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Tandem hydroboration/reduction of trisubstituted β,γ-unsaturated esters for the asymmetric synthesis of chiral 1,3-diols

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ABSTRACT

Treatment of a range of trisubstituted β,γ-unsaturated esters with 2 equiv of (−)-monoisopinocampheylborane results in hydroboration of their alkene functionalities and reduction of their ester groups to afford chiral 1,3-diols containing two new vicinal β,γ-(*anti*)-stereocentres in 67–85% enantiomeric excess.

The development of 'one-pot' protocols that enable reagents or catalysts to be used to transform two different functional groups in the same substrate represents an atom-efficient strategy. Borane reagents have been widely used to hydroborate substituted alkenes with good levels of regiocontrol, which upon oxidative work-up afford primary or secondary alcohols in good yields.[1] They may also be used to reduce the carbonyl functionalities of ester, aldehyde and ketone groups to afford primary and secondary alcohols, respectively.[2] Molander and Bobbitt have previously reported that treatment of a range of allyl-ketones with diisopinocampheylborane $((-)\text{-Ipc})_2BH$ **2** results in tandem hydroboration/reduction reactions to afford enantiomerically enriched chiral 1,4-diols.[3] For example, treatment of allyl-ketone **1** with 1.5 equiv of $(-)\text{-Ipc})_2BH$ **2** gave 1,4-diol **5** containing one new stereocentre in 88% enantiomeric excess (ee) (Scheme 1).[3] In this case, hydroboration of the allyl group of **1** results in a trialkylborane intermediate **3** that then undergoes stereoselective intramolecular reduction of its ketone group (with elimination of (+)-α-pinene) to afford a cyclic borinate ester **4** that on oxidative work-up affords 1,4-diol **5** (Scheme 1).

A review of the literature revealed that Martin and co-workers had reported that treatment of cyclic β,γ-unsaturated ester **6** with excess BH_3 resulted in tandem alkene hydroboration/ester reduction to afford diol **7** in a 6:1 diastereomeric ratio (dr) (Scheme 2, Eq. i).[4] Furthermore, Brown and coworkers had shown that hydroboration of trisubstituted arylalkene **8** with monoisopinocampheylborane ($(-)\text{-IpcBH}_2$) **9**,[5] followed by oxidative work-up, gave (*anti*)-alcohol **10** in 81% ee (Scheme 2, Eq. ii).[6] Therefore, it was decided to investigate whether treatment of methyl (*E*)-4-aryl-pent-3-enoates **11** with excess $(-)\text{-IpcBH}_2$ **9** would result in stereoselective tandem hydroboration/reduction reactions occurring to afford chiral 1,3-diols **12** containing two new stereocentres in good ee (Fig. 1).

A series of seven (*E*)-β,γ-unsaturated esters **11a–g** were prepared via Knoevanagel-type reaction of the enolate of malonic acid with a range of 2-arylpropionaldehydes **13a–g**[7] to afford their respective (*E*)-β,γ-unsaturated acids **14a–g**,[8] that were then subjected to acid catalysed esterification reactions with methanol (Scheme 3).[9] Treatment of methyl (*E*)-4-phenylpent-3-enoate **11a**[10a] with 2 equiv of $(-)\text{-IpcBH}_2$ **9** at −17 → 0 °C, followed by oxidation with alkaline hydrogen peroxide, resulted in the clean formation of (3*S*,4*R*)-4-phenylpentane-1,3-diol **12a**[10b] in 60% yield and 82% ee (Scheme 4).[11] The enantiomeric excess of diol **12a** was determined via treatment with 2-formylphenylboronic acid **16** and (*S*)-α-methylbenzylamine **17** that gave a mixture of diastereomeric imino-boronate esters **18** and **19**, whose 82% dr was determined by ^1H NMR spectroscopic analysis (Scheme 5).[12] The absolute configuration of (3*S*,4*R*)-4-phenylpentane-1,3-diol **12a** was determined via its two-step conversion into (2*R*,3*S*)-2-phenylpentan-3-ol **15**[10c] ($[\alpha]_D^{25}$ +6.3 (*c* 1.6, $CHCl_3$); (lit.[13] for (2*S*,3*R*)-**15** = −11.4 (neat)), involving mono-tosylation of its primary alcohol group, followed by subsequent reduction with $LiAlH_4$ (Scheme 4). This configurational assignment was consistent with the enantiofacial selectivity previously observed for hydroboration of the trisubstituted (*E*)-arylalkene functionality of (*E*)-trisubstituted alkene **8** with $(-)\text{-IpcBH}_2$ **9** (Scheme 2, Eq. ii).[6]

