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Uncatalyzed, Diastereoselective Vinylogous Mukaiyama Aldol Reactions on Aqueous Media: Pyrrole vs Furan 2-Silyloxy Dienes

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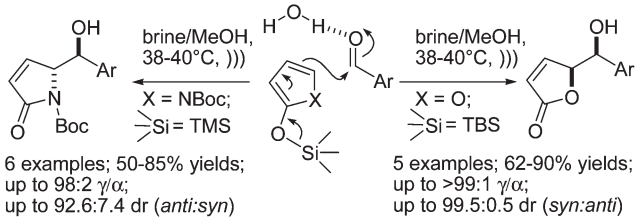

The first uncatalyzed, diastereoselective vinylogous Mukaiyama aldol reaction is reported, between pyrrole/furan-based dienoxy silanes and aromatic aldehydes on salty water/methanol medium, at almost human body temperature, under ultrasonic irradiation. With pyrrole dienes the reaction is *anti*-selective, while that of furan dienes is *syn*-selective. The dual role of water as both reaction medium and promoter is highlighted.

With a global volume of about 1.3 × 10^9 km^3, water is one of the most abundant chemical substances on the Earth's surface, where countless terrestrial and marine organisms live, grow, and propagate.[1] Water is a benign medium that assists the complex molecular machinery of living systems, and governs a myriad of vital biochemical transformations. From the times of ancient alchemy, organic chemists have had a troubled relationship with water, and it is only in recent times with old prejudices set aside that they have started to consider aqueous media as a plausible and clean alternative to customary organic solvents.[2]

For the past several years, we have been active in the vinylogous Mukaiyama-type aldol reaction (VMAR) domain exploiting a novel progeny of five-membered nitrogen, oxygen, and sulfur silyloxy diene heterocycles that emerged as a versatile d^4-donor pool with which highly decorated carbon segments and important molecular targets were realized.[3] On this wave, our aim here was to develop environmentally fair VMAR on aqueous media using pyrrole- and furan-based 2-silyloxy dienes, with the potential for preparation of varied butenolide-type functional frameworks.[4,5] To the best of our knowledge, this is the first report on uncatalyzed vinylogous Mukaiyama-type aldol addition reactions occurring in a heterogeneous aqueous environment.

At first, we set out to determine whether our proposal would allow access to vinylogous aldol products of type **3a**, by reacting *N*-Boc-2-(trimethylsilyloxy)pyrrole (**1a**) and benzaldehyde (**2a**) on aqueous media,[5] without the use of any other catalyst or promoter (Table 1). To ensure optimal conditions for a viable diastereoselective VMAR, we elected to survey a set of aqueous and nonaqueous reaction media vis-à-vis conventional control experiments in organic solvents. Using pure water[6] at ambient temperature, or better, at 38−40 °C in an open-air environment, at atmospheric pressure, the heterogeneous reaction proceeded under ultrasonic irradiation (US) and product **3a** was obtained after 8 h in 25−35% combined yield (entries 2 and 3), with almost complete γ-site selectivity and about 70:30 diastereomeric ratio in favor of the *anti*-configured isomer. On the contrary, without US irradiation (entry 1), the reactivity dropped, with a 15% yield of **3a** obtained after 24 h. Of note, control experiments carried out under neat conditions (entry 4), or uncatalyzed, homogeneous solutions in organic solvents such as CH_2Cl_2 and MeOH (entries 5 and 6), did not afford any appreciable result, thereby confirming the crucial role exerted by water in these processes. Next, we focused our attention on the optimization of yield and diastereomeric ratio. Inspired by the pioneering work of Breslow on the effect of hydrophobic interactions between organic reactants in an aqueous medium, we

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[1] (a) Gleick, P. H. In *Encyclopedia of Climate and Weather*; Schneider, S. H., Ed.; Oxford University Press: New York, 1996; Vol. 2, pp 817−823. (b) Debenedetti, P. G.; Stanley, H. E. *Phys. Today* **2003**, *56*, 40.

[2] For authoritative reviews about the state of the art of organic reactions carried out in/on aqueous media, see: (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blakie Academic & Professional: London, UK, 1998. (b) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. (c) Pirrung, M. C. *Chem.—Eur. J.* **2006**, *12*, 1312. (d) Lindström, U. M. *Organic Reactions in Water: Principles, Strategies and Applications*, 1st ed.; Blackwell Publishing: Oxford, UK, 2007. (e) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725. (f) Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302. For stereoselective organic reactions, see also: (g) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (h) Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33. (i) Mase, N.; Barbas, C. F., III *Org. Biomol. Chem.* **2010**, *8*, 4043.

