Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 525–535

Synthesis of atropisomeric 2,8-dioxygenated *N*,*N*-diisopropyl-1-naphthamides via kinetic resolution under Sharpless asymmetric dihydroxylation conditions

Wei-Min Dai,* Yan Zhang and Ye Zhang

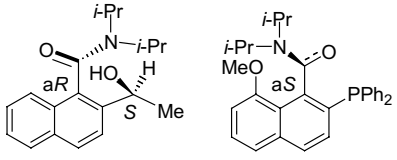
Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, SAR

Received 30 October 2003; accepted 27 November 2003

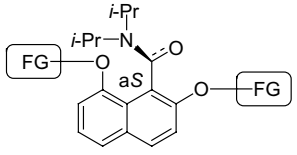
Abstract—A kinetic resolution approach under Sharpless asymmetric dihydroxylation conditions was used to synthesize enantio-enriched atropisomeric *N*,*N*-diisopropyl-1-naphthamides possessing oxygenated functionalities at both the C2 and C8 positions. A significant influence of the substrate structures on the efficiency of the kinetic resolution was observed. (+)-(a*S*)-*N*,*N*-Diisopropyl-2-[2′-(*E*)-butenoyloxy]-8-methoxy-1-naphthamide is obtained in 35% yield with 94.3% ee after treating the racemate with 3.5 mol% each of Os and $(DHQD)_2$–PHAL at 0 °C for 22 h.

1. Introduction

Atropisomers with rotationally restricted amide scaffolds has received considerable attention in recent years.[1] Reported examples of axially chiral amides include anilides,[2] *N*-arylimides,[3] benzamides,[4] and 1-naphthamides.[5] Preparation and application of these atropisomeric amides in stereo controlled reactions have been demonstrated by Curran et al.,[2a–d,3a] Beak et al.,[2e,5a] Simpkins et al.,[2f–2i] Taguchi et al.,[2j–2p] Uemura et al.,[2r,4a–4c] Clayden et al.,[2s,4e,5b–j] amongst others. The atropisomeric naphthalene derivatives possessing a nonamide substitution at C1 are also known. For example, C1-vinylnaphthalenes,[6] C1-arylsulfinylnaphthalenes,[7] and *tert*-butyl-1-(2-methyl-1-naphthyl)phosphine oxide[8] have been reported. Axially chiral thioanilides and related sulfur analogues have been reported as well.[9] In our previous studies,[10] we prepared enantiomerically pure, functionalized *N*,*N*-diisopropyl-1-naphthamides such as (−)-(a*R*)-*syn*-**1**,[10a] (−)-(a*S*)-**2**,[10b] and their antipodes via chemical resolution or separation over a chiral stationary phase. These chiral amides have been demonstrated as the 'chiral wall' templates in the desymmetrization of cyclic *meso* anhydrides with 100% diastereoselectivity[10a] and in the Pd-catalyzed asymmetric allylic alkylation with up to 94.7% ee.[10b] We herein report on the kinetic resolution[11] and stereochemical assignment of 2,8-dioxygenated *N*,*N*-diisopropyl-1-naphthamides such as (a*S*)-**3**, whose functional groups (FG) at C2 and C8 can be engineered for synthetic applications.



(-)-(a*R*)-*syn*-**1** (-)-(a*S*)-**2**



(a*S*)-**3**

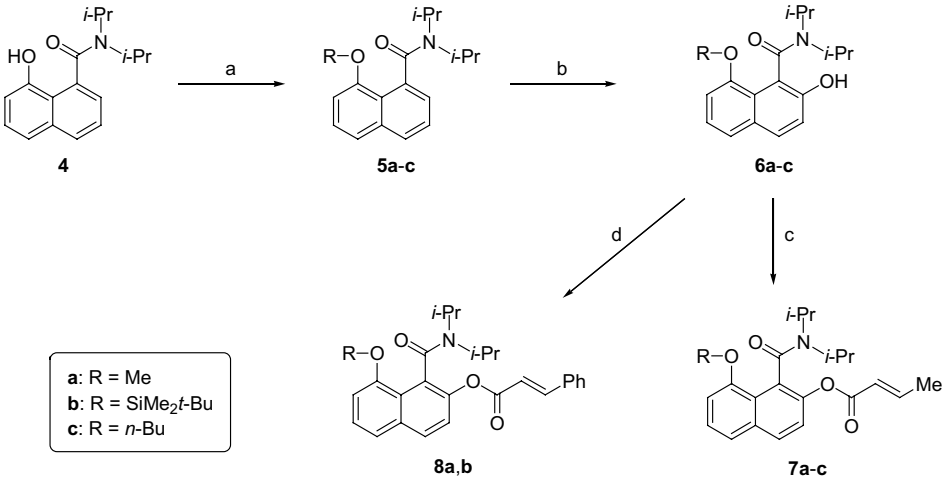
2. Results and discussion

2.1. Synthesis of racemic substrates

We prepared *N*,*N*,-diisopropyl-8-hydroxy-1-naphthamide **4** from 1,8-naphthalic anhydride according to the

* Corresponding author. Tel.: +852-2358-7365; fax: +852-2358-1594; e-mail: chdai@ust.hk

0957-4166/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2003.11.039



Scheme 1. Reagents and conditions: (a) K_2CO_3, MeI or *n*-BuBr, acetone, reflux, 24 h, 93% for **5a**, 91% for **5c**, or *t*-$BuMe_2SiCl$, imidazole, DMF, 45 °C, 20 h, 96% for **5b**; (b) *s*-BuLi, THF, −78 °C, 3 h; $B(Oi\text{-}Pr)_3$, 0 °C, 1 h; then glacial AcOH, H_2O_2, overnight, 92% for **6a**, 87% for **6b**, and 87% for **6c**; (c) *trans*-crotonyl chloride, Et_3N, CH_2Cl_2, rt, 3 h, 73% for **7a**, 81% for **7b**, and 74% for **7c**; (d) *trans*-cinnamoyl chloride, Et_3N, CH_2Cl_2, rt, 3 h, 97% for **8a** and 91% for **8b**.

reported method (Scheme 1).[12] Alkylation of the C8-hydroxyl group in **4** with MeI or *n*-BuBr in the presence of K_2CO_3 in refluxing acetone gave the 8-methoxy and 8-*n*-buthoxy derivatives **5a**[12a,13] and **5c**, respectively. Treatment of **4** with *t*-$BuMe_2SiCl$–imidazole in DMF afforded the silyl ether **5b**[10b] in 96% yield. Directed *ortho* deprotonation of **5a**–**c** was achieved with *s*-BuLi in THF at −78 °C with the resulting aryllithium species subjected to a reaction with $B(Oi\text{-}Pr)_3$ to form the organoboron intermediates. The latter, without isolation, were treated with $AcOH–H_2O_2$[14] at room temperature to furnish 2-hydroxy-1-naphthamides **6a**–**c** in 87–92% yields. The crotonates **7a**–**c** and cinnamates **8a** and **8b** were prepared from **6a**–**c** by treatment with *trans*-crotonyl chloride and *trans*-cinnamoyl chloride in the presence of Et_3N in good yields.

The structures of **6a** and **6b** and **7b** were confirmed by X-ray crystallographic analysis as shown in Figures 1–3. It is interesting to note that the silyl group and the *N*,*N*-diisopropyl moiety in **6b** and **7b** are oppositely oriented across the naphthalene ring thus minimizing steric repulsion (see Fig. 3b). Distortion of the naphthalene skeleton and *exo*-cyclic bonds in **6a** and **6b** and **7b** was observed. The dihedral angles θ_1–θ_4[13,15] associated with two *exo*-cyclic bonds, $C1_{Ar}$–C(O)N and $C8_{Ar}$–OR^1 are listed in Table 1. The through space distance *d* between the C8-oxygen and C1-carbonyl carbon is 2.750 Å for **6b** or 2.773 Å for **7b**. These distances are significantly longer when compared to the value of 2.599 Å for **6a** and other 8-methoxy-1-naphthamides (2.60–2.62 Å).[13,15] This implies that the electronic interaction between the C8-oxygen lone pair electrons and the π^* orbital of the amide is rather weak.[15] This may partially account for the fast racemization of enantioenriched **6b** with the free hydroxy group at the C2 position (vide infra).

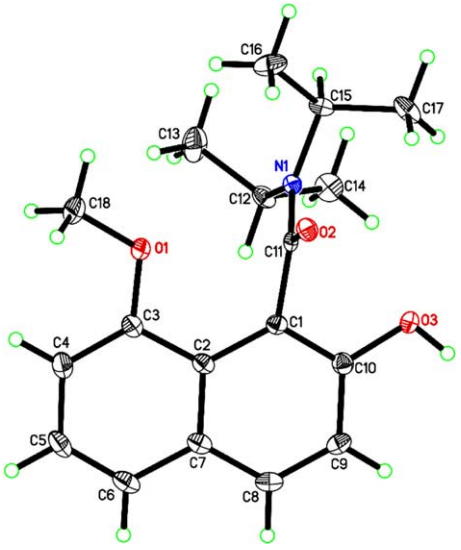


Figure 1. X-ray crystal structure of *rac*-**6a**.

