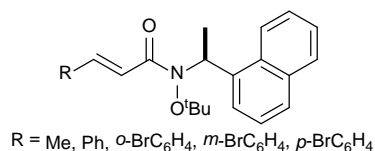


**Solid state conformations of  $\alpha,\beta$ -unsaturated hydroxamates derived from the ‘chiral Weinreb amide’ auxiliary (*S*)-*N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine**

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# Solid state conformations of $\alpha,\beta$ -unsaturated hydroxamates derived from the ‘chiral Weinreb amide’ auxiliary (*S*)-*N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine

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## Abstract

$\alpha,\beta$ -Unsaturated hydroxamates derived from the ‘chiral Weinreb amide’ auxiliary (*S*)-*N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine consistently adopt a defined conformation and undergo highly diastereoselective conjugate addition reactions with lithium amide reagents. The configuration of the *N*-1-(1'-naphthyl)ethyl group dictates the position of the *O*-*tert*-butyl group and also the configuration adopted by the pyramidal nitrogen atom via a ‘chiral relay’ effect. Conjugate addition of lithium amide reagents to these substrates proceeds on the face opposite to both the *O*-*tert*-butyl group and nitrogen lone-pair with high levels of diastereoselectivity.

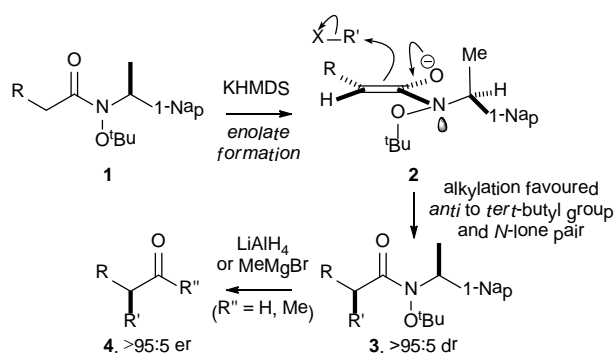
*Dedicated to the memory of Professor Howard D. Flack (1943–2017).*

**Keywords:** Hydroxamates, Weinreb amide, Michael acceptor.

## 1. Introduction

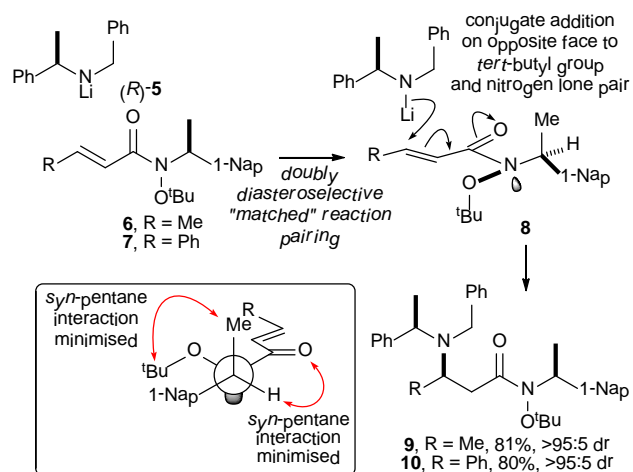
We have reported a protocol for the preparation of enantiopure  $\alpha$ -stereogenic aldehydes or ketones **4** via the alkylation of enolates derived from *N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxamates such as **1** (incorporating our ‘chiral Weinreb amide’ auxiliary), followed by treatment of the intermediate hydroxamates **3** with either  $\text{LiAlH}_4$  or  $\text{MeLi}$ .<sup>1,2</sup> A ‘chiral relay’<sup>3–5</sup> mechanism was proposed to rationalise the observed stereochemical outcome and a mechanistic study of this highly diastereoselective reaction revealed that a combination of evidence gained through experimental observations (including modification of the auxiliary structure), physical measurements, and molecular mechanics calculations, was found to validate this hypothesis.<sup>6</sup> In this ‘chiral relay’ model, the configuration of the *N*-1-(1'-naphthyl)ethyl group dictates the position of the *O*-*tert*-butyl group and also the configuration adopted by the pyramidal nitrogen atom. A fully staggered arrangement is adopted in which minimisation of steric interactions between the C(1')-methyl

