Synthesis and Separation of Diastereomeric Imino Alcohol Derivatives of Chiral Phthalides: A Method for Assignment of Phthalide Absolute Configurations

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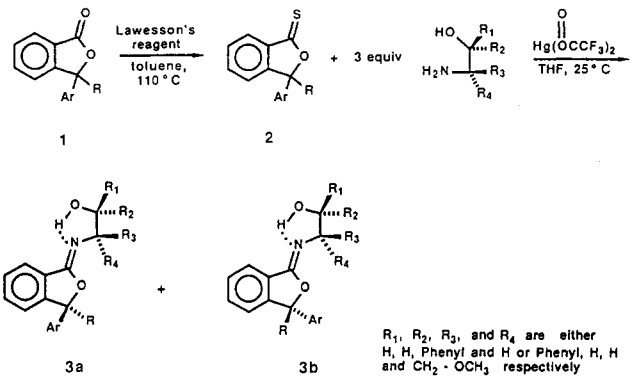
Representative members of a series of chiral type 1 phthalides were converted with Lawesson's reagent to the corresponding thionophthalides. On treatment with any of several configurationally known chiral amino alcohols in the presence of mercuric trifluoroacetate, diastereomeric imino alcohols are afforded. These prove to be readily separable by chromatography on either silica or chiral stationary phases derived from the *N*-3,5-dinitrobenzamides of (*R*)-phenylglycine or (*S*)-leucine. Both the elution order of these diastereomers from silica and their ^{1}H NMR chemical shift differences may be related to relative/absolute configurations. Hydrolysis of the separated imino alcohol diastereomers affords configurationally established phthalide enantiomers. On the basis of their CD spectra, it is concluded that the enantiomers of the entire series of phthalides elute from the chiral stationary phases in a uniform order.

In our continuing investigation into the chromatographic behavior of various racemates on chiral stationary phases (CSPs) developed in our laboratory,[1] we became interested in the separation of the enantiomers of type 1 3-substituted phthalides. A series of type 1 phthalides was prepared and the chromatographic behavior of each phthalide was monitored on CSPs derived from the *N*-3,5-dinitrobenzamides of (*R*)-phenylglycine or (*S*)-leucine.[2] The chromatographically derived data were utilized in the elucidation of the chiral recognition process employed by these CSPs for the separation of the phthalide enantiomers.[3] The proposed chiral recognition model relates elution order to absolute configuration. While several phthalides occur naturally[4] and others have been the subject of asymmetric syntheses,[5,6] no general methods for resolving or assigning absolute configurations to phthalides have been advanced. Moreover, knowledge of absolute configurations is essential to the testing of the chromatographic model. Herein, we report a general method for the determination of the absolute configurations of type 1 phthalides via separation of their diastereomeric imino alcohol derivatives and analysis of the NMR spectra of these derivatives. These diastereomeric imino alcohols are produced by a heretofore unknown mercuric ion-assisted coupling of an amino alcohol and a 1-thionophthalide.

Results and Discussion

Table I presents the relevant chromatographic data for the enantiomeric separations of a series of type 1 phthalides on the aforementioned CSPs. At the time of our initial chromatographic investigations, the absolute configurations of only a few type 1 phthalides had been established. The enantiomers of several configurationally established 3-phenyl-substituted phthalides, exemplified by **1a** and synthesized asymmetrically by Meyers and coworkers,[6] proved to be barely separable on the CSPs. Although the elution order of the enantiomers of **1a** conformed to our chiral recognition model, it seemed prudent not to rest the validity of this model (and hence the assignment of absolute configurations for the entire phthalide series) on the basis of the observed elution order of the enantiomers of one or two barely resolvable phthalides.

Scheme I



An intriguing facet of Meyer's asymmetric phthalide synthesis is the formation of intermediate diastereomeric imino lactones. These result from the spontaneous rearrangement of chiral *O*-acylaryloxazolines after alkyllithium addition to the prochiral *O*-acyl moiety. The relative stereochemistry of the imino lactone diastereomers and, after hydrolysis, the absolute configurations of the recovered phthalides were determined by the chemical shift differences noted in the NMR spectrum of the diastereomers and the known configuration of the chiral oxazoline precursor.

Unfortunately, attempts to extend Meyer's asymmetric phthalide synthesis to representative members of the 1-naphthyl- and 2-naphthyl-substituted phthalides in Table I failed, owing to low yields and the production of unidentified side products. Because our primary interest was not in the asymmetric synthesis of these phthalides but in the formation of the diastereomeric imino lactones from which the absolute configurations of the phthalides could

(1) For examples of racemates resolvable on the aforementioned CSPs, see: Pirkle, W. H.; Hamper, B. C.; Schreiner, J.; Pribish, J. R. *Asymmetric Reactions and Processes in Chemistry*; Eliel, E., Otsuka, S., Eds.; ACS Symposium Series 185; American Chemical Society: Washington, DC, 1982; 245.

(2) Columns containing the (*R*)-phenylglycine- and (*S*)-leucine-derived CSPs described herein are commercially available for Regis Chemical Co., 8210 Austin Ave., Morton Grove, IL 60053, and J. T. Baker, Phillipsburg, NJ 08865. The phenylglycine-derived CSP is also available from Sumitomo Chemical Co., Ltd., New Business Development Division, Sumitomo Blvd., 5-15 Kitahoma, Higashi-ku Osaka 541, Japan.

(3) For details of the phthalide chiral recognition model, see: Pirkle, W. H.; Sowin, T. J. *J. Chromatogr.* **1987**, *387*, 313.

(4) (a) Barton, D. H. R.; DeVries, J. X. *J. Chem. Soc.* **1963**, 916. (b) Elander, M.; Leander, K.; Luning, B. *Acta Chem. Scand.* **1969**, *23*, 2177.

(5) (a) Kolosov, M. N.; Guevich, A. I.; Shvestov, B. *Isv. Akad. Nauk SSSR, Ser. Khim.* **1963**, 701. (b) Jones, P. R.; Jarboe, C. J. *Tetrahedron Lett.* **1969**, 1849. (c) Mukaiyama, T.; Asami, M. *Chem. Lett.* **1980**, 17.

(6) Meyers, A. I.; Hanagan, M. A.; Trefonas, L. M.; Baker, R. J. *Tetrahedron* **1983**, *39*, 1991.

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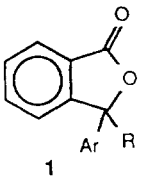
Table I. Resolution of Racemic Phthalides on Chiral Stationary Phases



1

			CSP					
			(*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine			(*S*)-*N*-(3,5-dinitrobenzoyl)leucine		
compd	Ar	R	α[a]	k_1'	$[\alpha]_D$[c]	α[a]	k_1'	$[\alpha]_D$[c]
1a	phenyl	CH_2CH_3	1.00	1.87[d]		1.03	4.35[d]	−
1b	1-naphthyl	H	1.09	1.95	+	1.19	5.86	−
1c	1-naphthyl	CH_3	1.57	4.00	−	2.03	5.71	+
1d	1-naphthyl	CF_3	1.15	1.43	−	1.30	1.43	+
1e	6,7-dimethyl-1-naphthyl	CH_3	2.03	4.71	−	2.84	6.29	+
1f	6,7-dimethyl-1-naphthyl	$CH(CH_3)_2$	2.89	2.57	−	4.39	3.29	+
1g	6,7-dimethyl-1-naphthyl	cyclohexyl	3.72	2.57	−	5.19	4.21	+
1h	3,7-dimethyl-1-naphthyl	CH_3	2.17	3.29	−	2.84	5.57	+
1i	3,4-dimethyl-1-naphthyl	phenyl	3.05	2.71	−	4.52	3.57	+
1j	4,7-dimethyl-1-naphthyl	H	1.15	6.57	+	1.36	7.14	−
1k	4,7-dimethyl-1-naphthyl	CH_3	2.06	4.61	−	2.70	5.50	+
1l	4,7-dimethyl-1-naphthyl	$(CH_2)_3CH_3$	2.39	2.57	−	3.96	3.57	+
1m	4,7-dimethyl-1-naphthyl	$(CH_2)_7CH_3$	2.55	2.07	−	4.09	3.00	+
1n	4,7-dimethyl-1-naphthyl	$C{\equiv}C(CH_2)_5CH_3$	2.42	2.71	−	3.80	5.00	+
1o	4,7-dimethyl-1-naphthyl	$(CH_2)_9CHCH_2$	2.75	2.00	−	4.37	3.50	+
1p	2-naphthyl	H	1.04	8.50[e]	+	1.00	7.75[e]	
1q	2-naphthyl	CH_3	1.03	6.06[e]	+	1.02	5.19[e]	−
1r	6,7-dimethyl-2-naphthyl	$CH(CH_3)_2$	1.00	2.43		1.17	2.07	−

