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Remote Asymmetric Induction about a Crowded Aromatic Core

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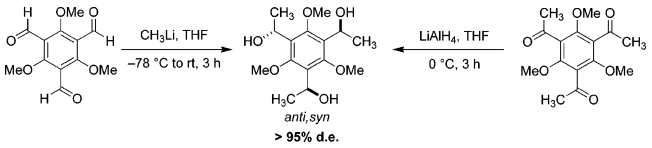
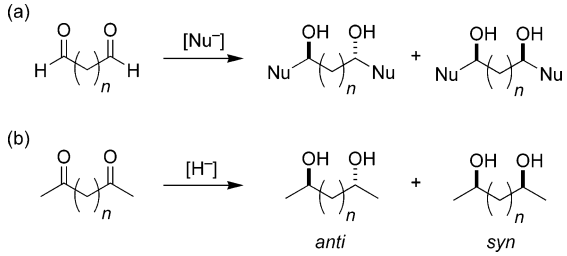
Received April 13, 2006



Described are among the first highly diastereoselective, one-pot organometallic addition and hydride reduction reactions (>95% de) involving three symmetry-equivalent carbonyl centers, each that bears a 1,5-relationship to its nearest neighbor. Three-fold methyllithium addition to 2,4,6-trimethoxybenzene-1,3,5-tricarbaldehyde gives the *anti*,*syn* triol exclusively (by ^{1}H NMR); addition of HMPA to the reaction or replacement of the substrate's methoxy groups with ethyl groups affords a statistical 3:1 (*anti*,*syn*:*syn*,*syn*) diastereomeric product ratio. Analogous asymmetric induction is found upon hydride reduction (using $LiAlH_4$ or $NaBH_4$) of the complementary triketone, 2,4,6-trimethoxybenzene-1,3,5-triethanone. Chelation and steric (gearing) effects about the crowded aromatic core contribute to the observed stereoselectivity.

Modern organic synthesis offers numerous strategies to exert stereocontrol in addition and reduction reactions at single prochiral carbonyl centers (i.e., aldehydes and ketones) in acyclic, achiral substrates and these have been extensively reviewed.[1] Suitable chiral additives (e.g., reagents or catalysts) can be used analogously to achieve high *anti*:*syn* diastereomeric ratios and high enantioselectivities (for the otherwise racemic diol product) in the addition[2] and reduction[3] reactions of two symmetry-equivalent carbonyl centers in one-pot reactions (Scheme 1). Unique to these substrates is the potential to realize moderate to excellent diastereomeric excesses even in the absence of a chiral additive. Such is the case for the addition

SCHEME 1 *Anti* and *Syn* Diastereomers that Arise from (a) Addition to Symmetrical Dialdehydes and (b) Reduction of Symmetrical Diketones



(Scheme 1a)[4] and reduction (Scheme 1b)[3b,5] reactions of symmetrical 1,2 ($n = 0$)- and 1,3 ($n = 1$)-dicarbonyl compounds (and even specialized 1,4 ($n = 2$)- or 1,5 ($n = 3$)-dicarbonyl substrates[1g,5e,6,7]) where cyclic (chelated) transition states[8] and/or rigid scaffolding are the basis for efficient communication between the two developing chiral centers. Diastereocontrol is generally lost, however, when the equivalent reactive centers are remote (>1,4-) and a statistical 1:1 *anti*:*syn* product mixture results.[3b,h,5e,9] Described in this Note are among the first highly

(1) (a) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994. (b) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338−344. (c) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856. (d) Sailes, H.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1785−1805. (e) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40−73. (f) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824. (g) Mikami, K.; Shimizu, M.; Zhang, H. C.; Maryanoff, B. E. *Tetrahedron* **2001**, *57*, 2917−2951. (h) Goldfuss, B. *Synthesis* **2005**, 2271−2280.

(2) (a) Soai, K.; Inoue, Y.; Takahashi, T.; Shibata, T. *Tetrahedron* **1996**, *52*, 13355−13362. (b) Ramachandran, P. V.; Chen, G. M.; Brown, H. C. *Tetrahedron Lett.* **1997**, *38*, 2417−2420.

