JOC The Journal of Organic Chemistry

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Diastereo- and Enantioselective Catalytic Vinylogous Mukaiyama-Mannich Reactions of Pyrrole-Based Silyl Dienolates with Alkyl-Substituted Aldehydes

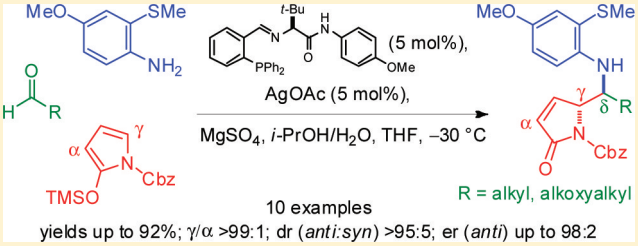
Beatrice Ranieri,[†] Claudio Curti,[†] Lucia Battistini,[†] Andrea Sartori,[†] Luigi Pinna,[‡] Giovanni Casiraghi,*[,†] and Franca Zanardi*[,†]

[†]Dipartimento Farmaceutico, Università degli Studi di Parma, Parco Area delle Scienze 27A, I-43124 Parma, Italy

[‡]Dipartimento di Chimica, Università degli Studi di Sassari, Via Vienna 2, I-07100 Sassari, Italy

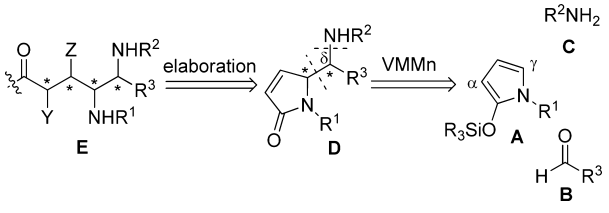
Supporting Information

ABSTRACT: A reliable, catalytic asymmetric vinylogous Mukaiyama–Mannich reaction of pyrrole-based silyl dienolates is introduced that is particularly apt for alkyl- and α-alkoxyalkyl-substituted aldehydes. The reaction course is effectively orchestrated by the Hoveyda–Snapper amino acid-based chiral ligand/silver(I) catalyst combination to produce valuable vicinal diamino carbonyl compounds in high yields, with virtually complete γ-site- and *anti*-selectivity and significant catalyst-to-product chirality transfer. The utility of the Mannich products can be seen in the synthesis of an unprecedented perhydrofuro[3,2-*b*]pyrrolone product, an aza-analogue of naturally occurring (+)-goniofufurone.



Chiral 1,2-diamino structures are the crucial motifs of several natural and non-natural compound classes, which often display distinctive chemical and biological properties.[1] Their utility as integral molecules or precursors in synthesis as well as ligands in asymmetric catalysis has stimulated chemists to design and realize qualifying methodologies to arrive at these constructs, some of which involve highly efficient and selective carbon–carbon bond formations.[1b–d,2] Among the most versatile and direct strategies available, the asymmetric, catalytic Mannich-type reactions of aldimines with carbon nucleophiles carrying an amino equivalent unit at the reacting site provide immediate access to these entities, which can be elaborated into important 1,2-diamino objectives.[3,4] Thus, easily available pyrrole-based silyl dienolates of type **A** are ideal carbon nucleophiles, as they contain a nitrogen atom close to the reacting γ-carbon (Scheme 1). Their Mukaiyama–Mannich–type vinylogous addition reaction (VMMn)[5] to an imine acceptor, generated in situ from an aldehyde **B** and an amine **C**, straightforwardly provides functionality-rich α,β-unsaturated pyrrolinone units **D**, which can be in turn elaborated to vicinal diamino fragments **E** in a number of ways.

Scheme 1. Disconnective Path of a Generic Open-Chain 1,2-Diamino Fragment E into the Corresponding Mannich Precursors A–C

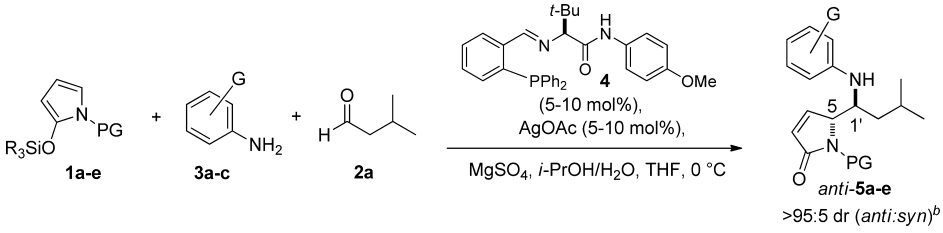


Along these lines, we recently reported on a catalytic, two-component asymmetric VMMn reaction of pyrrole silyl dienolates with aldimines[6] that allowed easy access to various δ-aminopyrrolinones of type **D** in a highly enantioenriched format. However, despite the efficiency and the distinct stereoselectivity experienced with aromatic aldimines, this method seemed to be limited in its application, as it did not perform adequately with imines derived from alkyl-substituted aldehydes. To complement that work, it is our aim herein to develop an improved asymmetric VMMn protocol especially applicable to aldimines derived from alkyl- and hydroxyalkyl-substituted aldehydes. In doing so, we have capitalized on the pioneering studies by Hoveyda and Snapper with silver-catalyzed, asymmetric VMMn reactions of furan-based silyl dienolates[7] and our own findings with pyrrole nucleophiles.[6] In this way, a reliable, enantioselective and diastereoselective procedure is open to a further palette of 1,2-bis-aminated pyrrolinone frameworks which bear diverse and versatile aliphatic units at the end of the carbon chain.

We initiated our journey by evaluating a model VMMn addition reaction between easily available and robust *N*-Boc-2-[(*tert*-butyldimethyl)silyloxy]pyrrole (**1a**), isovaleraldehyde (**2a**), and *o*-anisidine (**3a**) by adopting the skillful Hoveyda–Snapper chiral ligand **4** in conjunction with AgOAc as the

Received: September 15, 2011
Published: November 7, 2011

Table 1. Evaluation of *N*-Protected Trialkylsilyloxypyrroles and Aromatic Amines in the Enantioselective VMMn Reaction with Isovaleraldehyde (2a)[a]



entry	pyrrole: R_3Si/PG	amine	product	yield[c] (%)	er[d]
1	**1a**: TBS/Boc	**3a**: *o*-$OMeC_6H_4$			
2	**1b**: TMS/Boc	**3a**: *o*-$OMeC_6H_4$	**5a**	52 (70)	81:19
3	**1c**: TMS/Bn	**3a**: *o*-$OMeC_6H_4$			
4	**1d**: TMS/Ts	**3a**: *o*-$OMeC_6H_4$	**5b**	9 (12)	71:29
5	**1e**: TMS/Cbz	**3a**: *o*-$OMeC_6H_4$	**5c**	40 (50)	84:16
6	**1e**: TMS/Cbz	**3b**: *o*-$SMeC_6H_4$	**5d**	69 (85)	96:4
7	**1e**: TMS/Cbz	**3c**: *o*-SMe-*p*-$OMeC_6H_3$	**5e**	75 (90)	97:3
8[e]	**1e**: TMS/Cbz	**3c**: *o*-SMe-*p*-$OMeC_6H_3$	**5e**	58 (77)	90:10
9[f]	**1e**: TMS/Cbz	**3c**: *o*-SMe-*p*-$OMeC_6H_3$	**5e**	25 (30)	97:3
10[g]	**1e**: TMS/Cbz	**3c**: *o*-SMe-*p*-$OMeC_6H_3$	**5e**	80 (95)	97:3
11[g,h]	**1e**: TMS/Cbz	**3c**: *o*-SMe-*p*-$OMeC_6H_3$	**5e**	84 (92)	98:2
12[g,i]	**1e**: TMS/Cbz	**3c**: *o*-SMe-*p*-$OMeC_6H_3$	**5e**	46 (66)	92:8
13[g,h,j]	**1e**: TMS/Cbz	**3c**: *o*-SMe-*p*-$OMeC_6H_3$	**5e**	90 (97)	98:2

