Fluorescence-Based Screening of Asymmetric Acylation Catalysts through Parallel Enantiomer Analysis. Identification of a Catalyst for Tertiary Alcohol Resolution

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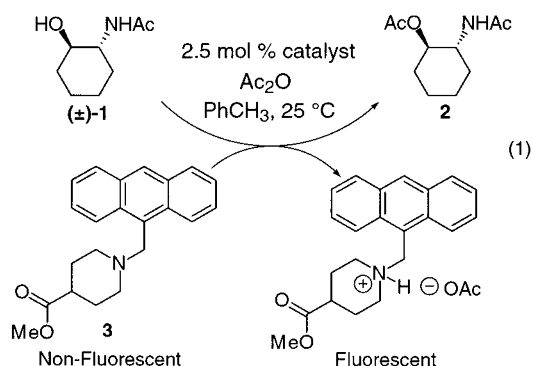
A technique for high-throughput screening of kinetic resolution catalysts is reported. The method relies on carrying simultaneous kinetic resolutions in a multiwell plate format wherein each well contains a unique catalyst and a small amount of a pH-activated fluorescent sensor (**3**). By conducting experiments such that each catalyst is evaluated in parallel in the presence of each isolated enantiomer, an indication of catalyst activity is obtained on a per enantiomer basis. Catalysts that are highly active for one enantiomer but modestly active for another are then reevaluated in conventional kinetic resolutions. From these screens, a highly selective (k_{rel} = 46) pentapeptide (**4**) was obtained for a model secondary alcohol (**1**). In addition, peptide **10** was found to afford excellent selectivities (k_{rel} > 20) for a number of alcohol substrates (**9a**–**9f**) in the traditionally challenging tertiary class.

Techniques that allow for the parallel preparation and simultaneous screening of numerous catalysts have gained particular attention as they promise to facilitate catalyst discovery.[1,2] Research in our laboratory has focused on the discovery of low molecular weight peptides that mimic enantioselective enzymes for use in asymmetric organic synthesis.[3] In particular, peptides containing the nucleophilic *N*-alkylimidazole moiety have been found to function as effective catalysts for the kinetic resolution of certain secondary alcohols.[4] Kinetic resolutions of **1** (eq 1) can be achieved with k_{rel} values > 50



(96% ee for the recovered starting material at 52% conversion).[5] To expand the substrate scope for this catalytic process, we planned high-throughput screens of libraries of potential catalysts. However, our conventional parallel screens were time-consuming because the chiral GC assay that separates both enantiomers of **1** and product **2** requires >30 min/reaction. To accelerate catalyst identification, we developed a fluorescence-based assay for catalyst activity.[6] A fluorescent sensor (**3**) that detects the acid byproduct generated during the reaction is employed as an additive (2.5 mM, 25 mol %). This allows for facile determination of the activity of multiple catalysts simultaneously by performing parallel reactions (in 96-well plates) in a commercially available fluorescence plate reader.

To obtain information concerning relative rates of reaction for two different enantiomers, we perform assays in which each catalyst is screened for reactivity against the isolated, optically pure enantiomers of the starting material. Reetz and co-workers have previously applied an IR thermography assay to isolated enantiomer screens of libraries of enzymatic catalysts with notable success.[7,8] In the present study, we use the fluorescence-based reactivity assay in a spatially segregated enantiomer screen that allows for direct measurement of catalytic rates for the isolated enantiomers. A multiwell plate is divided in half, with one enantiomer deposited in one-half of the wells (e.g., 48 of the wells in a 96-well plate); the other enantiomer is deposited in the remaining wells. A fluorescence plate reader therefore allows a simultaneous determination of the relative rates of 48 catalysts

(1) Jandeleit, B.; Schaefer, D. J.; Powers, T. S.; Turner, H. W.; Weinberg, W. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2494.
(2) For recent reviews of combinatorial catalysis, see: (a) Reetz, M. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 284. (b) Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Curr. Opin. Chem. Biol.* **1999**, *3*, 313. (c) Francis, M. B.; Jamison, T. F.; Jacobsen, E. N. *Curr. Opin. Chem. Biol.* **1998**, *2*, 422.
(3) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Elsevier Science Ltd.: Oxford, 1994.
(4) For reviews of catalytic kinetic resolution, see: (a) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*. 5. (b) Hoveyda, A. H.; Didiuk, M. T. *Curr. Org. Chem.* **1998**, *2*, 537.
(5) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638.
(6) Copeland, G. T.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 4306.
(7) Reetz, M. T.; Becker, M. H.; Kuhling, K. M.; Holzwarth, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2647.
(8) For other reports of combinatorial techniques that allow high-throughput assays for enantioselectivity, see: (a) Korbel, G. A.; Lalic, G.; Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 361. (b) Guo, J.; Wu, J.; Siuzdak, G.; Finn, M. G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1755. (c) Reetz, M. T.; Becker, M. H.; Klein, H.-W.; Stockigt, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1758.

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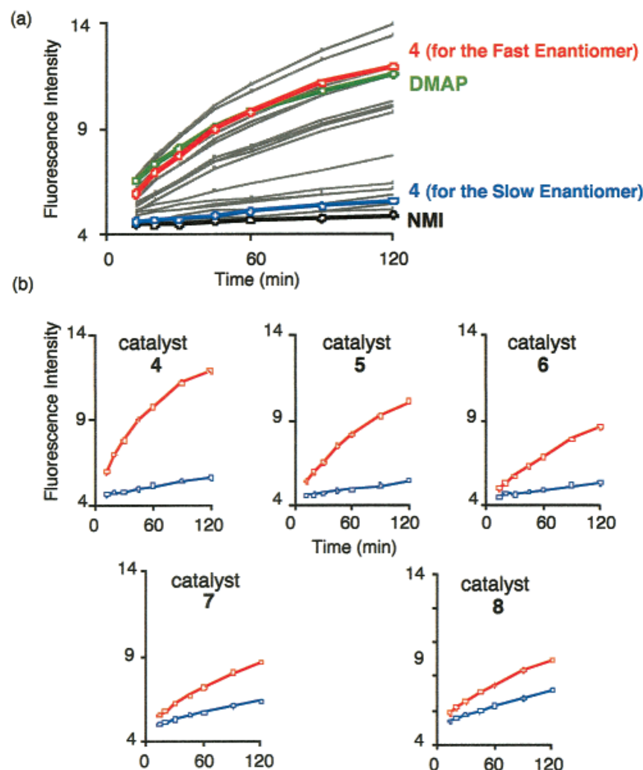


