JOC The Journal of Organic Chemistry

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Diastereo- and Enantioselective Three-Component Coupling Approach to Highly Substituted Pyrrolidines

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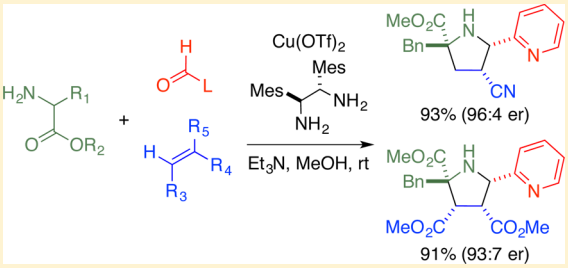
Supporting Information

ABSTRACT: The enantioselective synthesis of substituted pyrrolidines through a mild Lewis-acid catalyzed three-component coupling reaction between picolinaldehyde, amino acids, and activated olefins is reported. The reaction uses low catalyst loadings of commercially available chiral diamines and copper triflate proposed to self-assemble in conjunction with the chelating aldehydes, 4-substituted-2-picolinaldehydes or 4-methylthiazole-2-carboxaldehyde, to generate a catalyst complex. A model is provided to explain how this complex directs enantioselectivity. This work represents a significant advance in the ease, scope, and cost of producing highly substituted, enantioenriched pyrrolidines.



The direct and inexpensive construction of substituted heterocycles is critical to pharmaceutical development and discovery. Syntheses of pyrrolidines are particularly desirable due to their prevalence in pharmaceuticals and biologically active natural products (Figure 1).[1−5] Consistent with their

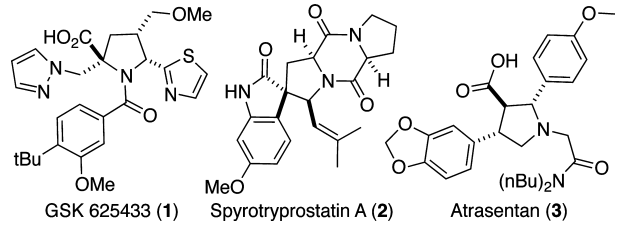


Figure 1. Representative biologically active pyrrolidines.

significance, numerous strategies toward their synthesis have been reported,[6−14] the most common of which involve 1,3-dipolar cycloadditions that generate them in a convergent and stereoselective manner.[15−27] Enantioselective syntheses using 1,3-dipolar cycloadditions were first established using chiral auxiliaries,[28] but the past decade has seen remarkable advances in catalytic asymmetric strategies.[16−20,29−40] Despite this progress, enantioselective access to pyrrolidines derived from amines less reactive than glycine, phenylglycine, or amino malonates remains limited by moderate enantioselectivities,[16−18,38] low temperatures,[16−18,37,38,40] synthetically inaccessible ligands,[37−40] poor scope,[16−18,38] or the requirement for multiple synthetic operations.[19,20,37−40] We report here a scalable, one-step, catalytic, and enantioselective synthesis of highly substituted pyrrolidines from chelating aldehydes, amino acid esters, and activated olefins using commercially available diamines and copper salts as recyclable catalysts, easing access to and lowering the cost of biologically significant pyrrolidines.

Although 1,3-dipolar cycloadditions of azomethine ylides and activated olefins are typically performed as two-step processes,[15−27] efforts to develop single-step strategies are desirable as they minimize handling, allow for improved chemoselectivity, and ease access to structural diversity. Reported strategies include the use of reactive amino acids such as amino malonates, glycine, and phenylglycine to facilitate ylide formation under the same conditions as Schiff-base formation,[41−43] the generation of reactive ylides *in situ* from diazoacetate derivatives,[44,45] and most recently, the organocatalytic enantioselective three-component coupling of amino acids, electron-poor aryl aldehydes, and electron-deficient olefins using 10−20 mol % of a bisphosphoric acid catalyst (available in 8 steps from commercially available sources).[39] Despite recent advances in three-component coupling approaches to pyrrolidine synthesis, this chemistry has remained limited in scope, providing cost-effective access only to pyrrolidines derived from highly activated amino acid or glycine derivatives.

Building on our studies of picolinaldehyde-based mimics of pyridoxal-5′-phosphate,[46,47] we recently reported the diastereoselective synthesis of pyrrolidines through a mild Lewis-acid catalyzed three-component coupling reaction between chelating aldehydes, amino acid esters, and activated olefins (Scheme 1).[48] We report here a catalytic enantioselective variant that provides single-step access to highly substituted, enantioenriched pyrrolidines using readily available chiral diamines and copper salts.

Following early screens that identified Cu(II) salts complexed with chiral 1,2-diamines such as (*S*,*S*)-1,2-bismesitylene-1,2-ethylene-diamine (**4**) as effective enantiose-

Received: June 10, 2013
Published: August 16, 2013

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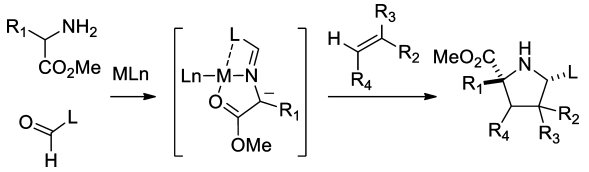
dx.doi.org/10.1021/jo401015y | J. Org. Chem. 2013, 78, 9471−9476

