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Asymmetric Induction in Hydrogen-Mediated Reductive Aldol Additions to α-Amino Aldehydes Catalyzed by Rhodium: Selective Formation of *syn*-Stereotriads Directed by Intramolecular Hydrogen-Bonding

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Abstract: Rhodium-catalyzed hydrogenation of methyl vinyl ketone and ethyl vinyl ketone in the presence of *N*-Boc-α-aminoaldehydes **3a**−**8a** at ambient temperature and pressure results in reductive C−C coupling to furnish aldol adducts **3b**−**8b** and **3c**−**8c**, respectively, which incorporate stereotriads that embody high levels of *syn*-aldol selectivity accompanied by high levels of *anti*-Felkin−Anh control. The collective data are consistent with a catalytic mechanism involving addition of the Z(*O*)-rhodium enolate to the sterically less-encumbered aldehyde π-face of an intramolecularly hydrogen-bonded chelate through a Zimmerman−Traxler type transition structure. Stereochemical assignments are supported by single-crystal X-ray diffraction analysis of **5b**-*O*-3,5-dinitrobenzoate, *iso*-**5b**, *N*-Me-*iso*-**5b**-*O*-3,5-dinitrobenzoate, and **7b**. As revealed by HPLC analysis, optical purity of the stereochemically labile α-aminoaldehydes is completely preserved under the conditions of hydrogen-mediated aldol coupling. Deletion of the intramolecular hydrogen bond, as in the case of *N*-methyl-*N*-Boc-L-leucinal *N*-Me-**5a**, inverts stereoselectivity to furnish the Felkin−Anh product *N*-Me-*iso*-**5b** in 17% yield. Additionally, reactions performed in the presence of *tert*-amyl alcohol (10 equiv) exhibit markedly lower levels of *anti*-Felkin−Anh control (7:1 versus ≥ 20:1). The collective studies suggest that intramolecular hydrogen bonding plays a key role in both activating the α-aminoaldehyde toward addition and directing facial selectivity.

Introduction

Discovered over a century ago,[1] the aldol reaction continues to challenge chemists, inspiring the development of increasingly effective protocols for stereocontrolled aldol addition.[2] The advent of metallic[3] and organic catalysts[4] for the direct enantioselective aldol addition of unmodified carbonyl compounds represents an especially significant milestone, as these processes herald a departure from the use of chiral auxiliaries and preformed enol(ate) derivatives. Nevertheless, for direct enantioselective aldol additions, the issue of regioselective or site-specific enolization remains largely unresolved.[5] As first reported by Stork et al., regiospecific enolate generation may be achieved through stoichiometric enone reduction,[6] enabling generation of enolate isomers that cannot be formed selectively through acid−base-mediated enolization.[7] Subsequently, the direct metal-catalyzed reductive coupling of enones to aldehydes was achieved, termed the "reductive aldol reaction".[8] To date, catalysts for reductive aldol coupling based on cobalt,[9] rhodium,[10,11] iridium,[12a] palladium,[12b] copper,[12c−g] and indium[12h] have been reported.

(1) Though largely attributed to Würtz, the aldol reaction was reported first by Borodin: (a) von Richter, V. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 552−554 (Borodin's earliest results are cited in this article). (b) Würtz, A. *Bull. Soc. Chim. Fr.* **1872**, *17*, 436−442. (c) Borodin, A. *Ber. Dtsch. Chem. Ges.* **1873**, *6*, 982−985. See also: Kane, R. *Ann. Phys. Chem. Ser. 2* **1838**, *44*, 475.

(2) For selected reviews on stereoselective aldol additions, see: (a) Heathcock, C. H. *Science* **1981**, *214*, 395−400. (b) Heathcock, C. H. *Am. Chem. Soc. Symp. Ser.* **1982**, *No. 185*, 55−72. (c) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1−115. (d) Machajewski, T. D.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352−1374. (e) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65−75.

(3) For a recent review on the use of metallic catalysts for direct enantioselective aldol additions, see: Shibasaki, M.; Matsunaga, S.; Kumagai, N. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 2, Chapter 6.

(4) For a recent review on the use of organic catalysts for direct enantioselective aldol addition, see: List, B. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 1, Chapter 4.

(5) Exposure of 2-butanone to both chiral organic or metallic catalysts for direct enantioselective aldol coupling results in preferential functionalization of C-1 rather than C-3. Such regioselectivity is incompatible with the synthesis of polypropionate natural products. Specific examples are cited in refs 3 and 4.

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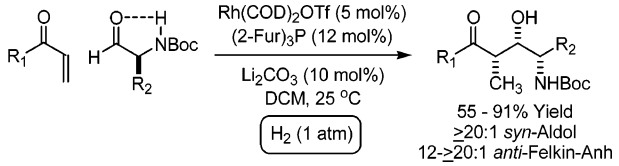
(7) A classical example of the subtle factors governing regioselective enolization of nonsymmetric ketones involves the deprotonation of steroidal ketones. Whereas cholesteran-3-one exhibits a thermodynamic preference for formation of the Δ_3-enolate, with little kinetic selectivity for formation of Δ_2-enolate, introduction of 7,8-unsaturation results in a thermodynamic preference for formation of the Δ_2-enolate, with little kinetic selectivity for formation of Δ_3-enolate. (a) Velluz, L.; Valls, J.; Nomine, G. *Angew. Chem. Int. Ed.* **1965**, *4*, 181−200. (b) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1955**, *77*, 2505−2509. (c) Berkoz, B.; Chavez, E. P.; Djerassi, C. *J. Chem. Soc.* **1962**, 1323−1329. (d) Mazur, Y. Sondheimer, F. *J. Am. Chem. Soc.* **1958**, *80*, 6296−6299.