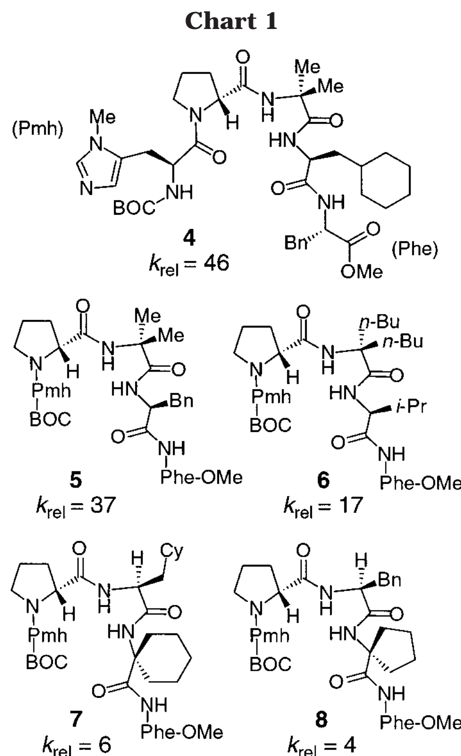
Figure 1. Parallel screen of acylation catalysts for activity and enantioselectivity. (a) Superimposed rate data on a single plot. (*R*,*R*)-**1** denoted (–), (*S*,*S*)-**1** denoted (–). (b) Deconvolution of raw fluorescence data plotted for unique catalysts with respect to reactions of single enantiomers.

simultaneously when a 96-well plate is used (192 catalysts when using a 384-well plate). Direct comparisons thus give a qualitative measure of the relative rates for the reactions of the two enantiomers with a wide variety of catalysts simultaneously.

To validate this approach, a biased library of 60 tetra- and pentapeptides that are capable of adopting β-turns was synthesized in parallel.[9–11] The catalysts were cleaved from the resin, and the unpurified peptides were used directly in screening assays.[12] Substrate **1** was evaluated as a test case. A sample of the data for an individual screen of 60 different catalysts is shown in Figure 1a. The rate profiles of three of the catalysts are shown with bold curves.

Two points merit discussion: (i) The catalytic activities of two control catalysts, *N,N*-(dimethylamino)pyridine (DMAP, green curve) and *N*-methylimidazole (NMI, black curve) parallel their well-established relative activities. (ii) Indexed deposition of peptide catalysts in the various wells allows for identification of those catalysts that afford the greatest rate differences for the two enantiomers of the substrate. For example, the catalyst labeled

Chart 1



4 effects substantially different rates of reaction for the two enantiomers (Chart 1). The rate of the acylation of the (*R*,*R*)-enantiomer (shown in red) is comparable to that of the DMAP-catalyzed control reaction; the reaction of the (*S*,*S*)-enantiomer (shown in blue) proceeds with a rate comparable to that of the NMI-catalyzed reaction. Further deconvolution of the superimposed data is shown in Figure 1b. For example, catalyst **8** affords much less difference in rate for the two enantiomers. The implication is that catalyst **4** will be a selective acylation catalyst in a kinetic resolution performed on the racemate, while catalyst **8** will be substantially less effective.[13] Indeed, rescreening of catalyst **4** with the racemate allows for a rigorous determination of selectivity by conventional chiral gas chromatography; catalyst **4** yields a substantial k_{rel} of 46. Catalyst **8** affords a k_{rel} of 4. The selectivity trends observed in the plate reader assay with other catalysts also correlate well with those observed in conventional GC assays in rescreening experiments. For example, comparison of the fluorescence traces generated with catalysts **4** and **5** suggests that catalyst **5**, while less selective than catalyst **4**, should still exhibit considerable rate differences for the two enantiomers. Indeed, catalyst **5** is appreciably selective, exhibiting a $k_{rel} = 37$. Further decreases in k_{rel} are observed with catalysts **6** and **7**, exhibiting selectivities of 17 and 6, respectively. Data generated in this fashion underscore the subtle factors within peptide structures that impact enantioselectivity.

With the validity of the approach established, we turned our attention toward the resolution of *tertiary* alcohols, a class that, to our knowledge, had been previously unexplored in the area of nonenzymatic asymmetric acylation catalysis.[14] In fact, even biocatalytic resolutions of *tertiary* carbinol centers are traditionally

(9) For this purpose, the library was biased with D-Pro in the *i*+1 position for the majority of the peptides. See: (a) Haque, T. S.; Little, J. C.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 6975. (b) Karle, I. L.; Awasthi, S. K.; Balaram, P. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 8189.

(10) The identity of each catalyst is listed in the Supporting Information.

(11) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17.

(12) Catalyst identities were confirmed by ES/MS. Resynthesis and full characterization of "hit" peptides was subsequently carried out. See Supporting Information for details.

(13) Phenomena such as enantiomer-specific substrate or product inhibition of the catalysts could lead to substantial differences in k_{rel} for reactions performed on racemates vs those conducted on single enantiomers. We have not observed large effects of this nature.