[a] Chromatographic separation factor. [b] Unless otherwise indicated, mobile phase was 10% 2-propanol in hexane. [c] Sign of rotation for first eluting enantiomer. [d] Mobile phase was 1% 2-propanol in hexane. [e] Mobile phase was 5% 2-propanol in hexane.

ultimately be derived, we considered alternative routes to these compounds.

An obvious approach, the production of these diastereomeric imino lactones by the direct coupling of phthalides with chiral amino alcohols of known configuration, failed under several sets of conditions. However, coupling was achieved by initially converting the phthalides to the corresponding 1-thiono derivatives (Scheme I).[7] Treatment of **1** with Lawesson's reagent gives the corresponding 1-thionophthalide **2** in high yield.[8] Mixing **2** with 3 equiv of chiral amino alcohol in the presence of 1 equiv of mercuric trifluoroacetate affords approximately a 50:50 mixture of the diastereomeric imino alcohols **3a** and **3b** along with a black precipitate of mercuric sulfide and the trifluoroacetate salt of the chiral amino alcohol. Diastereomers **3a** and **3b** are readily purified by flash chromatography on silica and were isolated in chemical yields in excess of 90%.

Diastereomers **3a** and **3b** are presumed to be conformationally biased, owing to intramolecular hydrogen bonding between the imine nitrogen and alcohol hydrogen.[9] An analogy to the early work of Helmchen[10] and Karger,[11] as well as studies performed in our own laborabory on the liquid chromatographic separation of diastereomeric carbamates,[12] allophanates[13] and ureides,[14] led us to believe that the relative/absolute stereochemistry of diastereomeric imino lactones such as **3a** and **3b** may by inferred from their elution orders on silica as well as from their ^1H NMR chemical shift differences. According to the concept of differential ease of approach to the adsorbant,[12] the most mobile imino alcohol diastereomer (on silica) should have the largest (repulsive toward silica) groups situated on the opposite faces of the approximately planar backbone of the imino alcohol. These repulsive groups inhibit adsorption onto silica from either face of the relatively polar imino alcohol. In this instance, group size and repulsive interaction with silica gel are related.

Presented in Table II are the results of both ^1H NMR and chromatographic studies of some diastereomeric imino alcohol pairs derived from several representative phthalides and (*R*)-phenylglycinol. The diastereomers of compounds **4a,b–7a,b** are readily separable on silica. In each case, the least retained diastereomers of compounds **4a–7a** are assigned the *R* configuration at C-3, since this places the large phenyl and naphthyl groups on opposite faces of the imino alcohol. The configurational assignments for the **4a,b–6a,b** pairs were also derived from the ^1H NMR chemical shift differences between diastereomers. The ^1H NMR chemical shifts of the methyl groups of **4a–6a** are substantially upfield of those of their counterparts, **4b–6b**, owing to shielding of the methyl groups in **4a–6a** by the syn phenyl substituent. Thus, assignments made by two independent methods coincide. The C-3 configurational assignments of **7a,b** are based solely on the order of elution

(7) The formation of acyclic imino esters is usually achieved by the alcoholysis of nitriles, treatment of amides with oxonium ions, or treatment of carboxylic acid ortho esters with amines. For more, see: March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985, p 1165. To the best of our knowledge, this is the first reported formation of a cyclic imino ester from the direct coupling of a thiono lactone and an amine.

(8) For a review on the use of Lawesson's reagent, see: Cara, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.

(9) Similar intramolecular hydrogen-bonding interactions have been invoked in assessing the preferred solution conformations of various compounds; see ref 10–14.

(10) Helmchen, G.; Ott, R.; Sauber, K. *Tetrahedron Lett.* **1972**, 3873.

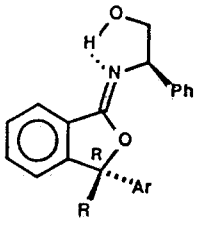
(11) (a) Karger, B. L.; Stern, R. L.; Rose, H. C.; Keane, W. *Gas Chromatography*; Littlewood, A. B., Ed.; Institute of Petroleum: London, 1967; p 240. (b) Karger, B. L.; Stern, R. L.; Keane, W.; Helpern, B.; Westly, J. W. *Anal. Chem.* **1967**, *39*, 228. (c) Westly, J. W.; Halpern, B.; Karger, B. L. *Anal. Chem.* **1968**, *40*, 2046.

(12) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 1839.

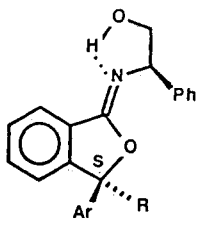
(13) Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1983**, *48*, 2520.

(14) Pirkle, W. H.; Robertson, M. R.; Hyun, M. H. *J. Org. Chem.* **1984**, *49*, 2433.

Table II. ^{1}H Nuclear Magnetic Resonance and Chromatographic Properties of Diastereomeric Imino Alcohols Derived from (*R*)-Phenylglycinol



a

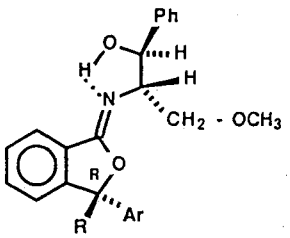


b

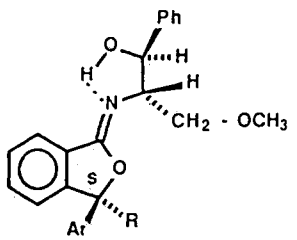
compd[a]	Ar	R	assigned confign at C-3	δ(R)	5-μm silica gel α^b	5-μm silica gel k′[c]	5-μm silica gel $[\alpha]_D$
4a	4,7-dimethyl-1-naphthyl	CH_3	*R*	1.874	1.33	2.70	+
4b	4,7-dimethyl-1-naphthyl	CH_3	*S*	2.302		3.60	−
5a	1-naphthyl	CH_3	*R*	1.926	1.25	1.50	+
5b	1-naphthyl	CH_3	*S*	2.170		1.88	−
6a	2-naphthyl	CH_3	*R*	1.921	2.33	0.75	−
6b	2-naphthyl	CH_3	*S*	2.046		1.75	+
7a	2-naphthyl	H	*R*	6.462	2.60	1.25	−
7b	2-naphthyl	H	*S*	6.449		3.25	+

[a] The stereochemistry represented in the drawings **a** and **b** is that assigned to the diastereomers designated as **a** or **b**. [b] Chromatographic separation factor. [c] Mobile phase was 10% 2-propanol in hexane.

