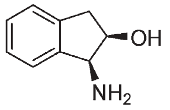
An outstanding catalyst for asymmetric transfer hydrogenation in aqueous solution and formic acid/triethylamine†

Daljit S. Matharu,[a] David J. Morris,[a] Guy J. Clarkson[b] and Martin Wills*[a]

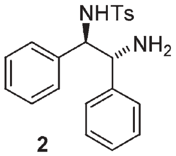
Received (in Cambridge, UK) 3rd May 2006, Accepted 5th June 2006
First published as an Advance Article on the web 23rd June 2006
DOI: 10.1039/b606288a

A Rh/tetramethylcyclopentadienyl complex containing a tethered functionality has been demonstrated to give excellent results in the asymmetric transfer hydrogenation of ketones in both aqueous and formic acid/triethylamine media.

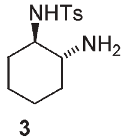
The reduction of ketones to enantiomerically-pure secondary alcohols is a fundamental chemical transformation which provides one of the most convenient methods for establishing chirality within target molecules and building blocks for complex target structures. Asymmetric transfer hydrogenation (ATH) is a highly efficient and practical method for this transformation.[1] Of the ATH catalysts reported within the last decade, the most widely used ligand classes are those based on 1,2-aminoalcohols[2–5] such as *cis*-aminoindanol **1**, and monosulfonylated diamines[5–8] such as *N*-tosyl-1,2-diphenylethane-1,2-diamine (TsDPEN) **2** and *N*-tosyl-1,2-diaminocyclohexane (TsDAC) **3**. The latter class is the more versatile, as it may be used in formic acid/triethylamine (FA/TEA) medium, resulting in an essentially irreversible reaction.



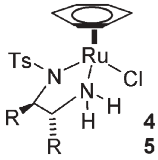
1



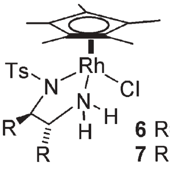
2



3



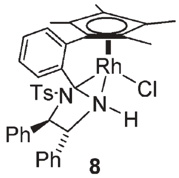
4 R=Ph
5 RR=$(CH_2)_4$



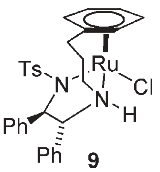
6 R=Ph
7 RR=$(CH_2)_4$

Aminoalcohols, by contrast, form less stable complexes and are limited to use in isopropanol, where the dilutions must be high in order to avoid troublesome reversible reactions. Of the metal complexes which may be formed with these ligands, those of arene/Ru(II) such as **4** and **5** have been studied most widely by researchers in academia and industry.[2,3,6,7] In general, Ru(II) catalysts are more versatile and more economical than the isoelectronic Cp′/Rh(III) or Ir(III) catalysts such as **6** and **7**.[4,5,8,9] Cp′/Rh(III) complexes have been commercialised by Avecia and marketed as 'CaTHy' catalysts.[4,5]

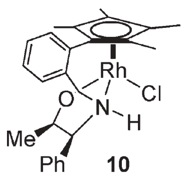
In certain cases, however, the Rh(III) catalysts are superior, notably in the case of reduction of α-chloro ketones.[8,9] These applications originate from 2001 when a binary system was introduced.[9a] This system and the associated procedure was significantly improved through the use of the preformed catalysts in 2002.[8d–8f] The system has also been demonstrated to be active in aqueous solution using either sodium formate or FA/TEA as the hydrogen source. In 2005, we reported an improved catalyst **8** which contained a tether between the cyclopentadienyl and TsDPEN components.[10] The performance of **8** was similar to that of the tethered Ru(II)TsDPEN catalyst **9** that we have previously reported[11] but represented a significant improvement over our earlier Rh(III) tethered catalyst **10** containing an amino alcohol ligand.[12]