(3) (a) Chong, J. M.; Clarke, I. S.; Koch, I.; Olbach, P. C.; Taylor, N. J. *Tetrahedron*: *Asymmetry* **1995**, *6*, 409−418. (b) Quallich, G. J.; Keavey, K. N.; Woodall, T. M. *Tetrahedron Lett.* **1995**, *36*, 4729−4732. (c) Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem.* **1996**, *61*, 3888−3889. (d) Kuwano, R.; Sawamura, M.; Shirai, J.; Takahashi, M.; Ito, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 485−496. (e) Ohtsuka, Y.; Kubota, T.; Ikeno, T.; Nagata, T.; Yamada, T. *Synlett* **2000**, 535−537. (f) Aldous, D. J.; Dutton, D. M.; Steel, P. G. *Tetrahedron*: *Asymmetry* **2000**, *11*, 2455−2462. (g) Zhou, H.-B.; Zhang, J.; Lü, S.-M.; Xie, R.-G.; Zhou, Z.-Y.; Choi, M. C. K.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron* **2001**, *57*, 9325−9333. (h) Lagasse, F.; Tsukamoto, M.; Welch, C. J.; Kagan, H. B. *J. Am. Chem. Soc.* **2003**, *125*, 7490−7491. (i) Sato, M.; Gunji, Y.; Ikeno, T.; Yamada, T. *Synthesis* **2004**, 1434−1438.

(4) (a) Clausen, C.; Wartchow, R.; Butenschon, H. *Eur. J. Org. Chem.* **2001**, 93−113. (b) Lemiègre, L.; Lesetre, F.; Combret, J.-C.; Maddaluno, J. *Tetrahedron* **2004**, *60*, 415−427.

(5) (a) Maier, G.; Roth, C.; Schmitt, R. K. *Chem. Ber.* **1985**, *118*, 704−721. (b) Maier, G.; Schmitt, R. K.; Seipp, U. *Chem. Ber.* **1985**, *118*, 722−728. (c) Barluenga, J.; Resa, J. G.; Olano, B.; Fustero, S. *J. Org. Chem.* **1987**, *52*, 1425−1428. (d) Tomooka, K.; Okinaga, T.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 6335−6338. (e) Harada, T.; Matsuda, Y.; Imanaka, S.; Oku, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1641−1643. (f) Bonini, C.; Bianco, A.; Difabio, R.; Mecozzi, S.; Proposito, A.; Righi, G. *Gazz. Chim. Ital.* **1991**, *121*, 75−80. (g) Stiasny, H. C. *Synthesis* **1996**, 259−264. (h) Yamada, M.; Horie, T.; Kawai, M.; Yamamura, H.; Araki, S. *Tetrahedron* **1997**, *53*, 15685−15690. (i) Ravikumar, K. S.; Sinha, S.; Chandrasekaran, S. *J. Org. Chem.* **1999**, *64*, 5841−5844. (j) Bartoli, G.; Bosco, M.; Bellucci, M. C.; Dalpozzo, R.; Marcantoni, E.; Sambri, L. *Org. Lett.* **2000**, *2*, 45−47. (k) Clerici, A.; Pastori, N.; Porta, O. *Eur. J. Org. Chem.* **2002**, 3326−3335.

(6) Although modest diastereomeric ratios are generally observed. Diastereoselectivity is definitively not found for alkene conjugated 1,4-diketones; see: Fleming, I.; Kuhne, H.; Takaki, K. *J. Chem. Soc., Perkin Trans. 1* **1986**, 725−728.

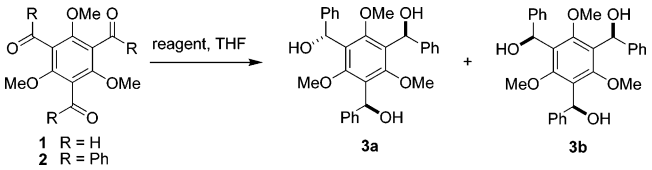
(7) The remote stereocontrol demonstrated in addition and reduction reactions involving 1,5- and 1,6-hydroxyketones (mediated by metal chelation) by Maryanoff and co-workers is mechanistically relevant: (a) Zhang, H.-C.; Harris, B. D.; Costanzo, M. J.; Lawson, E. C.; Maryanoff, C. A.; Maryanoff, B. E. *J. Org. Chem.* **1998**, *63*, 7964−7981. (b) Lawson, E. C.; Zhang, H. C.; Maryanoff, B. E. *Tetrahedron Lett.* **1999**, *40*, 593−596.