[3] (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. (b) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G. *Synlett* **2009**, 1525. See also: (c) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682. (d) Hosokawa, S.; Tatsuta, K. *Mini-Rev. Org. Chem.* **2008**, *5*, 1. (e) Brodmann, T.; Lorenz, M.; Schackel, R.; Simsek, S.; Kalesse, M. *Synlett* **2009**, 174.

[4] Despite the importance and the tremendous impact on organic synthesis, only a few reports on uncatalyzed, Mukaiyama-type aldol reactions promoted by an aqueous medium could be found in the literature: (a) Lubineau, A. *J. Org. Chem.* **1986**, *51*, 2142. (b) Lubineau, A.; Meyer, E. *Tetrahedron* **1988**, *44*, 6065. (c) Loh, T. P.; Feng, L. C.; Wei, L. L. *Tetrahedron* **2000**, *56*, 7309.

[5] The term "on aqueous media" refers to a heterogeneous reaction according to the definition given by Sharpless and co-workers: (a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275. (b) Klijn, J. E.; Engberts, B. F. N. *Nature* **2005**, *435*, 746. See also refs 2e and 2f.

[6] In the present work, the term "water" refers to deionized water obtained by reverse osmosis (conducibility: $0 < C < 50\,\mu S$). The term "brine" refers to saturated aqueous NaCl solution.

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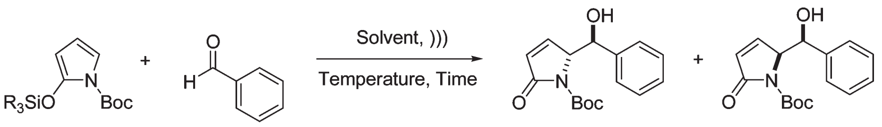
TABLE 1. Screening Conditions for Aqueous, Open-Air VMAR of Pyrrole Silyloxy Dienes 1a,b with Benzaldehyde 2a, Giving *anti*/*syn*-Configured Racemic Lactams 3a[a]



1a: R_3 = Me_3
1b: R_3 = *t*-BuMe_2
2a
anti-**3a**
syn-**3a**

entry	pyrrole	**1**:**2a** (equiv)	solvent	temp (°C)	time (h)	yield[b] (%)	γ/α	dr[c] (*anti*/*syn*)
1[d]	**1a**	1:1	H_2O	25−30	24	18 (15)	98/2	68.5/31.5
2	**1a**	1:1	H_2O	25−30	8	29 (25)	98/2	69.0/31.0
3	**1a**	1:1	H_2O	38−40	8	37 (35)	98/2	69.5/30.5
4	**1a**	1:1	neat	38−40	24	nd	nd	nd
5	**1a**	1:1	CH_2Cl_2	38−40	24	trace	nd	nd
6	**1a**	1:1	MeOH	38−40	8	trace	nd	nd
7	**1a**	1:1	sea water	38−40	8	42 (40)	95/5	85:15
8	**1a**	1:1	brine	38−40	8	51 (45)	90/10	92.0/8.0
9	**1a**	1:1	brine/MeOH (1:1)	38−40	8	69 (65)	95/5	84.0/16.0
10	**1b**	1:1	brine/MeOH (1:1)	38−40	8	13 (10)	nd	nd
11	**1a**	1:1	brine/MeOH (4:1)	38−40	8	65 (60)	95/5	88.2/11.8
12	**1a**	1:1	brine/MeOH (1:1)	55−60	8	38 (35)	98/2	80.0/20.0
13	**1a**	2:1	brine/MeOH (1:1)	38−40	8	56 (50)	98/2	80.0/20.0
14	**1a**	1:2	brine/MeOH (1:1)	38−40	3	80 (75)	98/2	83.3/16.7

[a] Unless otherwise noted, all reactions were carried out at atmospheric pressure under sonication (42 kHz ± 6%). For details, see the Supporting Information. [b] Determined by ^{1}H NMR analysis of the crude reaction product. Combined isolated yields in parentheses. [c] Determined by ^{1}H NMR analysis of the crude reaction product. [d] The reaction was carried out under vigorous stirring, without sonication.

