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1,5-Asymmetric Induction in Boron-Mediated Aldol Reactions of β-Alkoxy Methylketones

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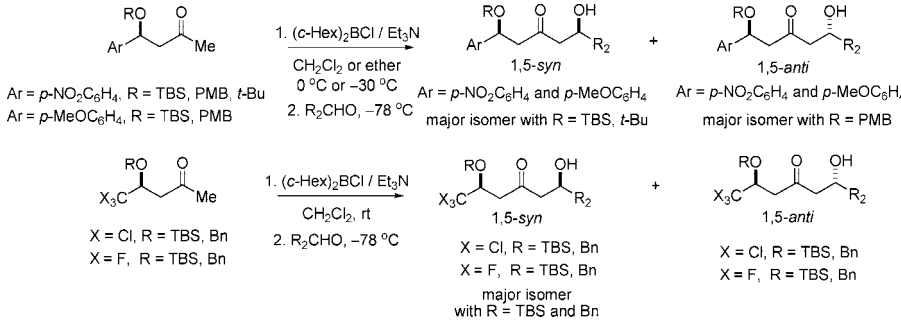

Good levels of substrate-controlled, 1,5-*syn*-stereoinduction are obtained in boron-mediated aldol reactions of β-trichloromethyl-β-alkoxy and β-trifluoromethyl-β-alkoxy methylketones with achiral aldehydes, independent of the nature of the β-alkoxy protecting group (TBS or PMB). In the case of boron aldol reactions of β-aryl-β-alkoxy methylketones, the 1,5-*anti*-adducts were obtained with high levels of diastereoselectivity only with a β-OPMB group.

Introduction

The aldol reaction between boron enolates generated from methylketones and aldehydes provides a very attractive method for carbon−carbon bond formation and has been applied for the synthesis of a wide variety of natural products with biological and pharmacological significance.[1] The presence of a β-heteroatom substituent in the boron enolates of methylketones influences the stereochemical outcome of the corresponding aldol reactions and controls the overall diastereoselectivity of the process leading to moderate to high levels of 1,5-*anti* stereoinduction.

The first evidence for 1,5-*anti* asymmetric induction in aldol reactions was described in 1989 by Masamune and co-workers[2] in their approach to the synthesis of the AB fragment [C1−C16] of bryostatin 1. In the past few years, the research groups of Paterson[3] and of Evans[4] made outstanding contributions and were responsible for the development of this area of remote 1,5-asymmetric induction.[5–7]

In these reactions, the less substituted boron enolate **2** is generated after treatment of the methylketone **1** with boron triflates or dialkyl chloroboranes, followed by addition of a tertiary amine in solvents such as CH_2Cl_2, Et_2O, or pentane (Scheme 1).[1] Usually, high levels of 1,5-*anti* selectivities are

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(1) (a) Dias, L. C.; Aguilar, A. M. *Chem. Soc. Rev.* **2008**, *37*, 451. (b) Dias, L. C.; Aguilar, A. M. *Quim. Nova* **2007**, *30*, 2007. (c) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1. (d) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317. (e) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press; New York, 1991; Vol. 2, p 181. (f) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press; New York, 1991; Vol. 2, p 239. (g) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.

(2) Blanchette, M. A.; Malamas, M. S.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S.; Kageyama, M.; Tamura, T. *J. Org. Chem.* **1989**, *54*, 2817.

(3) Paterson, I.; Oballa, R. M.; Norcross, R. D. *Tetrahedron Lett.* **1996**, *37*, 8581.

(4) Evans, D. A.; Côté, B.; Coleman, P. J.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10893.

(5) (a) Paterson, I.; Goodman, J. M. *Tetrahedron Lett.* **1989**, *30*, 997. (b) Paterson, I.; Florence, G. J. *Tetrahedron Lett.* **2000**, *41*, 6935. (c) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585. (d) Paterson, I.; Collett, L. A. *Tetrahedron Lett.* **2001**, *42*, 1187.