Table 1. Kinetic Resolutions of Tertiary Alcohols with Catalyst 10[a]

Catalyst **10**

Entry	*rac*-Substrate	Temp	k_{rel}[b] (Conv.)
1	**9a**	4 °C	20 (47)
		-23 °C	40 (37)
2	**9b**	4 °C	22 (52)
		-23 °C	>50 (48)
3	**9c**	4 °C	15 (54)
		-23 °C	32 (40)
4	**9d**	4 °C	14 (47)
		-23 °C	40 (35)
5	**9e**	4 °C	20 (51)
		-23 °C	39 (38)
6	**9f**	4 °C	9 (51)[c]
		-23 °C	19 (35)[c]
7	**9g**	25 °C	1 (51)

[a] Reactions were carried out in PhMe (10 mol % of **10**) and were quenched after 3 d. All data represent the average of 2−3 runs per substrate. [b] k_{rel} values determined according to the method of Kagan employing chiral HPLC or GC analyses. The fast-reacting enantiomer is shown (**9a**−**9f**). See Supporting Information for details. [c] Substrate **9f** reacts relatively slowly. These reactions were allowed to stir for 6 d.

difficult (k_{rel} values typically <10).[15,16] Our results with secondary alcohol acylation were promising for this objective since catalytic activities greater than that exhibited by DMAP had been observed, in an enantiomer-specific context.[17] We therefore conducted a screen analogous to that described above for tertiary alcohol substrate **9a**. Evaluation of the data indicated that imidazole-based catalyst **10** would prove to be selective. Indeed, peptide **10** functions in the resolution of **9a** (k_{rel} = 11, 52% conversion) when the reaction is conducted at 25 °C. Conducting reactions at lower temperatures resulted in enhanced k_{rel} values for **9a** and a range of other tertiary alcohol substrates (Table 1). For example, catalyst **10** affords k_{rel} = 20 and 40 for substrate **9a** at 4 and −23 °C, respectively (entry 1). Reaction rates are slow relative to those observed for secondary alcohols. Nevertheless, conversions of ~40−50% can be achieved for this and other tertiary alcohols within 72 h. *p*-Methyl-substituted substrate **9b** may be resolved with k_{rel} = 22 at 4 °C; selectivity is improved to k_{rel} > 50 at −23 °C (entry 2). *p*-Nitro-substituted substrate **9c** undergoes resolution with k_{rel} = 32 (entry 3, −23 °C). Naphthyl-substituted substrate **9d** affords a higher k_{rel} of 40 under these conditions (entry 4). Tetrahydronaphthalene **9e** is also a good substrate for catalyst **10**, undergoing resolution with k_{rel} = 39 at low temperature (entry 5). Cyclohexyl-bearing substrate **9f** undergoes kinetic resolution at a slower rate. Nevertheless, k_{rel} = 19 is observed at 35% conversion after reaction at −23 °C for 6 d (entry 6). Electron-withdrawing substituents appear to have a deleterious effect on resolution efficiency with catalyst **10**: ester-substituted substrate **9g** undergoes acylation without enantioselectivity under a variety of conditions (entry 7). This latter result emphasizes that a fully general catalyst remains an elusive goal.[18]

In summary, using a parallel enantiomer screening assay we have found a pentapeptide catalyst that enables nonenzymatic kinetic resolution of a number of tertiary alcohols. Such techniques may prove useful for the rapid identification of catalysts for the resolution of other alcohol classes that synthetic chemists may wish to resolve, including traditionally difficult substrates, such as tertiary alcohols.

Experimental Section

General Procedures. Proton NMR spectra were recorded on 400 or 300 NMR spectrometers. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.0) or with the solvent reference relative to TMS

(14) For a review, see: (a) Spivey, A. C.; Maddaford, A.; Redgrave, A. J. *Org. Prep. Proced. Int.* **2000**, *32*, 331. For lead references, see: (b) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813. (c) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412. (d) Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154. (e) Sano, T.; Miyata, H.; Oriyama, T. *Enantiomer* **2000**, *5*, 119.

(15) (a) O'Hagan, D.; Zaidi, N. A. *Tetrahedron: Asymmetry* **1994**, *5*, 1111. (b) Franssen, M. C. R.; Goetheer, E. L. V.; Jongenjan, H.; deGroot, A. *Tetrahedron Lett.* **1998**, *39*, 8345. (c) Brackenridge, I.; McCague, R.; Roberts, S. M.; Turner, N. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1093.

(16) A notable exception is the application of retroaldolase catalytic antibodies reported by Lerner and co-workers. List, B.; Shabat, D.; Zhong, G.; Turner, J. M.; Li, A.; Bui, T.; Anderson, J.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **1999**, *121*, 7283.

(17) DMAP is well-known to catalyze the acylation of tertiary alcohols, while NMI is notably less effective. (a) Guibe-Jampel, E.; Bram, G.; Vilkas, M. *Bull. Soc. Chim. Fr.* **1973**, 1021. (b) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

(18) A pentapeptide library (75 members, randomly chosen from a theoretical library size of 8192) that contained no β-turn bias was prepared to evaluate the role of the turn element. Each of the catalysts from this library that was tested exhibited k_{rel} < 2.0 (attempted resolution of **9a**). See Supporting Information for details.

employed as the internal standard ($CDCl_3$, δ 7.26 ppm; d_6-DMSO, δ 2.50; C_6D_6, δ 7.16 ppm). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants [Hz], integration). Carbon NMR spectra were recorded on 400 (100 MHz) or 300 (75 MHz) spectrometers with complete proton decoupling. Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, δ 77.0). NMR data were collected at ambient temperature, unless otherwise indicated. Infrared spectra were obtained on a FT-IR spectrometer. Analytical thin-layer chromatography (TLC) was performed using slica gel 60 Å F254 precoated plates (0.25 mm thickness). TLC R_f values are reported. Visualization was accomplished by irradiation with a UV lamp and/or staining with $KMnO_4$ or ceric ammonium molybdate (CAM) solutions. Flash column chromatography was performed using silica gel 60 Å (32−63 μm). Optical rotations were recorded at the sodium D line (path length 50 mm). Elemental analyses were performed by Robertson Microlit (Madison, NJ). High-resolution mass spectra were obtained at the Mass Spectrometry Facilities of either the University of Illinois (Urbana−Champaign, IL) or Boston College (Chestnut Hill, MA). The method of ionization is given in parentheses.

Analytical GC was performed by employing a flame ionization detector and the column specified in the individual experimental. Analytical and preparative reverse phase HPLC were performed with a single wavelength UV detector (214 nm). Analytical normal phase HPLC was performed on a chromatograph equipped with a diode array detector (214 and 254 nm). Fluorescence measurements were obtained using a Perkin-Elmer Wallac Victor F fluorescence reader equipped with a 380−15 nm band-pass excitation filter and a 420 nm long-pass emission filter.