Scheme 1. Racemic Three-Component Coupling Reaction



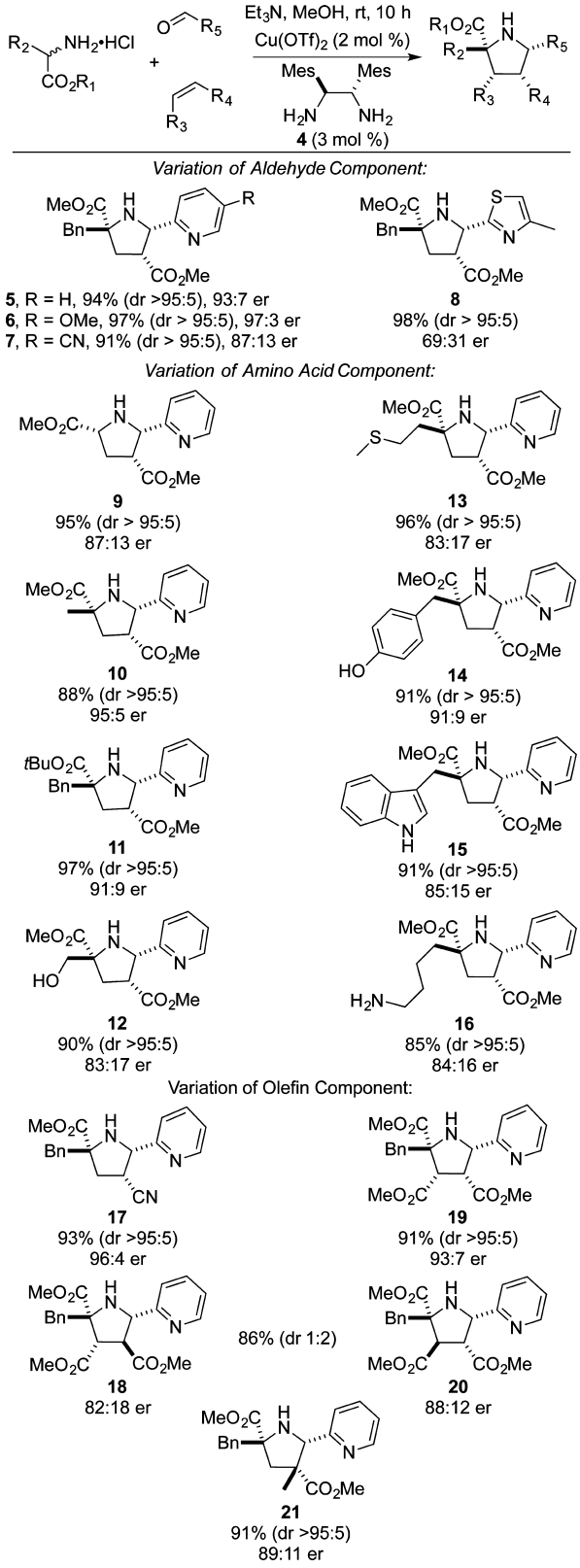
lective catalysts of this transformation (Tables S1 and S2 in the Supporting Information), we turned our attention to substrate scope (Table 1). In these studies, all substrates and reagents apart from the ethylene diamine ligands were either achiral or used in their racemic form. Using 2 mol % of $Cu(OTf)_2$ and 3 mol % of diamine **4**, various aldehydes were examined. These efforts revealed excellent reactivity, diastereoselectivity, and enantioselectivity with electron-rich and electron-poor picolinaldehyde derivatives, although a slight reduction in enantioselectivity was observed with the electron-poor system. Further modification of aldehyde structure maintained excellent yields but moderated enantioselectivity, producing thiazole derivative **8** in 69:31 er. Unfortunately, nonaromatic and nonchelating aldehydes such as benzaldehyde, 4-picolinaldehyde, and pivaldehyde gave minimal conversions under these reaction conditions. It should be noted that many of the pyrrolidines produced through this work are crystalline and that enantiopurities can likely be enhanced through recrystallization (this has been explicitly demonstrated for compound **17**, *vide infra*).

The reaction displays excellent substrate scope with regard to the amino acid ester. Amino acids were examined as the commercially available racemic hydrochloride salts in condensations with 2-picolinaldehyde and methyl acrylate. Amino acid esters bearing no additional functional groups displayed excellent yields, diastereoselectivities and enantioselectivities (**5**, **9**−**11**). Larger ester substituents have no discernible effect on yield or diastereoselectivity, but exhibit a slight erosion of enantioselectivity (**5** and **11**). Amino acid esters with unprotected or chelating functional groups such as serine (**12**), methionine (**13**), tyrosine (**14**), tryptophan (**15**), and lysine (**16**) also participated in moderate to good enantioselectivity, making this chemistry a rare example of azomethine ylide cycloadditions that incorporate reactive oxygen and nitrogen functionality in good yields without the need for protecting groups.[48−50]

Dipolarophiles were screened in reactions with phenylalanine methyl ester and 2-picolinaldehyde. Acrylonitrile, which exhibits poor diastereoselectivity under the previously reported calcium-catalyzed reactions,[48] participated in excellent yield, diastereo- and enantioselectivity to produce a single observable diastereoisomer (**17**). Similarly, dimethyl maleate participated with good yield, diastereo- and enantioselectivity to yield a single observable product (**19**), although dimethyl fumarate exhibited an erosion of endoselectivity to provide two major products (**18** and **20**) in good yields and enantioselectivities. The alkyl α-substituted α,β-unsaturated ester, methyl methacrylate, provided **21** in excellent yield and diastereo- and enantioselectivity.

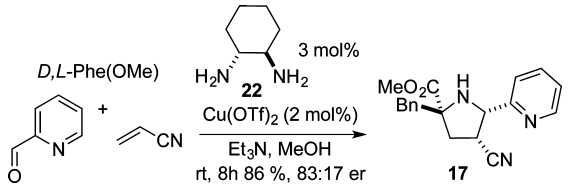
The scalability of the reaction and potential for catalyst recycling was examined in the context of pyrrolidine **17**. Accordingly, acrylonitrile, picolinaldehyde, and phenylalanine methyl ester were combined in a 1:1:1 mol ratio using 100 g of the hydrochloride salt of phenylalanine methyl ester (Scheme 2). As the enantioenrichment of pyrrolidine **17** can be increased by recrystallization, we chose to use the less expensive, albeit less selective (*R*,*R*)-trans-1,2-diaminocyclohexane (**22**). An aqueous extraction and initial recrystallization gave **17** in 86% yield with 83:17 er which, after further