[a]Unless noted otherwise, reactions were carried out using **1a–e** (0.3 mmol, 1.5 equiv), aldehyde **2a** (1.0 equiv), amine **3a–c** (1.0 equiv), $MgSO_4$ (2.0 equiv), ligand **4** (10 mol %), AgOAc (10 mol %), undistilled *i*-PrOH/H_2O (1.5 equiv each), and undistilled and stabilized THF (BHT, 250 ppm), in air, at 0 °C for 16 h, concentration 0.1 M referred to **1a–e**. [b]Determined by ^1H NMR analysis of the reaction crude. *Syn*-diastereoisomers not detected. [c]Isolated yields after chromatography; conversions in parentheses determined by ^1H NMR analysis of the reaction crude. [d]Determined by HPLC analysis on a chiral stationary phase. [e]No water added. [f]All-in-one execution, no $MgSO_4$ added. [g]Concentration, 0.4 M. [h]At −30 °C. [i]At −78 °C. [j]5.0 mol % catalyst used.

catalyst.[7] The result was disappointing (Table 1, entry 1), with little, if any, substrate conversion observed after 16 h at 0 °C. Thus, in searching for more reactive substrates and based on our precedents with pyrrole-based silyl dienolates,[8] we studied the reaction between less sterically demanding TMS-pyrrole **1b** with the imine derived from **2a** and **3a**. As shown in entry 2, with 10 mol % each of ligand **4** and AgOAc in undistilled THF at 0 °C, unsaturated lactam **5a** was obtained in 52% isolated yield (70% conversion) after silica gel chromatography, with virtually complete γ-site selectivity and diastereoselectivity in favor of the *anti*-configured isomer, albeit with a modest 81:19 er.[9] The reaction protocol was critical and mimicked the sequential addition mode previously established by the Hoveyda–Snapper group.[7b] Briefly, the procedure entailed the following steps: (1) neat aldehyde and amine (1.0 equiv each) were treated with anydrous $MgSO_4$ at rt, and then the mixture was diluted with THF; (2) the solution was taken and poured into a THF solution of ligand **4** and AgOAc (10 mol % each); (3) the mixture was supplemented with 2-propanol/water (1.5 equiv each); (4) after cooling to 0 °C, silyloxypyrrole (1.5 equiv) was added and the resulting combination allowed to react at 0 °C for 16 h.[10] Thus, aiming at improving yield and enantioselectivity, the effects of the pyrrole *N*-protecting groups were evaluated by uniformly adopting the above delineated VMMn protocol. The use of electron-releasing groups in the pyrrole proved detrimental (entry 3), while electron-withdrawing substituents were tolerated well. Among the three options tested, *tert*-butoxycarbonyl (entry 2), tosyl (entry 4), and benzyloxycarbonyl (entry 5), our choice fell on the Cbz-protected compound **1e**, due to the superior enantioselectivity displayed. Thus, *N*-Cbz TMS-pyrrole **1e** was advanced to a further optimization stage, where the effect of the amine component was analyzed with the hope that it would provide substantial improvement in this VMMn transformation. As previously demonstrated,[7b] success was attained with *o*-thiomethyl-*p*-anisidine (**3c**) (entry 7), where the Mannich adduct **5e** was obtained in a good 75% isolated yield (90% conversion), >95:5 dr, and 97:3 er.

The addition of water proved to have decisive effects on the reactivity, and excluding water in the solvent mixture decreased both yield and selectivity (entry 8).[11] Importantly, a more conventional all-in-one execution (entry 9) also proved detrimental, and only a 25% isolated yield was obtained after 16 h. Additional improvements were achieved by increasing the concentration of **1e** to 0.4 M (entry 10), as well as lowering the reaction temperature to −30 °C (entry 11), while a further temperature drop to −78 °C resulted in a sluggish reaction with no gain in enantioselectivity (entry 12). Tuning of the catalyst loading revealed that lowering the amount of the catalyst to 5.0 mol % for each ligand **4** and AgOAc did not alter the reaction course, and the Mannich adduct **5e** was obtained in a good 90% isolated yield, complete *anti*-selectivity, and excellent 98:2 er (entry 13).[12]

With optimum reaction conditions established, as in entry 13 of Table 1, the reaction scope with respect to the aldehyde component was studied next (Figure 1). It was demonstrated that a variety of substitution patterns on the aldehyde acceptors were compatible with the developed reaction, and the Mannich products **5e** and **6a–f** were obtained in good isolated yields, with complete γ-site selectivity, perfect diastereocontrol

dx.doi.org/10.1021/jo201875a | J. Org. Chem. 2011, 76, 10291–10298

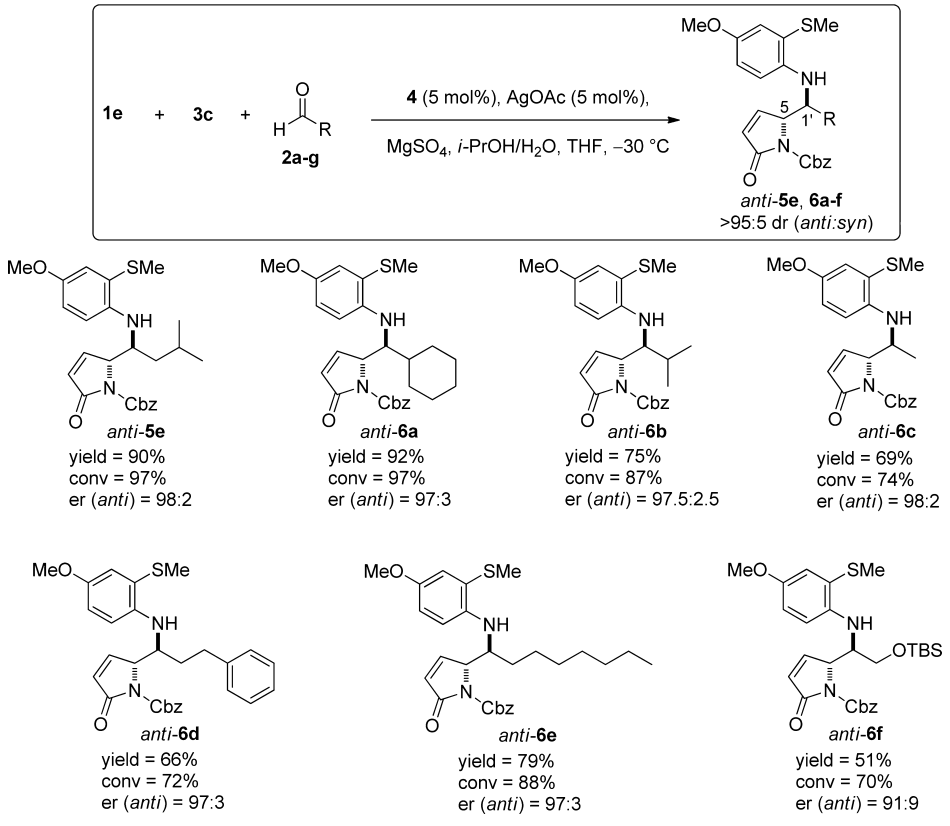


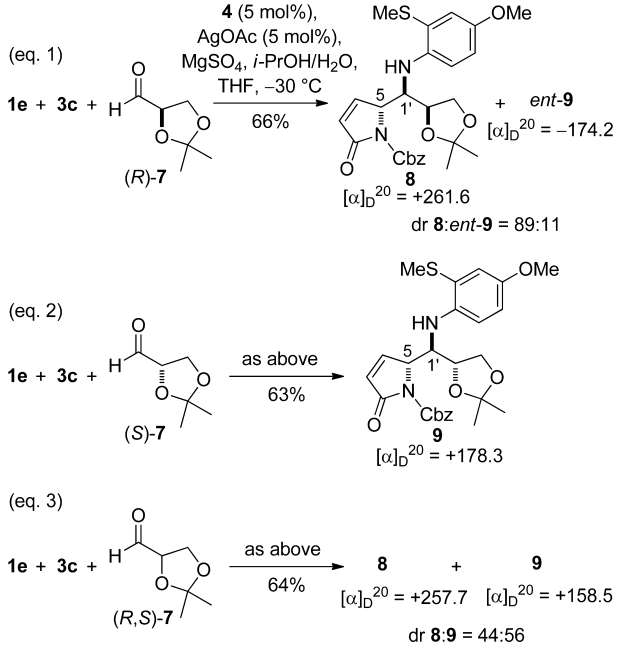
Figure 1. Profile of the asymmetric VMMn reaction of pyrrole **1e** and amine **3c** with alkyl- and hydroxyalkyl-substituted aldehydes **2a**–**g**. Yields refer to isolated vinylogous Mannich products. Conversions determined by ^{1}H NMR analysis of the reaction crude. Diastereomeric ratios determined by ^{1}H NMR analysis of reaction crude. *Syn*-diastereoisomers not detected. Enantiomeric ratios were determined by HPLC analysis on chiral stationary phase.

invariably favoring the *anti*-configured adducts, and remarkable enantiocontrol in the range 91:9 to 98:2 er.[13]

The ability of the silver-based chiral catalyst combination to orchestrate the stereochemical course of the present VMMn reaction was finally studied with a chiral aldehyde representative, adopting the popular three-carbon synthon 2,3-*O*-isopropylideneglyceraldehyde **7**. Scheme 2 analyzes the impact of the chirality resident in the aldehyde substrates on the VMMn coupling of pyrrole **1e** and aniline **3c**, with the aldehyde enantiomers (*R*)-**7** and (*S*)-**7** as well as the racemate (*R*,*S*)-**7**.