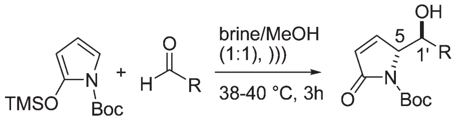
were confident that both the reaction rate and dr of the VMAR reaction could be improved by lowering the solubility of the reagents, enhancing as a consequence the hydrophobic interactions in the transition state.[7] This proved to be the case: exploiting the salting-out properties of NaCl,[8] we scrutinized salty water with increasing NaCl contents, from seawater to brine as the reaction medium (entries 7 and 8). The use of brine was the most effective, giving **3a** in 45% combined yield, 92:8 dr, and 90:10 γ/α site-selectivity.

Also, a number of additional parameters were investigated including variation of the nucleophile silyl group, temperature, **1a**:**2a** ratio, and methanol cosolvent amount (entries 9−14), to subtly balance chemical efficiency and selectivity. On the basis of these results, a set of optimal reaction conditions, in terms of both efficiency and regioselectivity, were screened out: namely, 0.4 mmol **1a** and 2.0 mol equiv of **2a** in 2.0 mL of a 1:1 brine:methanol medium, at 38−40 °C, under US irradiation (entry 14).

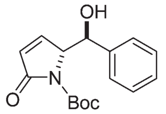
With optimal VMAR conditions in hand, the reaction scope with respect to the aldehyde acceptors in coupling reactions to silyloxy pyrrole **1a** in an aqueous, open-air environment was then investigated.

As shown in Table 2, the scope of this aqueous VMAR is large, and variations of the electronic nature of the substituents within the aromatic aldehyde component are well tolerated, providing *anti*-configured δ-hydroxy-α,β-unsaturated butyrolactams **3** in 50−85% range yields, very good γ-site selectivities, and, in most cases, > 80:20 *anti*:*syn* diastereoselectivities. A medium-scale protocol (2.0 mmol) proved to be equally viable and, as for the case of the coupling between **1a** and **2a**, quite productive leading to *anti*-**3a** in 65% isolated yield.[9]

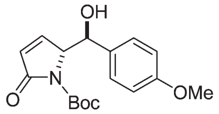
TABLE 2. Substrate Scope of *anti*-Selective VMAR of Pyrrole 1a with Respect to the Aldehyde Acceptors 2 Giving Racemic Lactams 3[a]



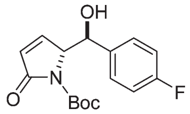
1a **2** *anti*-**3**



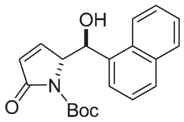
anti-**3a**
yield = 75%
γ:α = 98:2
dr = 83.3:16.7



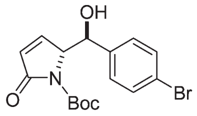
anti-**3b**
yield = 74%
γ:α = 95:5
dr = 82.0:18.0



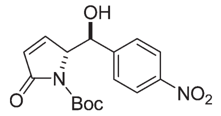
anti-**3c**
yield = 50%
γ:α = 95:5
dr = 81.0:19.0



anti-**3d**
yield = 80%
γ:α = 98:2
dr = 92.6:7.4



anti-**3e**
yield = 82%
γ:α = 95:5
dr = 74.0:26.0



anti-**3f**
yield = 85%
γ:α = 98:2
dr = 66.6:33.4

[a] Reactions were carried out at atmospheric pressure with pyrrole **1a** (0.4 mmol) and aldehyde **2** (2.0 mol equiv) dispersed in a 1:1 brine:methanol mixture, at 38−40 °C, under ultrasound irradiation (42 kHz ± 6%). Combined isolated yields. The γ/α and dr ratios (*anti*:*syn*) were determined by ^{1}H NMR analysis of the crude reaction mixture. For details, see the Supporting Information.

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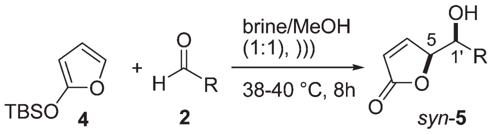
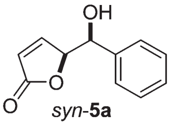
(7) (a) Breslow, R.; Rideout, D. C. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (b) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159 and references cited therein.

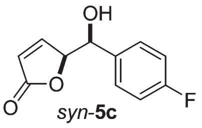
(8) (a) McDevit, W. F.; Long, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 1773. (b) Long, F. A.; McDevit, W. F. *Chem. Rev.* **1952**, *52*, 119.

