

Diastereodivergent Aldol Reactions of β -Alkoxy Ethyl Ketones: Modular Access to (1,4)-*syn* and -*anti* Polypropionates

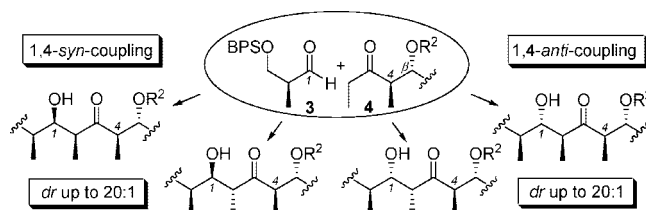
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ABSTRACT



Asymmetric substrate-controlled aldol reactions of ethyl ketones of type 4 with aldehyde 3 are reported. Modular access to all possible *syn*- and *anti*-aldol products was obtained by careful choice of reaction conditions. To achieve good selectivities in this diastereodivergent approach, selection of the protective group on the β -oxygen of the enolate (R^2) was of critical importance.

Polypropionates represent a rich class of natural products of broad structural diversity and complexity with a wide spectrum of potent biological activities.¹ This renders their synthesis an objective of high priority from the perspective of medicinal chemistry and drug discovery. As exemplified by the immunosuppressive macrolide brasilinolide A (**1**, Figure 1)² or the polyene antibiotic etnangien (**2**),³ they are characterized by a sequence of alternating methyl- and hydroxyl-bearing stereogenic centers that enable large numbers of possible stereochemical permutations.

The aldol reaction is widely considered as the most powerful and convergent method for the stereoselective synthesis of these stereogenic arrays.⁴ Particularly attractive are substrate-controlled variants where the selectivity relies on the stereoinduction from a pre-existing chiral center in the sense of a (1,*n*)-*syn* or -*anti* induction.^{5–10} Surprisingly,

(4) For recent reviews, see: (a) Yeung, K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237. (b) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506.

(5) According to the (1,*n*)-nomenclature, 1 denotes the newly formed stereogenic center, while *n* stands for the pre-existing chiral center.

(6) For a leading reference on substrate-controlled aldol reactions of enolates bearing different substitution patterns as compared to the one discussed herein, see ref 4b and Braun, M. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; pp 1–61.

(7) For selected references of aldol additions with substrate control of ethyl ketones which are structurally related to **4**, see: (a) McCarthy, P.; Kageyama, M. *J. Org. Chem.* **1987**, *52*, 4681. (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047. (c) Gustin, D. J.; VanNieuwenhze, M. S.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 3447. (d) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073. (e) Evans, D. A.; Cote, B.; Coleman, P. J.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10893.

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(1) For reviews on polyketide and polypropionate natural products, see: (a) O'Hagan, D. *The Polyketide Metabolites*; Ellis Horwood: Chichester, 1991. (b) O'Hagan, D. *Nat. Prod. Rep.* **1995**, *12*, 1.

(2) Komatsu, K.; Tsuda, M.; Tanaka, Y.; Mikami, Y.; Kobayashi, J. *J. Org. Chem.* **2004**, *69*, 1535.

(3) (a) Höfle, G.; Reichenbach, H.; Irschik, H.; Schummer, D. German Patent DE 196 30 980 A1: 1–7 (5.2. 1998). (b) Irschik, H.; Schummer, D.; Höfle, G.; Reichenbach, H.; Steinmetz, H.; Jansen, R. *J. Nat. Prod.* **2007**, *70*, 1060.

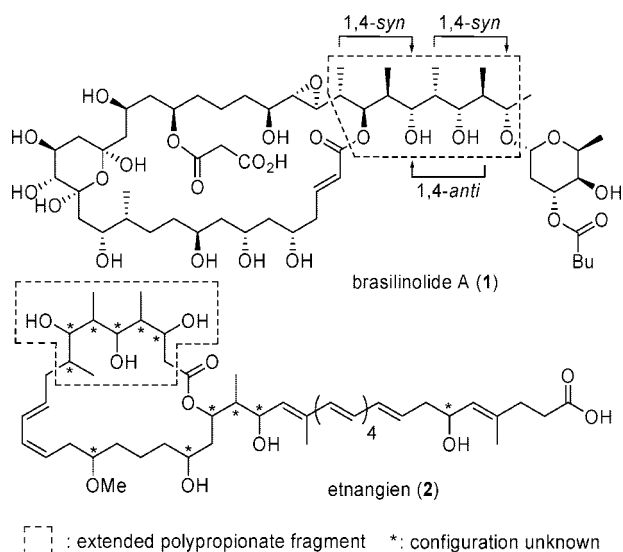


Figure 1. Contiguous arrays of methyl- and hydroxyl-bearing stereogenic centers in polypropionate natural products **1** and **2**: 1,4-*syn* versus 1,4-*anti* connectivity.