and *O-tert*-butyl groups leaves the C(1')-hydrogen and carbonyl oxygen atoms eclipsing, minimising *syn*-pentane interactions. Minimisation of lone pair-lone pair repulsion controls the configuration of the pyramidal nitrogen atom, with alkylation occurring on the face opposite to both the *O-tert*-butyl group (steric control) and nitrogen lone pair (stereoelectronic control) to give **3** with high levels of diastereoselectivity (Fig. 1).



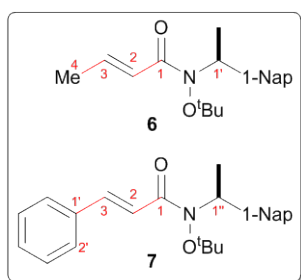
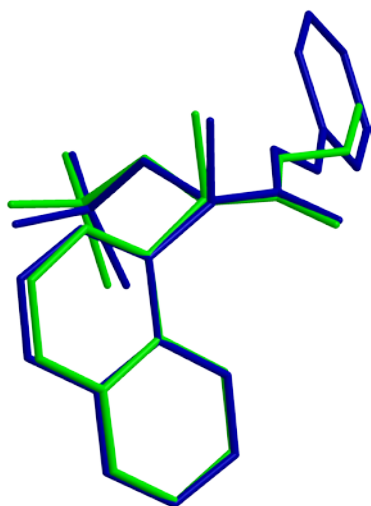
**Fig. 1.** Diastereoselective alkylation of hydroxamates **1**. [1-Nap = 1-naphthyl].

Based on these alkylation studies we envisaged that  $\alpha,\beta$ -unsaturated hydroxamates such as **6** and **7** (also derived from our ‘chiral Weinreb amide’ auxiliary) would undergo conjugate addition reactions of lithium amides<sup>7,8</sup> with high levels of diastereocontrol at the  $\beta$ -position. This was indeed found to be the case and we were able to propose reactive conformation **8** using the tool of double asymmetric induction as a mechanistic probe;<sup>9,10</sup> as expected, the doubly diastereoselective “matched” conjugate addition of (*R*)-**5** to  $\alpha,\beta$ -unsaturated hydroxamates **6** (R = Me) and **7** (R = Ph) occurs via conformation **8** (R = Me or Ph) on the face opposite to both the *O-tert*-butyl group and nitrogen lone-pair to give **9** (R = Me) and **10** (R = Ph) in  $\geq 80\%$  yield and >95:5 dr (Fig. 2).<sup>11</sup>



**Fig. 2.** The doubly diastereoselective "matched" conjugate addition of (*R*)-5 to  $\alpha,\beta$ -unsaturated hydroxamates **6** and **7**. [1-Nap = 1-naphthyl].

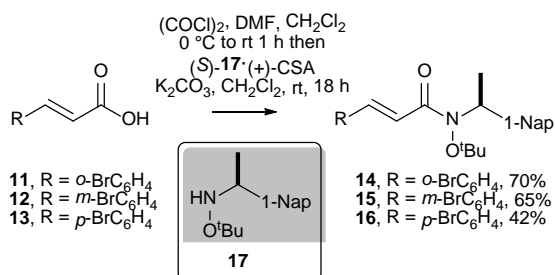
As part of this study we noticed some differences between the crystal structures of  $\alpha,\beta$ -unsaturated hydroxamates **6** and **7**: despite there being excellent parity between the conformation of the 'chiral Weinreb amide' auxiliary in both cases, the conformation of the alkenoyl substituent for **7** was found to deviate significantly from planarity [O–C(1)–C(2)–C(3) dihedral angle = 35.5°, C(2)–C(3)–C(1')–C(2') dihedral angle = 17.3°] (Fig. 3).<sup>12</sup> We therefore sought to examine this phenomenon further by analysing the conformations of a range of aryl substituted analogues and we selected the corresponding C(3)-*o*-bromophenyl, C(3)-*m*-bromophenyl and C(3)-*p*-bromophenyl substituted  $\alpha,\beta$ -unsaturated hydroxamates for this investigation.