TABLE 3. Substrate Scope of *syn*-Selective VMAR of Furan 4 with Respect to the Aldehyde Acceptors 2 Giving Racemic Butenolides 5[a]

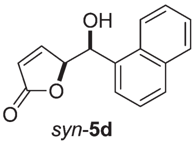




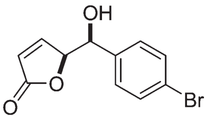
syn-**5a**
yield = 80%
γ:α >99:1
dr = 92.0:8.0



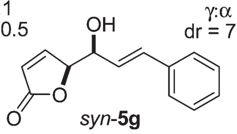
syn-**5c**
yield = 75%
γ:α >99:1
dr = 75.0:25.0



syn-**5d**
yield = 90%
γ:α >99:1
dr = 99.5:0.5



syn-**5e**
yield = 62%
γ:α >99:1
dr = 75.0:25.0



syn-**5g**
yield = 65%
γ:α = 98:2
dr = 99.5:0.5

[a]Reactions were carried out at atmospheric pressure with furan **4** (0.4 mmol) and aldehyde **2** (2.0 mol equiv) dispersed in a 1:1 brine:methanol mixture, at 38−40 °C, under ultrasound irradiation (42 kHz ± 6%). Combined isolated yields. The γ/α and dr ratios (*syn*:*anti*) were determined by ^{1}H NMR analysis of the crude reaction mixture. For details, see the Supporting Information.

Determining the product 5,1′-relative configuration simply required ^{1}H NMR measurements, since the C5−H and C1′−H resonances, as well as the vicinal H5−H1′ coupling constants are highly diagnostic ($^3J_{5,1'}$ = 2−4 Hz for *anti* vs $^3J_{5,1'}$ = 5−7 Hz for *syn* isomers).[10]

To validate this aqueous VMAR protocol with respect to the vinylogous donor component, we turned to furan-based dienoxy silanes, whose utility in conventional "organic solution" VMAR is widely documented.[3a−c] Due to rapid solvolysis of 2-(trimethylsilyloxy)furan in water,[11] robust TBS-protected furan **4** was scrutinized in addition reactions to several aromatic aldehydes (Table 3). Application of the same brine:methanol protocol previously optimized for pyrrole **1a** effectively advanced the vinylogous addition between **4** and benzaldehyde (**2a**). However, rather surprisingly, a striking switch of diastereoselectivity was observed in favor of *syn*-configured butenolide **5a**.

A nice 80% combined yield, complete γ-site selectivity, and good 92:8 *syn*/*anti* diastereoselectivity were attained. As for the VMAR with **1a**, substrate scope of the *syn*-selective addition of furan **4** was analyzed with a selected set of aromatic aldehyde components.

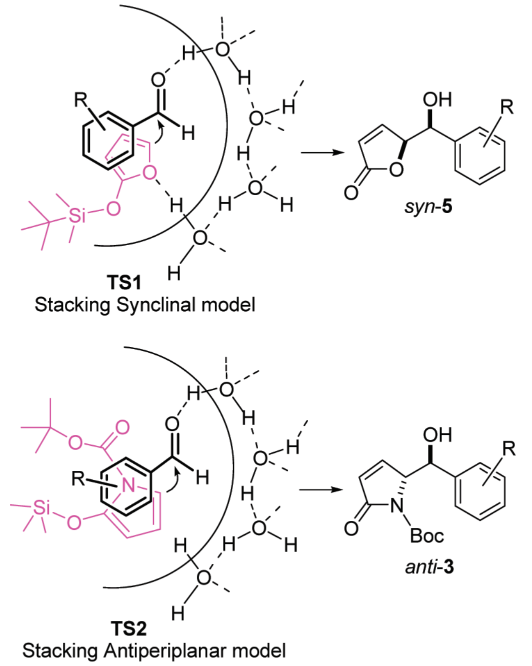


FIGURE 1. Proposed transition states **TS1** and **TS2** for the on water VMAR of silyloxy furan **4** and pyrrole **1a** with aromatic aldehydes.

Butenolide products **5** were recovered in useful yields with remarkable site- and *syn*-selectivities, reaching outstanding >99:1 γ/α and 75:25 to 99.5:0.5 *syn*/*anti* values.