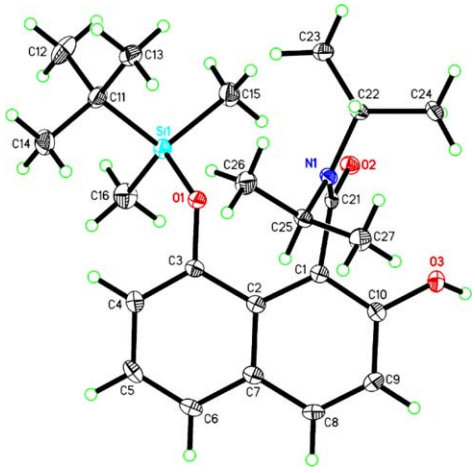


Figure 2. X-ray crystal structure of *rac*-**6b**.

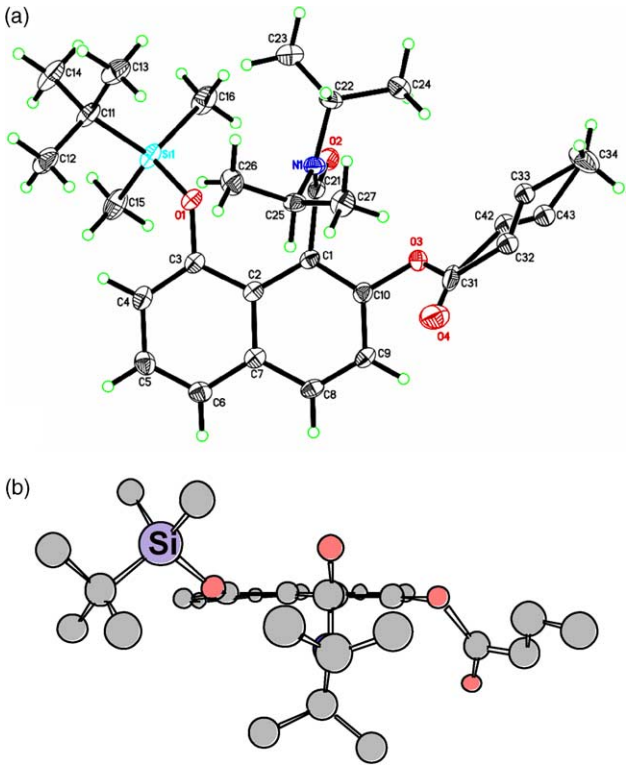
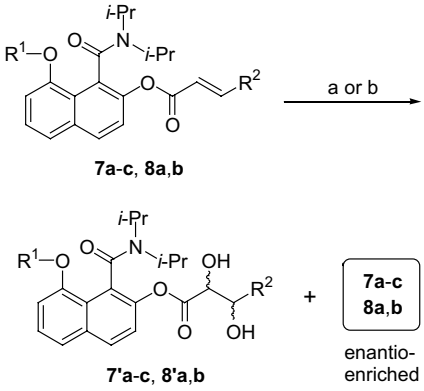


Figure 3. (a) X-ray crystal structure of *rac*-**7b**. C32/C33 and C42/C43 are representing the disorder of a pair of CH_2 groups with occupation factors of 65% and 35%, respectively. (b) Top view of *rac*-**7b** with occupation factors of 65%. Hydrogen atoms are omitted for clarity.

2.2. Kinetic resolution

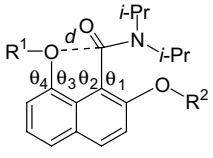
Recently, Walsh et al.[11] reported the kinetic resolution of atropisomeric benzamides and 1-naphthamides possessing an *ortho* vinyl group by using the Sharpless asymmetric dihydroxylation reaction.[16] For the benzamides, high k_{rel} values[17] of up to 32 were generally obtained whilst for an *N*,*N*-diisopropyl-1-naphthamide, k_{rel} values of 4.4 and 6.6 were reported by using AD-mix-α and AD-mix-β as the catalyst system, respectively. For the atropisomeric amides **7a–c** and **8a** and **8b**, the axis of chirality was incorporated into the ester moiety rather than being connected directly onto the olefin unit, where the asymmetric dihydroxylation takes place. After screening for different combinations of Os and chiral ligand loadings, we selected the following reaction conditions for the kinetic resolution of amides **7a–c** and **8a** and **8b**: 3.5 mol% $K_2OsO_4{\cdot}2H_2O$ and 3.5 mol% $(DHQ)_2$–PHAL (used in AD-mix-α) or $(DHQD)_2$–PHAL (used in AD-mix-β) in the presence of $K_3Fe(CN)_6$ and K_2CO_3 in *t*-BuOH–H_2O (1:1) at 0 °C (Scheme 2). Progress of the reaction and enantiomeric excess of the remaining substrate were monitored by HPLC analysis over a chiral stationary phase. The obtained average k_{rel} values[17] are listed in Table 2. For the kinetic resolution of **7a** given in entry 6, the measured k_{rel} values after reacting for 7, 11.5, and 22 h increase from 9.5, 10.5, to 13.5 with increased conversion of the substrate. At 61% conversion (0 °C, 22 h), (+)-**7a** was isolated in 35% yield and in 94.3% ee. The HPLC chromatogram of (+)-**7a** is shown in Figure 4.



Scheme 2. Reagents and conditions: (a) 3.5 mol% each of $K_2OsO_4{\cdot}2H_2O$ and $(DHQ)_2$–PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH–H_2O (1:1), 0 °C; (b) 3.5 mol% each of $K_2OsO_4{\cdot}2H_2O$ and $(DHQD)_2$–PHAL, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH–H_2O (1:1), 0 °C. $(DHQ)_2$–PHAL = 1,4-bis(9-*O*-dihydroquinine)phthalazine; $(DHQD)_2$–PHAL = 1,4-bis(9-*O*-dihydroquinidine)phthalazine.

A significant substituent effect on the efficiency of the kinetic resolution was observed. Replacement of the C8 methoxy group by the silyloxy group resulted in non-selective reactions for the amide **7b** compared to the amide **7a** (entries 1 and 6 vs entries 2 and 7). A decrease in k_{rel} values was observed for the C8 *n*-butyl ether **7c**

Table 1. Crystallographic measurements for 2,8-dioxygenated 1-naphthamides



Entry	Compound	*d* (Å)	Angle (°)			
			θ_1	θ_2	θ_3	θ_4
1	*rac*-**6a**	2.599	115.0	124.7	114.6	124.3
2	*rac*-**6b**	2.750	114.0	125.7	118.1	121.2
3	*rac*-**7b**	2.773	115.8	125.5	118.6	121.2
4	(a*S*)-(+)-**11**	2.802	115.6	126.6	119.3	119.8

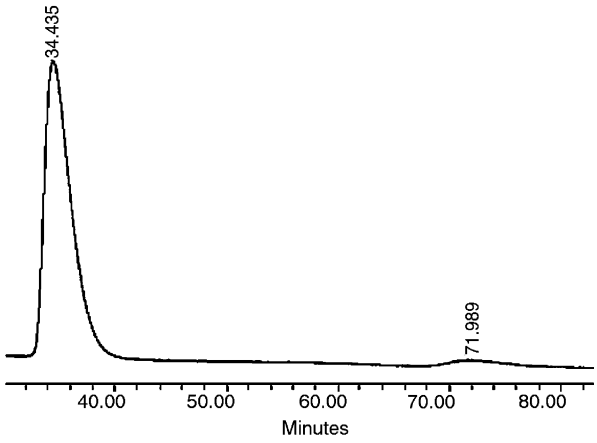
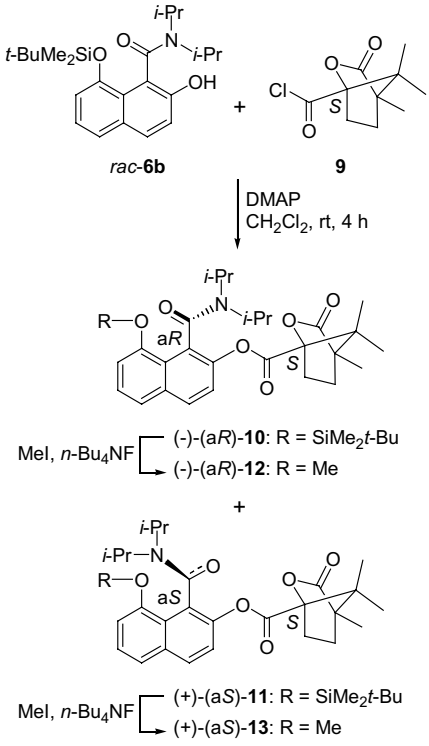


Figure 4. HPLC chromatogram of (+)-**7a** with 94.3% ee (HPLC setting: Chiralcel OD column eluted with 90:10 ratio of hexane–isopropanol at 0.5 mL/min and by UV detection at 254 nm).

(entries 3 and 8). The substituent at the β-position of the olefinic moiety is also sensitive toward the kinetic resolution. Two cinnamates **8a** and **8b** afforded no kinetic resolution under the asymmetric dihydroxylation conditions using either $(DHQ)_2$–PHAL or $(DHQD)_2$–PHAL as the chiral ligand (entries 4, 5, 9, and 10). Since the stereochemistry of the dihydroxylation products **7′a**–**c**, and **8′a** and **8′b** are complicated, we did not attempt to isolate these diols.