Table III. ^{1}H Nuclear Magnetic Resonance and Chromatographic Properties of Diasteromeric Imino Alcohols Derived from (1*S*,2*S*)-1-Phenyl-2-amino-3-methoxy-1-propanol



a



b

compd[a]	Ar	R	assigned confign at C-3	δ	α^b	k′[c]	sign of $[\alpha]_D$
8a	4,7-dimethyl-1-naphthyl	CH_3	R	3.081	1.18	5.00[d]	+
8b	4,7-dimethyl-1-naphthyl	CH_3	S	3.425		4.25[d]	−
9a	1-naphthyl	H	R	3.386	1.10	5.50	+
9b	1-naphthyl	H	S	3.413		5.00	−
10a	2-naphthyl	H	R	3.035	1.15	6.00	+
10b	2-naphthyl	H	S	3.389		6.88	−

[a] The stereochemistry represented in drawings **a** and **b** is that assigned to the diastereomers designated as **a** or **b**. [b] Chromatographic separation factor. [c] Unless otherwise indicated, mobile phase was 5% 2-propanol in hexane. [d] Mobile phase was 10% 2-propanol in hexane.

from silica for no ^{1}H NMR chemical shift difference is noted between the diastereomers for the C-3 protons. Examination of molecular models suggests that the phenyl group is too remote to influence the chemical shift of the C-3 hydrogen in either diastereomer.

The relative/absolute configuration of the diastereomeric imino alcohols produced from type 1 phthalides with C-3 hydrogens can be established by ^{1}H NMR if (1*S*,2*S*)-1-phenyl-2-amino-3-methoxy-1-propanol is used as the chiral amino alcohol rather than (*R*)-phenylglycinol. The relevant ^{1}H NMR chemical shift data and chromtographic data for these imino alcohols are shown in Table III. Diastereomeric pairs **9a,b** and **10a,b** are not separable on silica. However, they prove to be readily separable on the (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine CSP. Because of the different interactions involved, elution orders from this CSP are not necessarily the same as on silica. Diastereomers **9a** and **10a** are assigned the *R* configuration at C-3 owing to the upfield chemical shifts for their methoxy resonances relative to the methoxy resonances of the corresponding diastereomers, **9b** and **10b**. The upfield chemical shifts for the methoxy resonances of **9a** and **10a** result from shielding of the methoxy group by the syn naphthyl substituents. The methoxy and naphthyl groups of **9b** and **10b** are situated on opposite faces of the imino alcohol backbone.

Diastereomers **8a** and **8b** (Table III) were examined to test the view that imino alcohols derived from (1*S*,2*S*)-1-phenyl-2-amino-3-methoxy-1-propanol could also be utilized in determining the absolute configurations of type 1 3,3-disubstituted phthalides. Diastereomers **8a** and **8b** are readily separable on silica (α = 1.29; mobile phase 5% 2-propanol in hexane). The most mobile diastereomer, **8a**, is assigned the *R* configuration at C-3 for it is expected to have the phenyl and naphthyl substituents situated on opposite faces of its backbone. In addition, the C-3 methyl resonance of **8a**, found at δ 1.85, is upfield of the C-3 methyl resonance of **8b**, found at δ 2.14, owing to shielding by the syn phenyl group.

The separated diastereomers of imino alcohols **4a,b**–**10a,b** are readily hydrolyzed by aqueous oxalic acid, as described by Meyers,[6] to the corresponding phthalide

Table IV. Hydrolysis of Diastereomeric Imino Alcohols to Phthalide Enantiomers

imino alcohol	sign of $[\alpha]_D$	assigned confign at C-3	phthalide	sign of $[\alpha]_D$	assigned confign at C-3
4a	+	*R*	**1k**	+	*R*
4b	−	*S*	**1k**	−	*S*
5a	+	*R*	**1c**	+	*R*
5b	−	*S*	**1c**	−	*S*
6a	−	*R*	**1q**	−	*R*
6b	+	*S*	**1q**	+	*S*
7a	−	*R*	**1p**	−	*R*
7b	+	*S*	**1p**	+	*S*
8a	+	*R*	**1k**	+	*R*
8b	−	*S*	**1k**	−	*S*
9a	+	*R*	**1b**	−	*R*
9b	−	*S*	**1b**	+	*S*
10a	+	*R*	**1p**	−	*R*
10b	−	*S*	**1p**	+	*S*

enantiomers. In this procedure, the imino alcohol is heated (steam bath, capped vessel) in a 1:1 mixture of tetrahydrofuran-saturated aqueous oxalic acid. The course of the hydrolysis was monitored by thin-layer chromatography, most hydrolyses being complete within 3 h. *Protracted* heating was observed to lead to slight loss of phthalide enantiomeric purity as determined by HPLC using the chiral stationary phase columns. The results of these hydrolyses are reported in Table IV. The recovered phthalide enantiomers were chromatographed on the aforementioned CSPs and their chromatographic behavior was correlated with that of samples of the racemic phthalides used to generate the data in Table I. It is important to note that hydrolysis of either **7a** or **10a** gives the (−)-enantiomer of **1p**, consistent with the configurational assignments established by using either amino alcohol. Similarly, the hydrolysis of either **4a** or **8a** affords the (+)-enantiomer of **1k**.

Comparison of the results obtained from the phthalides, obtained from hydrolysis of imino alcohols **4a,b**–**10a,b** (Table IV) with the data presented in Table I indicates that, for the configurationally established phthalides, the *S* enantiomers are first eluted from the (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine CSP and the *R* enantiomers are first eluted from the (*S*)-*N*-(3,5-dinitrobenzoyl)leucine CSP.[15] These results are in full agreement with the a priori chiral recognition model proposed.[3] Moreover, correlation of the CD spectra of the configurationally established phthalides with the CD spectra of analogous but configurationally unassigned phthalide enantiomers in Table I indicates that the enantiomers of the entire phthalide series elute in a uniform order from the CSPs. For example, the CD spectra of configurationally established (*R*)-(+)-**1c** and (*R*)-(+)-**1k** were found to be almost identical with the CD spectra of the (+)-enantiomers of 3-(1-naphthyl)-3-alkylphthalides **1e,f,h,i,l,n,o**. In the same manner, the CD spectrum of configurationally established (*R*)-(−)-**1b** was found to be nearly the same as the CD spectrum of (−)-**1j**, and the CD spectrum of (*R*)-(−)-**1q** was found to be very similar to the CD spectrum of (−)-**1r**.[16] The CD characteristics for each of the above mentioned enantiomers are described in the Experimental Section.

(15) The elution orders from the two CSPs differ owing to the difference in absolute configuration of the CSPs.

(16) The CD spectra of the phthalide enantiomers belonging to different phthalide classes (i.e., 3-(1-naphthyl)-3-alkyl- vs. 3-(1-naphthyl)- vs. 3-(2-naphthyl)-3-alkylphthalides) are dissimilar owing to different spatial relationships between the transition dipole moment vectors of the naphthyl and benzo ring systems for each phthalide class; see: Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy*; University Science Books: Mill Valley, CA, 1983.

In addition, the absolute configurations of the 1-thionophthalide derivatives were determined from the established configurations of their phthalide precursors. Treatment of a pure phthalide enantiomer with Lawesson's reagent affords the corresponding 1-thionophthalide with complete retention of configuration at C-3. Thus, the phthalide enantiomers (*R*)-(−)-**1b**, (*R*)-(+)-**1c**, (*R*)-(+)-**1k**, (*R*)-(−)-**1p**, and (*R*)-(−)-**1q** give the 1-thionophthalide enantiomers (*R*)-(−)-**2b**, (*R*)-(+)-**2c**, (*R*)-(+)-**2k**, (*R*)-(−)-**2p**, and (*R*)-(−)-**2q**, respectively. The enantiomers of the 1-thionophthalides are separable on the aforementioned CSPs and, in accord with our chiral recognition model, exhibit the same elution order (and slightly lower separation factors) as do the corresponding phthalides. Treatment of a single thionaphthalide enantiomer with enantiomerically pure 1-phenyl-2-amino-3-methoxy-1-propanol and mercuric trifluoroacetate leads to but a single diastereomer of the imino alcohol.