All reactions were carried out under an argon atmosphere employing oven- and flame-dried glassware. All solvents were distilled from appropriate drying agents prior to use. Acetic anhydride was distilled prior to use and stored in a Schlenk tube for no more than 1 week. Racemic *trans*-2-acetamidocyclohexanol **1** was prepared according to the method of Hawkins.[19] Optically pure **1** was prepared via kinetic resolution of the racemic substrate utilizing peptidic acyl transfer catalysts as previously reported.[20] Racemic substrates **9a**−**f** were prepared via the corresponding epoxides[21] according to the method of Hawkins[22] or the method of Guy.[23] Substrate **9g** was prepared according to the method of Simona.[24] Optically pure **9a** was prepared according to the method of Sharpless.[25] Stereochemical assignments/proofs of absolute stereochemistry for **9a**, **9d**, and **9f** are described below. Assignments for **9b**, **9c**, and **9e** were made by analogy.

Library Synthesis. Peptides were synthesized on the solid support using commercially available Wang polystyrene resin preloaded with the appropriate amino acid (Advanced ChemTech). Couplings were performed using 4 equiv of amino acid derivative, 4 equiv of HBTU, and 8 equiv of Hunig's base in DMF, for 3 h. Deprotections were performed using 20% piperidine in DMF for 20 min (to minimize diketopiperazine formation, dipeptides were deprotected using 50% piperidine in DMF for 5 min). Peptides were cleaved from solid support using a mixture of MeOH:DMF:NEt_3 (9:1:1) for 4 days. The peptides were characterized by electrospray mass spectrometry and used in single enantiomer assays without further purification. Peptides which proved selective for resolution were purified by reverse phase HPLC techniques. Preparative HPLC was performed using a reverse phase RP-18 X Terra (Waters) column, eluting with 65−75% methanol in water, at a flow rate of 6 mL/min. The purity was checked by analytical HPLC under similar conditions, and the peptides were characterized by ^1H NMR and electrospray mass spectrometry. Data for peptides **4** and **10** follow. Representative data for the other peptides may be found in the Supporting Information.

Peptide 4. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.56 (broad s, 1H), 7.37 (broad d, J = 9.5 Hz, 1H), 7.29−7.20 (m, 5H), 6.92 (broad s, 1H), 6.89 (broad d, J = 6.2 Hz, 1H), 6.61 (broad d, J = 9.9 Hz, 1H), 6.29 (broad s, 1H), 4.80 (dd, J = 5.8 Hz, 13.3 Hz, 1H), 4.62 (dd, J = 8.1 Hz, 14.9 Hz, 1H), 4.47 (dd, J = 8.7 Hz, 14.8 Hz, 1H), 4.05 (t, J = 6.6 Hz, 1H), 3.69 (s, 3H), 3.63 (s, 3H), 3.57 (m, 1H), 3.41 (m, 1H), 3.21 (overlapping dd and m, J = 4.9 Hz, 13.7 Hz, 2H), 3.08 (dd, J = 6.6 Hz, 13.5 Hz, 1H), 2.94 (dd, J = 5.2 Hz, 14.4 Hz, 1H), 2.07 (m, 1H), 2.01 (m, 1H), 1.87 (m, 2H), 1.76−1.62 (m, 3H), 1.48 (s, 3H), 1.42 (s, 9H), 1.35−1.12 (overlapping s and m, 7H), 0.95 (m, 2H), 0.88 (m, 4H); TLC R_f 0.26 (8% MeOH/CH_2Cl_2). Exact mass calcd for $[C_{40}H_{59}N_7O_8 + H]^+$ requires m/z 766.4503. Found 766.4502 (ES+). Analytical HPLC. Purity of peptide **4** was assayed using a reverse phase RP-18 X Terra (Waters) column. Conditions: isocratic elution with 60% methanol in water, at a flow rate of 0.2 mL/min. Retention time = 2.63 min.

Peptide 10. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.38 (broad s, 1H), 7.30−7.16 (m, 6H), 6.84 (broad s, 1H), 6.72 (broad d, J = 8.1 Hz, 1H), 6.54 (broad d, J = 8.8 Hz, 1H), 6.37 (broad s, 1H), 4.86 (dd, J = 5.6 Hz, 14.0 Hz, 1H), 4.63 (m, 1H), 4.23 (m, 1H), 4.16 (t, J = 8.6 Hz, 1H), 3.66 (s, 3H), 3.65 (overlapping s and m, 4H), 3.29 (m, 1H), 3.12 (m, 3H), 2.96 (dd, J = 5.7 Hz, 14.8 Hz, 1H), 2.30 (broad d, J = 13.6 Hz, 1H), 2.09 (m, 2H), 2.01−1.93 (m, 3H), 1.84 (m, 2H), 1.76−1.47 (m, 7H), 1.42 (s, 9H), 1.34−1.02 (m, 7H), 1.01−0.80 (m, 3H); TLC R_f 0.32 (8% MeOH/CH_2Cl_2). Exact mass calcd for $[C_{42}H_{61}N_7O_8 + H]^+$ requires m/z 792.4660. Found 792.4659 (ES+). Analytical HPLC. Purity of peptide **10** was assayed using a reverse phase RP-18 X Terra (Waters) column. Conditions: isocratic elution with 60% methanol in water, at a flow rate of 0.2 mL/min. Retention time = 5.95 min.

Screening Experiments. The optimized conditions for the single enantiomer fluorescence assays are exemplified by the following experimental protocol for alcohol **1**. Each catalyst to be screened was dissolved in CH_2Cl_2, and an aliquot (10 μL, 0.125 μmol, 2.5 mol %) was delivered to each of two vials. A stock solution of each enantiomer of substrate **1** in 2:7 CH_2Cl_2:toluene was prepared, and an aliquot (0.45 mL, 0.0050 mmol) of the appropriate enantiomer was distributed to each vial. An aliquot of a solution of sensor **3** and acetic anhydride in toluene was added to each vial (40 μL, 0.00125 mmol sensor, 0.025 mmol acetic anhydride). The vials were capped and agitated at room temperature. Aliquots (50 μL) of the reaction mixtures were sampled into a custom-made 384-well black Teflon plate, and fluorescence measurements were taken at appropriate time intervals. Promising catalysts were chosen by examining first the rate of reaction of the slower enantiomer (giving preference to catalysts which showed reactivity in the same range as NMI) and second the difference in rate of reaction of the two enantiomers.