2.3. Determination of the stereochemistry

The stereochemistry of the enantioenriched (+)-**7a** obtained from the kinetic resolution given in entry 6 of Table 2 was determined by chemical correlation. We first prepared the diastereomeric esters (−)-(a*R*)-**12** and (+)-(a*S*)-**13** from the reaction of (−)-(1*S*)-camphanic chloride **9** with racemic **6a**. Unfortunately, the diastereomers could not be easily separated by column chromatography over silica gel. Alternatively, the camphanates (−)-(a*R*)-**10** (38%) and (+)-(a*S*)-**11** (42%) were synthesized from *rac*-**6b** and **9** as shown in Scheme 3. Diastereomerically pure compounds were obtained after column chromatographic separation. The structure of (+)-(a*S*)-**11** was determined by X-ray crystallographic analysis (Fig. 5) with the chiral axis determined to be a*S*. In contrast, the diastereomer (−)-(a*R*)-**10** was not stable in solution and cleavage of the ester bond was observed. It is analogous to a camphanate of 8-hydroxy-1-naphthamide reported in our previous study.[10b] Removal of



Scheme 3. Chemical resolution of *rac*-**6b**.

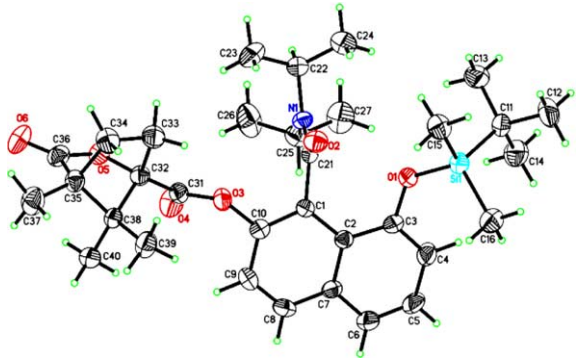


Figure 5. X-ray crystal structure of (+)-(a*S*)-**11**.

the C8 silyl group in (−)-(a*R*)-**10** by *n*-Bu_4NF and methylation of the resulting alkoxide was performed in a 'one pot' fashion to give (−)-(a*R*)-**12** (82%) with improved chemical stability toward ester bond cleavage compared to the silyl ether (−)-(a*R*)-**10**. Similarly, (+)-

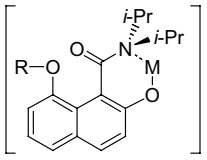
Table 2. Kinetic resolution of atropisomeric 1-naphthamides under Sharpless asymmetric dihydroxylation conditions[a]

Entry	Amide	Chiral ligand	k_{rel}[b]	Entry	Amide	Chiral ligand	k_{rel}[b]
1	**7a**	$(DHQ)_2$–PHAL	4.2	6	**7a**	$(DHQD)_2$–PHAL	11.2
2	**7b**	$(DHQ)_2$–PHAL	1.2	7	**7b**	$(DHQD)_2$–PHAL	1.0
3	**7c**	$(DHQ)_2$–PHAL	1.8	8	**7c**	$(DHQD)_2$–PHAL	2.5
4	**8a**	$(DHQ)_2$–PHAL	1.1	9	**8a**	$(DHQD)_2$–PHAL	1.1
5	**8b**	$(DHQ)_2$–PHAL	1.1	10	**8b**	$(DHQD)_2$–PHAL	1.1

[a] The reaction was carried out at 0 °C with 3.5 mol% each of the chiral ligand and $K_2OsO_4 \cdot H_2O$.
[b] Average values.

(a*S*)-**13** was obtained from (+)-(a*S*)-**11** with an overall yield of 89% (Scheme 3).

The camphanate (+)-(a*S*)-**11** was hydrolyzed with 10% aqueous KOH to give 89% yield of **6b** (Scheme 4), which was found to be in its racemic form as confirmed by HPLC analysis over a chiral stationary phase. A dynamic HPLC chromatogram of **6b** is shown in Figure 6 in which a plateau between the peaks indicates a low energy barrier for rotation.[18] The facile racemization of **6b** is unexpected when considering the half-lives of 19 h[19] and 12 days[15] at 20 °C estimated for 2-methoxy-1-naphthamide and 8-methoxy-1-naphthamide, respectively. This can be explained by a transition state[19] of bond rotation around $C1_{Ar}$–C(O)N with reduced activation energy. This may result from the interaction between the C2 hydroxyl group and the pyramidal nitrogen[19] of the amide in the transition state **14** via a hydrogen bond or through metal chelation as in the case of ester hydrolysis. It should be emphasized that the amide nitrogen is not in conjugation with C=O in **14**.



14: R = Me, *t*-BuMe$_2$Si
M = H or metal

Conversion of the silyl ether (+)-(a*S*)-**11** into the methoxy ether (+)-(a*S*)-**13** followed by ester hydrolysis (rt, 40 min) gave (+)-(a*S*)-**6a**. The latter was found to be partially racemized (86.8% ee) by HPLC analysis immediately after purification but to a much lesser extent when compared with the silyl ether **6b**. Compound (+)-(a*S*)-**6a** of 42.2% ee was also obtained by ester cleavage (rt, 8.5 h) of the enantioenriched (+)-(a*S*)-**7a** (94.3% ee) prepared by kinetic resolution. The stereochemistry of (+)-(a*S*)-**7a** was thus determined to be a*S*. We found that racemization of (+)-(a*S*)-**6a** took place during the saponification of (+)-(a*S*)-**7a** and (+)-(a*S*)-**13** with the enantiomeric excess of (+)-(a*S*)-**6a** dependent on the reaction time. Two HPLC chromatograms from the samples of (+)-(a*S*)-**6a** obtained by hydrolysis of (+)-(a*S*)-**7a** and (+)-(a*S*)-**13** are given in Figure 7.

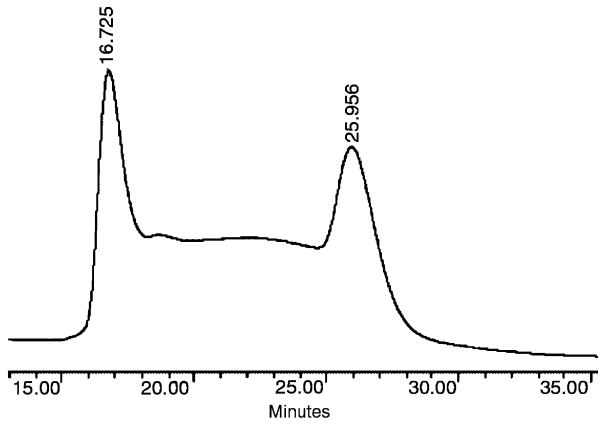
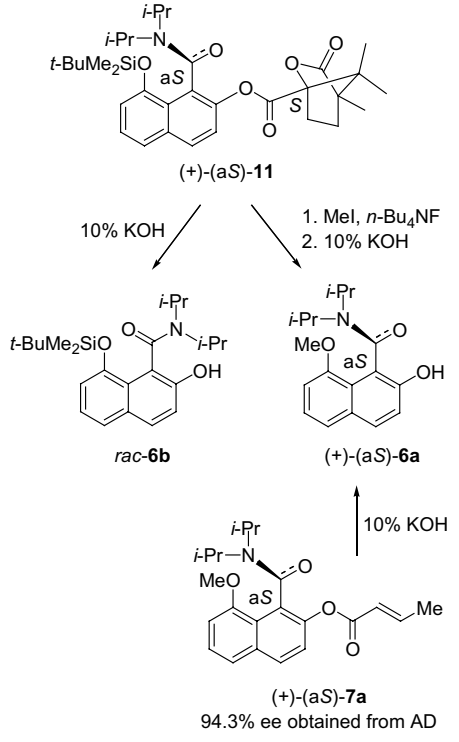


Figure 6. Dynamic HPLC chromatogram of **6b** (HPLC setting: Chiralpak AD column eluted with 99:1 ratio of hexane–isopropanol at 0.3 mL/min and by UV detection at 254 nm).



Scheme 4. Determination of stereochemistry of (+)-(a*S*)-**7a**.

3. Conclusion

In summary, we have synthesized a series of 2,8-dioxygenated *N*,*N*-diisopropyl-1-naphthamides for kinetic resolution under Sharpless asymmetric dihydroxylation conditions. A significant substituent effect on the efficiency of the kinetic resolution was observed. After treatment of the racemate with 3.5 mol% each of Os and $(DHQD)_2$–PHAL at 0 °C for 22 h, (+)-(a*S*)-*N*,*N*-diisopropyl-2-[2′-(*E*)-butenoyloxy]-8-methoxy-1-naphthamide (+)-(a*S*)-**7a** was obtained in 35% yield with 94.3% ee. The stereochemistry of (+)-(a*S*)-**7a** was determined to be a*S* by chemical correlation with the camphanate (+)-(a*S*)-**11**, whose stereochemistry was established by X-ray crystallographic analysis. Application of the enantioenriched atropisomeric amide in asymmetric synthesis is in progress and the results will be reported elsewhere.

4. Experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively) with $CHCl_3$ as the internal reference. IR spectra were taken

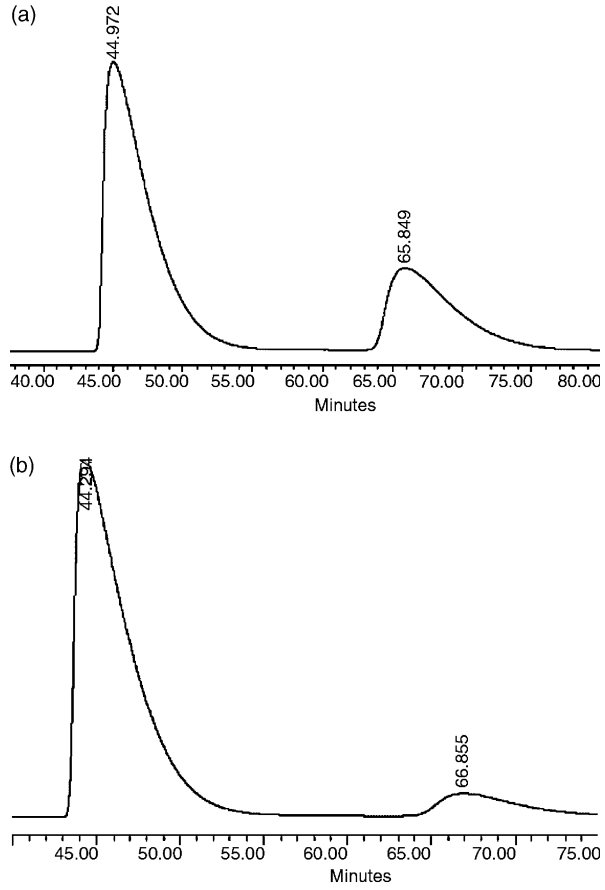


Figure 7. HPLC chromatograms of (+)-(a*S*)-**6a**. (a) The sample obtained from hydrolysis of (+)-(a*S*)-**7a** with an enantiomer ratio of 71.1:28.9 and (b) the sample obtained from hydrolysis of (+)-(a*S*)-**13** with an enantiomer ratio of 93.4:6.6 (HPLC setting: Chiralpak AD column eluted with 97:3 ratio of hexane–isopropanol at 0.3 mL/min and by UV detection at 254 nm).

on a FT-IR spectrophotometer. Mass spectra (MS) were measured by the CI method. Elemental analyses were performed by Zhejiang University. All reactions were carried out under a nitrogen atmosphere and monitored by thin-layer chromatography on 0.25-mm E. Merck silica gel plates (60 F-254) using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. All reagents were obtained commercially and used as received. Room temperature is around 25 °C.

4.1. Synthesis

4.1.1. *N*,*N*-Diisopropyl-8-butoxy-1-naphthamide 5c. To a suspension of K_2CO_3 (2.07 g, 15.0 mmol) and *N*,*N*-diisopropyl-8-hydroxy-1-naphthamide **4** (814.1 mg, 3.0 mmol) in acetone (30 mL) under a nitrogen atmosphere was added 1-bromobutane (3.2 mL, 30.0 mmol) followed by refluxing for 24 h. The reaction mixture was filtered off through Celite and the filtrate evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 3.2% EtOAc–CH_2Cl_2) to give **5c** (894.0 mg, 91%) as a colorless crystalline solid; mp 88–89 °C (CH_2Cl_2–hexane); $R_f = 0.48$ (3.2% EtOAc–CH_2Cl_2); IR ($CHCl_3$): 2960, 2928, 1637, 1326, 1259, 1107 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76 (d, $J = 8.1$ Hz, 1H), 7.46–7.35 (m, 3H), 7.19 (dd, $J = 6.6$, 0.9 Hz, 1H), 6.88 (dd, $J = 7.5$, 1.5 Hz, 1H), 4.31–4.14 (m, 2H), 3.56 (octet, $J = 6.6$ Hz, 2H), 1.95–1.85 (m, 2H), 1.68 (d, $J = 6.9$ Hz, 3H), 1.62 (d, $J = 6.9$ Hz, 3H), 1.56–1.43 (m, 2H), 1.10 (d, $J = 6.9$ Hz, 3H), 1.00 (d, $J = 6.6$ Hz, 3H), 0.98 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 154.7, 135.3, 134.7, 127.8, 126.1, 125.6, 123.6, 121.8, 120.5, 106.4, 68.9, 50.7, 45.4, 30.9, 20.9, 20.6, 20.1 (×2), 19.3, 14.0; MS (+FAB): m/z 328 (M+H$^+$, 76), 171 (100). Anal. Calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 77.25; H, 8.83; N, 4.82.

4.1.2. General procedure for the synthesis of 2-hydroxy-1-naphthamides: preparation of *N*,*N*-diisopropyl-2-hydroxy-8-methoxy-1-naphthamide 6a. To a solution of *N*,*N*-diisopropyl-8-methoxy-1-naphthamide **5a** (2.0 mmol) in dry THF (20 mL) cooled in a dry ice–acetone bath (−78 °C) under a nitrogen atmosphere was added dropwise a solution of *sec*-butyllithium (4.62 mL, 1.3 M in hexanes, 6.0 mmol) via a syringe followed by stirring at the same temperature for 3 h to form the aryllithium species. To a solution of triisopropyl borate (1.42 mL, 6.0 mmol) in THF (30 mL) cooled in a dry ice–acetone bath (−78 °C) under a nitrogen atmosphere was added the above aryllithium solution via a syringe. The resultant mixture was slowly warmed to 0 °C and kept while stirring at the same temperature for another 1 h. Glacial acetic acid (0.4 mL) was added into the reaction mixture followed by the dropwise addition of aqueous 30% H_2O_2 (1 mL). The mixture turned to a milky solution and was stirred at ambient temperature overnight. EtOAc (30 mL) and H_2O (30 mL) were added, and the white precipitate dissolved to form a clear solution. After extraction with EtOAc (30×3 mL), the combined organic layer was washed with aqueous solution of $FeCl_2$, saturated aqueous NH_4Cl, and 5% aqueous solution of KOH (5×3 mL). The organic layer was discarded and the combined aqueous layer acidified with 5% aqueous HCl and extracted with EtOAc (20×3 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 25% EtOAc–CH_2Cl_2) to give **6a** (555.0 mg, 92%) as a pale yellow crystalline solid; mp 247–248 °C (CH_2Cl_2–hexane); $R_f = 0.28$ (25% EtOAc–CH_2Cl_2); IR ($CHCl_3$): 3100 (br), 2921, 1597, 1580, 1256 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.56 (s, 1H), 7.65 (d, $J = 8.7$ Hz, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.17 (t, $J = 7.9$ Hz, 1H), 7.12 (d, $J = 9.0$ Hz, 1H), 6.85 (d, $J = 7.5$ Hz, 1H), 3.78 (s, 3H), 3.61 (quintet, $J = 6.6$ Hz, 1H), 3.50 (quintet, $J = 6.6$ Hz, 1H), 1.53 (d, $J = 6.3$ Hz, 3H), 1.48 (d, $J = 6.3$ Hz, 3H), 1.07 (d, $J = 6.3$ Hz, 3H), 0.94 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 154.1, 150.8, 128.9, 128.5, 122.9, 122.4, 120.3, 118.2, 117.2, 105.6, 54.9, 50.4, 44.4, 20.6, 20.5, 20.4, 19.5; MS (+FAB): m/z 302 (M+H$^+$,

100%). Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.53; H, 7.65; N, 4.74.

4.1.3. *N*,*N*-Diisopropyl-8-(*tert*-butyldimethylsilyloxy)-2-hydroxy-1-naphthamide 6b. The reaction mixture was extracted with EtOAc (20×3 mL) and the combined organic layer washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 6% EtOAc–CH_2Cl_2) to afford **6b** (87%) as a colorless crystalline solid; mp 176–177 °C (CH_2Cl_2–hexane); $R_f = 0.31$ (6% EtOAc–CH_2Cl_2); IR ($CHCl_3$): 3100 (br), 2930, 1603, 1578, 1262 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.83 (br s, 1H), 7.55 (d, $J = 9.0$ Hz, 1H), 7.34 (d, $J = 8.1$ Hz, 1H), 7.14 (t, $J = 7.5$ Hz, 1H), 7.10 (d, $J = 9.3$ Hz, 1H), 6.92 (d, $J = 7.2$ Hz, 1H), 3.61 (quintet, $J = 6.6$ Hz, 1H), 3.40 (quintet, $J = 6.6$ Hz, 1H), 1.65 (d, $J = 7.2$ Hz, 3H), 1.52 (d, $J = 6.6$ Hz, 3H), 1.06 (d, $J = 6.6$ Hz, 3H), 0.99 (s, 9H), 0.79 (d, $J = 6.6$ Hz, 3H), 0.42 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 152.5, 150.6, 129.9, 129.8, 124.9, 122.9, 121.6, 119.0, 115.7, 115.2, 50.5, 46.5, 27.0 (×3), 22.1, 20.6, 20.3, 20.1, 19.4, −2.5, −3.9; MS (+FAB): m/z 402 ($M+H^+$, 24), 344 (100). Anal. Calcd for $C_{23}H_{35}NO_3Si$: C, 68.78; H, 8.78; N, 3.49. Found: C, 68.75; H, 8.91; N, 3.94.