diversity-oriented applications of such methods for the divergent assembly of polypropionates are much less reported,^{11,12} despite their importance for library synthesis and in enabling flexible routes to natural products with unassigned configurations,¹³ such as **2**.³ Primarily, they rely on chiral auxiliaries¹⁴ or are not fully diverse, i.e., allowing access to all possible stereoisomeric permutations.^{6,7a,c,d,8b} Herein, we report diastereodivergent asymmetric aldol couplings of ethylketones of type **4** with aldehyde **3** (Scheme 1) to access all possible aldol products by careful choice of reaction conditions, purely by substrate control.

(8) For selected reference of aldol additions with substrate control from chiral methyl ketones, which are structurally related to **4**, see: (a) Evans, D. A.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 6129. (b) Gustin, D. J.; VanNieuwenhze, M. S.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 3443. (c) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585. (d) Evans, D. A.; Coleman, P. J.; Cote, B. J. *Org. Chem.* **1997**, *62*, 788. (e) Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; Scott, J. P.; Sereinig, N. *Org. Lett.* **2003**, *5*, 35. (f) Paton, R. S.; Goodman, J. M. *Org. Lett.* **2006**, *8*, 4299.

(9) For a review on asymmetric boron-mediated aldol reactions, see: Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1.

(10) For leading references on the stereochemical influence of the α - and β -chiral center of the aldehyde in aldol reactions, see: (a) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151. (b) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462. (c) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

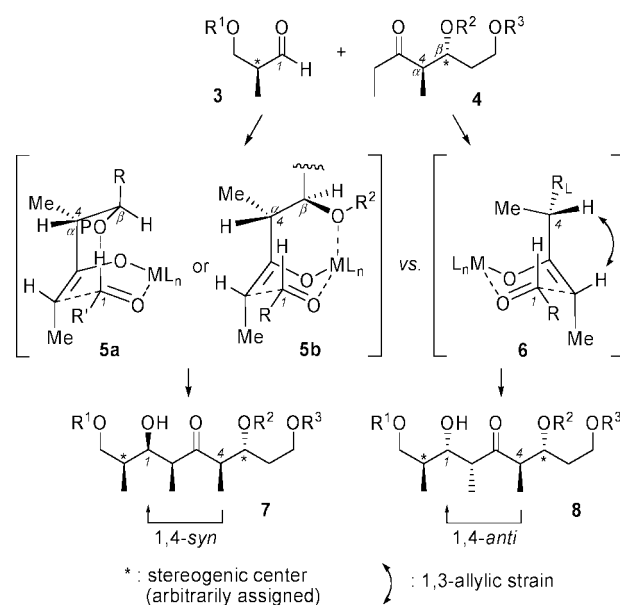
(11) For recent examples of diversity-oriented polyketide library synthesis, see: (a) Reggelin, M.; Brenig, V. *Tetrahedron Lett.* **1996**, 6851. (b) Paterson, I.; Temal-Laib, T. *Org. Lett.* **2002**, *4*, 2473. (c) Barun, O.; Sommer, S.; Waldmann, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3195. (d) Kesavan, S.; Su, Q.; Shao, J.; Porco, J. A., Jr.; Panek, J. S. *Org. Lett.* **2005**, *7*, 4435. (e) Shang, S.; Iwadare, H.; Macks, D. E.; Ambrosini, L. M.; Tan, D. S. *Org. Lett.* **2007**, *9*, 1895.

(12) For diversity oriented aldol-couplings of α -chiral silyloxy-ketones, see: Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. T. *J. Org. Chem.* **1996**, *56*, 2499.

(13) For an example, see: Paterson, I.; Britton, R.; Ashton, K.; Knust, H.; Stafford, J. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 11986.

(14) (a) Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173. (b) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797. (c) Evans, D. A.; Ng, H. P.; Clark, S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127.