8

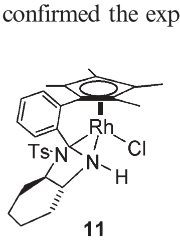


9

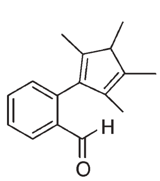


10

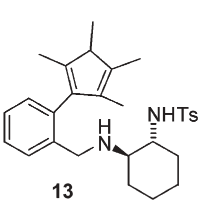
Upon examination of the publications in this area, we noted that, in contrast to the Ru(II)/TsDPEN **2** system, several successful catalysts based on Rh(III)/monotosylated diamines are derived from TsDAC **3**.[8,9] We therefore sought to prepare the 'tethered' catalyst **11** from this diamine. Following our procedure for the synthesis of **8**, monotosylated diamine *R,R*-**3** was reductively alkylated with aldehyde **12**[10] to give intermediate **13**. Upon reaction of **13** with $RhCl_3$ in methanol, catalyst **11** was formed and isolated in pure form by column chromatography on silica gel and recrystallisation. The ^1H-NMR spectrum of **11** exhibited a distinct pattern of four singlets from the methyl groups on the cyclopentadienyl ring with a fifth from the methyl of the tosyl group. An X-ray crystal structure of **11** was obtained which confirmed the expected structure (Fig. 1).[13]



11



12



13

Complex **11** proved to be an excellent catalyst for the reduction of a wide range of ketones in FA/TEA media (Scheme 1, Table 1). Reductions were generally complete within times as short as 30 min (for S/C = 200), although some substrates took longer to be fully reduced. In the majority of cases, the product e.e.s were over 90%,

---

[a] *Asymmetric Catalysis Group, Coventry, UK CV4 7AL. E-mail: m.wills@warwick.ac.uk; Fax: +44 24 7652 4112; Tel: +44 24 7652 3260*
[b] *X-ray Crystallography Unit, Department of Chemistry, The University of Warwick, Coventry, UK CV4 7AL*

† Electronic supplementary information (ESI) available: Experimental procedures and characterisation data for catalyst intermediates and reduction products. See DOI: 10.1039/b606288a

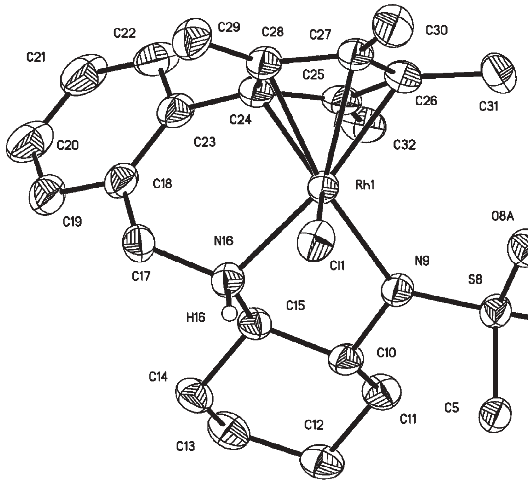
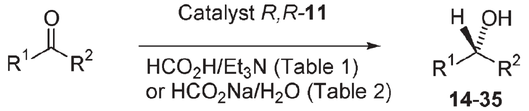


Fig. 1 X-Ray crystallographic structure of *R,R*-**11** (pTol replaced with Me, and hydrogen atoms removed, for clarity).



Scheme 1 Asymmetric reduction of ketones using *R,R*-**11**.

and in many cases higher than those we had previously observed with **8**. In the case of substrates not containing an *ortho*-substituent, e.e.s were consistently high (entries 1–4). *ortho*-Chloro acetophenone was reduced in 85% e.e., compared to 77% using **8**, whilst 2-(methoxy)acetophenone was reduced in 94% e.e. compared to 90% with **8**.

