

Enantioselective Nucleophilic Aromatic Substitution with Small-Molecule Chiral Selectors

by Seth E. Snyder*, Alex B. Shvets, and William H. Pirkle*

School of Chemical Sciences, University of Illinois at Urbana-Champaign, Urbana, Illinois, 61801
(tel.: 217-333-3896; e-mail: sesnyder@uiuc.edu)

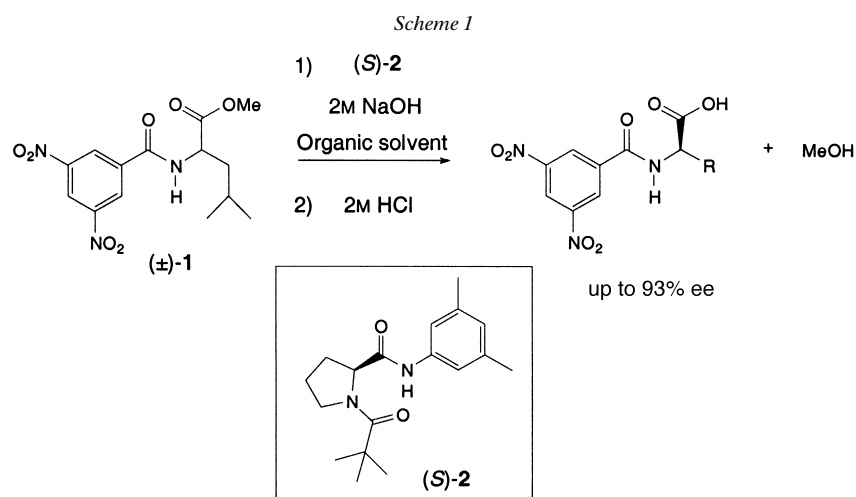
Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

Small-molecule rationally designed chiral selectors have been shown to influence the stereochemical outcome of a variety of organic transformations. For instance, in a recent report, we demonstrated that a chiral selector (in conjunction with an achiral phase-transfer catalyst) could selectively inhibit one enantiomer of electron-deficient aromatic amides from forming *Meisenheimer* adducts (*Scheme 2*). We now extend this methodology to performing enantioselective nucleophilic aromatic substitutions. Initial studies involved biphasic kinetic resolutions with a chiral selector in conjunction with an achiral phase-transfer catalyst (*Scheme 3*). The results are consistent with previous data taken for biphasic reactions (*e.g.*, *Scheme 1*) where the chiral selector effectively shields the more highly complexed enantiomer from reaction. With neutral nucleophiles such as amines, the enantioselective nucleophilic aromatic substitutions can also be conducted in single-phase systems. Several examples are given.

Introduction. – Principles of chiral recognition have been manipulated with remarkable efficiency in the design of small-molecule chiral selectors used in the preparation of chiral stationary phases (CSPs), leading to the ability to separate, with significant selectivity factors, the enantiomers of many classes of racemic analytes [1]. Since early studies involving chiral separations were carried out in these laboratories, a variety of CSPs have been produced that utilize readily available naturally occurring enantiomers such as polysaccharides, cyclodextrins, proteins, alkaloids, and antibiotics (for a review, see [2]). Nonetheless, the rationally designed CSPs developed from small, relatively simple chiral selectors offer several advantages. For instance, the selectors are inexpensive, quite stable, available in both enantiomeric forms, and can be recovered for re-use. Furthermore, the selectors usually operate through well-defined chiral-recognition mechanisms [3]. Chiral discrimination is rationalized through the formation of energetically nonequivalent transient diastereoisomeric complexes and generally relies on intermolecular interactions such as H-bonding, electrostatic forces, steric effects, and π - π interactions. Since the total structure of each of these selectors can be controlled, they can be tailored and optimized to the extent that one understands the mechanisms by which they differentiate between enantiomers. These principles will undoubtedly find application in the design of small-molecule enzyme-like catalysts and inhibitors (for reviews, see [4]). In this context, we are investigating the utilization of chiral selectors in a variety of enantioselective organic transformations.

In an earlier report, we described a method of performing highly enantioselective kinetic resolutions in biphasic media [5]. When organic solutions of an *N*-(3,5-

dinitrobenzoyl) ester of a racemic amino acid (e.g., ($\pm$)-**1**) and chiral selector (*S*)-**2** were added to 2M NaOH, enantioselective hydrolysis ensued (*Scheme 1*). Enantioselectivity increases with increasing amount of selector, a result that suggests selective inhibition of the more strongly complexed enantiomer. Reaction rates and enantioselectivities of hydrolysis are greatest in nonpolar organic solvents such as hexane or CCl₄. Typically, the utility of a kinetic resolution (for reviews, see [6]) is measured by the stereoselectivity factor (*s*), which gives the relative rates of reaction of the two enantiomers. Kinetic resolution is considered a practical and general route to optical resolution of chiral compounds when *s* > 10. Stereoselectivity factors for hydrolysis of ($\pm$)-**1** in hexane (at 0°) approach 100 (ee greater than 90% at 50% conversion), although one or more molar equivalents of (*S*)-**2** are required. Addition of a quaternary ammonium phase-transfer catalyst (PTC) results in the formation of a burgundy colored, sludge-like salt as a by-product of the reaction, initially suspected of being a *Meisenheimer* adduct.



Attempts to hydrolyze racemic amides such as ($\pm$)-**3** and ($\pm$)-**4** (*Fig. 1*) under biphasic conditions in the presence of (*S*)-**2** were not successful. However, when reactions were carried out under PTC conditions in hexane, the burgundy colored, sludge-like salt was formed. In halogenated solvents such as CH₂Cl₂ or CCl₄, the organic layer turns red, but no salt precipitates. In all cases, monitoring the unreacted amide in the organic layer by chiral HPLC revealed that the process is quite enantioselective, the more highly associated enantiomer once again being sequestered from reaction. Upon acidic workup, the dark red color vanishes, and a significant quantity of the starting amide is regenerated. Subsequent analysis shows that the colored species is a *Meisenheimer* adduct **6** (*Scheme 2*). The unusual stability of the complex is attributed to an ion-pairing interaction between the anionic *Meisenheimer* adduct and the quaternary ammonium cation [7]. Indeed, the overall equilibrium is dependent upon the quantity of PTC added. With acetate as a nucleophile, the C-adducts are formed even more readily, most likely a result of the added stability in comparison with the corresponding O-adducts (e.g., **6**) [8]. As with enantioselective