Conclusion

Diastereomeric imino alcohols of type **3a** and **3b** are now accessible by the reaction of type **2** 1-thionophthalides with chiral amino alcohols in the presence of mercuric trifluoroacetate. These show appreciable degrees of chromatographic separability and ^1H NMR chemical shift differences, both of which can be correlated with their relative/absolute configurations. With careful selection of the chiral amino alcohol, it should be possible to separate and determine the absolute configurations of a wide range of chiral phthalides and possibly other chiral lactones as well. Furthermore, the full synthetic potential of this new route to imino esters has not yet been realized and investigations into the synthetic scope of this reaction are now in progress.

Experimental Section

Chromatography was performed with an Altex 100A pump, Altex 210 injector, and an Altex Model 152 dual-wavelength (254 and 280 nm) detector. Either a Kipp and Zonen BD 41 or Altex Model C-R1A integrating recorder was used. A Rudolph Autopol III digital polarimeter containing a 20-cm flow cell was used in series with the ultraviolet detector to simultaneously monitor the sign of $[\alpha]_D$ as the enantiomers or diastereomers eluted. Flash chromatography was performed with Grace, Grade 951, silica gel (58 μm). Regis covalent (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine Pirkle 1-A and Baker covalent (*S*)-*N*-(3,5-dinitrobenzoyl)leucine chiral stationary phases (250 × 4.6 mm columns) were used to generate the data in Tables I, III, and IV. A Rainin Microsorb silica HPLC column (250 × 4.6 mm) was used to generate the data in Table III. Melting points were obtained with a Büchi apparatus and are uncorrected. Microanalyses were performed by J. Nemeth and Associates, University of Illinois. Mass spectra were obtained by J. C. Cook and Associates, University of Illinois, on a Varian MAT CH-5 spectrometer (low-resolution, electron-impact) and a Varian Model 731 (high-resolution, electron-impact) mass spectrometer. Proton NMR spectra were recorded on either a Varian XL-200 (200 MHz) or a GE-QE 300 (300 MHz) spectrometer using tetramethylsilane as an internal reference. All proton NMR spectra were obtained with deuteriochloroform as solvent. IR spectra were recorded on either an IBM IR-32 FT-IR or a Nicolet 7000 FT-IR spectrophotometer. CD spectra were obtained on a Jasco J-40 recording spectropolarimeter using a 1-mm path length cell and spectrophotometric grade methanol as solvent. Sample concentrations for CD analysis were typically (1–4) × 10^{-4} M. Enantiomerically enriched samples were obtained directly by semipreparative (5–15 mg) HPLC using a Beckman 100A pump, an Altex 210 injector equipped with a 225-μL sample loop, a Beckman Model 153 dual-wavelength detector, and a covalently bonded (*S*)-*N*-(3,5-dinitrobenzoyl)leucine (250 mm × 10 mm) column. CD samples were greater than 98% ee (enantiomeric enrichment) except for (*R*)-(+)-**1c** (45.5% ee) and

(*S*)-(+)-**1r** (48.4% ee). In these instances, CD values have been corrected to 100% ee. Phthalide **1a**, enriched in the *S* enantiomer, was obtained from A. I. Meyers, Colorado State University.

General Procedures for the Synthesis of Phthalides. Procedure A. The procedure was adapted from that of Parham.[17] To a stirred solution of *o*-bromobenzoic acid in anhydrous THF at −100 °C, maintained under a nitrogen atmosphere, was slowly added 2 equiv of *n*-butyllithium (via syringe) over a 20-min period. The solution was warmed to −78 °C, the appropriate ketone or aldehyde, dissolved in a small volume of anhydrous THF, was slowly added via syringe, and the solution was allowed to warm to room temperature over a 1-h period. The reaction mixture was poured into H_2O and the resulting mixture washed with ether. The aqueous phase was isolated, acidified to pH 1 with concentrated aqueous HCl, and extracted with ether. The ether layer was isolated, washed with cold 5% aqueous NaOH and H_2O, and dried over $MgSO_4$. The ether was removed in vacuo to give the desired phthalide. Purification, if needed, was achieved by flash chromatography on silica or by recrystallization from ethanol.

Procedure B. To a stirred solution of the appropriate keto acid in anhydrous THF, cooled to −78 °C and maintained under a nitrogen atmosphere, was slowly added either $NaBH_4$ or 2 equiv of the desired Grignard or lithium reagent. The solution was warmed to 25 °C (over a 1-h period) and quenched by addition to H_2O. The reaction was then worked up as in procedure A.

3-(1-Naphthyl)phthalide (1b) was obtained in 85% yield by procedure B with 2-(1-naphthoyl)benzoic acid[18] and $NaBH_4$ and isolated as a white solid: mp 135–137 °C (lit. mp 137–138 °C).[19] Anal. Calcd for $C_{18}H_{12}O_2$: C, 83.06; H, 4.65. Found: C, 83.12; H, 4.63. ^1H NMR ($CDCl_3$) δ 7.21–8.33 (m, 12 H); CD [λ_{ext}, nm ($\Delta\epsilon$)] *R*-(−)-enantiomer, 207.5 (−18.2), 220.0 (+32.74), 225.0 (0.0), 231.0 (−49.4), 27.0 (+5.3), 296.0 (−0.8).

3-(1-Naphthyl)-3-methylphthalide (1c) was obtained in 71% yield by procedure B with 2-(1-naphthoyl)benzoic acid and methyllithium and isolated as a white solid: mp 151–153 °C (lit. mp 151–152 °C).[20] Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.19; H, 5.14. Found: C, 83.15; H, 5.27. ^1H NMR ($CDCl_3$) δ 2.23 (s, 3 H), 7.31–7.97 (m, 10 H), 8.52 (d, 1 H, J = 8.52 Hz); CD [λ_{ext}, nm ($\Delta\epsilon$)] *R*-(+)-enantiomer, 229.0 (+72.7), 275.0 (+3.7).

3-(1-Naphthyl)-3-(trifluoromethyl)phthalide (1d) was obtained in 34% yield by procedure A with trifluoromethyl 1-naphthyl ketone and isolated as a white solid: mp 104–105 °C. Anal. Calcd for $C_{19}H_{11}F_3O_2$: C, 69.51; H, 3.38; F, 17.36. Found: C, 69.68; H, 3.56; F, 17.13. ^1H NMR ($CDCl_3$) δ 7.21–8.12 (m, 11 H); IR ($CHCl_3$) 3100–3000, 1789 (C=O), 1487, 1279, 1180, 089, 1012 cm^{-1}.

3-(6,7-Dimethyl-1-naphthyl)-3-methylphthalide (1e) was obtained in 33% yield by Procedure A with 1-acetyl-6,7-dimethylnaphthalene[21] and isolated as a white solid: mp 210–213 °C. Anal. Calcd for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00. Found: C, 83.16; H, 6.07. ^1H NMR ($CDCl_3$) δ 2.22 (s, 3 H), 2.40 (s, 3 H), 2.45 (s, 3 H), 7.10–8.20 (m, 9 H); IR ($CHCl_3$) 3100–2900, 1757 (C=O), 1288, 1269, 1095 cm^{-1}; CD [λ_{ext}, nm ($\Delta\epsilon$)] *R*-(+)-enantiomer, 232.5 (+71.6), 279.0 (+4.4); *S*-(−)-enantiomer, 232.5 (−72.11), 279 (−3.8).

3-(6,7-Dimethyl-1-naphthyl)-3-isopropylphthalide (1f) was obtained in 32% yield by procedure A with isopropyl 6,7-dimethyl-1-naphthyl ketone[22] and isolated as a white solid: mp 125–130 °C. Anal. Calcd for $C_{23}H_{22}O_2$: C, 83.60 H, 6.71. Found: C, 83.35; H, 6.99. ^1H NMR ($CDCl_3$) δ 1.32 (d, 6 H), 2.40 (s, 3 H), 2.45 (s, 3 H), 3.45 (m, 1 H), 7.22–8.22 (m, 9 H); IR ($CHCl_3$) 3100–2820, 1760 (C=O), 1467, 1290, 1254, 1132, 1077, 987, 949 cm^{-1}; CD [λ_{ext}, nm Δε)] *R*-(+)-enantiomer, 232.5 (+78.9), 279.0 (+5.8); *S*-(−)-enantiomer, 232.5 (−60.1), 279.0 (−4.5).