(8) For reviews encompassing catalytic reductive aldol reactions, see: (a) Motherwell, W. B. *Pure Appl. Chem.* **2002**, *74*, 135−142. (b) Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, 12−21. (c) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *Chemtracts* **2003**, *16*, 554−559. (d) Jang, H.-Y.; Krische, M. J. *Eur. J. Org. Chem.* **2004**, *19*, 3953−3958. (e) Jang, H.-Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653−661. (f) Chiu, P. *Synthesis* **2004**, 2210−2215.

While highly diastereoselective[9b,c,d,10c,11e,12e,h,i] and enantioselective[10d,g,h,12a,f,g] reductive aldolizations have been achieved, enantioselective variants have only been realized in connection with the use of acrylates as enolate precursors. Asymmetric aldol additions involving vinyl ketones have not been described. Further, substrate-directed asymmetric induction in reductive aldol couplings to α-chiral aldehydes remains entirely unexplored.[13,14] Here, we disclose that hydrogenation of vinyl ketones in the presence of α-amino aldehydes at ambient temperature and pressure using tri-2-furylphosphine ligated rhodium catalysts results in highly stereoselective aldolization to afford the *syn*-aldol *anti*-Felkin−Anh products.[15] The collective studies suggest that persistence of an intramolecular hydrogen bond under the conditions of hydrogen-mediated coupling both activates the aldehyde toward addition and directs facial selectivity through chelation control.[16]



Results and Discussion

Hydrogen-Mediated Aldol Coupling of Vinyl Ketones to α-Aminoaldehydes. Recently, a catalytic system enabling highly *syn*-diastereoselective hydrogen-mediated reductive aldol coupling methyl vinyl ketone (MVK) and ethyl vinyl ketone (EVK) was developed in our laboratory.[11e] High levels of *syn*-aldol selectivity were found to depend critically upon the use of tri-2-furylphosphine as ligand.[17] These studies set the stage for the generation of stereotriads by way of reductive aldol couplings to optically enriched α-chiral aldehydes. Hence, the hydrogenation of vinyl ketones in the presence of α-alkoxy aldehydes[13] was explored. Here, it was found that for certain substrate combinations, useful levels of *anti*-Felkin−Anh selectivity could be attained. Such *anti*-Felkin−Anh selectivity is often observed in aldol additions of *Z*(O)-enolates to α-chiral aldehydes that proceed through Zimmerman−Traxler type transition structures and is presumed to arise as a consequence of *syn*-pentane interactions evident in the alternate Felkin−Anh mode of approach.[18] However, as demonstrated by the formation of **1b** versus **2b**, the extent of *anti*-Felkin−Anh selectivity was found to be highly substrate dependent, and for most systems examined, synthetically useful levels of selectivity were not obtained. It was reasoned that *anti*-Felkin−Anh selectivity might be enhanced if chelation could be established between the α-heteroatom and the oxygen atom of the aldehyde carbonyl. Use of an intramolecular hydrogen bond was deemed feasible, as hydrogen-mediated aldol coupling occurs under essentially neutral conditions in a low dielectric medium (dichloromethane, DCM). Boc-protected α-amino aldehydes **3a** and **4a** incorporate an internal hydrogen-bond donor in the form of the carbamate N−H. In the event, hydrogenation of MVK in the presence of α-amino aldehydes **3a** and **4a** delivers aldol adducts **3b** and **4b** with high levels of *syn*-aldol selectivity accompanied by high levels of *anti*-Felkin−Anh control (Scheme 1).

To further challenge the hypothesis that intervention of an intramolecular hydrogen bond is responsible for directing *anti*-Felkin−Anh selectivity, *N*-Boc-L-leucinal **5a** and the corresponding *N*-methylated compound *N*-Me-**5a** were subjected to conditions for hydrogen-mediated aldol coupling with MVK. In the former case, the *syn*-aldol *anti*-Felkin−Anh product **5b** was the major isomer obtained (20:1 dr). The *syn*-aldol Felkin−Anh product *iso*-**5b** is the minor isomer produced under these conditions. The stereochemical assignments of **5b** and *iso*-**5b** were corroborated by single-crystal X-ray diffraction analysis. In contrast, the major isomer observed in the reductive aldol coupling of MVK to *N*-Me-**5a** is the *syn*-aldol Felkin−Anh product *N*-Me-*iso*-**5b** (10:1). The stereochemical assignment of *N*-Me-*iso*-**5b**-*O*-3,5-dinitrobenzoate was corroborated by single-crystal X-ray diffraction analysis. Of additional interest is the fact that the isolated yield in the coupling of the intramolecularly hydrogen-bonded aldehyde **5a** (66% yield) is substantially higher

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(14) For selected reviews encompassing additions to α-amino and *β*-amino aldehydes, see: (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149−164. (b) Reetz, M. T. *Angew. Chem. Int. Ed.* **1991**, *30*, 1531−1546. (c) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121−1162.

(15) For examples of aldol additions to α-amino aldehydes, see: (a) Narita, M.; Otsuka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1982**, *23*, 525−528. (b) Reetz, M. T.; Rivadeneira, E.; Niemeyer, C. *Tetrahedron Lett.* **1990**, *31*, 3863−3866. (c) Hayashi, K.; Hamada, K. Y.; Shioiri, T. *Tetrahedron Lett.* **1991**, *32*, 7287−7290. (d) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Consolandi, E. *J. Org. Chem.* **1992**, *57*, 456−461. (e) Gennari, C.; Pain, G.; Moresca, D. *J. Org. Chem.* **1995**, *60*, 6248−6249. (f) Nagafuji, P.; Cushman, M. *J. Org. Chem.* **1996**, *61*, 4999−5003. (g) Kohli, R. M.; Burke, M. D.; Tao, J.; Walsh, C. T. *J. Am. Chem. Soc.* **2003**, *125*, 7160−7161. (h) Espelt, L.; Parella, T.; Bujons, J.; Solans, C.; Joglar, J.; Delgado, A.; Clapés, P. *Chem. Eur. J.* **2003**, *9*, 4887−4889. (i) Marco, J. A.; Carda, M.; Diaz-Oltra, S.; Murga, J.; Falomir, E.; Roeper, H. *J. Org. Chem.* **2003**, *68*, 8577−8582.

