Tetrahedron: *Asymmetry* 19 (2008) 1250–1255

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: http://www.elsevier.com/locate/tetasy

Synthesis of a series of novel *N,N*-dialkyl-TsDPEN ligands and their application to enantioselective addition of dialkylzinc to benzaldehyde

José E. D. Martins, Martin Wills *

Department of Chemistry, The University of Warwick, Coventry, CV4 7AL, UK

ARTICLE INFO

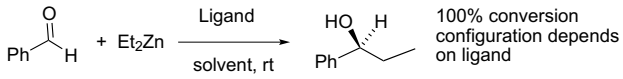
Article history:
Received 8 April 2008
Accepted 16 April 2008
Available online 26 May 2008

ABSTRACT

A series of mono- and dialkylated derivatives of *C*2-symmetric *N*-tosyl-1,2-diphenylethylene diamines have been prepared and used as ligands for the enantiomeric control of the addition of diethylzinc to aldehydes. Addition products of up to 79% ee were formed.

1. Introduction

The addition of dialkylzincs to aldehydes (Scheme 1) is a well-established synthetic reaction, which provides a means for the preparation of secondary alcohols in high enantioselectivities. Ligands (Fig. 1) which have been reported for this application include homochiral 1,2-, 1,3- and 1,4-aminoalcohols such as **1**–**4**, and also diamines and disulfonylated compounds.[1–3] The observation of non-linear chirality transfer effects when using DAIB **1** led to the identification of a mechanism which involved the formation of dimeric ligand/zinc intermediate. The high stability of the *meso* dimer led to enrichment of the active catalytic reagent in situ.[3a–c] Whilst it is possible to achieve high enantioselectivities in this reaction through the use of a wide range of chiral amino alcohols, disulfonylated derivatives are more frequently employed as titanium(IV) complexes for optimum results.[4]



Scheme 1. Asymmetric addition of diethylzinc to aldehydes.

The use of diamine **5** gave an addition product in 80% ee; other derivatives of the diamine were more effective.[2d,e] The titanium(IV) complex **6**, of a *C*2-symmetric bistrifluoromethylsulfonamide **7**, catalyzed the addition of alkylzincs to aldehydes in excellent enantioselectivity, and was more efficient than the use of the ligand alone.[4b–d]

A large number of examples of N,N′-disulfonylated derivatives of *C*2-symmetric diamines, including 1,2-diphenylethylene-1,2-diamine **8**,[4h] have now been tested in dialkylzinc additions,[4] and this area has been extensively reviewed.[1,4b,c] Detailed studies of

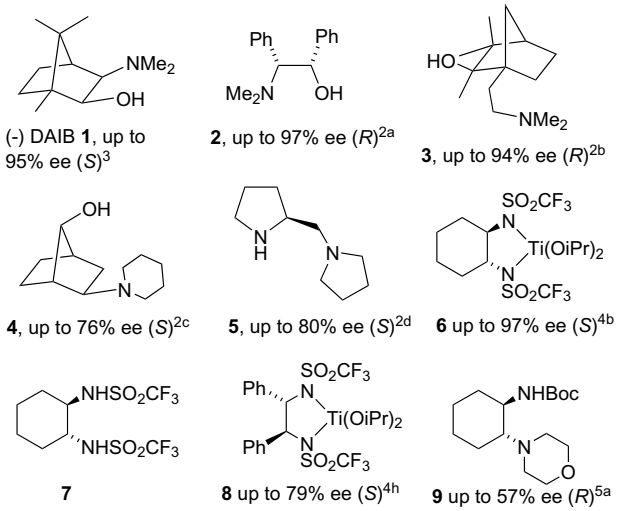


Figure 1. Representative ligands used in diethylzinc addition reactions.

second order effects have been reported, leading to methods for asymmetric amplification.[4g]

Although the ditosylated diamine derivatives have been extensively researched, the use of unsulfonylated diamines is less well established, although there are a number of reports in the literature on the use of these as catalysts,[1] including some recent examples.[5a,b] A paper by Rebolledo[5a] concluded that N,N-dialkylated-N′-acylated (or carboxylated) derivatives of *C*2-symmetric diamines such as **9** were effective catalysts for diethylzinc addition to benzaldehyde, although the best results were obtained using dimeric derivatives of the ligands.[4a]

Despite the many diamines which have been tested in diethylzinc addition reactions, we were not aware of any investigations on derivatives which contained a combination of a monosulfonylated amine and a basic amine, that is, which combine features of both

* Corresponding author. Tel.: +44 24 7642 3260; fax: +44 24 7652 4112.
E-mail address: m.wills@warwick.ac.uk (M. Wills).

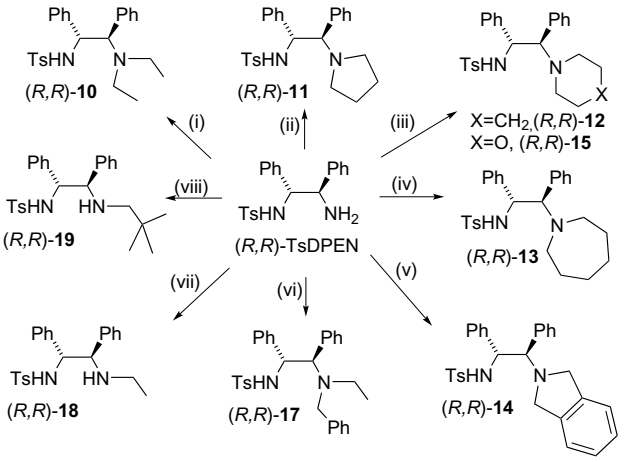
0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.04.020

sets of known ligands. In order to establish whether such derivatives might be effective, in this work we prepared a series of candidate ligands from readily available *N*-tosyl-1,2-diphenylethylene-1,2-diamine (TsDPEN), a popular ligand for asymmetric transfer hydrogenation, which is commercially available in either enantiomeric form,[6] and evaluated them as catalysts in the asymmetric addition of diethylzinc to benzaldehyde.