Scheme 1. Working Model for Diastereodivergent 1,4-*syn* versus 1,4-*anti* Aldol Coupling (Exemplarily Shown for Z-Enolates **5/6**)



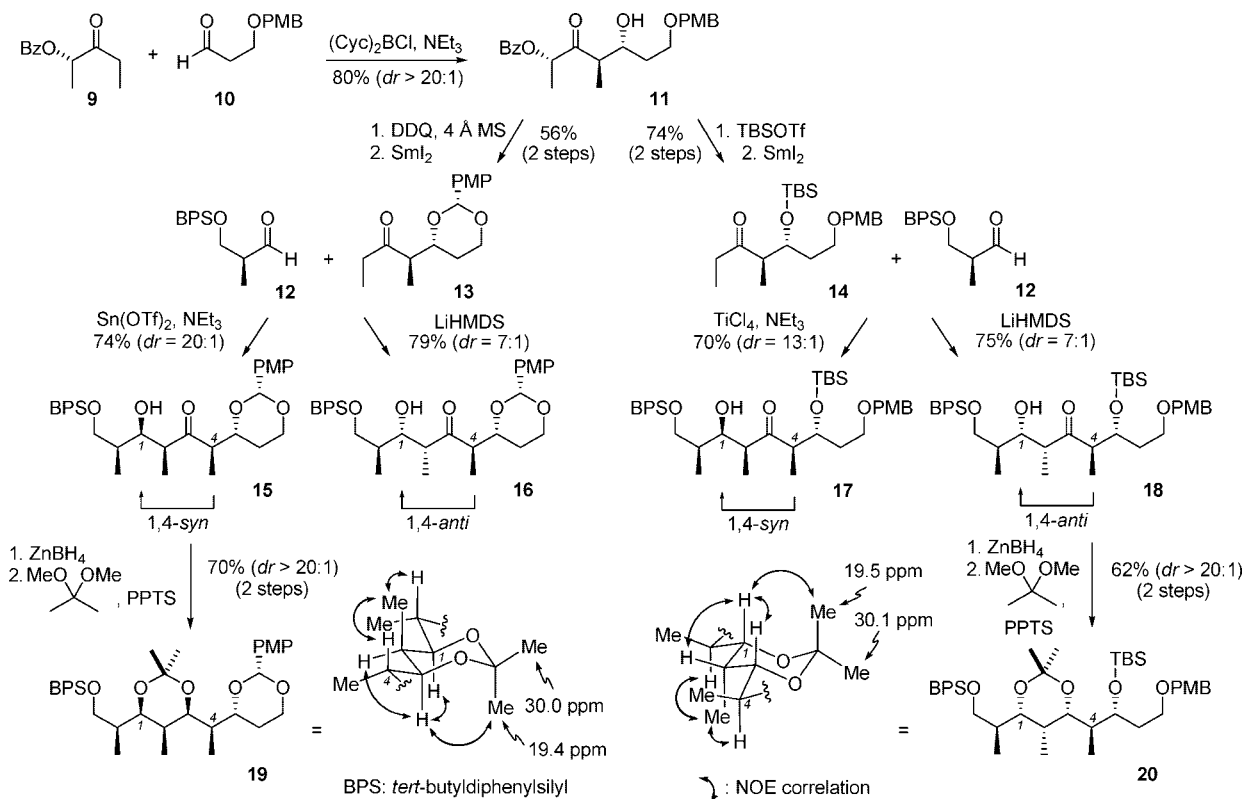
To obtain useful levels of stereoselectivity in substrate-controlled aldol couplings, it is usually necessary to impart stereocontrol from the enolate, as the asymmetric induction from the chiral aldehyde alone is usually insufficient to lead to highly stereoselective aldol reactions.^{7–10} Results indicate that the α -methyl group of ethyl ketones plays a more important role as compared to the β -stereocenter.^{7–10,14c,15} Consequently, our working model, as shown in Scheme 1, was based on the stereoinduction from the α -methyl group of ketone **4** to give after coupling with aldehyde **3** either the 1,4-*syn* or 1,4-*anti* product.¹⁶ To access the 1,4-*syn* diastereomer **7**, a chelation-controlled coupling was envisioned. In analogy to recent calculations of Goodman on boron-mediated aldol reactions of β -oxygenated methyl ketones, albeit without an α -substituent,^{8f} it was envisioned that a similar hydrogen bond interaction between the formyl hydrogen of the aldehyde and the β -oxygen substituent, as depicted in **5a**, may also be present in related reactions of ethyl ketones with an α -methyl group, such as **4**. Alternatively, the β -oxygen may also internally coordinate to the metal counterion giving intermediate **5b**. In both cases, diastereoselectivity should then be governed to minimize steric interaction of the α -methyl group leading to the should be obtained via a nonchelation transition model.¹⁷ In order to reduce allylic strain, the respective enolate was expected to reside in a conformation depicted as **6**. Diastereofacial

(15) In 1,5-*anti* aldol reactions of certain β -alkoxyketones, the β -substituent appears to be more influential as compared to the α -substituent; see ref 8f and literature cited therein.