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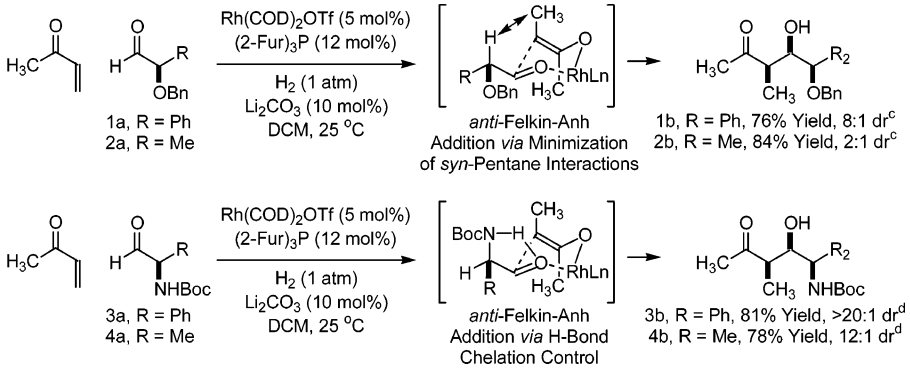
(17) For tri-2-furylphosphine effects in metal catalyzed reactions, see: (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595. (b) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73−78. (c) Anderson, N. G.; Keay, B. A. *Chem. Rev.* **2001**, *101*, 997−1030.

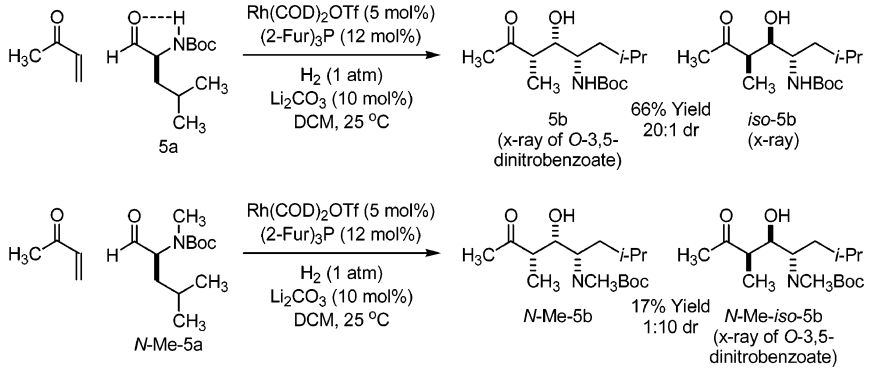
(18) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151−4157.

Scheme 1. Directing Anti-Felkin−Anh Selectivity in Hydrogen-Mediated Aldol Couplings to α-Alkoxy and α-Aminoaldehydes[a,b]



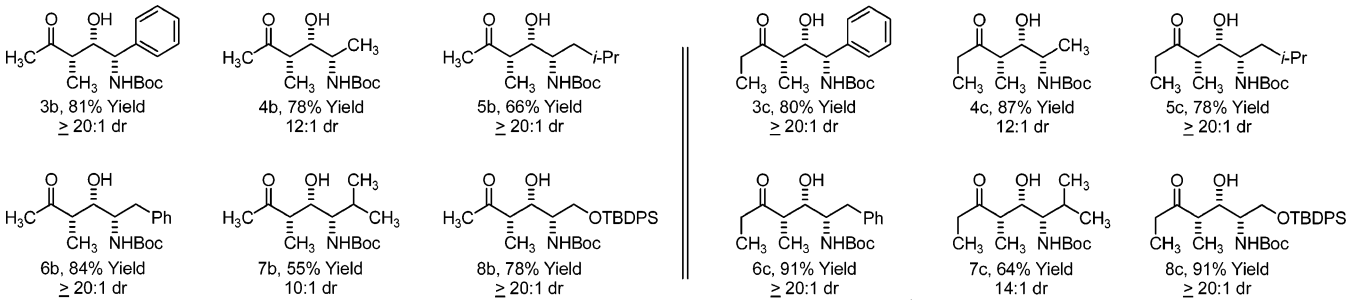
[a] In order to depict a clear cross-comparison, the enantiomeric amino aldehydes **3a** and **4a** are indicated. The L-α-amino aldehydes were actually used. [b]Cited yields are of material isolated by SiO_2 chromatography. Diastereomeric ratios were determined by ^1H NMR analysis of the crude reaction mixtures. See Experimental Section for detailed procedures. [c]The diastereomeric ratio refers to the indicated major isomer versus all other isomers combined. [d]The diastereomeric ratio refers to the indicated major isomer vs the *syn*-aldol Felkin−Anh product. Other isomers were not observed.

Scheme 2. Inversion of Diastereoselectivity in Hydrogen-Mediated Aldol Couplings to α-Aminoaldehydes in Response to Deletion of an Intramolecular Hydrogen Bond[a]



[a] Cited yields are of material isolated by SiO_2 chromatography. Diastereomeric ratios were determined by ^1H NMR analysis of the crude reaction mixtures. The stereochemical assignments of **5b**, *iso*-**5b**, and *N*-Me-*iso*-**5b** have been corroborated by single-crystal X-ray diffraction analysis.