Table 1. Substrate scope



dx.doi.org/10.1021/jo401015y | J. Org. Chem. 2013, 78, 9471−9476

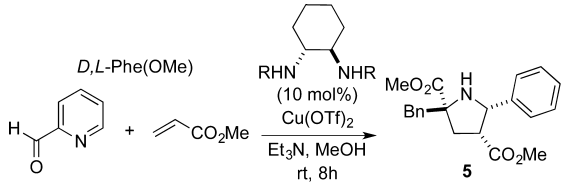
Scheme 2. 100 g Scale Synthesis of Pyrrolidine 17



recrystallization, provided 82.2 g (55%) of **17** in >99:1 er, demonstrating the scalability of this reaction. Moreover, lyophilization of the aqueous wash resulted in 42 g of a blue solid, 42 mg (0.1%) of which catalyzed the condensation of 100 mg phenylalanine methyl ester (0.1% of the scale of the original reaction) to produce **17** in 74% yield and 86:14 er, demonstrating the recyclability of the catalyst system. Unfortunately, this blue solid, likely comprising a complex mixture of copper salts, sodium bicarbonate, triethylammonium salts, chiral diamine, and residual starting material, proved resistant to purification, with all efforts resulting in catalytically inactive materials. Finally, crystallization of **17** provided X-ray quality crystals that allowed the determination of the absolute stereochemistry of this product (Figure S2).

Given that the reactions are run under conditions conducive to Schiff-base formation, we hypothesized that the diamine ligands bind copper as the corresponding picolinaldehyde imines. This hypothesis might help explain the significant loss of enantioselectivity observed using thiazole-derived aldehydes, as these substrates play multiple roles in the transition state. To test our hypothesis, we examined the reactivity and enantioselectivity of substituted analogs of ligand **22** in the condensation of phenylalanine methyl ester, methyl acrylate, and 2-picolinaldehyde (Table 2). Consistent with our

Table 2. Efforts at Ligand Tuning



	R	yield	er
23	Bn	65%	56:44
24	2-picoline	98%	83:17

hypothesis, a reaction using dibenzyl substituted **23** exhibited moderate yields and dramatically diminished enantioselectivity, whereas dipicolinated **24** produced pyrrolidine **5** in excellent yields and enantioselectivities similar (albeit slightly diminished) to those observed using unsubstituted trans-1,2-cyclohexyldiamine. These results are consistent with the hypothesis that the active catalyst incorporates picolinaldehyde as a component of the ligand structure.

Building on our hypothesis that the catalyst complex involved the picolinaldehyde Schiff base of the diamine ligand, we sought to establish a model of the active catalyst complex. In our previous studies of Lewis acid promoted azomethine ylide formation, we found that intermediate species bind the Lewis acid in a tridentate manner.[46] Accordingly, we examined the ground state conformations of a series of complexes between copper, substrate-derived tridentate ylides, and tridentate (*S*,*S*)-1,2-bismesitylene-1,2-ethylenediamine bound to one or two additional molecules of picolinaldehyde as the corresponding Schiff Base (Figure S3). For each complex, the relative energies of two possible diastereoisomers were established to identify the dominant species. Reactions were then hypothesized to occur at the most exposed face of the bound substrate, allowing presumed enantioselectivities to be determined accordingly. These predictions were consistent with experimental results for **17** in the context of the bis-Schiff base, but not the mono, suggesting that the active catalyst species derives from a bis-Schiff base complex such as **25**. This is unsurprising, as bis-Schiff base complex **25** is anticipated to be dicationic, likely increasing the Lewis acidity of the bound copper catalyst relative to the corresponding monocationic mono-Schiff base.

Examination of the proposed catalyst model provides clear insights into the origins of selectivity: unfavorable interactions with the highlighted methyl of the α-mesitylene blocks binding of pyridine at the adjacent site, forcing the substrate to bind in the manner shown (Figure 2). Upon complexation, the bound

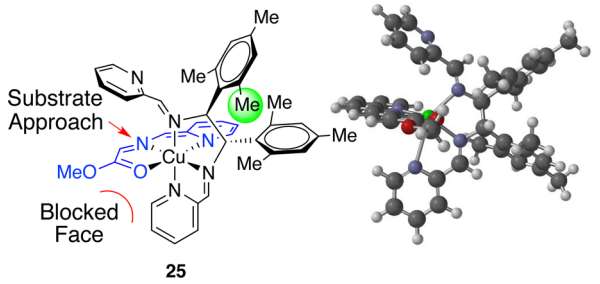


Figure 2. Proposed model of the catalyst complex, bound substrate shown in blue.

pyridine ring of the ligand blocks the bottom face of the substrate, forcing the dipolarophile to approach from the top face adjacent to the more flexible pyridine ring (Figure 2). Based on this model, we can readily explain the observed loss of enantioselectivity with bulky ester **11**, as steric bulk at this position likely erodes the diastereoselectivity of complex formation. This model provides a clear avenue for predicting the enantioselectivity of these and future reactions, as well as laying critical groundwork for the development of future 1,3-dipolar cycloaddition catalysts.

In conclusion, we have developed a mild three-component variant of (3 + 2) cycloaddition reactions to synthesize highly substituted pyrrolidines containing either a 2-pyridyl 2-thiazolyl substituent at the 2-position in an enantio-, diastereo-, and regioselective manner. The reaction can be run in a cost-effective manner, employing commercially available copper salts, chiral ligands, amino acid esters, α-chelating aldehydes, and dipolarophiles and running in an inexpensive and readily disposed solvent. Finally, the observation that the catalyst complex can be recycled further indicates the potential utility of this chemistry in practical applications, whether by simply using lower catalyst loadings or through a direct recycling program.