4.1.4. *N*,*N*-Diisopropyl-8-butoxy-2-hydroxy-1-naphthamide 6c. Prepared in 87% yield as described for **6a** as white needles; mp 207–208 °C (CH_2Cl_2–hexane); $R_f = 0.21$ (14% EtOAc–CH_2Cl_2); IR ($CHCl_3$): 3100 (br), 2919, 1597, 1579 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 9.55 (br s, 1H), 7.64 (d, $J = 9.0$ Hz, 1H), 7.31 (d, $J = 7.8$ Hz, 1H), 7.15 (t, $J = 7.8$ Hz, 1H), 7.11 (d, $J = 8.7$ Hz, 1H), 6.88 (d, $J = 7.8$ Hz, 1H), 4.21–4.02 (m, 2H), 3.64–3.48 (m, 2H), 1.81–1.65 (m, 2H), 1.54 (d, $J = 6.6$ Hz, 3H), 1.48 (d, $J = 6.9$ Hz, 3H), 1.50–1.35 (m, 2H), 1.05 (d, $J = 6.9$ Hz, 3H), 0.98 (d, $J = 6.3$ Hz, 3H), 0.90 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.6, 153.2, 150.9, 129.1, 128.6, 122.9, 122.8, 120.2, 118.2, 117.3, 106.6, 67.8, 50.3, 44.5, 30.3, 20.9, 20.4, 20.0, 19.9, 18.8, 13.9; MS (+FAB): m/z 344 ($M+H^+$, 100). Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.40; H, 8.51; N, 4.39.

4.1.5. General procedure for the synthesis of esters of 2-hydroxy-1-naphthamides: preparation of *N*,*N*-diisopropyl-2-[2′-(*E*)-butenoyloxy]-8-methoxy-1-naphthamide 7a. To a solution of 2-naphthols **6a-c** (1.5 mmol) and Et_3N (0.42 mL, 3.0 mmol) in dry CH_2Cl_2 (30 mL) cooled in an ice–H_2O bath (ca. 0 °C) under a nitrogen atmosphere was added dropwise *trans*-crotonyl or *trans*-cinnamoyl chloride (3.0 mmol). The resultant mixture was allowed to warm to room temperature and then stirred at the same temperature for 3 h. The reaction mixture was filtered through a pad of silica gel with washing by 33% EtOAc–CH_2Cl_2 (10 mL). The combined filtrate was evaporated under reduced pressure, and the residue purified by flash column chromatography over silica gel to give the esters **7a–c** and **8a** and **8b**, respectively. **7a**: prepared in 73% yield after flash column chromatography (silica gel, 9.1% EtOAc–CH_2Cl_2) as a colorless crystalline solid; mp 203–204 °C (CH_2Cl_2–hexane); $R_f = 0.28$ (9.1% EtOAc–CH_2Cl_2); IR ($CHCl_3$): 2929, 1738, 1635, 1316, 1212, 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, $J = 9.3$ Hz, 1H), 7.43 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.38 (d, $J = 7.5$ Hz, 1H), 7.33 (d, $J = 8.7$ Hz, 1H), 7.23 (dq, $J = 15.6$, 6.9 Hz, 1H), 6.85 (dd, $J = 7.2$, 1.2 Hz, 1H), 6.05 (dq, $J = 15.6$, 1.5 Hz, 1H), 3.91 (s, 3H), 3.60 (septet, $J = 6.6$ Hz, 1H), 3.51 (septet, $J = 6.6$ Hz, 1H), 1.96 (dd, $J = 6.9$, 1.5 Hz, 3H), 1.67 (d, $J = 6.6$ Hz, 3H), 1.56 (d, $J = 6.9$ Hz, 3H), 1.01 (d, $J = 6.9$ Hz, 3H), 1.00 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 164.3, 155.3, 147.5, 144.3, 133.0, 128.6, 125.9, 124.6, 122.2, 122.1, 121.6, 120.8, 106.2, 55.3, 50.8, 45.7, 20.7, 20.7, 20.4, 19.8, 18.3; MS (+FAB): m/z 370 ($M+H^+$, 100). Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.53; H, 7.34; N, 4.25.

4.1.6. *N*,*N*-Diisopropyl-2-[2′-(*E*)-butenoyloxy]-8-(*tert*-butyldimethylsilyloxy)-1-naphthamide 7b. Prepared in 81% yield after flash column chromatography (silica gel, 1:20:20 EtOAc–CH_2Cl_2–hexane) as a colorless crystalline solid; mp 187–188 °C (CH_2Cl_2–hexane); $R_f = 0.20$ (1:20:20 EtOAc–CH_2Cl_2–hexane); IR ($CHCl_3$): 2928, 1739, 1645, 1308, 1211, 1149 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, $J = 9.0$ Hz, 1H), 7.45 (d, $J = 7.8$ Hz, 1H), 7.33–7.16 (m, 3H), 6.98 (d, $J = 6.9$ Hz, 1H), 6.03 (dd, $J = 15.3$, 1.5 Hz, 1H), 3.72 (septet, $J = 6.9$ Hz, 1H), 3.26 (septet, $J = 6.6$ Hz, 1H), 1.95 (dd, $J = 7.2$, 1.5 Hz, 3H), 1.64 (d, $J = 6.9$ Hz, 3H), 1.48 (d, $J = 7.2$ Hz, 3H), 1.03 (d, $J = 6.9$ Hz, 3H), 1.02 (s, 9H), 0.88 (d, $J = 6.9$ Hz, 3H), 0.46 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 164.5, 152.0, 147.4, 145.0, 133.1, 129.0, 125.4, 124.7, 124.6, 122.1, 121.7, 121.6, 115.9, 50.5, 45.8, 27.2 (×3), 22.7, 21.0, 20.6, 20.3, 19.5, 18.3, −2.4, −3.8; MS (+FAB): m/z 471 ($M+H^+$, 22), 470 (M^+, 60), 412 (100). Anal. Calcd for $C_{27}H_{39}NO_4Si$: C, 69.04; H, 8.37; N, 2.98. Found: C, 69.38; H, 8.43; N, 2.66.

4.1.7. *N*,*N*-Diisopropyl-2-[2′-(*E*)-butenoyloxy]-8-butoxy-1-naphthamide 7c. Prepared in 74% yield after flash column chromatography (silica gel, 3.8% EtOAc–CH_2Cl_2) as a pale green crystalline solid; mp 104–105 °C (CH_2Cl_2–hexane); $R_f = 0.33$ (3.8% EtOAc–CH_2Cl_2); IR ($CHCl_3$): 2930, 1738, 1635, 1313, 1210, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, $J = 8.7$ Hz, 1H), 7.35–7.07 (m, 4H), 6.82 (d, $J = 7.2$ Hz, 1H), 5.95 (d, $J = 15.3$ Hz, 1H), 4.25–4.03 (m, 2H), 3.52–3.41 (m, 2H), 1.87 (d, $J = 7.2$ Hz, 3H), 1.82–1.66 (m, 2H), 1.58 (d, $J = 6.9$ Hz, 3H), 1.45 (d, $J = 6.9$ Hz, 3H), 1.46–1.32 (m, 2H), 0.95 (d, $J = 6.3$ Hz, 3H), 0.90 (d, $J = 6.9$ Hz, 3H), 0.86 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 164.4, 154.5, 147.5, 144.6, 133.1, 128.9, 125.9, 124.3, 122.7, 122.2, 121.6, 120.6, 107.6, 69.1, 50.9, 46.0, 30.6, 20.7, 20.6, 20.4, 20.1, 19.3, 18.3, 14.0; MS (+FAB): m/z 413 ($M+H^+$, 28), 412 (M^+, 100). Anal. Calcd for $C_{25}H_{33}NO_4$: C, 72.96; H, 8.08; N, 3.40. Found: C, 73.04; H, 8.07; N, 3.88.

4.1.8. *N*,*N*-Diisopropyl-8-methoxy-2-[2′-(*E*)-3′-phenylpropenoyloxy]-1-naphthamide 8a. Prepared in 97% yield after flash column chromatography (silica gel, 9.1% EtOAc–CH_2Cl_2) as white needles; mp 210–211 °C (CH_2Cl_2–hexane); $R_f = 0.46$ (9.1% EtOAc–CH_2Cl_2); IR ($CHCl_3$): 2924, 1731, 1634, 1315, 1212, 1132 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (d, $J = 15.9$ Hz, 1H), 7.81 (d, $J = 9.0$ Hz, 1H), 7.62–7.53 (m, 2H), 7.48–7.36 (m, 6H), 6.88 (d, $J = 7.5$ Hz, 1H), 6.65 (d, $J = 15.9$ Hz, 1H), 3.93 (s, 3H), 3.66 (quintet, $J = 6.6$ Hz, 1H), 3.51 (quintet, $J = 6.6$ Hz, 1H), 1.68 (d, $J = 6.6$ Hz, 3H), 1.58 (d, $J = 6.6$ Hz, 3H), 1.04 (d, $J = 5.7$ Hz, 3H), 1.02 (d, $J = 5.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 165.3, 155.6, 147.3, 144.7, 134.3, 133.4, 131.0, 129.2 (×2), 129.1, 128.5 (×2), 126.4, 124.8, 122.5, 122.5, 121.2, 117.1, 106.6, 55.7, 51.2, 46.2, 21.1, 21.1, 20.7, 20.2; MS (+FAB): m/z 432 ($M+H^+$, 100). Anal. Calcd for $C_{27}H_{29}NO_4$: C, 75.15; H, 6.77; N, 3.25. Found: C, 75.15; H, 6.76; N, 3.54.