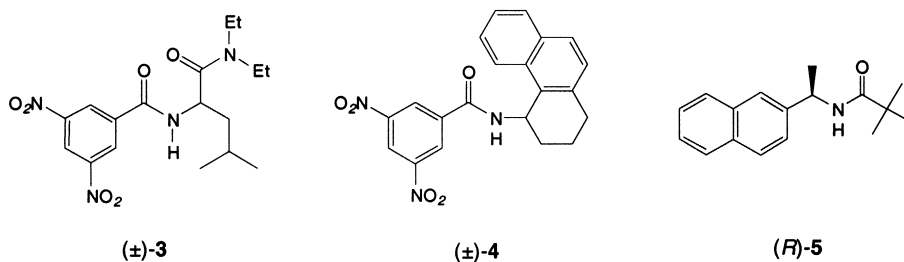
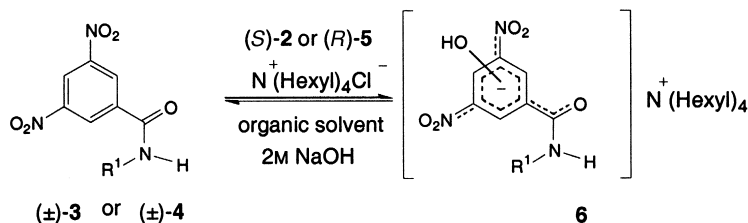


Fig. 1. Racemic amides and chiral selector used in kinetic resolutions

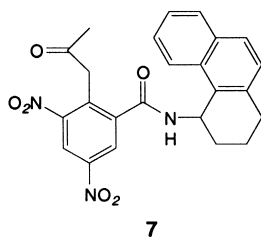
Scheme 2



hydrolysis, s factors for these kinetic resolutions are substantial when at least 1 mol-equiv. of the chiral selector is used, exceeding 100 for kinetic resolutions of $(\pm)$ -3 and 10 for kinetic resolutions of $(\pm)$ -4 (at 0°). Furthermore, enantioselective *Meisenheimer* adducts are formed enantioselectively with a variety of chiral selectors. With selector (R) -5 (2 mol-equiv.), kinetic resolutions of $(\pm)$ -4 give s factors exceeding 15. Here, we report a novel method to perform enantioselective nucleophilic aromatic substitution (S_NAr), a reaction known to proceed through the formation of a *Meisenheimer* complex (for reviews, see [9]).

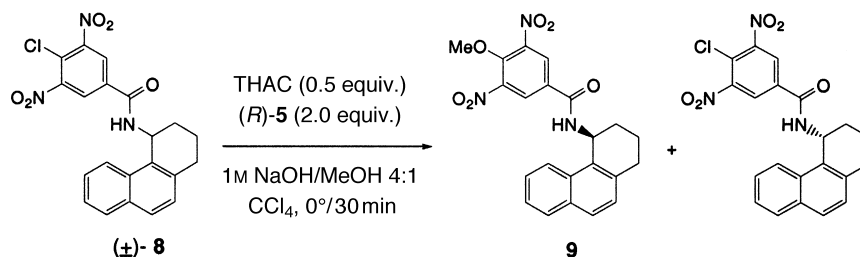
Results and Discussion. – Although NMR, EPR, and UV/VIS spectra of **6** are consistent with previous data for *Meisenheimer* adducts [10], isolation of the ion pairs is difficult owing to slow reversion to the starting amide or oxidation of the adduct (particularly when reactions are not performed under O_2 -free conditions.) For reactions in CCl_4 , where the organic layer remains homogeneous, the oxidative by-products could be isolated. For instance, reaction of $(\pm)$ -4 with acetate as a nucleophile results, after stirring for several hours, in oxidation of the C-adduct. When reactions are performed in the presence of selector (R) -5, the isolated *Janovsky* product (**7**; Fig. 2) is enriched in enantiomer from the less strongly complexed enantiomer of $(\pm)$ -4, while the residual unreacted amide (following acidic workup) is enriched in the more strongly complexed enantiomer.

These results prompted us to investigate nucleophilic aromatic substitution (S_NAr), reactions that proceed through the formation of intermediate *Meisenheimer* adducts. Nucleophilic aromatic substitution is an important step in the syntheses of a variety of pharmaceuticals, including hypotensive drugs, antidepressants, and antitumor agents [11]. An enantioselective approach to performing these reactions may prove to have

Fig. 2. Isolated Janovsky product from kinetic resolution of ($\pm$)-**4**

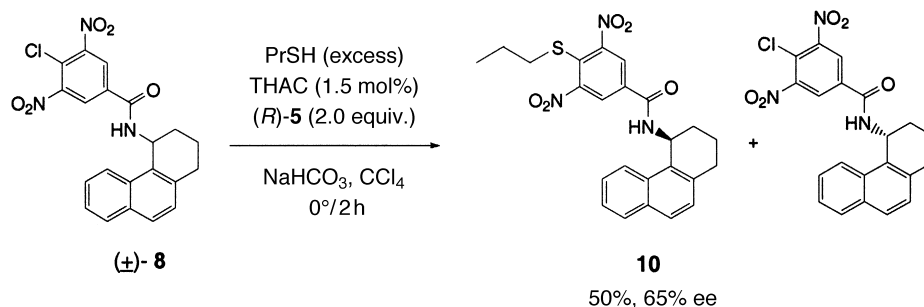
some synthetic utility. As an initial demonstration, a CCl_4 solution of the *p*-Cl-substituted dinitrobenzamide ($\pm$)-**8**, when treated with a methanolic NaOH solution in the presence of selector (*R*)-**5** and tetrahexylammonium chloride (THAC), affords the enantiomerically enriched MeO-substituted product **9** (Scheme 3). After 10 min, 50% of ($\pm$)-**8** had been converted to **9** as well as to a small quantity of the phenol resulting from replacement of the Cl by OH. The ee of both the residual **8** and product **9** was *ca.* 60%, enriched in the most and least strongly complexed enantiomers respectively. At 72% conversion, the ee of residual **8** was 96%. The reaction can also be conducted with catalytic amounts of THAC, giving nearly identical enantioselectivities. Reactions run with NaOH solutions proceed with similar enantioselectivity, although stoichiometric amounts of THAC are required owing to the stable ion-pair formed between the quaternary ammonium cation and the product phenolate anion. Thiols, which are considerably more nucleophilic and acidic than the corresponding alcohols, react readily with ($\pm$)-**8** in a mildly basic saturated NaHCO_3 solution (Scheme 4). Reactions proceed cleanly under phase-transfer conditions (*e.g.*, with 1.5-mol-% THAC) with no catalyst poisoning owing to the lack of production of the phenolate by-product. Stereoselectivity factors for kinetic resolutions appear to be independent of whether the nucleophile is an alcohol or a thiol. To our knowledge, these are the first examples of nonenzymatic enantioselective $\text{S}_\text{N}\text{Ar}$ reactions yet reported.

