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The effects of aromatic substituents on the chromatographic enantioseparation of diarylmethyl esters with the Whelk-O1 chiral stationary phase

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Abstract

Members of a series of diarylmethanols, diarylmethyl pivalates, and diarylmethyl acetates (analyte sets **1**–**26**) were enantioresolved with the (*S*,*S*)-Whelk-O1 chiral stationary phase (CSP). An analogue of the (*S*,*S*)-Whelk-O1 selector was combined with enantioenriched samples of the various diarylmethyl pivalates and thereby used as a chiral solvating agent (CSA) for high field ^{1}H NMR studies. The absolute configurations of a number of chiral diarylmethyl pivalates were assigned using this approach, and hydrolysis of the pivalates allowed assignment of the absolute configurations of the corresponding diarylmethanols. Chromatographic, ^{1}H NMR, and X-ray evidence are given in support of a chiral recognition model for the enantioresolution of diarylmethyl esters on this CSP.

Keywords: Benzhydrol; Diarylmethanol; Diarylcarbinol; Chiral chromatography; Chiral solvating agent; Chiral recognition; π–π interactions

1. Introduction

The development of methods for obtaining enantiomerically enriched diarylmethanols, determining their enantiomeric purities, and determining their absolute configurations continues to attract attention. These efforts are not solely of academic interest, for some pharmaceuticals are derived from chiral diarylmethanols [1]. Methods for asymmetric reduction of diarylmethanones (benzophenones) [2–6] and classical resolution of diarylmethanols [7] are frequently limited by moderate yields, moderate enantiomeric excess, narrow scope, or lack of stereochemical rationale. Diphenylzinc [8] and aryltitanium reagents [9] have been added to aryl aldehydes under conditions affording chiral diarylmethanols in high yield and high enantiomeric excess, but the use of aryl Grignard intermediates precludes the presence of certain functional groups. Alternatively, one might obtain diarylmethanols in high enantiomeric purity by liquid chromatography on a chiral stationary phase. For example, Maier and Uray [10,11] have resolved many chiral diarylmethanols using a slight variation of the commercially available ULMO CSP. The Whelk-O1 CSP can utilize subtle substituent effects to differentiate between enantiomers and thus seemed a natural choice for the enantioresolution of diarylmethanols. Although the Whelk-O1 CSP does resolve a number of these compounds, the corresponding pivalate and acetate esters are generally better resolved. Moreover, analysis of the chromatographic behavior of the diarylmethyl esters has yielded

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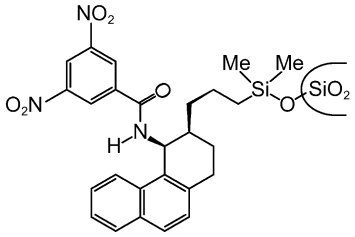


Fig. 1. (*S*,*S*)-Whelk-O1. Although sold as the (*S*,*S*)-Whelk-O1, the true configuration is (3*R*,4*S*) as shown above. The incorrect assignment is a remnant of the original Whelk-O CSP wherein the selector was bound to silicon with an undecyl linkage and thus correctly assigned the (*S*,*S*) configuration.

much information about the chiral recognition mechanism of the Whelk-O selector.

The (*S*,*S*)-Whelk-O1 CSP, shown in Fig. 1, was designed to separate the enantiomers of compounds that have a hydrogen bond acceptor and a π-electron system near a stereogenic center. NMR and chromatographic data [12–14] indicate that the enantioresolution afforded by the Whelk-O CSP is attributable to the chiral cleft conformation of the Whelk-O selector shown in Fig. 2 which depicts (*S*)-(4-methoxyphenyl)phenylmethyl pivalate [(*S*)-**2b**] interacting with the (*S*,*S*)-Whelk-O selector. The "wall" and "floor" of the selector cleft are formed by the dinitrobenzoyl (DNB) group and naphthyl portion of the selector, respectively. The amide proton of the selector provides the site for the dominant interaction between the selector and the analyte, a hydrogen bond with the ester carbonyl oxygen. While a diarylmethyl ester molecule is hydrogen bonded to the selector, only one of its aromatic rings can be placed in the cleft such that the ring participates in two additional stabilizing interactions: a face-to-face π–π interaction with the DNB group and an edge-to-face π–π interaction with the naphthyl group. The identity of the aromatic ring that fits into the cleft depends on the handedness of the diarylmethyl ester that is hydrogen bonded to the selector. This chiral recognition mechanism is illustrated in Fig. 3 with a generic pivalate ester. Two complexes are shown; the first is the complex of the (*S*,*S*)-Whelk-O selector with the ester MRE (last eluting, more retained enantiomer on the (*S*,*S*)-Whelk-O1 CSP). The second is the complex of the (*S*,*S*)-Whelk-O selector with the ester LRE (first eluting, less retained enantiomer on the (*S*,*S*)-Whelk-O1 CSP). In each

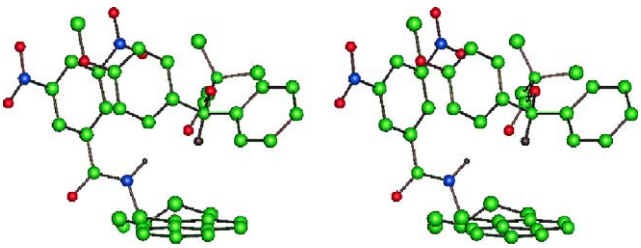


Fig. 2. Stereoview of a selector–analyte complex. (*S*,*S*)-Whelk-O: (*S*)-(4-methoxyphenyl)phenylmethyl pivalate [(*S*)-**2b**]. All hydrogens except the selector amide proton and the analyte methine proton have been omitted for clarity.

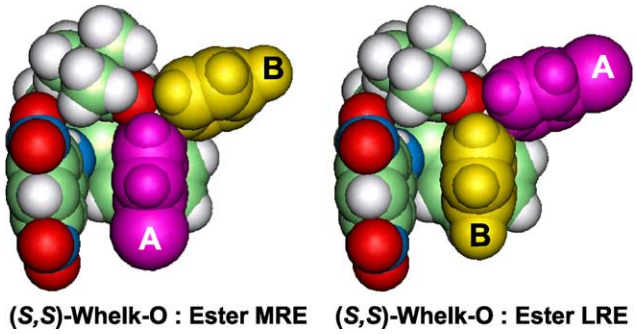


Fig. 3. Proposed chiral recognition mechanism. These are idealized depictions of complexes of the (*S*,*S*)-Whelk-O selector and a diarylmethyl ester's enantiomers. MRE: more retained enantiomer on the (*S*,*S*)-Whelk-O1 CSP; LRE: less retained enantiomer on the (*S*,*S*)-Whelk-O1 CSP. The inclusion priority is ring A > ring B; aromatic ring A forms a more stable complex with the Whelk-O selector than does aromatic ring B. There is no correlation between inclusion priority and Cahn-Ingold-Prelog priority. Although a pivalate ester analyte is depicted, the model also applies to acetate esters.

complex, one ring of the ester is included in the cleft and the other ring is excluded from the cleft. In the MRE complex, the A-ring is included and the B-ring is excluded; these roles are exchanged in the LRE complex. It then follows that the degree of enantioresolution of a diarylmethyl ester by the Whelk-O selector is determined, to a good approximation, by the differences in π–π interactions for the two complexes in Fig. 3.

So far, we have tacitly assumed that the conformation of the diarylmethyl ester shown in Figs. 2 and 3 is representative of the low energy conformation of this class of analytes. We are interested in low energy conformations of the esters since any energetically favorable interactions between the selector and an analyte in a high energy conformation would be offset by the intramolecular strain of the analyte molecule. To identify pertinent low energy conformations of a diarylmethyl ester, the rotations about four bonds must be analyzed. Two of these bonds, those of the sp^3 oxygen, define the relative positions of the ester carbonyl and methine proton. In our series of analytes, the NMR signal of a diarylmethanol's methine proton consistently lies upfield of the corresponding methine NMR signals of its esters. This acylation shift has been documented [15] and indicates an energetic minimum in which the methine proton lies approximately in the plane of the carbonyl as shown in Fig. 2. The other two bonds to consider are those between the methine carbon and its adjacent aromatic carbons; rotation about these bonds affects the ability of the analyte's aromatic rings to interact with the selector cleft. The conformation of the diarylmethyl ester in Figs. 2 and 3 has been referred to as "booklike" [10] and is described by the following $C_{ortho}-C_{ipso}-C_{methine}-H_{methine}$ dihedral angles (θ): $\theta_{included} \approx +25^\circ$, $\theta_{excluded} \approx -25^\circ$. The proposed recognition model requires that the included ring be held in a "book" conformation, but there is no such constraint on the excluded ring. Indeed, a "half-book" conformation would not invalidate the chiral recognition model as long as the two "half-book" conformations for a diarylmethyl ester were

energetically equivalent. Analyte (*S*)-**2b** was modeled using CHARMm minimization software, and three low energy conformations were identified. The global energetic minimum for **2b** is the "book" conformation. CHARMm modeling also identified two local minima within 0.2 kcal/mol of the global minimum; these conformations correspond roughly to the two "half-book" conformations [16]. Modeling of other *meta*- and/or *para*-substituted diarylmethyl acetates and pivalates gave similar results. This finding is consistent with the X-ray crystal structures of diarylmethyl phthalates [17–19]; some variation in the aromatic ring dihedral angles is observed, but all structures lie close to one of the three low energy conformations above. However, analytes with an *ortho* substituent are more conformationally rigid and are better represented by a single, biased "half-book" conformation in which only the *ortho*-substituted ring may be held in the selector cleft as described earlier. As will be shown, this assertion is supported by both X-ray data and modeling.

