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anti-Selective, Catalytic Asymmetric Vinylogous Mukaiyama Mannich Reactions of Pyrrole-Based Silyl Dienolates with *N*-Aryl Aldimines

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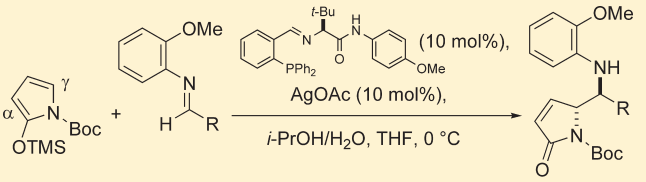
Supporting Information

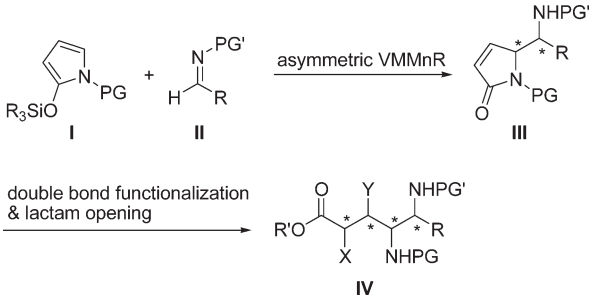
ABSTRACT: Pyrrole-based silyl dienolates undergo asymmetric vinylogous Mukaiyama Mannich reactions with a series of *N*-aryl aldimines in the presence of the Hoveyda−Snapper amino acid-derived silver(I) catalysts. The Mannich products—α,β-unsaturated δ-amino-γ-butyrolactams—are typically obtained in high yields, excellent γ-site selectivities and *anti*-diastereoselectivities, and up to 80% enantioselectivity.



The vinylogous, asymmetric Mukaiyama Mannich-type reactions (VMMnR) of imines with silicon dienolates provide very effective ways to construct δ-amino-α,β-unsaturated carbonyl frameworks, which are versatile building blocks for a myriad of important multifunctional fragments and target compounds.[1−6] There are only a few reported studies in this emerging area of research that utilize both acyclic and heterocyclic silicon dienolates reacting with preformed or in situ-generated imine components. In a closely related series of papers, Schneider[1] and Akiyama[2a] independently investigated the Brønsted acid-catalyzed, enantioselective VMMnR of acyclic silyl dienolates with aldimines exploiting varied axially chiral BINOL phosphoric acid catalysts, while a disclosure by Feng and Liu[3] centered upon a three-component VMMnR catalyzed by chiral scandium(III) *N*,*N*′-dioxide complexes. The utility of the heterocyclic furan-based silicon dienolates in asymmetric VMMnR with aldimines was scrutinized with copper(I) ferrocenyl complexes,[4] silver(I) diphenylphosphino binaphthyl complexes,[5] and iodinated dinaphthyl phosphoric acids.[2b] A notable advance in this technique was recently reached by Hoveyda and Snapper,[6] who utilized furan-based silyloxy dienes in the presence of designed, amino acid-derived silver(I) catalysts. Highly valuable, chiral nonracemic δ-aminated γ-butenolide fragments formed in this way, with unprecedented levels of chemical efficiency and site-, diastereo-, and enantiocontrol.

Complementary to these seminal works, herein we describe our efforts to expand the scope of catalytic, asymmetric VMMnR to involve pyrrole-based silicon dienolates, a d_4 donor progeny whose utility in this domain is still substantially unexplored.[7] As illustrated in Scheme 1, the reaction between a generic pyrrole **I** and imine **II** can deliver enantioenriched α,β-unsaturated δ-amino-γ-butyrolactam adducts of type **III** that can be viewed as

Scheme 1. The Synthetic Potential of the Asymmetric VMMnR As Applied to Pyrrole Silicon Dienolates



precursor candidates to be manipulated into a huge number of structurally and stereochemically diverse aminated carbon entities as, for example, open chain α,β-substituted-γ,δ-diamino carbonyls of type **IV** bearing up to four contiguous carbon stereocenters.

With this goal in mind, we began with the model reaction between *N*-Boc-2-[(*tert*-butyldimethyl)silyloxy]pyrrole (**1a**) and preformed arylimine **2a** (Table 1), which was scrutinized with the chiral catalysts **C1**−**C7** displayed in Figure 1.