**Fig. 3.** Overlaid molecular structures of **6** [green] and **7** [blue], all H atoms are omitted for clarity.

## 2. Results and discussion

Bromo-substituted  $\alpha,\beta$ -unsaturated hydroxamates **14–16** were prepared by coupling our ‘chiral Weinreb amide’ auxiliary (*S*)-*N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **17** [which is stored as the corresponding (+)-camphorsulfonic acid salt **17**·(+)-CSA] with commercially available bromo-substituted *trans*-cinnamic acids **11–13**, via the intermediacy of the corresponding acid chlorides, to give **14–16** in 42–70% yield after chromatographic purification (Scheme 1).



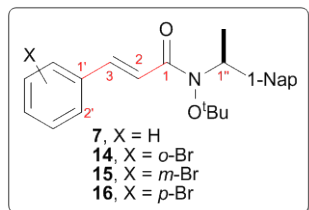
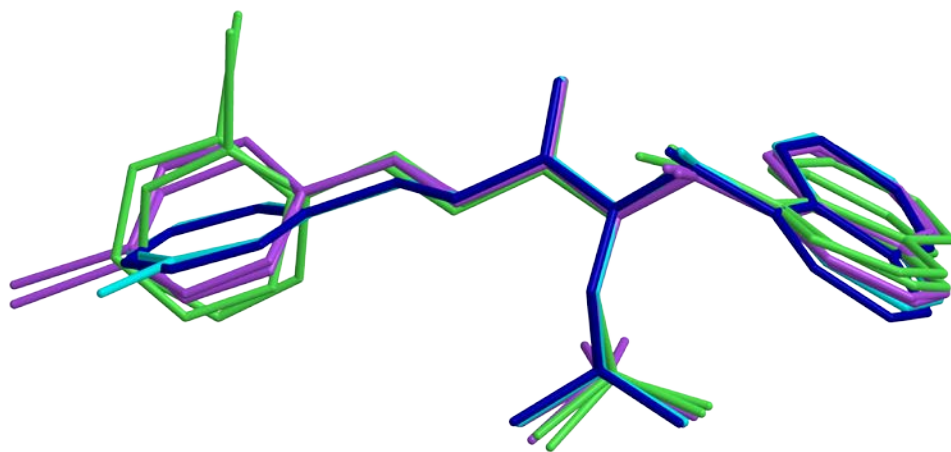
**Scheme 1.** [1-Nap = 1-naphthyl].

Recrystallisation of **14–16** from  $\text{CHCl}_3$ /heptane gave, in each case, colourless blocks which were subjected to separate X-ray diffraction analyses. Selected structural details for **14**, **15** and **16** are included in Table 1. For all structures, the Flack  $x$  parameter<sup>13,14</sup> was refined and was found to satisfy the criteria for a reliable