(8) (a) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1245−1249. (b) Cram, D. J.; Wilson, D. R. *J. Am. Chem. Soc.* **1963**, *85*, 1249−1257. (c) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462−468. (d) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223.

(9) (a) Neudeck, H.; Schlögl, K. *Monatsh. Chem.* **1975**, *106*, 229−259. (b) Rodríguez, D.; Castedo, L.; Domínguez, D.; Saá, C. *Org. Lett.* **2003**, *5*, 3119−3121.

10.1021/jo060794l CCC: $33.50
Published on Web 06/22/2006

TABLE 1. Organometallic Addition and Reduction Reactions of Crowded Aromatic Aldehyde 1 and Ketone 2



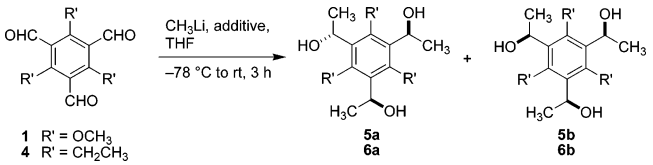
entry	aldehyde/ ketone	reagent	temp	major product	yield (%)	dr (**3a**:**3b**)
1	**1**	PhLi	−78 °C to rt	**3a**	67[a]	>20:1[b]
2	**1**	PhMgBr	0 °C to rt	**3a**	52[a]	>20:1[b]
3[12]	**2**	$LiAlH_4$	rt	**3a**	64	–[c]

[a] Isolated yield of the major product after chromatography on silica gel. [b] Ratio determined by ^1H NMR analysis of the crude reaction mixture. [c] Only **3a** was isolated upon purification of the crude reaction mixture. See ref 12 for details.

diastereoselective organometallic addition and hydride reduction reactions (>95% diastereoselectivity) involving three symmetry-equivalent carbonyl centers, each that bears a 1,5-relationship ($n = 3$) to its neighbor.

Two experimental observations initiated our studies (Table 1, entries 1 and 2). In work that employs phloroglucinol derivatives as synthons for functionalized donor-σ-acceptor molecules,[10] we found that treatment of 2,4,6-trimethoxybenzene-1,3,5-tricarbaldehyde (**1**) with excess phenyllithium or phenlymagnesium bromide at low temperature provided a greater than 20:1 diastereomeric ratio (dr) in favor of the racemic *anti*,*syn* stereoisomer **3a**.[11] Expected from this reaction, particularly given the remote 1,5-relationship between the prochiral aldehydes, is a statistical 3:1 *anti*,*syn* (**3a**):*syn*,*syn* (**3b**) ratio. A thorough search of the literature then revealed one example of the complementary reduction reaction (Table 1, entry 3), whereby Biali and Siegel reported isolating (following recrystallization) diastereomer **3a** upon treatment of triketone **2** with $LiAlH_4$.[12] Obvious commonalties between the two sets of reactions, and their substrates, prompted us to consider the role of both chelation (presumably involving the flanking methoxy groups) and sterics at the origin of efficient stereochemical control. Surprisingly, while congested aromatic rings have long been regarded as useful stereochemical relay scaffolds[13−15] and conformationally well-defined platforms for molecular recognition and ligand design,[16] there have been no systematic attempts to control the stereochemical outcome of reactions at multiple equivalent sites around such cores.

TABLE 2. Methyllithium Addition to Crowded Aromatic Aldehydes 1 and 4[a]



entry	aldehyde	additive	major product	yield[b] (%)	dr[c] (**5/6a**:**5/6b**)
1	**1**	none	**5a**	67	>20:1
2	**1**	HMPA[d]	**5a**	60	3.0:1
3	**4**	none	**6a**	86	3.2:1
4	**4**	HMPA[d]	**6a**	99	3.1:1

[a] Reactions were run in the presence of 5.0 equiv (1.7 equiv per carbonyl group) of CH_3Li. [b] Overall isolated yield of the stereoisomeric mixture (**a** + **b**). [c] Ratio determined by ^1H NMR analysis of the crude reaction mixture and verified by isolation of the individual diastereomers (entries 2−4) by column chromatography. [d] 5.0 equiv of HMPA were used (i.e., 1:1 HMPA:CH_3Li).