The stereochemical relationship between the heteroatom substituents in the major compounds **5** is 5,1′-*syn*, as confidentially ascertained by ^{1}H NMR measurements ($^3J_{5,1'}$ = 6−8 Hz for *syn* vs $^3J_{5,1'}$ = 2−4 Hz for *anti* isomers).[10]

As far as the role of water in the present diastereoselective on water heterogeneous VMAR is concerned, we assumed that the reaction occurs at the boundary between water and dispersed droplets of the lipophilic reactants, as observed in other related reactions occurring on aqueous media.[12] One or more water molecules in the outer aqueous layer are speculated to work as H-bond donor species to activate the aldehyde acceptor and control the mutual position of the reactants in the transition state. With furan-based nucleophiles, a stacking synclinal transition state model **TS1** leading to *syn*-isomers **5** would seem favored (Figure 1), with both the aldehyde carbonyl and furan oxygen exposed to the aqueous interface (*re*-*re* face trajectory). An analogous model applied to pyrroles would expose the bulky *N*-*tert*-butoxycarbonyl group toward water, thus destabilizing this transition state. On the contrary, by reverting the donor diastereoface (*si*-*re* face trajectory) as in **TS2**, the same Boc group is shifted away from the water interface entering the inner pocket of the reactant droplets, thus reverting diastereocontrol (*anti*-**3** isomers preferred).[13]

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(9) While this protocol was focused on reactions involving aromatic aldehyde acceptors, preliminary experiments with pyrrole **1a** and 2-methylpropanal or 2,3-*O*-isopropylidene-D-glyceraldehyde were successfully executed, giving rise to the expected 5,1′-*anti*-configured vinylogous lactams in acceptable yields and diastereoselectivities.

(10) The C5-C1′ relative configurations of lactams of type **3** and butenolides of type **5** have been recently unambiguously certified by X-ray analysis: Curti, C.; Ranieri, B.; Battistini, L.; Rassu, G.; Zambrano, V.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *Adv. Synth. Catal.* **2010**, *352*, 2011.

(11) On the contrary, solvolysis of 2-(trimethylsilyloxy)pyrrole **1a** is negligible under the optimized reaction conditions reported for VMAR in Table 1.

(12) (a) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492. (b) Lützenkirchen, I.; Preočanin, T.; Kallay, N. *Phys. Chem. Chem. Phys.* **2008**, *10*, 4946. (c) Tiwari, S.; Kumar, A. *J. Phys. Chem. A* **2009**, *113*, 13685. (d) Beattie, J. K.; McErlean, C. S. P.; Phippen, C. B. W. *Chem.—Eur. J.* **2010**, *16*, 8972 and references cited therein. See also, ref 2.

In conclusion, we have reported a novel, efficient, and diastereoselective VMAR involving pyrrole- and furan-based 2-silyloxy dienes **1a** and **4** and several aromatic aldehydes that occurs on aqueous media, in open-air, under ultrasound irradiation at 38−40 °C.

A remarkable switch of simple diastereoselectivity was observed when passing from pyrrole **1a** (*anti*-selective) to furan **4** (*syn*-selective), highlighting how the bulkiness of the heteroatom substituent in the silyl dienolate donor critically impacts diastereocontrol. Future work will involve conveying the ambitions of this reaction to Mannich and Michael acceptors, and examining the rationale of the transition states postulated above by using theoretical calculations. Furthermore, we hope to develop an asymmetric catalytic VMAR procedure utilizing the same aqueous methodology, with the use of water-tolerant chiral catalysts to control facial selectivity.

Experimental Section

Representative Procedure A (Suitable for Liquid Aldehydes). (5*R,1′*S**)-*N*-(*tert*-Butoxycarbonyl)-5-[hydroxy(phenyl)methyl]-1*H*-pyrrol-2(5*H*)-one (*anti*-3a).** To an emulsion of benzaldehyde (**2a**) (0.08 mL, 0.80 mmol) in 1.5 mL of brine/MeOH (1:0.5 mixture), under sonication at 38−40 °C, was slowly added a solution of *N*-Boc-2-(trimethylsilyloxy)pyrrole (**1a**) (100 mg, 0.40 mmol) dissolved in MeOH (0.5 mL). The reaction, kept under sonication at the same temperature for 3 h, was cooled to room temperature, then added with ice, and the resulting slurry mixture was extracted with EtOAc (3 × 20 mL). The organic layers were collected, dried with MgSO$_4$, filtered, and concentrated in vacuo. The diastereomeric ratio of the addition products was determined to be 83.3/16.7 (*anti*/*syn*) by ^{1}H NMR analysis of the crude reaction mixture. The crude residue, dissolved in anhydrous ethanol, was filtered through a Whatman Anotop 10 LC filter, and purified by semipreparative HPLC (CN-10 μm, 250 × 10 mm, hexane/anhydrous EtOH 90:10, flow rate 3.0 mL/min, detection at 254 nm, R_t *anti*-**3a** = 12.79 min), yielding major isomer *anti*-**3a** (72 mg, 63% yield) as a glassy solid: TLC R_f 0.27 (hexanes/EtOAc, 60:40); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.31−7.41 (5H, m, Ph), 6.95 (1H, dd, J = 6.2, 2.0 Hz, H4), 6.15 (1H, dd, J = 6.2, 1.6 Hz, H3), 5.50 (1H, d, J = 2.1 Hz, H1′), 4.91 (1H, dd, J = 1.6, 2.1 Hz, H5), 1.64 (9H, s, *t*-Bu, Boc); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.6 (Cq, C2), 150.5 (Cq, Boc), 146.7 (CH, C4), 139.5 (Cq, Ph), 128.7 (2C, CH, Ph), 128.5 (CH, Ph), 128.2 (CH, C3), 125.7 (2C, CH, Ph), 84.0 (Cq, *t*-Bu, Boc), 71.9 (CH, C1′), 69.0 (CH, C5), 28.4 (3C, CH$_3$, *t*-Bu, Boc); MS (ES+, 50 eV) *m*/*z* 290.2 (M + H$^+$), 312.3 (M + Na$^+$). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.38; H, 6.67; N, 4.88.