EXPERIMENTAL SECTION

General Procedure. Catalyst was generated in a 4 mL vial by mixing $Cu(OTf)_2$ (3.6 mg, 0.010 mmol), (1*S*,2*S*)-1,2-bis(2,4,6-trimethylphenyl)ethylenediamine dihydrochloride (5.5 mg, 0.015 mmol), and triethylamine (4 μL, 0.03 mmol) in methanol (0.25 mL) and stirred (shaken) for 20 min. Esters of racemic amino acids (0.5 mmol) were weighed in a second 4 mL vial and dissolved in methanol (0.75 mL). To this solution, triethylamine (70 μL, 0.50

dx.doi.org/10.1021/jo401015y | J. Org. Chem. 2013, 78, 9471−9476

mmol unless otherwise indicated), aldehyde (0.50 mmol), olefin (0.60 mmol), and the catalyst solution were added (final concentration in MeOH 0.5 M). The vial was capped and shaken for 14 h unless otherwise indicated. Crude reaction mixtures were concentrated *in vacuo* and purified with flash silica column chromatography. HPLC data were taken by dissolving 1 mg of the compound in 0.5 mL 10% 2-propanol/hexanes solution and running them through the indicated chiral columns.

*(2S,4R,5S)-Dimethyl 2-benzyl-5-(pyridin-2-yl)pyrrolidine-2,4-dicarboxylate (**5**).* Followed the general procedure, R_f = 0.4 (ethyl acetate/hexanes 40:60); 167.0 mg, 94%, >95:5 dr, 95:5 er; colorless solid; $[\alpha]_D^{20}$ + 15.8° (*c* 0.92, $CHCl_3$); mp 83−86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48−8.45 (m, 1H), 7.57 (dt, *J* = 7.6, 2.0 Hz, 1H), 7.29−7.19 (m, 6H), 7.10 (ddd, *J* = 7.2, 4.8, 1.2 Hz, 1H), 4.48 (d, 6.8 Hz, 1H), 3.69 (s, 3H), 3.54 (bs, 1H), 3.22 (s, 3H), 3.17 (dt, *J* = 7.2, 4.8 Hz, 1H), 3.08 (d, *J* = 13.2 Hz, 1H), 2.93 (d, *J* = 13.2 Hz, 1H), 2.82 (dd, *J* = 13.6, 5.6 hz, 1H), 2.19 (dd, *J* = 13.6, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 172.8, 158.8, 148.8, 136.9, 136.1, 130.3, 127.9, 126.7, 122.3, 122.0, 70.5, 66.1, 52.1, 51.2, 49.5, 46.2, 38.3; IR (thin film, cm^{-1}): 3308, 3027, 2950, 1733, 1593, 1435, 1258, 1199, 1175; HRMS: (ESI-quadrupole) *m*/*z* calculated for $C_{20}H_{23}N_2O_4$ $[M+H]^+$ 355.1658, found 355.1651.

*(2S,4R,5S)-Dimethyl 2-benzyl-5-(5-methoxypyridin-2yl)-pyrrolidine-2,4-dicarboxylate (**6**).* Followed the general procedure, R_f = 0.3 (ethyl acetate/hexanes 40:60); 186.4 mg, 97%, >95:5 dr, 97:3 er; colorless solid; $[\alpha]_D^{20}$ + 2.1° (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 2.8 Hz, 1H), 7.29−7.07 (m, 7H), 4.48 (d, *J* = 7.2 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.62 (bs, 1H), 3.26 (s, 3H), 3.15 (td, *J* = 7.6, 5.6 Hz, 1H), 3.08 (d, *J* = 13.2 Hz, 1H), 2.96 (d, *J* = 12.8 Hz, 1H), 2.82 (dd, *J* = 14.0, 5.6 Hz, 1H), 2.19 (dd, *J* = 14.0, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 172.8, 154.7, 150.5, 136.8, 136.1, 130.3, 127.9, 126.7, 122.3, 120.7, 70.5, 65.4, 55.4, 52.1, 51.3, 49.3, 46.1, 38.2; IR (thin film, cm^{-1}): 3428, 2950, 1732, 1645, 1494, 1435, 1201; HRMS: (ESI-quadrupole) *m*/*z* calculated for $C_{21}H_{25}N_2O_5$ $[M+H]^+$ 385.1763, found 385.1772.

*(2S,4R,5S)-Dimethyl 2-benzyl-5-(5-cyanopyridin-2-yl)pyrrolidine-2,4-dicarboxylate (**7**).* Followed the general procedure, R_f = 0.3 (ethyl acetate/hexanes 40:60); 172.6 mg, 91%, >95:5 dr, 88:12 er; colorless solid; $[\alpha]_D^{20}$ + 5.3° (*c* 1.00, $CHCl_3$); mp 163−164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, *J* = 1.6 Hz, 1H), 7.85 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.42 (d, *J* = 8.4 hz, 1H), 7.28−7.20 (m, 5H), 5.23 (t, *J* = 6.4 Hz, 1H), 3.70 (s, 3H), 3.35 (d, *J* = 5.2 Hz, 1H), 3.28 (s, 3H), 3.21 (dt, *J* = 14.0, 7.6 Hz, 1H), 3.09 (d, *J* = 13.2 Hz, 1H), 2.91 (d, *J* = 12.8 Hz, 1H), 2.82 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.24 (dd, *J* = 14.0, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 172.1, 164.1, 151.4, 139.3, 136.5, 130.2, 128.1, 126.9, 122.3, 116.6, 108.4, 70.2, 65.6, 52.3, 51.5, 49.1, 46.2, 37.7; IR (thin film, cm^{-1}): 2989, 2898, 2232, 1727, 1449, 1392, 1360, 1142; HRMS: (ESI-quadrupole) *m*/*z* calculated for $C_{21}H_{22}N_3O_4$ $[M+H]^+$ 380.1610, found 380.1591.