Scheme 3



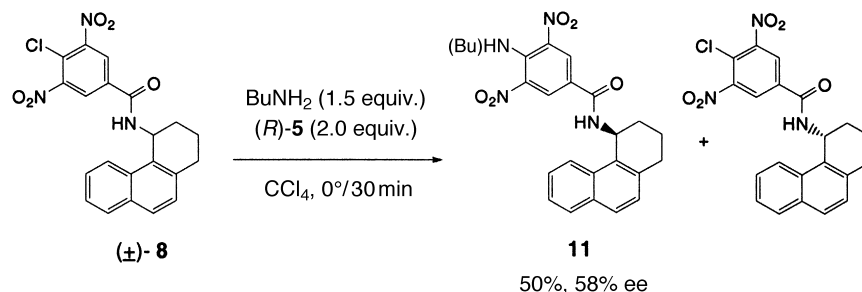
The results from enantioselective aromatic substitutions are consistent with those of the enantioselective hydrolyses (Scheme 1). In both cases, the chiral selector apparently inhibits one enantiomer from reaction. Although differential complexation of enantiomers appeared to be the governing factor accounting for the enantioselectivities observed in these biphasic reactions, one cannot rule out the occurrence of a

Scheme 4



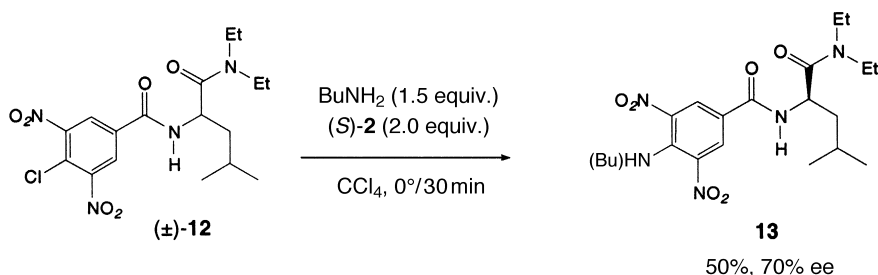
special interfacial orientation owing to the presence of the selector. Hence, reactions performed in a monophasic environment were expected to be informative. Since $S_N\text{Ar}$ reactions can be achieved readily with neutral nucleophiles such as amines, this reaction provides a convenient means of studying the monophasic counterpart to the biphasic kinetic resolutions discussed above. An example is provided in *Scheme 5*. As with the biphasic reactions, the more highly complexed enantiomer is sequestered from reaction. Enantioselectivities are similar to those of the biphasic reaction, suggesting that differential complexation is the dominant enantiomer-differentiating factor for both the biphasic and the monophasic reactions. Interestingly, dilution or concentration of reagents (with the same number of mol-equiv. of selector and racemic amide) does not have a profound effect on enantioselectivity of these systems. Reactions run at 0° show increased enantioselectivity over those run at room temperature. However, lowering the temperature to -16° does not significantly further enhance enantioselectivity. Kinetic resolutions of an electron-deficient amide derived from leucine (**(±)-12**) with selector (*S*)-**2** as a chiral complexing agent also show reasonably high *s* factors (*Scheme 6*).

Scheme 5



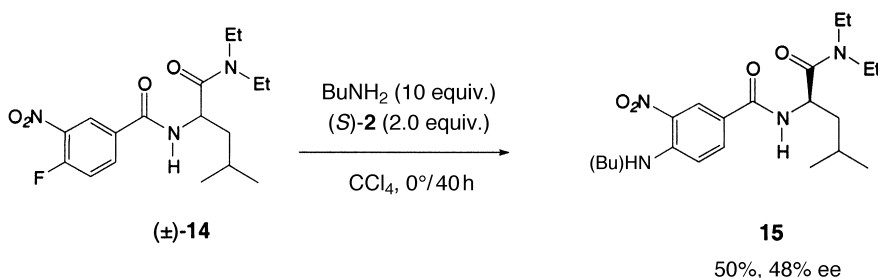
The synthetic utility and generality of the enantioselective aromatic substitution reaction would be extended significantly if reactions could be performed on reagents containing only one NO_2 group on the aromatic moiety. Fluorinated aromatic compounds containing but one NO_2 substituent tend to react readily with a variety of nucleophiles. Addition of BuNH_2 to **(±)-14** in the presence of selector (*S*)-**2**

Scheme 6



(Scheme 7) gives the aromatic amine **15** with modest enantioselectivity (*s* factor *ca.* 4.5). The reduced enantioselectivity of the reaction, relative to the kinetic resolution of (±)-**12**, is likely the result of reduced complexation of (±)-**14** with the selector. These types of reactions are currently being investigated with other racemic substrates and chiral selectors.

Scheme 7



Conclusions. – Results presented in this manuscript display our initial attempts to utilize small-molecule chiral selectors to effect enantioselective processes. Although substrates were chosen to demonstrate ‘proof of principle’, it is clear that the impressive stereoselectivity factors obtained can potentially bring these reactions into the realm of practical kinetic resolutions. Furthermore, the methodology provides a simplistic means of screening numerous chiral selectors that could find application as both CSPs and chiral catalysts. As understanding of the requirements for high levels of chiral recognition advances, the sophistication and generality in the design and utilization of chiral selectors is expected to follow suit.