2. Results and discussion

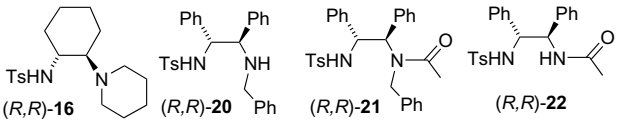
A search of the literature revealed very little work on the synthesis of monotosylated DPEN derivatives containing a tertiary basic amine group. Nagao et al. have reported the synthesis of N-sulfonylated, N′,N′-dimethylated derivatives of homochiral DPEN in enantioselective acyl transfer reactions; however, this appears to be the major catalytic application of such reagents to be reported to date.[7] In contrast, several examples of monotosylated DPENs containing secondary basic amines have been reported.[8] These include their use as ligands in Ru(II) complexes for asymmetric catalysis of reduction reactions,[8a–c] Fe-catalyzed epoxidation[8d] and silacycle-catalyzed Diels–Alder reactions.[8e]

Ligands **10**–**15** and **17** were identified as a diverse range of derivatives of the class of ligand we wished to investigate, that is, TsDPEN derivatives containing a tertiary amine basic group. In addition, the analogous 1,2-diaminocyclohexane derivative **16** and secondary amine derivatives **18** and **19** were also prepared for purposes of comparison. Ligand **12** was prepared in both enantiomerically pure forms from the precursor tosylated diamine. The ligands were prepared following the methods illustrated in Scheme 2 and are, with the exception of **18**,[8c] novel compounds.

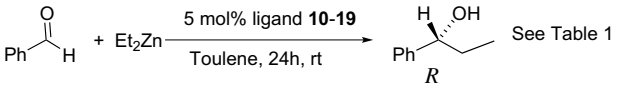


Scheme 2. Synthesis of ligands. Reagents and conditions: (i) CH_3CHO, AcOH, $NaBH_3CN$, MeOH, 74%; (ii) 1,4-diiodobutane, K_2CO_3, MeOH, reflux, 63%; (iii) X = CH_2, 1,5-diiodopentane, K_2CO_3, MeOH, reflux, 68%, X = O, di(2-iodoethyl)ether, K_2CO_3, MeOH, reflux, 52%; (iv) 1,6-diiodohexane, K_2CO_3, MeOH, reflux, 65%; (v) phthaldialdehyde, AcOH, $NaBH_3CN$, MeOH, 53%; (vi) (a) PhCHO, $NaBH_3CN$, MeOH, 88%; (b) CH_3COCl, Et_3N, DCM, 93%; (c) $LiAlH_4$, THF, reflux, 54%; (vii) (a) CH_3COCl, Et_3N, DCM, quant; (b) $LiAlH_4$, THF, reflux, 75%; (viii) trimethylacetaldehyde, AcOH $NaBH_3CN$, MeOH, 77%.

Ligands **11**–**13**, **15** and **16** were efficiently prepared by substitution of the appropriate dielectrophile by the basic nitrogen of TsDPEN, whilst **10**, **14** and **19** were formed by reductive amination with aldehydes using sodium cyanoborohydride as the reducing agent. Ligand **17** was prepared by a three-step process, via benzylation to give **20**, then acylation to **21** and finally reduction with lithium aluminium hydride. Ligand **18** was formed via **22** followed by reduction. In all cases, the ligands were formed in good to excellent yields and were fully characterized.



With a diverse range of ligands in hand, we then examined the use of each of them in the ethylation of benzaldehyde, which is known to be a useful prototype reaction for comparison with other catalysts (Scheme 3, Table 1). Each of the ligands proved to be effective at promoting the addition reaction; however, the best results in terms of both conversion and ee were obtained with those containing a tertiary amine within a heterocyclic ring. The highest ee (79%, *R*) was obtained using the azepan derivative **13**, in quantitative yield. Ligands containing acyclic substituents at the basic amine did not give quantitative yields, although the less hindered ligand **10** gave a product in higher conversion than **17**. The cyclohexane-derived ligand **16** gave a product in lower ee than the analogous TsDPEN-derived diamine.



Scheme 3. Asymmetric addition of diethylzinc to benzaldehyde catalyzed by ligands **10**–**19**.

Table 1
Results of asymmetric benzaldehyde ethylation catalyzed by **10**–**19**[a]

Ligand	Yield (%)	ee[a] (%)	*R*/*S*[a]
(*R*,*R*)-**10**	96	68	(*R*)
(*R*,*R*)-**11**	100	65	(*R*)
(*R*,*R*)-**12**	100	77	(*R*)
(*S*,*S*)-**12**	100	77	(*S*)
(*R*,*R*)-**13**	99	79	(*R*)
(*R*,*R*)-**14**	100	64	(*R*)
(*R*,*R*)-**15**	99	76	(*R*)
(*R*,*R*)-**16**	100	53	(*R*)
(*R*,*R*)-**17**	55	66	(*R*)
(*R*,*R*)-**18**	62	8	(*R*)
(*R*,*R*)-**19**	46	13	(*R*)

[a] Determined by GC analysis (Chrompac cyclodextrin-β-236M-19 50m), T = 115 °C, P = 15 psi, benzaldehyde: 6.0 min; 1-phenylpropanol: t_R (*R*) = 21.6 min, t_R (*S*) = 22.4 min.

The ligands containing a secondary basic amine were inferior in this application and delivered products in low yield and very low ee (only 8–13% for the two examples tested). It therefore appears that the presence of a tertiary basic amine is essential for optimum results in this application, which mirrors the results obtained using aminoalcohols as catalysts.

The results demonstrate that relatively simple dialkylated derivatives of TsDPEN are effective for the catalysis of benzaldehyde alkylation with diethylzinc. As regards the mechanism (Fig. 2), we anticipate that the active catalytic species is likely to be zinc complex such as **23** (which may reversibly dimerize), containing a 1:1 combination of Zn:ligand, and that this reacts with a further molecule of diethylzinc through a transition state similar to that depicted in **24**.

Assuming that co-ordination of the diethylzinc molecule is to the face of the metallocycle *trans* to the adjacent phenyl ring, together with π-stacking between the substrate arene and the further phenyl ring, delivery of an ethyl group to the exposed face of the aldehyde will deliver a product of correct configuration (*R*).