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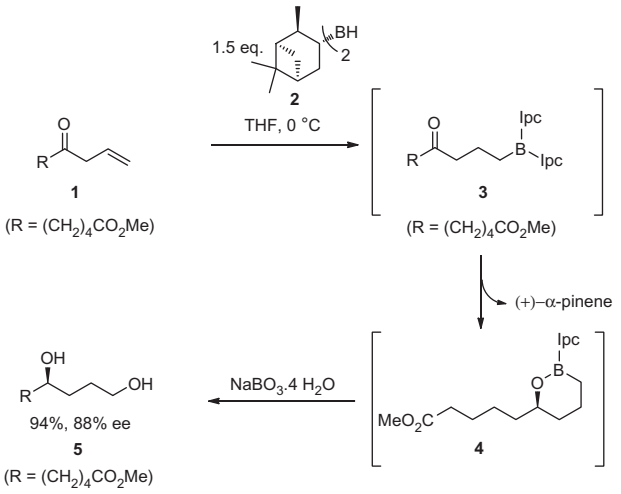
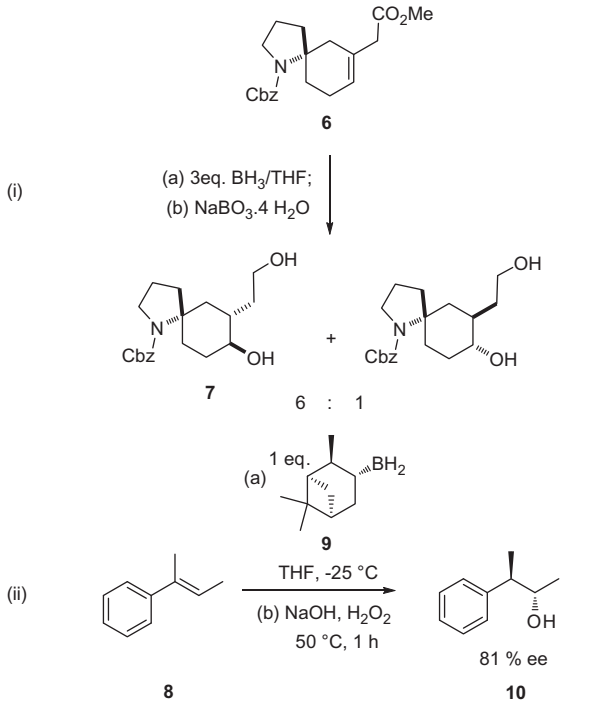


Scheme 1. Hydroboration of allyl-ketone **1** with 1.5 equiv of $((-)\text{-Ipc})_2BH$ **2**, followed by oxidative work-up, affords 1,4-diol **5** in 88% ee.



Scheme 2. (i) Hydroboration of cyclic β,γ-unsaturated ester **6** with excess BH_3 affords diol **7** in a 6:1 dr;[4] (ii) Hydroboration of (*E*)-2-phenyl-2-butene **8** with $(-)$-$IpcBH_2$ **9** affords (2*S*,3*R*)-3-phenylbutan-2-ol **10** in 81% ee.[6]

Modification of the reaction conditions employed for hydroboration, involving the treatment of ester **11a** with 2 equiv of $(-)$-$IpcBH_2$ **9** in THF at −25 °C over a period of 48 h, followed by