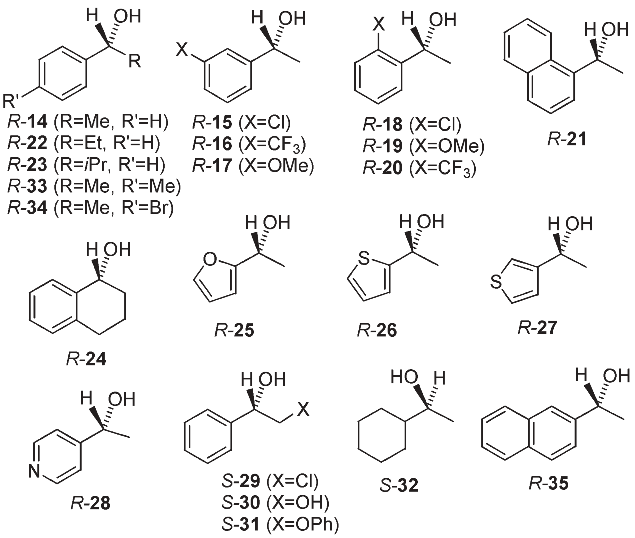
Although still moderate, the 62% e.e. for 2-(trifluoromethyl)-acetophenone represented a sharp improvement on that of 17% using **8**. The e.e.s of 96% and 75% for propiophenone and isobutyrophenone (entries 9 and 10), respectively, compare well to results obtained using other catalysts, including **8**. Tetralone was reduced in exceptionally high e.e. of 99.4%, a result comparable to that obtained using **8**. Heterocyclic ketones also proved to be excellent substrates: 2-acetylfuran gave a product of 98% e.e, 2-acetylthiophene 97% e.e, 3-acetylthiophene 93% e.e and 4-acetyl pyridine 95% e.e., respectively (entries 12–15).

Table 1 Ketone reductions in formic acid/triethylamine

Entry[a]	Product	Time[b]	Conversion	e.e. (*R*/*S*)
1	**14**	2 h	100%	96% *R*
2	**15**	1 h	100%	95% *R*
3	**16**	30 min	100%	96% *R*
4	**17**	4 h	99%	94% *R*
5	**18**	8 h	100%	85% *R*
6	**19**	22 h	100%	94% *R*
7	**20**	48 h	47%	62% *R*
8	**21**	48 h	99%	84% *R*
9	**22**	6 h	99%	96% *R*
10	**23**	48 h	27%	75% *R*
11	**24**	4 h	100%	99.4% *R*
12	**25**	3.5 h	100%	98% *R*
13	**26**	4.5 h	100%	97% *R*
14	**27**	8 h	99%	93% *R*
15	**28**	1.5 h	100%	95% *R*
16[c]	**29**	45 min	100%	96% *S*
17	**30**	2 h	100%	99.5% *S*
18	**31**	1 h	100%	92% *S*
19	**32**	26 h	96%	87% *S*

[a] Catalyst *R,R*-**11**, S/C = 200, 28 °C. [b] Time taken to reach conversion indicated. [c] S/C = 1000.

α-Substituted ketones are highly compatible with Rh(III) catalysts, as has been previously demonstrated. In this work, **11** reduced α-chloroacetophenone in 96% e.e. (catalyst loading lowered to 0.1 mol%), α-hydroxyacetophenone in 99.5% e.e. and α-phenoxy acetophenone in 92% e.e. A final significant result was the reduction of cyclohexylmethyl ketone in 87% e.e., representing one of the highest selectivities observed for this class of ketone. Of note was the observation that **32** was formed as the *S*-enantiomer. This represents a reverse in selectivity relative to the aryl/alkyl examples and mirrors our previous observation with catalyst **9**.[11a] These results again suggest that the reduction of alkyl/alkyl ketones by tethered catalysts operates through a predominantly sterically controlled mechanism. In our examples, we employed a typical catalyst loading of 0.5 mol%, however, this could be reduced to 0.1 mol% without loss of enantioselectivity.



Encouraged by these results, we extended our studies to the reduction of ketones in water.[14,15] In our tests, we employed sodium formate as the reducing agent. Again, the reactions were generally rapid and highly enantioselective (Scheme 1, Table 2). Again, consistently high enantiomeric excesses were obtained in reductions of relatively unhindered aryl/alkyl ketones (entries 1–7), with full conversions in reaction times of 3–6 h at a S/C of 200.

The reduction of *ortho*-substituted ketones was typically less selective (entry 8) although the challenging cyclohexyl/methyl ketone was reduced in 84% e.e., which again compares well with other methods for this substrate (entry 9). Again, the absolute configuration of the reduction product was reversed relative to the aryl/alkyl ketones. The most remarkable feature of the catalyst is, however, its longevity, since in all cases the catalyst loading could be lowered significantly without suffering deterioration of the e.e. This is illustrated for 2-acetylthiophene and -furan, respectively, in entries 10 through 14. In all cases, increasing the S/C from 200 (already twice that typically used for ATH catalysts in aqueous systems) to 1,000 and even as high as 10,000 necessitated longer reaction times but *without any decrease in* enantioselectivity.