Table 1. Hydrogen-Mediated Reductive Aldol Coupling of Methyl Vinyl Ketone (left) and Ethyl Vinyl Ketone (right) to Representative *N*-Boc Protected L-α-Aminoaldehydes[a]



[a] Cited yields are of material isolated by SiO_2 chromatography. Diastereomeric ratios were determined by ^1H NMR analysis of the crude reaction mixtures. All α-amino aldehydes were prepared via DIBAL reduction of the corresponding esters. See Experimental Section for general procedures.

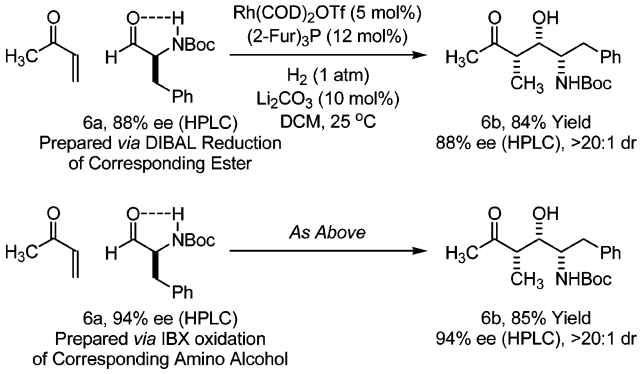
than that involving *N*-Me-**5a** (17% yield), which is lacking the intramolecular hydrogen bond. These data suggest that intramolecular hydrogen bonding not only directs *anti*-Felkin−Anh selectivity but also plays a key role in enhancing aldehyde reactivity through stabilization of the incipient alkoxide in the transition structure (Scheme 2).

To assess the scope and limitation of this process, a range of α-amino aldehydes were subjected to conditions for hydrogen-mediated aldol coupling using commercially available MVK and EVK as pronucleophiles. As demonstrated by the formation of **3b**, **3c**, **6b**, and **6c**, the α-amino aldehydes *N*-Boc-L-phenylglycinal and *N*-Boc-L-phenylalaninal, which possess aromatic side chains, undergo highly stereoselective coupling to provide the *syn*-aldol *anti*-Felkin−Anh products. α-Amino aldehydes that incorporate aliphatic side chains (*N*-Boc-L-alaninal, *N*-Boc-L-leucinal, and *N*-Boc-L-valinal) provide the aldol products **4b**, **4c**, **5b**, **5c**, **7b**, and **7c**, respectively. Couplings to *N*-Boc-L-serinal also occur in a highly stereoselective manor to furnish **8b** and **8c**. As revealed by a survey of counterion ($Rh(COD)_2X$, where X = OTf, BF_4, SbF_6, BARF = {3,5-$(CF_3)_2C_6H_3$}$_4B^{\theta}$), $Rh(COD)_2OTf$ is the optimum precatalyst for couplings of this type. $Rh(COD)_2OTf$ purchased from Umicore

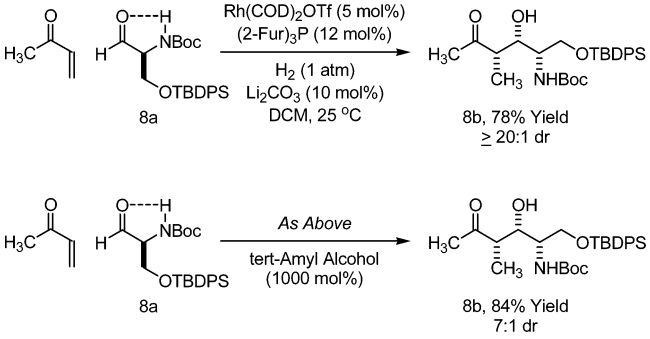
was found to be superior to other commercial sources. Finally, it is noteworthy that the diastereoselectivities observed in the present hydrogen-mediated aldol additions, which are conducted at ambient temperature, exceed those observed in related aldol additions to α-amino aldehydes involving stoichiometrically preformed enolates (Table 1).[15]

Most α-aminoaldehydes are configurationally unstable, especially under basic reaction conditions.[19] To assess whether the optical integrity of the *N*-Boc-protected α-amino aldehydes is preserved under the conditions of hydrogen-mediated aldol coupling, the optical purities of *N*-Boc-L-phenylalaninal **6a** and the corresponding aldol adduct **6b** were evaluated by chiral stationary phase HPLC using authentic samples of racemic **6a** and **6b** as standards. The α-amino aldehyde *N*-Boc-L-phenylalaninal **6a** was chosen specifically for this test, as it is notoriously prone toward racemization.[20] Starting with L-phenylalanine of >98% optical purity, *N*-Boc-L-phenylalaninal **6a** was prepared via DIBAL reduction of the corresponding ethyl ester in 88% enantiomeric excess after isolation by silica gel chromatography. Hydrogen-mediated aldol coupling using MVK as pronucleophile provides the aldol coupling product **6b** in 88% enantiomeric excess, thus demonstrating complete preservation of optical purity under the conditions of hydrogen-mediated aldol coupling. More highly optically enriched *N*-Boc-L-phenylalaninal **6a** may be prepared through oxidation of the corresponding α-aminoalcohol using IBX (α-iodoxybenzoic acid).[21b]

Specifically, L-phenylalanine of ≥98% purity was reduced using $NaBH_4$-I_2,[21a] and the resulting amino alcohol was subject to IBX oxidation[21b] to furnish *N*-Boc-L-phenylalaninal **6a** in 94% enantiomeric excess. Hydrogen-mediated aldol coupling of this material using MVK as pronucleophile provides the aldol adduct **6b** in 85% yield and 94% enantiomeric excess.