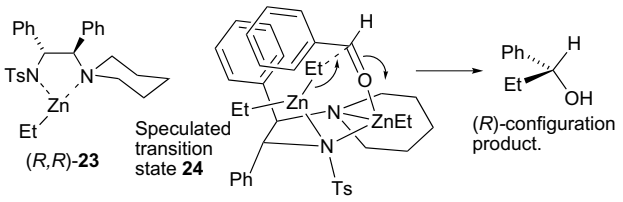


Figure 2. Proposed mechanism for Et_2Zn addition to benzaldehyde catalyzed by TsDPEN derivatives.

3. Conclusions

In conclusion, we have investigated the synthesis of a series of novel tertiary amine derivative of the popular TsDPEN chiral diamine and have found these to be effective in the control of the addition reaction of diethylzinc to benzaldehyde. The results are superior to those obtained using the secondary amine analogues. The ligands described in this paper are likely to be of value in other asymmetric catalytic applications, and studies of their applications continues.

4. Experimental

4.1. *N*-(2-Diethylamino-1,2-diphenyl-ethyl)-4-methyl-benzenesulfonamide (*R*,*R*)-10

To a stirred solution of (1*R*,2*R*)-TsDPEN (0.20 g, 0.54 mmol) and molecular sieves (1 g) in dried methanol (8 mL) was added acetaldehyde (0.06 mL, 1.2 mmol) followed by three drops of glacial acetic acid. The reaction was followed by TLC until the imine was formed (3 h) and then sodium cyanoborohydride (0.13 g, 2.2 mmol) was added, and the reaction mixture was left to stir overnight at room temperature. The molecular sieves were filtered through filter paper and the solution was concentrated under reduced pressure to remove the methanol. The residue was dissolved in chloroform (50 mL), washed with saturated $NaHCO_3$ solution (30 mL) and then dried over anhydrous $MgSO_4$. The solvent was removed to give a crude solid, which was purified by silica gel column chromatography (0→30% v/v ethyl acetate/hexane) to afford the product **10** as a white solid (0.17 g, 0.40 mmol, 74%). Mp 79–82 °C; $[\alpha]_D^{20} = +11.4$ (*c* 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1}: 3058, 3029, 2934, 2823, 1328, 1600, 1495, 1453, 1388, 1328, 1158, 1049, 937, 818, 725, 705; δ_H (300 MHz; $CDCl_3$)/ppm: 7.49–6.88 (15H, m, Ar-H + NH), 4.66 (1H, d, *J* 10.9 PhC*H*NHTs), 3.75 (1H, d, *J* 10.9 PhCHNR$_2$), 2.61 (2H, m, CH_2), 2.34 (3H, s, CH_3), 2.05 (2H, m, CH_2), 1.11 (6H, t, *J* 7.0 $2CH_3$). δ_C (75 MHz; $CDCl_3$)/ppm: 142.7, 138.5, 137.2, 133.2, 129.6, 128.9, 128.3, 128.2, 127.8, 127.6, 127.2, 127.0 (Ar-C), 68.6 (CH), 57.2 (CH), 42.6 ($2CH_2$), 21.4 (CH_3), 13.8 ($2CH_3$). HRMS calcd for $C_{25}H_{31}N_2SO_2$ $[M+H]^+$ 423.2096, found 423.2101 (1.1 ppm error).

4.2. *N*-(1,2-Diphenyl-2-pyrrolidin-1-yl-ethyl)-4-methyl-benzenesulfonamide (*R*,*R*)-11

To a stirred solution of (1*R*,2*R*)-TsDPEN (0.1 g, 0.27 mmol) and potassium carbonate (0.09 g, 0.7 mmol) in acetonitrile (2 mL) was added 1,4-diiodobutane (0.04 mL, 0.31 mmol), and the reaction mixture was left to stir overnight under reflux. The reaction mixture was filtered in filter paper and the acetonitrile was evaporated under reduced pressure. The residue was dissolved in chloroform (20 mL), washed with water (20 mL) and then dried over anhydrous $MgSO_4$. The solvent was removed to afford the product **11** as a white solid, which was purified by silica gel column chromatography (0→30% v/v ethyl acetate/hexane) to afford the product as a white solid (0.072 g, 0.17 mmol, 63%). Mp 116–119 °C; $[\alpha]_D^{20} = -1.6$ (*c* 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1}: 3286, 3029, 2905, 1599, 1494, 1454, 1439, 1321, 1152, 1094, 1063, 936, 812, 762, 697, 662; δ_H (300 MHz; $CDCl_3$)/ppm: 7.52–6.88 (15H, m, Ar-H + NH), 4.60 (1H, d, *J* 10.6 PhC*H*NHTs), 3.81 (1H, d, *J* 10.6 PhCHNR$_2$), 2.40–2.24 (7H, m, $2CH_2$ and CH_3 singlet overlapping at 2.33), 1.62 (4H, m, $2CH_2$). δ_C (75 MHz; $CDCl_3$)/ppm: 142.2, 137.8, 136.5, 131.2, 129.4, 128.4, 127.6, 127.1, 127.0, 126.6, 126.4 (Ar-C), 68.7 (CH), 57.6 (CH), 46.7 (CH_2), 22.0 (CH_2), 20.8 (CH_3). HRMS calcd for $C_{25}H_{28}N_2O_2S$ $[M+H]^+$ 421.1940, found 421.1994 (12.0 ppm error).