Table 2 Ketone reductions using sodium formate in water

Entry[a]	Product	Time[b]	Conversion	e.e. (*R*/*S*)
1	**14**	3 h	100%	96% *R*
2	**16**	3 h	100%	96% *R*
3	**33**	3 h	100%	94% *R*
4	**34**	3 h	100%	93% *R*
5	**17**	3 h	98%	97% *R*
6	**22**	4 h	100%	96% *R*
7	**35**	6 h	98%	91% *R*
8	**20**	8 h	96%	51% *R*
9	**32**	24 h	100%	84% *S*
10	**26**	1.5 h	100%	97% *R*
11[c]	**26**	5 h	100%	97% *R*
12	**25**	1 h	100%	98% *R*
13[c]	**25**	4 h	100%	98% *R*
14[d]	**25**	7 days	100%	98% *R*
15[c]	**16**	16 h	100%	97% *R*

[a] Catalyst *R,R*-**11**, S/C = 200, 28 °C. [b] Time taken to reach conversion indicated. [c] S/C = 1,000. [d] =S/C = 10 000.

These results highlight the high stability of tethered catalyst **11**, which can continue to turnover a reaction at exceptionally low loading in the face of virtually zero background reaction. We believe that this is one of the first examples of a Rh(III) transfer hydrogenation system in which the catalyst loadings can be decreased to levels typically associated with the best of pressure hydrogenation catalysts.

We thank the EPSRC for generous support of this work through postdoctoral funding (to DJM) and Doctoral Training Funds (to DSM). Dr B. Stein of the EPSRC MS service at Swansea is thanked for HRMS analysis of certain compounds. The use of the EPSRC Chemical Database Service at Daresbury is acknowledged.[16] We thank Arran Chemicals for donation of homochiral diamines.

Notes and references

1 (*a*) M. J. Palmer and M. Wills, *Tetrahedron: Asymmetry*, 1999, **10**, 2045; (*b*) R. Noyori and S. Hashiguchi, *Acc. Chem. Res.*, 1997, **30**, 97; (*c*) S. E. Clapham, A. Hadzovic and R. H. Morris, *Coord. Chem. Rev.*, 2004, **248**, 2201; (*d*) S. Gladiali and E. Alberico, *Chem. Soc. Rev.*, 2006, **35**, 226; (*e*) T. Ikariya, K. Murata and R. Noyori, *Org. Biomol. Chem.*, 2006, **4**, 393; (*f*) J. S. M. Samec, J.-M. Backvall, P. G. Andersson and P. Brandt, *Chem. Soc. Rev.*, 2006, **35**, 237.

2 (*a*) J. Takehara, S. Hashiguchi, A. Fujii, S.-I. Inoue, T. Ikariya and R. Noyori, *Chem. Commun.*, 1996, 233; (*b*) M. Yamakawa, I. Yamada and R. Noyori, *Angew. Chem., Int. Ed.*, 2001, **40**, 2818.

3 (*a*) M. J. Palmer, T. Walsgrove and M. Wills, *J. Org. Chem.*, 1997, **62**, 5226; (*b*) M. J. Palmer, J. A. Kenny, T. Walsgrove, A. M. Kawamoto and M. Wills, *J. Chem. Soc., Perkin Trans. 1*, 2002, 416; (*c*) R. V. Wisman, J. G. de Vriue, B.-J. Deelman and H. J. Heeres, *Org. Process Res. Dev.*, 2006, **10**, 423; (*d*) K. B. Hansen, J. R. Chilenski, R. Desmond, P. N. Devine, E. J. J. Grabowski, R. Heid, M. Kubryk, D. J. Mathre and R. Varsolona, *Tetrahedron: Asymmetry*, 2003, **14**, 3581; (*e*) J. W. Faller and A. R. Lavoie, *Organometallics*, 2002, **21**, 2010; (*f*) K. Everaere, A. Mortreux, M. Bulliard, J. Brussee, A. van der Gen, G. Nowogrocki and J. F. Carpentier, *Eur. J. Org. Chem.*, 2001, 275; (*g*) D. A. Alonso, S. J. M. Nordin, P. Roth, T. Tarnai and P. G. Andersson, *J. Org. Chem.*, 2000, **65**, 3116; (*h*) M. Hennig, K. Puntener and M. Scalone, *Tetrahedron: Asymmetry*, 2000, **11**, 1849; (*i*) P. Brandt, P. Roth and P. G. Andersson, *J. Org. Chem.*, 2004, **69**, 4885.