3-(6,7-Dimethyl-1-naphthyl)-3-cyclohexylphthalide (1g) was obtained in 16% yield by procedure A with cyclohexyl 6,7-dimethyl-1-naphthyl ketone[22] and isolated as a white solid: mp 160–161 °C; high-resolution mass spectrum, calcd for $C_{26}H_{26}O_2$ 370.1940, found 370.1936; ^1H NMR ($CDCl_3$) δ 1.00–1.81 (m, 11 H), 2.44 (s, 3 H), 2.53 (s, 3 H), 7.03–8.52 (m, 9 H); IR ($CHCl_3$) 3000–2800, 1751 (C=O), 1291, 1282, 1119, 951 cm^{-1}.

3-(3,7-Dimethyl-1-naphthyl)-3-methylphthalide (1h) was obtained in 33% yield by procedure A with 1-acetyl-3,7-dimethylnaphthalene[23] and isolated as a white solid: mp 161–162 °C. Anal. Calcd for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00. Found: C, 83.34; H, 62. ^1H NMR ($CDCl_3$) δ 2.24 (s, 3 H), 2.38 (s, 3 H), 2.54 (s, 3 H), 7.18–8.29 (m, 9 H); IR (KBr) 3100–2900, 1759 (C=O), 1612, 1261, 1113, 1024, 966 cm^{-1}; CD [λ_{ext}, nm ($\epsilon\epsilon$)] *R*-(+)-enantiomer, 232.5 (+78.1), 279.0 (+5.0).

3-(3,7-Dimethyl-1-naphthyl)-3-phenylphthalide (1i) was obtained in 48% yield by procedure B with phenyllithium and 2-(3,7-dimethyl-1-naphthoyl)benzoic acid[24] and isolated as a white solid: mp 160–161 °C; high-resolution mass spectrum; calcd for $C_{26}H_{20}O_2$ 364.1463, found 364.1462; ^1H NMR ($CDCl_3$) δ 2.25 (s, 3 H), 2.39 (s, 3 H), 7.22–8.03 (m, 14 H); IR ($CHCl_3$) 3100–2900, 1760 (C=O), 1466, 1288, 1255, 1098, 961 cm^{-1}; CD [λ_{ext}, nm ($\Delta\epsilon$)] *R*-(+)-enantiomer; 210.0 (+20.9), 232.5 (+51.9), 279.0 (+5.8).

3-(4,7-Dimethyl-1-naphthyl)phthalide (1j) was obtained in 90% yield by procedure B with 2-(4,7-dimethylnaphthoyl)benzoic acid[24] and $NaBH_4$ and isolated as a white solid: mp 135–137 °C. Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.30; H, 5.59. Found: C, 83.11; H, 5.23. ^1H NMR ($CDCl_3$) δ 2.55 (s, 3 H), 2.60 (s, 3 H), 7.00–7.95 (m, 10 H); IR (KBr) 3100–2900, 1772 (C=O), 1599, 1464, 1282, 1263, 1213, 955 cm^{-1}; CD [λ_{ext}, nm ($\Delta\epsilon$)] *R*-(−)-enantiomer, 211.0 (−11.4), 226.0 (+38.0), 233.0 (0.0), 239.0 (−32.3), 279.0 (+5.2), 306.0 (−0.9); *S*-(+)-enantiomer, 211.0 (+14.6), 226.0 (−37.9), 233 (0.0), 239.0 (+37.1), 279.0 (−5.8), 306.0 (+1.4).

3-(4,7-Dimethyl-1-naphthyl)-3-methylphthalide (1k) was obtained in 90% yield by procedure B with methylmagnesium bromide and 2-(4,7-dimethyl-1-naphthoyl)benzoic acid and isolated as a white solid: mp 176–178 °C. Anal. Calcd for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00. Found: C, 83.27; H, 6.01. ^1H NMR ($CDCl_3$) δ 2.23 (s, 3 H), 2.56 (s, 3 H), 2.63 (s, 3 H), 7.07–7.97 (m, 8 H), 8.38 (s, 1 H); IR ($CHCl_3$) 3100–2850, 1757 (C=O), 1466, 1289, 1268, 1129, 1094, 915 cm^{-1}; CD [λ_{ext}, nm ($\Delta\epsilon$)] *R*-(+)-enantiomer, 232.5 (+84.0), 279.0 (+4.6).

3-(4,7-Dimethyl-1-naphthyl)-3-phthalide (1l) was obtained in 91% yield by procedure B with *n*-butyllithium and 2-(4,7-dimethyl-1-naphthoyl)benzoic acid and isolated as a white solid: mp 105–107 °C. Anal. Calcd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02. Found: C, 83.83; H, 7.10. ^1H NMR ($CDCl_3$) δ 0.51–1.53 (m, 9 H), 255 (s, 3 H), 2.63 (s, 3 H), 7.05–8.00 (m, 8 H), 8.40 (s, 1 H); IR (KBr) 3100–2900, 1761 (C=O), 1464, 1287, 1266, 1076, 951 cm^{-1}; CD [λ_{ext}, nm ($\Delta\epsilon$)] *R*-(+)-enantiomer, 232.5 (+93.4), 279.0 (+9.2); *S*-(−)-enantiomer, 232.5 (−88.8), 279.0 (−6.3).

3-(4,7-Dimethyl-1-naphthyl)-3-octylphthalide (1m) was obtained in 95% yield by procedure B with *n*-octyllithium and 2-(4,7-dimethyl-1-naphthoyl)benzoic acid and isolated as a colorless oil: high-resolution mass spectrum, calcd for $C_{28}H_{32}O_2$ 400.2402, found 400.2397; ^1H NMR ($CDCl_3$) δ 0.73–1.60 (m, 17 H), 2.55 (s, 3 H), 2.63 (s, 3 H), 7.01–8.00 (m, 8 H), 8.40 (s, 1 H); IR (neat) 3050–2900, 1765 (C=O), 1464, 1287, 1260, 1086, 926 cm^{-1}.

3-(4,7-Dimethyl-1-naphthyl)-3-(1-octynyl)phthalide (1n) was obtained in 76% yield by procedure B with 1-octynyllithium and 2-(4,7-dimethyl-1-naphthoyl)benzoic acid and isolated as a white solid: mp 145–174 °C. Anal. Calcd for $C_{28}H_{28}O_2$: C, 84.60; H, 7.35. Found: C, 84.46; H, 7.20. ^1H NMR ($CDCl_3$) δ 0.62–1.43 (m, 11 H), 2.14 (t, 2 H), 2.53 (s, 3 H), 2.63 (s, 3 H), 7.01–8.00 (m, 8 H), 8.69 (s, 1 H); IR (KBr) 3000–2850, 2150, 1765 (C=O), 1464, 1286, 1252, 1101, 916 cm^{-1}; CD [λ_{ext}, nm ($\Delta\epsilon$)] *R*-(+)-enantiomer, 202.0 (67.1), 221.5 (0.0), 232.5 (+64.1), 279.0 (+7.0).