(16) Selection of **3** and **4** was based on preliminary studies on the configurational assignment of etnangien in our own laboratories.

(17) This noncyclic transition state is in agreement with that proposed by Evans for a boron-mediated aldol reaction.^{14c} For titanium-mediated aldol couplings, a different noncyclic model has been discussed.^{7b}

Scheme 2. 1,4-*syn* versus 1,4-*anti* Aldol Coupling of Z-Enolates



attack should then be governed by the relative sizes of the two residues at C-4, the methyl group (= small) and the large β -chain (R_L). Attack of the aldehyde would then proceed from the *si* face of this enolate to minimize steric interactions, leading to the desired 1,4-*anti* product **8**.

Such a noncyclic transition state should be favored by sterically demanding, electron-withdrawing protecting groups on the β -oxygen, while electron-donating groups R^2 should favor transition states **5a/b**. Accordingly, both the PMP- and the TBS-protected ethyl ketones **13** and **14** were prepared. As shown in Scheme 2⁴, their synthesis was based on a dicyclohexyl-boron mediated Paterson *anti*-aldol reaction⁹ of lactate-derived ethyl-ketone **9** with PMB-protected aldehyde **10**, which proceeds with excellent diastereoselectivity and good yields. Intramolecular protection of the newly generated hydroxyl of **11** as the PMP-acetal and reductive removal of the benzoate (using SmI_2)¹⁸ gave ethyl ketone **13**. The TBS congener **14** was prepared accordingly (TBSOTf, SmI_2).

To initiate our studies for diastereodivergent aldol couplings,¹⁹ we first focused to obtain the all-*syn* aldol product **15**, which should be most readily accessible by reaction of PMP-ketone **13** with Roche ester derived aldehyde **12**.

Optimum results in terms of diastereoselectivity, yield, and preparative practicability among those screened²⁰ were obtained by using a tin-mediated coupling.²¹ Enolisation was best performed under modified Mukaiyama conditions using freshly prepared $\text{Sn}(\text{OTf})_2$ (1.3. equiv) and Et_3N (1.6 equiv) in CH_2Cl_2 at -20°C for 1 h and performing the aldol coupling at -78°C for 1 h giving the desired isomer **15** with very high levels of stereoinduction ($dr > 20:1$)²² and yield (74%). The configuration of **15** was rigorously assigned by NMR analysis on acetonide **19**, readily available by 1,3-*syn* reduction using a freshly prepared ethereal solution of $\text{Zn}(\text{BH}_4)_2$ and treatment with dimethoxypropane. When employing these same conditions to TBS-ketone **14**, the analogous TBS-protected 1,4-*syn* adduct **17** was likewise obtained as the major product, albeit with decreased selectivity (dr 6:1, see Supporting Information), in agreement with our working model. This result, however, could be improved by switching to titanium enolates.²³ By employing slightly modified Evans conditions²⁴ using 1.1 equiv of Hünig's base

(20) Analogous boron⁹ and titanium^{7b} gave lower π -face selectivity and/or proceeded with lower yields.

(21) Tin enolates were first introduced by Mukaiyama: Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381.

(22) In all cases, dr refers to the diastereomeric ratio of the 1,4-*syn* to the 1,4-*anti* aldol products.

(23) For a leading reference on titanium-mediated aldol reactions, see: Ghosh, A. K.; Shevlin, M. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; pp 63–125.

(24) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446.

(18) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639.

(19) Mukaiyama-type aldol reactions were not evaluated within this study because of practicality, as they require separate silyl-enol-ether formation.

and 1.15 equiv of TiCl_4 , for enolization at $-78\text{ }^\circ\text{C}$ (1 h) and performing the aldol coupling at $-78\text{ }^\circ\text{C}$ (2 h) and $-25\text{ }^\circ\text{C}$ (5 min), the desired aldol adduct **17** was obtained with very good levels of selectivity (*dr* 13:1) and yield (70%). This favorable result is in agreement with excellent selectivities previously reported for very similar substrates in titanium-mediated aldol reactions.^{7b,24}

The corresponding 1,4-*anti*-aldol products **16** and **18** were best accessible by use of lithium enolates. Treatment of **13** and **14** with LiHMDS at $-78\text{ }^\circ\text{C}$ and subsequent addition of aldehyde **12** gave the 1,4-*anti*-aldol products **16** and **18**, respectively, as the major isomers with preparatively useful levels of selectivity and yield.²⁵ The configuration of the newly generated stereocenters in the major products was assigned in an analogous fashion as described above by conversion to the corresponding acetonides, such as **20**. While the selectivity of the aldol reaction of ketone **14** may be explicable by model **6**, the very similar levels of π -selectivity of ketone **13** were surprising, as lithium aldol reactions of structurally related β -alkoxy-enolates with donating protective groups, albeit without an α -chiral center, had resulted in high degrees of 1,5-*anti* induction.²⁶ These results may suggest that the α -methyl group has a more pronounced influence and/or alternative transition models have to be considered.^{7a,27}