Single Enantiomer Fluorescence Assays of Reaction of Alcohol 9a. Reactions were performed in the same manner as for alcohol **1**. Each catalyst to be screened was dissolved in CH_2Cl_2, and an aliquot (10 mL, 0.00075 mmol, 10 mol %) was delivered to each of two vials. Stock solutions of each enantiomer of substrate **9a** in 2:3 CH_2Cl_2:toluene were prepared, and an aliquot (0.45 mL, 0.0075 mmol) of the appropriate enantiomer was distributed to each vial. An aliquot of a solution of sensor **3** and acetic anhydride in toluene was added to each vial (40 μL, 0.00125 mmol of sensor, 0.375 mmol of acetic anhydride). The vials were capped and agitated at room temperature. Fluorescence measurements were taken as with alcohol **1**.

Kinetic Resolutions. Standard Conditions for Resolution of Substrate 1. Alcohol (±)-**1** (21.0 mg, 0.133 mmol) was

(19) Hawkins, L. R.; Bannard, R. A. B. *Can. J. Chem.* **1958**, *36*, 220.
(20) Reference 5.
(21) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
(22) Reference 19.
(23) Guy, A.; Doussot, J.; Ferroud, C.; Garreau, R.; Godefroy-Falguieres, A. *Synthesis* **1992**, *9*, 821.
(24) Simona, D.; Invidiata, F. P.; Manfredini, S.; Ferroni, R.; Lampronti, I.; Roberti, M.; Pollini, G. P. *Tetrahedron Lett.* **1997**, *38*, 2749.
(25) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (b) Fleming, P. R.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 2869.

dissolved in 22.2 mL of toluene. This stock solution was distributed in 1.0 mL aliquots to reaction vessels containing peptide catalysts (0.00015 mmol in 10 mL of CH_2Cl_2). A solution of acetic anhydride in toluene (40 μL, 0.024 mmol) was then introduced. The reactions were allowed to stir at room temperature. Aliquots were removed, quenched with methanol, and directly assayed by chiral GC analysis to determine k_{rel} values as previously reported.[26]

Standard Conditions for Resolution of Substrate 9a. Alcohol (±)-**9a** (17 mg, 0.088 mmol) was dissolved in 2.3 mL of CH_2Cl_2, and 3.5 mL toluene was added. This stock solution was distributed in 1.0 mL aliquots to reaction vessels containing peptide catalysts (0.0015 mmol in 20 μL of CH_2Cl_2). Acetic anhydride (70.8 μL, 0.75 mmol) and triethylamine (42 μL, 0.30 mmol) were then introduced. The reactions were allowed to stir at room temperature. Aliquots were removed and quenched with methanol, and solvent and amine were removed in vacuo. The residue was dissolved in 10% 2-propanol in hexanes and assayed by chiral HPLC analysis to determine k_{rel} values as above.

Standard Conditions for Resolution of Substrates with Product Isolation. Alcohol (±)-**9d** (46 mg, 0.189 mmol) was dissolved in 4.8 mL of CH_2Cl_2, and 7.6 mL of toluene was added. A solution of peptide catalyst **10** (15 mg, 0.0189 mmol in 250 μL of CH_2Cl_2) was added. The mixture was stirred and cooled to −20 °C. Acetic anhydride (895 μL, 9.47 mmol) and triethylamine (534 μL, 3.79 mmol) were then introduced. Reaction progress was monitored by chiral HPLC analysis as described in standard runs. After 82 h, methanol (5 mL) was added and the reaction mixture was concentrated in vacuo. The residue was purified by silica gel flash column chromatography (0.25−4% MeOH/CH_2Cl_2) to give **9d-Ac** (18 mg, 93% ee), recovered **9d** (30 mg, 35% ee), and recovered catalyst **10** (11 mg).

Substrate 9a. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, J = 7.0 Hz, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.27 (t, J = 8.4 Hz, 1H), 5.70 (broad s, 1H), 3.74 (dd, J = 14.1 Hz, 6.8 Hz, 1H), 3.40 (dd, 13.9 Hz, 5.1 Hz, 1H), 3.38 (s, 1H), 1.95 (s, 3H), 1.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6, 145.4, 128.1, 126.8, 124.8, 74.7, 51.2, 27.9, 23.1; IR (film, cm^{-1}) 3409, 3315, 3089, 3061, 2977, 2928, 1648; TLC R_f 0.31 (4% methanol/CH_2Cl_2); $[\alpha]_D$ −38.2 (c 1.0, CH_2Cl_2, at 49% ee). Anal. Calcd for $C_{11}H_{15}N_1O_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.15; H, 7.93; N, 7.14. Exact mass calcd for $[C_{11}H_{15}N_1O_2]^+$ requires m/z 193.1103. Found 193.1108 (EI+).

Product 9a-Ac. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (m, 5H), 5.90 (broad s, 1H), 3.78 (dd, J = 14.5 Hz, 6.8 Hz, 1H), 3.64 (dd, J = 14.3 Hz, 5.5 Hz, 1H), 2.11 (s, 3H), 1.96 (s, 3H), 1.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 169.5, 141.8, 128.4, 127.4, 124.5, 83.6, 49.3, 23.4, 22.3; IR (film, cm^{-1}) 3390, 3301, 1738, 1659; TLC R_f 0.35 (4% methanol/CH_2Cl_2); $[\alpha]_D$ −17.6 (c 1.0, CH_2Cl_2, at 96% ee). Anal. Calcd for $C_{13}H_{17}N_1O_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.16; H, 7.34; N, 5.69. Exact mass calcd for $[C_{13}H_{17}N_1O_3]^+$ requires m/z 235.1208. Found 235.1206 (EI+).

Assay of Enantiomeric Purity. Enantiomers of product **9-Ac** were separated by chiral HPLC employing a Chiracel OJ column (Alltech), eluting at a flow rate of 1 mL/min with the following gradient: 15% 2-propanol/hexanes for 5 min, ramp to 30% 2-propanol/hexanes over 7 min, hold until 50 min. Retention times: **9a**, $R_{t(S)}$ = 6.3 min; $R_{t(R)}$ = 7.9 min. Retention rimes: **9a-Ac**, $R_{t(S)}$ = 21.4 min; $R_{t(R)}$ = 40.3 min. Product **9a-Ac** was obtained with 96% ee; recovered **9a** was produced with 49% ee (33% conversion).