For synthetic convenience we began further explorations into this unexpected asymmetric induction using methyllithium additions to **1** (Table 2). Upon treatment of the trialdehyde with excess organolithium reagent (5.0 equiv), again only the *anti*,*syn* triol (**5a**) is identified by ^1H NMR analysis of the crude reaction mixture and subsequently isolated by column chromatography (entry 1). The steric size (CH_3 versus Ph) and hybridization (sp^3 versus sp^2)[17] of the organolithium reagent appears of no consequence to the overall diastereoselectivity.[18] The greater than 95% dr of entry 1 is abolished upon addition of just 5.0 equiv of HMPA (1:1 HMPA:CH_3Li), as evidenced by the statistical 3:1 **5a**:**5b** product mixture of epimeric triols that results (entry 2)—metal coordination is likely central to the asymmetric induction.[19] Equally telling, triethyl-functionalized **4** (entries 3 and 4) displays no diastereoselective induction, either with or without HMPA. Thus, the methoxy group oxygen[20] is required for stereoselectivity and sterics alone, despite the generally predictable conformational gearing behavior of the persubstituted 1,3,5-triethylbenzene core,[16] are not sufficient to engender the result (vide infra).

Triketones **7** and **8**, accessible via high-yielding PCC oxidation of triols **5** and **6**, respectively, provide substrates for exploring the complementary hydride reductions (Table 3). Trimethoxytriethanone **7** undergoes diastereoselective hydride reduction to give the *anti*,*syn* triol **5a** as the only isolable product with both $LiAlH_4$ (entry 1) and $NaBH_4$ (entry 2). Notably, the reaction of **7** with $LiAlH_4$ must be kept at temperatures ≤0 °C to avoid chelation-promoted demethylation (to the phenolate)

(10) (a) Li, H. F.; Homan, E. A.; Lampkins, A. J.; Ghiviriga, I.; Castellano, R. K. *Org. Lett.* **2005**, *7*, 443−446. (b) Lampkins, A. J.; Abdul-Rahim, O.; Li, H. F.; Castellano, R. K. *Org. Lett.* **2005**, *7*, 4471−4474.

(11) Throughout the paper, the *anti*,*syn* diastereomer refers to the RRS/SSR (triol) racemate and the *syn*,*syn* diastereomer refers to the RRR/SSS (triol) racemate.

(12) Simaan, S.; Siegel, J. S.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 3699−3701. Although the paper states that the RRS/SSR stereoisomer is formed preferentially (Table 1, entry 3), there is no discussion of the diastereomeric composition of the crude reaction mixture, only what appears to be the purified product (following recrystallization).

(13) For "chiral relay" systems in general see: Corminboeuf, O.; Quaranta, L.; Renaud, P.; Liu, M.; Jasperse, C. P.; Sibi, M. P. *Chem. Eur. J.* **2003**, *9*, 29−35 and references therein.

(14) (a) Mills, R. J.; Taylor, N. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372−4385. (b) Jimeno, C.; Rios, R.; Carroll, P. J.; Walsh, P. J. *Tetrahedron* **2004**, *60*, 4543−4548.

(15) (a) Clayden, J. *Synlett* **1998**, 810−816. (b) Clayden, J. *Chem. Commun.* **2004**, 127−135. (c) Clayden, J.; Lund, A.; Vallverdu, L. S.; Helliwell, M. *Nature* **2004**, *431*, 966−971.

(16) Hennrich, G.; Anslyn, E. V. *Chem. Eur. J.* **2002**, *8*, 2219−2224.

(17) (a) Jeyaraj, D. A.; Yadav, V. K.; Parvez, M.; Gauniyal, H. M. *J. Org. Chem.* **1998**, *63*, 3831−3837. (b) Dixon, D. J.; Krause, L.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2516−2518.

(18) The typical sensitivity (see: Bailey, W. F.; Reed, D. P.; Clark, D. R.; Kapur, G. N. *Org. Lett.* **2001**, *3*, 1865−1868 and ref 17b) to the nature of the organometallic reagent (Grignard versus organolithium) is also not found in these systems.