Given the shielding diamagnetic anisotropy of the Whelk-O cleft, NMR is an apt method for studying the association of selector and analyte. An (*S*,*S*)-Whelk-O selector analogue which lacks the 3-alkyl substituent that tethers the selector to silica was synthesized [20], resolved, and used as a chiral solvating agent for NMR. For each CSA experiment, the (*S*)-CSA was combined in $CDCl_3$ with a diarylmethyl ester enantioenriched on a semi-preparative (*S*,*S*)-Whelk-O1 column. The NMR spectrum exhibited proton chemical shift differences between the analyte enantiomers that could be correlated to the proposed complexes of selector and analyte enantiomers.

2. Experimental

2.1. Instrumental

HPLC analyses were performed using a Beckman 110B HPLC pump, a Rheodyne Model 7125 injector with a 20 μL injection loop, a Linear Instruments Uvis 200 variable wavelength detector set at 254 nm, and a Hewlett-Packard HP 3390A integrator. All chromatographic solvents were HPLC grade. Optical rotations were measured in $CHCl_3$ using an Autopol IV polarimeter (Rudolph Research). The columns used in this study were brush-type (*S*,*S*)-Whelk-O1 (analytical: 4.6 mm × 25 cm, 5 μm/100 Å silica; semi-prep: 10 mm × 25 cm, 10 μm/100 Å silica) obtained from Regis Technologies. Analytical chromatography was performed at a flow rate of 2.0 mL/min at 0 °C unless otherwise noted; the mobile phase was isopropyl alcohol:hexane (1:99). The void volume marker for the analytical column was 1,3,5-tri-*tert*-butyl benzene. Resolution of the unbound selector CSA was achieved on a preparative column derived from the *N*,*N*-diallyl amide of (*S*)-naproxen (2.5 cm × 78 cm, 40 μm PQ silica).

NMR spectra for compound identification were obtained using a Varian Unity 400 NMR instrument at ambient temperature. NMR spectra of the CSA studies were obtained on a Varian Unity 500 NMR instrument (at ambient temperature unless otherwise noted) or on a Varian Unity Inova 750 NMR instrument (at low temperatures). The nOe experiments were conducted at 20 °C using a Varian Unity Inova 500NB NMR instrument. $CDCl_3$ was the solvent for all NMR experiments. Proton chemical shifts are reported with reference to TMS, and carbon chemical shifts are reported with reference to the solvent peak at δ 77.23.

Gas-phase molecular simulations were conducted with the program CHARMm® distributed by Molecular Simulations Incorporated, San Diego, CA, USA. The steepest descents minimization method was used to identify local minima; the global minimum was identified by both the conjugate gradient and the Newton–Raphson methods. For all analyses, multiple runs from several starting points were performed.

2.2. Synthesis

Unless otherwise noted, all reagents are commercially available. Diarylmethanols were synthesized either by reduction [21–23] of the parent diarylmethanones or by Grignard reaction [24]. The following diarylmethanols were synthesized by Grignard reaction: **4a**, **13a** (*p*-bromotoluene); **12a**, **18a**, **20a**, **23a**, **24a** (bromobenzene); **14a** (2-bromomesitylene). The procedure of van de Bunt [25] was used to chlorinate *p*-aminobenzaldehyde which was then diazotized and converted to 3,5-dichlorobenzaldehyde by reaction with H_3PO_2 [26].

Parent diarylmethanones of **5a**–**11a**, **15a**–**17a**, **21a**, **22a**, **25a**, and **26a** were synthesized by Friedel–Crafts acylation [27]. Acid chlorides were prepared by heating the corresponding benzoic acids at reflux in thionyl chloride. These acid chlorides were reacted with benzene [**7a** (solvent), **8a**, **9a** (solvent), **10a** (solvent), **16a**, **21a**, **22a**], anisole [**6a**,**11a** (4 eq.)], chlorobenzene [**17a**, **25a**, **26a**], toluene [**5a**], or mesitylene [**15a**]. 3,5-Dichlorobenzoic acid was prepared by oxidation of 3,5-dichlorobenzaldehyde with Jones' reagent [28]. The parent diarylmethanones of the following diarylmethanols were reduced by $NaBH_4$: **1a**–**3a**, **5a**–**7a**, **9a**–**11a**, **15a**–**17a**, **19a**, **21a**, **22a**, and **25a**. The parent diarylmethanone of **8a** was reduced with $LiAlH_4$ and the parent diarylmethanone of **26a** was reduced with $THF{\cdot}BH_3$.

Esters were synthesized by slow addition of the appropriate acid chloride to a solution of the diarylmethanol in CH_2Cl_2 and triethylamine. Acetylation reactions were cooled to −78 °C and pivalation reactions were catalyzed by DMAP. Enantioenriched esters were hydrolyzed in a solution of 2 M NaOH and EtOH (1:2, v:v) with heating and sonication. All compounds were purified by silica gel chromatography using CH_2Cl_2 or CH_2Cl_2–hexanes mixtures as the eluent.

2.3. ^1H NMR, selected ^{13}C NMR, and optical rotation data

1a (4-Methylphenyl)phenylmethanol, δ 2.20 (s, 1H), 2.34 (s, 3H), 5.81 (s, 1H), 7.15 (d, 2H, J = 7.8 Hz), 7.26 (d,