We then turned our attention to the corresponding *E*-enolates. As shown in Scheme 3, the dicyclohexyl-boron

mainly from a favorable 1,5-*anti* induction in analogy to the Goodman model^{8f} for methyl ketones, whereas the 1,4-*syn* induction should be less attenuated.²⁸ Notably, related systems with silyl-protecting groups on the β -oxygen have previously resulted in high 1,5-*syn* induction,^{8d,9} in agreement with our general working model (Scheme 1). The low stereochemical induction of the aldehyde in such boron-mediated aldol reactions has been amply demonstrated.^{9,10a} This strong 1,5-*anti* bias toward **21** is no longer present in the aldol reaction of the corresponding TBS-protected ketone **14**, due to the bulk of the protecting group and the electron-poor oxygen. The respective 1,4-*anti* product was obtained as the major product, albeit with only low selectivity (*dr* 1.8:1). This low degree of asymmetric induction was surprising, as a very similar aldol coupling had previously resulted in excellent 1,4-*anti* selectivity,^{14c} which suggests that only subtle structural differences may result in highly variable degrees in aldol couplings of this type. Nevertheless, the high chemical yield of this reaction allowed access to diastereomerically pure **22** in 62% isolated yield (see Supporting Information), which renders this transformation still preparatively useful. Therefore, the valuable option of late stage-diversification by substrate control depending on the choice of the β -alkoxy substituent may still be considered even in this case. In general, these results suggest that the β -oxygenated stereocenter appears to impart a stronger influence on the stereoselectivity of dicyclohexyl-boron mediated aldol reactions of ethyl ketones than originally suggested.^{9,14c}

In summary, we have devised substrate-controlled aldol reactions of β -oxygenated chiral ethyl ketones of type **4** with chiral aldehyde **12** to give all possible 1,2-/1,4-*syn* and -*anti* aldol products, with excellent to preparatively useful selectivities in all cases. The protective group on the β -oxygen was shown to impart a crucial influence on the stereochemical outcome in these reactions. Applications of these findings to substrate-controlled aldol-type approaches to etnangien are in progress. It is expected that these findings will be beneficial in devising future modular synthetic approaches and will stimulate further research in divergent aldol couplings.

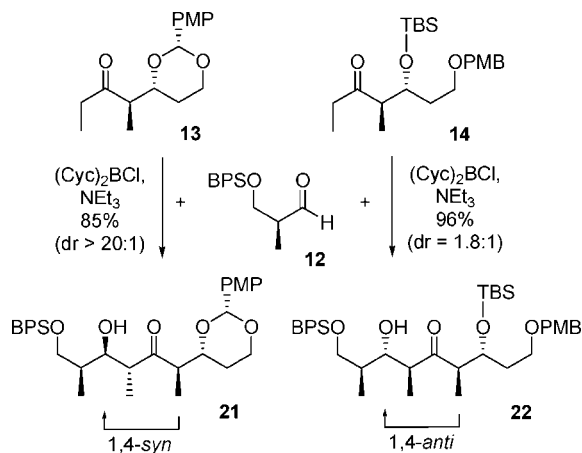
Acknowledgment. This work was supported by the “Fonds der Chemischen Industrie” (“Liebig-Stipendium” to D.M., Stipend to F.A.), the DFG, the Wild-Stiftung, and the HZI. We thank Antje Ritter and Tatjana Arnold (both HZI) for technical support.

Supporting Information Available: Experimental details, spectral data and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL801292T

(28) Dias, L. C.; Baú, R. Z.; se Sousa, M. A.; Zukerman-Schpector, J. *Org. Lett.* **2002**, *4*, 4325.

Scheme 3. 1,4-*syn* versus 1,4-*anti* Aldol Coupling of *E*-Enolates



mediated aldol reaction of PMP-protected ethyl ketone **13** with aldehyde **12** enabled a very efficient access to the 1,4-*syn* adduct **21**. The high selectivity is expected to result

(25) For good stereoselectivities, short reaction times were beneficial.^{7c}

(26) Schinzer, D.; Limberg, A.; Bauer, A.; Böhm, O. M.; Cordes, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 523.

(27) Schinzer, D. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; pp 311–328.