assignment of absolute configuration of a material known to be enantiopure. In accordance with our previous observations concerning derivatives of (*S*)-*N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine **17**<sup>1,2,6,11</sup> the conformation of the 'chiral Weinreb amide' auxiliary was found to be very similar in all cases: minimisation of steric interactions between the C(1')-methyl and *O*-*tert*-butyl groups leaves the C(1')-hydrogen and carbonyl oxygen atoms eclipsing, minimising *syn*-pentane interactions. The nitrogen atom is pyramidalised, and minimisation of lone pair-lone pair repulsion controls its configuration (Fig. 4). However, there were again variations observed in the conformation of the alkenoyl substituents.<sup>15</sup> In this respect the structures of the parent C(3)-phenyl substituted compound **7** and the C(3)-*m*-bromophenyl substituted analogue **15** were found to be very similar in that they both exhibit significant deviations from planarity about the C(1)–C(2) bond with O–C(1)–C(2)–C(3) dihedral angles of >35° in both cases. For the C(3)-*o*-bromophenyl and C(3)-*p*-bromophenyl substituted analogues **14** and **16** the O–C(1)–C(2)–C(3) dihedral angle was less than 20° in each case (both structures have two distinct conformations present within the asymmetric unit), although the C(2)–C(3)–C(1')–C(2') dihedral angle was greater for C(3)-*o*-bromophenyl substituted **14** which may be due to minimisation of allylic strain (Table 2). The conformations of **6**, **7** and **14–16** were also investigated by IR and UV spectroscopic analyses. Whilst there were no significant trends observed in the UV spectroscopic data (in CHCl<sub>3</sub>), it was interesting to note the discrepancy between the IR spectra recorded in the solid state (KBr disc) and solution phase (CHCl<sub>3</sub> cell) for the C(3)-phenyl and C(3)-*m*-bromophenyl substituted compounds **7** and **15**: for both compounds the  $\nu_{\text{max}}$  values for the absorptions corresponding to the C=C bonds were found to be anomalously high in the solid state. This may be indicative of a reduced degree of conjugation which would be consistent with the crystal structure data for these compounds as both structures have large (>35°) O–C(1)–C(2)–C(3) dihedral angles. The  $\nu_{\text{max}}$  values for the absorptions corresponding to the C=C bonds in solution (CHCl<sub>3</sub> cell) showed greater parity and may be indicative of a greater degree of conjugation in solution than in the solid state (Table 2).

Compound	14	15	16
Empirical formula	C <sub>25</sub> H <sub>26</sub> BrNO <sub>2</sub>	C <sub>25</sub> H <sub>26</sub> BrNO <sub>2</sub>	C <sub>25</sub> H <sub>26</sub> BrNO <sub>2</sub>
Formula weight	452.39	452.39	452.39
Crystal habit, colour	Block, colourless	Block, colourless	Block, colourless
Crystal system	Monoclinic	Orthorhombic	Triclinic
Space group	P2 <sub>1</sub>	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	P1
<i>a</i> (Å)	13.8684(3)	8.1480(2)	9.6178(8)
<i>b</i> (Å)	7.8789(2)	10.1341(2)	11.079(1)
<i>c</i> (Å)	19.8764(4)	26.5460(5)	11.8824(11)
$\alpha$ (°)	90	90	63.168(4)
$\beta$ (°)	90.714(1)	90	83.430(4)
$\gamma$ (°)	90	90	86.420(3)
Volume (Å <sup>3</sup> )	2171.68(8)	2191.97(8)	1122.31(18)
<i>Z</i>	4	4	2
Density (calc. g cm <sup>-3</sup> )	1.384	1.371	1.339
Temperature (K)	150	150	150
Radiation type/ $\lambda$ (Å)	Mo K $\alpha$ /0.71073	Mo K $\alpha$ /0.71073	Mo K $\alpha$ /0.71073
Absorption coeff. (mm <sup>-1</sup> )	1.913	1.896	1.851
<i>F</i> (000)	936	936	468
Crystal size (mm)	0.18 × 0.23 × 0.28	0.12 × 0.16 × 0.20	0.10 × 0.14 × 0.25
Reflections measured	28077	23566	17907
Independent reflections	8355	4741	5639
Observed reflns. [ <i>I</i> > 2.0 $\sigma$ ( <i>I</i> )]	6996	3504	4733
Number of parameters	524	263	524
Goodness-of-fit on <i>F</i> <sup>2</sup>	0.930	0.993	1.009
Final <i>R</i> indices [ <i>I</i> > 2.0 $\sigma$ ( <i>I</i> )]	<i>R</i> <sub>1</sub> = 0.038, <i>wR</i> <sub>2</sub> = 0.072	<i>R</i> <sub>1</sub> = 0.037, <i>wR</i> <sub>2</sub> = 0.070	<i>R</i> <sub>1</sub> = 0.089, <i>wR</i> <sub>2</sub> = 0.240
<i>R</i> indices [all data]	<i>R</i> <sub>1</sub> = 0.052, <i>wR</i> <sub>2</sub> = 0.082	<i>R</i> <sub>1</sub> = 0.051, <i>wR</i> <sub>2</sub> = 0.075	<i>R</i> <sub>1</sub> = 0.098, <i>wR</i> <sub>2</sub> = 0.247
<i>x</i> (Flack)	0.008(8)	0.001(8)	0.080(2)
$\Delta\rho_{\max}$ , $\Delta\rho_{\min}$ (e Å <sup>-3</sup> )	0.80, -0.76	0.55, -0.63	1.59, -0.78
CCDC deposition no.	817636	817637	817638