2H, J = 8.1 Hz), 7.35 (m, 5H). $[\alpha]_D^{25}$ −10.0 (c 1.19) [17]: $[\alpha]_D^{25}$ −9.0 (c 0.70, $CHCl_3$) for the *S* enantiomer. **1b** (4-Methylphenyl)phenylmethyl pivalate, δ 1.25 (s, 9H), 2.32 (s, 3H), 6.79 (s, 1H), 7.13 (d, 2H, J = 7.8 Hz), 7.21 (d, 2H, J = 7.8 Hz), 7.30 (m, 5H). MRE: $[\alpha]_D^{26}$ −21.0 (c 0.51). **1c** (4-Methylphenyl)phenylmethyl acetate, δ 2.15 (s, 3H), 2.33 (s, 3H), 6.85 (s, 1H), 7.14 (d, 2H, J = 8.3 Hz), 7.23 (d, 2H, J = 8.1 Hz), 7.30 (m, 5H). MRE: $[\alpha]_D^{26}$ −26.7 (c 1.26). **2a** (4-Methoxyphenyl)phenylmethanol, δ 2.23 (s, 1H), 3.79 (s, 3H), 5.81 (s, 1H), 6.87 (d, 2H, J = 8.8 Hz), 7.27 (m, 5H), 7.29 (d, 2H, J = 8.5 Hz). MRE: $[\alpha]_D^{24}$ +19.4 (c 0.31) [17]: $[\alpha]_D^{25}$ −18.8 (c 5.0, benzene) for the *S* enantiomer. **2b** (4-Methoxyphenyl)phenylmethyl pivalate, δ 1.23 (s, 9H), 3.77 (s, 3H), 6.79 (s, 1H), 6.86 (d, 2H, J = 8.8 Hz), 7.25 (d, 2H, J = 8.5 Hz), 7.30 (m, 5H). MRE: $[\alpha]_D^{23}$ −39.3 (c 1.26). **2c** (4-Methoxyphenyl)phenylmethyl acetate, δ 2.15 (s, 3H), 3.79 (s, 3H), 6.85 (s, 1H), 6.86 (d, 2H, J = 8.8 Hz), 7.26 (d, 2H, J = 8.5 Hz), 7.30 (m, 5H). MRE: $[\alpha]_D^{26}$ −50.8 (c 0.37). **3a** (4-Nitrophenyl)phenylmethanol, δ 2.44 (s, 1H), 5.90 (s, 1H), 7.33 (m, 5H), 7.56 (d, 2H, J = 8.5 Hz), 8.17 (d, 2H, J = 8.8 Hz). MRE: $[\alpha]_D^{25}$ +79.0 (c 0.84) [17]: $[\alpha]_D^{20}$ +79.5 (c 1.3, $CHCl_3$) for the *S* enantiomer. **3b** (4-Nitrophenyl)phenylmethyl pivalate, δ 1.27 (s, 9H), 6.86 (s, 1H), 7.34 (m, 5H), 7.51 (d, 2H, J = 8.6 Hz), 8.20 (d, 2H, J = 8.7 Hz). MRE: $[\alpha]_D^{26}$ −25.6 (c 2.57). **3c** (4-Nitrophenyl)phenylmethyl acetate, δ 2.20 (s, 3H), 6.91 (s, 1H), 7.34 (m, 5H), 7.52 (d, 2H, J = 8.8 Hz), 8.20 (d, 2H, J = 8.8 Hz). MRE: $[\alpha]_D^{24}$ −20.9 (c 1.36). **4a** (4-Methoxyphenyl)-(4-methylphenyl)methanol, δ 2.10 (s, 1H), 2.33 (s, 3H), 3.79 (s, 3H), 5.79 (s, 1H), 6.86 (d, 2H, J = 8.8 Hz), 7.14 (d, 2H, J = 8.1 Hz), 7.26 (d, 2H, J = 7.8 Hz), 7.29 (d, 2H, J = 8.8 Hz). ^{13}C NMR: δ 21.3, 55.5, 75.9, 114.0, 126.6, 128.0, 129.3, 136.5, 137.3, 141.4, 159.2. MRE: $[\alpha]_D^{24}$ +5.9 (c 2.28). **4b** (4-Methoxyphenyl)-(4-methylphenyl)methyl pivalate, δ 1.23 (s, 9H), 2.32 (s, 3H), 3.78 (s, 3H), 6.75 (s, 1H), 6.85 (d, 2H, J = 8.8 Hz), 7.13 (d, 2H, J = 8.1 Hz), 7.20 (d, 2H, J = 8.3 Hz), 7.24 (d, 2H, J = 8.8 Hz). MRE: $[\alpha]_D^{26}$ −23.0 (c 0.56). **4c** (4-Methoxyphenyl)-(4-methylphenyl)methyl acetate, δ 2.14 (s, 3H), 2.34 (s, 3H), 3.79 (s, 3H), 6.83 (s, 1H), 6.87 (d, 2H, J = 8.9), 7.15 (d, 2H, J = 7.9), 7.23 (d, 2H, J = 8.1 Hz), 7.26 (d, 2H, J = 8.5 Hz). MRE: $[\alpha]_D^{24}$ −25.7 (c 2.19). **5a** (4-Methylphenyl)-(4-nitrophenyl)methanol, δ 2.34 (s, 3H), 2.40 (s, 1H), 5.88 (s, 1H), 7.17 (d, 2H, J = 7.8 Hz), 7.22 (d, 2H, J = 8.1 Hz), 7.57 (d, 2H, J = 8.5 Hz), 8.17 (d, 2H, J = 8.8 Hz). ^{13}C NMR: δ 21.3, 75.4, 123.7, 126.8, 127.1, 129.7, 138.4, 139.9, 147.1, 151.2. MRE: $[\alpha]_D^{26}$ +72.4 (c 1.11). **5b** (4-Methylphenyl)-(4-nitrophenyl)methyl pivalate, δ 1.27 (s, 9H), 2.33 (s, 3H), 6.83 (s, 1H), 7.16 (d, 2H, J = 8.3 Hz), 7.21 (d, 2H, J = 8.3 Hz), 7.51 (d, 2H, J = 8.5 Hz), 8.19 (d, 2H, J = 8.8 Hz). MRE: $[\alpha]_D^{26}$ −42.6 (c 3.69). **5c** (4-Methylphenyl)-(4-nitrophenyl)methyl acetate, δ 2.19 (s, 3H), 2.34 (s, 3H), 6.89 (s, 1H), 7.17 (d, 2H, J = 8.1 Hz), 7.22 (d, 2H, J = 8.1 Hz), 7.52 (d, 2H, J = 8.8 Hz), 8.20 (d, 2H, J = 9.0 Hz). MRE: $[\alpha]_D^{24}$ −57.0 (c 4.04). **6a** (4-Methoxyphenyl)-(4-nitrophenyl)methanol, δ 2.50 (s, 1H), 3.80 (s, 3H), 5.87 (s, 1H), 6.88 (d, 2H, J = 8.3 Hz), 7.23 (d, 2H, J = 8.1 Hz), 7.54 (d, 2H, J = 9.0 Hz), 8.15 (d, 2H, J = 8.8 Hz). ^{13}C NMR: δ 55.5, 75.2, 114.4, 123.8, 127.1, 128.3, 135.2, 147.2, 151.3, 159.7. MRE: $[\alpha]_D^{24}$ +95.9 (c 0.92). **6b** (4-Methoxyphenyl)-(4-nitrophenyl)methyl pivalate, δ 1.25 (s, 9H), 3.79 (s, 3H), 6.83 (s, 1H), 6.87 (d, 2H, J = 8.8 Hz), 7.23 (d, 2H, J = 8.5 Hz), 7.50 (d, 2H, J = 8.3 Hz), 8.19 (d, 2H, J = 8.8 Hz). MRE: $[\alpha]_D^{24}$ −68.8 (c 2.27). **6c** (4-Methoxyphenyl)-(4-nitrophenyl)methyl acetate, δ 2.18 (s, 3H), 3.78 (s, 3H), 6.86 (d, 2H, J = 8.8 Hz), 6.88 (s, 1H), 7.24 (d, 2H, J = 8.5 Hz), 7.50 (d, 2H, J = 8.5 Hz), 8.18 (d, 2H, J = 8.8 Hz). MRE: $[\alpha]_D^{27}$ −84.8 (c 3.32). **7a** (3,5-Dimethoxyphenyl)phenylmethanol, δ 2.37 (s, 1H), 3.76 (s, 6H), 5.74 (s, 1H), 6.36 (t, 1H, J = 2.2 Hz), 6.55 (d, 2H, J = 2.2 Hz), 7.32 (m, 5H). MRE: $[\alpha]_D^{24}$ +14.3 (c 3.49) [19]: $[\alpha]_D^{25}$ +16.6 (c 1.02, $CHCl_3$) for the *S* enantiomer. **7b** (3,5-Dimethoxyphenyl)phenylmethyl pivalate, δ 1.26 (s, 9H), 3.75 (s, 6H), 6.36 (t, 1H, J = 2.1 Hz), 6.49 (d, 2H, J = 2.4 Hz), 6.73 (s, 1H), 7.30 (m, 5H). MRE: $[\alpha]_D^{23}$ +9.0 (c 12.6). **8a** (3,5-Dinitrophenyl)phenylmethanol, δ 2.60 (s, 1H), 6.00 (s, 1H), 7.33 (m, 5H), 8.60 (d, 2H, J = 2.0 Hz), 8.93 (t, 1H, J = 2.2 Hz). ^{13}C NMR: δ 75.0, 117.9, 126.6, 126.9, 129.3, 129.6, 141.8, 148.5, 148.7. MRE: $[\alpha]_D^{26}$ +86.9 (c 3.89). **8b** (3,5-Dinitrophenyl)phenylmethyl pivalate, δ 1.30 (s, 9H), 6.93 (s, 1H), 7.38 (m, 5H), 8.53 (d, 2H, J = 2.1 Hz), 8.95 (t, 1H, J = 2.1 Hz). MRE: $[\alpha]_D^{26}$ −42.8 (c 5.65). **9a** (3,5-Dimethylphenyl)phenylmethanol, δ 2.35 (s, 6H), 2.51 (s, 1H), 5.76 (s, 1H), 6.96 (s, 1H), 7.03 (s, 2H), 7.31 (m, 1H), 7.38 (m, 2H), 7.42 (m, 2H). ^{13}C NMR: δ 21.4, 76.1, 124.4, 126.6, 127.3, 128.4, 129.2, 137.9, 143.9, 144.1. MRE: $[\alpha]_D^{24}$ −6.1 (c 2.55). **9b** (3,5-Dimethylphenyl)phenylmethyl pivalate, δ 1.27 (s, 9H), 2.29 (s, 6H), 6.75 (s, 1H), 6.91 (s, 1H), 6.95 (s, 2H), 7.31 (m, 5H). MRE: $[\alpha]_D^{23}$ −6.4 (c 4.21). **10a** (3-Methoxyphenyl)phenylmethanol, δ 2.24 (s, 1H), 3.79 (s, 3H), 5.82 (s, 1H), 6.81 (dd, 1H, J = 8.1 Hz, 2.7 Hz), 6.96 (m, 2H), 7.26 (m, 1H), 7.36 (m, 5H). MRE: $[\alpha]_D^{23}$ +16.6 (c 5.91) [19]: $[\alpha]_D^{25}$ +14.5 (c 0.97, $CHCl_3$) for the *S* enantiomer. **10b** (3-Methoxyphenyl)phenylmethyl pivalate, δ 1.27 (s, 9H), 3.78 (s,3H), 6.79 (s, 1H), 6.81 (dd, 1H, J = 8.3 Hz, 3.2 Hz), 6.90 (t, 1H, J = 2.2 Hz), 6.93 (d, 1H, J = 7.6 Hz), 7.25 (t, 1H, J = 7.8 Hz), 7.30 (m, 5H). MRE: $[\alpha]_D^{24}$ +7.8 (c 2.82). **11a** (3-Methoxyphenyl)-(4-methoxyphenyl)methanol, δ 2.45 (s, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 5.77 (s, 1H), 6.82 (dd, 1H, J = 8.1 Hz, 2.4 Hz), 6.88 (d, 2H, J = 8.5 Hz), 6.96 (m, 2H), 7.26 (t, 1H, J = 8.1 Hz), 7.29 (d, 2H, J = 8.8 Hz). ^{13}C NMR: δ 55.4, 55.5, 75.9, 112.1, 113.0, 114.1, 118.9, 128.1, 129.7, 136.2, 145.9, 159.2, 159.9. MRE: $[\alpha]_D^{24}$ +30.5 (c 1.69). **11b** (3-Methoxyphenyl)-(4-methoxyphenyl)methyl pivalate, δ 1.28 (s, 9H), 3.79 (s, 3H), 3.80 (s, 3H), 6.77 (s, 1H), 6.82 (dd, 1H, J = 8.3 Hz, 2.4 Hz), 6.87 (d, 2H, J = 8.8 Hz), 6.89 (t, 1H, J = 2.2 Hz), 6.92 (d, 1H, J = 7.6 Hz), 7.26 (t, 1H, J = 7.8 Hz), 7.27 (d, 2H, J = 8.5 Hz). MRE: $[\alpha]_D^{24}$ −43.7 (c 1.26). **12a** (2,4,6-Trimethylphenyl)phenylmethanol, δ 2.17 (s, 1H), 2.23 (s, 6H), 2.28 (s, 3H), 6.32 (s, 1H), 6.86 (s, 2H), 7.26 (m, 5H). LRE: $[\alpha]_D^{26}$ +143 (c 1.59) [29]: $[\alpha]_D^{26}$ +144 (c 1.01, $CHCl_3$) for the *R* enantiomer. **12b** (2,4,6-Trimethylphenyl)phenylmethyl pivalate, δ 1.30 (s, 9H), 2.27 (s, 3H), 2.32 (s, 6H), 6.85 (s, 2H), 7.11 (m, 2H), 7.23 (m, 3H), 7.31 (s, 1H). MRE: $[\alpha]_D^{23}$ −119 (c 1.04). **12c** (2,4,6-