The enantioselective $S_N\text{Ar}$ reactions discussed above are a significant advance. Besides the potential practical value, the reactions provide a means of comparing the biphasic enantioselective reactions with single-phase reactions. Obviously, kinetic studies of monophasic reactions are far less complicated than the corresponding biphasic reactions, a fact that could be important in elucidating the mechanistic basis of the observed enantioselectivities. Ongoing studies in this area are focused on expanding the scope of substrates (*e.g.*, heterocyclic aromatic amines) and organic reactions that can be influenced by chiral selectors.

Experimental Part

General. The following compounds and solvents used in the studies were purchased from the manufacturers: tetrahexylammonium chloride (THAC), triethylamine (NEt₃), Et₂NH, leucine, di(*tert*-butyl) dicarbonate, dicyclohexylcarbodiimide (DCC), 4-fluoro-3-nitrobenzoic acid from *Aldrich*; NaOH, NaHCO₃, THF, DMF, CH₂Cl₂, CCl₄ (old supply), acetone, MeOH from *Fisher*. 4-Chloro-3,5-dinitrobenzoic acid was available from previous studies and used in the synthesis without further purification: (m.p. 161–163°; [12]: 159–162°). All solvents were distilled prior to use. Anhyd. CH₂Cl₂ and Et₃N were distilled from CaH₂. THF was distilled from Na, benzophenone was added as an indicator. DMF was distilled from CaO and stored over activated molecular sieves (4 Å). Distilled H₂O was obtained from a *Millipore* water purification system. H₂O was collected when resistivity reached 14 MΩ. TLC: 0.2-mm silica-gel glass-coated plates (*Merck*) with *F*₂₅₄ indicator. Flash chromatography (FC): *Merck* 40–63-μm silica gel. HPLC was conducted with the following equipment: injectors: *Beckman*, *Rheodyne*; pumps: *Rainin Rabbit-HPX*, *Beckman 110B*, *Alcott 760*; fixed-wavelength UV detectors: *LDC/Milton Roy*, *Altech 450* at 254 nm, variable-wavelength UV detector: *Linear UVIS 200*; recorder/integrator: *HP 3390A*. Chromatographic runs were conducted at ambient temp. with the flow rate of 2 ml/min, dimensions of all anal. HPLC columns were 24 cm × 4.6 mm (unless otherwise indicated). The void volume was determined by injecting 1,3,5-tris(*tert*-butyl)benzene. The retention factor (*k*_n) was calculated on the basis of the following equation:

$$k_n = (t_n - t_0)/t_0$$

where *t*_n is the retention time of an analyte (enantiomer) and *t*₀ is the retention time of 1,3,5-tris(*tert*-butyl)benzene. The separation factor (*α*) is a ratio of the retention factors of two enantiomers and calculated according to the equation:

$$\alpha = k_2/k_1 = (t_2 - t_0)/(t_1 - t_0)$$

Calculation of the stereoselectivity factor (*s*) was accomplished according to the equation:

$$s = \ln [1 - C(1 + ee)] / \ln [1 - C(1 - ee)]$$

where *C* is the extent of conversion of starting material and *ee* is enantiomeric excess of the remaining starting material. For all chromatographic assays, conversion was determined with the selector as an internal standard. ¹H- and ¹³C-NMR spectra: *Varian Unity 400* or *500* spectrometers at 'The *Varian Oxford Instruments Center for Excellence in NMR Laboratory*' at the University of Illinois School of Chemical Science; all chemical shifts are reported in ppm (*δ*) with the solvent reference CDCl₃ (*δ* 7.26 ppm) for ¹H and CDCl₃ (*δ* 77.0) for ¹³C spectra; coupling constants (*J*) in Hz; ¹³C-NMR proton-decoupled. Low- (*ZAB-SE* instrument) and high-resolution (*70-SE-4F* instrument) fast atom bombardment (FAB) mass spectra (MS) as well as matrix-assisted laser desorption ionization (MALDI, 'Voyager' instrument) MS were obtained in the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. Elemental analyses were performed at the Analytical Laboratories of the University of Illinois, School of Chemical Science.

Reaction of 3,5-Dinitro-N-(1,2,3,4-tetrahydrophenanthren-4-yl)benzamide (4) with Acetone. Racemic **4** (0.52 mmol) and THAC (0.4 mmol) were dissolved in 10 ml of benzene in a scintillation flask equipped with a *Teflon* lining and a magnetic stir bar. Acetone (30 μl) was added *via* syringe followed with 10 ml of 2M NaOH. The mixture turned dark blue immediately on mixing. The vial was capped and vigorously stirred for 4 h. Phases were separated. The aq. phase was acidified with 2M HCl. The brown gel precipitate was removed by filtration through 'Whatman' #4 paper. The solid was dissolved in CH₂Cl₂, dried (Na₂SO₄), and analyzed by MALDI-MS. Clusters of peaks were observed, these being separated by molecular-weight increments close to the molecular weight of the starting material. This indicates that some oligomerization is occurring. The org. phase was quenched with 2M HCl for ca. 50 min. The color very slowly changed from dark blue to red and finally to yellow. The org. phase was dried (Na₂SO₄) and concentrated under vacuum. The majority of the starting material was recovered by crystallization from THF/hexane. The mother liquor was collected, concentrated under vacuum, and chromatographed on silica gel with pure CH₂Cl₂, followed with 10% acetone in CH₂Cl₂. All recovered starting material was combined, yielding a total of 172 mg (86%). *Janovsky* product **7** (5 mg) was isolated as a white solid.