(19) (a) Solomon, M.; Jamison, W. C. L.; McCormick, M.; Liotta, D.; Cherry, D. A.; Mills, J. E.; Shah, R. D.; Rodgers, J. D.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 3702−3704. (b) Reich, H. J.; Goldenberg, W. S.; Gudmundsson, B. O.; Sanders, A. W.; Kulicke, K. J.; Simon, K.; Guzei, I. A. *J. Am. Chem. Soc.* **2001**, *123*, 8067−8079.

(20) For anisole coordination to organolithium reagents see: (a) Saá, J. M.; Deyá, P. M.; Suñer, G. A.; Frontera, A. *J. Am. Chem. Soc.* **1992**, *114*, 9093−9100. (b) Slocum, D. W.; Dumbris, S.; Brown, S.; Jackson, G.; LaMastus, R.; Mullins, E.; Ray, J.; Shelton, P.; Walstrom, A.; Wilcox, J. M.; Holman, R. W. *Tetrahedron* **2003**, 8275−8284.

SCHEME 2. Partial Addition of Methyllithium to 1 at Low Temperature

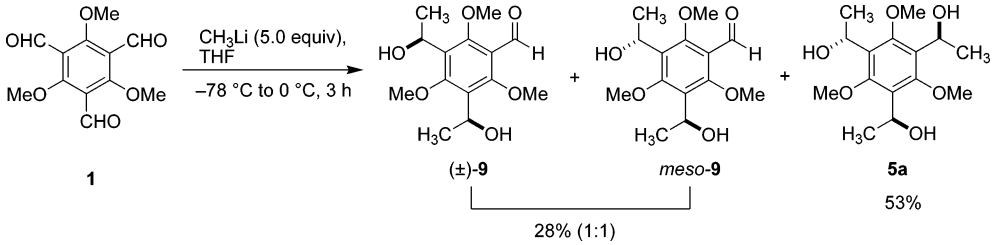
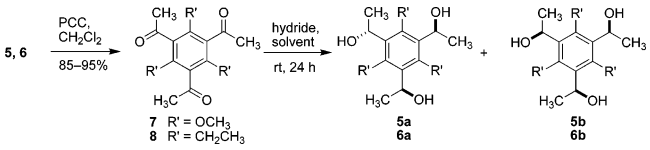


TABLE 3. Hydride Reduction of Crowded Aromatic Ketones 7 and 8



entry	ketone	hydride[a]	solvent	major product	yield[b] (%)	dr[c] (**5/6a**:**5/6b**)
1	**7**	$LiAlH_4$	THF[d]	**5a**	83	>20:1
2	**7**	$NaBH_4$	EtOH, THF	**5a**	75	>20:1
3	**8**	$LiAlH_4$	THF	**6a**	82	2.9:1
4	**8**	$NaBH_4$	EtOH, THF	**6a**	N.R.	–

[a] Reactions were run in the presence of 10 equiv (3.3 equiv per carbonyl group) of hydride reagent. [b] Overall isolated yield of the stereoisomeric mixture (**a** + **b**). [c] Ratio determined by ^{1}H NMR analysis of the crude reaction mixture and verified by isolation of the individual diastereomers (entry 3) by column chromatography. [d] Reaction performed at 0 °C for 3 h.

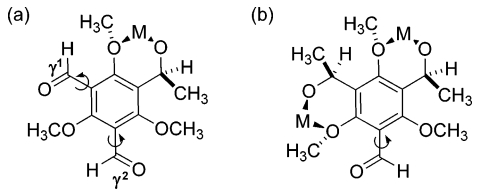


FIGURE 1. Chelation, steric gearing effects, and a directional sense about the core are apparent contributors to the observed asymmetric induction: putative intermediates following the first (a) and second (b) methyllithium addition to **1** or hydride reduction of **7**.

by excess hydride.[21] When the triethyl isostere **8** is subjected to identical $LiAlH_4$ reduction conditions, no asymmetric induction is observed (entry 3). Then, somewhat surprisingly, if **8** is treated with $NaBH_4$ no reaction occurs at room temperature (entry 4), in sharp contrast to its trimethoxy counterpart **7**. Thus, the methoxy groups of **7** not only promote diastereoselective addition reactions in these crowded molecules, but also dramatically increase the rate of reduction for an otherwise unreactive[22] triketone with $NaBH_4$.[14c,23]