Trimethylphenyl)phenylmethyl acetate, δ 2.17 (s, 3H), 2.28 (s, 3H), 2.30 (s, 6H), 6.86 (s, 2H), 7.12 (m, 2H), 7.26 (m, 3H), 7.39 (s, 1H). MRE: $[\alpha]_D^{24}$ −121 (c 1.51). **13a** (2,4,6-Trimethylphenyl)-(4-methylphenyl)methanol, δ 2.20 (s, 1H), 2.26 (s, 6H), 2.31 (s, 3H), 2.36 (s, 3H), 6.31 (s, 1H), 6.89 (s, 2H), 7.13 (d, 2H, J = 8.1 Hz), 7.19 (d, 2H, J = 8.1 Hz). ^{13}C NMR: δ 20.8, 21.1, 21.2, 71.2, 125.6, 129.0, 130.2, 136.2, 136.7, 137.2, 137.4, 140.2. MRE: $[\alpha]_D^{25}$ −125 (c 1.66). **13b** (2,4,6-Trimethylphenyl)-(4-methylphenyl)methyl pivalate, δ 1.30 (s, 9H), 2.29 (s, 3H), 2.31 (s, 6H), 2.34 (s, 3H), 6.86 (s, 2H), 7.01 (d, 2H, J = 7.8 Hz), 7.11 (d, 2H, J = 8.1 Hz), 7.29 (s, 1H). MRE: $[\alpha]_D^{24}$ −98.6 (c 1.78). **13c** (2,4,6-Trimethylphenyl)-(4-methylphenyl)methyl acetate, δ 2.17 (s, 3H), 2.28 (s, 9H), 2.33 (s, 3H), 6.86 (s, 2H), 7.00 (d, 2H, J = 8.1 Hz), 7.10 (d, 2H, J = 8.1 Hz), 7.33 (s, 1H). MRE: $[\alpha]_D^{26}$ −92.5 (c 0.65). **14a** (4-Methoxyphenyl)-(2,4,6-trimethylphenyl)methanol, δ 2.15 (s, 1H), 2.25 (s, 6H), 2.29 (s, 3H), 3.80 (s, 3H), 6.29 (s, 1H) 6.84 (d, 2H, J = 8.8 Hz), 6.86 (s, 2H), 7.19 (d, 2H, J = 8.8 Hz). ^{13}C NMR: δ 20.7, 21.0, 55.3, 70.8, 113.6, 126.9, 130.1, 135.3, 136.7, 137.0, 137.2, 158.3. MRE: $[\alpha]_D^{26}$ −102 (c 1.86). **14b** (4-Methoxyphenyl)-(2,4,6-trimethylphenyl)methyl pivalate, δ 1.28 (s, 9H), 2.27 (s, 3H), 2.30 (s, 6H), 3.78 (s, 3H), 6.82 (d, 2H, J = 9.0 Hz), 6.84 (s, 2H), 7.02 (d, 2H, J = 8.1 Hz), 7.25 (s, 1H). MRE: $[\alpha]_D^{24}$ −77.5 (c 4.53). **14c** (4-Methoxyphenyl)-(2,4,6-trimethylphenyl)methyl acetate, δ 2.23 (s, 3H), 2.35 (s, 3H), 2.37 (s, 6H), 3.83 (s, 3H), 6.90 (d, 2H, J = 8.8 Hz), 6.94 (s, 2H), 7.13 (d, 2H, J = 8.8 Hz), 7.40 (s, 1H). MRE: $[\alpha]_D^{24}$ −70.9 (c 0.86). **15a** (2,4,6-Trimethylphenyl)-(4-nitrophenyl)methanol, δ 2.22 (s, 6H), 2.29 (s, 3H), 2.40 (s, 1H), 6.35 (s, 1H), 6.88 (s, 2H), 7.47 (d, 2H, J = 9.0 Hz), 8.16 (d, 2H, J = 9.0 Hz). ^{13}C NMR: δ 20.7, 21.1, 70.7, 123.6, 126.5, 130.5, 135.7, 137.2, 138.4, 146.8, 151.2. MRE: $[\alpha]_D^{24}$ +157 (c 1.80). **15b** (2,4,6-Trimethylphenyl)-(4-nitrophenyl)methyl pivalate, δ 1.30 (s, 9H), 2.28 (s, 9H), 6.87 (s, 2H), 7.30 (d, 2H, J = 8.8 Hz), 7.33 (s, 1H), 8.16 (d, 2H, J = 8.8 Hz). MRE: $[\alpha]_D^{25}$ −124 (c 0.99). **15c** (2,4,6-Trimethylphenyl)-(4-nitrophenyl)methyl acetate, δ 2.23 (s, 3H), 2.28 (s, 6H), 2.29 (s, 3H), 6.89 (s, 2H), 7.32 (d, 2H, J = 8.2 Hz), 7.39 (s, 1H), 8.16 (d, 2H, J = 8.8 Hz). MRE: $[\alpha]_D^{24}$ −113 (c 1.49). **16a** (2-Chlorophenyl)phenylmethanol, δ 2.60 (s, 1H), 6.20 (s, 1H), 7.31 (m, 8H), 7.61 (dd, 1H, J = 7.8 Hz, 1.5 Hz). LRE: $[\alpha]_D^{26}$ −23.2 (c 1.60) [6]: $[\alpha]_D^{20}$ −21.5 (c 1.14, $CHCl_3$) for the *S* enantiomer. **16b** (2-Chlorophenyl)phenylmethyl pivalate, δ 1.26 (s, 9H), 7.19 (s, 1H), 7.30 (m, 8H), 7.45 (dd, 1H, J = 7.6 Hz, 2.0 Hz). MRE: $[\alpha]_D^{24}$ +7.2 (c 6.71). **17a** (2-Chlorophenyl)-(4-chlorophenyl)methanol, δ 2.43 (s, 1H), 6.20 (s, 1H), 7.24 (td, 1H, J = 7.5 Hz, 1.7 Hz), 7.30 (d, 2H, J = 8.8 Hz), 7.30 (td, 1H, J = 7.9 Hz, 2.3 Hz), 7.33 (d, 2H, J = 9.4 Hz), 7.35 (dd, 1H, J = 7.9 Hz, 1.3 Hz), 7.56 (dd, 1H, J = 7.7 Hz, 1.7 Hz). ^{13}C NMR: δ 72.2, 127.4, 128.1, 128.5, 128.8, 129.2, 129.8, 132.6, 133.7, 140.8, 140.8. MRE: $[\alpha]_D^{22}$ +38.2 (c 2.40). **17b** (2-Chlorophenyl)-(4-chlorophenyl)methyl pivalate, δ 1.29 (s, 9H), 7.16 (s, 1H), 7.25 (td, 1H, J = 7.7 Hz, 1.9 Hz), 7.30 (td, 1H, J = 7.5 Hz, 1.5 Hz), 7.32 (s, 4H), 7.38 (dd, 1H, J = 7.9 Hz, 1.5 Hz), 7.47 (dd, 1H, J = 7.7 Hz, 1.7 Hz). MRE: $[\alpha]_D^{23}$ +16.1 (c 3.71). **18a** (4-Fluorophenyl)phenylmethanol, δ 2.23 (s, 1H), 5.83 (s, 1H), 7.02 (t, 2H, J = 8.5 Hz), 7.32 (m, 7H). ^{13}C NMR: δ 75.7, 115.4 (d, J_{CF} = 21.9 Hz), 126.6, 127.9, 128.4 (d, J_{CF} = 8.1 Hz), 128.7, 139.7 (d, J_{CF} = 2.9 Hz), 143.8, 162.3 (d, J_{CF} = 245.9 Hz). MRE: $[\alpha]_D^{26}$ +6.7 (c 0.51). **18b** (4-Fluorophenyl)phenylmethyl pivalate, δ 1.26 (s, 9H), 6.82 (s, 1H), 7.02 (t, 2H, J = 8.5 Hz), 7.31 (m, 7H). MRE: $[\alpha]_D^{26}$ +16.8 (c 0.50). **19a** (4-Chlorophenyl)phenylmethanol, δ 2.50 (s, 1H), 5.78 (s, 1H), 7.32 (m, 9H). MRE: $[\alpha]_D^{26}$ +20.3 (c 0.95) [30]: $[\alpha]_D^{20}$ +22.0 (c 0.9, $CHCl_3$) for the *S* enantiomer. **19b** (4-Chlorophenyl)phenylmethyl pivalate, δ 1.25 (s, 9H), 6.78 (s, 1H), 7.32 (m, 9H). MRE: $[\alpha]_D^{25}$ −11.3 (c 2.60). **19c** (4-Chlorophenyl)phenylmethyl acetate, δ 2.18 (s, 3H), 6.84 (s, 1H), 7.32 (m, 9H). MRE: $[\alpha]_D^{25}$ −7.1 (c 3.02). **20a** (4-Bromophenyl)phenylmethanol, δ 2.21 (s, 1H), 5.80 (s, 1H), 7.26 (d, 2H, J = 8.5 Hz), 7.31 (m, 5H), 7.46 (d, 2H, J = 8.5 Hz). MRE: $[\alpha]_D^{25}$ +18.6 (c 0.24) [18]: $[\alpha]_D^{22}$ +19.8 (c 5, benzene) for the *S* enantiomer. **20b** (4-Bromophenyl)phenylmethyl pivalate, δ 1.25 (s, 9H), 6.78 (s, 1H), 7.21 (d, 2H, J = 8.3 Hz), 7.33 (m, 5H), 7.45 (d, 2H, J = 8.3 Hz). MRE: $[\alpha]_D^{25}$ −11.2 (c 3.08). **21a** (4-Iodophenyl)phenylmethanol, δ 2.59 (s, 1H), 5.71 (s, 1H), 7.10 (d, 2H, J = 8.1 Hz), 7.32 (m, 5H), 7.65 (d, 2H, J = 8.3 Hz). ^{13}C NMR: δ 75.9, 93.3. 126.7, 128.1, 128.6, 128.9, 137.7, 143.5, 143.6. MRE: $[\alpha]_D^{25}$ +16.5 (c 1.05). **21b** (4-Iodophenyl)phenylmethyl pivalate, δ 1.25 (s, 9H), 6.75 (s, 1H), 7.08 (d, 2H, J = 8.3 Hz), 7.31 (m, 5H), 7.66 (d, 2H, J = 8.5 Hz). MRE: $[\alpha]_D^{26}$ −13.8 (c 3.24). **22a** (3-Chlorophenyl)phenylmethanol, δ 2.72 (broad s, 1H), 5.73 (s, 1H), 7.24 (m, 3H), 7.33 (m, 5H), 7.39 (m, 1H). ^{13}C: δ 76.1, 125.0, 127.024, 127.031, 128.1, 128.4, 129.1, 130.2, 134.8, 143.6, 146.1. The two peaks at δ 127.0 could be resolved by reducing the spectral window to 60–160 ppm, increasing the number of points to 524k, and processing with a Fourier number of 512k and no line broadening. The resolution of these peaks was further aided by processing the fid with a shifted sine bell. Pertinent Varian parameters: np = 524k, sw = 9575.1, tof = 1920.7, fn = 512k, lb = 0, sb = −1.508, sbs = −0.374. Opt. Rot. LRE: $[\alpha]_D^{23}$ −34.9 (c 0.17). **22b** (3-Chlorophenyl)phenylmethyl pivalate, δ 1.26 (s, 9H), 6.77 (s, 1H), 7.27 (m, 9H). **22c** (3-Chlorophenyl)phenylmethyl acetate, δ 2.18 (s, 3H), 6.84 (s, 1H), 7.28 (m, 9H). MRE: $[\alpha]_D^{25}$ −19.0 (c 1.37). **23a** (3,4-Dichlorophenyl)phenylmethanol, δ 2.31 (s, 1H), 5.78 (s, 1H), 7.19 (dd, 1H, J = 8.3 Hz, 2.2 Hz), 7.32 (m, 5H), 7.39 (d, 1H, J = 8.3 Hz), 7.51 (d, 1H, J = 2.0 Hz). ^{13}C NMR: δ 75.0, 125.9, 126.6, 128.2, 128.4, 128.8, 130.4, 131.4, 132.5, 142.7, 143.9. MRE: $[\alpha]_D^{26}$ +45.9 (c 2.83). **23b** (3,4-Dichlorophenyl)phenylmethyl pivalate, δ 1.26 (s, 9H), 6.75 (s, 1H), 7.18 (dd, 1H, J = 8.3 Hz, 2.0 Hz), 7.33 (m, 5H), 7.41 (d, 1H, J = 8.3 Hz), 7.42 (d, 1H, J = 2.0 Hz). MRE: $[\alpha]_D^{24}$ −0.94 (c 4.78). **24a** (3,5-Dichlorophenyl)phenylmethanol, δ 2.29 (s, 1H), 5.76 (s, 1H), 7.25 (t, 1H, J = 2.0 Hz), 7.29 (dd, 2H, J = 2.0 Hz, 0.7 Hz), 7.35 (m, 5H). ^{13}C NMR: δ 75.4, 125.1, 126.8, 127.8, 128.5, 129.1, 135.2, 142.8, 147.1. MRE: $[\alpha]_D^{26}$ +50.7 (c 3.27). **24b** (3,5-Dichlorophenyl)phenylmethyl pivalate, δ