**Table 1.** Crystallographic data and refinement details for compounds **14–16**.



**Fig. 4.** Overlaid molecular structures of **7** [blue], **14** [green], **15** [cyan] and **16** [purple], all H atoms are omitted for clarity.

Compound	<b>6</b>	<b>7</b>	<b>14<sup>a</sup></b>	<b>15</b>	<b>16<sup>a</sup></b>
C(3)-Substituent	Me	Ph	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub>	<i>m</i> -BrC <sub>6</sub> H <sub>4</sub>	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>
O–C(1)–C(2)–C(3) Dihedral	6.4, 1.0	35.5	4.8, 1.4	39.5	16.3, 14.7
C(2)–C(3)–C(1')–C(2') Dihedral	--	17.3	36.6, 20.5	18.4	10.6, 2.0
IR $\nu_{\max}$ (C=O, KBr)/cm <sup>-1</sup>	1657	1648	1650	1649	1654
IR $\nu_{\max}$ (C=O, CHCl <sub>3</sub> )/cm <sup>-1</sup>	1658	1649	1650	1650	1654
IR $\nu_{\max}$ (C=C, KBr)/cm <sup>-1</sup>	1624	1623	1612	1624	1616
IR $\nu_{\max}$ (C=C, CHCl <sub>3</sub> )/cm <sup>-1</sup>	1623	1609	1611	1614	1613
UV $\lambda_{\max}$ /nm ( $\epsilon$ /M <sup>-1</sup> cm <sup>-1</sup> )	293 (5298)	309 (20715)	315 (22441)	299 (18772)	310 (19521)

**Table 2.** Selected structural parameters and IR and UV spectroscopic analyses for compounds **6**, **7** and **14–16**. [<sup>a</sup> The crystal structures of **6**, **14** and **16** all contain two molecules within the asymmetric unit].

### 3. Conclusion

The crystal structures of  $\alpha,\beta$ -unsaturated hydroxamates, derived from (*S*)-*N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine, were studied by X-ray diffraction. In each case the conformation of the *N*-*tert*-butoxy and *N*-1-(1'-naphthyl)ethyl groups was found to be very similar: minimisation of steric interactions between the C(1')-methyl and *O*-*tert*-butyl groups leaves the C(1')-hydrogen and carbonyl oxygen atoms eclipsing, minimising *syn*-pentane interactions. In addition, the nitrogen atom is pyramidalised, and minimisation of lone pair-lone pair repulsion controls its configuration. Whilst there were significant deviations observed in the conformations of the alkenoyl substituents, these findings are consistent with our previous observations concerning the (*S*)-*N*-1-(1'-naphthyl)ethyl-*O*-*tert*-butylhydroxylamine chiral auxiliary, where a 'chiral relay' effect may be proposed to rationalise this trend. In each case, the conformation of the  $\alpha,\beta$ -unsaturated



hydroxamate is consistent with highly selective conjugate addition of lithium amide reagents on the face opposite to both the *O*-*tert*-butyl group and nitrogen lone-pair, as observed experimentally.