4.3. *N*-(1,2-Diphenyl-2-piperidin-1-yl-ethyl)-4-methyl-benzenesulfonamide (*R*,*R*)-12

To a stirred solution of (1*R*,2*R*)-TsDPEN (0.2 g, 0.54 mmol) and potassium carbonate (0.19 g, 1.4 mmol) in acetonitrile (3 mL) was added 1,5-diiodobutane (0.09 mL, 0.62 mmol), and the reaction mixture was left to stir overnight under reflux. The reaction mixture was filtered in filter paper and the acetonitrile was evaporated under reduced pressure. The residue was dissolved in chloroform (30 mL), washed with water (25 mL) and then dried over anhydrous $MgSO_4$. The solvent was removed to afford the product **12** as a white solid, which was purified by silica gel column chromatography (0→30% v/v ethyl acetate/hexane) to afford the product as a white solid (0.16 g, 0.37 mmol, 68%). Mp 108–110 °C; $[\alpha]_D^{20} = +3.3$ (*c* 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1}: 3279, 3029, 2935, 2858, 2807, 1600, 1492, 1455, 1347, 1334, 1303, 1200, 1150, 1090, 1061, 932, 811, 793, 760, 697, 660; 7.52–6.88 (15H, m, Ar-H + NH), 7.56–6.88 (14H, m, Ar-H), 4.61 (1H, d, *J* 11.0 PhC*H*NHTs), 3.52 (1H, d, *J* 11.0 PhCHNR$_2$), 2.36 (3H, s, CH_3), 2.23 (4H, m, $2CH_2$), 1.56 (4H, m, $2CH_2$), 1.28 (2H, m, CH_2). δ_C (75 MHz; $CDCl_3$)/ppm: 142.8, 138.5, 137.0, 132.1, 129.6, 129.0, 128.3, 127.6, 127.2, 127.0 (Ar-C), 74.6 (CH), 56.7 (CH), 26.4 (CH_2), 24.1 ($2CH_2$), 21.5 (CH_3). HRMS calcd for $C_{26}H_{31}N_2O_2S$ $[M+H]^+$ 435.2096, found 435.2130 (7.8 ppm error).

4.4. *N*-(1,2-Diphenyl-2-piperidin-1-yl-ethyl)-4-methyl-benzenesulfonamide (*S*,*S*)-12

To a stirred solution of (1*S*,2*S*)-TsDPEN (0.15 g, 0.4 mmol) and potassium carbonate (0.14 g, 1.0 mmol) in acetonitrile (3 mL) was added 1,5-diiodobutane (0.07 mL, 0.47 mmol), and the reaction mixture was left to stir overnight under reflux. The reaction mixture was filtered in filter paper and the acetonitrile was evaporated under reduced pressure. The residue was dissolved in chloroform (30 mL), washed with water (25 mL) and then dried over anhydrous $MgSO_4$. The solvent was removed to afford the product as a white solid, which was purified by silica gel column chromatography (0→30% v/v ethyl acetate/hexane) to afford the product **12** as a white solid (0.086 g, 0.19 mmol, 58%). Mp 108–110 °C; $[\alpha]_D^{25} = -3.3$ (*c* 0.5, $CHCl_3$). ν_{max} (neat)/cm^{-1}: 3279, 3031, 2933, 2853, 2807, 1598, 1494, 1453, 1349, 1334, 1303, 1202, 1151, 1090, 1056, 1028, 933, 812, 794, 759, 697, 657; δ_H (300 MHz; $CDCl_3$)/ppm: 7.52–6.88 (15H, m, Ar-H + NH), 4.61 (1H, d, *J* 11.0 PhC*H*NHTs), 3.52 (1H, d, *J* 11.0 PhCHNR$_2$), 2.36 (3H, s, CH_3), 2.23 (4H, m, $2CH_2$), 1.56 (4H, m, $2CH_2$), 1.28 (2H, m, CH_2). δ_C (75 MHz; $CDCl_3$)/ppm: 142.8, 138.5, 137.0, 132.1, 129.6, 129.0, 128.3, 127.6, 127.2, 127.0 (Ar-C), 74.6 (CH), 56.7 (CH), 26.4 (CH_2), 24.1 ($2CH_2$), 21.5 (CH_3). HRMS calcd for $C_{30}H_{30}N_2NaO_3S$ $[M+H]^+$ 435.2096, found 435.2114 (4.1 ppm error).

4.5. *N*-(2-Azepan-1-yl-1,2-diphenyl-ethyl)-4-methyl-benzenesulfonamide (*R*,*R*)-13

To a stirred solution of (1*R*,2*R*)-TsDPEN (0.2 g, 0.54 mmol) and potassium carbonate (0.15 g, 1.1 mmol) in acetonitrile (3 mL) was added 1,6-diiodohexane (0.10 mL, 0.65 mmol), and the reaction

mixture was left to stir overnight under reflux. The reaction mixture was filtered in filter paper and the acetonitrile was evaporated under reduced pressure. The residue was dissolved in chloroform (25 mL), washed with water (20 mL) and then dried over anhydrous $MgSO_4$. The solvent was removed to afford the crude product, which was purified by silica gel column chromatography (0→20% v/v ethyl acetate/hexane) to afford the product **13** as a clear oil (0.16 g, 0.36 mmol, 65%). $[\alpha]_D^{20} = +39$ (*c* 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1}: 3030, 2923, 2853, 1599, 1495, 1453, 1312, 1151, 1091, 1077, 1056, 931, 810, 754, 696, 664; δ_H (300 MHz; $CDCl_3$)/ppm: 7.47–6.86 (15H, m, Ar-H + NH), 4.64 (1H, d, *J* 10.9, PhC*H*NHTs), 3.63 (1H, d, *J* 10.9, $PhCHNR_2$), 2.54 (2H, m, CH_2), 2.42 (2H, m, CH_2), 2.33 (3H, s, CH_3), 1.73–1.52 (8H, m, $4CH_2$). δ_C (75 MHz; $CDCl_3$)/ppm: 142.6, 138.1, 137.2, 133.6, 129.4, 128.9, 128.4, 127.7, 127.6, 127.2, 127.0 (Ar-C), 75.0 (CH), 57.5 (CH), 51.3 ($2CH_2$), 29.0 ($2CH_2$), 26.5 ($2CH_2$), 21.4 (CH_3). HRMS calcd for $C_{27}H_{33}N_2O_2S$ $[M + H]^+$ 449.2252, found 449.2268 (3.5 ppm error).