*(2S,4R,5S)-Dimethyl 2-benzyl-5-(4-methylthiazol-2-yl)pyrrolidine-2,4-dicarboxylate (**8**).* Followed the general procedure, R_f = 0.3 (ethyl acetate/hexanes 40:60); 183.4 mg, 98%, >95:5 dr, 69:31 er; colorless solid; $[\alpha]_D^{20}$ − 1.5° (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−7.11 (m, 5H), 6.71 (s, 1H), 4.76 (d, *J* = 7.6 Hz, 1H), 3.69 (s, 3H), 3.42 (s, 3H), 3.33−3.15 (m, 1H), 3.06 (d, *J* = 13.2 Hz, 1H), 2.88 (d, *J* = 13.2 Hz, 1H), 2.80 (dd, *J* = 13.2 Hz, 8.8 Hz, 1H), 2.32 (s, 3H), 2.18 (dd, *J* = 13.6 Hz, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 171.7, 170.5, 152.5, 136.3, 130.1, 128.2, 126.9, 113.5, 69.5, 61.5, 52.1, 51.6, 48.6, 46.1, 35.8, 17.0; IR (thin film, cm^{-1}): 3420, 2952, 2924, 2360, 2341, 1740, 1667, 1526, 1467, 1439, 1268, 1207; HRMS: (ESI-quadrupole) *m*/*z* calculated for $C_{19}H_{22}N_2O_4NaS$ $[M+Na]^+$ 397.1198, found 397.1191.

*(2R,4R,5S)-Dimethyl 5-(pyridin-2-yl)pyrrolidine-2,4-dicarboxylate (**9**).* Followed the general procedure but substituting 8 h instead of 12 h reaction time, R_f = 0.4 (ethyl acetate/hexanes 40:60); 125.5 mg, 95%, >95:5 dr, 92:8 er; colorless solid; $[\alpha]_D^{20}$ + 19.7° (*c* 1.00, $CHCl_3$); mp 50−54 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, *J* = 4.4 Hz, 1H), 7.60 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.14−7.09 (m, 1H), 4.55 (d, *J* = 7.6 Hz, 1H), 3.98 (t, *J* = 8.0 Hz, 1H), 3.76 (s, 3H), 3.30 (dd, *J* = 13.2, 7.6 Hz, 1H), 3.22 (s, 3H), 3.05 (bs, 1H), 2.46−2.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 172.9, 158.0, 148.9, 136.3, 122.5, 122.2, 66.8, 60.0, 52.2, 51.3, 49.1, 33.5; IR (thin film, cm^{-1}): 3522, 2951, 2921, 1736, 1593, 1437, 1376, 1203, 1175; HRMS: (CI-ion trap) *m*/*z* calculated for $C_{13}H_{17}N_2O_4$ $[M+H]^+$ 265.1183, found 265.1174.

*(2R,4R,5S)-Dimethyl 2-methyl-5-(pyridin-2-yl)pyrrolidine-2,4-dicarboxylate (**10**).* Followed the general procedure, R_f = 0.4 (ethyl acetate/hexanes 40:60); 122.4 mg, 88%, >95:5 dr, 96:4 er; colorless solid; $[\alpha]_D^{20}$ + 9.1° (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48−8.45 (m, 1H), 7.58 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.10 (ddd, *J* = 7.2, 4.8, 1.2 Hz, 1H), 4.63 (d, *J* = 7.2 Hz, 1H), 3.76 (s, 3H), 3.75 (bs, 1H), 3.35 (dt, *J* = 7.2, 5.6 Hz, 1H), 3.22 (s, 3H), 2.76 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.02 (dd, *J* = 13.6, 7.6 Hz, 1H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 172.8, 158.1, 148.8, 136.1, 122.4, 122.2, 66.0, 65.9, 52.4, 51.2, 50.0, 40.4, 27.9; IR (thin film, cm^{-1}): 3304, 2952, 2360, 1732, 1593, 1571, 1436, 1375, 1263, 1202, 1137; HRMS: (ESI-quadrupole) *m*/*z* calculated for $C_{14}H_{19}N_2O_4$ $[M+H]^+$ 279.1345, found 279.1350.

*(2S,4R,5S)-2-tert-Butyl 4-methyl 2-benzyl-5-(pyridin-2-yl)-pyrrolidine-2,4-dicarboxylate (**11**).* Followed the general procedure, R_f = 0.4 (ethyl acetate/hexanes 40:60); 192.2 mg, yield 97%, >95:5 dr, 92:8 er; colorless solid; $[\alpha]_D^{20}$ + 4.0° (*c* 1.00, $CHCl_3$); mp 80−82 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48−8.44 (m, 1H), 7.57 (td, *J* = 7.6, 1.6 Hz, 1H), 7.37−7.34 (m, 1H), 7.26−7.16 (m, 5H), 7.09 (ddd, *J* = 7.2, 4.4, 1.2 Hz, 1H), 4.45 (d, *J* = 7.6 Hz, 1H), 3.24 (s, 3H), 3.50 (bs, 1H), 3.15 (td, *J* = 7.7, 6.4 Hz, 1H), 3.03 (d, *J* = 13.6 Hz, 1H), 2.93 (d, *J* = 13.6 Hz, 1H), 2.76 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.15 (dd, *J* = 13.6, 7.6 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 172.8, 159.2, 148.8, 137.3, 136.0, 130.5, 127.7, 126.5, 122.2, 121.9, 81.2, 70.3, 66.0, 51.1, 49.5, 45.9, 38.6, 27.9; IR (thin film, cm^{-1}): 3300, 2977, 2948, 1731, 1593, 1434, 1368, 1256, 1161, 1117; HRMS: (ESI-quadrupole) *m*/*z* calculated for $C_{23}H_{29}N_2O_4$ $[M+H]^+$ 397.2127, found 397.2133.