(6) (a) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788. (b) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *29*, 8671. (c) Tanimoto, N.; Gerritz, S. W.; Sawabe, A.; Noda, T.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 673. (d) Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A.; Scheidt, K. A. *J. Org. Chem.* **2002**, *67*, 4275.

(7) (a) Denmark, S. E.; Fujimori, S.; Pham, S. M. *J. Org. Chem.* **2005**, *70*, 10823. (b) Denmark, S. E.; Fujimori, S. *Synlett* **2001**, 1024. (c) Denmark, S. E.; Fujimori, S. *J. Am. Chem. Soc.* **2005**, *127*, 8971.

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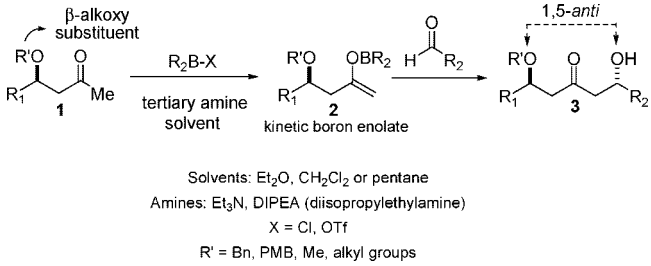
SCHEME 1. General Scheme for Aldol Reactions of β-Alkoxy Boron Enolates



obtained in aldol reactions of β-alkoxy methylketones when the β-alkoxy substituent is an alkyloxy group, a benzyloxy group (OBn, OPMB), or a part of benzylidene acetal. With a β-silicon protecting group, the aldol reaction gives little or no selectivity.[1–4]

In order to understand the principles that control the 1,5-diastereoselectivity in aldol reactions of boron enolates generated from β-alkoxy methylketones, we decided to study the influence of the substituents at the β-position of the boron enolate by using β-*p*-nitrophenyl and β-*p*-methoxyphenyl groups as well as β-trichloromethyl and β-trifluoromethyl groups.[8] In addition, trichloromethyl and trifluoromethyl compounds are precursors for the synthesis of various useful products such as α-substituted carboxylic acids and terminal alkynes.[9]

We wish to report here our results in aldol reactions using the less substituted boron enolates of β-alkoxy-β-aryl, β-alkoxy-β-trichloromethyl, and β-alkoxy-β-trifluoromethyl methylketones with achiral aldehydes.[7] Methylketones with *tert*-butyldimethylsilyl (TBS), benzyl (Bn), *p*-methoxybenzyl (PMB), and *tert*-butyl protecting groups at the β-position were employed to evaluate the potential steric and electronic impact of the β-alkoxy substituents.[8]

Results and Discussion

Aldol Reactions of β-Aryl-β-alkoxy Methylketones. The preparation of β-alkoxy-β-aryl methylketones **5** (R = PMB), **6** (R = TBS), **8** (R = PMB), and **9** (R = TBS) is described in Scheme 2. The racemic methylketones **4** and **7** were prepared in good yields by aldol reactions between acetone and *p*-nitrobenzaldehyde or *p*-methoxybenzaldehyde, respectively (Scheme 2).[10] Treatment of methylketone **4** with PMB-acetimidate in the presence of catalytic amounts of TfOH gave methylketone **5** in 64% yield.[11] Protection of the β-oxygen in **4** as its TBS ether was achieved by using TBSCl and $AgNO_3$ in DMF at room tempertaure for 16 h, providing **6** in 92% yield (Scheme 2).[12]

Methylketone **7** was treated under similar reaction conditions to provide the protected β-alkoxy methylketones **8** (R = PMB) and **9** (R = TBS) in good yields (Scheme 2).