3-(4,7-Dimethyl-1-naphthyl)-3-(10-undecenyl)phthalide (1o) was obtained in 45% yield by procedure B with 10-undecenylmagnesium chloride and 2-(4,7-dimethyl-1-naphthoyl)benzoic acid and isolated as a colorless oil: high-resolution mass spectrum, calcd for $C_{31}H_{36}O_2$ 440.2715, found 440.2715; ^1H NMR ($CDCl_3$) δ 0.92–15.3 (m, 16 H), 1.83 (m, 2 H), 2.55 (s, 3 H), 2.64 (s, 3 H), 2.84 (m, 2 H), 5.65 (m, 1 H), 7.01–8.00 (m, 8 H), 8.60 (s, 1 H); IR (neat) 3050–2900, 1765 (C=O), 1599 (C=C), 1464, 1260, 1111,

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928 cm^{-1}; CD [λ_{ext}, nm ($\Delta\epsilon$)] *R*-(+)-enantiomer, 232.5 (+77.0), 279.0 (+4.6).

3-(2-Naphthyl)phthalide (1p) was obtained in 56% yield by procedure B with $NaBH_4$ and 2-(2-naphthoyl)benzoic acid[25] and isolated as a white solid: mp 148–150 °C. Anal. Calcd for $C_{18}H_{12}O_2$: C, 83.06; H, 4.65. Found: C, 83.07; H, 4.75. ^1H NMR ($CDCl_3$) δ 6.57 (s, 1 H), 7.15–8.02 (m, 11 H); IR (KBr) 3050–2950, 1754 (C=O), 1586, 1451, 1266, 1041, 990 cm^{-1}.

3-(2-Naphthyl)-3-methylphthalide (1q) was obtained in 92% yield by procedure B with methylmagnesium bromide and 2-(2-naphthoyl)benzoic acid and isolated as a white solid: mp 126–128 °C. Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.19; H, 5.14. Found: C, 83.16; H, 5.18. ^1H NMR ($CDCl_3$) δ 2.15 (s, 3 H), 7.47–7.94 (m, 11 H); IR (KBr) 3050–2850, 1755 (C=O), 1605, 1474, 1313, 1287, 1032, 930 cm^{-1}; CD [λ_{ext}, nm ($\Delta\epsilon$)] *R*-(−)-enantiomer, 231.0 (+19.5), 242.0 (−8.3), 279.0 (−9.6).

3-(6,7-Dimethyl-2-naphthyl)-3-isopropylphthalide (1r) was obtained in 16% yield by procedure A with 6,7-dimethyl-1-naphthyl isopropyl ketone[22] and isolated as a white solid: mp 122–126 °C. Anal. Calcd for $C_{23}H_{22}O_2$: C, 83.60; H, 6.71. Found: C, 83.45; H, 7.13. ^1H NMR ($CDCl_3$) δ 1.34 (d, 6 H), 2.40 (s, 3 H), 2.45 (s, 3 H), 3.45 (m, 1 H), 7.21–8.24 (m, 9 H); IR (KBr) 3100–2850, 1754 (C=O), 1612, 1261, 1113, 1024, 966 cm^{-1}; CD [λ_{ext}, nm ($\Delta\epsilon$)] *R*-(−)-enantiomer, 232.5 (+26.2), 245.5 (−3.3), 284.0 (−12.4); *S*-(+)-enantiomer, 232.5 (−20.46), 245.5 (+2.3), 284.0 (+9.1).

General Procedure for the Synthesis of 1-Thionophthalides. 1-Thiono-3-(1-naphthyl)phthalide (2b). Phthalide **1b** (1.1 g, 4.22 mmol) was dissolved in 50 mL of toluene and the solution azeotropically dried by using a Dean–Stark trap. The solution was allowed to cool, Lawesson's reagent (0.85 g, 2.11 mmol) was added, and the mixture was heated at reflux for either 12 h or until no more starting material could be detected by TLC. After concentration (rotary evaporator), the crude mixture was flash chromatographed on silica (40% CH_2Cl_2/hexane) to afford 0.81 g (90%) of 1-thionophthalide **2b** as a yellow solid. Further purification, if needed, was accomplished by recrystallization from hexane/ethyl acetate: mp 102–105 °C. Anal. Calcd for $C_{18}H_{12}OS$: C, 78.23; H, 4.38; S, 11.60. Found: C, 78.17; H, 4.47; S, 11.78. ^1H NMR ($CDCl_3$) δ 7.24 (s, 1 H), 7.37–7.95 (m, 9 H), 8.15 (d, 1 H, J = 7.8 Hz), 8.22 (d, 1 H, J = 8.4 Hz). IR (KBr) 3050–2950, 1320, 1273, 1161, 771 cm^{-1}.

1-Thiono-3-(1-naphthyl)-3-methylphthalide (2c). Recrystallization from hexane/ethyl acetate afforded an 86% yield of **2c** as a bright yellow solid: mp 182–185 °C. Anal. Calcd for $C_{19}H_{14}OS$: C, 78.59; H, 4.86; S, 11.04. Found: C, 78.51; H, 5.00; S, 11.24. ^1H NMR ($CDCl_3$) δ 2.29 (s, 3 H), 7.25–7.89 (m, 9 H), 8.13 (d, 1 H, J = 7.5 Hz), 8.47 (d, 1 H, J = 8.1 Hz). IR (KBr) 3100–3000, 1320, 1258, 1196, 1038, 776 cm^{-1}; CD [λ_{ext}, nm ($\Delta\epsilon$)] *R*-(+)-enantiomer, 212.0 (+26.6), 221.5 (−15.58), 232.5 (+106.3), 279.0 (+14.7), 310.0 (−8.2).

1-Thiono-3-(4,7-dimethyl-1-naphthyl)-3-methylphthalide (2k). Recrystallization from hexane/ethyl acetate afforded a 92% yield of **2k** as a yellow solid: mp 133–135 °C. Anal. Calcd for $C_{21}H_{18}OS$: C, 79.21; H, 5.70; S, 10.07. Found: C, 79.06; H, 5.82; S, 10.18. ^1H NMR ($CDCl_3$) δ 2.26 (s, 3 H), 2.50 (s, 3 H), 2.63 (s, 3 H), 7.07–8.14 (m, 8 H), 8.16 (s, 1 H); IR (KBr) 3100–2900, 1318, 1242, 1210, 1154, 1111, 1046, 826 cm^{-1}.

1-Thiono-3-(2-naphthyl)phthalide (2p). Recrystallization from hexane/ethyl acetate afforded a 70% yield of **2p** as a light yellow solid: mp 137–139 °C. Anal. Calcd for $C_{18}H_{12}OS$: C, 78.23; H, 4.38; S, 11.60. Found: C, 78.56; H, 4.42; S, 11.98. ^1H NMR ($CDCl_3$) δ 6.79 (s, 1 H), 7.18–7.83 (m, 10 H), 8.12 (d, 1 H, J = 7.8 Hz); IR (KBr) 3050–2950, 1325, 1273, 1163, 818 cm^{-1}.

1-Thiono-3-(2-naphthyl)-3-methylphthalide (2q). Recrystallization from hexane/ethyl acetate afforded a 90% yield of **2q** as a yellow solid: mp 133–135 °C. Anal. Calcd for $C_{19}H_{14}OS$: C, 78.59; H, 4.86; S, 11.04. Found: C, 78.66; H, 4.99; S, 11.09. ^1H NMR ($CDCl_3$) δ 2.20 (s, 3 H), 7.41–7.84 (m, 9 H), 7.91 (s, 1 H), 8.07 (d, 1 H, J = 7.5 Hz); IR (KBr) 3050–2950, 1469, 1318, 1248, 1186, 1074, 1041, 814 cm^{-1}.