Proof of Absolute Stereochemistry for 9a. Recovered starting material was compared to authentic (R)-**9a** prepared according to the method of Sharpless.[27] Asymmetric dihydroxylation of 2-phenylpropene[25a] was followed by conversion to the azido alcohol.[25b] Hydrogenation and acetylation provided (R)-**9a** that was found to exhibit $[\alpha]_D$ = −82.8 (c 1.0, CH_2Cl_2 at 95% ee). Recovered starting material **9a** from kinetic resolution with catalyst **10**: $[\alpha]_D$ = −38.2 (c 1.0, CH_2Cl_2, at 49% ee).

Substrate 9b. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 6.10 (broad s, 1H), 3.80 (broad s, 1H), 3.65 (dd, J = 13.9 Hz, 6.6 Hz, 1H), 3.39 (dd, J = 14.1 Hz, 5.3 Hz, 1H), 2.33 (s, 3H), 1.90 (s, 3H), 1.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 142.5, 136.4, 128.8, 124.7, 74.6, 51.1, 27.9, 23.1, 21.0; IR (film, cm^{-1}) 3316, 3096, 3026, 2980, 2925, 1656; TLC R_f 0.33 (6% methanol/CH_2Cl_2); $[\alpha]_D$ −43.6 (c 1.0, $CHCl_3$, at 88% ee). Anal. Calcd for $C_{12}H_{17}N_1O_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.60; H, 8.13; N, 6.50. Exact mass calcd for $[C_{12}H_{17}N_1O_2 + H]^+$ requires m/z 208.1338. Found 208.1337 (FAB+).

Product 9b-Ac. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.17 (m, 4H), 5.83 (broad s, 1H), 3.77 (dd, J = 14.3 Hz, 7.0 Hz, 1H), 3.63 (dd, J = 14.3 Hz, 5.5 Hz, 1H), 2.33 (s, 3H), 2.09 (s, 3H), 1.96 (s, 3H), 1.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7, 169.5, 138.8, 137.0, 129.0, 124.4, 83.6, 49.3, 23.4, 23.3, 22.3, 21.2; IR (film, cm^{-1}) 3308, 3063, 2986, 2986, 1739, 1659; TLC R_f 0.32 (6% methanol/CH_2Cl_2); $[\alpha]_D$ −27.2 (c 1.0, $CHCl_3$, at 91% ee). Anal. Calcd for $C_{14}H_{19}N_1O_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.16; H, 7.34; N, 5.69. Exact mass calcd for $[C_{14}H_{19}N_1O_3 + H]^+$ requires m/z 272.1263. Found 272.1266 (ESI+).

Assay of Enantiomeric Purity. Enantiomers of product **9b-Ac** were separated by chiral HPLC employing a Chiracel OD column (Alltech), eluting with 5% 2-propanol/hexanes at a flow rate of 1.0 mL/min and a temperature of 10 °C. Retention times: **9b**, $R_{t(R)}$ = 22.9 min; $R_{t(S)}$ = 28.3 min. Retention times: **9b-Ac**, $R_{t(S)}$ = 32.4 min; $R_{t(R)}$ = 37.3 min. Product **9b-Ac** was obtained with 91% ee. Recovered **9b** was produced with 83% ee (45% conversion).

Substrate 9c. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.1 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 9.1 Hz, 2H), 5.75 (broad s, 1H), 4.28 (broad s, 1H), 3.73 (dd, J = 14.3 Hz, 6.2 Hz, 1H), 3.47 (dd, J = 14.3 Hz, 6.2 Hz, 1H), 1.95 (s, 3H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3, 153.1, 146.6, 126.1, 123.3, 75.3, 51.5, 28.0, 23.0; IR (film, cm^{-1}) 3385, 3316, 3114, 3083, 2978, 2932, 1652; TLC R_f 0.143 (4% methanol/CH_2Cl_2); $[\alpha]_D$ −39.6 (c 1.0, CH_2Cl_2, at 47% ee). Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.34; H, 5.82; N, 11.79. Exact mass calcd for $[C_{11}H_{14}N_2O_4 + H]^+$ requires m/z 239.1032. Found 239.1033 (EI+).

Product 9c-Ac. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.21 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 8.3 Hz, 2H), 5.91 (broad s, 1H), 3.79 (dd, J = 14.4 Hz, 6.6 Hz, 1H), 3.67 (dd, J = 14.6 Hz, 5.8 Hz, 1H), 2.15 (s, 3H), 1.98 (s, 3H), 1.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.0, 169.6, 149.3, 147.2, 125.8, 123.7, 83.2, 48.9, 23.2 (2C), 21.9; IR (film, cm^{-1}) 3396, 3301, 3083, 2989, 2935, 1742, 1662; TLC R_f 0.32 (4% methanol/CH_2Cl_2); $[\alpha]_D$ −40.0 (c 0.58, CH_2Cl_2, at 96% ee). Anal. Calcd for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.71; H, 5.68; N, 10.07. Exact mass calcd for $[C_{13}H_{16}N_2O_5 + H]^+$ requires m/z 281.1137. Found 281.1137 (EI+).

Assay of Enantiomeric Purity. Enantiomers of starting material **9c** were separated by chiral HPLC employing a Chiracel OB-H column (Alltech), eluting with 10% 2-propanol/hexanes at a flow rate of 1.0 mL/min. Retention times: **9c**, $R_{t(S)}$ = 33.9 min; $R_{t(R)}$ = 39.8 min. Enantiomers of product **9c-Ac** were separated by chiral HPLC employing a Chiracel AD column (Alltech), eluting with 9% 2-propanol/hexanes at a flow rate of 1.0 mL/min. Retention times: **9c-Ac**, $R_{t(R)}$ = 23.9 min; $R_{t(S)}$ = 25.9 min. Product **9c-Ac** was obtained with 96% ee. Recovered **9c** was produced with 47% ee (33% conversion).