4.1.9. *N*,*N*-Diisopropyl-8-(*tert*-butyldimethylsilyloxy)-2-[2′-(*E*)-3′-phenylpropenoyloxy]-1-naphthamide 8b. Prepared in 91% yield after flash column chromatography (silica gel, 1:1:10 EtOAc–CH_2Cl_2–hexane) as white needles; mp 149–150 °C (CH_2Cl_2–hexane); $R_f = 0.26$ (1:1:10 EtOAc–CH_2Cl_2–hexane); IR ($CHCl_3$): 2929, 1735, 1637, 1308, 1210, 1131 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, $J = 15.6$ Hz, 1H), 7.81 (d, $J = 8.7$ Hz, 1H), 7.60–7.53 (m, 2H), 7.48 (d, $J = 8.1$ Hz, 1H), 7.44–7.39 (m, 3H), 7.35 (d, $J = 8.7$ Hz, 1H), 7.23 (t, $J = 8.1$ Hz, 1H), 7.01 (d, $J = 7.2$ Hz, 1H), 6.63 (d, $J = 15.9$ Hz, 1H), 3.73 (quintet, $J = 6.6$ Hz, 1H), 3.31 (quintet, $J = 6.6$ Hz, 1H), 1.65 (d, $J = 6.6$ Hz, 3H), 1.51 (d, $J = 6.9$ Hz, 3H), 1.06 (d, $J = 6.3$ Hz, 3H), 1.04 (s, 9H), 0.93 (d, $J = 6.0$ Hz, 3H), 0.48 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 165.1, 152.0, 146.9, 145.0, 134.1, 133.1, 130.5, 129.1, 128.9 (×2), 128.2 (×2), 125.5, 124.7, 124.5, 122.0, 121.6, 117.0, 116.0, 50.5, 45.9, 27.2 (×3), 25.7, 22.7, 21.0, 20.7, 20.3, 19.5, −2.4, −3.7; MS (+FAB): m/z 533 ($M+H^+$, 33), 532 (M^+, 60), 474 (100). Anal. Calcd for $C_{32}H_{41}NO_4Si$: C, 72.28; H, 7.77; N, 2.63. Found: C, 72.23; H, 7.79; N, 3.11.

4.1.10. General procedure for kinetic resolution under the Sharpless dihydroxylation conditions: preparation of (+)-(a*S*)-*N*,*N*-diisopropyl-2-[2′-(*E*)-butenoyloxy]-8-methoxy-1-naphthamide (+)-(a*S*)-7a. Modified AD catalyst system: The commercial AD-mix-α or AD-mix-β (1.0 g) was modified by adding $K_2OsO_4{\cdot}2H_2O$ (10.6 mg) and $(DHQ)_2$–PHAL or $(DHQD)_2$–PHAL (16.0 mg) to contain 3.0×10^{-2} mmol of $K_2OsO_4{\cdot}2H_2O$ and 3.0×10^{-2} mmol of $(DHQ)_2$–PHAL or $(DHQD)_2$–PHAL.

To a solution of the modified AD-mix-β [140.0 mg, 4.2×10^{-3} mmol each of Os and $(DHQD)_2$–PHAL] and methanesulfonamide (9.5 mg, 0.1 mmol) in *t*-BuOH–H_2O (1.2 mL, 1:1) cooled in an ice–H_2O bath (ca. 0 °C) was added amide **7a** (44.3 mg, 0.12 mmol). *N*,*N*-Diisopropyl-1-naphthamide (15.3 mg, 6.0×10^{-2} mmol) was added as an internal reference for the purpose of HPLC analysis (*N*,*N*-dicyclohexyl-1-naphthamide was used for the AD reaction of amide **7c**). The resultant mixture was stirred vigorously at 0 °C for 22 h and the reaction was quenched by adding aqueous sodium sulfite (0.4 g/mL, 0.38 mL) with stirring for another 20 min. The reaction mixture was extracted with EtOAc (10 × 3 mL), and the combined organic layer washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product mixture was purified by flash column chromatography (silica gel, 9.1% EtOAc–CH_2Cl_2) to give the enantioenriched amide (+)-**7a** (15.5 mg, 35%). Before purification a small portion of the crude product was dissolved in EtOAc and the solution filtered through a short pad of silica gel with elution by EtOAc. The combined filtrate was evaporated and the residue subjected to HPLC analysis over a chiral stationary phase. It was determined that 61% of amide **7a** was consumed in the AD reaction while the remaining (+)-**7a** had 94.3% ee. The HPLC chromatogram of (+)-**7a** is found in Figure 4.

Enantiomerically pure **7a** was obtained by HPLC resolution of racemic **7a** over a chiral stationary phase under the conditions given in Figure 4. (+)-(a*S*)-**7a**: $[\alpha]_D^{25} = +59.9$ (*c* 0.81, $CHCl_3$). (−)-(a*R*)-**7a**, $[\alpha]_D^{25} = -59.4$ (*c* 0.81, $CHCl_3$).

For the kinetic measurements given in Table 2, aliquots of the reaction mixture were taken at selected time intervals for HPLC analysis of both conversion and enantiomeric ratio of the amide. The HPLC settings are as follows:

For amide **7a**: Chiralcel OD column eluted with a 90:10 ratio of hexane–isopropanol at 0.5 mL/min and by UV detection at 254 nm. $t_R = 17.8$ min for *N*,*N*-diisopropyl-1-naphthamide; $t_R = 32.0$ min for (−)-(a*R*)-**7a**; $t_R = 47.3$ min for (+)-(a*S*)-**7a**.

For amide **7b**: Chiralcel OD column eluted with a 95:5 ratio of hexane–isopropanol at 0.5 mL/min and by UV detection at 254 nm. $t_R = 23.6$ min for *N*,*N*-diisopropyl-1-naphthamide; $t_R = 9.4$ and 13.3 min for both enantiomers of **7b**.

For amide **7c**: Chiralcel OD plus Chiralcel OD-H columns eluted with a 99:1 ratio of hexane–isopropanol at 0.2 mL/min and by UV detection at 254 nm. $t_R = 122.6$ min for *N*,*N*-dicyclohexyl-1-naphthamide (internal reference); $t_R = 140.2$ and 150.7 min for both enantiomers of **7c**.

For amide **8a**: Chiralcel OD column eluted with a 98:2 ratio of hexane–isopropanol at 0.2 mL/min and by UV detection at 254 nm. $t_R = 40.6$ min for *N*,*N*-diisopropyl-1-naphthamide; $t_R = 147.2$ and 163.2 min for both enantiomers of **8a**.

For amide **8b**: Chiralcel OD column eluted with a 99:1 ratio of hexane–isopropanol at 0.3 mL/min and by UV detection at 254 nm. $t_R = 53.2$ min for *N*,*N*-diisopropyl-1-naphthamide; $t_R = 27.3$ and 31.1 min for both enantiomers of **8b**.

4.1.11. (−)-(a*R*,1′*S*,4′*R*)-*N*,*N*-Diisopropyl-8-(*tert*-butyldimethylsilyloxy)-2-{4′,7′,7′-trimethyl-3′-oxo-2′-oxabicyclo-[2.2.1]heptanecarbonyloxy}-1-naphtamide (−)-(a*R*)-10 and (+)-(a*S*,1′*S*,4′*R*)-*N*,*N*-diisopropyl-8-(*tert*-butyldimethylsilyloxy)-2-{4′,7′,7′-trimethyl-3′-oxo-2′-oxabicyclo[2.2.1]heptanecarbonyl-oxy}-1-naphtamide (+)-(a*S*)-11. A solution of racemic amide **6b** (401.0 mg, 1.0 mmol) and dimethylaminopyridine (244.0 mg, 2.0 mmol) in dry CH_2Cl_2 (20 mL) cooled in an ice–H_2O bath (ca. 0 °C) under a nitrogen atmosphere was added a solution of camphanic chloride (433.0 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) via a syringe. The resulting mixture was allowed to warm to room temperature followed by stirring for 4 h. The reaction mixture was filtered through a pad of silica gel with washing by CH_2Cl_2–EtOAc (3:1, 20 mL). The combined filtrate was evaporated under reduced pressure, and the residue purified by flash column chromatography (silica gel, 1.4–2.4% EtOAc–CH_2Cl_2) to give (−)-(a*R*)-**10** (223.0 mg, 38%) and (+)-(a*S*)-**11** (242.0 mg, 42%).

(−)-(a*R*)-**10**: A yellow gum (ester bond cleavage was observed during attempted crystallization in CH_2Cl_2–hexane or NMR measurement in $CDCl_3$); $[\alpha]_D^{25} = -88.4$ (*c* 1.0, $CHCl_3$); $R_f = 0.26$ (2.4% EtOAc–CH_2Cl_2); IR ($CHCl_3$): 2928, 1789, 1262 cm^{-1}; MS (+FAB): *m*/*z* 582 ($M+H^+$, 52), 344 (100).

(+)-(a*S*)-**11**: A white crystalline solid; mp 199–200 °C (CH_2Cl_2–hexane); $[\alpha]_D^{25} = +114.5$ (*c* 1.0, $CHCl_3$); $R_f = 0.34$ (2.4% EtOAc–CH_2Cl_2); IR ($CHCl_3$): 2918, 1794, 1764, 1739, 1635, 1257, 1049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, $J = 8.9$ Hz, 1H), 7.46 (d, $J = 7.6$ Hz, 1H), 7.34 (t, $J = 7.9$ Hz, 1H), 7.10 (d, $J = 8.9$ Hz, 1H), 7.01 (dd, $J = 7.6$, 0.7 Hz, 1H), 3.76 (septet, $J = 6.9$ Hz, 1H), 3.18 (septet, $J = 6.6$ Hz, 1H), 2.63 (ddd, $J = 13.7$, 10.7, 4.2 Hz, 1H), 2.21 (ddd, $J = 13.7$, 9.4, 4.6 Hz, 1H), 1.97 (ddd, $J = 13.2$, 10.7, 4.6 Hz, 1H), 1.73 (ddd, $J = 13.2$, 9.4, 4.2 Hz, 1H), 1.63 (d, $J = 6.6$ Hz, 3H), 1.56 (d, $J = 6.8$ Hz, 3H), 1.16 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H), 1.02 (s, 9H), 1.00 (d, $J = 7.5$ Hz, 3H), 0.95 (d, $J = 6.6$ Hz, 3H), 0.45 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 177.0, 165.9, 164.6, 151.3, 144.1, 132.9, 129.5, 126.1, 124.6, 123.6, 123.5, 121.5, 116.0, 89.9, 54.7, 54.3, 49.8, 45.0, 30.4, 28.2, 26.8 (×3), 22.1, 20.4, 20.3, 19.8, 19.1, 16.6, 16.4, 9.5, −2.7, −3.9; MS (+FAB): *m*/*z* 582 ($M+H^+$, 88), 524 (100). Anal. Calcd for $C_{33}H_{47}NO_6Si$: C, 68.12; H, 8.14; N, 2.41. Found: C, 67.97; H, 8.18; N, 2.39.