## 4. Experimental

All reagents were used as supplied without prior purification. Melting points were recorded on a Gallenkamp Hot Stage apparatus and are uncorrected. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as KBr discs. Selected characteristic peaks are reported in  $\text{cm}^{-1}$ . NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. Spectra were recorded at rt. The field was locked by external referencing to the relevant deuteron resonance. Low-resolution mass spectra were recorded on either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m  $\times$  0.25 mm) using amyl acetate as a lock mass.

### 4.1. General Procedure

A solution of the requisite carboxylic acid (2.5 equiv) in  $\text{CH}_2\text{Cl}_2$  at 0 °C was treated with  $(\text{COCl})_2$  (5.0 equiv) and DMF (1 drop). The reaction mixture was allowed to warm to rt over 1 h then concentrated in vacuo. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  and the resultant mixture was added to a stirred solution of (*S*)-**17**·(+)-CSA<sup>1</sup> (1.0 equiv) and  $\text{K}_2\text{CO}_3$  (10.0 equiv) in  $\text{CH}_2\text{Cl}_2$  at 0 °C. The reaction mixture was then allowed to warm to rt and stirred at rt for 18 h. Satd aq  $\text{NaHCO}_3$  was then added and the resultant mixture was extracted with three portions of  $\text{CH}_2\text{Cl}_2$ . The combined organic extracts were washed with brine, then dried and concentrated in vacuo.

### 4.2. (*S*)-*N*-*tert*-Butoxy-*N*-1''-(1'''-naphthyl)ethyl (*E*)-3-(2'-bromophenyl)propenamide **14**

Following the *general procedure*, a solution of *trans*-2-bromocinnamic acid **11** (1.20 g, 5.25 mmol) in  $\text{CH}_2\text{Cl}_2$  (12 mL) was reacted with  $(\text{COCl})_2$  (0.71 mL, 8.40 mmol) and a mixture of (*S*)-**17**·(+)-CSA<sup>1</sup> (1.00 g, 2.10 mmol) and  $\text{K}_2\text{CO}_3$  (2.90 g, 21.0 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL). Purification via flash column chromatography (gradient elution, 1%→20%  $\text{Et}_2\text{O}$  in 30–40 °C petrol) gave **14** as a white solid (665 mg, 70%); mp 110–112 °C;  $[\alpha]_{\text{D}}^{25}$  –56.9 (*c* 1.0 in  $\text{CHCl}_3$ );  $\nu_{\text{max}}$  (KBr) 1650 (C=O), 1612 (C=C);  $\delta_{\text{H}}$  (500 MHz,  $\text{PhMe-}d_8$ , 343 K) 0.76 (9H, s,  $\text{CMe}_3$ ), 1.76 (3H, d, *J* 6.9, C(1'')*Me*), 6.46–6.58 (1H, br m, C(1'')*H*), 6.67–6.73 (1H, m, *Ar*), 6.83–6.89 (1H, m, *Ar*), 6.98–7.45 (6H, m, C(2)*H*, *Ar*), 7.58–7.67 (3H, m, *Ar*), 8.41 (1H, d, *J*

15.8, C(3)*H*), 8.56–8.74 (1H, br m, *Ar*);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 16.3 (C(1'')*Me*), 27.8 (*CMe*<sub>3</sub>), 55.8 (C(1'')), 83.1 (*CMe*<sub>3</sub>), 120.2, 123.0, 124.4, 124.9, 125.7, 126.1, 126.6, 126.8, 128.6, 130.6, 132.6, 133.6, 136.0, 137.2, 137.5 (*Ar*), 130.4 (C(2)), 141.4 (C(3)), 173.1 (C(1)); *m/z* (ESI<sup>+</sup>) 927 ([M(<sup>79</sup>Br)+M(<sup>81</sup>Br)+Na]<sup>+</sup>, 100%), 476 ([M(<sup>81</sup>Br)+Na]<sup>+</sup>, 50%), 474 ([M(<sup>79</sup>Br)+Na]<sup>+</sup>, 50%); HRMS (ESI<sup>+</sup>) C<sub>25</sub>H<sub>26</sub><sup>81</sup>BrNNaO<sub>2</sub><sup>+</sup> ([M(<sup>81</sup>Br)+Na]<sup>+</sup>) requires 476.1020; found 476.1010; HRMS (ESI<sup>+</sup>) C<sub>25</sub>H<sub>26</sub><sup>79</sup>BrNNaO<sub>2</sub><sup>+</sup> ([M(<sup>79</sup>Br)+Na]<sup>+</sup>) requires 474.1039; found 474.1024.