4.6. *N*-[2-(1,3-Dihydro-isoindol-2-yl)-1,2-diphenyl-ethyl]-4-methyl-benzenesulfonamide (*R*,*R*)-14

To a stirred solution of (1*R*,2*R*)-TsDPEN (0.20 g, 0.54 mmol) and molecular sieves (1 g) in dried methanol (6 mL) was added phthaldialdehyde (0.08 g, 0.60 mmol) followed by 3 drops of glacial acetic acid. The reaction was followed by TLC until the imine was formed (4 h) and then sodium cyanoborohydride (0.13 g, 2.1 mmol) was added, and the reaction mixture was left to stir overnight at room temperature. The molecular sieves were filtered through filter paper and the solution was concentrated under reduced pressure to remove the methanol. The residue was dissolved in chloroform (30 mL), washed with saturated $NaHCO_3$ solution (20 mL) and then dried over anhydrous $MgSO_4$. The solvent was removed to give a crude solid, which was purified by silica gel column chromatography (0→30% v/v ethyl acetate/hexane) to afford the product **14** as a light yellow solid (0.13 g, 0.27 mmol, 53%). Mp 69–72 °C; $[\alpha]_D^{23} = +16.5$ (*c* 0.2, $CHCl_3$); ν_{max} (neat)/cm^{-1}: 3029, 2802, 1598, 1494, 1453, 1320, 1152, 1091, 932, 811, 743, 700, 663; δ_H (300 MHz; $CDCl_3$)/ppm: 7.50–6.94 (19H, m, Ar-H + NH), 4.77 (1H, d, *J* 10.1, PhC*H*NHTs), 4.00 (1H, d, *J* 10.1, $PhCHNR_2$), 3.91 (2H, d, *J* 10.5, NCH_aH_b), 3.75 (2H, d, *J* 10.5, NCH_aH_b), 2.35 (3H, s, CH_3). δ_C (75 MHz; $CDCl_3$)/ppm: 142.2, 138.2, 137.5, 136.6, 132.0, 129.3, 128.5, 127.7, 127.5, 127.2, 127.1, 126.7, 126.6, 126.2, 121.6 (Ar-C), 69.2 (CH), 57.6 (CH), 52.6 ($2CH_2$), 20.9 (CH_3). HRMS calcd for $C_{29}H_{29}N_2SO_2$ $[M+H]^+$ 469.1940, found 469.1982 (8.9 ppm error).

4.7. 4-Methyl-*N*-(2-morpholin-4-yl-1,2-diphenyl-ethyl)-benzenesulfonamide (*R*,*R*)-15

To a stirred solution of (1*R*,2*R*)-TsDPEN (0.2 g, 0.54 mmol) and potassium carbonate (0.15 g, 1.1 mmol) in acetonitrile (3 mL) was added 2-iodoethylether (0.09 mL, 0.65 mmol), and the reaction mixture was left to stir overnight under reflux. The reaction mixture was filtered in filter paper and the acetonitrile was evaporated under reduced pressure. The residue was dissolved in chloroform (25 mL), washed with water (20 mL) and then dried over anhydrous $MgSO_4$. The solvent was removed to afford the crude product **15**, which was purified by silica gel column chromatography (0→30% v/v ethyl acetate/hexane) to afford the product as a light yellow solid (0.12 g, 0.28 mmol, 52%). Mp 147–149 °C; $[\alpha]_D^{20} = +12.7$ (*c* 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1}: 3196, 3032, 2918, 2852, 1598, 1495, 1454, 1390, 1325, 1151, 1114, 1092, 999, 931, 867, 800, 750, 697, 661; δ_H (300 MHz; $CDCl_3$)/ppm: 7.53–6.88 (15H, m, Ar-H + NH), 4.69 (1H, d, *J* 11.0, PhC*H*NHTs), 3.65 (4H, m, $2CH_2$), 3.54 (1H, d, *J* 11.0, $PhCHNR_2$), 2.34 (3H, s, CH_3), 2.28 (4H, m, $2CH_2$). δ_C (75 MHz; $CDCl_3$)/ppm: 143.0, 138.0, 137.0, 131.3, 129.6, 129.1, 128.3, 128.0, 127.9, 127.7, 127.2 (Ar-C), 74.1 (CH), 67.1 ($4CH_2$), 56.5 (CH), 21.4 (CH_3). HRMS calcd for $C_{25}H_{29}N_2O_3S$ $[M+H]^+$ 437.1889, found 437.1894 (1.1 ppm error).

4.8. 4-Methyl-*N*-(2-piperidin-1-yl-cyclohexyl)-benzenesulfonamide (*R*,*R*)-16

To a stirred solution of (1*R*,2*R*)-(−)-*N*-*p*-tosyl-1,2-cyclohexanediamine (0.2 g, 0.74 mmol) and potassium carbonate (0.26 g, 2.0 mmol) in acetonitrile (3 mL) was added 1,5-diiodobutane (0.13 mL, 0.86 mmol), and the reaction mixture was left to stir overnight under reflux. The reaction mixture was filtered in filter paper and the acetonitrile was evaporated under reduced pressure. The residue was dissolved in chloroform (30 mL), washed with water (25 mL) and then dried over anhydrous $MgSO_4$. The solvent was removed to afford the product **16** as a white solid, which was purified by silica gel column chromatography (0→30% v/v ethyl acetate/hexane) to afford the product as a white solid (0.15 g, 0.44 mmol, 58%). Mp 82–84 °C; $[\alpha]_D^{20} = -92$ (*c* 1, $CHCl_3$); ν_{max} (neat)/cm^{-1}: 3195, 2919, 2854, 1598, 1493, 1401, 1345, 1319, 1163, 1066, 952, 904, 810, 768, 689; δ_H (300 MHz; $CDCl_3$)/ppm: 7.76 (2H, d, *J* 8.2 Ar-H), 7.30 (2H, d, *J* 7.9 Ar-H), 2.62 (1H, m, CH), 2.09 (5H, m, NH + $2CH_2$), 1.72 (4H, m, $2CH_2$), 1.44–0.78 (10H, $5CH_2$). δ_C (75 MHz; $CDCl_3$)/ppm: 143.1, 136.6, 129.4, 127.2 (Ar-C), 67.3 (CH), 53.3 (CH), 32.7 (CH_2), 26.5 (CH_2), 25.3 (CH_2), 24.5 (CH_2), 24.2 (CH_2), 22.6 (CH_2), 21.5 (CH_3). HRMS calcd for $C_{18}H_{29}N_2O_2S$ $[M+H]^+$ 337.1940, found 337.1952 (3.5 ppm error).

