)RhCl]_2$ and $AgBF_4$. This resulted in 44% conversion and 8:1 diastereoselectivity.

17 The reaction was also tested using a ligand with an additional oxygen atom i.e. methoxyethoxy group in place of the methoxy group, but this showed no advantages.

18 The use of the acetate to probe for hydrogen bonding was inspired by H. B. Henbest, R. A. L. Wilson, *J. Chem. Soc.* **1957**, 1958-1965.

19 J. Garcia, F. Urpí, J. Vilarrasa, *Tetrahedron Lett.* **1984**, *25*, 4841-4844.

20 Preliminary DFT calculations indicate that the hydrogen bond provides stabilisation of about 1.3 kcal mol^{-1}. See the S.I. for further details.

21 (a) B. J. Magerlein, R. D. Birkenmeyer, U.S. Patent 3,282,957, **1966**; (b) N. M. Brahme, J. E. Gonzalez, J. P. Rolls, E. J. Hessler, S. Mizsak, L. H. Hurley, *J. Am. Chem. Soc.* **1984**, *106*, 7873-7878; (c) J. Zemlicka, M. C. Fernandez-Moyano, M. Ariatti, G. E. Zurenko, J. E. Grady, J. P. G. Ballesta, *J. Med. Chem.* **1993**, *36*, 1239-1244; (d) M.-P. Collin, S. N. Hobbie, E. C. Böttinger, A. Vasella, *Acta Chim. Helv.* **2008**, *91*, 1838-1848; (e) M.-P. Collin, S. N. Hobbie, E. C. Böttinger, A. Vasella, *Acta Chim. Helv.* **2009**, *92*, 230-266.

22 J. C. Rech, M. Yato, D. Duckett, B. Ember, P. V. LoGrasso, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2007**, 129, 490-491. Careful control of the reaction temperature during Grignard addition was found to be essential to obtain consistent diastereoselectivity.

23 Allylation of **20** with bromide **8c** could be achieved in 67% yield using KHMDS in the presence of KI. Subsequent ring closing metathesis (Grubbs' II catalyst, toluene, 70 °C) only proceeded to 50% conversion.

24 A. K. Ganguly, S. S. Alluri, C.-H. Wang, A. Antropow, A. White, D. Caroccia, D. Biswas, E. Kang, L.-K. Zhang, S. S. Carroll, C. Burlein, J. Fay, P. Orth, C. Strickland, *Tetrahedron* **2014**, *70*, 2894-2904.

25 Y. Y. Kozyrkov, O. G. Kulinkovich, *Synthesis*, **2002**, 443-446.

26 P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936-3938. $CHCl_3$ was used in place of carbon tetrachloride.

27 S. Ji, L. B. Gortler, A. Waring, A. J. Battisti, S. Bank, W. D. Closson, P. A. Wriede, *J. Am. Chem. Soc.* **1967**, *89*, 5311-5312.

28 L. Aurelio, J. S. Box, R. T. C. Brownlee, A. B. Hughes, M. M. Sleebs, *J. Org. Chem.* **2003**, *68*, 2652-2667.

29 (a) J. Cossy, D. Belotti, *Tetrahedron Lett.* **2001**, *42*, 2119-2120; (b) J. Cossy, D. Belotti, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1989-1992.

30 (a) C. Agami, F. Bisaro, S. Comesse, S. Guesné, C. Kadouri-Puchot, R. Morgentin, *Eur. J. Org. Chem.* **2001**, 2385-2389; (b) C. Alegret, F. Santacana, A. Riera, *J. Org. Chem.* **2007**, *72*, 7688-7692; (c) P. Ferrabischi, M. De Mieri, P. Grisenti, M. Lotz, U. Nettekoven, *Tet. Asymmetry* **2011**, *22*, 1626-1631.

31 For an example, see L. Albrecht, G. Dickmeiss, C. F. Weise, C. Rodríguez-Escrich, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2012**, *51*, 13109-13113.

32 (a) In hydroformylation: T. Šmejkal, B. A. Breit, *Angew. Chem. Int. Ed.* **2008**, *47*, 311-315; (b) in asymmetric hydrogenation: Q. Zhao, S. Li, K. Huang, R. Wang, X. Zhang, *Org. Lett.* **2013**, *15*, 4014-4017; (c) in C-H borylation: Y. Kuninobu, H. Ida, M. Nishi, M. Kanai, *Nat. Chem.* **2015**, *7*, 712-717; (d) P. C. Roosen, V. A. Kallepalli, B. Chattopadhyay, D. A. Singleton, R. E. Maleczka, Jr., M. R. Smith III, *J. Am. Chem. Soc.* **2012**, *134*, 11350-11353; (e) in hydrometallation: S. M. Rummelt, K. Radkowski, D.-A. Roşca, A. Fürstner, *J. Am. Chem. Soc.* **2015**, *137*, 5506-5519; (f) in organometallic photocatalysis, see K. L., Skubi, J. B. Kidd, H. Jung, I. A. Guzei, M.-H. Baik, T. P. Yoon, *J. Am. Chem. Soc.* **2017**, *139*, 17186-17192.

33 H. J. Davis, R. J. Phipps, *Chem. Sci.* **2017**, *8*, 864-877.