1.27 (s, 9H), 6.72 (s, 1H), 7.21 (dd, 2H, J = 2.0 Hz, 0.7 Hz), 7.27 (t, 1H, J = 2.0 Hz), 7.35 (m, 5H). MRE: $[\alpha]_D^{26}$ −16.6 (c 3.16). **25a** (3-Chlorophenyl)-(4-chlorophenyl)methanol, δ 2.22 (s, 1H), 5.77 (s, 1H), 7.22 (m, 1H), 7.26 (m, 2H), 7.29 (d, 2H, J = 8.8 Hz), 7.32 (d, 2H, J = 8.8 Hz), 7.37 (m, 1H). ^{13}C NMR: δ 75.2, 124.8, 126.8, 128.1, 128.2, 129.0, 130.1, 133.9, 134.8, 141.8, 145.5. MRE: $[\alpha]_D^{23}$ +16.9 (c 2.70). **25b** (3-Chlorophenyl)-(4-chlorophenyl)methyl pivalate, δ 1.25 (s, 9H), 6.74 (s, 1H), 7.20 (m, 1H), 7.26 (d, 2H, J = 8.5 Hz), 7.27 (m, 2H), 7.30 (m, 1H), 7.32 (d, 2H, J = 8.5 Hz). MRE: $[\alpha]_D^{27}$ −21.9 (c 1.56). **25c** (3-Chlorophenyl)-(4-chlorophenyl)methyl acetate, δ 2.17 (s, 3H), 6.78 (s, 1H), 7.18 (m, 1H), 7.26 (d, 2H, J = 8.1 Hz), 7.27 (m, 2H), 7.31 (m, 1H), 7.32 (d, 2H, J = 8.6 Hz). MRE: $[\alpha]_D^{26}$ −26.7 (c 0.42). **26a** (3,5-Dichlorophenyl)-(4-chlorophenyl)methanol, δ 2.29 (s, 1H), 5.74 (s, 1H), 7.25 (dd, 2H, J = 1.9 Hz, 0.6 Hz), 7.27 (t, 1H, J = 1.7 Hz), 7.28 (d, 2H, J = 8.4 Hz), 7.34 (d, 2H, J = 8.6 Hz). ^{13}C NMR: δ 74.8, 125.1, 1281, 128.2, 129.2, 134.3, 135.4, 141.2, 146.8. MRE: $[\alpha]_D^{23}$ +28.4 (c 6.60). **26b** (3,5-Dichlorophenyl)-(4-chlorophenyl)methyl pivalate, δ 1.25 (s, 9H), 6.68 (s, 1H), 7.18 (d, 2H, J = 1.5 Hz), 7.24 (d, 2H, J = 8.3 Hz), 7.28 (t, 1H, J = 2.0 Hz), 7.34 (d, 2H, J = 8.5 Hz). MRE: $[\alpha]_D^{23}$ −24.4 (c 3.55).

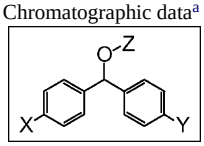
3. Results and discussion

3.1. Analytes with meta- and/or para-methoxy, methyl, or nitro substituents

Although the simultaneous π–π interactions between the Whelk-O selector and an analyte may be synergistic, the interaction between the π-acidic selector DNB group and the aromatic analyte moiety correlates with enantioresolution of analytes possessing a single aromatic substituent. For example, enantioresolutions of 5-arylhydantoins generally improve as the π-basicity of the aromatic moiety increases [31]. Accordingly, an intuitive view of π-basicity gives the following stability sequence for face-to-face association of a *para*-substituted aryl group with the selector DNB group and, by extension, the priority for inclusion of the aryl group in the Whelk-O cleft: 4-OMe > 4-Me > H > 4-NO_2.

Using the π-basicity sequence above, one would assign A = 4-methoxyphenyl and B = phenyl for analyte **2b**; it then follows that the MRE-**2b** on an (*S*,*S*)-Whelk-O1 column should be the *S* enantiomer and should yield the known [17] levorotatory compound (*S*)-(4-methoxyphenyl)phenylmethanol [(*S*)-**2a**] upon hydrolysis. This prediction was verified, and (*S*)-**2a** was found to be the LRE of that analyte as shown in Table 1. Hydrolysis of the acetate ester MRE-2c yielded (*S*)-**2a** as well. The absolute configurations of (4-methylphenyl)phenylmethanol (**1a**) and (4-nitrophenyl)phenylmethanol (**3a**) are also known [17], and studies of their ester derivatives also support the chiral recognition model for diarylmethyl esters.

Table 1
Chromatographic data[a] for analyte sets **1**–**6**



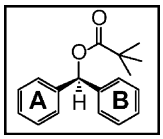
Analyte	X	Y	Z	k'_1	α	Configuration of MRE[b]
1a	H	Me	H	2.95	1.00	–
1b			Pivalyl	2.50	1.45	*S*-(−)
1c			Acetyl	2.99	1.25	*S*-(−)
2a	H	OMe	H	5.58	1.05	*R*-(+)[c]
2b			Pivalyl	3.57	2.42	*S*-(−)
2c			Acetyl	4.79	2.00	*S*-(−)
3a	H	NO_2	H	7.72	1.09	*S*-(+)[c]
3b			Pivalyl	3.70	1.13	*R*-(−)
3c			Acetyl	5.10	1.12	*R*-(−)
4a	Me	OMe	H	6.16	1.03	*R*-(+)
4b			Pivalyl	4.99	1.76	*S*-(−)
4c			Acetyl	6.09	1.68	*S*-(−)
5a	Me	NO_2	H	7.67	1.13	*S*-(+)
5b			Pivalyl	3.72	1.58	*R*-(−)
5c			Acetyl	5.19	1.38	*R*-(−)
6a	OMe	NO_2	H	15.08	1.16	*R*-(+)
6b			Pivalyl	5.37	2.46	*S*-(−)
6c			Acetyl	8.28	2.03	*S*-(−)

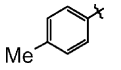
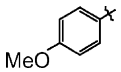
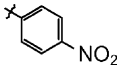
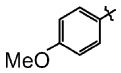
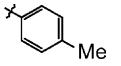
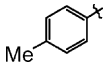
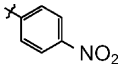
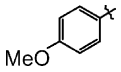
[a] Mobile phase: 2-propanol:hexane (1:99). Temperature: 0 °C. Flow rate: 2 mL/min.
[b] MRE: more retained enantiomer on the (*S*,*S*)-Whelk-O1 CSP.
[c] Known absolute configuration [17].