4.9. *N*-(2-Benzylamino-1,2-diphenyl-ethyl)-4-methyl-benzenesulfonamide (*R*,*R*)-20[8d]

To a stirred solution of (1*R*,2*R*)-TsDPEN (0.30 g, 0.82 mmol) and molecular sieves (1 g) in dried methanol (8 mL) was added benzaldehyde (0.10 mL, 0.98 mmol) followed by three drops of glacial acetic acid. The reaction was followed by TLC until the imine was formed (3 h) and then sodium cyanoborohydride (0.15 g, 2.4 mmol) was added, and the reaction mixture was left to stir overnight at room temperature. The molecular sieves were filtered through filter paper and the solution was concentrated under reduced pressure to remove the methanol. The residue was dissolved in chloroform (50 mL), washed with saturated $NaHCO_3$ solution (30 mL) and then dried over anhydrous $MgSO_4$. The solvent was removed to give a crude solid, which was purified by silica gel column chromatography (0→30% v/v ethyl acetate/hexane) to afford the product **20** as a white solid (0.33 g, 0.72 mmol, 88%). Mp 136 −138 °C (lit.[8d] 139 °C); $[\alpha]_D^{20} = -33$ (*c* 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1}: 3247, 3027, 2847, 1601, 1493, 1454, 1438, 1332, 1275, 1261, 1159, 916, 840, 807, 763, 697, 671; δ_H (300 MHz; $CDCl_3$)/ppm: 7.40–6.88 (10H, m, Ar-H), 6.19 (1H, br s, NH), 4.31 (1H, d, *J* 7.8, PhC*H*NHTs), 3.68 (1H, d, *J* 7.8 PhC*H*NHBn), 3.61 (1H, d, *J* 13.2, CH_aH_b), 3.40 (1H, d, *J* 13.2, CH_aH_b), 2.30 (3H, s, CH_3), 1.80 (1H, br s, NH). δ_C (75 MHz; $CDCl_3$)/ppm: 142.7, 139.6, 138.8, 138.2, 136.9, 129.1, 128.5, 128.4, 128.0, 127.9, 127.6, 127.5, 127.3, 127.2, 127.1 (Ar-C), 66.8 (CH), 63.1 (CH), 50.8 (CH_2), 21.4 (CH_3). HRMS calcd for $C_{28}H_{29}N_2O_2S$ $[M+H]^+$ 457.1940, found 457.1944 (0.8 ppm error).

4.10. *N*-Benzyl-*N*-[1,2-diphenyl-2-(toluene-4-sulfonylamino)-ethyl]-acetamide (*R*,*R*)-21

(*R*,*R*)-**20** (0.12 g, 0.26 mmol) was dissolved in dichloromethane (4 mL) and then acetylchloride (0.022 mL, 0.3 mmol) and triethylamine (0.037 mL, 0.26 mmol) were added, and the reaction mixture was left to stir overnight at room temperature. The mixture was washed with water (10 mL), extracted with chloroform (3×15 mL) and then dried over anhydrous $MgSO_4$. The solvent was removed to afford the product as a yellow oil, which was puri-

fied by silica gel column chromatography (0→40% v/v ethyl acetate/hexane) to afford the product **21** as yellow oil (0.122 g, 0.24 mmol, 93% yield). Mp 42–44 °C; $[\alpha]_D^{25} = -46$ (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1}: 3030, 2924, 1733, 1619, 1495, 1454, 1416, 1327, 1157, 1092, 1061, 951, 930, 858, 809, 758, 728, 696, 666. δ_H (300 MHz; $CDCl_3$)/ppm: 7.42–6.66 (20H, m, Ar-H + NH), 5.16 (1H, dd, *J* 9.0, 10.0, PhC*H*NHTs), 4.72 (2H, AB system, *J* 18.0, $PhCH_2NR$), 2.25 (3H, s, CH_3), 2.10 (3H, s, CH_3), 1.25 (2H, s, CH_2). δ_C (75 MHz; $CDCl_3$)/ppm: 173.8 (C=O), 141.6, 137.8, 137.6, 136.5, 134.6, 129.0, 128.3, 127.8, 127.6, 127.4, 127.2, 126.5, 126.1, 126.0, 125.3 (Ar-C), 60.7 (CH), 58.0 (CH), 47.9 (CH_2), 22.0 (CH_3), 20.7 (CH_3). HRMS calcd for $C_{30}H_{30}N_2NaO_3S$ $[M+Na]^+$ 521.1864, found 521.1870 (1.1 ppm error).

4.11. *N*-[2-(Benzyl-ethyl-amino)-1,2-diphenyl-ethyl]-4-methyl-benzenesulfonamide (*R*,*R*)-17

To a stirred solution of (*R*,*R*)-**21** (0.1 g, 0.2 mmol) in dry THF (7 mL), a 2 M solution of $LiAlH_4$ (0.4 mL, 0.8 mmol) was added dropwise. The system was refluxed for 4 h and then 1 mL of water followed by 0.12 g (0.44 mmol) of Rochelle salt (Na/K tartarate) was added, and the reaction mixture was stirred for additional 2 h. The product was extracted with chloroform (3 × 15 mL) and the combined organic fractions were washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography (0→20% v/v ethyl acetate/hexane) to afford the product **17** as a white solid (0.05 g, 0.1 mmol, 54%). Mp 115–117 °C; $[\alpha]_D^{20} = -33$ (*c* 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1}: 3236, 3062, 3031, 2972, 2926, 2829, 1598, 1494, 1455, 1377, 1347, 1150, 1075, 1089, 1052, 933, 814, 761, 699, 666. δ_H (300 MHz; $CDCl_3$)/ppm: 7.45–6.78 (20H, m, Ar-H + NH), 4.74 (1H, d, *J* 10.9, PhC*H*NHTs), 3.86 (1H, d, *J* 13.6, CH_aH_b), 3.73 (1H, d, *J* 10.9, $PhCHNR_2$), 2.99 (1H, d, *J* 13.6, CH_aH_b), 2.53 (1H, m, CH_aH_b), 2.30 (3H, s, CH_3), 2.20 (1H, m, CH_aH_b), 1.19 (3H, *t* 7.0, CH_3). δ_C (75 MHz; $CDCl_3$)/ppm: 142.6, 138.5, 138.2, 137.1, 132.6, 129.9, 128.8, 128.7, 128.3, 127.9, 127.7, 127.6, 127.2, 127.0 (Ar-C), 67.6 (CH), 57.2 (CH), 53.2 (CH_2), 42.6 (CH_2), 21.4 (CH_3), 13.8 (CH_3). HRMS calcd for $C_{30}H_{33}N_2O_2S$ $[M+H]^+$ 485.2252, found 485.2259 (1.4 ppm error).