Interestingly, it was found that irrespective of the chirality of the aldehyde component, the catalytic, asymmetric VMMn reaction using either enantiomers of glyceraldehydes gave the desired products **8** and **9** with almost the same conversion and the same relative, and hence absolute, steric disposition of the two newly formed C5 and C1′ stereocenters (both *anti*- and 5*R*,1′*R*-configured). In addition, use of the racemate did result in a nearly balanced mixture of the adducts, namely the overall contribution of the separate experiments with enantiopure aldehyde enantiomers. Although a small matched/mismatched effect was observed in favor of (*S*)-**7**, no appreciable kinetic resolution of the racemate was detected. This result demonstrates that the chirality of the ligand in the silver catalyst plays a crucial role in the asymmetric induction, with an almost perfect ligand-to-product chirality relay which largely overrides the inherent chirality of the substrates. In truth, the optical rotation value of **9** in eq 3, arising from (*R*,*S*)-**7**, was slightly lower than that measured for the same isomer arising from (*S*)-**7** (eq 2) ($[\alpha]^{20}_D$ = +158.5 vs $[\alpha]^{20}_D$ = +178.3), and this suggests that a minute amount of *ent*-**9**, the minor product with (*R*)-**7** in eq 1, contaminates this isomer, lowering its optical rotation value to some extent.

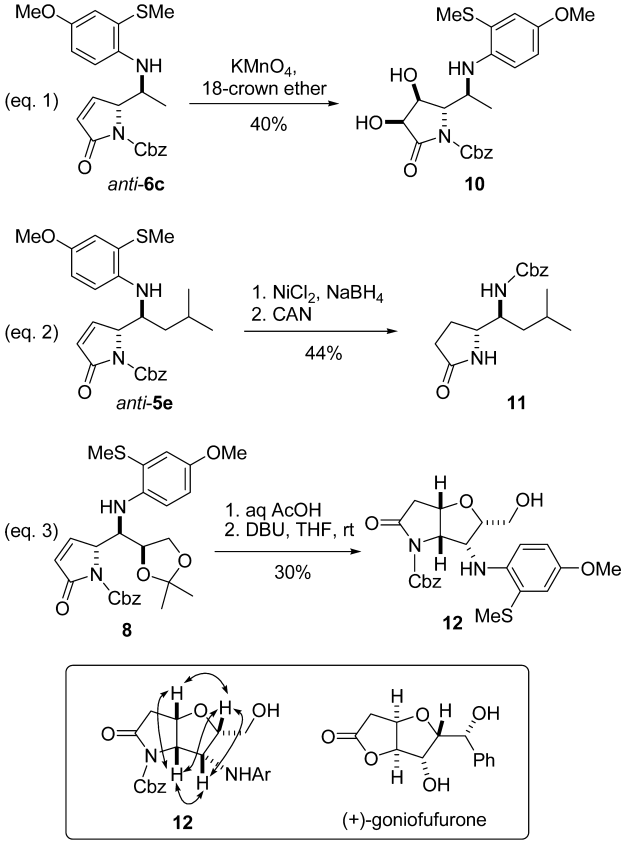
Scheme 2. Impact of the Glyceraldehyde Chirality for the Asymmetric VMMn Addition of Pyrrole 1e and Amine 3c Catalyzed by Silver-Based Catalyst 4·AgOAc



dx.doi.org/10.1021/jo201875a | *J. Org. Chem.* 2011, 76, 10291–10298

To highlight the versatility of the unsaturated lactam products in synthesis, basic manipulations were performed on their molecular framework, which invariably resulted in formation of enantiomerically pure vicinal diamine structures (Scheme 3). These include a diastereoselective dihydroxylation

Scheme 3. Skeletal Elaboration of Mannich Products to Functionality-Rich 1,2-Diaminated Scaffolds



of the lactam double bond within **6c** to 3,4-*cis*:4,5-*trans*-configured diol **10** (eq 1); a three-step hydrogenation/dearylation/*N*,*N*-Cbz-migration[14] sequence to pyrrolidinone **11** (eq 2); and, importantly, a chemo- and diastereoselective oxa-Michael annulation to rare hexahydrofuro[3,2-*b*]pyrrolone **12** (eq 3). Extensive 1D and 2D NMR analyses including NOESY correlation experiments of this last compound provided confirmation of the relative (hence absolute) configuration of the four embodied stereocenters and, ultimately, established the precursor **8** to have the 5*R*,1′*R*,2′*S*-stereochemistry, as indicated. As for the isomeric candidate **9**, the relative and absolute configuration was inferred to be 5*R*,1′*R*,2′*R* (5,1′-*anti*:1′,2′-*anti*) by chiro-optical considerations[15] and strict ^{1}H and ^{13}C NMR spectral analogy to a known, related compound.[9] All structures in Figure 1 were assigned by analogy, in accordance with the stereoinduction trend dictated by the chiral ligand in the silver catalyst, featuring preferential attack of the diene nucleophile (*Si*-face) at the *Re*-face of the imine component.[7,16]

In summary, we present a highly efficient, catalytic diastereo- and enantioselective vinylogous Mukaiyama–Mannich reaction to provide rapid access to various enantioenriched 1,2-diamino carbonyl frameworks. This process, which is skilfully governed by the silver-based Hoveyda–Snapper catalyst **4**·AgOAc, is especially valuable with aliphatic aldehydes and α-alkoxyaldehydes which are, on the whole, poorly suited to similar vinylogous Mannich-type transformations. The synthetic utility of the process has been established by basic framework manipulations of the formed Mannich adducts, which include a chemo- and stereocontrolled oxa-Michael annulation to an unprecedented fused furopyrrolone heterocycle, an aza-analogue, reminiscent of the structure of the fully oxygenated, naturally occurring (+)-goniofufurone.[17]