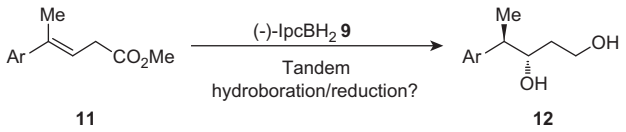
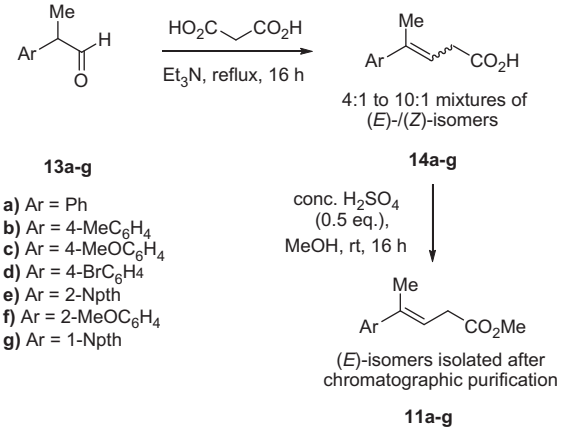
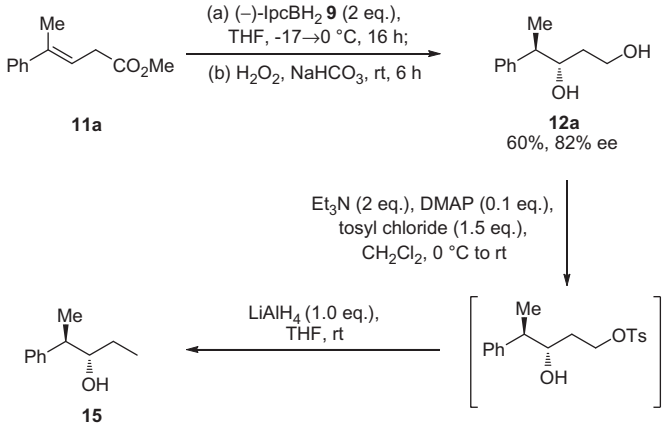


Figure 1. Proposed tandem hydroboration/reduction of trisubstituted β,γ-unsaturated esters **11** to afford chiral 1,3-diols **12** containing two new stereocentres.



Scheme 3. Knoevanagel-type synthesis of (*E*)-β,γ-unsaturated esters **11a–g**.



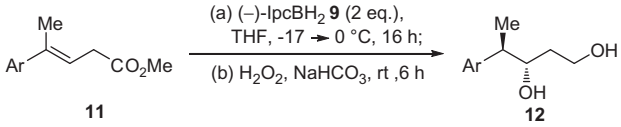
Scheme 4. Asymmetric synthesis of (3*S*,4*R*)-4-phenylpentane-1,3-diol **12a** and its conversion into (2*R*,3*S*)-2-phenylpentan-3-ol **15**.

quenching with methanol at −25 °C and oxidative work-up with alkaline H_2O_2, resulted in the clean formation of methyl (3*S*,4*R*)-3-hydroxy-4-phenylpentanoate **20**[10d] in 75% ee (Scheme 6).[14,15] This demonstrates that the alkene functionality of **11a** is hydroborated at a significantly faster rate than its ester group is reduced. This implies that hydroboration of **11a** occurs to afford a chiral organoborane intermediate **21**, the ester group of which is then reduced via intramolecular hydride transfer to give a cyclic borinate ester **22**. Subsequent loss/addition of the methoxide group of intermediate **22** would then occur to afford boronate-coordinated aldehyde **23** that is then reduced by excess $(-)$-$IpcBH_2$ **9** (Fig. 2).

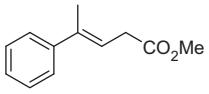
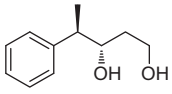
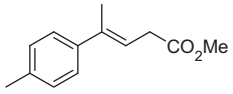
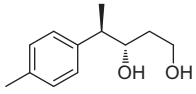
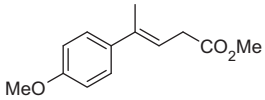
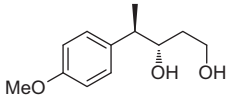
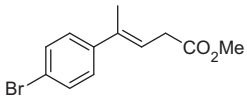
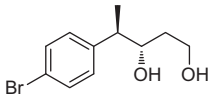
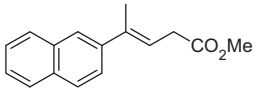
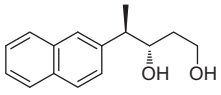
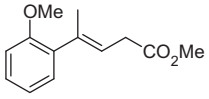
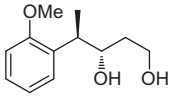
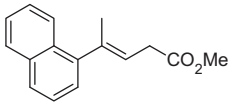
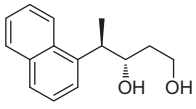
The remaining β,γ-unsaturated esters **11b–g** were then subjected to our standard reaction conditions using two equivalents of $(-)$-$IpcBH_2$ **9** in THF at −17 to 0 °C, over 16 h, followed by oxidative work-up with $H_2O_2/NaHCO_3$ to afford their corresponding chiral diols **12b–g** in 41–77% isolated yields and 67–85% ees (Table 1).