3,5-Dinitro-2-(2-oxopropyl)-N-(1,2,3,4-tetrahydrophenanthren-4-yl)benzamide ((±)-7). M.p. > 239° (dec.). ¹H-NMR (400 MHz, CDCl₃): 1.58 (s, 3 H); 1.82 (m, 1 H); 2.05 (m, 2 H); 2.32 (m, 1 H); 2.98 (m, 2 H); 3.84 (d, *J*_{AB} = 17.1, 1 H); 3.99 (d, *J*_{AB} = 17.1, 1 H); 6.00 (m, 1 H); 6.98 (d, *J* = 9.0, 1 H); 7.24 (d, *J* = 8.5, 1 H); 7.50 (ddd, *J* = 7.1, 7.1, 0.7, 1 H); 7.59 (ddd, *J* = 7.7, 7.7, 1.2, 1 H); 7.73 (d, *J* = 8.5, 1 H); 7.84 (d, *J* = 7.8, 1 H); 8.06 (d, *J* = 8.5, 1 H); 8.58 (d, *J* = 2.4, 1 H); 8.81 (d, *J* = 2.4, 1 H). ¹³C-NMR (100 MHz, CDCl₃): 17.8; 29.1; 29.5; 29.7; 43.8; 44.37; 120.9; 122.5; 125.5; 126.97; 127.03; 128.36; 128.41; 128.8; 129.1; 131.6; 132.6; 133.7; 136.2; 142.9; 146.8; 149.4; 163.6; 205.0. HR-FAB-MS 448.1509; ([*M* + 1]⁺, C₂₄H₂₁N₃O₆; calc. 448.1509).

4-Chloro-3,5-dinitro-N-(1,2,3,4-tetrahydrophenanthren-4-yl)benzamide ((±)-8). 2.0 g of 4-chloro-3,5-dinitrobenzoic acid was suspended in 10 ml of SOCl₂. 0.1 ml of dry DMF was added, and the mixture was brought to reflux for 5 h. SOCl₂ was distilled and residual liquid was poured into dry hexane. However, the acid chloride oiled out and did not crystallize. Hexane and residual SOCl₂ were removed under vacuum to yield 2.3 g of viscous oil as a product. The crude acid chloride 355 mg (1.34 mmol) was combined with the HCl salt of the amine (1,2,3,4-tetrahydrophenanthren-4-amine; 0.67 mmol) [1] and suspended in 3 ml of dry CH₂Cl₂. The mixture was cooled in an ice/NaCl bath to –10° and 0.19 ml of dry Et₃N was added dropwise *via* syringe. All solid material dissolved, and the solution turned a clear light yellow color. A precipitate began to develop after *ca.* 10 min. The soln. was stirred under N₂ in an ice bath for 1 h. A thick slurry formed. The resulting suspension was diluted with *ca.* 3 ml of hexane and filtered. The resulting solid (product along with HCl salt of Et₃N) was dissolved in *ca.* 100 ml of CHCl₃ and extracted in sequence with 5% NaHCO₃, 1M HCl, sat. NaCl soln. and distilled H₂O. The org. phase was dried (MgSO₄), filtered, and concentrated under vacuum. The resulting solid was recrystallized from CH₂Cl₂/hexane to yield 201 mg (70%) of (±)-8. White solid. M.p. > 248° (dec.). ¹H-NMR (400 MHz, CDCl₃): 1.89 (m, 1 H); 2.03 (m, 2 H); 2.41 (m, 1 H); 3.03 (m, 2 H); 5.95 (m, 1 H); 6.50 (d, *J* = 7.3, 1 H); 7.27 (d, *J* = 8.5, 1 H); 7.45 (ddd, *J* = 7.6, 6.2, 1.4, 1 H); 7.50 (ddd, *J* = 8.1, 6.8, 1.6, 1 H); 7.77 (d, *J* = 8.5, 1 H); 7.82 (dd, *J* = 7.8, 1.5, 1 H); 7.84 (d, *J* = 8.3, 1 H); 8.30 (s, 2 H). ¹³C-NMR (100 MHz, 1,4-(D₈)dioxane): 18.3; 30.1; 30.8; 45.1; 123.1; 123.6; 126.1; 127.3; 127.7; 128.7; 129.1; 129.4; 130.6; 133.2; 133.5; 136.0; 136.9; 150.4; 161.7. HR-FAB-MS: 426.0856 ([*M* + 1]⁺, C₂₁H₁₆ClN₃O₅; calc. 426.0857). Anal. calc. for C₂₁H₁₅ClN₃O₅: C 59.23, H 3.79, N 9.87, Cl 8.33; found: C 59.41, H 3.86, N 9.54, Cl 8.41.

When conditions are not controlled as specified above, some formation of an adduct of the starting amine at the *p*-position of **8** is observed (by ¹H-NMR). This by-product can be separated from the product by chromatography on a semi-prep. 'Pirkle Covalent D,L-Phenylglycine' HPLC column (Regis Technologies) with hexane/CH₂Cl₂ 1:1 at a flow rate of 8.5 ml/min and ambient temp.

4-Methoxy-3,5-dinitro-N-(1,2,3,4-tetrahydrophenanthren-4-yl)benzamide ((±)-9). Racemic **8** (0.05 mmol), chiral selector (*R*)-**5** (0.1 mmol), and THAC (0.025 mmol) were dissolved in 0.5 ml of CH₂Cl₂ and 4.5 ml of CCl₄. The reaction was carried out in a 25-ml scintillation vial with a Teflon cover under the cap. The soln. was cooled in an ice bath. A separate soln. of 1M NaOH (4 ml) and pure MeOH (1 ml) was prepared and also cooled. The cold aq. soln. was added to the org. soln. all at once, and the mixture was stirred vigorously in a capped vial. Color slowly developed, at first light orange, then changing to raspberry-pink. The soln. remained transparent throughout the reaction. The reaction was monitored by chiral HPLC with a column available from Regis Technologies. CSP: (S,S)-ULMO, mobile phase: 15% of *i*-PrOH in hexane, detection at λ = 254 nm, starting material: *k*₁ = 3.24, *k*₂ = 5.05; product: *k*₁ = 4.01, *k*₂ = 6.84. Selector (*R*)-**5** [7] was used as an internal standard. HPLC Assay after 15 min reaction time indicated 68% conversion. After 30 min, the phases were separated, and the org. phase was quenched with 1M HCl. The org. phase turned light yellow. The org. phase was dried (Na₂SO₄) and concentrated under vacuum. The crude mixture was chromatographed on silica gel in 1% Et₂O/CH₂Cl₂. Starting amide **8** was recovered: 5.2 mg (24%) with ee of 96%. Product **9** (15.7 mg, 72%) was obtained as a white solid with ee 36%. M.p. > 236° (dec.) (ee 36%). ¹H-NMR (400 MHz, CDCl₃): 1.90 (m, 1 H); 2.02 (m, 2 H); 2.39 (m, 1 H); 3.02 (m, 2 H); 4.08 (s, 3 H); 6.46 (d, *J* = 7.6, 1 H); 7.27 (d, *J* = 9.3, 1 H); 7.45 (ddd, *J* = 7.3, 7.3, 1.0, 1 H); 7.49 (ddd, *J* = 6.7, 6.7, 1.3, 1 H); 7.82 (dd, *J* = 8.3, 1.5, 1 H); 7.86 (d, *J* = 8.3, 1 H); 8.37 (s, 2 H). ¹³C-NMR (100 MHz, CDCl₃): 18.1; 29.1; 29.9; 44.7; 65.0; 114.7; 122.4; 125.5; 127.2; 127.5; 127.9; 128.7; 128.79; 128.81; 130.2; 131.8; 132.5; 136.3; 145.0; 161.1. HR-FAB-MS: 422.1354 ([*M* + H]⁺, C₂₂H₂₀N₃O₆; calc. 422.1353). The percent of remaining starting material calculated from HPLC data obtained just prior to isolation was 26%. A strongly adsorbed yellow band was eluted from silica gel after the initial chromatography with pure MeOH, followed by pure CH₂Cl₂. The yellow org. soln. was dried (Na₂SO₄) and concentrated under vacuum to yield 5.5 mg of a mixture of THAC and *p*-OH derivative of **8**. The by-product was analyzed by ¹H-NMR and negative FAB-MS. Although the alkyl proton region is obscured with signals from THAC, the aromatic region is similar to that of the starting material. MS Data indicates that the by-product is a phenol derived from the starting material. FAB-MS: 406.0 ([*M* – 1][–]; calc. for C₂₁H₁₇N₃O₆ (*M*⁺) 407.1).