EXPERIMENTAL SECTION

Representative VMMn Procedure. (*R*)-1-(Benzyloxycarbonyl)-5-[(*S*)-1-[4-methoxy-2-(methylthio)phenylamino]-3-methylbutyl]-1*H*-pyrrol-2(5*H*)one (*anti*-5e) (Table 1, Entry 13). Chiral phosphine **4** (5.3 mg, 0.01 mmol) and AgOAc (1.7 mg, 0.01 mmol) were dissolved in undistilled BHT-stabilized (250 ppm) THF (208 μL), and the mixture was allowed to stir for 10 min at 22 °C. A separate vial was charged with 4-methoxy-2-(methylthio)aniline (**3c**) (35.1 mg, 0.21 mmol) and $MgSO_4$ (50 mg, 0.41 mmol) into which aldehyde **2a** (21.7 μL, 0.21 mmol) was added at room temperature. The resulting mixture was allowed to stir for 10 min; the crude imine was diluted with undistilled THF (830 μL) and transferred to the above silver–peptide complex solution, followed by the addition of a mixture of *i*-PrOH (23.7 μL, 0.31 mmol)/H_2O (5.6 μL, 0.31 mmol). The resulting mixture was allowed to stir at −30 °C for 10 min. 2-(Trimethylsilyloxy)pyrrole (**1e**) (90.0 mg, 0.31 mmol) was diluted with undistilled THF (776 μL) and then added in one portion, and the resulting mixture was allowed to stir at −30 °C for 16 h. The reaction was quenched upon addition of buffer solution (pH 7, 1.0 mL), followed by warming to 25 °C with vigorous stirring for 10 min. The mixture was extracted with EtOAc (3 × 10 mL), and the organic layers were collected, dried with $MgSO_4$, filtered, and concentrated in vacuo. The diastereomeric ratio of the Mannich products **5e** was determined to be >95:5 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 70:30) to yield 85.9 mg (90%) of *anti*-**5e** as a light red resin: TLC, R_f = 0.40 (petroleum ether/EtOAc = 70:30); $[\alpha]^{20}_{D}$ = +174.2 (*c* = 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.33 (m, 5H, Cbz), 7.28 (dd, *J* = 6.2, 1.6 Hz, 1H, H4), 6.92 (d, *J* = 2.9 Hz, 1H, H3″), 6.55 (dd, *J* = 8.9, 2.9 Hz, 1H, H5″), 6.42 (brd, *J* = 8.9 Hz, 1H, H6″), 6.30 (dd, *J* = 6.2, 1.6 Hz, 1H, H3), 5.35 (d, *J* = 12.3 Hz, 1H, Cbz), 5.21 (d, *J* = 12.4 Hz, 1H, Cbz), 4.88 (brs, 1H, H5), 4.44 (m, 1H, H1′), 3.69 (s, 3H, OMe), 2.25 (s, 3H, SMe), 1.74 (m, 1H, H3′), 1.50 (t, *J* = 7.0 Hz, 2H, H2′), 0.96 (d, *J* = 6.6 Hz, 3H, CH_3), 0.92 (d, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (Cq), 151.7 (Cq), 151.4 (Cq), 146.7 (CH), 141.8 (Cq), 135.4 (Cq), 129.8 (CH), 128.8 (2CH), 128.6 (CH), 128.5 (2CH), 121.4 (Cq), 119.5 (CH), 115.4 (CH), 111.9 (CH), 68.2 (CH_2), 66.6 (CH), 55.9 (CH_3), 52.6 (CH), 43.3 (CH_2), 25.5 (CH), 23.0 (CH_3), 22.6 (CH_3), 18.6 (CH_3); ESI-MS *m*/*z* 477.30 $[M + Na]^+$ (calcd 477.20 $[M + Na]^+$). Anal. Calcd for $C_{25}H_{30}N_2O_4S$: C, 66.05; H, 6.65; N, 6.16. Found: C, 66.09; H, 6.70; N, 6.13. Chiral HPLC: (1′*S*,5*R*)-**5e**, t_R 21.65 min (97.9%); (1′*R*,5*S*)-**5e**, t_R 28.26 min (2.1%) (Whelk-O1, hexane/EtOH = 80:20, 0.9 mL/min, 254 nm).

(*R*)-1-(Benzyloxycarbonyl)-5-[(*S*)-[4-methoxy-2-(methylthio)-phenylamino](cyclohexyl)methyl]-1*H*-pyrrol-2(5*H*)one (*anti*-6a). Prepared according to the representative procedure, utilizing aldehyde **2b** (25.4 μL, 0.21 mmol), aniline **3c** (35.5 mg, 0.21 mmol), and pyrrole **1e** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be >95:5 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 70:30) to yield 92.8 mg (92%) of the *anti*-**6a** as a red resin: TLC, R_f = 0.39 (petroleum ether/EtOAc = 70:30); $[\alpha]^{20}_{D}$ = +233.3 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.35 (m, 5H, Cbz), 7.27 (dd, *J* = 6.2, 1.8 Hz, 1H, H4), 6.91 (d, *J* = 2.8 Hz, 1H, H3″), 6.52 (dd, *J* = 8.9, 2.8 Hz, 1H, H5″), 6.33 (d, *J* = 10.4 Hz, 1H, H6″), 6.30 (dd, *J* = 6.4, 1.3 Hz, 1H, H3), 5.30 (d, *J* = 12.4 Hz, 1H, Cbz), 5.16 (d, *J* = 12.4 Hz, 1H, Cbz), 5.09 (s, 1H, H5), 4.13 (dd, *J* = 8.8, 2.3 Hz, 1H, H1′), 3.68 (s, 3H,

dx.doi.org/10.1021/jo201875a | *J. Org. Chem.* 2011, 76, 10291–10298

OMe), 2.24 (s, 3H, SMe), 1.88 (m, 2H, alkyl), 1.69 (m, 2H, alkyl), 1.47 (m, 1H, alkyl), 1.28−1.21 (m, 5H, alkyl), 1.02 (m, 1H, alkyl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (Cq), 151.3 (2Cq), 146.5 (CH), 142.9 (Cq), 135.5 (Cq), 129.9 (CH), 128.8 (2CH), 128.5 (CH), 128.4 (2CH), 120.6 (Cq), 119.5 (CH), 115.5 (CH), 111.6 (CH), 68.1 (CH_2), 64.6 (CH), 58.8 (CH), 55.9 (CH_3), 43.0 (CH), 31.0 (CH_2), 30.5 (CH_2), 26.4 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 18.7 (CH_3); ESI-MS m/z 503.30 $[M + Na]^+$ (calcd 503.20 $[M + Na]^+$). Anal. Calcd for $C_{27}H_{32}N_2O_4S$: C, 67.47; H, 6.71; N, 5.83 Found: C, 67.22; H, 6.75; N, 5.84. Chiral HPLC: (1′*S*,5*R*)-**6a**, t_R 21.82 min (97.0%); (1′*R*,5*S*)-**6a**, t_R 29.14 min (3.0%) (Whelk-O1, hexane/EtOH = 80:20, 0.9 mL/min, 254 nm).

(*R*)-1-(Benzyloxycarbonyl)-5-[(*S*)-1-[4-methoxy-2-(methylthio)phenylamino]-2-methylpropyl]-1*H*-pyrrol-2(5*H*)-one (*anti*-6b). Prepared according to the representative procedure, utilizing aldehyde **2c** (19.2 μL, 0.21 mmol), aniline **3c** (35.5 mg, 0.21 mmol), and pyrrole **1e** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be >95:5 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 70:30) to yield 69.4 mg (75%) of the *anti*-**6b** as a red resin: TLC, R_f = 0.40 (petroleum ether/EtOAc = 70:30); $[\alpha]^{20}_D$ = +202.7 (c = 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.32 (m, 5H, Cbz), 7.27 (dd, J = 7.3, 2.0 Hz, 1H, H4), 6.91 (d, J = 2.8 Hz, 1H, H3″), 6.53 (dd, J = 8.9, 2.9 Hz, 1H, H5″), 6.34 (d, J = 8.5 Hz, 1H, H6″), 6.30 (dd, J = 6.1, 1.4 Hz, 1H, H3), 5.30 (d, J = 12.4 Hz, 1H, Cbz), 5.17 (d, J = 12.4 Hz, 1H, Cbz), 5.09 (s, 1H, H5), 4.04 (dd, J = 9.1, 2.5 Hz, 1H, H1′), 3.68 (s, 3H, OMe), 2.25 (s, 3H, SMe), 1.77 (m, 1H, H2′), 1.17 (d, J = 6.7 Hz, 3H, CH_3), 1.03 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (Cq), 151.3 (2Cq), 146.4 (CH), 142.8 (Cq), 135.4 (Cq), 130.0 (CH), 128.8 (2CH), 128.5 (CH), 128.3 (2CH), 120.6 (Cq), 119.4 (CH), 115.5 (CH), 111.6 (CH), 68.1 (CH_2), 64.9 (CH), 60.3 (CH), 55.9 (CH_3), 33.7 (CH), 21.0 (CH_3), 20.2 (CH_3), 18.8 (CH_3); ESI-MS m/z 463.30 $[M + Na]^+$ (calcd 463.18 $[M + Na]^+$). Anal. Calcd for $C_{24}H_{28}N_2O_4S$: C, 65.43; H, 6.41; N, 6.36. Found: C, 65.20; H, 6.49; N, 6.39. Chiral HPLC: (1′*S*,5*R*)-**6b**, t_R 22.47 min (97.7%); (1′*R*,5*S*)-**6b**, t_R 27.97 min (2.3%) (Whelk-O1, hexane/EtOH = 80:20, 0.9 mL/min, 254 nm).