In the analyte sets of (4-methoxyphenyl)-(4-methylphenyl)methanol (**4a**), (4-methylphenyl)-(4-nitrophenyl)methanol (**5a**), and (4-methoxyphenyl)-(4-nitrophenyl)methanol (**6a**), the effects the substituents exert on enantioselectivity reinforce each other when the substituents on the rings have opposite propensities, with respect to phenyl, for inclusion in the selector cleft and oppose each other when they have similar propensities with respect to phenyl. Thus, ester **6b** has a greater α value than either **2b** or **3b** while the α value of **4c** lies between the α values of **1c** and **2c**.

The NMR spectrum of the (*S*)-Whelk-O CSA combined with analyte **2b**—enriched in the MRE on the (*S*,*S*)-Whelk-O1 CSP—exhibits two analyte methine signals. The larger methine signal of the MRE lies upfield of the smaller methine signal of the LRE ($\Delta\delta = \delta$ MRE $- \delta$ LRE = −0.072, Table 2). Even with high field NMR and the low temperatures sometimes used in the CSA studies, fast exchange occurs and only a single, averaged signal is observed for the methine proton of each enantiomer. Upon association with the Whelk-O CSA, the enantiotopic protons of a chiral diarylmethyl ester become diastereotopic, and in principle nonequivalent by NMR. In practice, however, the magnitude of this non-equivalence will not be large if the diastereotopic protons experience similar magnetic environments. Because the LRE methine proton and the MRE methine proton are presumed to be in very similar positions in the Whelk-O cleft in the respective complexes,

Table 2
Proton NMR chemical shift non-equivalence data from CSA studies of pivalate esters **1b–6b**



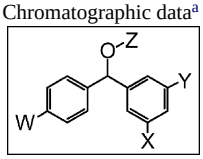
Analyte	A-ring structure	Δδ values[a]							B-ring structure	Pivalyl Δδ[a]	[(*S*)-CSA] /mM	[Analyte] /mM(ee)[b]
		A *para*	A *meta*	A *ortho*	Methine	B *ortho*	B *meta*	B *para*				
1b		−0.025	−0.041	−0.038	−0.037	obsc	obsc	obsc		+0.002	21	32 (47)
2b		−0.020	−0.050	−0.051	−0.072	obsc	obsc	obsc		+0.003	19	34 (47)
3b		obsc	obsc	obsc	−0.034	obsc	+0.007	–		0	7	9(47)
4b		−0.018	−0.041	−0.038	−0.036	+0.013	+0.027	+0.018		0	18	27 (48)
5b		−0.018	−0.031	−0.038	−0.069	−0.009	+0.008	–		+0.002	17	36 (22)
6b		−0.015	−0.037	−0.048	−0.090	−0.014	+0.005	–		+0.003	17	58 (35)

[a] Δδ: δ MRE − δ LRE, ambient temperature, 500 MHz, obsc: obscured.
[b] The enantiomer present in excess is that shown, the MRE on the (*S*,*S*)-Whelk-O1 CSP.

the magnetic environments for these two diastereotopic protons are expected to be similar. Therefore, one may wonder why the magnitude of methine non-equivalence for an ester is consistently similar to or greater than the magnitudes of non-equivalences observed for the aromatic ring protons which presumably experience very different magnetic environments in the two complexes. An explanation for this occurrence is the difference in association constants for the complexes of the Whelk-O selector with the MRE or LRE of a diarylmethyl ester. At any moment, the fraction of MRE molecules associated with the selector is greater than the fraction of LRE molecules associated with the selector; consequently, the methine proton of the MRE experiences a greater average shielding than the methine proton of the LRE. This explanation is consistent with the correlation between separation factor and methine non-equivalence. Despite variations in the conditions of the CSA studies, a general trend of increasing methine non-equivalence with increasing separation factor is evident.

The methine non-equivalence does not help in assigning absolute configurations to the enantiomers, since to make such assignments one must observe chemical shift non-equivalence for protons on the aromatic rings or the aromatic ring substituents. The signals of the 4-methoxy protons and the neighboring *meta* protons of **2b** have negative Δδ values (Table 2), indicating that the 4-methoxyphenyl ring of the MRE experiences greater shielding than the 4-methoxyphenyl ring of the LRE. One may then conclude that A = 4-methoxyphenyl and B = phenyl. This same conclusion was reached earlier on the grounds of π-basicity and was found to agree with the established absolute configuration of analyte **2a**. The analytes of known absolute configuration provide a means for validating the CSA data. This is a gratifying result since fidelity of the chiral recognition mechanism of the unbound selector relative to that of the bound selector was not assured beforehand. Back-face interaction of an analyte with the DNB ring of the selector has always been suspected to occur, thus allowing the excluded A-ring of an ester LRE to undergo, simultaneously, hydrogen bonding and the face-to-face π–π interaction but not the edge-to-face π–π interaction. In fact, an X-ray crystal structure of a 1:1 co-crystal of one enantiomer of the Whelk-O selector and the LRE of an amide analyte shows a back-face interaction whereas a co-crystal of the same Whelk-O enantiomer and the amide MRE shows inclusion in the cleft [32]. For the CSP, the short tether is thought to position the back face of the selector close enough to the silica to impede approach of the LRE to the back face, thereby increasing enantioselectivity by reducing retention of the LRE [33]. While the CSA offers no such impediment, consideration of NMR spectra, chromatographic behavior, and X-ray crystallographic data supports analyte inclusion in the cleft as the major enantioselective interaction between the diarylmethyl esters and either the Whelk-O CSA or CSP.

Table 3
Chromatographic data[a] for analyte sets **7**–**11**



Analyte	*W*	*X*	*Y*	*Z*	k'_1	α	Configuration of MRE[b]
7a	H	OMe	OMe	H	7.83	1.13	*S*-(+)[c]
7b				Pivalyl	4.74	3.93	*S*-(+)
8a	H	NO_2	NO_2	H	11.80	1.38	*S*-(+)
8b				Pivalyl	3.15	2.54	*R*-(−)
9a	H	Me	Me	H	2.85	1.09	*S*-(−)
9b				Pivalyl	2.50	2.76	*S*-(−)
10a[d]	H	H	OMe	H	4.70	1.02	*S*-(+)[c]
10b				Pivalyl	3.38	2.06	*S*-(+)
11a	OMe	H	OMe	H	10.17	1.04	*S*-(+)
11b				Pivalyl	9.40	1.16	*R*-(−)

[a] Mobile phase: 2-propanol: hexane (1:99). Temperature: 0 °C. Flow rate: 2 mL/min.
[b] MRE: more retained enantiomer on the (*S*,*S*)-Whelk-O1 CSP.
[c] Known absolute configuration [19].
[d] Flow rate: 1.5 mL/min.

The small downfield shift often observed for the MRE pivalate signal relative to that of the LRE is also consistent with the chiral recognition model. In the model, a pivalate ester associated with the selector has one of the pivalate methyl groups in the plane of the selector DNB, one methyl group at the border of the DNB shielding cone, and the third methyl group outside regions of significant diamagnetic influence. A slight deshielding of the pivalate signal of the MRE is expected. The magnitude of this non-equivalence is small and, in the case of (2-chlorophenyl)-(4-chlorophenyl)methyl pivalate (**17b**) its sense is reversed. For this analyte, A = 2-chlorophenyl and the steric demands of an *ortho*-Cl substituent may prevent the MRE from closely associating with the selector, thereby altering somewhat the structure of the complex as compared to those of *para*- and/or *meta*-substituted analytes. Similarly, the bulk of the mesityl group may be the cause of the sense of non-equivalence found for the single acetate ester subjected to the CSA studies [(2,4,6-trimethylphenyl)-(4-nitrophenyl)methyl acetate, **15c**].

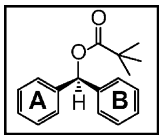
Because of the complexity of the signals in the aromatic region of the NMR spectra, 500 MHz or 750 MHz spectrometers, multiple low temperatures, and varied ratios of the enantiomers were used to unravel the spectra sufficiently to make configuration assignments. Although the signals from protons on an unsubstituted ring could not be deconvoluted with confidence, the non-equivalence for protons on the substituted rings was usually discernable. Because the chemical shifts of the *ortho* protons on a ring might be influenced by the diamagnetic anisotropy of the other ring and because the *ortho* protons or substituents on the excluded ring may be affected by the selector's naphthyl group anisotropy, the sense of any non-equivalence noted for an *ortho* proton or substituent was not considered a reliable indicator of absolute configuration. An example of an NMR spectrum from a similar CSA study can be found in an earlier publication [34].

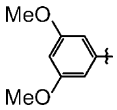
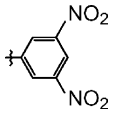
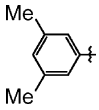
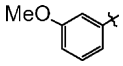
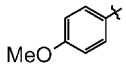
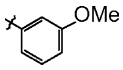
The analytes discussed thus far are all substituted at the *para* position. Substitution at the *para* position is not expected to impede entry of any analyte into the selector cleft, and space-filling models suggest that small substituents in the *meta* position should not prevent an aromatic ring of a diarylmethyl ester from entering the selector cleft. Several analytes bearing *meta* substituents were enantioresolved (Table 3) and subjected to CSA studies (Table 4). These data provide an expanded priority sequence for inclusion in the selector cleft: 3,5-diOMe > 3,5-diMe > 4-OMe > 3-OMe > 4-Me > H > 4-NO_2 > 3,5-diNO_2. In the course of this study, the absolute configurations of (3,5-dimethoxyphenyl)phenylmethanol (**7a**) and (3-methoxyphenyl)phenylmethanol (**10a**) indicated by the CSA studies were verified by X-ray crystallography [19].