*(2S,4R,5S)-Dimethyl 2-(hydroxymethyl)-5-(pyridin-2-yl)-pyrrolidine-2,4-dicarboxylate (**12**).* Followed the general procedure, R_f = 0.4 (ethyl acetate/hexanes 50:50); 132.4 mg, yield 90%, >95:5 dr, 80:20 er; colorless solid; $[\alpha]_D^{20}$ + 11.0° (*c* 1.00, $CHCl_3$); mp 122−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, *J* = 4.4 Hz, 1H), 7.63 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.18−7.14 (m, 1H), 4.56 (d, *J* = 6.4 Hz, 1H), 3.79 (s, 3H), 3.75 (d, *J* = 10.8 Hz, 1H), 3.58 (bs, 2H), 3.52 (d, *J* = 10.8 Hz, 1H), 3.28−3.23 (m, 1H), 3.23 (s, 3H), 2.67−2.60 (m, 1H), 2.04 (dd, *J* = 14.0, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 172.9, 156.9, 149.0, 136.4, 122.7, 122.4, 71.0, 67.6, 65.9, 52.7, 51.4, 49.9, 36.0; IR (thin film, cm^{-1}): 3350, 2953, 1729, 1436, 1211, 1123, 1052; HRMS: (ESI-quadrupole) *m*/*z* calculated for $C_{14}H_{19}N_2O_5$ $[M+H]^+$ 295.1294, found 295.1286.

*(2S,4R,5S)-Dimethyl 2-(2-(methylthio)ethyl)-5-(pyridin-2-yl)-pyrrolidine-2,4-dicarboxylate (**13**).* Followed the general procedure, R_f = 0.4 (ethyl acetate/hexanes 40:60); 162.4, 96%, >95:5 dr, 84:16 er; colorless solid; $[\alpha]_D^{20}$ + 5.3° (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (d, *J* = 4.4 Hz, 1H), 7.59 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.15−7.09 (m, 1H), 4.55 (d, *J* = 6.4 Hz, 1H), 3.88 (bs, 1H), 3.78 (s, 3H), 3.27 (dt, *J* = 7.2, 4.4 Hz, 1H), 3.20 (s, 3H), 2.77 (dd, *J* = 13.6, 4.0 Hz, 1H), 2.67 (ddd, *J* = 12.4, 11.6, 4.8 Hz, 1H), 2.33 (dt, *J* = 11.6, 5.2 Hz, 1H), 2.12 (ddd, *J* = 13.2, 11.6, 5.2 Hz, 1H), 2.04 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.05 (s, 3H), 1.87 (ddd, *J* = 13.2, 11.2, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.4, 172.8, 157.6, 148.9, 136.2, 122.5, 122.3, 69.4, 66.3, 52.4, 51.3, 49.9, 40.6, 40.3, 29.6, 15.5; IR (thin film, cm^{-1}): 3300, 2950, 2917, 1732, 1593, 1435, 1198, 1170; HRMS: (ESI-quadrupole) *m*/*z* calculated for $C_{16}H_{23}N_2O_4S$ $[M+H]^+$ 339.1379, found 339.1375.

*(2S,4R,5S)-Dimethyl 2-(4-hydroxybenzyl)-5-(pyridin-2-yl)-pyrrolidine-2,4-dicarboxylate (**14**).* Followed the general procedure, R_f = 0.4 (ethyl acetate/hexanes 40:60); 168.5 mg, 91%, >95:5 dr, 91:9 er; colorless solid; $[\alpha]_D^{20}$ + 13.5° (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, *J* = 3.6 Hz, 1H), 7.59 (dt, *J* = 8.0, 1.6 hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.20 (bs, 1H), 7.11 (ddd, *J* = 7.6, 5.2 Hz, 0.8 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.61 (d, *J* = 8.4 Hz, 2H), 4.54 (d, *J* = 7.6 Hz, 1H), 3.70 (s, 3H), 3.50 (bs, 1H), 3.22 (ddd, *J* = 12.4, 7.2, 5.2 Hz, 1H), 3.18 (s, 3H), 3.02 (d, *J* = 13.6 Hz, 1H), 2.84 (d,

dx.doi.org/10.1021/jo401015y | *J. Org. Chem.* 2013, 78, 9471−9476

J = 13.2 Hz, 1H), 2.78 (dd, J = 13.6, 5.2 Hz, 1H), 2.19 (dd, J = 13.6, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 172.9, 158.6, 155.5, 148.4, 136.6, 131.1, 127.7, 122.6, 122.1, 115.2, 70.5, 65.6, 52.3, 51.3, 49.3, 45.1, 38.2; IR (thin film, cm^{-1}): 3415, 2950, 2356, 1734, 1647, 1514, 1437, 1203; HRMS: (ESI-quadrupole) m/z calculated for $C_{20}H_{23}N_2O_5$ $[M+H]^+$ 371.1607, found 371.1607.

*(2S,4R,5S)-Dimethyl 2-((1H-indol-3-yl)methyl)-5-(pyridin-2-yl)-pyrrolidine-2,4-dicarboxylate (**15**).* Followed the general procedure, R_f = 0.4 (ethyl acetate/hexanes 40:60); 179.0 mg, 91%, >95:5 dr, 89:11 er); colorless solid; $[\alpha]_D^{20}$ + 3.6° (c 1.00, $CHCl_3$); mp 156−159 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (d, J = 4.0 Hz, 1H), 8.26 (bs, 1H), 7.64 (d, J = 7.2 hz, 1H), 7.56 (dt, J = 7.6, 2.0 Hz, 1H), 7.30−7.22 (m, 2H), 7.18−7.04 (m, 4H), 4.56 (d, J = 7.2 Hz, 1H), 3.64 (s, 3H), 3.62 (bs, 1H), 3.29 (d, J = 14.0 Hz, 1H), 3.27−3.21 (m, 1H), 3.22 (s, 3H), 2.83 (dd, J = 13.2, 5.2 Hz, 1H), 2.57 (dd, J = 13.6, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.1, 172.9, 158.5, 148.7, 136.2, 135.8, 128.2, 123.9, 122.4, 122.0, 121.6, 119.3, 118.9, 111.1, 110.6, 70.6, 66.1, 52.3, 51.3, 49.6, 38.3, 35.8; IR (thin film, cm^{-1}): 3376, 2920, 2362, 2342, 1724, 1591, 1433, 1199, 1172, 1091; HRMS: (ESI-quadrupole) m/z calculated for $C_{22}H_{24}N_3O_4$ $[M+H]^+$ 394.1767, found 394.1751.