(*R*)-1-(Benzyloxycarbonyl)-5-[(*S*)-1-[4-methoxy-2-(methylthio)phenylamino]ethyl]-1*H*-pyrrol-2(5*H*)one (*anti*-6c). Prepared according to the representative procedure, utilizing aldehyde **2d** (11.8 μL, 0.21 mmol), aniline **3c** (35.5 mg, 0.21 mmol), and pyrrole **1e** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be >95:5 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 70:30−60:40) to yield 59.8 mg (69%) of the *anti*-**6c** as a red resin: TLC, R_f = 0.20 (petroleum ether/EtOAc = 70:30); $[\alpha]^{20}_D$ = +240.7 (c = 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.28 (m, 6H, Cbz, H4), 6.94 (d, J = 2.9 Hz, 1H, H3″), 6.61 (dd, J = 8.85, 3.0 Hz, 1H, H5″), 6.41 (d, J = 8.9 Hz, 1H, H6″), 6.33 (dd, J = 6.1, 1.4 Hz, 1H, H3), 5.34 (1/2 ABq, J = 12.4 Hz, 1H, Cbz), 5.27 (1/2 ABq, J = 12.4 Hz, 1H, Cbz), 4.86 (s, 1H, H5), 4.45 (m, 1H, H1′), 3.71 (s, 3H, OMe), 2.25 (s, 3H, SMe), 1.34 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (Cq), 151.8 (Cq), 151.5 (Cq), 146.7 (CH), 141.5 (Cq), 135.5 (Cq), 129.6 (CH), 128.8 (2CH), 128.5 (CH), 128.3 (2C), 122.0 (Cq), 119.3 (CH), 115.3 (CH), 112.3 (CH), 68.3 (CH_2), 67.2 (CH), 56.0 (CH_3), 49.6 (CH), 18.8 (CH_3), 18.3 (CH_3); ESI-MS m/z 435.20 $[M + Na]^+$ (calcd 435.15 $[M + Na]^+$). Anal. Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.06; H, 5.86; N, 6.79. Found: C, 64.11; H, 5.90; N, 6.73. Chiral HPLC: (1′*S*,5*R*)-**6c**, t_R 30.01 min (97.8%); (1′*R*,5*S*)-**6c**, t_R 36.09 min (2.2%) (Whelk-O1, hexane/EtOH = 80:20, 0.9 mL/min, 254 nm).

(*R*)-1-(Benzyloxycarbonyl)-5-[(*S*)-1-[4-methoxy-2-(methylthio)phenylamino]-3-phenylpropyl]-1*H*-pyrrol-2(5*H*)-one (*anti*-6d). Prepared according to the representative procedure, utilizing aldehyde **2e** (27.7 μL, 0.21 mmol), aniline **3c** (35.5 mg, 0.21 mmol), and pyrrole **1e** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be >95:5 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica gel flash chromatography (petroleum ether/EtOAc elution gradient from 80:20 to 75:25) to yield 69.7 mg (66%) of the *anti*-**6d** as a red resin: TLC, R_f = 0.20 (petroleum ether/EtOAc = 70:30); $[\alpha]^{20}_D$ = +154.9 (c = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.23 (m, 10H, Cbz, Ph), 7.17 (d, J = 7.1 Hz, H4), 6.92 (d, J = 2.9 Hz, 1H, H3″), 6.50 (dd, J = 8.9, 2.9 Hz, 1H, H5″), 6.30 (m, 2H, H6″ and H3), 5.27 (d, J = 12.4 Hz, 1H, Cbz), 5.17 (d, J = 12.3 Hz, 1H, Cbz), 4.87 (s, 1H, H5), 4.38 (m, 1H, H1′), 3.68 (s, 3H, OMe), 2.85 (m, 1H, H3′), 2.71 (m, 1H, H3′), 2.27 (s, 3H, SMe), 2.07 (m, 1H, H2′), 1.84 (m, 1H, H2′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0 (Cq), 151.4 (Cq), 151.1 (Cq), 146.2 (CH), 142.1 (Cq), 141.1 (Cq), 135.2 (Cq), 129.7 (CH), 128.6 (4CH), 128.4 (2CH), 128.3 (CH), 128.2 (2CH), 126.2 (CH), 121.1 (Cq), 119.1 (CH), 115.1 (CH), 111.8 (CH), 68.0 (CH_2), 66.5 (CH), 55.7 (CH_3), 53.9 (CH), 36.3 (CH_2), 33.0 (CH_2); 18.5 (CH_3); ESI-MS m/z 525.21 $[M + Na]^+$ (calcd 525.19 $[M + Na]^+$). Anal. Calcd for $C_{29}H_{30}N_2O_4S$: C, 69.30; H, 6.02; N, 5.57. Found: C, 69.05; H, 6.04; N, 5.58. Chiral HPLC: (1′*S*,5*R*)-**6d**, t_R 30.03 min (96.8%); (1′*R*,5*S*)-**6d**, t_R 36.91 min (3.2%) (Whelk-O1, hexane/EtOH = 80:20, 0.9 mL/min, 254 nm).

(*R*)-1-(Benzyloxycarbonyl)-5-[(*S*)-1-[4-methoxy-2-(methylthio)phenylamino]octyl]-1*H*-pyrrol-2(5*H*)one (*anti*-6e). Prepared according to the representative procedure, utilizing aldehyde **2f** (32.8 μL, 0.21 mmol), aniline **3c** (35.5 mg, 0.21 mmol), and pyrrole **1e** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be >95:5 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 75:25−70:30) to yield 82.4 mg (79%) of the *anti*-**6e** as a red resin: TLC, R_f = 0.30 (petroleum ether/EtOAc = 70:30); $[\alpha]^{20}_D$ = +151.5 (c = 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.33 (m, 5H, Cbz), 7.29 (dd, J = 6.2, 2.1 Hz, 1H, H4), 6.92 (d, J = 2.9 Hz, 1H, H3″), 6.56 (dd, J = 8.9, 2.9 Hz, 1H, H5″), 6.39 (brd, J = 8.7 Hz, 1H, H6″), 6.31 (dd, J = 6.2, 1.6 Hz, 1H, H3), 5.32 (d, J = 12.4 Hz, 1H, Cbz), 5.21 (d, J = 12.4 Hz, 1H, Cbz), 4.91 (brs, 1H, H5), 4.33 (m, 1H, H1′), 3.69 (s, 3H, OMe), 2.25 (s, 3H, SMe), 1.68 (m, 2H, H2′), 1.50 (m, 2H, H3′), 1.28 (m, 8H, H4′, H5′, H6′, H7′), 0.89 (dd, J = 7.0, 6.5 Hz, 3H, H8′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (Cq), 151.6 (Cq), 151.4 (Cq), 146.7 (CH), 142.8 (Cq), 135.4 (Cq), 129.7 (CH), 128.8 (2CH), 128.5 (CH), 128.4 (2CH), 120.6 (Cq), 119.3 (CH), 115.4 (CH), 111.6 (CH), 68.2 (CH_2), 66.5 (CH), 55.9 (CH_3), 53.5 (CH), 33.7 (CH_2), 31.9 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 26.9 (CH_2), 22.8 (CH_2), 18.6 (CH_3), 14.3 (CH_3); ESI-MS m/z 519.20 $[M + Na]^+$ (calcd 519.24 $[M + Na]^+$). Anal. Calcd for $C_{28}H_{36}N_2O_4S$: C, 67.71; H, 7.31; N, 5.64. Found: C, 67.65; H, 7.33; N, 5.62. Chiral HPLC: (1′*S*,5*R*)-**6e**, t_R 15.93 min (97.0%); (1′*R*,5*S*)-**6e**, t_R 19.38 min (3.0%) (Whelk-O1, hexane/EtOH = 80:20, 0.9 mL/min, 254 nm).