The catalyst choice was mainly based upon two criteria: (1) documented efficiency in related asymmetric, catalyzed vinylogous Mukaiyama-type Mannich or aldol processes and (2) easy access from readily available natural or synthetic sources. Thus, catalysts included amino acid-derived silver(I) complexes **C1**−

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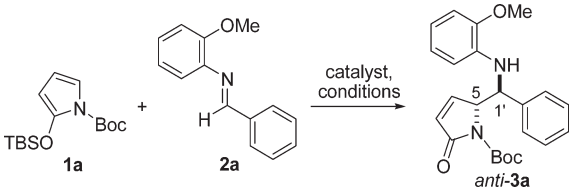
Table 1. Initial Catalyst Screening Studies of the Asymmetric VMMnR of Pyrrole 1a with *N*-Arylimine 2a[a]



entry	catalyst	conv (%)[b]	dr[c] (*anti*:*syn*)	er[d] (*anti*)
1	**C1**·AgOAc	20	99:1	58:42
2	**C2**·AgOAc	15	99:1	55:45
3	**C3**·AgOAc	30	99:1	63:37
4	**C4**	95	60:40	55:45[e]
5	**C5**	71	65:35	55:45[e]
6	**C6**·$SiCl_4$	80	55:45	51:49[e]
7	**C7**·TFA	30	80:20	52:48[e]

[a] For each catalyst, almost the same conditions previously utilized in the original works were adopted: entries 1−3, ref 6a; entries 4 and 5, ref 1; entry 6, refs 8 and 9; and entry 7, ref 10. [b] Conversion determined by ^{1}H NMR analysis of the crude reaction product. [c] Determined by HPLC analysis of the crude reaction mixture. [d] Determined by HPLC analysis, using a Chiralcel OD-H column. [e] Absolute configuration not determined.

C3·AgOAc developed by the Hoveyda and Snapper group,[6] the axially chiral BINOL phosphoric acids **C4** and **C5** widely exploited by Schneider et al.,[1] Denmark's bisphosphoramide/silicon tetrachloride dual system **C6**·$SiCl_4$,[8,9] and the cinchona-thiourea organocatalyst **C7**·TFA, successfully utilized by Deng et al.[10]

As the results in Table 1 indicate, the initial move was less rewarding and, although high diastereoselectivity in favor of the *anti*-configured adduct *anti*-**3a** was attained with the three silver complexes **C1**−**C3**·AgOAc (entries 1−3), reactions were inefficient (15−30% conversion after 16 h) and enantioselectivity was low (<65:35 dr in favor of the 5*R*,1′*S*-configured isomer). With catalysts **C4** and **C5**, reaction rates increased (entries 4 and 5) but neither the relative nor absolute stereocontrol were substantially detected. The dual bisphosphoramide/$SiCl_4$ system **C6**·$SiCl_4$, which proved an excellent catalyst in directing asymmetric vinylogous aldol-type processes with pyrrole- and furan-based dienoxy silanes,[9] failed with the Mannich variant, and a balanced mixture of racemic adducts *anti*-**3a** and *syn*-**3a** was formed (entry 6). Similarly, bifunctional alkaloid-thiourea salt **C7**·TFA proved to be an inefficient catalyst that afforded poor yields of racemates (entry 7).

At this point, in recognizing how the nature of the pyrrole donor component could impact both the efficiency and stereocontrol in similar vinylogous additions to aldehyde acceptors,[9] we next wondered whether the low yield and enantioselectivity of the silver-catalyzed reaction in entry 3 of Table 1 leading to *anti*-**3a** could be improved here by altering the nitrogen and silicon functionalities in the donor pyrrole substrates. This proved to be the case, indeed, as shown in entry 3 of Table 2. After the VMMnR between *N*-Boc-trimethylsilyl-substituted pyrrole **1c** with imine **2a** had been conducted in the presence of the silver catalyst **C3**·AgOAc, *anti*-**3a** was formed in 60% yield with almost