3.2. Analytes with ortho substituents

To explore the steric aspect of chiral recognition by the Whelk-O1 CSP, diarylmethyl esters containing a 2,4,6-trimethylphenyl (mesityl) moiety were enantioresolved (Table 5) and subjected to CSA studies (Table 6). The CSA data indicate that A = 2,4,6-trimethylphenyl for these esters, as the $\Delta\delta$ values of the *meta* protons on the mesityl ring are negative for all. Initially, these data were puzzling because the steric bulk of the mesityl ring was expected to impede its entry into the selector cleft; the bulkiness of these molecules is evident in their short chromatographic retention times. However, the X-ray crystallographic data for a camphorsultam phthalic acid derivative of (2,4,6-

Table 4
Proton NMR chemical shift non-equivalence data from CSA studies of pivalate esters **7b**–**11b**



Analyte	A-ring structure	Δδ values[a]							B-ring structure	Pivalyl Δδ[a]	[(*S*)-CSA] /mM	[Analyte] /mM (ee)[b]
		A *para*	A *meta* (3,5)	A *ortho* (2,6)	Methine	B *ortho* (2,6)	B *meta* (3,5)	B *para*				
7b		−0.098	−0.047	−0.115	−0.229	obsc	obsc	obsc		+0.009	48	37 (36)
8b		obsc	obsc	obsc	−0.186	−0.034	–	+0.005		+0.002	42	42 (33)
9b		−0.043	−0.056	−0.082	−0.112	obsc	obsc	obsc		+0.004	41	31 (62)
10b[c]		−0.061	−0.033, −0.060	−0.067, −0.057	−0.085	obsc	obsc	obsc		+0.003	40	33 (34)
11b[d]		−0.034	−0.077	−0.060	−0.034	obsc, obsc	+0.032, +0.053	obsc		+0.004	45	35 (28)

[a] Δδ: δ MRE − δ LRE, ambient temperature, 500 MHz, obsc: obscured.
[b] The enantiomer present in excess is that shown, the MRE on the (*S*,*S*)-Whelk-O1 CSP.
[c] Proton assignments for **10b** were made with an nOe difference experiment. Irradiation of the methoxy singlet at δ3.78 gave a 6.9% enhancement at δ6.90 (*t*, *J* = 2.2 Hz) and a 6.8% enhancement at δ6.81 (dd, *J* = 8.3, 3.2 Hz). A 1.3% indirect nOe signal was observed at δ7.25 (*t*, *J* = 7.8 Hz); a 0.2 % indirect nOe was observed at δ6.93 (d, *J* = 7.6 Hz).
[d] Assignments for **11b** were made by comparison of its spectrum with that of **10b**.

trimethylphenyl)phenylmethanol (**12a**) verified the absolute configuration of **12a** indicated by the CSA data of **12b** [29]. Absolute configurations for the other mesityl analyte sets were assigned by comparison of their CSA data and chromatographic behavior with the data for analyte set 12.

As stated earlier, the "book" conformation does not accurately represent the conformation of the mesityl analytes. A drawing of the only low energy conformer of (*S*)-(2,4,6-trimethylphenyl)phenylmethyl pivalate [(*S*)-**12b**] generated by CHARMm minimization is shown in Fig. 4. The mesityl ring assumes a "book" conformation but the phenyl ring is turned significantly and cannot participate in the π–π interactions with the selector cleft. This configuration agrees with that revealed by the X-ray data. Modeling identified a "book" conformation approximately 6 kcal/mol higher in energy; the other "half-book" conformation, which would permit only the phenyl B-ring to interact with the selector cleft as previously described, is even more energetically unfavorable [35].

Two other *ortho*-substituted analytes in this study, (2-chlorophenyl)phenylmethyl pivalate (**16b**) and (2-chlorophenyl)-(4-chlorophenyl)methyl pivalate (**17b**), also behave in a manner consistent with a biased "half-book" low energy conformation. The absolute configuration of (2-chlorophenyl)phenylmethanol (**16a**) is known [6] and hydrolysis of MRE-**16b** demonstrates that A = 2-chlorophenyl for the ester; the NMR data for **17b** show that A = 2-chlorophenyl for this analyte as well. Similar separation factors of **16b** (α = 1.96) and **17b** (α = 1.91) signify that the inclusion priorities of the phenyl and 4-chlorophenyl moieties are nearly identical for these analytes. Clearly this

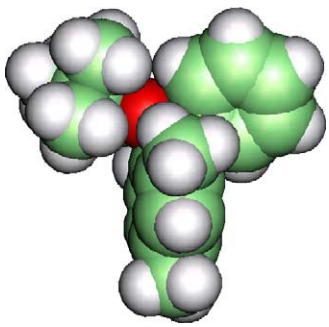
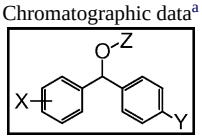


Fig. 4. Space-filling model of (*S*)-(2,4,6-trimethylphenyl)phenylmethyl pivalate [analyte (*S*)-**12b**].

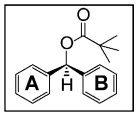
Table 5
Chromatographic data[a] for analyte sets **12**–**17**

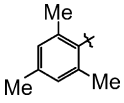
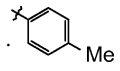
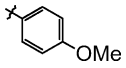
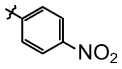
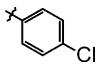


Analyte	*X*	*Y*	*Z*	k'_1	α	Configuration of MRE[b]
12a	Mesityl	H	H	1.42	1.07	*S*-(−)[c]
12b			Pivalyl	0.48	1.68	*S*-(−)
12c			Acetyl	0.77	2.43	*S*-(−)
13a	Mesityl	Me	H	1.44	1.09	*S*-(−)
13b			Pivalyl	0.57	1.47	*S*-(−)
13c			Acetyl	0.83	2.46	*S*-(−)
14a	Mesityl	OMe	H	2.69	1.09	*S*-(−)
14b			Pivalyl	0.94	1.42	*S*-(−)
14c			Acetyl	1.49	2.22	*S*-(−)
15a	Mesityl	NO_2	H	4.23	1.05	*R*-(+)
15b			Pivalyl	0.74	1.68	*S*-(−)
15c			Acetyl	1.49	2.06	*S*-(−)
16a	2-Cl	H	H	2.28	1.15	*R*-(+)[d]
16b			Pivalyl	0.78	1.96	*S*-(+)
17a	2-Cl	Cl	H	2.41	1.21	*R*-(+)
17c			Pivalyl	0.74	1.91	*S*-(+)

[a] Mobile phase: 2-propanol: hexane (1:99). Temperature: 0 °C. Flow rate: 2 mL/min.
[b] MRE: more retained enantiomer on the (*S*,*S*)-Whelk-O1 CSP.
[c] Known absolute configuration [29].
[d] Known absolute configuration [6].

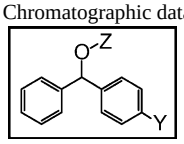
Table 6
Proton NMR chemical shift non-equivalence data from CSA studies of esters **12b**–**14b**, **15c** and **17b**



Analyte	A-ring structure	Δδ values[a]							B-ring structure	Pivalyl Δδ[a]	[(*S*)-CSA] /mM	[Analyte] /mM (ee)[b]
		A *para*	A *meta* (3,5)	A *ortho* (2,6)	Methine	B *ortho*	B *meta*	B *para*				
12b[c]		0	−0.006	−0.012	obsc	obsc	obsc	obsc		Upfield shoulder	15	27 (23)
13b		0	−0.007	−0.014	−0.039	−0.009	0	0		+0.002	11	19(35)
14b		0	−0.008	−0.016	−0.036	−0.011	0	0		+0.001	13	25 (36)
15c[d]		0	−0.010	−0.018	−0.053	−0.010	0	–		−0.013[e]	18	25(61)
17b[f]		obsc	−0.033, obsc	–, obsc	−0.057	obsc	obsc	–		−0.005	44	35 (27)

[a] Δδ: δ MRE − δ LRE, −20 °C, 750 MHz, obsc: obscured.
[b] The enantiomer present in excess is that shown, the MRE on the (*S*,*S*)-Whelk-O1 CSP.
[c] Ambient temperature, 500 MHz.
[d] −10 °C, 500 MHz.
[e] Analyte **15c** is an acetate ester.
[f] Proton assignments for **17b** were made with an nOe difference experiment. Irradiation of the methine singlet at δ 7.16 gave a 3% enhancement at δ 7.47 (dd, *J* = 7.7, 1.7 Hz).

Table 7
Chromatographic data[a] for analyte sets **18**–**21**



Analyte	*Y*	*Z*	k'_1	α	Configuration of MRE[b]
18a	F	H	2.65	1.04	*S*-(+)
18b		Pivalyl	2.11	1.07	*R*-(+)
19a	Cl	H	2.73	1.06	*S*-(+)[c]
19b		Pivalyl	2.24	1.46	*S*-(−)
19c		Acetyl	2.69	1.43	*S*-(−)
20a	Br	H	2.98	1.05	*S*-(+)[d]
20b		Pivalyl	2.37	1.67	*S*-(−)
21a[e]	I	H	4.99	1.06	*S*-(+)
21b		Pivalyl	2.49	1.86	*S*-(−)

[a] Mobile phase: 2-propanol: hexane (1:99). Temperature: 0 °C. Flow rate: 2 mL/min.
[b] MRE: more retained enantiomer on the (*S*,*S*)-Whelk-O1 CSP.
[c] Known absolute configuration [30].
[d] Known absolute configuration [18].
[e] Temperature: −25 °C.