4 J. Blacker and J. Martin, Scale up studies in Asymmetric Transfer Hydrogenation, in *Asymmetric Catalysis on an Industrial Scale: Challenges, Approaches and Solutions*, ed. H. U. Blaser, E. Schmidt, Wiley, 2004, pp. 201–216.

5 X. Sun, G. Manos, J. Blacker, J. Martin and A. Gavriilidis, *Org. Process Res. Dev.*, 2004, **8**, 909.

6 (*a*) S. Hashiguchi, A. Fujii, J. Takehara, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 7562; (*b*) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 2521; (*c*) K. J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya and R. Noyori, *Angew. Chem.*, 1997, **109**, 297; *Angew. Chem., Int. Ed.*, 1997, **36**, 285; (*d*) M. Watanabe, K. Murata and T. Ikariya, *J. Org. Chem.*, 2002, **67**, 1712; (*e*) K. Murata, K. Okano, M. Miyagi, H. Iwane, R. Noyori and T. Ikariya, *Org. Lett.*, 1999, **1**, 1119; (*f*) K. Matsumura, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1997, **119**, 8738.

7 (*a*) M. Li, J. Scott and G. A. O'Doherty, *Tetrahedron Lett.*, 2004, **45**, 1005; (*b*) J. A. Marshall and K. Ellis, *Tetrahedron Lett.*, 2004, **45**, 1351; (*c*) I. C. Lennon and J. A. Ramsden, *Org. Process Res. Dev.*, 2005, **9**, 110; (*d*) H. Yamashita, T. Ohtani, S. Morita, K. Otsubo, K. Kan, J. Matsubara, K. Kitano, Y. Kawano, M. Uchida and F. Tabusa, *Heterocycles*, 2002, **56**, 123; (*e*) M. Miyagi, J. Takehara, S. Collet and K. Okano, *Org. Process Res. Dev.*, 2000, **4**, 346; (*f*) J. Cossrow and S. Rychnovsky, *Org. Lett.*, 2002, **4**, 147; (*g*) Y. Yamano, Y. Watanabe, N. Watanabe and M. Ito, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2833; (*h*) M. Mogi, K. Fuji and M. Node, *Tetrahedron: Asymmetry*, 2004, **15**, 3715; (*i*) I. C. Lennon and J. A. Ramsden, *Org. Process Res. Dev.*, 2005, **9**, 110; (*j*) K. Maki, R. Motoki, K. Fujii, M. Kanai, T. Kobayashi and M. Shibasaki, *J. Am. Chem. Soc.*, 2005, **127**, 17111; (*k*) J. A. Kenny, M. J. Palmer, A. R. C. Smith, T. Walsgrove and M. Wills, *Synlett*, 1999, 1615; (*l*) A. M. Kawamoto and M. Wills, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1916; (*m*) N. J. Alcock, I. Mann, P. Peach and M. Wills, *Tetrahedron: Asymmetry*, 2002, **13**, 2485.

8 (*a*) K. Mashima, T. Abe and K. Tani, *Chem. Lett.*, 1998, 1199; (*b*) K. Murata, T. Ikariya and R. Noyori, *J. Org. Chem.*, 1999, **64**, 2186; (*c*) K. Mashima, T. Abe and K. Tani, *Chem. Lett.*, 1998, 1201; (*d*) T. Hamada, T. Torii, K. Izawa, R. Noyori and T. Ikariya, *Org. Lett.*, 2002, **4**, 4373; (*e*) T. Hamada, T. Torii, K. Izawa and T. Ikariya, *Tetrahedron*, 2004, **60**, 7411; (*f*) T. Hamada, T. Torii, T. Onishi, T. ??, K. Izawa and T. Ikariya, *J. Org. Chem.*, 2004, **69**, 7391.