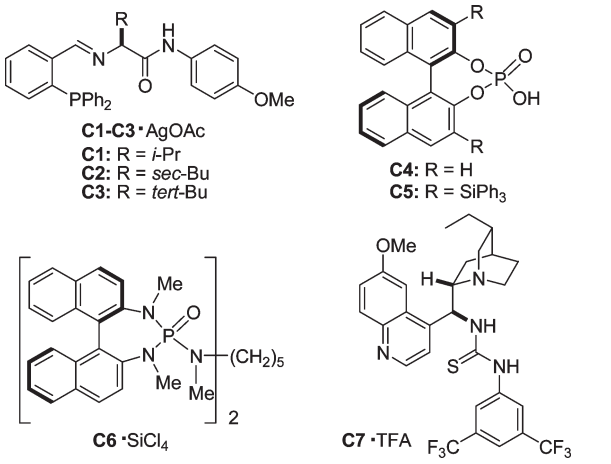
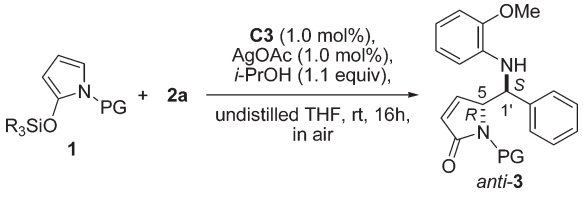


Figure 1. Structures of the chiral catalyst systems of this study.

Table 2. Examination of Silyloxypyrrole Donors 1 Bearing Different Silicon Substituents and *N*-Protecting Groups[a]



entry	pyrrole	R_3Si	PG	yield (%)[b]	dr[c] (*anti*:*syn*)	er[d] (*anti*)
1	**1a**	TBS	Boc	30	99:1	63:37
2	**1b**	TES	Boc	34	99:1	65:35
3	**1c**	TMS	Boc	60	99:1	68:32
4	**1d**	TBS	allyl	20	99:1	51:49
5	**1e**	TBS	Me	—[e]		
6	**1f**	TMS	Me	—[e]		

[a] The reaction was performed with pyrrole **1**/aldehyde **2a** (1.0/1.0 equiv), ligand **C3** (1.0 mol %), AgOAc (1.0 mol %), undistilled *i*-PrOH (1.1 equiv), undistilled and stabilized (BHT, 250 ppm) THF, in air, at 25 °C for 16 h (0.21 mmol scale). [b] Isolated yield of the vinylogous Mannich products. [c] Determined by HPLC analysis of the crude reaction mixture. [d] Determined by HPLC analysis, using a Chiralcel OD-H column. [e] No Mannich product obtained.

complete γ-site selectivity and *anti*-selectivity, with moderate enantioselectivity (68:32 er) in favor of the 5*R*,1′*S*-isomer.

To optimize the reaction conditions further, the effects of the catalyst loading, the donor:acceptor ratio, the reaction temperature, and the additive were finally investigated by using catalyst **C3**, with the results grouped in Table 3. When the reaction between **1c** (1.5 equiv excess) and **2a** was performed at 0 °C in THF, using a 10.0 mol % ligand **C3**, in the presence of isopropanol/water (entry 7), the enantioselectivity of the Mannich product *anti*-**3a** was good (90:10 er), the yield high, and both γ-site- and diastereoselectivity excellent. In comparison, in the absence of water (entry 6), enantioselectivity diminished to 80:20, but yield was almost maintained. Increasing the amount of water to 3.0 equiv did not cause any additional improvement, but more water (10.0 equiv) was detrimental for both yield and enantioselectivity (entries 4 and 5). The dramatic role of water

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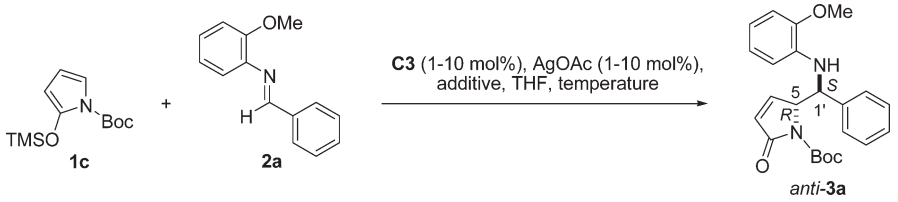
Table 3. Further Optimization of the Asymmetric VMMnR of Pyrrole 1c with *N*-Arylimine 2a, Using Silver(I) Catalyst C3·AgOAc[a]