#### 4.3. (*S*)-*N*-*tert*-Butoxy-*N*-1''-(1'''-naphthyl)ethyl (*E*)-3-(3'-bromophenyl)propenamide **15**

Following the *general procedure*, a solution of *trans*-3-bromocinnamic acid **12** (400 mg, 1.76 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was reacted with (COCl)<sub>2</sub> (0.24 mL, 2.82 mmol) and a mixture of (*S*)-**17**·(+)-CSA<sup>1</sup> (336 mg, 0.70 mmol) and K<sub>2</sub>CO<sub>3</sub> (974 mg, 7.04 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL). Purification via flash column chromatography (gradient elution, 1%→20% Et<sub>2</sub>O in 30–40 °C petrol) gave **15** as a white solid (190 mg, 65%); mp 98–100 °C;  $[\alpha]_{\text{D}}^{25}$  –26.9 (*c* 1.0 in CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (KBr) 1649 (C=O), 1624 (C=C);  $\delta_{\text{H}}$  (500 MHz, PhMe-*d*<sub>8</sub>, 343 K) 0.75 (9H, s, *CMe*<sub>3</sub>), 1.78 (3H, d, *J* 6.9, C(1'')*Me*), 6.43–6.63 (1H, br m, C(1'')*H*), 6.69–6.78 (1H, m, *Ar*), 6.99–7.54 (7H, m, C(2)*H*, *Ar*), 7.56–7.68 (3H, m, *Ar*), 7.71 (1H, d, *J* 15.8, C(3)*H*), 8.55–8.77 (1H, br m, *Ar*);  $\delta_{\text{C}}$  (125 MHz, CDCl<sub>3</sub>) 16.4 (C(1'')*Me*), 27.8 (*CMe*<sub>3</sub>), 55.8 (C(1'')), 83.0 (*CMe*<sub>3</sub>), 121.5, 123.7, 124.4, 124.9, 125.6, 125.7, 126.1, 126.6, 127.5, 128.6, 132.6, 133.3, 133.5, 133.6, 135.3, 136.0 (*Ar*), 130.7 (C(2)), 141.4 (C(3)), 173.1 (C(1)); *m/z* (ESI<sup>+</sup>) 927 ([M(<sup>79</sup>Br)+M(<sup>81</sup>Br)+Na]<sup>+</sup>, 100%), 476 ([M(<sup>81</sup>Br)+Na]<sup>+</sup>, 50%), 474 ([M(<sup>79</sup>Br)+Na]<sup>+</sup>, 50%); HRMS (ESI<sup>+</sup>) C<sub>25</sub>H<sub>26</sub><sup>81</sup>BrNNaO<sub>2</sub><sup>+</sup> ([M(<sup>81</sup>Br)+Na]<sup>+</sup>) requires 476.1020; found 476.1024; HRMS (ESI<sup>+</sup>) C<sub>25</sub>H<sub>26</sub><sup>79</sup>BrNNaO<sub>2</sub><sup>+</sup> ([M(<sup>79</sup>Br)+Na]<sup>+</sup>) requires 474.1039; found 474.1031.