Representative Procedure B (Suitable for Solid Aldehydes). (5*R,1′*S**)-*N*-(*tert*-Butoxycarbonyl)-5-[hydroxy(4-bromophenyl)-methyl]-1*H*-pyrrol-2(5*H*)-one (*anti*-3e).** To a solution of 4-bromobenzaldehyde (**2e**) (145 mg, 0.80 mmol) in 0.50 mL of MeOH, under sonication at room temperature, was added brine (1.0 mL) then the temperature was raised to 38−40 °C. After 10 min, a white suspension was formed and a solution of *N*-Boc-2-(trimethylsilyloxy)pyrrole (**1a**) (100 mg, 0.40 mmol) in 0.50 mL of MeOH was slowly added. The suspension readily disappeared giving an emulsion that was kept under sonication at the same temperature for 3 h. The reaction was cooled to room temperature, added with ice, and the resulting slurry mixture was extracted with EtOAc (3 × 15 mL). The organic layers were collected, dried with MgSO$_4$, filtered, and concentrated in vacuo. The diastereomeric ratio (*anti*/*syn*) of the addition products was determined to be 74.0/26.0 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue, dissolved in anhydrous ethanol, was filtered through a Whatman Anotop 10 LC filter, and purified by semipreparative HPLC (CN-10 μm, 250 × 10 mm, hexane/anhydrous EtOH 95:5, flow rate 5.0 mL/min, detection at 254 nm, R_t *anti*-**3e** = 12.22 min), yielding major isomer *anti*-**3e** (90 mg, 61%) as a glassy solid: TLC R_f 0.36 (hexanes/EtOAc, 60:40); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.50 (2H, m, Ar), 7.29 (2H, m, Ar), 6.88 (1H, dd, J = 6.2, 2.0 Hz, H4), 6.08 (1H, dd, J = 6.2, 1.7 Hz, H3), 5.48 (1H, d, J = 1.5 Hz, H1′), 4.79 (1H, ddd, J = 1.9, 1.9, 1.9 Hz, H5), 1.60 (9H, s, *t*-Bu, Boc); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.8 (Cq, C2), 150.3 (Cq, Boc), 146.7 (CH, C4), 138.8 (Cq, Ar), 131.8 (2C, CH, Ar), 128.5 (CH, C3), 127.6 (2C, CH, Ar), 121.9 (Cq, Ar), 84.1 (Cq, *t*-Bu, Boc), 71.4 (CH, C1′), 69.2 (CH, C5), 28.4 (3C, CH3, *t*-Bu, Boc); MS (ES+, 50 eV) *m*/*z* 308.1 (M + H$^+$), 330.2 (M + Na$^+$). Anal. Calcd for $C_{16}H_{18}BrNO_4$: C, 52.19; H, 4.93; N, 3.80. Found: C, 52.15; H, 4.96; N, 3.78.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds and copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Changing benzyl for Boc protecting group in the pyrrole donor did not perturb the *anti*-diastereopreference of the reaction, suggesting that it is the steric demand of the donor heteroatom site (oxygen vs *N*-Boc or *N*-Bn) that is likely responsible for the observed reversal of stereochemistry. We are grateful to the reviewers for drawing this point to our attention.