entry	**1c**:**2a** (equiv)	**C3**·AgOAc (mol %)	temp (°C)	additive (equiv)	yield (%)[b]	γ:α	dr[c] (*anti*:*syn*)	er[d] (*anti*) (5*R*,1′*S*:5*S*,1′*R*)
1	1:1	1.0	25	*i*-PrOH (1.1)	60	>99:1	99:1	68:32
2	1.5:1	1.0	0	*i*-PrOH (1.5)	65	>99:1	99:1	80:20
3	1.5:1	10.0	−30	*i*-PrOH (1.1)	15	>99:1	99:1	92:8
4	1.5:1	10.0	0	*i*-PrOH (1.5), H_2O (10.0)	40	>99:1	99:1	68:32
5	1.5:1	10.0	0	*i*-PrOH (1.5), H_2O (3.0)	70	>99:1	99:1	78:22
6	1.5:1	10.0	0	*i*-PrOH (1.5)	72	>99:1	99:1	80:20
7	1.5:1	10.0	0	*i*-PrOH (1.5), H_2O (1.5)	80	>99:1	99:1	90:10

[a] The reactions were performed with ligand **C3**/AgOAc (1:1), undistilled *i*-PrOH, undistilled and stabilized (BHT, 250 ppm) THF, in air, for 16 h at the indicated temperature (0.21 mmol scale). [b] Isolated yield of the vinylogous Mannich products. [c] Determined by HPLC analysis of the crude reaction mixture. [d] Determined by HPLC analysis, using a Chiralcel OD-H column.

and protic additives on the efficiency and stereocontrol of these processes is noteworthy, yet precedented in similar catalytic reactions.[1a,5,6a] As a plausible explanation, one can argue that during the catalytic cycle (vide infra, Figure S2 in the Supporting Information) protic additives act as scavengers of the evolving silicon ion species to form inactive silanol or silyl ether byproducts. This results in catalyst turnover enhancement and, more importantly, in depletion of the competitive racemic background reaction catalyzed by the silicon ions themselves.

Lowering the reation temperature to −30 °C did decrease the yield significantly (15%) with only marginal benefit of the enantioselectivity (entry 3). Catalyst loading affected significantly both yield and enantioselectivity (see entry 2 vs 6), and the reactants ratio proved to be equally decisive (entry 2 vs 1). In summary, the optimized reaction conditions were established as 10.0 mol % silver catalyst **C3**·AgOAc (1:1 ligand:silver salt molar ratio), using 1.5 equiv excess pyrrole **1c** and 1.5 equiv of isopropanol/water (1:1 molar ratio) in commercial grade, undistilled BHT-stabilized THF, in an open-air vessel at 0 °C.

On the basis of the optimization efforts presented above, the scope of the acceptor substrate of the catalytic asymmetric VMMnR catalyzed by silver(I) catalyst **C3**·AgOAc was carried out (Table 4). In general, all the examined substrates could furnish the desired 5,1′-bis-aminated adducts in synthetically useful yields and selectivities.

A variety of aromatic aldehyde imines with either electron-donating or electron-withdrawing substituents in the aromatic ring underwent the asymmetric VMMnR to afford the respective *anti*-configured adducts as the exclusive products in 65−99% yields with excellent site-selectivities (>99:1 γ:α) and diastereomeric ratios (dr >98:2), with acceptable levels of enantiocontrol ranging from 71:29 to 90:10 er. The substitution pattern of the phenyl ring in **2** did not impact stereocontrol significantly, and heteroaromatic aldehyde imine **2f** was a viable substrate too, as was the 2-naphthaldehyde-derived imine **2e**.

To enlarge the scope of the reaction further, VMMnR involving two aliphatic aldimines, **2g** and **2h**, were scrutinized, giving rise to the expected amino lactams *anti*-**3g** and *anti*-**3h**. In these instances, while γ-site regiocontrol, *anti*-diastereopreference, and enantiocontrol proved similar to those displayed by aromatic imines, the efficiency declined, with isolated yields ranging from 52% to 36%.

The relative configuration of the major Mannich adduct *anti*-**3a** was assigned by single crystal X-ray analysis of the racemate (Supporting Information), while those of the remainder adducts *anti*-**3b**−*anti*-**3h** were proposed by analogy. The absolute configuration of *anti*-**3a** was unambiguously determined via chemical correlation to the known 5*S*,1′*S*-configured *syn*-butyrolactam (−)-(*S*)-*N*-(*tert*-butoxycarbonyl)-5-[(*S*)-hydroxy(phenyl)methyl]-1*H*-pyrrol-2(5*H*)-one,[9] as detailed in Scheme S1 (Supporting Information). By analogy (all the Mannich products were dextrorotatory), the absolute configuration of the other adducts *anti*-**3b**/*anti*-**3h** was proposed as shown in Table 4.