To further corroborate the role of intramolecular hydrogen bonding as a stereochemical control element, the coupling of MVK and *N*-Boc-L-serinal **8a** was performed in DCM in the presence of *tert*-amyl alcohol (1000 mol %). Whereas in neat DCM aldol adduct **8b** is produced a ≥20:1 diastereomeric ratio, in the presence of *tert*-amyl alcohol a 7:1 diasteromeric ratio is observed. Significant erosion in diastereoselectivity in response to the presence of competitive hydrogen-bond donors represents additional evidence in support of substrate-directed asymmetric induction via intramolecular hydrogen bonding.



Summary

In summary, we report a highly diastereoselective catalytic reductive aldol coupling of vinyl ketones to *N*-Boc-α-aminoaldehydes, wherein high levels of *syn*-aldol selectivity are accompanied by exceptional levels of *anti*-Felkin−Anh control. This method enables generation of amine containing aldol stereotriads with control of both relative and absolute stereochemistry. Because catalytic hydrogen-mediated aldol coupling occurs under essentially neutral conditions (10 mol % of Li_2CO_3, a heterogeneous base in DCM), even very sensitive *N*-Boc-α-aminoaldehydes, such as *N*-Boc-L-phenylalaninal **6a**, participate in the coupling without detectable loss of optically purity. Future studies will focus on the development of related transformations, including enantioselective hydrogen-mediated aldol couplings employing chirally modified rhodium catalysts.

Experimental Section

General. Anhydrous solvents were transferred by an oven-dried syringe. Flasks were flame-dried and cooled under a stream of nitrogen. Dichloromethane (DCM) was distilled from calcium hydride. Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F_{254}). Preparative column chromatography employing silica gel was performed according to the method of Still. ^{1}H NMR spectra were recorded with a Varian Mercury 400 (400 MHz) or Unity+ 300 (300 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian Mercury 400 (100 MHz) or Unity+ 300 (75 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.0 ppm for deuteriochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling. High-resolution mass spectra were obtained on a Micromass ZAB-E spectrometer. FT−IR spectra were obtained using a Nicolet Impact 410 spectrometer. Melting points were obtained on a Thomas-Hoover Unimelt apparatus and are uncorrected.

Representative Procedure for the Reductive Coupling of Enones to *N*-Boc-Protected α-Amino Aldehydes. To a 13 mm × 100 mm test tube charged with Li_2CO_3 (2.8 mg, 0.038 mmol, 10 mol %), (2-furyl)$_3$P (10.7 mg, 0.046 mmol, 12 mol %), Rh(COD)$_2$OTf (9.0 mg, 0.019 mmol, 5 mol %), and *N*-Boc-L-phenylglycinal **3a** (90 mg, 0.38 mmol, 100 mol %) was added dichloromethane (380 μL, 1.0 M). The test tube was sealed, and Ar(g) was bubbled through the reaction mixture followed by H_2(g) for 20 s each. The reaction mixture was placed under an atmosphere of hydrogen using a balloon. MVK (94 μL, 1.15 mmol, 300 mol %) was added to the reaction mixture, and

(19) For selected discussions of the configurational stability of various N-protected α-aminoaldehydes, see: (a) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236−239. (b) Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000**, *41*, 1359−1362.

(20) (a) Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487−1492. (b) Rittle, K. E.; Homnick, C. F.; Ponticello, G. S.; Evans, B. E. *J. Org. Chem.* **1982**, *47*, 3016−3018.

(21) (a) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568−3571. (b) Ocejo, M.; Vicario, J. L.; Badia, D.; Carrillo, L.; Reyes, E. *Synlett.* **2005**, 2110−2112.

the reaction mixture was allowed to stir at 25 °C for 16 h. The reaction mixture was evaporated onto silica, and the residue was purified via flash chromatography (SiO_2: EtOAc/hexane) to furnish the aldol coupling product **3b** (95 mg, 0.31 mmol) in 84% yield.

(1*S*,2*S*,3*S*)-(2-Hydroxy-3-methyl-4-oxo-1-phenylpentyl)carbamic Acid *tert*-Butyl Ester, "MVK-*N*-Boc-L-phenylglycinal Adduct" (3b). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.26−7.37 (m, 5H), 5.42 (d, J = 7.9 Hz, 1H), 4.65 (br, 1H), 4.11 (br, 1H), 2.67 (br, 1H), 2.56−2.63 (m, 1H), 2.17 (s, 3H), 1.42 (br, 9H), 1.23 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 212.3, 156.0, 140.4, 128.7, 127.6, 126.6, 79.7, 74.9, 56.9, 48.6, 29.2, 28.3, 11.8. HRMS: [M + 1] calcd for $C_{17}H_{25}NO_4$, 308.1862; found, 308.1862. FTIR (film): 3440, 3155, 2981, 2253, 1794, 1705, 1494, 1369, 1251, 1167, 1094, 904 cm^{-1}. $[\alpha]_D$ = +30.0 (c = 0.50, $CHCl_3$).

(1*S*,2*S*,3*S*)-(2-Hydroxy-3-methyl-4-oxo-1-phenylhexyl)carbamic Acid *tert*-Butyl Ester, "EVK-*N*-Boc-L-phenylglycinal Adduct" (3c). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.23−7.35 (m, 5H), 5.46 (d, J = 8.2 Hz, 1H), 4.62 (br, 1H), 4.08 (br, 1H), 2.76 (br, 1H), 2.66 (quintet, J = 6.9 Hz, 1H), 2.54 (dq, A of ABX, J_{AB} = 18.1 Hz, J_{AX} = 7.2 Hz, 1H), 2.42 (dq, B of ABX, J_{AB} = 18.1 Hz, J_{BX} = 7.2 Hz, 1H), 1.41 (br, 9H), 1.20 (d, J = 7.2 Hz, 3H), 1.03 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 215.0, 155.8, 140.6, 128.6, 127.4, 126.5, 79.7, 75.1, 56.7, 47.8, 35.2, 28.2, 12.4, 7.5. HRMS: [M + 1] calcd for $C_{18}H_{27}NO_4$, 322.2018; found, 322.2020. FTIR (film): 3155, 2982, 2384, 2254, 1794, 1708, 1602, 1550, 1468, 1381, 1166, 1095, 911 cm^{-1}. MP: 88−89 °C. $[\alpha]_D$ = +21.7 (c = 0.69, $CHCl_3$).