To further understand the mechanism of stereochemical transmission in the addition (and by analogy, reduction) reactions, intermediate diols were isolated from the methyllithium addition reaction of trialdehyde **1** (Scheme 2). By keeping the reaction temperature below 0 °C, epimeric diols (±)-**9** and *meso*-**9** could be obtained as an inseparable mixture (28% isolated yield as an oil) in a 1:1 ratio (based on ^{1}H NMR analysis).[24] The only other product identified was *anti*,*syn* triol **5a**, obtained in 53% isolated yield. Implied from the experiment, and consistent with the addition being under kinetic control, is the conversion of both epimeric diols **9** to the same *anti*,*syn* **5a**. For *meso*-**9**, neither the mechanism of addition nor the conformation of the putative lithium coordinated intermediate is of consequence; all conceivable pathways will afford **5a**. Such is not the case for (±)-**9**; the final addition must itself occur with the greater than 95% diastereoselectivity observed for the overall reaction.

The data collected thus far allow us only to construct a tentative model for asymmetric induction in these systems. Addition to one of the three equivalent carbonyl centers of **1** likely begins to establish a rigid steric environment about the core; Figure 1a shows the intermediate that might arise from delivery of the methyl group via a transition state that involves β-chelation between one methoxy group and the developing alkoxide.[20,25] A similar intermediate would be formed from reduction of **7**. Potential differences in subsequent reactivity between carbonyls γ^1 and γ^2, free rotation about the carbon–carbon bonds indicated, and chelate conformation and stability complicate further analysis to elucidate the precise 1:1 ratio of epimeric diols (±)- and *meso*-**9** reported in Scheme 2.

It is tempting then to assume that subsequent methyllithium additions would occur to ensure an alternation of OCH_3 groups and CH_3 groups, consistent with classical steric gearing models in analogous systems. Unfortunately, while these gearing phenomena are well-understood for persubstituted 1,3,5-triethylbenzene cores,[16] they are poorly described for the isosteric 1,3,5-trimethoxybenzene systems.[12,26] At the current time we can only propose intermediates such as the one shown in Figure 1b, which must be converted with >95% diastereoselectivity to the *anti*,*syn* product. Both the conformation of the remaining aldehyde moiety and face of attack ultimately govern the stereochemistry of the final prochiral center.

In conclusion, we have demonstrated excellent 1,5-diastereocontrol in nucleophilic addition reactions and hydride reductions of carbonyl groups positioned on the periphery of the 1,3,5-trimethoxybenzene platform. While elucidation of the ultimate origin of asymmetric induction in the processes will require further study, implicated are chelation and steric control (potentially through a gearing phenomenon) afforded by the crowded aromatic core. Our near-term goals involve mechanistic probing through molecular modeling and NMR approaches. We

(21) A competing side reaction that diminishes the isolated yields of the trimethoxy versus triethyl compounds in this work; see also: Kimura, K.; Tanaka, M.; Iketani, S.; Shono, T. *J. Org. Chem.* **1987**, *52*, 836–844.

(22) Delair, P.; Kanazawa, A. M.; deAzevedo, M. B. M.; Greene, A. E. *Tetrahedron*: *Asymmetry* **1996**, *7*, 2707–2710.

(23) Kizirian, J. C.; Cabello, N.; Pinchard, L.; Caille, J. C.; Alexakis, A. *Tetrahedron* **2005**, *61*, 8939–8946.

(24) Condensation of the (±)-**9**/*meso*-**9** mixture with benzylamine (performed quantitatively) also did not allow chromatographic separation or crystallization of the corresponding imines.

(25) Mori, S.; Kim, B. H.; Nakamura, M.; Nakamura, E. *Chem. Lett.* **1997**, 1079–1080.

(26) Karle, I. L.; Flippen-Anderson, J. L.; Chiang, J. F.; Lowrey, A. H. *Acta Crystallogr., Sect. B* **1984**, *40*, 500–506.

then hope to extend this methodology to diverse reactions at the core, derivatives capable of diastereoselective recognition and/or catalysis, and ultimately more general asymmetric synthesis.