On the basis of the relative and absolute configuration of our major adducts *anti*-**3a**/*anti*-**3h** and the previous paradigmatic studies by the Hoveyda and Snapper group with asymmetric VMMnR of furan-based silyl dienolates,[6] the simple *anti*-selectivity and the facial 5*R*-selectivity observed in the silver-catalyzed asymmetric VMMnR of pyrrole silyl dienolates with *N*-arylimines can be rationalized by the catalytic mechanistic cycle depicted in Figure S2 in the Supporting Information.

To conclude, we have reported the first example of a catalytic, asymmetric VMMnR of pyrrole-based silyl dienolates with a series of *N*-arylimines. The efficient amino acid-derived silver(I) catalyst system, previously exploited by Hoveyda and Snapper[6] with furan-based silyl dienolates, exhibited good performance, giving rise to diverse *anti*-configured γ,δ-diamino α,β-unsaturated carbonyls in good yields, virtually complete γ-site- and diastereoselectivities, with up to 80% enantioselectivities. Exploitation of these findings in asymmetric synthesis of relevant multifunctional target molecules which contain vicinal diamino motifs is planned, and research in this direction is under way.

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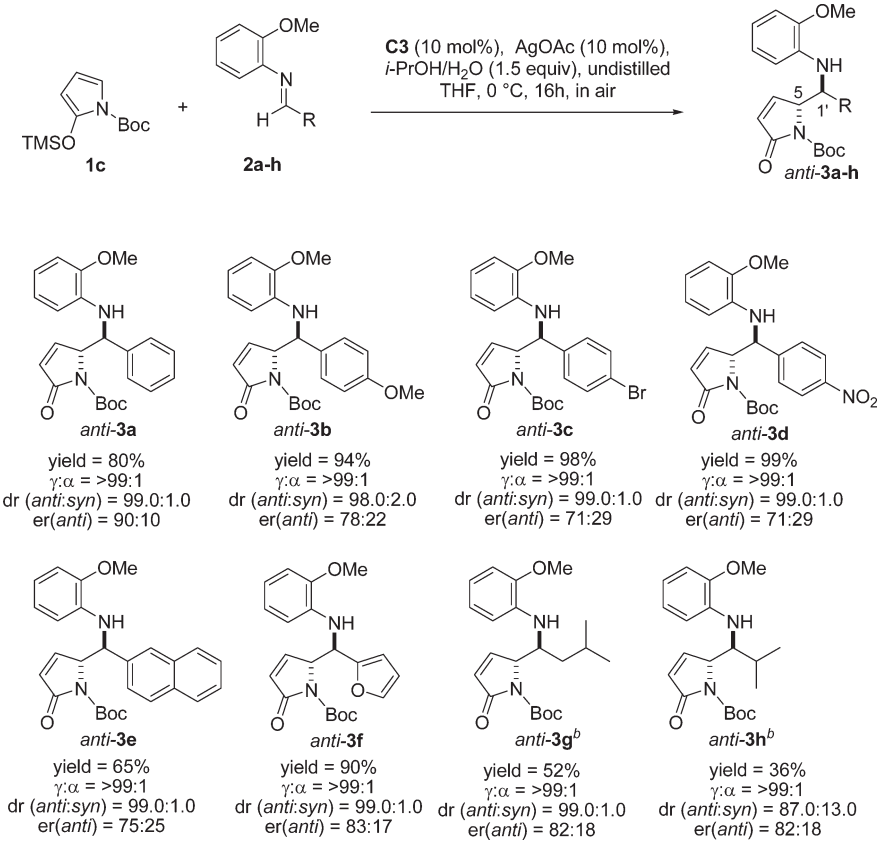
Table 4. Asymmetric VMMnR of Pyrrole 1c with Various Aromatic, Heteroaromatic, and Aliphatic *N*-Arylimines 2a−h Catalyzed by Silver(I) Complex C3·AgOAc[a]



[a] Conditions of entry 7 in Table 3. Yields refer to isolated vinylogous Mannich products. Diastereomeric ratios were determined by HPLC analysis of the crude reaction mixtures. Enantiomeric ratios were determined by HPLC analysis, using a Chiralcel OD-H column. [b] Three-component procedure, with the aliphatic imine component formed in situ. For details, see the Supporting Information.