The enolization of methylketone **5** (R = PMB) was performed with $(c\text{-Hex})_2BCl$ and Et_3N in Et_2O or CH_2Cl_2 as solvent at 0 °C. Aldol reactions with aldehydes **10a**−**f**, at −78 °C, provided the corresponding 1,5-*anti* (**11a**−**f**) and 1,5-*syn* (**12a**−**f**) aldol adducts (Scheme 3, Table 1).[13]

The boron-mediated aldol reactions of methylketone **5** (R = PMB) were found to proceed with good yields and high degrees of remote 1,5-*anti* stereoinduction. In all the cases studied with methylketone **5** (R = PMB), 1,5-*anti* isomers **11a**−**f** were isolated as the major products.[14]

In the case of methylketone **6** (R = TBS), the corresponding boron enolate addition to aldehydes **10a**−**f** gave a mixture of aldol adducts **13a**−**f** and **14a**−**f** favoring the 1,5-*syn* aldol adducts **14a**−**f** (Scheme 3, Table 1).[8] The best selectivity was observed with benzaldehyde (entry 6, *anti:syn* = 29:71). It is clear from these examples that the presence of a TBS protecting group at the β-oxygen of the boron enolate weakly favored the formation of the 1,5-*syn* product, indicating a low level of influence on the selectivity by the resident β-OTBS group.

The relative stereochemistry for aldol adducts **11a**−**f** (R = PMB) was confirmed after conversion of **11a** to the corresponding benzylidene acetal **16** and isopropylidene acetal **17** (Scheme 4). Selective 1,3-*anti* reduction of **11a** provided diol **15** in 54% yield and >95:05 diastereoselectivity (via transition state **A**).[15] Diol **15** was treated with DDQ in CH_2Cl_2 in the presence of molecular sieves to give benzylidene acetal **16** in 83% yield (Scheme 4).[16] Analysis of the ^1H NMR coupling constants, specifically $J_{Ha\text{-}Hc}$ = 11.2 Hz, $J_{Ha\text{-}Hd}$ = 2.7 Hz, $J_{Hb\text{-}Hc}$ = 11.2 Hz, and $J_{Hb\text{-}Hd}$ = 2.5 Hz, together with the illustrated NOE data, proved that Ha, Hb, and Hc are all axial in **16**. Treatment of diol **15** with $Me_2C(OMe)_2$ and catalytic amounts of CSA provided the isopropylidene acetal **17** in 77% yield (Scheme 4).[17] Analysis of the ^{13}C NMR spectra showed resonances at 24.3, 25.0, and 100.2 for **17**, characteristic of a 1,3-*anti*-acetonide.[17]

The next step involved the assignment of the relative stereochemistry for aldol adducts obtained from methylketone **6** (R = TBS). Treatment of aldol adduct **11a** with DDQ, gave diol 1,5-*anti*-**18** in 36% nonoptimized yield (Scheme 5).[16] As we were able to separate the 34:66 mixture of *anti* and *syn* aldol adducts **13a** and **14a** (R = TBS) by flash column chromatography, both aldols were independently treated with HF in CH_3CN/H_2O (4/1) to give diols **18** and **19**, respectively, in excellent yields. At this point, by comparison of their ^1H and ^{13}C NMR spectra, we observed that the diol **18**, prepared from the minor aldol adduct **13a**, was identical in all respects with the 1,5-*anti*-diol prepared from PMB removal of **11a**. This proved that the 1,5-*syn*-isomer is the major product in the aldol reactions with a TBS protecting group (Scheme 5).

(8) Dias, L. C.; Marchi, A. A.; Ferreira, M. A. B.; Aguilar, A. M. *Org. Lett.* **2007**, *9*, 4869.

(9) (a) Gouverneur, V.; Purser, S.; Moore, P. R.; Swallow, S. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Bonnet-Delpon, D.; Bégué, J. P. *J. Fluorine Chem.* **2006**, *127*, 992.

(10) (a) Chimni, S. S.; Mahajan, D. *Tetrahedron* **2005**, *61*, 5019. (b) Zhang, F.; Su, N.; Gong, Y. *Synlett* **2006**, 1703.

(11) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535.

(12) (a) Hakimelahi, G. H.; Proba, Z. A.; Ogilvie, K. K. *Tetrahedron Lett.* **1981**, *22*, 4775. (b) Cossy, J.; Bauer, D.; Bellosta, V. *Tetrahedron* **2002**, *58*, 5909.