Substrate 9d. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (s, 1H), 7.85−7.82 (m, 3H), 7.52−7.46 (m, 3H), 5.76 (broad s, 1H), 3.83 (dd, J = 14.1 Hz, 6.8 Hz, 1H), 3.72 (broad s, 1H), 3.50 (d, J = 14.1 Hz, 5.3 Hz, 1H), 1.90 (s, 3H), 1.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.7, 142.8, 133.0, 132.3, 128.1, 128.0, 127.4, 126.1, 125.8, 123.7, 123.2, 75.2, 51.4, 28.2, 23.2; IR (film, cm^{-1}) 3317, 3061, 2976, 2928, 1656; TLC R_f 0.16 (4% methanol/CH_2Cl_2); $[\alpha]_D$ +3.4 (c 1.0, EtOH, at 35% ee). Anal. Calcd for $C_{15}H_{17}N_1O_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.86; H,

(26) (a) S values were calculated according to the method of Kagan. See: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249. (b) See also: ref 5.
(27) See ref 25.

6.79; N, 5.76. Exact mass calcd for $[C_{15}H_{17}N_1O_2 + Na]^+$ requires *m/z* 266.1157. Found 266.1150 (ESI+).

Product 9d-Ac. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85−7.80 (m, 3H), 7.75 (s, 1H), 7.51−7.45 (m, 2H), 7.41 (d, J = 8.8 Hz, 1H), 5.94 (br s, 1H), 3.87 (dd, J = 14.3 Hz, 6.6 Hz, 1H), 3.77 (dd, J = 14.3 Hz, 5.5 Hz, 1H), 2.16 (s, 3H), 1.96 (s, 3H), 1.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9, 169.5, 139.2, 132.8, 132.4, 128.2, 128.0, 127.3, 126.2, 126.0, 123.6, 122.4, 83.7, 49.1, 23.4, 23.3, 22.3; IR (film, cm^{-1}) 3302, 3060, 2986, 2935, 1736, 1655; TLC R_f 0.28 (4% methanol/CH_2Cl_2); $[\alpha]_D$ −15.3 (*c* 0.67, EtOH, at 86% ee). Anal. Calcd for $C_{17}H_{19}N_1O_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.17; H, 6.43; N, 4.71. Exact mass calcd for $[C_{17}H_{19}N_1O_3 + Na]^+$ requires *m/z* 308.1263. Found 308.1258 (ESI+).

Assay of Enantiomeric Purity. Enantiomers of product **9d-Ac** were separated by chiral HPLC employing a Chiracel OJ column (Alltech), eluting at a flow rate of 1.0 mL/min with the following gradient: 12% 2-propanol/hexanes for 23 min, ramp to 20% 2-propanol/hexanes over 2 min, hold until 105 min. Retention times: **9d**, $R_{t(S)}$ = 15.3 min; $R_{t(R)}$ = 17.5 min. Retention times: **9d-Ac**, $R_{t(S)}$ = 34.0 min; $R_{t(R)}$ = 90.6 min. Product **9d-Ac** was obtained with 35% ee. Recovered **9d** was produced with 86% ee (29% conversion).

Proof of Absolute Stereochemistry for 9d: recovered starting material as compared to authentic (*R*)-**9d** prepared in analogy to the method employed for substrate **9a**. Authentic (*R*)-**9d** was found to exhibit $[\alpha]_D$ +10.3 (*c* 1.0, EtOH, at 97% ee). Recovered starting material **9d** from kinetic resolution with catalyst **10**: $[\alpha]_D$ = +3.4 (*c* 1.0, EtOH, at 35% ee).

Substrate 9e. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.14 (d, J = 9.5 Hz, 2H), 7.05 (d, J = 7.7 Hz, 1H), 5.78 (broad s, 1H), 3.74 (dd, J = 14.1 Hz, 7.1 Hz, 1H), 3.36 (dd, J = 13.9 Hz, 5.1 Hz, 1H), 3.17 (s, 1H), 2.76 (broad m, 4H), 1.96, (s, 3H), 1.80 (broad s, 4H), 1.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4, 142.5, 136.9, 135.7, 128.9, 125.4, 121.8, 74.6, 51.5, 29.7, 29.1, 28.0, 23.3 (2C), 23.2; IR (film, cm^{-1}) 3314, 3094, 2976, 2928, 2857, 1650; TLC R_f 0.26 (6% MeOH/CH_2Cl_2); $[\alpha]_D$ −29.0 (*c* 1.0 $CHCl_3$, at 40% ee). Anal. Calcd for $C_{15}H_{21}N_1O_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.61; H, 8.23; N, 5.45. Exact mass calcd for $[C_{15}H_{21}N_1O_2 + Na]^+$ requires *m/z* 270.1470. Found 270.1465 (ESI+).

Product 9e-Ac. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.00 (m, 3H), 5.87 (broad s, 1H), 3.77 (dd, J = 14.3 Hz, 7.0 Hz, 1H), 3.60 (dd, J = 14.3 Hz, 5.5 Hz, 1H), 2.74 (broad m, 4H), 2.10 (s, 3H), 1.98 (s, 3H), 1.78 (broad s, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 169.6, 138.8, 137.1, 136.4, 129.1, 125.2, 121.6, 83.6, 49.4, 29.7, 29.1, 23.5, 23.4, 23.2 (2C), 22.4; IR (film, cm^{-1}) 3305, 3081, 2986, 2928, 2859, 1736, 1656; TLC R_f 0.34 (6% MeOH/CH_2Cl_2); $[\alpha]_D$ −25.0 (*c* 1.0, $CHCl_3$, at 89% ee). Anal. Calcd for $C_{17}H_{23}N_1O_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.48; H, 7.95; N, 4.92. Exact mass calcd for $[C_{17}H_{23}N_1O_3 + Na]^+$ requires *m/z* 312.1576. Found 312.1573 (ESI+).