4.12. *N*-[1,2-Diphenyl-2-(toluene-4-sulfonylamino)-ethyl]-acetamide (*R*,*R*)-22

(1*R*,2*R*)-TsDPEN (0.5 g, 1.3 mmol) was dissolved in dichloromethane (10 mL) and then acetylchloride (0.1 mL, 1.5 mmol) and triethylamine (0.2 mL, 1.3 mmol) were added, and the reaction mixture was left to stir overnight at room temperature. The mixture was washed with water (20 mL), extracted with chloroform (3 × 30 mL) and then dried over anhydrous $MgSO_4$. The solvent was removed to afford the product **22** as a white solid (0.55 g, 1.3 mmol, quantitative yield). Mp 222–224 °C; $[\alpha]_D^{20} = +7$ (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1}: 3304, 3033, 1651, 1539, 1319, 1154, 1058, 1087, 922, 808, 696, 670; δ_H (300 MHz; $CDCl_3$)/ppm: 7.48–6.84 (15H, m, Ar-H + NH), 5.30 (1H, dd, *J* 8.0, 9.0, PhC*H*NHTs), 4.62 (1H, dd, *J* 9.0, 8.5, PhC*H*NHR), 2.27 (3H, s, CH_3), 2.07 (3H, s, CH_3). δ_C (75 MHz; $CDCl_3$)/ppm: 170.8 (C=O), 142.0, 138.3, 137.3, 137.2, 128.5, 127.7, 127.4, 127.0, 126.8, 126.9, 126.7, 126.1 (Ar-C), 62.4 (CH), 58.3 (CH), 22.6 (CH_3), 20.7 (CH_3). HRMS calcd for $C_{23}H_{24}N_2NaO_3S$ $[M+Na]^+$ 431.1396, found 431.1405 (2.0 ppm error).

4.13. *N*-(2-Ethylamino-1,2-diphenyl-ethyl)-4-methyl-benzenesulfonamide (*R*,*R*)-18[8c]

To a stirred solution of (*R*,*R*)-**22** (0.25 g, 0.6 mmol) in dry THF (15 mL), a 2 M solution of $LiAlH_4$ (0.6 mL, 1.2 mmol) was added dropwise. The system was refluxed for 4 h and then 2 mL of water followed by 0.39 g (1.4 mmol) of Rochelle salt (Na/K tartarate) was added and the reaction mixture was stirred for additional 2 h. The product was extracted with chloroform (3 × 30 mL) and the combined organic fractions were washed with brine (2 × 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography (0→20% v/v ethyl acetate/hexane) to afford the product **18** as a white solid (0.18 g, 0.46 mmol, 75%). Mp 116–118 °C; $[\alpha]_D^{20} = -11.5$ (*c* 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1}: 3228, 3064, 2972, 2858, 1598, 1493, 1437, 1454, 1324, 1148, 1081, 1039, 925, 908, 847, 810, 770, 752, 695, 667; δ_H (300 MHz; $CDCl_3$)/ppm: 7.41–6.87 (15H, m, Ar-H + NH), 4.23 (1H, d, *J* 8.0 PhC*H*NHTs), 3.61 (1H, d, *J* 8.0 PhC*H*NHR), 2.50–2.28 (5H, m, CH_2 and CH_3 singlet overlapping at 2.34), 1.0 (3H, t, *J* 7.1 CH_3). δ_C (75 MHz; $CDCl_3$)/ppm: 142.7, 139.3, 138.3, 137.0, 129.0, 128.2, 127.8, 127.6, 127.4, 127.2, 127.1 (Ar-C), 67.6 (CH), 63.0 (CH), 41.4 (CH_2), 21.4 (CH_3), 15.2 (CH_3). HRMS calcd for $C_{23}H_{27}N_2O_2S$ $[M+H]^+$ 395.1784, found 395.1797 (3.2 ppm error).

4.14. *N*-[2-(2,2-Dimethyl-propylamino)-1,2-diphenyl-ethyl]-4-methyl-benzenesulfonamide (*R*,*R*)-19

To a stirred solution of (1*R*,2*R*)-TsDPEN (0.30 g, 0.82 mmol) and molecular sieves (1 g) in dried methanol (8 mL) was added trimethylacetaldehyde (0.1 mL, 0.90 mmol) followed by three drops of glacial acetic acid. The reaction was followed by TLC until the imine was formed (4 h) and then sodium cyanoborohydride (0.15 g, 2.4 mmol) was added, and the reaction mixture was left to stir overnight at room temperature. The molecular sieves were filtered through filter paper and the solution was concentrated under reduced pressure to remove the methanol. The residue was dissolved in chloroform (50 mL), washed with saturated $NaHCO_3$ solution (30 mL) and then dried over anhydrous $MgSO_4$. The solvent was removed to give a crude solid, which was purified by silica gel column chromatography (0→30% v/v ethyl acetate/hexane) to afford the product **19** as a white solid (0.28 g, 0.66 mmol, 77%). Mp 97–99 °C; $[\alpha]_D^{20} = -37$ (*c* 0.5, $CHCl_3$); ν_{max} (neat)/cm^{-1}: 3180, 2954, 1600, 1495, 1470, 1456, 1373, 1319, 1148, 1092, 945, 931, 811, 784, 751, 699, 660; δ_H (300 MHz; $CDCl_3$)/ppm: 7.43–6.83 (15H, m, Ar-H + NH), 4.22 (1H, d, *J* 8.0 PhC*H*NHTs), 3.53 (1H, d, *J* 8.0 PhC*H*NHR), 2.34 (3H, s, CH_3), 2.14 (1H, d, *J* 11.3 CH_aH_b), 1.95 (1H, d, *J* 11.3 CH_aH_b), 0.84 (9H, s, $3CH_3$). δ_C (75 MHz; $CDCl_3$)/ppm: 142.7, 139.4, 138.4, 136.9, 129.1, 128.3, 127.9, 127.5, 127.4, 127.2, 127.1 (Ar-C), 68.5 (CH), 63.4 (CH), 59.4 (CH_2), 31.5 (C), 27.6 (CH_3), 21.4 ($3CH_3$). HRMS calcd for $C_{26}H_{33}N_2O_2S$ $[M+H]^+$ 437.2252, found 437.2260 (1.8 ppm error).