In conclusion, we have shown that treatment of a range of trisubstituted β,γ-unsaturated esters **11** with an excess of the chiral hydroborating agent $(-)$-$IpcBH_2$ **9** results in 'one-pot' hydroboration of their alkene functionalities, followed by the reduction of their ester groups, to afford chiral 1,3-diols **12** containing two new vicinal β,γ-(*anti*)-stereocentres in 67–85% enantiomeric excess.

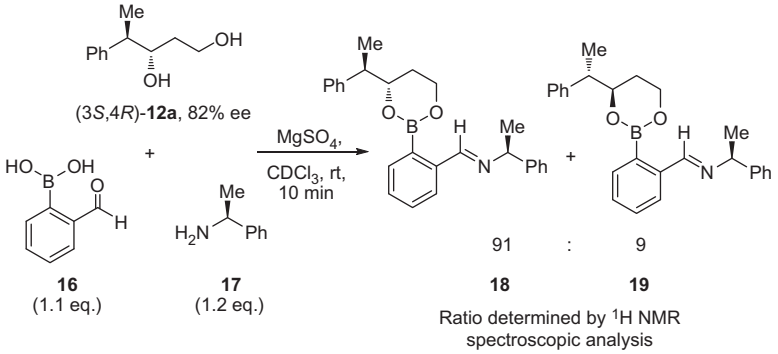
Table 1
Treatment of trisubstituted β,γ-unsaturated esters **11a–g** with (−)-IpcBH$_2$ results in formation of 1,3-diols **12a–g**



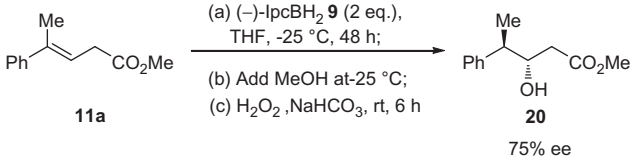
11 **12**

Entry	β,γ-Unsaturated ester (**11a–g**)	1,3-Diol (**12a–g**)	Yield[a] (%)	ee[b] (%)
1	 **11a**	 **12a**	60	82
2	 **11b**	 **12b**	66	78
3	 **11c**	 **12c**	77	84
4	 **11d**	 **12d**	61	85
5	 **11e**	 **12e**	62	83
6	 **11f**	 **12f**	54	75
7	 **11g**	 **12g**	41[c]	67

[a]Isolated yields for chromatographically purified diols.
[b]ees determined via derivatisation with 2-formylphenylboronic acid **16** and (*S*)-α-methyl-benzylamine **17**, followed by ^{1}H NMR spectroscopic analysis of the dr of the resultant diastereomeric imino-boronate esters (see Scheme 5).[12]
[c]Lower 41% yield due to competing formation of a 10% yield of its corresponding β-hydroxy ester.



Scheme 5. The ee of diol **12a** was determined via ^{1}H NMR spectroscopic analysis of the dr of iminoboronate ester derivatives **18** and **19**.



Scheme 6. Hydroboration of β,γ-ester **11a** to afford (3*S*,4*R*)-β-hydroxy ester **20**.

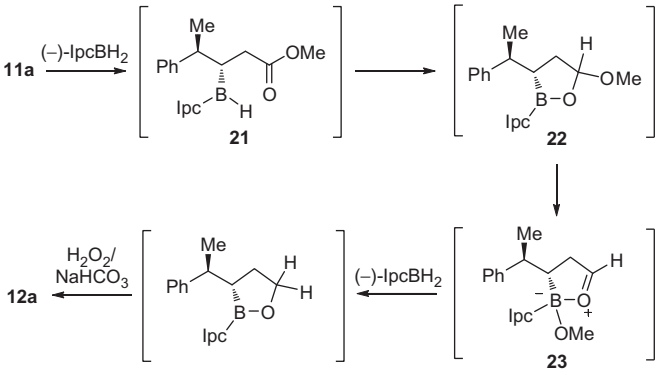


Figure 2. Proposed mechanism for the tandem hydroboration/reduction of β,γ-unsaturated ester **11a**.