4.1.12. General procedure for the synthesis of 8-methoxy-1-naphthamides via a one-pot desilylation–methylation sequence: preparation of (−)-(a*R*,1′*S*,4′*R*)-*N*,*N*-diisopropyl-8-methoxy-2-{4′,7′,7′-trimethyl-3′-oxo-2′-oxabicyclo[2.2.1]heptanecarbonyloxy}-1-naphtamide (−)-(a*R*)-12. To a solution of (−)-(a*R*)-**10** (174.0 mg, 0.3 mmol) in THF (10 mL) cooled in an ice–H_2O bath (ca. 0 °C) was added MeI (94 μL, 1.5 mmol) and a solution of tetrabutylammonium fluoride (0.3 mL, 1 M in THF, 0.3 mmol). The resulting mixture was allowed to warm to room temperature gradually and then stirred for another 5 h. The reaction mixture was filtered through a pad of silica gel with washing by EtOAc. The combined filtrate was evaporated under reduced pressure and the residue purified by flash column chromatography (silica gel, 5.9% EtOAc–CH_2Cl_2) to give (−)-(a*R*)-**12** (118.0 mg, 82%) as a yellow gum; $[\alpha]_D^{25} = -7.8$ (*c* 0.6, $CHCl_3$); $R_f = 0.18$ (7.7% EtOAc–CH_2Cl_2); IR ($CHCl_3$): 2918, 1790, 1634, 1316, 1262, 1042 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, $J = 9.0$ Hz, 1H), 7.46–7.38 (m, 2H), 7.25 (d, $J = 8.7$ Hz, 1H), 6.90 (dd, $J = 6.6$, 1.2 Hz, 1H), 3.91 (s, 3H), 3.59 (quintet, $J = 6.6$ Hz, 1H), 3.48 (quintet, $J = 6.6$ Hz, 1H), 2.54 (ddd, $J = 19.2$, 10.5, 4.2 Hz, 1H), 2.24 (ddd, $J = 13.2$, 9.6, 4.5 Hz, 1H), 1.99 (ddd, $J = 18.9$, 10.8, 4.5 Hz, 1H), 1.77 (ddd, $J = 13.2$, 9.0, 4.2 Hz, 1H), 1.66 (d, $J = 7.5$ Hz, 3H), 1.63 (d, $J = 7.2$ Hz, 3H), 1.17 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H), 1.13 (d, $J = 7.8$ Hz, 3H), 0.98 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.7, 166.5, 166.0, 155.7, 144.0, 133.3, 128.8, 126.5, 125.0, 122.2, 121.6, 120.8, 106.8, 90.5, 55.5, 54.9, 54.7, 51.0, 46.1, 31.9, 29.2, 21.3, 21.0, 20.2, 19.7, 17.1, 17.0, 9.8; MS (+FAB): *m*/*z* 482 ($M+H^+$, 100).

4.1.13. (+)-(a*S*,1′*S*,4′*R*)-*N*,*N*-Diisopropyl-8-methoxy-2-{4′,7′,7′-trimethyl-3′-oxo-2′-oxabicyclo[2.2.1]heptanecarbonyloxy}-1-naphtamide (+)-(a*S*)-13. Prepared from (+)-(a*S*)-**11** in 89% yield as a yellow solid; $[\alpha]_D^{25} = +21.7$ (*c* 0.45, $CHCl_3$); $R_f = 0.24$ (7.7% EtOAc–CH_2Cl_2); IR ($CHCl_3$): 2919, 1793, 1759, 1636, 1316, 1262, 1211, 1052 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.79 (d, $J = 9.0$ Hz, 1H), 7.46 (dd, $J = 8.1$, 1.8 Hz, 1H), 7.42 (t, $J = 8.1$ Hz, 1H), 7.19 (d, $J = 9.0$ Hz, 1H), 6.90 (dd, $J = 6.9$, 1.8 Hz, 1H), 3.92 (s, 3H), 3.55 (septet, $J = 6.6$ Hz, 2H), 2.58 (ddd, $J = 13.8$, 10.5, 4.2 Hz, 1H), 2.20 (ddd, $J = 13.2$, 9.6, 4.5 Hz, 1H), 1.98 (ddd, $J = 13.2$, 10.8, 4.5 Hz, 1H), 1.74 (ddd, $J = 13.8$, 9.3, 4.2 Hz, 1H), 1.66 (dd, $J = 6.9$ Hz, 3H), 1.65 (d, $J = 6.9$ Hz, 3H), 1.17 (s, 6H), 1.16 (s, 3H), 1.14 (d, $J = 6.9$ Hz, 3H), 0.99 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.8, 166.3, 166.0, 155.6, 143.9, 133.3, 129.2, 126.5, 124.7, 122.2, 121.5, 120.8, 106.8, 90.6, 55.5, 55.0, 55.0, 51.2, 46.2, 30.9, 29.1, 21.0, 20.7, 20.2, 19.7, 17.1, 17.0, 9.9; MS (+FAB): *m*/*z* 482 ($M+H^+$, 100).

4.1.14. General procedure for ester hydrolysis: preparation of racemic *N*,*N*-diisopropyl-8-(*tert*-butyldimethylsilyloxy)-2-hydroxy-1-naphthamide 6b from (+)-(a*S*)-11. To a solution of (+)-(a*S*)-**11** (58.2 mg, 0.1 mmol) in THF (2 mL) at room temperature was added 10% aqueous KOH (0.22 mL, 0.4 mmol) followed by stirring at room temperature for 40 min. Saturated aqueous NH_4Cl (5 mL) was added to the reaction mixture. The resulting mixture was extracted with EtOAc (15 × 3 mL) and the combined organic layer washed with brine, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 5.9% EtOAc–CH_2Cl_2) to give **6b** (35.7 mg, 89%) in racemic form.

4.1.15. Preparation of (+)-(a*S*)-*N*,*N*-diisopropyl-2-hydroxy-8-methoxy-1-naphthamide (+)-(a*S*)-6a via hydrolysis of (+)-(a*S*)-13. Hydrolysis of the ester (+)-(a*S*)-**13**

(48.2 mg, 0.1 mmol) at room temperature for 40 min gave (+)-(a*S*)-**6a** (25.6 mg, 85%) in 87.8% ee; $[\alpha]_D^{25} = +20.7$ (*c* 1.0, $CHCl_3$). The HPLC chromatogram is given in Figure 7b. Enantiomer excess and specific rotation of (+)-(a*S*)-**6a** are time-dependent due to facile racemization at room temperature.

4.1.16. Preparation of (+)-(a*S*)-*N*,*N*-diisopropyl-2-hydroxy-8-methoxy-1-naphthamide (+)-(a*S*)-6a via hydrolysis of (+)-(a*S*)-7a. Hydrolysis of the ester (+)-(a*S*)-**7a** (36.9 mg, 94.3% ee, 0.1 mmol) at room temperature for 8.5 h gave (+)-(a*S*)-**6a** (16.0 mg, 53%) in 42.1% ee; The HPLC chromatogram is given in Figure 7a. A portion of the ester (+)-(a*S*)-**7a** (14.8, 40%) was recovered from the hydrolysis reaction with no racemization of (+)-(a*S*)-**7a** being detected under hydrolysis conditions.

4.1.17. X-ray crystallographic structural determination of *rac*-6a, *rac*-6b, *rac*-7b, and (a*S*)-(+)-11. The X-ray crystal structures of *rac*-**6a**, *rac*-**6b**, *rac*-**7b**, and (a*S*)-(+)-**11** are given in Figures 1, 2, 3 and 5 and the crystal data were deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 219621, CCDC 219197, CCDC 219196, and CCDC 219198, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB12 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

This work is supported by the Department of Chemistry, HKUST and the Research Grants Council of the Hong Kong Special Administration Region, China (through a Competitive Earmarked Research Grant, HKUST 6129/01P).