EXPERIMENTAL SECTION

Representative Experimental Procedure for Ag-Catalyzed VMMnR. Preparation of (*R*)-5-(*N*-*tert*-Butoxycarbonyl)-[(*S*)-(2-methoxyphenylamino)(phenyl)methyl]-1*H*-pyrrol-2(5*H*)-one (*anti*-3a). Chiral phosphine **C3** (14.0 mg, 0.02 mmol, 0.10 equiv) and AgOAc (3.5 mg, 0.02 mmol, 0.10 equiv) were dissolved in undistilled BHT-stabilized (250 ppm) THF (4 mL) and allowed to stir for 5 min at 22 °C. A solution of imine **2a** (44.0 mg, 0.21 mmol, 1.0 equiv) in THF (1.0 mL) was added followed by addition of a mixture of *i*-PrOH (24.0 μL, 0.31 mmol, 1.5 equiv)/H_2O (6.0 μL, 0.31 mmol, 1.5 equiv) and the reaction vessel was capped with a septum. The mixture was allowed to cool to 0 °C and **1c** (82 mg, 0.31 mmol, 1.5 equiv) in THF (1.0 mL) was added. After 16 h the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (0.5 mL). The mixture was allowed to warm to 22 °C with vigorous stirring for 10 min, and finally extracted with EtOAc. The organic layers were collected, dried with $MgSO_4$, filtered, and concentrated in vacuo. The diastereomeric ratio of the addition products **3a** was determined to be 99:1 by analytical HPLC (CN-100, 5 μm, hexane/anhydrous EtOH 95:5, 1.0 mL/min, 254 nm): *anti*-**3a**, R_t 11.71 min (99.0%); *syn*-**3a**, R_t 14.33 min (1.0%). The crude residue was then purified by silica gel flash chromatography (hexane/Et_2O 70:30), to yield 62 mg (80%) of (+)-*anti*-**3a** as colorless crystals: TLC, R_f 0.38 (petroleum ether/EtOAc 70:30); chiral HPLC (Chiralcel OD-H, hexane/anhydrous EtOH 90:10, 1.0 mL/min, 254 nm): (5*R*,1′*S*)-**3a**, R_t 8.99 min (90.0%); (5*S*,1′*R*,)-**3a**, R_t 10.14 min (10.0%); $[\alpha]^{20}_D$ +99.5 (*c* 0.99, EtOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.30 (m, 5H, Ph), 6.92 (dd, *J* = 6.1, 2.0 Hz, 1H, H4), 6.77 (dd, *J* = 7.4, 2.1 Hz, 1H, H3″), 6.70 (ddd, *J* = 7.5, 7.5, 1.8 Hz, 1H, H5″), 6.65 (ddd, *J* = 7.5, 7.5, 1.9 Hz, 1H, H4″), 6.32 (dd, *J* = 7.2, 2.1 Hz, 1H, H6″), 6.30 (dd, *J* = 6.0, 1.6 Hz, 1H, H3), 5.44 (bd, *J* = 3.3 Hz, 1H, H1′), 5.06 (ddd, *J* = 3.6, 1.8, 1.8 Hz, 1H, H5), 4.44 (bs, 1H, NH), 3.86 (s, 3H, CH_3), 1.56 (s, 9H, *t*-Bu, Boc); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0 (Cq, C2), 149.6 (Cq, Boc), 147.3 (Cq, C2″), 146.1 (CH, C4), 139.7 (Cq, C1″), 136.9 (Cq, Ph), 129.3 (CH, C3), 129.1 (2C, CH, Ph), 128.0 (CH, Ph), 126.6 (2C, CH Ph), 121.2 (CH, C5″), 117.7 (CH, C4″), 111.6 (CH, C6″), 109.8 (CH, C3″), 83.7 (Cq, Boc), 67.7 (CH, C5), 57.3 (CH, C1′), 53.6 (CH_3, OMe), 28.3 (3C, CH_3, Boc). ESI-MS *m*/*z* 417.38 [M + Na^+] (calcd 417.18 [M + Na^+]). Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 70.13; H, 6.78; N, 6.95.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures, spectroscopic data for all new compounds, chiral HPLC traces, crystallographic data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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