General Procedure for the Synthesis of Racemic 12 and 14. Synthesis began from racemic leucine by first protecting the amine functionality with a Boc group ((Boc)₂O) [13], followed by DCC-mediated coupling to diethylamide [14], deprotection with TFA [14] and finally acylation with one of the activated acids (analogously to preparation of (±)-8). 4-Fluoro-3-nitrobenzoyl chloride was prepared similarly to 4-chloro-3,5-dinitrobenzoyl chloride as in the preparation of 8 and used in the reaction without further purification.

4-Chloro-N-[1-(diethylcarbamoyl)-3-methylbutyl]-3,5-dinitrobenzamide ((±)-12) was obtained as a white solid. M.p. 183–186°. ¹H-NMR (400 MHz, CDCl₃): 0.95 (d, *J* = 6.6, 3 H); 1.01 (d, *J* = 6.6, 3 H); 1.14 (t, *J* = 7.1, 3 H); 1.38 (t, *J* = 7.1, 3 H); 1.41 (m, 1 H); 1.80 (m, 2 H); 3.18 (dq, *J* = 13.8, 7.0, 1 H); 3.38 (dq, *J* = 14.8, 7.4, 1 H); 3.48 (dq, *J* = 15.0, 7.5, 1 H); 3.67 (dq, *J* = 13.9, 7.0, 1 H); 5.09 (ddd, *J* = 11.1, 8.1, 2.9, 1 H); 8.43 (s, 2 H). ¹³C-NMR (100 MHz): 12.7; 14.0; 21.2; 23.4; 24.9; 40.9; 41.0; 42.3; 49.3; 123.2; 126.3; 133.7; 149.2; 161.2; 172.5. FAB-MS: 415.1 ([*M* + 1]⁺; calc. for *M*⁺, 414.13). Anal. calc. for C₁₇H₂₃ClN₄O₆: C 49.22, H 5.59, N 13.51; found: C 49.05, H 5.52, 13.25.

N-[1-(Diethylcarbamoyl)-3-methylbutyl]-4-fluoro-3-nitrobenzamide ((±)-14) was obtained as a white solid: 57% yield. M.p. 109–110°. ¹H-NMR (400 MHz, CDCl₃): 0.95 (d, *J* = 6.6, 3 H); 1.03 (d, *J* = 6.6, 3 H); 1.15 (t, *J* = 7.2, 3 H); 1.34 (t, *J* = 7.2, 3 H); 1.42 (m, 1 H); 1.79 (m, 2 H); 3.23 (dq, *J* = 13.8, 7.0); 3.41 (dq, *J* = 14.7, 7.4); 3.47 (dq, *J* = 14.7, 7.4); 3.63 (dq, *J* = 13.8, 7.0); 5.11 (ddd, *J* = 11.1, 8.1, 2.9); 7.25 (dd, *J* = 10.1, 8.7, 1 H); 7.97 (d, *J* = 8.1, 1 H); 8.05 (ddd, *J* = 8.7, 4.2, 2.3, 1 H); 8.52 (dd, *J* = 7.0, 2.3, 1 H). ¹³C-NMR (100 MHz, +40°): 13.1; 14.6; 21.9; 23.7; 25.2; 40.9; 42.3; 42.7; 48.8; 118.7 (d, *J*(C,F) = 21.4); 125.6 (d, *J*(C,F) = 1.5); 131.2 (d, *J*(C,F) = 3.8); 134.4 (d, *J*(C,F) = 9.2); 137.5 (d, *J*(C,F) = 5.8); 157.3 (d, *J*(C,F) = 270.1); 163.7; 172.2. FAB-MS: 354 ([*M* + 1]⁺; calc. for *M*⁺, 353.18). Anal. calc. for C₁₇H₂₄FN₃O₄: C 57.78, H 6.85, N 11.89; found: C 57.45, H 6.70, N 11.82.

General Procedure for the Syntheses of Racemic 10, 11, 13, and 15. The starting material (compounds 8, 12, and 14) was dissolved in dry CH₂Cl₂ (concentration range: 0.025–0.15M) and placed in a dry sealed tube equipped with a stir bar. Nucleophile (BuNH₂ or PrSH) was added in 10-fold excess. Dry K₂CO₃ was used as a base (in equimolar quantity to thiol) for preparation of 10. The color of the reaction solns. became quickly yellow as product was being formed. The reactions were stirred at r.t. for 10–12 h in a sealed tube. The reaction temp. for preparation of 15 was 40°. At the end of the reaction time, the contents of the reaction soln. were diluted with 20 ml of CH₂Cl₂ and extracted sequentially with 1M HCl, brine, and distilled H₂O. Org. phase was dried (MgSO₄), filtered, and concentrated under vacuum. Compounds 10 and 11 were directly recrystallized from hexane/CH₂Cl₂. Compounds 13 and 15 were chromatographed on silica gel in 1% Et₂O/5% Acetone/CH₂Cl₂, followed by crystallization from hexane/CH₂Cl₂. Reported yields are after crystallization.