*(2R,4R,5S)-Dimethyl 2-(4-aminobutyl)-5-(pyridin-2-yl)pyrrolidine-2,4-dicarboxylate (**16**).* Followed the general procedure substituting 140 μL (1.0 mmol) of triethylamine instead of 70 μL (0.5 mmol), R_f = 0.2 (ethyl acetate/hexanes/diethyl amine 58:40:2); 142.5 mg, 85%, >95:5 dr, 85:15 er; colorless solid; $[\alpha]_D^{20}$ + 12.4° (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (d, J = 4.0 Hz, 1H), 7.64 (td, J = 7.6, 1.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.15 (ddd, J = 7.2, 4.8, 0.8 Hz, 1H), 4.71 (d, J = 7.2 Hz, 1H), 3.78 (s, 3H), 3.30 (td, J = 7.6, 3.6 Hz, 1H), 3.20 (s, 3H), 2.84 (t, J = 6.8 Hz, 2H), 2.75 (dd, J = 14.0, 4.0 Hz, 1H), 2.11 (dd, J = 13.6, 7.6 Hz, 1H), 1.88−1.60 (m, 4H), 1.60−1.46 (m, 1H), 1.58 (bs, H2O), 1.28−1.16 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 175.8, 173.0, 156.7, 148.3, 136.6, 122.8, 122.7, 69.4, 65.5, 51.6, 50.4, 49.9, 39.9, 39.6, 38.8, 26.9, 21.5; IR (thin film, cm^{-1}): 3374, 2921, 1733, 1592, 1435, 1260, 1204; HRMS: (ESI-quadrupole) m/z calculated for $C_{17}H_{26}N_3O_4$ $[M+H]^+$ 336.1923, found 336.1915.

*(2S,4R,5S)-Methyl 2-benzyl-4-cyano-5-(pyridin-2-yl)pyrrolidine-2-carboxylate (**17**).* Followed the general procedure, R_f = 0.4 (ethyl acetate/hexanes 40:60); 149.4 mg, 93%, >95:5 dr, 98:2 er; colorless solid; $[\alpha]_D^{20}$ + 18.6° (c 1.00, $CHCl_3$); mp 96−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, J = 4.8 Hz, 1H), 7.67 (td, J = 7.6, 1.6 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.30−7.18 (m, 6H), 4.44 (d, J = 6.0 Hz, 1H), 3.73 (s, 3H), 3.42 (bs, 1H), 3.16 (dt, J = 7.2, 5.6 Hz, 1H), 3.08 (d, J = 13.2 Hz, 1H), 2.94 (d, J = 12.8 Hz, 1H), 2.86 (dd, J = 14.0, 5.6 Hz, 1H), 2.36 (dd, J = 14.0, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 157.7, 149.2, 136.7, 136.1, 130.2, 128.2, 127.0, 123.1, 121.6, 118.9, 69.7, 65.1, 52.4, 45.6, 38.7, 35.4; IR (thin film, cm^{-1}): 3307, 2951, 2239, 1733, 1593, 1571, 1494, 1474, 1436, 1257, 1206, 1123, 1092; HRMS: (ESI-quadrupole) m/z calculated for $C_{19}H_{20}N_3O_2$ $[M+H]^+$ 322.1556, found 322.1546.

*(2S,4R,5S)-Methyl 2-benzyl-4-cyano-5-(pyridin-2-yl)pyrrolidine-2-carboxylate (**17**) (Large Scale).* To a solution of phenylalanine methyl ester hydrochloride (100.0 g, 0.464 mol), triethylamine (71.0 mL, 0.510 mol), pyridine-2-carboxaldehyde (44.3 mL, 0.464 mol), and acrylonitrile (36.7 mL, 0.556 mol) in methanol (463 mL) was added a solution of $Cu(OTf)_2$ (3.35 g, 9.27 mmol) and (*R,R*)-*trans*-1,2-diaminocyclohexane hydrochloride (1.59 g, 13.9 mmol) in methanol (927 mL). The reaction mixture was stirred at rt for 14 h. After which the reaction mixture was concentrated under reduced pressure. The remaining residue was brought up in 500 mL 1/2 saturated $NaHCO_3$ (*aq.*) and extracted with (300 mL × 4) ethyl acetate. The aqueous layers were combined and lyophilized to provide the "blue solid" described in the text. The organic layers were combined, dried with Na_2SO_4, and concentrated under reduced pressure to yield a dark oil (crude methyl 2-benzyl-4-cyano-5-(pyridin-2-yl)pyrrolidine-2-carboxylate (86% via NMR, >83:17 er)). Crystallization of this material was not optimized, likely increasing the number of total recrystallizations required for purification. Initial crystallizations were performed from pure methanol at −20 °C and seeded with enantioenriched product (~2 mg) when required. The first three crystallizations were recrystallized three times each in methanol with at least two crops collected. Subsequent crystallizations were performed using methanol and diisopropyl ether in which purified materials were combined and recrystallized four times in methanol and diisopropyl ether with at least two crops collected for each recrystallization. The combined crystallization crops yielded methyl 2-benzyl-4-cyano-5-(pyridin-2-yl)pyrrolidine-2-carboxylate (82.2 g, 0.256 mol, 55%, >95:5 dr, >99:1 er) as a colorless solid.