General Procedure for the Synthesis of Diastereomeric Imino Alcohols. Diastereomeric Imino Alcohols 4a and 4b. 1-Thionophthalide **2k** (0.16 g, 0.50 mmol) and (*R*)-phenylglycinol (0.21 g, 1.50 mmol) were dissolved in 30 mL of anhydrous THF and stirred under nitrogen. Mercuric trifluoroacetate (0.21 g, 0.50 mmol) was added in one portion to the stirred solution at room temperature, and a black precipitate of mercuric sulfide was immediately produced. This mixture was allowed to stir 30 min at room temperature, filtered through sintered glass, and concentrated on a rotary evaporator, affording a viscous yellow oil. This oil was dissolved in 20 mL of CH_2Cl_2, and after 1–3 min, a white precipitate of the trifluoroacetate salt of (*R*)-phenylglycinol fell from solution. The mixture was filtered and concentrated on a rotary evaporator, affording 0.21 g (98%) of an equamolar mixture of **4a** and **4b** as a yellowish oil. Diastereomers **4a** and **4b** were simultaneously separated and purified by flash chromatography (20% ethyl acetate/CH_2Cl_2). Further purification, if needed, was achieved by recrystallization from hexane/ethyl acetate. The first eluted diastereomer, **4a**, was isolated as a white solid: mp 169–170 °C; mass spectrum (70 eV), *m/e* (relative intensity) 421 (2, M^+), 391 (35), 390 (100), 285 (65), 270 (47), 255 (12); high-resolution mass spectrum, calcd for $C_{29}H_{27}NO_2$ 421.2041, found 421.2035; ^1H NMR ($CDCl_3$) δ 1.71 (br s, 1 H), 1.87 (s, 3 H, CCH_3), 2.63 (s, 3 H, $ArCH_3$), 2.69 (s, 3 H, $ArCH_3$), 3.76–3.88 (m, 2 H), 4.97 (m, 1 H), 7.04–7.51 (m, 11 H), 7.93 (d, 1 H, J = 7.8 Hz), 7.98 (d, 1 H, J = 8.4 Hz), 8.23 (s, 1 H, naphthyl 9-H); IR (melt) 3100–3050, 2950–2800, 1686 (C=N), 1603, 1466, 1302, 1273, 1134, 1049 cm^{-1}. The second diastereomer eluted from silica was **4b**, isolated as a colorless oil: mass spectrum (70 eV), *m/e* (relative intensity) 421 (2, M^+), 390 (100), 285 (62), 270 (42), 255 (10); high-resolution mass spectrum, calcd for $C_{27}H_{29}NO_2$ 421.2041, found 421.2035; ^1H NMR ($CDCl_3$) δ 1.62 (br s, 1 H), 2.38 (s, 3 H, C-CH_3), 2.56 (s, 3 H, $ArCH_3$), 2.68 (s, 3 H, ArCH), 3.93 (dd, 1 H, J = 8.1, 4.2 Hz), 4.32 (m, 1 H), 5.33 (dd, 1 H, J = 6.0, 4.2 Hz), 7.01–7.98 (m, 13 H), 8.63 (d, 1 H, J = 7.8 Hz); IR (neat) 3100–3030, 1682 (C=N), 1631, 1491, 1466, 1267, 1115, 1030 cm^{-1}.

Diastereomeric imino alcohols 5a and 5b were obtained in the form of a yellow oil as an equimolar mixture (97%) and separated by flash chromatography on silica (25% ethyl acetate/CH_2Cl_2). The first eluted diastereomer, **5a**, was recrystallized from hexane/ethyl acetate and isolated as a white solid: mp 82–85 °C. Anal. Calcd for $C_{27}H_{23}NO_2$: C, 82.41; H, 5.89; N, 3.56. Found: C, 82.25; H, 6.04; N, 3.47. ^1H NMR ($CDCl_3$) δ 1.93 (s, 3 H), 2.58 (br s, 1 H), 3.78 (m, 2 H), 4.90 (dd, 1 H, J = 2.7, 5.1 Hz), 7.26–7.58 (m, 12 H), 7.81–8.13 (m, 3 H), 8.31 (m, 1 H); IR (KBr) 3400–3200, 3050–2800, 1682 (C=N), 1591, 1450, 1260, 1112, 1041 cm^{-1}. The second eluted diastereomer, **5b**, was recrystallized from hexane/ethyl acetate and isolated as a white solid: mp 175–178 °C. Anal. Calcd for $C_{27}H_{23}NO_2$: C, 82.41; H, 5.89; N, 3.56. Found: C, 82.19; H, 6.10; N, 3.41. ^1H NMR ($CDCl_3$) δ 2.17 (s, 3 H), 2.53 (br s, 1 H), 3.92 (m, 2 H), 5.14 (dd, 1 H, J = 2.4, 5.4 Hz), 6.96–7.81 (m, 14 H), 8.12 (m, 1 H), 8.22 (d, 1 H, J = 8.7 Hz); IR (KBr) 3400–3200, 3042–2866, 1675 (C=N), 1457, 1260, 1112, 1041 cm^{-1}.

Diastereomeric imino alcohols 6a and 6b were obtained as an equimolar mixture in the form of a viscous yellowish oil (98%) and separated by flash chromatography on silica (15% ethyl acetate/CH_2Cl_2). The first eluted diastereomer, **6a**, was recrystallized from hexane/ethyl acetate and isolated as a white solid: mp 51–55 °C. Anal. Calcd for $C_{27}H_{23}NO_2$: C, 82.41; H, 5.89; N, 3.56. Found: C, 82.44; H, 6.25; N, 3.26. ^1H NMR ($CDCl_3$) δ 1291 (s, 3 H), 2.38 (br s, 1 H), 3.92 (m, 2 H), 5.23 (m, 1 H), 7.17–7.96 (m, 16 H); IR (KBr) 3400–3200, 3050–3000, 1683 (C=N), 1468, 1272, 1128, 1044 cm^{-1}. The second eluted diastereomer, **6b**, was recrystallized from hexane/ethyl acetate and isolated as a white solid: mp 208–209 °C. Anal. Calcd for $C_{27}H_{23}NO_2$: C, 82.41; H, 5.89; N, 3.56. Found: C, 82.54; H, 6.05; N, 3.41. ^1H NMR ($CDCl_3$) δ 2.05 (s, 3 H), 2.67 (br s, 1 H), 3.94 (m, 2 H), 5.17 (dd, 1 H, J = 3.3, 4.8 Hz), 7.14–7.73 (m, 15 H), 7.97 (m, 1 H); IR (KBr) 3400–3200, 3050–3000, 1683 (C=N), 1464, 1268, 1124, 1060 cm^{-1}.

Diastereomeric imino alcohols 7a and 7b were obtained as an equimolar mixture in the form of a yellow oil (95%) and separated by flash chromatography on silica (15% ethyl acetate/CH_2Cl_2). The first eluted diastereomer, **7a**, was recrystallized from hexane/ethyl acetate and isolated as a white solid: mp 156–158 °C. Anal. Calcd for $C_{26}H_{21}NO_2$: C, 82.29; H, 5.58; N, 3.69. Found: C, 82.64; H, 5.73; N, 3.62. Mass spectrum (70 eV), *m/e* (relative intensity) 379 (14, M^+), 348 (100), 243 (27), 217 (33); high-resolution mass spectrum, calcd for $C_{26}H_{21}NO_2$ 379.1572, found 379.1579; ^1H NMR ($CDCl_3$) δ 2.39 (br s, 1 H), 3.881 (m,

(25) Fieser, L. F.; Hershberg, E. B. *J. Am. Chem. Soc.* **1940**, *62*, 49.

2 H), 5.17 (m, 1 H), 6.46 (s, 1 H), 7.17–8.03 (m, 16 H); IR (KBr) 3200–3000, 2950–2800, 1677 (C=N), 1602, 1470, 1289, 1170, 1063, 1006 cm^{-1}. The second eluted diastereomer, **7b**, was recrystallized from hexane/ethyl acetate and isolated as a white solid: mp 141–143 °C. Anal. Calcd for $C_{26}H_{21}NO_2$: C, 82.29; H, 5.58; N, 3.69. Found: C, 82.51; H, 5.52; N, 3.62. Mass spectrum (70 eV), *m/e* (relative intensity) 379 (6, M^+), 348 (100), 243 (38), 217 (43), 215 (32); high-resolution mass spectrum, calcd for $C_{26}H_{21}NO_2$ 379.1572, found 379.1571; ^1H NMR ($CDCl_3$) δ 2.92 (br s, 1 H), 3.98 (m, 2 H), 5.16 (dd, 1 H, J = 3.6, 4.8), 6.45 (s, 1 H), 6.96–8.04 (m, 16 H); IR (KBr) 3200–300, 2950–2800, 1683 (C=N), 1595, 1458, 1326, 1289, 1069, 994 cm^{-1}.