4.15. General procedure for enantioselective addition of diethylzinc to benzaldehyde[2c]

A solution of ligand (*R*,*R*)-**13** (0.022 mmol) in dry toluene (1 mL) was stirred under N_2 in a flame-dried schlenk tube at 25 °C for 10 min. The system was cooled to −78 °C and then diethylzinc 1 M solution was added (1.1 mmol). The system was stirred at that temperature for 1 h and then the cooling bath was removed, and the system was stirred for another 1 h at room temperature when benzaldehyde was added (0.44 mmol). The system was stirred at room temperature and monitored by GC. The reaction was quenched with aqueous HCl (10%, 5 mL) and extracted with Et_2O, dried over $MgSO_4$, filtered and concentrated in vacuum to give the crude reaction mixture, which was analyzed by GC. $[\alpha]_D^{24} = +36$ (*c* 0.72, $CHCl_3$) 79% ee (*R*) (lit.[6a] $[\alpha]_D^{20} = +47.0$ (*c* 1.4, $CHCl_3$) 95% ee (*R*)); δ_H (400 MHz; $CDCl_3$)/ppm: 7.36–7.24 (5H, m, Ar-H), 4.57 (1H, t, *J* 6.5,$PhCH(OH)CH_2$), 2.00 (1H, br s, OH), 1.86-1.68 (2H, m, CH_2), 0.90 (3H, t, *J* 7.4, CH_3); δ_C (100.6 MHz; $CDCl_3$)/ppm: 144.6, 128.4, 127.5, 126.0 (Ar-C), 76.0 (CH), 31.9 (CH_2), 10.2 (CH_3).

Acknowledgments

We thank Coordenação de Aperfeiçoamento de Pessoal de Ensinol Superior (CAPES) for the scholarship to J.E.D.M. We thank the EPSRC Mass Spectrometry Service (Swansea) for analysis of certain ligands and intermediates and the use of the EPSRC Chemical Database Service at Daresbury.[9]

References

1. (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824; (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856.
2. (a) Li, S.; Jiang, Y.; Mi, A. *Tetrahedron: Asymmetry* **1992**, *3*, 1467–1474; (b) Hanyu, N.; Mino, T.; Sakamoto, M.; Fujita, T. *Tetrahedron Lett.* **2000**, *41*, 4587–4590; (c) Martins, J. E. D.; Mehlecke, C. M.; Gamba, M.; Costa, V. E. U. *Tetrahedron: Asymmetry* **2006**, *17*, 1817–1823; (d) Asami, M.; Inoue, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1687–1690; (e) Asami, M.; Watanabe, H.; Honda, K.; Inoue, S. *Tetrahedron: Asymmetry* **1998**, *9*, 4165–4173.
3. (a) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832–4842; (b) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922–2959; (c) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800–9809; (d) Soai, K.; Kawasaki, T. *Chirality* **2006**, *18*, 469–478; (e) Buono, F.; Walsh, P. J.; Blackmond, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 13652–13653.
4. (a) Ramon, D. J.; Yus, M. *Chem. Rev.* **2006**, *106*, 2126–2208; (b) Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, 8275; (c) Knochel, P. *Synlett* **1995**, 393–403; (d) Yoshioka, M.; Kawakita, T.; Ohno, M. *Tetrahedron Lett.* **1989**, *13*, 1657–1660; (e) Bisai, A.; Singh, P. K.; Singh, V. K. *Tetrahedron* **2007**, *63*, 598–601; (f) Yus, M.; Ramon, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2003**, *14*, 1103–1114; (g) Satyanarayana, T.; Ferber, B.; Kagan, H. B. *Org. Lett.* **2007**, *9*, 251–253; (h) Costa, A. M.; Garcia, C.; Carroll, P. J.; Walsh, P. J. *Tetrahedron* **2005**, *61*, 6442–6446.
5. (a) Gonzalez-Sabin, J.; Gotor, V.; Rebolledo, F. *Tetrahedron: Asymmetry* **2006**, *17*, 449–454; (b) Johansson, A.; Wingstrand, E.; Hakansson, M. *J. Organomet. Chem.* **2005**, *690*, 3846–3853.
6. (a) Hayes, A. M.; Morris, D. J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2005**, *127*, 7318–7319; (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97–102; (c) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226–236; (d) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562–7563; (e) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521–2522.
7. (a) Honjo, T.; Sano, S.; Shiro, M.; Nagao, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5838–5841; (b) Honjo, T.; Nakao, M.; Sano, S.; Shiro, M.; Yamaguchi, K.; Sei, Y.; Nagao, Y. *Org. Lett.* **2007**, *9*, 509–512.
8. (a) Kioke, T.; Ikariya, T. *Adv. Synth. Catal.* **2004**, *346*, 37–41; (b) Kioke, T.; Ikariya, T. *J. Organomet. Chem.* **2007**, *692*, 408–419; (c) Xue, D.; Chen, Y.-C.; Cui, X.; Wang, Q.-W.; Zhu, J.; Deng, J.-G. *J. Org. Chem.* **2005**, *70*, 3584–3591; (d) Gelalcha, F. G.; Bitterlich, B.; Anilkumar, G.; Tse, M. K.; Beller, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7293–7296; (e) Katsumi, K.; Hamblett, C. L.; Wang, X.; Leighton, J. L. *Tetrahedron* **2006**, *62*, 11397–11401.
9. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746–749.