3,5-Dinitro-4-(propylsulfanyl)-N-(1,2,3,4-tetrahydrophenantren-4-yl)benzamide ((±)-10) was obtained from (±)-8 as a pale yellow solid: 68% yield. M.p. > 180° (dec.). ¹H-NMR (500 MHz, CDCl₃): 0.93 (t, *J* = 7.4, 3 H); 1.54 (tq, *J* = 7.7, 7.3, 2 H); 1.57 (m, 1 H); 1.89 (m, 1 H); 2.02 (m, 2 H); 2.38 (d, *J* = 12.9, 1 H); 2.81 (t, *J* = 7.4, 2 H); 3.02 (m, 2 H); 5.93 (m, 1 H); 6.53 (d, *J* = 7.1, 1 H); 7.25 (d, *J* = 8.4, 1 H); 7.44 (dd, *J* = 7.3, 7.3, 1 H); 7.49 (ddd, *J* = 7.7, 7.7, 1.4, 1 H); 7.74 (d, *J* = 8.4, 1 H); 7.80 (d, *J* = 7.7, 1 H); 7.85 (d, *J* = 8.4, 1 H); 8.15 (s, 2 H). ¹³C-NMR (125 MHz): 13.0; 18.1; 22.8; 29.0; 29.8; 38.5; 44.7; 122.4; 124.8; 125.5; 127.2; 127.9; 128.6; 128.79; 128.80; 131.8; 132.5; 135.2; 136.4; 154.3; 161.1; 169.0. FAB-MS: 466.1 ([*M* + 1]⁺; calc. for *M*⁺, 465.14).

4-(Butylamino)-N-(1,2,3,4-tetrahydrophenantren-4-yl)benzamide ((±)-11) was obtained from (±)-8 as a yellow solid: 78% yield. M.p. > 225° (dec.). ¹H-NMR (400 MHz, CDCl₃): 0.92 (t, *J* = 7.3, 3 H); 1.38 (tq, *J* = 7.5, 7.5, 2 H); 1.64 (t, *J* = 7.3, 7.3, 2 H); 1.95 (m, 2 H); 2.36 (d, *J* = 10.5, 1 H); 5.93 (m, 1 H); 6.45 (d, *J* = 7.6, 1 H); 7.25 (d, *J* = 7.6, 1 H); 7.42 (ddd, *J* = 7.4, 7.4, 1.1, 1 H); 7.47 (ddd, *J* = 7.6, 7.6, 1.5, 1 H); 7.73 (d, *J* = 8.5, 1 H); 7.79 (dd, *J* = 7.8, 1.2, 1 H); 7.87 (d, *J* = 8.3); 8.52 (s, 2 H); 8.58 (br. s, 1 H). ¹³C-NMR (100 MHz): 13.6; 18.1; 19.8; 29.2; 29.9; 31.9; 44.3; 46.3; 119.6; 122.6; 125.3; 127.1; 127.9; 128.5; 128.6; 129.1; 130.6; 131.9; 132.5; 136.2; 136.8; 141.3; 161.8. FAB-MS: 463.5 ([*M* + 1]⁺; calc. for *M*⁺, 462.50).

4-(Butylamino)-N-[1-(diethylcarbamoyl)-3-methylbutyl]-3,5-dinitrobenzamide ((±)-13) was obtained from (±)-12 as a yellow solid: 53% yield. M.p. 135–137°. ¹H-NMR (400 MHz, CDCl₃): 0.94 (d, *J* = 6.1, 6 H); 0.97 (t, *J* = 7.3, 3 H); 1.14 (t, *J* = 7.1, 3 H); 1.30 (td, *J* = 10.9, 2.8, 1 H); 1.44 (t, *J* = 7.1, 3 H); 1.46 (m, 2 H); 1.72 (t, *J* = 7.4, 7.4, 2 H); 1.86 (ddd, *J* = 10.0, 6.7, 3.5, 1 H); 1.95 (ddd, *J* = 13.8, 12.1, 3.4, 1 H); 2.96 (m, 1 H); 3.05 (m, 2 H); 3.34 (dq, *J* = 14.6, 7.3, 1 H); 3.52 (dq, *J* = 14.6, 7.3, 1 H); 3.97 (dq, *J* = 13.9, 7.0, 1 H); 5.04 (ddd, *J* = 11.1, 8.2, 2.9, 1 H); 8.47 (s, 2 H); 8.58 (t, *J* = 4.5, 1 H); 9.25 (d, *J* = 7.6, 1 H). ¹³C-NMR (100 MHz): 12.7; 13.7; 13.9; 19.9; 21.1; 23.5; 24.9; 31.9; 40.7; 40.9; 42.1; 46.2; 49.0; 118.0; 130.6; 136.4; 140.9; 162.6; 173.1. FAB-MS: 452.2 ([*M* + 1]⁺; calc. for *M*⁺, 451.24). Anal. calc. for C₂₁H₃₃N₅O₆: C 55.86, H 7.37, N 15.51; found: C 55.53, H 7.41, N 15.13.