*(2S,3S,4S,5S)-Trimethyl 2-benzyl-5-(pyridin-2-yl)pyrrolidine-2,3,4-tricarboxylate (**18**) (minor isomer) and (2R,3R,4R,5S)-Trimethyl 2-benzyl-5-(pyridin-2-yl)pyrrolidine-2,3,4-tricarboxylate (**20**) (major isomer).* Followed the general procedure, R_f = 0.4 (ethyl acetate/hexanes 40:60), 1:2 mixture (as determined by crude ^{1}H NMR using resonances at 4.82 ppm for **20** and 4.42 ppm for **18**) of **18** (90:10 er) and **20** (86:14 er); 177.3 mg, 86%, 2:1 dr; Small amounts of the compounds **18** and **20** were separated using preparatory HPLC for the characterization. (**20**) (major isomer) colorless solid; $[\alpha]_D^{20}$ + 4.4° (c 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (d, J = 5.2 Hz, 1H), 7.53 (td, J = 7.6, 1.6 Hz, 1H), 7.24−7.10 (m, 6H), 7.03 (ddd, J = 7.2, 4.8, 0.8 Hz, 1H), 4.82 (d, J = 8.0 Hz, 1H), 4.12 (d, J = 9.2 Hz, 1H), 3.93 (t, J = 8.8 Hz, 1H), 3.76 (s, 3H), 3.54 (s, 3H), 3.23 (s, 3H), 2.99 (d, J = 13.2 Hz, 1H), 2.84 (d, J = 13.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 171.9, 171.3, 159.3, 148.6, 136.3, 136.2, 130.2, 127.9, 126.7, 122.7, 122.4, 715, 63.7, 53.7, 52.3, 52.3, 53.2, 51.5, 40.0; IR (thin film, cm^{-1}): 3298, 3029, 2952, 1735, 1593, 1436, 1261, 1218, 1171; HRMS: (ESI-quadrupole) m/z calculated for $C_{22}H_{25}N_2O_6$ $[M+H]^+$ 413.1713, found 413.1733. (**18**) (minor isomer) colorless solid; $[\alpha]_D^{20}$ + 6.1° (c 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6): δ 8.34 (d, J = 4.4 Hz, 1H), 7.52 (d, J = 7.2 Hz, 1H), 7.20−7.01 (m, 6H), 6.96 (td, J = 7.6, 1.6 Hz, 1H), 4.42 (d, J = 9.6 Hz, 1H), 3.94 (dd, J = 10.8, 9.6 Hz, 1H), 3.86 (d, J = 11.2 Hz, 1H), 3.45 (d, J = 13.6 Hz, 1H), 3.39 (s, 3H), 3.29 (d, J = 13.2 Hz, 1H), 3.24 (s, 3H), 3.14 (s, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ 172.9, 171.8, 171.5, 158.8, 149.3, 136.8, 135.8, 131.0, 126.8, 122.4, 122.2, 73.0, 66.0, 57.7, 55.4, 51.7, 51.5, 51.1, 44.1; IR (thin film, cm^{-1}): 3296, 3029, 2951, 2362, 2279, 1733, 1593, 1436, 1323, 1217, 1171, 1015; HRMS: (ESI-quadrupole) m/z calculated for $C_{22}H_{25}N_2O_6$ $[M+H]^+$ 413.1713, found 413.1708.

*(2R,3S,4R,5S)-Dimethyl 2-benzyl-5-(pyridin-2-yl)pyrrolidine-2,3,4-tricarboxylate (**19**).* Followed the general procedure, R_f = 0.4 (ethyl acetate/hexanes 40:60); 187.6 mg, 91%, 95:5 dr, 94:6 er; colorless solid; $[\alpha]_D^{20}$ + 21.7° (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, J = 4.8 Hz, 1H), 7.59 (td, J = 7.6, 1.6 Hz, 1H), 7.50−7.45 (m, H), 7.31−7.19 (m, 5H), 7.15−7.10 (m, 1H), 4.43 (d, J = 10.7 Hz, 1H), 4.06 (dd, J = 10.7, 5.6 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.33 (d, J = 6.4 Hz, 1H), 3.26 (s, 3H), 3.23 (d, J = 12.8 Hz, 1H), 3.18 (d, J = 12.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.0, 171.1, 170.7, 156.5, 148.8, 136.1, 136.0, 131.2, 128.0, 126.9, 121.8, 72.5, 64.7, 54.1, 52.6, 52.1, 51.6, 51.1, 44.9; IR (thin film, cm^{-1}): 3304, 3027, 2950, 2852, 1736, 1593, 1435, 1236, 1200, 1173, 1120, 1087; HRMS: (ESI-quadrupole) m/z calculated for $C_{22}H_{25}N_2O_6$ $[M+H]^+$ 413.1713, found 413.1704.

*(2R,4R,5S)-Dimethyl 2-benzyl-4-methyl-5-(pyridin-2-yl)-pyrrolidine-2,4-dicarboxylate (**21**).* Followed the general procedure, R_f = 0.4 (ethyl acetate/hexanes 40:60); 167.6 mg, 91%, >95:5 dr, 90:10 er; colorless solid; $[\alpha]_D^{20}$ + 12.1° (c 1.00, $CHCl_3$); mp 88−93 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51−8.45 (m, 1H), 7.57 (dt, J = 8.0, 2.0 Hz, 1H), 7.33−7.29 (m, 2H), 7.26−7.19 (m, 3H), 7.13 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.10−7.07 (m, 1H), 3.76 (s, 1H), 3.70 (s, 3H), 3.63 (bs, 1H), 3.24 (s, 3H), 3.08 (d, J = 14.0 Hz, 1H), 3.06 (d, J = 12.8 Hz, 1H), 2.94 (d, J = 12.8 Hz, 1H), 1.95 (d, J = 14.0 Hz, 1H), 1.21 (s, 3H); ^{13}CNMR (100 MHz, $CDCl_3$): δ 175.9, 174.7, 156.7, 148.9, 137.1, 136.0, 130.5, 127.8, 126.6, 122.6, 122.2, 73.6, 69.9, 55.2, 52.1, 51.3, 48.0, 47.1, 21.4; IR (thin film, cm^{-1}): 3483, 2952, 2926, 1737, 1593, 1455, 1435, 1259, 1203, 1125; HRMS: (ESI-quadrupole) m/z calculated for $C_{21}H_{25}N_2O_4$ $[M+H]^+$ 369.1814, found 369.1799.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional tables referenced in the text, materials, general methods, X-ray crystallographic data for **17**, DFT calculations,

dx.doi.org/10.1021/jo401015y | J. Org. Chem. 2013, 78, 9471−9476

chiral HPLC traces and spectra for all compounds generated through this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We acknowledge the financial support of Indiana University.

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