(13) (a) Dias, L. C.; Baú, R. Z.; de Sousa, M. A.; Zuckerman-Schpector, J. *Org. Lett.* **2002**, *4*, 4325. (b) Dias, L. C.; Aguilar, A. M.; SallesJr, A. G.; Steil, L. J.; Roush, W. R *J. Org. Chem.* **2005**, *70*, 10461. (c) Dias, L. C.; Aguilar, A. M. *Org. Lett.* **2006**, *8*, 4629.

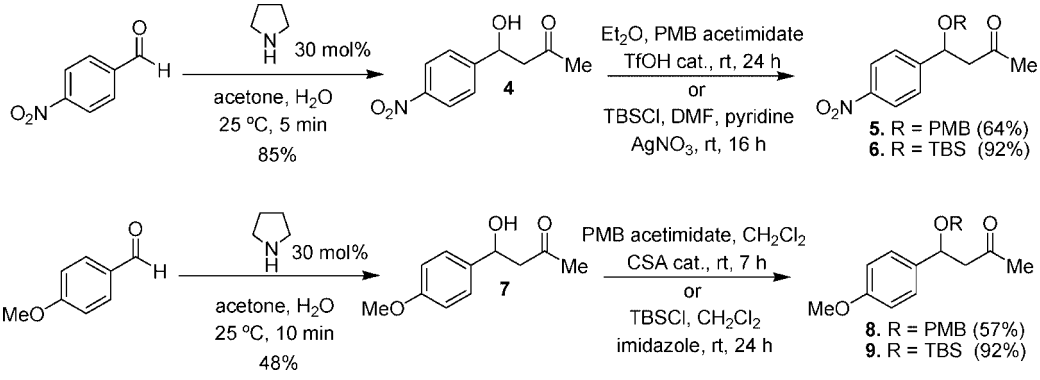
(14) (a) The ratios were determined by ^1H and ^{13}C NMR spectroscopic analysis of the unpurified product mixture. (b) All of the percentage values represent data obtained from at least three individual trials.

(15) (a) Evans, D. A; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939. (b) Evans, D. A; Chapman, K. T.; Carreira, E. M *J. Am. Chem. Soc.* **1988**, *110*, 3560. (c) Dias, L. C.; de Oliveira, L. G.; Vilcachagua, J. D.; Nigsch, F. *J. Org. Chem.* **2005**, *70*, 2225. (d) Dias, L. C.; de Oliveira, L. G. *Org. Lett.* **2004**, *6*, 2587. (e) Dias, L. C.; de Oliveira, L. G.; de Sousa, M. A. *Org. Lett.* **2003**, *5*, 265.

(16) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889.

(17) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099. (c) Tormena, C. F.; Dias, L. C.; Rittner, R. *J. Phys. Chem. A* **2005**, *109*, 6077. (d) Dias, L. C.; Giacomini, R. *Tetrahedron Lett.* **1998**, *39*, 5343. (e) Dias, L. C.; Diaz, G.; Ferreira, A. A.; Meira, P. R. R.; Ferreira, E. *Synthesis* **2003**, 603.