#### 4.4. (*S*)-*N*-*tert*-Butoxy-*N*-1''-(1'''-naphthyl)ethyl (*E*)-3-(4'-bromophenyl)propenamide **16**

Following the *general procedure*, a solution of *trans*-4-bromocinnamic acid **13** (300 mg, 1.32 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was reacted with (COCl)<sub>2</sub> (0.18 mL, 2.11 mmol) and a mixture of (*S*)-**17**·(+)-CSA<sup>1</sup> (250 mg, 0.52 mmol) and K<sub>2</sub>CO<sub>3</sub> (725 mg, 5.25 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL). Purification via flash column chromatography (gradient elution, 1%→20% Et<sub>2</sub>O in 30–40 °C petrol) gave **16** as a white solid (96 mg, 42%); mp 102–104 °C;  $[\alpha]_{\text{D}}^{25}$  –17.2 (*c* 0.5 in CHCl<sub>3</sub>);  $\nu_{\text{max}}$  (KBr) 1654 (C=O), 1616 (C=C);  $\delta_{\text{H}}$  (500 MHz, PhMe-*d*<sub>8</sub>, 343 K) 0.77 (9H, s, *CMe*<sub>3</sub>), 1.76 (3H, d, *J* 6.9, C(1'')*Me*), 6.47–6.63 (1H, br m, C(1'')*H*), 6.92–7.32 (7H, m, C(2)*H*, *Ar*), 7.39–7.49 (1H, m, *Ar*), 7.56–7.68 (3H, m, *Ar*), 7.75 (1H, d, *J* 15.8, C(3)*H*), 8.53–8.78

(1H, br m, Ar);  $\delta_C$  (125 MHz, CDCl<sub>3</sub>) 16.3 (C(1'')Me), 27.8 (CMe<sub>3</sub>), 55.7 (C(1')), 83.1 (CMe<sub>3</sub>), 119.4 (C(2)), 124.0, 124.4, 124.9, 125.7, 126.1, 126.5, 128.6, 129.1, 129.4, 132.1, 132.6, 133.6, 134.2, 136.0 (Ar), 141.7 (C(3)), 173.3 (C(1));  $m/z$  (ESI<sup>+</sup>) 476 ([M(<sup>81</sup>Br)+Na]<sup>+</sup>, 100%), 474 ([M(<sup>79</sup>Br)+Na]<sup>+</sup>, 100%); HRMS (ESI<sup>+</sup>) C<sub>25</sub>H<sub>26</sub><sup>81</sup>BrNNaO<sub>2</sub><sup>+</sup> ([M(<sup>81</sup>Br)+Na]<sup>+</sup>) requires 476.1020; found 476.1010; HRMS (ESI<sup>+</sup>) C<sub>25</sub>H<sub>26</sub><sup>79</sup>BrNNaO<sub>2</sub><sup>+</sup> ([M(<sup>79</sup>Br)+Na]<sup>+</sup>) requires 474.1039; found 474.1021.

#### 4.5. Single Crystal X-ray Diffraction

Single crystal diffraction data for **14–16** were collected using a Nonius  $\kappa$ -CCD diffractometer (Mo-K $\alpha$  radiation,  $\lambda$ = 0.71073 Å) at 150(2) K with an Oxford Cryosystems Cryostream N<sub>2</sub> open-flow cooling device<sup>16</sup> and processed using the DENZO-SMN package,<sup>17</sup> including unit cell parameter refinement and inter-frame scaling (which were carried out using SCALEPACK within DENZO-SMN).

The structures were solved using SIR92.<sup>18</sup> Refinement was carried out using full-matrix least-squares within the CRYSTALS suite,<sup>19</sup> on F<sup>2</sup>. All non-hydrogen atoms were refined with anisotropic displacement parameters. The positions and isotropic displacement parameters of hydrogen atoms were refined using restraints prior to inclusion into the model with riding constraints.<sup>20</sup> For all structures the Flack  $x$  parameter<sup>13,14</sup> was refined and was found to satisfy the criteria for a reliable assignment of absolute configuration of a material known to be enantiopure.

Full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 817636, 817637 and 817638, respectively. Copies of these data can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

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