Experimental Section

Representative Methyllithium Addition and Hydride Reduction Reactions. Preparation of (*anti,syn*)-1,1′,1″-(2,4,6-Trimethoxybenzene-1,3,5-triyl)triethanol (5a). Method A (Table 2, entry 1): To a stirring solution of methyllithium (1.6 M in ether, 3.0 mmol) in dry THF (15 mL) at −78 °C under a blanket of argon was slowly added a solution of **1** (0.15 g, 0.60 mmol, dissolved in 5 mL of dry THF) via syringe. The resulting mixture was maintained at −78 °C for an additional hour, and then allowed to gradually warm to room temperature over 2 h. The reaction was then quenched by dropwise addition of dilute HCl, and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to a crude residue (^{1}H NMR analysis of this crude residue shows no signs of epimer **5b**), which was purified via flash chromatography (4:1 EtOAc/hexanes) to afford **5a** (0.12 g, 67%) as a colorless oil.

Method B (Table 3, entry 1): To a stirring mixture of $LiAlH_4$ (0.194 g, 5.10 mmol) in dry THF (40 mL) at 0 °C under an argon atmosphere was slowly added a solution of **7** (0.150 g, 0.510 mmol, in 10 mL of dry THF). The resulting suspension was allowed to stir at 0 °C for 2 h, after which it was quenched via portionwise addition of $Na_2SO_4 \cdot 10H_2O$ until evolution of hydrogen gas ceased. The solid material was removed by suction filtration and the filtrate dried over $MgSO_4$, filtered, and concentrated to a crude residue, which was purified as in Method A to afford **5a** (0.127 g, 83%).

Method C (Table 3, entry 2): To a stirring solution of **7** (0.050 g, 0.17 mmol) in THF/EtOH (5 mL/3 mL) was added $NaBH_4$ (0.065 g, 1.7 mmol) and the resulting solution was allowed to stir at ambient temperature for 24 h. The reaction was then diluted with water and extracted with EtOAc (3 × 20 mL). All organics were combined, washed with brine, and concentrated to a crude residue, which was purified as in Method A to afford **5a** (0.038 g, 75%). **5a**: IR (film) ν_{max} 3422, 2971, 1573, 1128 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.57 (m, 9H), 3.74 (br s, 3H), 3.86 (s, 6H), 3.88 (s, 3H), 5.14 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 24.2, 24.5, 64.0, 64.2, 64.3, 64.4, 128.1, 128.2, 156.9, 157.4; HRMS (ESI) calcd for $C_{15}H_{24}O_6$ $(M + Na)^+$ 323.1465, found 323.1478.

Preparation of (*syn,syn*)-1,1′,1″-(2,4,6-Trimethoxybenzene-1,3,5-triyl)triethanol (5b; Table 2, entry 2). To a stirring solution of methyllithium (1.6 M in ether, 3.0 mmol) and HMPA (0.52 mL, 3.0 mmol) in dry THF (15 mL) at −78 °C under a blanket of argon was slowly added a solution of **1** (0.15 g, 0.60 mmol, dissolved in 5 mL of dry THF) via syringe. The resulting mixture was maintained at −78 °C for an additional hour, and then allowed to gradually warm to room temperature over 2 h. The reaction was then quenched by dropwise addition of dilute HCl, and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to a crude residue, which was purified via flash chromatography (4:1 EtOAc/hexanes eluent system) to afford **5a** (0.081 g, 45%) and **5b** (0.027 g, 15%) as colorless oils. **5b**: IR (film) ν_{max} 3406, 2935, 1573, 1128 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.63 (d, J = 6.6 Hz, 9H), 3.89 (s, 9H), 3.68−4.02 (br s, 3H), 5.17 (q, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 24.1, 64.1, 64.2, 128.4, 157.1; HRMS (ESI) calcd for $C_{15}H_{24}O_6$ $(M + Na)^+$ 323.1465, found 323.1478.

Acknowledgment. This work was financially supported by the National Science Foundation CAREER program (CHE-0548003) and the University of Florida. A.J.L. was supported by a University of Florida Alumni Graduate Fellowship.

Supporting Information Available: Full synthetic details and compound characterization for all new compounds, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060794L