References and notes

1. Clayden, J. *Angew. Chem., Int. Ed.* **1997**, *36*, 949–951.
2. Selected examples of axially chiral anilides, see: (a) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131–3132; (b) Curran, D. P.; Hale, G. R.; Geib, S. J.; Balog, A.; Cass, Q. B.; Degani, A. L. G.; Hernandes, M. Z.; Freitas, L. C. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3955–3975; (c) Curran, D. P.; Liu, W.; Chen, C. H.-T. *J. Am. Chem. Soc.* **1999**, *121*, 11012–11013; (d) Ates, A.; Curran, D. P. *J. Am. Chem. Soc.* **2001**, *123*, 5130–5131; (e) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552–560; (f) Hughes, A. D.; Price, D. A.; Shishkin, O.; Simpkins, N. S. *Tetrahedron Lett.* **1996**, *37*, 7607–7610; (g) Hughes, A. D.; Simpkins, N. S. *Synlett* **1998**, 967–968; (h) Hughes, A. D.; Price, D. A.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1295–1304; (i) Godfrey, C. R. A.; Simpkins, N. S.; Walker, M. D. *Synlett* **2000**, 388–390; (j) Kitagawa, O.; Izawa, H.; Taguchi, T.; Shiro, M. *Tetrahedron Lett.* **1997**, *38*, 4447–4450; (k) Kitagawa, O.; Izawa, H.; Sato, K.; Dobashi, A.; Taguchi, T.; Shiro, M. *J. Org. Chem.* **1998**, *63*, 2634–2640; (l) Fujita, M.; Kitagawa, O.; Izawa, H.; Dobashia, A.; Fukaya, H.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 1949–1952 (Corrigendum: Fujita, M., Kitagawa, O., Izawa, H., Dobashia, A., Fukaya, H., Taguchi, T. *Tetrahedron Lett.* **2000**, *41*, 4997); (m) Kitagawa, O.; Momose, S.; Fushimi, Y.; Taguchi, T. *Tetrahedron Lett.* **1999**, *40*, 8827–8831; (n) Fujita, M.; Kitagawa, O.; Yamada, Y.; Izawa, H.; Hasegawa, H.; Taguchi, T. *J. Org. Chem.* **2000**, *65*, 1108–1114; (o) Kitagawa, O.; Fujita, M.; Kohriyama, M.; Hasegawa, H.; Taguchi, T. *Tetrahedron Lett.* **2000**, *41*, 8539–8544; (p) Kitagawa, O.; Kohriyama, M.; Taguchi, T. *J. Org. Chem.* **2002**, *67*, 8682–8684; (q) Bach, T.; Schröder, J.; Harms, K. *Tetrahedron Lett.* **1999**, *40*, 9003–9004; (r) Hata, T.; Koide, H.; Taniguchi, N.; Uemura, M. *Org. Lett.* **2000**, *2*, 1907–1910; (s) Clayden, C.; Lund, A.; Youssef, L. H. *Org. Lett.* **2001**, *3*, 4133–4136; (t) Clayden, J.; Johnson, P.; Pink, J. H. *J. Chem Soc., Perkin Trans. 1* **2001**, *1*, 371–375; (u) Clayden, J.; Mitjans, D.; Youssef, L. H. *J. Am. Chem. Soc.* **2002**, *124*, 5266–5267.
3. Selected examples of axially chiral *N*-arylimides, see: (a) Curran, D. P.; Geib, S.; DeMello, N. *Tetrahedron* **1999**, *55*, 5681–5704; (b) Kondo, K.; Fujita, H.; Suzuki, T.; Murakami, Y. *Tetrahedron Lett.* **1999**, *40*, 5577–5580; (c) Shimizu, K. D.; Freyer, H. O.; Adams, R. D. *Tetrahedron Lett.* **2000**, *41*, 5431–5434, Also see Refs. 2a,k.
4. Selected examples of axially chiral benzamides, see: (a) Koide, H.; Uemura, M. *Chem. Commun.* **1998**, 2483–2484; (b) Koide, H.; Uemura, M. *Tetrahedron Lett.* **1999**, *40*, 3443–3446; (c) Koide, H.; Hata, T.; Uemura, M. *J. Org. Chem.* **2002**, *67*, 1929–1935; (d) Li, X.; Schenkel, L. B.; Kozlowski, M. C. *Org. Lett.* **2000**, *2*, 875–878; (e) Clayden, J.; Johnson, P.; Pink, J. H.; Helliwell, M. *J. Org. Chem.* **2000**, *65*, 7033–7040.
5. Selected examples of axially chiral 1-naphthamides, see: (a) Thayumanavan, S.; Beak, P.; Curran, D. P. *Tetrahedron Lett.* **1996**, *37*, 2899–2902; (b) Clayden, J. *Synlett* **1998**, *5*, 810–816, and references cited therein; (c) Clayden, J.; Westlund, N.; Frampton, C. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1379–1385, and references cited therein; (d) Clayden, J.; Lai, L. W. *Angew. Chem., Int. Ed.* **1999**, *38*, 2556–2558; (e) Clayden, J.; McCarthy, C.; Cumming, J. G. *Tetrahedron Lett.* **2000**, *41*, 3279–3283; (f) Clayden, J.; Helliwell, M.; McCarthy, C.; Westlund, N. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3232–3249; (g) Clayden, J.; Lai, L. W. *Tetrahedron Lett.* **2001**, *42*, 3163–3166; (h) Clayden, J.; Helliwell, M.; Pink, J. H.; Westlund, N. *J. Am. Chem. Soc.* **2001**, *123*, 12449–12457; (i) Bragg, R. A.; Clayden, J.; Morris, G. a.; Pink, J. H. *Chem. Eur. J.* **2002**, *8*, 1279–1289; (j) Anstiss, M.; Clayden, J.; Grube, A.; Youssef, L. H. *Synlett* **2002**, 290–294.
6. Atropisomeric naphthalene derivatives possessing a vinyl group at C1, see: (a) Kawabata, T.; Yahiro, K.; Fuji, K. *J. Am. Chem. Soc.* **1991**, *113*, 9694–9696; (b) Fuji, K.; Kawabata, T. *Chem. Eur. J.* **1998**, *4*, 373–376.
7. Atropisomeric naphthalene derivatives possessing an arylsulfinyl group at C1, see: (a) Hiroi, K.; Suzuki, Y. *Tetrahedron Lett.* **1998**, *39*, 6499–6502; (b) Nakamura, S.; Yasuda, H.; Watanabe, Y.; Toru, T. *Tetrahedron Lett.* **2000**, *41*, 4157–4160; (c) Nakamura, S.; Yasuda, H.; Watanabe, Y.; Toru, T. *J. Org. Chem.* **2000**, *65*, 8640–8650; (d) Nakamura, S.; Yasuda, H.; Toru, T. *Tetrahedron: Asymmetry* **2002**, *13*, 1509–1518.
8. (a) Gasparrini, F.; Lunazzi, L.; Mazzanti, A.; Pierini, M.; Pietrusiewicz, K. M.; Villani, C. *J. Am. Chem. Soc.* **2000**,

122, 4776–4780; (b) Wang, F.; Wang, Y.; Polavarapu, P. L.; Li, T.; Drabowicz, J.; Pietrusiewicz, K. M.; Zygo, K. *J. Org. Chem.* **2002**, *67*, 6539–6541.
9. For an example of axially chiral thioanilides, see: (a) Dantale, S.; Reboul, V.; Metzner, P.; Philouze, C. *Chem. Eur. J.* **2002**, *8*, 632–640; Also, see: (b) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Silvero, G.; Valencia, C. *Tetrahedron* **1999**, *55*, 4377–4400; (c) Avalos, M.; Babiano, R.; Cintas, P.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C.; Silvero, G.; Valencia, C. *Tetrahedron* **1999**, *55*, 4401–4426.
10. (a) Dai, W.-M.; Yeung, K. K. Y.; Chow, C. W.; Williams, I. D. *Tetrahedron: Asymmetry* **2001**, *12*, 1603–1613; (b) Dai, W.-M.; Yeung, K. K. Y.; Liu, J.-T.; Zhang, Y.; Williams, I. D. *Org. Lett.* **2002**, *4*, 1615–1618; Also see: (c) Dai, W.-M.; Lau, C. W. *Tetrahedron Lett.* **2001**, *42*, 2541–2544.
11. A recent example of kinetic resolution on atropisomeric amides under Sharpless asymmetric dihydroxylation conditions, see: Rios, R.; Jimeno, C.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10272–10273.
12. (a) Clayden, J.; Frampton, C. S.; McCarthy, C.; Westlund, N. *Tetrahedron* **1999**, *55*, 14161–14184; Also see: (b) Birch, A. J.; Salahud-Din, M.; Smith, D. C. C. *J. Chem. Soc. (C)* **1966**, *6*, 523–527.
13. Schweizer, W. B.; Procter, G.; Kaftory, M.; Dunitz, J. D. *Helv. Chim. Acta* **1978**, *61*, 2783–2808.
14. Simon, J.; Salzbrunn, S.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *J. Org. Chem.* **2001**, *66*, 633–634.
15. Clayden, J.; McCarthy, C.; Helliwell, M. *Chem. Commun.* **1999**, *8*, 2059–2060.
16. VanNieuwenhze, M. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 7864–7865.
17. For discussion on k_{rel} value in a recent review, see: Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5–26.
18. (a) Gasparrini, F.; Misiti, D.; Pierini, M.; Villani, C. *Tetrahedron: Asymmetry* **1997**, *8*, 2069–2073; (b) Schurig, V.; Keller, F.; Reich, S.; Fluck, M. *Tetrahedron: Asymmetry* **1997**, *8*, 3475–3480.
19. Ahmed, A.; Bragg, R. A.; Clayden, J.; Lai, L. W.; McCarthy, C.; Pink, J. H.; Westlund, N.; Yasin, S. A. *Tetrahedron* **1998**, *54*, 13277–13294.