(1*S*,2*S*,3*S*)-(2-Hydroxy-1,3-dimethyl-4-oxopentyl)carbamic Acid *tert*-Butyl Ester, "MVK-*N*-Boc-L-phenylalaninal Adduct" (4b). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.84 (d, J = 8.5 Hz, 1H), 3.73−3.76 (m, 1H), 3.68 (br, 1H), 3.15 (br, 1H), 2.70 (quintet, J = 7.0 Hz, 1H), 2.21 (s, 3H), 1.44 (s, 9H), 1.20 (d, J = 7.2 Hz, 3H), 1.18 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 212.7, 156.1, 79.4, 74.8, 49.4, 48.5, 29.2, 28.3, 18.6, 12.1. HRMS: [M + 1] calcd for $C_{12}H_{23}NO_4$, 246.1705; found, 246.1707. FTIR (film): 3435, 3055, 2981, 2935, 2305, 1703, 1506, 1454, 1393, 1367, 1266, 1167, 1079, 1024, 992, 896 cm^{-1}. $[\alpha]_D$ = −24.3 (c = 2.47, $CHCl_3$).

(1*S*,2*S*,3*S*)-(2-Hydroxy-1,3-dimethyl-4-oxohexyl)carbamic Acid *tert*-Butyl Ester, "EVK-*N*-Boc-L-phenylalaninal Adduct" (4c). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.71 (br, 1H), 3.73−3.77 (m, 1H), 3.65 (br, 1H), 2.85 (br, 1H), 2.67−2.74 (m, 1H), 1.44 (s, 9H), 1.18 (d, J = 7.2 Hz, 3H), 1.05 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 215.4, 156.0, 79.4, 75.0, 48.5, 35.0, 28.5, 28.3, 18.8, 12.3, 7.5. HRMS: [M + 1] calcd for $C_{13}H_{25}NO_4$, 260.1862; found, 260.1860. FTIR (film): 3435, 3055, 2980, 2937, 1703, 1506, 1456, 1367, 1266, 1166, 1102, 1025, 976, 896 cm^{-1}. $[\alpha]_D$ = −24.0 (c = 2.08, $CHCl_3$).

(1*S*,2*S*,3*S*)-(2-Hydroxy-1-isobutyl-3-methyl-4-oxopentyl)carbamic Acid *tert*-Butyl Ester, "MVK-*N*-Boc-L-leucinal Adduct" (5b). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.70 (d, J = 9.2 Hz, 1H), 3.76−3.80 (m, 1H), 3.60−3.66 (m, 1H), 2.90 (d, J = 5.8 Hz, 1H), 2.72 (quintet, J = 7.2 Hz, 1H), 2.21 (s, 3H), 1.60−1.68 (m, 1H), 1.44−1.50 (m, 1H), 1.44 (s, 9H), 1.26−1.34 (m, 1H), 1.20 (d, J = 7.2 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 212.9, 156.2, 79.3, 74.0, 50.9, 49.5, 41.9, 29.4, 28.3, 24.8, 23.0, 22.1, 12.9. HRMS: [M + 1] calcd for $C_{15}H_{29}NO_4$, 288.2175; found, 288.2178. FTIR (film): 3374, 2960, 2871, 1711, 1564, 1502, 1453, 1367, 1251, 1166, 1042, 955, 868 cm^{-1}. $[\alpha]_D$ = −42.5 (c = 2.24, $CHCl_3$).

(1*S*,2*R*,3*R*)-(2-Hydroxy-1-isobutyl-3-methyl-4-oxopentyl)carbamic Acid *tert*-Butyl Ester, "MVK-*N*-Boc-L-leucinal Adduct" (*iso*-5b). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.33 (d, J = 9.0 Hz, 1H), 3.71−3.76 (m, 1H), 3.58−3.64 (m, 1H), 3.12 (br, 1H), 2.73−2.77 (m, 1H), 2.21 (s, 3H), 1.60−1.70 (m, 1H), 1.44−1.50 (m, 1H), 1.44 (s, 9H), 1.24 (d, J = 7.0 Hz, 3H), 1.19−1.24 (m, 1H), 0.93 (d, J = 6.5 Hz, 3H), 0.91−0.94 (m, 1H), 0.91 (d, J = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 213.8, 155.9, 79.5, 74.4, 51.2, 48.7, 40.6, 28.8, 28.3, 24.7, 23.8, 21.4, 11.0. HRMS: [M + 1] calcd for $C_{15}H_{29}NO_4$, 288.2175; found, 288.2182. FTIR (film): 3350, 2967, 2875, 2100, 1686, 1525, 1459, 1378, 1311, 1272, 1237, 1176, 1124, 1078, 1035, 1004, 965, 908, 876 cm^{-1}. MP: 102−103 °C. $[\alpha]_D$ = −11.8 (c = 0.85, $CHCl_3$).