(*R*)-1-(Benzyloxycarbonyl)-5-[(*R*)-1-[4-methoxy-2-(methylthio)phenylamino]-2-(*tert*-butyldimethylsilyl)-oxyethyl]-1*H*-pyrrol-2(5*H*)one (*anti*-6f). Prepared according to the representative procedure, utilizing aldehyde **2g** (38.8 μL, 0.21 mmol), aniline **3c** (35.5 mg, 0.21 mmol), and pyrrole **1e** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be >95:5 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica gel flash chromatography (petroleum ether/EtOAc 70:30) to yield 58.1 mg (51%) of the *anti*-**6f** as a yellow resin: TLC, R_f = 0.38 (petroleum ether/EtOAc = 70:30); $[\alpha]^{20}_D$ = +106.9 (c = 0.57, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, J = 6.2, 2.1 Hz, 1H, H4), 7.43−7.40 (m, 2H, Cbz), 7.38−7.30 (m, 3H, Cbz), 6.92 (d, J = 2.9 Hz, 1H, H3″), 6.55 (dd, J = 8.9, 2.9 Hz, 1H, H5″), 6.40 (brd, J = 9.0 Hz, 1H, H6″), 6.21 (dd, J = 6.2, 1.6 Hz, 1H, H3), 5.34 (d, J = 12.4 Hz, 1H, Cbz), 5.26 (d, J = 12.4 Hz, 1H, Cbz), 5.09 (brs, 1H, H5), 4.46 (dt, J = 5.6, 2.8, 2.8 Hz, 1H, H1′), 3.89 (dd, J = 10.6, 2.2 Hz, 1H, H2′), 3.74 (dd, J = 10.6, 5.8 Hz, 1H, H2′) 3.70 (s, 3H, OMe), 2.23 (s, 3H, SMe), 0.92 (s, 9H, ^{t}Bu), 0.06 (s, 3H, CH_3), 0.05 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5 (Cq), 151.5 (Cq), 151.2 (Cq), 148.2 (CH), 141.3 (Cq), 135.3 (Cq), 128.6 (2CH), 128.3 (CH), 128.2 (CH), 128.1 (2CH), 121.6 (Cq), 119.4 (CH), 115.2 (CH), 111.7 (CH), 67.9 (CH_2), 65.8 (CH), 63.7 (CH_2), 55.8 (CH_3), 54.6 (CH), 25.9 (CH_3), 18.1 (Cq), 18.1 (CH_3), −5.6 ($2CH_3$); ESI-MS m/z 565.30 $[M + Na]^+$ (calcd 565.23 $[M + Na]^+$). Anal. Calcd for $C_{28}H_{38}N_2O_5SSi$: C, 61.96; H, 7.06; N, 5.16.

Found: C, 62.0; H, 7.10; N, 5.19. Chiral HPLC: (1′*S*,5*R*)-**6f**, t_R 15.24 min (91.0%); (1′*R*,5*S*)-**6f**, t_R 17.90 min (9.0%) (Whelk-O1, hexane/EtOH = 80:20, 0.9 mL/min, 254 nm).

(*R*)-1-(Benzyloxycarbonyl)-5-[(*R*)-[4-methoxy-2-(methylthio)-phenylamino][(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl]-1*H*-pyrrol-2(5*H*)one (8) and (*S*)-(1-benzyloxycarbonyl)-5-[(*S*)-[4-methoxy-2-(methylthio)phenylamino][(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl]-1*H*-pyrrol-2(5*H*)one (*ent*-9) (Scheme 2, eq 1). Prepared according to the representative procedure, utilizing aldehyde (*R*)-**7** (27.3 mg, 0.21 mmol), aniline **3c** (35.5 mg, 0.21 mmol), and pyrrole **1e** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be 89:11 (**8**:*ent*-**9**) by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica gel flash chromatography (petroleum ether/EtOAc elution gradient from 80:20 to 75:25) to yield 61.5 mg (59%) of **8** and 7.6 mg (7%) of *ent*-**9** as a light yellow resin: TLC, R_f = 0.30 (petroleum ether/EtOAc=70:30). Analitycally pure samples were then obtained by semipreparative HPLC (CN 100A 10 μ, hexane/EtOH = 98:2, 3.0 mL/min, 254 nm, t_R 57.17 for **8** and t_R 63.29 for *ent*-**9**). Data for **8**: $[\alpha]^{20}_D$ = +261.6 (*c* = 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 6.2, 2.1 Hz, 1H, H4), 7.46−7.35 (m, 5H, Cbz), 6.94 (d, *J* = 2.9 Hz, 1H, H3″), 6.44 (dd, *J* = 8.9, 2.9 Hz, 1H, H5″), 6.23 (d, *J* = 9.0 Hz, 1H, H6″), 6.19 (dd, *J* = 6.3, 1.6 Hz, H3), 5.35 (1/2 ABq, *J* = 12.4 Hz, 1H, Cbz), 5.29 (1/2 ABq, *J* = 12.4 Hz, 1H, Cbz), 4.91 (dd *J* = 4.3, 2.2 Hz, 1H, H5), 4.73 (brs, 1H, NH), 4.49 (m, 2H, H1′, H2′), 4.05 (dd, *J* = 8.0, 6.6 Hz, 1H, H3′), 3.68 (s, 3H, OMe), 3.61 (dd, *J* = 7.8, 7.7 Hz, 1H, H3′), 2.25 (s, 3H, SMe), 1.51 (s, 3H, CH_3), 1.42 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (Cq), 151.9 (Cq), 151.4 (Cq), 149.1 (CH), 142.2 (Cq), 135.5 (Cq), 128.8 (2CH), 128.6 (CH), 128.4 (2CH), 128.2 (CH), 120.9 (Cq), 120.0 (CH), 115.3 (CH), 110.6 (Cq), 110.4 (CH), 76.8 (CH), 68.3 (CH_2), 67.5 (CH), 66.8, (CH_2), 56.0 (CH_3), 53.3 (CH), 26.5 (CH_3), 25.7 (CH_3), 18.7 (CH_3); ESI-MS *m*/*z* 521.23 $[M + Na]^+$ (calcd 521.18 $[M + Na]^+$). Anal. Calcd for $C_{26}H_{30}N_2O_6S$: C, 62.63; H, 6.06; N, 5.62. Found: C, 62.51; H, 6.11; N, 5.68. Data for *ent*-**9**: $[\alpha]^{20}_D$ = −174.2 (*c* = 0.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.35 (m, 6H, Cbz, H4), 6.90 (d, *J* = 2.9 Hz, 1H, H3″), 6.56 (dd, *J* = 8.9, 2.9 Hz, 1H, H5″), 6.43 (d, *J* = 8.9 Hz, 1H, H6″), 6.35 (dd, *J* = 6.2, 1.6 Hz, H3), 5.25 (d, *J* = 12.3 Hz, 1H, Cbz), 5.24 (m, 1H, H5), 5.15 (d, *J* = 12.3 Hz, 1H, Cbz), 4.47 (m, 1H, H1′), 4.07 (m, 2H, H2′, H3′), 3.91 (m, 1H, H3′), 3.69 (s, 3H, OMe), 2.27 (s, 3H, SMe), 1.54 (s, 3H, CH_3), 1.40 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (Cq), 152.2 (2Cq), 146.5 (CH), 141.3 (Cq), 135.3 (Cq), 130.1 (CH), 128.8 (2CH), 128.5 (CH), 128.3 (2CH), 122.0 (Cq), 119.0 (CH), 115.2 (CH), 112.4 (CH), 110.6 (Cq), 76.8 (CH), 68.2 (2C, CH_2/CH), 66.3 (CH), 57.1 (CH), 55.9 (CH_3), 27.2 (CH_3), 25.4 (CH_3), 18.9 (CH_3); ESI-MS *m*/*z* 521.14 $[M + Na]^+$ (calcd 521.18 $[M + Na]^+$). Anal. Calcd for $C_{26}H_{30}N_2O_6S$: C, 62.63; H, 6.06; N, 5.62. Found: C, 62.41; H, 6.11; N, 5.67.

(*R*)-1-(Benzyloxycarbonyl)-5-[(*R*)-[4-methoxy-2-(thiomethyl)-phenylamino][(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl]-1*H*-pyrrol-2(5*H*)one (9) (Scheme 2, eq 2). Prepared according to the representative procedure, utilizing aldehyde (*S*)-**7** (27.3 mg, 0.21 mmol), aniline **3c** (35.5 mg, 0.21 mmol), and pyrrole **1e** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be >95:5 by ^{1}H NMR analysis of the crude reaction mixture (no other isomers detected). The crude residue was purified by silica gel flash chromatography (petroleum ether/EtOAc elution gradient from 80:20 to 75:25) to yield 65.9 mg (63%) of **9** as a light yellow resin: TLC, R_f = 0.30 (petroleum ether/EtOAc = 70:30). Data for **9**: $[\alpha]^{20}_D$ = +178.3 (*c* = 0.18, $CHCl_3$); for ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$), see compound *ent*-**9**; ESI-MS *m*/*z* 521.21 $[M + Na]^+$ (calcd 521.18 $[M + Na]^+$). Anal. Calcd for $C_{26}H_{30}N_2O_6S$: C, 62.63; H, 6.06; N, 5.62. Found: C, 62.52; H, 6.06; N, 5.61.