Diastereomeric imino alcohols 8a and 8b were produced by the general procedure except that (1*S*,2*S*)-1-phenyl-2-amino-3-methoxy-1-propanol[26] was used in place of (*R*)-phenylglycinol. Diastereomers **8a** and **8b** were obtained as a slightly yellow oily equimolar mixture (90%) and separated by flash chromatography on silica (10% ethyl acetate/CH_2Cl_2). The first eluted diastereomer, **8a**, was isolated as a colorless oil: mass spectrum (70 eV), *m/e* (relative intensity) 465 (46, M^+), 358 (100), 327 (87), 326 (100), 286 (92), 285 (100), 270 (99), 181 (100); high-resolution mass spectrum; calcd for $C_{31}H_{31}NO_3$ 465.2304, found 465.2304; ^1H NMR ($CDCl_3$) δ 1.86 (s, 3 H, CCH_3), 2.50 (s, 3 H, $ArCH_3$), 2164 (s, 3 H, $ArCH_3$), 3.08 (s, 3 H, OCH_3), 3.22 (m, 1 H), 3.51 (m, 1 H), 4.31 (m, 1 H), 5.05 (m, 1 H), 7.08–7.71 (m, 11 H), 7.92–8.08 (m, 3 H); IR (neat) 3200–3050, 3000–2850, 1686 (C=N), 1598, 1458, 1274, 1058, 1024 cm^{-1}. The second diastereomer eluted, **8b**, was isolated as a colorless oil: mass spectrum (70 eV), *m/e* (relative intensity) 465 (51, M^+), 358 (100), 327 (89), 326 (100), 286 (96), 285 (100), 270 (100), 181 (100); high-resolution mass spectrum, calcd for $C_{31}H_{31}NO_3$ 465.2304, found 465.2304; ^1H NMR ($CDCl_3$) δ 2.14 (s, 3 H, CCH_3), 2.43 (s, 3 H, $ArCH_3$), 2.66 (s, 3 H, $ArCH_3$), 3.43 (s, 3 H, OCH_3), 3.56 (m, 1 H), 3.70 (m, 1 H), 4.28 (m, 1 H), 4.86 (m, 1 H), 6.85–6.96 (m, 2 H), 7.09–7.65 (m, 10 H), 7.95 (m, 1 H), 8.05 (s, 1 H); IR (neat) 3200–3050, 3000–2850, 1683 (C=N), 1589, 1459, 1269, 1062, 1024 cm^{-1}.

Diastereomeric imino alcohols 9a and 9b were produced according to the general procedure except that (1*S*,2*S*)-1-phenyl-2-amino-3-methoxy-1-propanol was used in place of (*R*)-phenylglycinol. The diastereomers were obtained as a yellow oily equimolar mixture and purified by flash chromatography (20% ethyl acetate/CH_2Cl_2) to afford **9a** and **9b** (96%) as a colorless oil. The diastereomers **9a** and **9b** were not readily separable by liquid chromatography on silica but were readily separated by semipreparative HPLC (10% 2-propanol in hexane) using a covalently bonded (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine CSP (250 mm × 10 mm column). The second diastereomer eluted, **9a**, was isolated as a colorless oil: mass spectrum (70 eV), *m/e* (relative intensity) 423 (8, M^+), 316 (34), 284 (31), 275 (67), 259 (100), 215 (66), 133 (50), 105 (97); high-resolution mass spectrum, calcd for $C_{28}H_{25}NO_3$ 423.1834, found 423.1833; ^1H NMR ($CDCl_3$) δ 3.39 (s, 3 H), 3.60 (m, 1 H), 3.64 (m, 1 H), 4.43 (m, 1 H), 4.98 (br s, 1 H), 5.58 (d, 1 H, J = 7.2 Hz), 6.83 (m, 1 H), 6.89 (s, 1 H), 7.26–8.07 (m, 15 H); IR ($CHCl_3$) 3050–2800, 1690 (C=N), 1633, 1443, 1393, 1316, 1112, 1048 cm^{-1}. The first diastereomer eluted, **9b**, was isolated as a colorless oil: mass spectrum (70 eV), *m/e* (relative intensity) 423 (16, M^+), 316 (71), 284 (71), 275 (100), 215 (100), 133 (97), 105 (100); high-resolution mass spectrum; calcd for $C_{28}H_{25}NO_3$ 423.1834, found 423.1829; ^1H NMR ($CDCl_3$) δ 3.41 (s, 3 H), 3.66 (m, 1 H), 3.74 (m, 1 H), 4.45 (m, 1 H), 4.98 (br s, 1 H), 5.64 (d, 1 H, J = 6.3 Hz), 6.77 (d, 1 H, J = 7.8 Hz), 6.84 (s, 1 H), 7.18–8.05 (m, 15 H); IR ($CHCl_3$) 3050–2800, 1693 (C=N), 1640, 1598, 1452, 1395, 1329, 1126, 1054 cm^{-1}.

Diastereomeric imino alcohols 10a and 10b were produced according to the general procedure except that (1*S*,2*S*)-1-phenyl-2-amino-3-methoxy-1-propanol was used in place of (*R*)-phenylglycinol. The diastereomers were obtained as a yellow oil, which was purified by flash chromatography (20% ethyl acetate/CH_2Cl_2) affording an equimolar mixture of **10a** and **10b** (95%) as a colorless oil. The diastereomers were separated by semipreparative HPLC (5% 2-propanol in hexane) using a covalently bonded (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine CSP (250 mm × 10 mm column). The first diastereomer eluted, **10a**, was isolated as a colorless oil: mass spectrum (70 eV), *m/e* (relative intensity) 423 (19, M^+), 316 (67), 275 (100), 259 (100), 215 (98), 105 (100), 91 (100); high-resolution mass spectrum, calcd for $C_{28}H_{25}NO_3$ 423.1834, found 423.1833; ^1H NMR ($CDCl_3$) δ 2.63 (dd, 1 H, J = 1.5, 7.8 Hz), 3.04 (s, 3 H), 3.30 (m, 1 H), 4.29 (m, 1 H), 4.39 (br s, 1 H), 5.26 (d, 1 H, J = 6.3 Hz), 6.17 (s, 1 H), 7.26–7.53 (m, 11 H), 7.76–7.84 (m, 4 H), 8.05 (d, 1 H, J = 8.4 Hz); IR ($CHCl_3$) 3300–3100, 3050–250, 1698 (C=N), 1644, 1454, 1328, 1124, 1056 cm^{-1}. The second diastereomer eluted, **10b**, was isolated as a colorless oil: mass spectrum (70 eV), *m/e* (relative intensity) 423 (7, M^+), 259 (100), 125 (46), 105 (95), 91 (100); high-resolution mass spectrum, calcd for $C_{28}H_{25}NO_3$ 423.1834, found 423.1833; ^1H NMR ($CDCl_3$) δ 3.39 (s, 3 H), 3.60 (m, 2 H), 4.01 (m, 1 H), 5.32 (d, 1 H, J = 7.2 Hz), 6.09 (s, 1 H), 6.55 (d, 1 H, J = 7.5 Hz), 6.82 (m, 1 H), 7.09 (m, 1 H), 7.27–7.53 (m, 7 H), 7.74–7.91 (m, 6 H); IR ($CHCl_3$) 3300–3200, 3150–2850, 1683 (C=N), 1640, 1450, 1330, 1266, 1119, 1048 cm^{-1}.

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(26) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567.