(1*S*,2*R*,3*R*)-(2-Hydroxy-1-isobutyl-3-methyl-4-oxopentyl)methylcarbamic Acid *tert*-Butyl Ester, "MVK-*N*-Me-*N*-Boc-L-leucinal Adduct" (*N*-Me-*iso*-5b). ^{1}H NMR (400 MHz, DMSO, mixture of rotamers, δ): 4.80−5.01 (m, 1H), 3.86−4.08 (m, 1H), 3.74−3.86 (m, 1H), 3.52−3.74 (m, 1H), 2.54−2.68 (m, 3H), 2.32−2.40 (m, 1H), 2.07−2.10 (m, 3H), 1.42−1.49 (m, 1H), 1.25−1.40 (m, 10H), 0.93−1.00 (m, 3H), 0.81−0.91 (d, 6H). ^{13}C NMR (100 MHz, DMSO, mixture of rotamers, δ): 210.8, 210.7, 210.5, 210.1, 210.0, 155.8, 155.4, 155.0, 78.7, 78.6, 78.4, 78.2, 75.0, 74.6, 73.0, 72.7, 72.4, 72.1, 71.9, 71.6, 71.4, 71.0, 70.9, 55.2, 54.5, 50.1, 49.5, 49.1, 48.9, 37.5, 37.3, 37.0, 36.9, 34.6, 29.4, 28.8, 28.6, 28.2, 28.1, 28.1, 28.0, 28.0, 27.5, 24.6, 24.3, 24.1 24.0, 23.9, 23.6, 23.4, 21.7, 21.3, 21.2, 21.1, 13.0, 12.9, 10.6, 9.4, 9.0. HRMS: [M + 1] calcd for $C_{16}H_{31}NO_4$, 302.2331; found, 302.2337. FTIR (film): 3945, 3673, 3446, 3055, 2984, 2686, 2306, 1684, 1456, 1422, 1394, 1367, 1326, 1266, 1152, 1109, 1048, 984, 897 cm^{-1}. $[\alpha]_D$ = −31.6 (c = 0.79, $CHCl_3$).

(1S,2S,3S)-(2-Hydroxy-1-isobutyl-3-methyl-4-oxohexyl)carbamic Acid *tert*-Butyl Ester, "EVK-*N*-Boc-L-leucinal Adduct" (5c). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.67 (d, J = 9.6 Hz, 1H), 3.78−3.81 (m, 1H), 3.56−3.62 (m, 1H), 2.80 (br, 1H), 2.73 (quintet, J = 7.2 Hz, 1H), 2.48−2.63 (m, 2H), 1.58−1.68 (m, 1H), 1.44 (s, 9H), 1.40−1.50 (m, 1H), 1.26−1.35 (m, 1H), 1.19 (d, J = 7.2 Hz, 3H), 1.05 (t, J = 7.2 Hz, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 215.5, 156.1, 79.1, 73.9, 50.8, 48.7, 42.1, 35.1, 28.3, 24.7, 22.9, 22.2, 13.2, 7.4. HRMS: [M + 1] calcd for $C_{16}H_{31}NO_4$, 302.2331; found, 301.2334. FTIR (film): 3440, 2961, 1711, 1564, 1502, 1453, 1367, 1250, 1170, 1109, 1021, 975, 867 cm^{-1}. $[\alpha]_D$ = −26.2 (c = 1.72, $CHCl_3$).

(1*S*,2*S*,3*S*)-(1-Benzyl-2-hydroxy-3-methyl-4-oxopentyl)carbamic Acid *tert*-Butyl Ester, "MVK-*N*-Boc-L-phenylalaninal Adduct" (6b). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.30−7.32 (m, 2H), 7.19−7.21 (m, 3H), 4.80 (d, J = 8.5 Hz, 1H), 3.75−3.83 (m, 2H), 3.03 (br, 1H), 2.80−2.94 (m, 2H), 2.70 (quintet, J = 7.1 Hz, 1H), 2.15 (s, 3H), 1.39 (s, 9H), 1.19 (d, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 213.1, 156.1, 138.1, 129.2, 128.4, 126.5, 79.5, 72.3, 54.1, 49.8, 38.8, 29.3, 28.3, 12.8. HRMS: [M + 1] calcd for $C_{18}H_{27}NO_4$, 322.2018; found, 322.2015. FTIR (film): 3451, 2977, 2933, 2865, 2805, 2606, 1961, 1714, 1494, 1445, 1383, 1351, 1296, 1248, 1153, 1121, 1076, 1043, 934, 845 cm^{-1}. $[\alpha]_D$ = −29.0 (c = 2.07, $CHCl_3$, 94% ee).

(1S,2S,3S)-(1-Benzyl-2-hydroxy-3-methyl-4-oxohexyl)carbamic Acid *tert*-Butyl Ester, "EVK-*N*-Boc-L-phenylalaninal Adduct" (6c). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.26−7.30 (m, 2H), 7.18−7.23 (m, 3H), 4.79 (d, J = 9.2 Hz, 1H), 3.79−3.83 (m, 1H), 3.72−3.78 (m, 1H), 3.07 (br, 1H), 2.95−2.83 (m, 2H), 2.83 (br, 1H), 2.71 (quintet, J = 7.2 Hz, 1H), 2.38−2.61 (m, 2H), 1.38 (s, 9H), 1.17 (d, J = 7.2 Hz, 3H), 1.01 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 215.7, 156.0, 138.2, 129.2, 128.4, 126.3, 79.5, 72.5, 65.8, 54.0, 48.9, 39.0, 35.1, 28.3, 15.2, 13.2, 7.5. HRMS: [M + 1] calcd for $C_{19}H_{29}NO_4$, 336.2175; found, 336.2175. FTIR (film): 3432, 3055, 2980, 2937, 1704, 1499, 1456, 1392, 1367, 1266, 1169, 1080, 1023, 976, 895 cm^{-1}. $[\alpha]_D$ = −30.9 (c = 1.78, $CHCl_3$).