Compounds 8 and 9 (Scheme 2, eq 3). Prepared according to the representative procedure, utilizing aldehyde (*R*,*S*)-**7** (27.3 mg, 0.21 mmol), aniline **3c** (35.5 mg, 0.21 mmol), and pyrrole **1e** (90.0 mg, 0.31 mmol). The diastereomeric ratio of the addition products was determined to be 44:56 (**8**:**9**) by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 80:20−75:25) to yield 29.5 mg (28%) of **8** and 37.5 mg (36%) of **9** as a light yellow resin: TLC, R_f = 0.30 (petroleum ether/EtOAc = 0:30). Analytically pure samples were then obtained by semipreparative HPLC (CN 100A 10 μ, hexane/EtOH = 98:2, 3.0 mL/min, 254 nm, t_R 57.17 for **8** and t_R 63.29 for **9**). Data for **8**: $[\alpha]^{20}_D$ = +257.7 (*c* = 0.8, $CHCl_3$); data for **9**: $[\alpha]^{20}_D$ = +158.5 (*c* = 0.18, $CHCl_3$).

(3*S*,4*S*,5*S*)-1-(Benzyloxycarbonyl)-5-[(*S*)-1-[4-methoxy-2-(thiomethyl)phenylamino]ethyl]-3,4-dihydroxypyrrolidin-2-one (10). To a stirred solution of the lactam *anti*-**6c** (50 mg, 0.12 mmol) in dry CH_2Cl_2 (2.0 mL) were added dicyclohexano-18-crown-6 ether (22.6 mg, 0.06 mmol) and powdered $KMnO_4$ (30 mg, 0.19 mmol) at room temperature. After 2 h, the reaction was quenched by the addition of saturated aqueous Na_2SO_3 and citric acid solutions to the reaction mixture until the brown color disappeared. The resulting colorless solution was extracted with EtOAc (3 × 10 mL), and the organic layers were collected, dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by silica gel flash chromatography (petroleum ether/EtOAc = 40:60−30:70) to yield 21.4 mg (40%) of **10** as a red resin: TLC, R_f = 0.88 (petroleum ether/EtOAc = 40:60); $[\alpha]^{20}_D$ = +112.7 (*c* = 0.19, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48−7.38 (m, 5H, Cbz,), 6.89 (d, *J* = 2.8 Hz, 1H, H3″), 6.41 (dd, *J* = 8.8, 2.7 Hz, 1H, H5″), 6.20 (d, *J* = 8.8 Hz, 1H, H6″), 5.36 (s, 2H, Cbz), 4.70 (d, *J* = 4.9 Hz, 1H, H3), 4.52 (d, *J* = 4.9 Hz 1H, H4), 4.20 (d, *J* = 1.8 Hz, 1H, H5), 3.94 (m, 1H, H1′), 3.70−3.90 (brs, 1H, OH), 3.71 (s, 3H, OMe), 3.45 (brs, 1H, OH), 2.28 (s, 3H, SMe), 1.33 (d, *J* = 6.5 Hz, 1H, CH_3, H2′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7 (Cq), 152.5 (Cq), 151.9 (Cq), 140.9 (Cq), 135.5 (Cq), 128.9 (2CH), 128.7 (3CH), 123.2 (Cq), 118.5 (CH), 114.6 (CH), 112.3 (CH), 71.7 (CH), 70.5 (CH), 69.2 (CH_2), 66.6 (CH), 56.0 (CH_3), 50.6 (CH), 19.2 (CH_3), 18.4 (CH_3); ESI-MS *m*/*z* 469.18 $[M + Na]^+$ (calcd 469.15 $[M + Na]^+$). Anal. Calcd for $C_{22}H_{26}N_2O_6S$: C, 59.18; H, 5.87; N, 6.27. Found: C, 59.11; H, 5.93; N, 6.24.

(*R*)-5-[(*S*)-1-[(Benzyloxycarbonyl)amino]-3-methylbutyl]-pyrrolidin-2-one (11). To a solution of *anti*-**5e** (29 mg, 0.06 mmol) in MeOH (1.0 mL), cooled to 0 °C into an ice bath, was added $NiCl_2 \cdot 7H_2O$ (11.4 mg, 0.05 mmol), and the resulting solution was allowed to vigorously stir at the same temperature. After 10 min $NaBH_4$ (6.0 mg, 0.16 mmol) was added in one portion with the occurrence of a vigorous gas evolution. Stirring was continued, and the reaction was monitored by TLC. After 6 h, the reaction mixture was quenched and neutralized by adding a saturated aqueous NH_4Cl solution (8 mL), and the resulting biphasic mixture was stirred vigorously for an additional 30 min. The phases were separated, and the aqueous layer was washed with CH_2Cl_2 (3 × 10 mL). The organic layers were collected, dried over $MgSO_4$, filtered, and concentrated in vacuo. The reaction crude was purified by silica gel flash chromatography (Et_2O) to yield 21.5 mg (74%) of a saturated lactam intermediate as yellow resin. In a 10 mL round-bottom flask containing the previously prepared lactam intermediate (21.5 mg, 0.05 mmol, 1.0 equiv) were added CAN (62 mg, 0.11 mmol, 2.4 equiv), MeCN (250 μL), and H_2O (40 μL). The mixture was allowed to stir at 0 °C for 10 min. Aqueous HCl 1 N (60 μL) was added, and the resulting solution was warmed to 22 °C and allowed to stir at the same temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with aqueous HCl 1 N (3 × 3 mL). Aqueous NaOH 2 N was added to the collected aqueous layers until pH = 10 was reached. The basified aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the organic phases were collected, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 5.7 mg (40%, two steps from *anti*-**5e**) of **11** as a red resin: TLC, R_f = 0.33 (EtOAc/MeOH = 95:5); $[\alpha]^{20}_D$ = −33.9 (*c* = 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO) δ 7.57 (s, 1H, NH), 7.39−7.28 (m, 5H, Ph), 7.11 (d, *J* = 9.4 Hz, 1H, NH), 5.04 (s, 2H, Cbz), 3.52 (m, 1H, H1′), 3.41 (m, 1H, H5), 2.11−1.93 (m, 3H, H3, H4), 1.79 (m, 1H, H3), 1.57 (m, 1H, H3′), 1.24 (m, 2H, CH_2, H2′), 0.87 (d, *J* = 6.7 Hz, 3H, CH_3), 0.84 (d, *J* = 6.5 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3 (Cq), 156.8 (Cq), 136.4 (Cq), 128.8 (2CH), 128.4 (CH), 128.3 (2CH), 67.2 (CH_2), 58.7 (CH), 52.0 (CH), 39.3 (CH), 30.1 (CH_2), 24.9

(CH), 23.7 (CH_2), 22.5 (CH_3), 21.8 (CH_3); ESI-MS m/z 327.5 $[M + Na]^+$ (calcd 327.18 $[M + Na]^+$). Anal. Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 66.95; H, 7.97; N, 9.18.