Acknowledgment

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7. 2-Arylpropionaldehydes **13a–g** were prepared from their corresponding acetophenones via a two-step Wittig C_1-homologation/enol ether hydrolysis protocol, see: Pelphrey, P. M.; Popov, V. M.; Joska, T. M.; Beierlein, J. M.; Bolstad, E. S. D.; Fillingham, Y. A.; Wright, D. L.; Anderson, A. C. *J. Med. Chem.* **2007**, *50*, 940–950.
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9. General procedure for the two-step synthesis of β,γ-unsaturated esters **11a–g**. *Step 1:* A mixture of dry Et_3N (1.5 equiv, 27.5 mmol, 3.9 mL), malonic acid (1.0 equiv, 18.3 mmol, 1.90 g) and 2-aryl-propionaldehyde **13** (1.0 equiv, 18.3 mmol) was heated at reflux for 16 h. The crude reaction mixture was cooled to rt, acidified to pH 1.0, extracted with Et_2O (3 × 30 mL) and the combined organic phases washed with $NaCl_{(aq)}$, dried ($MgSO_4$) and the solvent removed under reduced pressure. The resultant crude product was dissolved in 0.1 M aqueous NaOH solution, washed with Et_2O (2 × 30 mL), acidified to pH 1.0 and the precipitated acid extracted with CH_2Cl_2 (4 × 30 mL). The combined organic solvent was dried ($MgSO_4$) and removed under reduced pressure to afford the desired 4-arylpent-3-enoic acid **14**. *Step 2:* 98% H_2SO_4 (0.5 equiv) was added dropwise to a rapidly stirred solution of 4-arylpent-3-enoic acid **14** in MeOH (0.5 M), and the resulting solution stirred at rt for 16 h. The solution was neutralised by the addition of solid $NaHCO_3$ and the solvent evaporated under reduced pressure. The crude product was partitioned between H_2O and CH_2Cl_2, the aqueous layer re-extracted with CH_2Cl_2, the combined organic layers dried ($MgSO_4$) and solvent removed under reduced pressure. The resultant mixture of (*E*)/(*Z*)-isomers was purified via chromatography (petrol/Et_2O (9:1), SiO_2) to afford the desired methyl (*E*)-4-arylpent-3-enoate **11**.
10. Spectroscopic data for selected compounds: (a) **Methyl (*E*)-4-phenylpent-3-enoate 11a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.44 (5H, m, Ar*H*), 5.95 (1H, tq, *J* = 7.1 and 1.4 Hz, C=C*H*), 3.72 (3H, s, OCH_3), 3.27 (2H, d, *J* = 7.1 Hz, CH_2), 2.05–2.08 (3H, m, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 143.1, 138.1, 128.3, 127.1, 125.8, 119.2, 52.0, 34.3, 16.2; IR (neat): 1730 (C=O), 1160 (C–O) cm^{-1}; (b) **(3*S*,4*R*)-4-Phenylpentane-1,3-diol 12a**: 82% ee; $[\alpha]_D^{25}$ +6.4 (*c* 4.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.38 (5H, m, Ar*H*), 3.77–3.97 (3H, m, CH_2(OH) and *CH*(OH)), 2.79 (app. p, *J* = 7.0 Hz, *CH*CH_3), 2.17 (2H, br s, 2 × O*H*), 1.82–1.95 (1H, m, CH_AH_B), 1.58–1.74 (1H, m, CH_AH_B), 1.28 (3H, d, *J* = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 128.8, 128.1, 126.9, 76.8, 61.9, 46.6, 35.6, 17.6; IR (neat): 3350 (O–H) cm^{-1}; HRMS (ES): *m/z* $[C_{11}H_{16}NaO_2]^+$ requires 203.1043, found 203.1052; (c) **(2*R*,3*S*)-2-Phenylpentan-3-ol 15:** 82% ee; $[\alpha]_D^{25}$ +6.3 (*c* 1.6, $CHCl_3$), (lit.