(1*S*,2*S*,3*S*)-(2-Hydroxy-1-isopropyl-3-methyl-4-oxopentyl)carbamic Acid *tert*-Butyl Ester, "MVK-*N*-Boc-L-valinal Adduct" (7b). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.78 (d, J = 9.2 Hz, 1H), 3.99−4.03 (m, 1H), 3.17−3.22 (m, 1H), 2.66−2.73 (m, 2H), 2.20 (s, 3H), 1.81−1.89 (m, 1H), 1.45 (s, 9H), 1.20 (d, J = 7.2 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 213.2, 156.5, 79.2, 71.3, 58.2, 57.3, 49.9, 38.4, 30.3, 29.5, 28.3, 19.7, 19.0, 12.8. HRMS: [M + 1] calcd for $C_{14}H_{27}NO_4$, 274.2018; found, 274.2019. FTIR (film): 3436, 3054, 2985, 2685, 2410, 2305, 1707, 1606, 1549, 1501, 1422, 1367, 1265, 1170, 896 cm^{-1}. MP: 120−121 °C. $[\alpha]_D$ = −16.4 (c = 1.22, $CHCl_3$).

(1*S*,2*S*,3*S*)-(2-Hydroxy-1-isopropyl-3-methyl-4-oxohexyl)carbamic Acid *tert*-Butyl Ester, "MVK-*N*-Boc-L-valinal Adduct" (7c). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 4.80 (d, J = 9.2 Hz, 1H), 4.00−4.03 (m, 1H), 3.13−3.18 (m, 1H), 2.76 (br, 1H), 2.71 (quintet, J = 7.2 Hz, 1H), 2.44−2.61 (m, 2H), 1.80−1.89 (m, 1H), 1.44 (s, 9H), 1.18 (d, J = 7.2 Hz, 3H), 1.04 (t, J = 7.2 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 215.8, 156.5, 79.2, 71.5, 58.2, 49.1, 35.2, 30.6, 28.3, 19.7. 19.0. 13.0. 7.5. HRMS: [M + 1] calcd for $C_{15}H_{29}NO_4$, 288.2175; found, 288.2173. FTIR (film): 3436, 3055, 2978, 2877, 2409, 2348, 1703, 1502, 1461, 1391, 1367, 1266, 1171, 1021, 975, 895 cm^{-1}. MP: 96−98 °C. $[\alpha]_D = -10.8$ (c = 1.39, $CHCl_3$).

(1*S*,2*S*,3*S*)-[1-(*tert*-Butyl-diphenylsilanyloxymethyl)-2-hydroxy-3-methyl-4-oxopentyl]carbamic Acid *tert*-Butyl Ester, "MVK-*N*-Boc-L-serinal Adduct" (8b). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.63−7.68 (m, 4H), 7.37−7.47 (m, 6H), 5.11 (d, J = 9.2 Hz, 1H), 4.14−4.17 (m, 1H), 3.84 (dd, A of ABX, J_{AB} = 10.6 Hz, J_{AX} = 3.8 Hz, 1H), 3.78 (dd, B of ABX, J_{AB} = 10.6 Hz, J_{BX} = 4.1 Hz, 1H), 3.65−3.67 (m, 1H), 3.26 (d, J = 2.7 Hz, 1H), 2.72 (quintet, J = 7.2 Hz, 1H), 2.18 (s, 3H), 1.44 (s, 9H), 1.20 (d, J = 6.8 Hz, 3H), 1.07 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 211.9, 155.9, 135.5, 135.5, 132.4, 130.0, 127.9, 79.4, 2.9, 66.7, 52.4, 49.2, 29.5, 28.3, 26.8, 19.1, 12.9. HRMS: [M + 1] calcd for $C_{28}H_{41}NO_5Si$, 500.2832; found, 500.2834. FTIR (film): 3441, 3053, 2965, 2933, 2860, 2306, 1963, 1709, 1589, 1501, 1473, 1428, 1392, 1367, 1266, 1170, 1113, 913, 872, 823 cm^{-1}. $[\alpha]_D = +11.8$ (c = 2.96, $CHCl_3$).

(1*S*,2*S*,3*S*)-[1-(*tert*-Butyldiphenylsilanyloxymethyl)-2-hydroxy-3-methyl-4-oxohexyl]carbamic Acid *tert*-Butyl Ester, "EVK-*N*-Boc-L-serinal Adduct" (8c). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.63−7.69 (m, 4H), 7.38−7.46 (m, 6H), 5.17 (d, J = 9.2 Hz, 1H), 4.15−4.18 (m, 1H), 3.82 (dd, A of ABX, J_{AB} = 10.6 Hz, J_{AX} = 3.8 Hz, 1H), 3.78 (dd, B of ABX, J_{AB} = 10.6 Hz, J_{BX} = 4.3 Hz, 1H), 3.59−3.61 (m, 1H), 3.30 (d, J = 2.7 Hz, 1H), 2.75 (quintet, J = 7.3 Hz, 1H), 2.41−2.60 (m, 2H), 1.44 (s, 9H), 1.18 (d, J = 6.5 Hz, 3H), 1.07 (s, 9H), 1.03 (d, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 214.6 155.7, 135.5, 135.5, 132.4, 129.9, 127.8, 79.3, 73.1, 66.7, 52.4, 48.4, 35.4, 28.3, 26.8, 13.3, 7.5. HRMS: [M] calcd for $C_{29}H_{43}NO_5Si$, 514.2989; found, 514.2991. FTIR (film): 3443, 3072, 3052, 2977, 2934, 2860, 1962, 1900, 1822, 1705, 1590, 1502, 1462, 1428, 1392, 1367, 1263, 1170, 1112, 1043, 1025, 975, 857, 824 cm^{-1}. MP: 102−103 °C. $[\alpha]_D = +9.8$ (c = 2.05, $CHCl_3$).

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Supporting Information Available: Spectral data for all new compounds. Single-crystal X-ray diffraction data for **5b**-*O*-3,5-dinitrobenzoate, *iso*-**5b**, *iso*-*N*-Me-**5b**-*O*-3,5-dinitrobenzoate, and **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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