4-(Butylamino)-N-[1-(diethylcarbamoyl)-3-methylbutyl]-3-nitrobenzamide ((±)-15) was obtained from (±)-14 as a pale orange solid: 45% yield. M.p. 112–113°. ¹H-NMR (400 MHz, CDCl₃): 0.94 (d, *J* = 6.6, 3 H); 0.98 (t, *J* = 7.3, 3 H); 1.02 (d, *J* = 6.6, 3 H); 1.13 (t, *J* = 7.1, 3 H); 1.31 (t, *J* = 7.2, 3 H); 1.42 (m, 1 H); 1.47 (tq, *J* = 7.5, 7.5, 2 H); 1.73 (m, 3 H); 3.24 (dq, *J* = 13.7, 6.9, 1 H); 3.32 (q, *J* = 6.2, 2 H); 3.44 (q, *J* = 7.2, 2 H); 3.56

(*dq*, *J* = 13.6, 6.9, 1 H); 5.14 (*ddd*, *J* = 11.1, 7.9, 3.0, 1 H); 6.79 (*d*, *J* = 9.0, 1 H); 7.33 (*d*, *J* = 7.6, 1 H); 7.88 (*dd*, *J* = 8.9, 1.6, 1 H); 8.23 (*t*, *J* = 4.4, 1 H); 8.64 (*d*, *J* = 2.0, 1 H). ¹³C-NMR (100 MHz): 12.9; 13.7; 14.4; 20.1; 21.7; 23.5; 24.8; 30.8; 40.6; 42.0; 42.7; 42.9; 47.9; 113.5; 120.6; 126.5; 130.9; 134.6; 147.0; 164.9; 172.2. FAB-MS: 407.2 (*[M* + 1]⁺; calc. for *M*⁺, 406.26). Anal. calc. for C₂₁H₃₄N₄O₄: C 62.04, H 8.43, N 13.78; found: C 61.84, H 8.43, N 13.57.

General Procedure for Biphasic Enantioselective Nucleophilic Aromatic Substitution of (±)-8 with PrSH (Scheme 4). To a stirred soln. of (±)-8 (0.009 mmol), (R)-5 (0.018 mmol), and THAC (0.0002 mmol) in 2 ml of CCl₄ were added 1.0 ml of sat. NaHCO₃ soln. and 0.05 ml of PrSH at 0°. The reaction progress was monitored by the FUSE-4 chiral stationary phase¹⁾ developed in these laboratories under the following conditions: mobile phase 12% i-PrOH in hexane, detection at λ = 254 nm, (R)-5: *k* = 0.8, (R)-8: *k* = 3.7, (S)-8: *k* = 9.8, (S)-10: *k* = 2.8, (R)-10: *k* = 9.8. The extent of conversion was monitored by HPLC with (R)-5 as an internal standard. After 2 h (at ca. 50% conversion), the soln. was diluted with CCl₄ and H₂O, and the layers were separated. The org. layer was washed with 2M HCl and H₂O, and then dried (MgSO₄).

General Procedure for Monophasic Enantioselective Nucleophilic Aromatic Substitution of (±)-8 with BuNH₂ (Scheme 5). To a stirred soln. of (±)-8 (0.009 mmol) and (R)-5 (0.018 mmol) in 1 ml of CCl₄ and 0.02 ml of CH₂Cl₂ was added 0.013 mmol of BuNH₂. The soln. was stirred for 30 min, diluted with CCl₄, and washed sequentially with 2M HCl and H₂O. The extent of conversion was determined with a Pirkle Covalent D,L-Phenylglycine column (20% i-PrOH in hexane) available from Regis Technologies. Selector (R)-5 was used as an internal standard. Enantiomeric excess was determined with an (R,R)-Whelk O1 column (Regis Technologies) under the following conditions: mobile phase 25% i-PrOH in hexane, detection at δ = 254 nm, (R)-5: *k* = 58, (R)-8: *k* = 2.1, (S)-8: *k* = 2.5, (S)-11: *k* = 4.5, (R)-11: *k* = 5.7.

General Procedure for Monophasic Enantioselective Nucleophilic Aromatic Substitution of (±)-12 with BuNH₂ (Scheme 6). To a stirred soln. of (±)-12 (0.009 mmol) and (S)-2 (0.018 mmol) in 1 ml of CCl₄ and 0.02 ml of CH₂Cl₂ was added 0.013 mmol of BuNH₂. The soln. was stirred for 30 min, diluted with CCl₄, and washed sequentially with 2M HCl and H₂O. The extent of conversion and the enantiomeric excess were determined with an (R,R)-Whelk O1 column (Regis Technologies) under the following conditions: mobile phase 3% i-PrOH in 97% hexane, detection at λ = 280 nm, (S)-2: *k* = 7.9, (S)-12: *k* = 2.96, (R)-12: *k* = 5.1, (R)-13: *k* = 6.4, (S)-13: *k* = 12.3. Selector (S)-2 was used as an internal standard.

General Procedure for Monophasic Enantioselective Nucleophilic Aromatic Substitution of (±)-14 with BuNH₂ (Scheme 7). To a stirred soln. of (±)-14 (0.009 mmol) and (S)-2 (0.018 mmol) in 1 ml of CCl₄ and 0.02 ml of CH₂Cl₂ was added 0.09 mmol BuNH₂. The soln. was stirred for 40 h, diluted with CCl₄, and washed sequentially with 2M HCl and H₂O. Assays were analyzed periodically by HPLC with an (S)-α-Burke column (Regis Technologies) under the following conditions: mobile phase 3% i-PrOH in 97% hexane, detection at λ = 248 nm, (S)-2: *k* = 9.5, (S)-14: *k* = 3.2, (R)-14: *k* = 4.0, (R)-15: *k* = 5.3, (S)-15: *k* = 6.9. Selector (S)-2 was used as an internal standard.

Determination of Absolute Configuration. Abs. configurations were assigned by comparison with authentic enantiomerically pure samples (1, 3, and 4). When authentic enantiomerically pure samples were not available, it was assumed that chromatographic behavior of structural analogues of 3 (e.g., 12, 13, 14, and 15) and of 4 (e.g., 7, 8, 9, 10, and 11) resembled the parent compounds 3 and 4. Structural analogues of 3 were resolved on the CSP derived from (S)-2 [15] with large enantiomer-separation factors. Similarly, analogues of 4 were resolved on the CSP derived from (R)-5 (FUSE-3)²⁾ with large enantioseparation factors.

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¹⁾ Chiral stationary phase FUSE-4 was made from an analogue of Betti amine ((2-(Methoxynaphthalen-1-yl)benzylamine) according to an earlier described procedure [15], resolved with D-malic acid [15], and immobilized as carboxamide of 2,2-dimethylpent-4-enoic acid by a previously described method [16].

²⁾ Chiral stationary phase FUSE-3 was prepared from commercially available (+)-(R)-1-(2-Naphthyl)ethylamine (Lancaster) and immobilized as carboxamide of 2,2-dimethylpent-4-enoic acid by a previously described method [15].

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