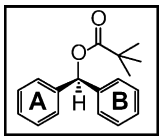
is inconsistent with the large separation factor for analyte **19b** [(4-chlorophenyl)phenylmethyl pivalate, α = 1.46]. A plausible explanation is that the *o*-Cl substituent prevents significant inclusion of the other ring; as with the mesityl analytes, CHARMm modeling supports this hypothesis [36].

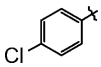
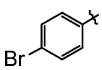
3.3. Analytes with meta- and/or para-halogen substituents

Prior work has shown that enantioresolution of analytes possessing a *para*-halophenyl group increases as the polarizability of the halogen increases [14,31]. Chromatographic and NMR data of analyte sets **18–21** (Tables 7 and 8) agree with this observation; (4-chlorophenyl)phenylmethanol (**19a**) and (4-bromophenyl)phenylmethanol (**20a**) provide more support for the recognition model since their absolute configurations are known [18,30].

Overlap of aromatic proton NMR signals confounded CSA studies of the (3-chlorophenyl)phenylmethanol (**22a**) series; the NMR spectra of the other *meta*-chlorinated analytes in Table 9 were more easily interpreted. The CSA data for (3,4-dichlorophenyl)phenylmethyl pivalate (**23b**) show that A = 3,4-dichlorophenyl (Table 10); by analogy, the chlorinated ring of (3,5-dichlorophenyl)phenylmethyl

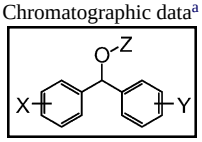
Table 8
Proton NMR chemical shift non-equivalence data from CSA studies of pivalate esters **18b**–**21b**



Analyte	A-ring structure	$\Delta\delta$ values[a]							B-ring structure	Pivalyl $\Delta\delta$[a]	[(*S*)-CSA] /mM	[Analyte][b] /mM (ee)
		A *para*	A *meta*	A *ortho*	Methane	B *ortho*	B *meta*	B *para*				
18b		obsc	obsc	obsc	−0.008	obsc	+0.013	–		0	12	33 (23)
19b		–	−0.035	−0.034	−0.035	obsc	obsc	obsc		+0.003	19	24 (59)
20b		–	−0.037	−0.039	−0.048	obsc	obsc	obsc		+0.002	11	11 (70)
21b		–	−0.044	−0.048	−0.065	obsc	obsc	obsc		+0.004	15	19 (41)

[a] $\Delta\delta$: δ MRE − δ LRE, ambient temperature, 500 MHz, obsc: obscured.
[b] The enantiomer present in excess is that shown, the MRE on the (*S*,*S*)-Whelk-O1 CSP.

Table 9
Chromatographic data[a] for analyte sets **22**–**26**

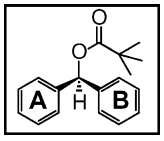


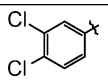
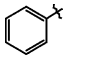
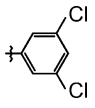
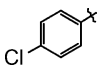
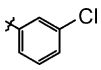
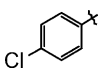
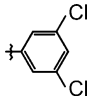
Analyte	X	Y	Z	k'_1	α	Configuration of MRE[b]
22a	H	3-Cl	H	2.50	1.13	*S*-(+)[c]
22b			Pivalyl	2.66	1.00	–
22c			Acetyl	2.72	1.13	*R*-(−)
23a	H	3,4-diCl	H	2.81	1.16	*S*-(+)
23b			Pivalyl	2.50	1.48	*S*-(−)
24a	H	3,5-diCl	H	1.94	1.34	*S*-(+)
24b			Pivalyl	1.94	1.35	*R*-(−)
25a	3-Cl	4-Cl	H	2.88	1.09	*S*-(+)
25b			Pivalyl	2.46	1.51	*R*-(−)
25c			Acetyl	2.70	1.65	*R*-(−)
26a	4-Cl	3,5-diCl	H	2.22	1.30	*S*-(+)
26b			Pivalyl	1.87	1.99	*R*-(−)

[a] Mobile phase: 2-propanol: hexane (1:99). Temperature: 0 °C. Flow rate: 2 mL/min.
[b] MRE: more retained enantiomer on the (*S*,*S*)-Whelk-O1 CSP.
[c] Assignment is not directly supported by CSA data.

pivalate (**24b**) was expected to have a greater inclusion priority than the phenyl ring. However, CSA data for 24b indicate that B = 3,5-dichlorophenyl. The chromatographic and NMR data for **19b**, **24b**, and **26b** [(3,5-dichlorophenyl)-(4-chlorophenyl)methyl pivalate] are consistent with B = 3,5-dichlorophenyl for both **24b** and **26b**. Because of the similarity of relative elution orders of each diarylmethanol and its esters and the similarity of optical rotations in analyte sets **22** and **24**, the absolute configuration of **22a** has been tentatively assigned as indicated in Table 9. The chromatographic data for the sets of **19a**, **22a**, and **25a** [(3-chlorophenyl)-(4-chlorophenyl)methanol] support the assignment of absolute configuration for **22a** in the manner discussed in Section 3.1. Whereas the inclusion priorities for 3-methoxyphenyl and

Table 10
Proton NMR chemical shift non-equivalence data from CSA studies of pivalate esters **23b**–**26b**



Analyte	A-ring structure	Δδ values[a]							B-ring structure	Pivalyl Δδ[a]	[(*S*)-CSA] /mM	[Analyte][b] /mM (ee)
		A *para*	A *meta* (3,5)	A *ortho* (2,6)	Methane	B *ortho* (2,6)	B *meta* (3,5)	B *para*				
23b		–	−0.029	obsc, −0.040	−0.041	obsc	obsc	obsc		+0.002	45	70 (59)
24b[c]		obsc	obsc	obsc	−0.098	+0.044	–	+0.107		+0.003	42	32 (32)
25b		–	−0.092	−0.091	−0.085	obsc, obsc	obsc	obsc		+0.005	46	38 (28)
26b		–	−0.091	−0.099	−0.127	Upfield shoulder	–	+0.045		+0.006	41	30 (37)

[a] Δδ: δ MRE − δ LRE, ambient temperature, 500 MHz, obsc: obscured.
[b] The enantiomer present in excess is that shown, the MRE on the (*S*,*S*)-Whelk-O1 CSP.
[c] Temperature: −5 °C.

4-methoxyphenyl are described by the sequence 4-OMe > 3-OMe > H, the inclusion priorities for 3-chlorophenyl and 4-chlorophenyl are described by the sequence 4-Cl > H > 3-Cl.

4. Conclusion

With few exceptions, the Whelk-O1 CSP provides baseline separations of the enantiomers of the diarylmethyl esters in this study, thus affording these compounds in high enantiomeric excess. This study further demonstrates the scope of the Whelk-O1 CSP and provides additional insight on the electronic and steric interactions influencing enantioresolution on this CSP. Assignment of absolute configuration to an enantiomer based on its elution order from a chiral column is a goal of chiral chromatography. Low molecular weight chiral selectors such as the Whelk-O1 CSP offer hope for attaining this goal, since reducing the number of significant chiral interactions simplifies the task of determining the chiral recognition mechanism.

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[16] Although a dihedral angle $\theta_{\text{included}} = +25^\circ$ is optimal, values of θ_{included} approaching 0° will still allow an aromatic ring to interact with the selector cleft as described. Thus, the "book" conformation may be generously delineated as $0^\circ < \theta_{\text{included}} < +30^\circ$ and $-30^\circ < \theta_{\text{excluded}} < 0^\circ$. The low-energy conformations found for (*S*)-**2b** are as follows. A "book" conformation: $\theta_{\text{included}} = +22^\circ$, $\theta_{\text{excluded}} = -29^\circ$, $E = -20.3$ kcal/mol. Two "half-book" conformations: $\theta_{\text{included}} = +10^\circ$, $\theta_{\text{excluded}} = -42^\circ$, $E = -20.3$ kcal/mol; $\theta_{\text{included}} = +40^\circ$, $\theta_{\text{excluded}} = -15^\circ$, $E = -20.2$ kcal/mol.
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[35] The low-energy "half-book" conformation of (*S*)-**12b**: $\theta_{\text{included}} = -6^\circ$, $\theta_{\text{excluded}} = -77^\circ$, $E = -31.1$ kcal/mol. The other approximately "half-book" conformation: $\theta_{\text{included}} = +74^\circ$, $\theta_{\text{excluded}} = +8^\circ$, $E = -23.5$ kcal/mol. "Book" conformation: $\theta_{\text{included}} = +12^\circ$, $\theta_{\text{excluded}} = -30^\circ$, $E = -25.6$ kcal/mol.
[36] For this molecule, the θ_{included} is defined as the torsional angle $C_{ortho(Cl)}-C_{ipso}-C_{methine}-H_{methine}$; the asymmetric ring substitution creates three possible "half-book" conformations. The two favorable conformations of (*S*)-**16b** include one "book" conformation ($\theta_{\text{included}} = +21^\circ$, $\theta_{\text{excluded}} = -32^\circ$, $E = -26.3$ kcal/mol) and one "half-book" conformation permitting inclusion of the 2-chlorophenyl ring in the cleft ($\theta_{\text{included}} = +18^\circ$, $\theta_{\text{excluded}} = -42^\circ$, $E = -26.3$ kcal/mol); thus a slight bias towards inclusion of the 2-chlorophenyl ring is indicated. Perhaps more importantly though, the related "half-book" conformation in which the chlorine substituent is pointing away from the methine proton ($\theta_{\text{included}} \approx -160^\circ$) is approximately 3 kcal/mol higher in energy; all such conformations were found to be unfavorable. Furthermore, modeling suggests that the o-chlorine substituent is more of a steric impediment to association with the selector when present on the excluded ring than it is when present on the included ring of an analyte when the chlorine substituent is pointing in the same direction as the methine proton.