(2*S*,3*R*,3a*S*,6a*S*)-3-[4-Methoxy-2-(methylthio)phenylamino]-4-(benzyloxycarbonyl)-hexahydro-2-(hydroxymethyl)furo[3,2-*b*]pyrrol-5-one (12). Lactam **8** (21 mg, 0.04 mmol) was treated with 80% aq acetic acid (750 μL), and after being stirred at 40 °C for 18 h, the resulting solution was concentrated under vacuo. The reaction crude was purified by silica gel flash chromatography (petroleum ether/EtOAc 30:70) to yield 6.0 mg (30%) of a partially deprotected diol intermediate as a yellow resin. To a solution of the previously prepared lactam intermediate (6.0 mg, 0.013 mmol) in dry THF (1.7 mL), DBU (3.0 μL, 0.02 mmol) was added, and the resulting solution was stirred for 19 h at room temperature. The reaction mixture was then filtered through a short pad of silica gel that was washed with EtOAc (15 mL). After concentration in vacuo, the crude residue was purified by silica gel flash chromatography (petroleum ether/EtOAc 20:80) to yield 6.0 mg (quantitative yield) of **12** as a brownish resin: TLC, R_f = 0.60 (EtOAc); $[\alpha]^{20}_D$ = +14.0 (c = 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.37 (m, 5H, Cbz,), 7.01 (d, J = 8.9 Hz, 1H, H6′), 6.98 (d, J = 2.9 Hz, 1H, H3′), 6.69 (dd, J = 8.8, 2.9 Hz, 1H, H5′), 5.39 (1/2 ABq, J = 12.8 Hz, 1H, Cbz), 5.35 (1/2 ABq, J = 13.0 Hz, 1H, Cbz), 4.87 (td, J = 5.1, 2.6 Hz, 1H, H6a), 4.73 (s, 1H, OH), 4.57 (dd, J = 5.4, 0.8 Hz, 1H, H3a), 4.36 (brd, J = 4.1 Hz, 1H, H3), 4.30 (q, J = 4.4 Hz, 1H, H2), 3.96 (1/2 ABq, J = 12.3, 4.4 Hz, 1H, CH_2OH), 3.91 (1/2 ABq, J = 12.2, 4.6 Hz, 1H, CH_2OH), 3.83 (s, 1H, NH), 3.78 (s, 3H, OMe), 2.80−2.78 (m, 2H, H6), 2.37 (s, 3H, SMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5 (Cq), 152.7 (Cq), 151.9 (Cq), 139.8 (Cq), 136.5 (Cq), 128.9 (2CH), 128.8 (CH), 128.5 (2CH), 123.3 (Cq), 118.6 (CH), 114.2 (CH), 113.1 (CH), 79.3, (CH), 72.6 (CH), 68.8 (CH_2), 67.7 (CH), 61.5 (CH_2), 60.9 (CH), 56.0 (CH_3), 40.0 (CH_2), 17.8 (CH_3); ESI-MS m/z 481.3 $[M + Na]^+$ (calcd 481.15 $[M + Na]^+$); HRMS (NSI) calcd for $C_{23}H_{27}N_2O_6S$ $[M + H]^+$ 459.1590, found 459.1601.

■ ASSOCIATED CONTENT

Supporting Information

General experimental information, full list of the optimization experiments, chiral HPLC traces, transition-state models, and copies of NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: giovanni.casiraghi@unipr.it; franca.zanardi@unipr.it.

■ ACKNOWLEDGMENTS

Funding from Università degli Studi di Parma is gratefully acknowledged. We thank the Centro Interdipartimentale Misure "G. Casnati" (Università degli Studi di Parma) for instrumental facilities. We are grateful to Silvia Migliari (Università degli Studi di Parma) for preliminary experiments.

■ REFERENCES

(1) For leading reviews on vicinal diamines in organic synthesis and medicinal chemistry, see: (a) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161. (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. (c) Viso, A.; de la Pradilla, R. F.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167. (d) Saibabu Kotti, S. R. S; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101.

(2) (a) Zhong, Y.-W.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2004**, *6*, 4747. (b) Ooi, T.; Takeuchi, M.; Kato, D.; Uematsu, Y.; Tayama, E.; Sakai, D.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 5073.

(3) (a) Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504. (b) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843. (c) Rondot, C.; Zhu, J. *Org. Lett.* **2005**, *7*, 1641. (d) Chowdari, N. S.; Ahmad, M.; Albertshofer, K.; Tanaka, F.; Barbas, C. F. III. *Org. Lett.* **2006**, *8*, 2839.

(4) For examples on catalytic asymmetric Mannich-type reactions of glycine-derived Schiff bases, see: (a) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583. (b) Ooi, T.; Kameda, M.; Fuji, J.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397. (c) Hernández-Toribio, J.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 16150. (d) Shang, D.; Liu, Y. L.; Zhou, X.; Liu, X.; Feng, X. *Chem.—Eur. J.* **2009**, *15*, 3678. (e) Liang, G.; Tong, M.-C.; Tao, H.; Wang, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 1851.

(5) For selected reviews on the vinylogous Mannich reaction, see: (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. (b) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221. (c) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895. (d) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G. *Synlett* **2009**, 1525. (e) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev* **2011**, *111*, 3076. For recent examples on Mukaiyama-Mannich vinylogous reaction, see: (f) Dudot, B.; Chiaroni, A.; Royer, J. *Tetrahedron Lett.* **2000**, *41*, 6355. (g) DeGoey, D. A.; Chen, H.-J.; Flosi, W. J.; Grampovnik, D. J.; Yeung, C. M.; Klein, L. L.; Kempf, D. J. *J. Org. Chem.* **2002**, *67*, 5445. (h) Yang, Y.; Phillips, D. P.; Pan, S. *Tetrahedron Lett.* **2011**, *52*, 1549. (i) Ruan, S.-T.; Luo, J.-M.; Du, Y.; Huang, P.-Q. *Org. Lett.* **2011**, *13*, 4938.

(6) Curti, C.; Battistini, L.; Ranieri, B.; Pelosi, G.; Rassu, G.; Casiraghi, G.; Zanardi, F. *J. Org. Chem.* **2011**, *76*, 2248.

(7) (a) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7230. (b) Mandai, H.; Mandai, K.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 17961. (c) Wieland, L. C.; Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 570.

(8) Curti, C.; Ranieri, B.; Battistini, L.; Rassu, G.; Zambrano, V.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Adv. Synth. Catal.* **2010**, *352*, 2011.

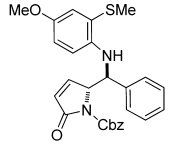
(9) The relative 5*R**,1′*S**-*anti*-configuration of **5a** was established by single crystal X-ray analysis of the racemate. See: Sartori, A.; Dell'Amico, L.; Curti, C.; Battistini, L.; Pelosi, G.; Rassu, G.; Casiraghi, G.; Zanardi, F. *Adv. Synth. Catal.* **2011**, in press.

(10) Strictly speaking, this VMMn procedure lies between a two-component stepwise modality (the imine intermediate is isolated) and a three-component one-pot execution (all reagents are mixed together from the beginning).

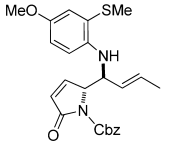
(11) As protic scavenger of the evolving silicon ion species, water may concur in depletion of the competitive racemic background reaction catalyzed by the silicon ions themselves, thus resulting in improved stereoselectivity. See also refs 6 and 7a.

(12) The complete progress toward the optimized conditions for the enantioselective VMMn reaction is detailed in Tables S1 and S2 in the Supporting Information.

(13) As illustrated by the examples below, by following the reaction conditions of entry 13 in Table 1, the catalytic asymmetric VMMn reaction with aldimines derived from aromatic or α,β-unsaturated



yield = 12%; conv = 18% (*anti*)
dr (*anti*:*syn*) = 67:23
er (*anti*) = 90:10



yield = 5%; conv = 8%

aldehydes proceed in lower yields and with modest diastereo- and enantioselectivity.

(14) For other examples on *N*-Cbz group-migration, see: (a) Bunch, L.; Norrby, P.-O.; Frydenvang, K.; Krogsgaard-Larsen, P.; Madsen, U. *Org. Lett.* **2001**, *3*, 433. (b) Quijada, F. J.; Gotor, V.; Rebolledo, F. *Org. Lett.* **2010**, *12*, 3602.

(15) (a) Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P.; Gasparri Fava, G.; Ferrari Belicchi, M. *Tetrahedron* **1990**, *46*, 5807. (b) Gawroński, J.; Gawrońska, K.; Kwit, M.; Kacprzak, K.; Rychlewska, U. *Chirality* **2004**, *16*, 405. (c) Cuiper, A. D.; Brzostowska, M.; Gawroński, J. K.; Smeets, W. J. J.; Spek, A. L.; Hiemstra, H.; Kellogg, R. M.; Feringa, B. L. *J. Org. Chem.* **1999**, *64*, 2567.

(16) For plausible transition-state models, see Figure S1 in the Supporting Information.

(17) Prasad, K. R.; Gholap, S. L. *J. Org. Chem.* **2008**, *73*, 2.