9 (*a*) D. J. Cross, J. A. Kenny, I. Houson, L. Campbell, T. Walsgrove and M. Wills, *Tetrahedron: Asymmetry*, 2001, **12**, 1801; (*b*) K. Polborn and K. Severin, *Eur. J. Org. Chem.*, 2000, **65**, 1687; (*c*) D. Sterk, M. S. Stephan and B. Mohar, *Tetrahedron: Asymmetry*, 2002, **13**, 2605; (*d*) M. Zaidlezicz, A. Tafelska-Kaczmarek and A. Prewysz-Kwinto, *Tetrahedron: Asymmetry*, 2005, **16**, 3205.

10 D. M. Matharu, D. J. Morris, A. M. Kawamoto, G. J. Clarkson and M. Wills, *Org. Lett.*, 2005, **7**, 5489.

11 (*a*) A. M. Hayes, D. J. Morris, G. J. Clarkson and M. Wills, *J. Am. Chem. Soc.*, 2005, **127**, 7318; (*b*) J. Hannedouche, G. J. Clarkson and M. Wills, *J. Am. Chem. Soc.*, 2004, **126**, 986; (*c*) F. K. Cheung, A. M. Hayes, J. Hannedouche, A. S. Y. Yim and M. Wills, *J. Org. Chem.*, 2005, **70**, 3188.

12 D. J. Cross, I. Houson, A. M. Kawamoto and M. Wills, *Tetrahedron Lett.*, 2004, **45**, 843.

13 Crystal data for *R,R*-**11**; $C_{29}H_{36}N_2O_2Cl$, M = 615.02, orange block, 0.40 × 0.30 × 0.08 mm, Orthorhombic, $P2(1)2(1)2(1)$ (No 19), a = 10.0963(12), b = 13.7861(16), c = 19.923(2) Å, T = 180 K , μ(Mo-Kα) = 0.077 mm^{-1}, U = 2773.1(6) Å^3, Z 4, D_{cal} = 1.473 g cm^{-3}, 27747 reflections measured, 6969 unique [R_{int} = 0.0312]. Final residuals for 327 parameters were R_1 [$I > 2\sigma(I)$] = 0.0294, wR_2 [$I > 2\sigma(I)$] = 0.0712 and R_1 = 0.0309, wR_2 = 0.0718 for all 6969 data. CCDC 603515. For crystallographic data in CIF format or other electronic format see DOI: 10.1039/b606288a.

14 (*a*) X. Li, X. Wu, W. Hems, W. Chen, F. E. Hancock, F. King and J. Xiao, *Org. Lett.*, 2004, **6**, 3321; (*b*) X. Wu, X. Li, F. King and J. Xiao, *Angew. Chem., Int. Ed.*, 2005, **44**, 3407; (*c*) X. Wu, X. Li, W. Hems, F. King and J. Xiao, *Org. Biomol. Chem.*, 2004, **2**, 1818; (*d*) P. Liu, N. J. G. Deng, Y. Q. Tu and S. H. Wang, *Chem. Commun.*, 2004, 2070; (*e*) T. Thorpe, J. Blacker, S. M. Brown, C. Bubert, J. Crosby, S. Fitzjohn, J. P. Muxworthy and J. M. J. Williams, *Tetrahedron Lett.*, 2001, **42**, 4037; (*f*) J. Mao, B. Wan, F. Wu and S. Lu, *Tetrahedron Lett.*, 2005, **46**, 7341; (*g*) H. Y. Rhyoo, H.-J. Park, W. H. Suh and Y. K. Chung, *Tetrahedron Lett.*, 2002, **43**, 269; (*h*) F. Wang, H. Liu, L. Cun, J. Zhu, J. Deng and Y. Jiang, *J. Org. Chem.*, 2005, **70**, 9424; (*i*) X. Wu, X. Li, M. McConville, O. Saidi and J. Xiao, *J. Mol. Catal. A: Chem.*, 2006, **247**, 153.

15 (*a*) X. Wu, D. Vinci, T. Ikariya and J. Xiao, *Chem. Commun.*, 2005, 4447; (*b*) T. Thorpe, J. Blacker, S. M. Brown, C. Bubert, J. Crosby, S. Fitzjohn, J. P. Muxworthy and J. M. J. Williams, *Tetrahedron Lett.*, 2001, **42**, 4041.

16 D. A. Fletcher, R. F. McMeeking and D. Parkin, *J. Chem. Inf. Comput. Sci.*, 1996, **36**, 746.