Assay of Enantiomeric Purity. Enantiomers of product **9e-Ac** were separated by chiral HPLC employing a Chiracel OJ column (Alltech), eluting at a flow rate of 1 mL/min with the following gradient: 3% 2-propanol/hexanes for 54 min, ramp to 10% 2-propanol/hexanes over 1.5 min, hold until 70 min. Retention times: **9e**, $R_{t(R)}$ = 29.0 min; $R_{t(S)}$ = 31.5 min. Retention times: **9e-Ac**, $R_{t(S)}$ = 52.3 min; $R_{t(R)}$ = 63.0 min. Product **9e-Ac** was obtained with 89% ee. Recovered **9e** was produced with 40% ee (30% conversion).

Substrate 9f. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.21 (broad s, 1H); 3.33 (dd, J = 13.9 Hz, 6.6 Hz, 1H), 3.24 (dd, J = 13.6 Hz, 5.1 Hz, 1H), 2.69 (s, 1H), 2.03 (s, 3H), 1.87−1.67 (broad m, 5H), 1.36 (m, 1H), 1.25−0.96 (broad m, 5H), 1.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 74.6, 47.7, 46.5, 27.9, 26.8 (2C), 26.7, 26.5, 23.4, 21.6; IR (film, cm^{-1}) 3308, 3093, 2973, 2925, 2852, 1650; TLC R_f 0.08 (4% MeOH/CH_2Cl_2); $[\alpha]_D$ +1.6 (*c* 2.5, $CHCl_3$, at 48% ee). Anal. Calcd for $C_{11}H_{21}N_1O_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.16; H, 10.38; N, 6.91. Exact mass calcd for $[C_{11}H_{21}N_1O_2 + Na]^+$ requires *m/z* 222.1470. Found 222.1465 (ESI+).

Product 9f-Ac. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.56 (broad s, 1H), 3.75 (dd, J = 14.8 Hz, 7.1 Hz, 1H), 3.45 (dd, J = 14.9 Hz, 4.9 Hz, 1H), 2.04 (s, 3H), 2.01, (s, 3H), 1.95 (m, 1H), 1.78 (broad m, 2H), 1.69 (broad m, 3H), 1.29 (s, 3H), 1.25−1.00 (broad m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 169.8, 87.6, 45.0, 44.1, 27.5, 27.0, 26.6, 26.5 (2C), 23.6, 22.4, 19.5; IR (film, cm^{-1}) 3295, 3090, 2929, 2856, 1727, 1654; TLC R_f 0.15 (4% MeOH/CH_2Cl_2); $[\alpha]_D$ +9.2 (*c* 1.0, $CHCl_3$, at 88% ee). Anal. Calcd for $C_{13}H_{23}N_1O_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.68; H, 9.45; N, 5.56. Exact mass calcd for $[C_{13}H_{23}N_1O_3 + Na]^+$ requires *m/z* 264.1576. Found 264.1576 (ESI+).

Assay of Enantiomeric Purity. Enantiomers of product **9f-Ac** were separated by chiral GC employing a 40 m CHIRALDEX B-DM column (Advanced Separation Technologies, Inc.) connected in-line to a 30 m achiral precolumn (HP-5, Hewlett-Packard), with a He pressure of 40 psi at the following temperature gradient: 150 °C for 25 min, followed by a 2 min ramp to 120 °C for 45 min followed by a 1 min ramp to 135 °C for 15 min, followed by an additional 1 min ramp to 145 °C for 45 min Retention times: **9e**, $R_{t(S)}$ = 105.0 min; $R_{t(R)}$ = 109.4 min. Retention times: **9f-Ac**, $R_{t(R)}$ = 76.6 min; $R_{t(S)}$ = 78.3 min. Product **9f-Ac** was obtained with 88% ee. Recovered **9f** was produced with 48% ee (35% conversion).

Proof of Absolute Stereochemistry for 9f. Recovered starting material was compared to authentic (*S*)-**9f** prepared according to the method of Jacobsen[28] that was found to exhibit: $[\alpha]_D$ = −3.2 (*c* 2.8, $CHCl_3$, at >99% ee). Recovered starting material **9f** from the kinetic resolution with catalyst **10**: $[\alpha]_D$ +1.6 (*c* 2.5, $CHCl_3$, at 48% ee).

Substrate 9g. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 (d, J = 8.1 Hz, 2H), 7.36 (m, 3H), 5.92 (broad s, 1H), 4.50 (s, 1H), 4.22 (dd, J = 13.9 Hz, 7.0 Hz, 1H), 3.79 (s, 3H), 3.62 (dd, J = 13.9 Hz, 4.8 Hz, 1H), 1.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.6, 171.0, 138.7, 128.2, 125.2, 78.7, 53.3, 47.6, 23.0; IR (film, cm^{-1}) 3308, 3066, 2951, 1734, 1655; TLC R_f 0.06 (2% MeOH/CH_2Cl_2). Anal. Calcd for $C_{12}H_{15}N_1O_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.69; H, 6.23; N, 5.80. Exact mass calcd for $[C_{12}H_{15}N_1O_4 + Na]^+$ requires *m/z* 260.0899. Found 260.0898 (ESI+).

Product 9g-Ac. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (m, 2H), 7.37 (m, 3H), 5.58 (broad s, 1H), 4.41 (dd, J = 14.6 Hz, 7.3 Hz, 1H), 3.94 (dd, J = 14.6 Hz, 5.5 Hz, 1H), 3.71 (s, 3H), 2.21 (s, 3H), 1.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.0, 169.8, 169.7, 135.6, 128.6, 128.6, 124.9, 82.4, 52.8, 44.1, 23.2, 21.2; IR (film, cm^{-1}) 3393, 3298, 3071, 3028, 2956, 1742, 1659; TLC R_f 0.14 (2% MeOH/CH_2Cl_2). Anal. Calcd for $C_{14}H_{17}N_1O_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.01; H, 5.90; N, 4.87. Exact mass calcd for $[C_{14}H_{17}N_1O_5 + Na]^+$ requires *m/z* 302.1004. Found 302.1004. (ESI+).

Assay of Enantiomeric Purity. Enantiomers of product **9g-Ac** were separated by chiral HPLC employing a Chiracel AD column (Alltech), eluting with 4% 2-propanol/hexanes at a flow rate of 0.8 mL/min. Retention times: **9g**, R_t = 68.6 min; R_t = 78.0 min. Retention times: **9g-Ac**, R_t = 52.7 min; R_t = 62.6 min.

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