[13] $[\alpha]_D^{25}$ for (2*S*,3*R*)-**15** = −11.4(neat)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12–7.30 (5H, m, Ar*H*), 3.52 (1H, ddd, *J* = 8.2, 7.1 and 3.5 Hz, *CH*(OH)), 2.69 (app. p, *J* = 7.1 Hz, CH_3*CH*), 1.49–1.65 (1H, m, CH_AH_B), 1.44 (1H, br s, O*H*), 1.24-1.38 (1H, m, CH_AH_B), 1.21 (3H, d, *J* = 7.1 Hz, CH*CH*$_3$), 0.92 (3H, t, *J* = 7.3 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 128.6, 128.2, 126.7, 77.4, 45.7, 27.3, 18.0, 10.0; IR (neat): 3387 (O–H), 1602 cm^{-1}; HRMS (ES): *m/z* $[C_{11}H_{16}NaO]^+$ requires 187.1099, found 187.1092; (d) **Methyl (3*S*,4*R*)-3-hydroxy-4-phenylpentanoate 20:** 75% ee; $[\alpha]_D^{25}$ −11.7 (*c* 3.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13–7.30 (5H, m, Ar*H*), 4.11 (1H, ddd, *J* = 9.4, 6.2 and 3.0 Hz, *CH*(OH)), 3.61 (3H, s, OCH_3), 2.78 (1H, app. p, *J* = 7.0 Hz, *CH*CH_3), 2.97 (1H, dd, *J* = 16.0 and 3.0 Hz, CH_AH_B), 2.29 (1H, dd, *J* = 16.0 and 9.6 Hz, CH_AH_B), 1.25 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 142.6, 128.5, 128.2, 126.8, 72.3, 51.8, 45.2, 38.8, 17.2; IR (neat): 3657 (O–H), 1727 (C=O) cm^{-1}; HRMS (ES): *m/z* $[C_{12}H_{16}NaO_3]^+$ requires 231.0997, found 231.0999.
11. *General procedure for the asymmetric hydroboration/reduction of β,γ-unsaturated esters **11a–g**:* $BF_3{\cdot}OEt_2$ (2.0 equiv, 5.26 mmol, 0.65 mL) was added dropwise to a solution of 2IpcBH$_2$.TMEDA[16] (1.05 equiv, 2.76 mmol, 1.15 g) in dry THF (3.8 mL). The resulting solution was stirred at rt for 3 h and then cooled to −17 °C (MeOH/finely crushed ice). A solution of ester **11** (1.0 equiv, 2.63 mmol) in THF (1.0 mL) was then added dropwise and the reaction mixture allowed to warm to 0 °C overnight. The resultant solution was then treated with 30% aqueous H_2O_2 (13.8 mL) and saturated $NaHCO_3$ solution (84 mL), followed by stirring at rt for 6 h. The reaction mixture was then extracted with Et_2O, the combined organics washed with water, dried ($MgSO_4$) and the solvent removed under reduced pressure to afford a crude product that was purified via chromatography (petrol/Et_2O (1:1), SiO_2) to afford the desired 4-arylpentane-1,3-diol **12**.
12. For a detailed discussion of how to determine the ee of diols using this derivatisation method, see: (a) Kelly, A. M.; Pérez-Fuertes, Y.; Arimori, S.; Bull, S. D.; James, T. D. *Org. Lett.* **2006**, *8*, 1971–1974; (b) Kelly, A. M.; Pérez-Fuertes, Y.; Fossey, J. S.; Yeste, S. L.; Bull, S. D.; James, T. D. *Nat. Protoc.* **2008**, *3*, 215–219.
13. Cram, D. J. *J. Am. Chem. Soc.* **1952**, *74*, 2159–2165.
14. The ee of β-hydroxy-ester **20** was determined via reduction with $LiAlH_4$ to afford 1,3-diol **12a** whose ee was then determined using the ^{1}H NMR derivatisation method described in Scheme 5.

15. For related studies describing rhodium-catalysed asymmetric hydroboration reactions of trisubstituted β,γ-unsaturated amides using pinacolborane that gave chiral β-hydroxy amides in good yields and high ee, see: (a) Smith, S. M.; Takacs, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 1740–1741; (b) Smith, S. M.; Takacs, J. M. *Org. Lett.* **2010**, *12*, 4612–4615.

16. (a) Brown, H. C.; Mandal, A. K.; Yoon, N. M.; Singaram, B.; Schwier, J. R.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47*, 5069–5074; (b) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *J. Org. Chem.* **1982**, *47*, 5074–5083.