SCHEME 2. Preparation of β-Alkoxy Methylketones 5−9



SCHEME 3. Aldol Reactions of β-Alkoxy Methylketones 5 and 6

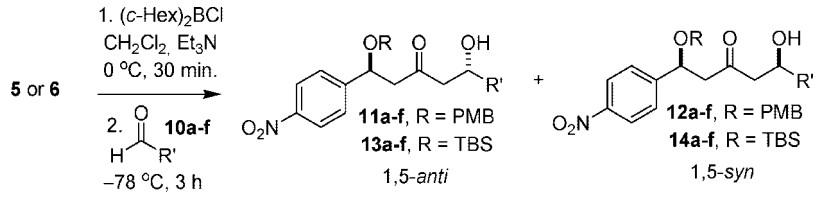


TABLE 1. Aldol Reactions of 5 and 6 with R′CHO

entry	R (ketone)	aldehyde (R′)	ds[a](1,5-*anti*:1,5-*syn*)	yield (%)[b]
1[c]	PMB (**5**)	**10a**, ^{i}-Pr	96:04 (**11a**:**12a**)	70
2	PMB (**5**)		96:04 (**11a**:**12a**)	78
3	TBS (**6**)		34:66 (**13a**:**14a**)	91
4	PMB (**5**)	**10b**, Ph	>95:05 (**11b**:**12b**)	65
5[d]	PMB (**5**)		87:13 (**11b**:**12b**)	74
6	TBS (**6**)		29:71 (**13b**:**14b**)	81
7	PMB (**5**)	**10c**, Et	92:08 (**11c**:**12c**)	51
8	TBS (**6**)		41:59 (**13c**:**14c**)	65
9	PMB (**5**)	**10d**, C(Me)=CH$_2$	93:07 (**11d**:**12d**)	54
10	TBS (**6**)		41:59 (**13d**:**14d**)	70
11	PMB (**5**)	**10e**, *p*-C$_6$H$_4$OMe	>95:05 (**11e**:**12e**)	63
12	TBS (**6**)		37:63 (**13e**:**14e**)	67
13	PMB (**5**)	**10f**, *p*-C$_6$H$_4$NO$_2$	>95:05 (**11f**:**12f**)	56
14	TBS (**6**)		43:57 (**13f**:**14f**)	69

[a] Ratio was determined by ^{1}H NMR analysis of the diastereoisomeric mixture of adducts. [b] Isolated yields of both *syn* and *anti* isomers after SiO$_2$ flash chromatography. [c] Et$_2$O as solvent. [d] Aldehyde addition was performed at 0 °C.

We next moved to investigate the aldol reactions of methylketones **8** (R = PMB) and **9** (R = TBS). The aldol reactions of the methylketones **8** and **9** with aldehydes **10a**−**f** were investigated using (*c*-Hex)$_2$BCl and Et$_3$N in CH$_2$Cl$_2$ as solvent for enolization to give the 1,5-*anti*- and 1,5-*syn*-aldol adducts (Scheme 6, Table 2).[8,13] The enolizations were performed at 0 °C, and the addition of the aldehyde was at −78 °C. As observed before, these boron-mediated aldol reactions were found to proceed with good yields and high degrees of remote 1,5-*anti*-stereoinduction for methylketone **8** (R = PMB).

Following the same trend observed for methylketone **6** (R = TBS), the reaction of the boron enolate generated from methylketone **9** (R = TBS) with aldehydes **10a**−**f** led to a mixture of aldol adducts **22a**−**f** and **23a**−**f** favoring the 1,5-*syn*-aldol adducts **23a**−**f** (Scheme 6, Table 2).[8] The best selectivity was observed with propionaldehyde (entry 6, *anti:syn* = 29:71). The presence of a TBS protecting group at the β-oxygen of the methylketone **9** again favored the formation of the 1,5-*syn*-aldol adduct.

The 1,5-*anti*-relative stereochemistry for aldol adducts **20a**−**f** was unambiguously established after conversion of **20a** to the corresponding benzylidene acetal **25** (Scheme 7). Selective reduction of **20a** to the 1,3-*anti*-diol **24** (52% yield) followed by treatment of **24** with DDQ in CH$_2$Cl$_2$ gave benzylidene acetal **25** in 25% nonoptimized yield.[15,16] Analysis of the ^{1}H NMR coupling constants, specifically $J_{Ha\text{-}He}$ = 11.1 Hz, $J_{Ha\text{-}Hd}$ = 2.4 Hz, $J_{Hb\text{-}He}$ = 11.1 Hz, and $J_{Hb\text{-}Hd}$ = 2.7 Hz, together with the illustrated NOE interactions between Ha, Hb, and Hc, proved that Ha, Hb, and Hc are all axial in **25**.

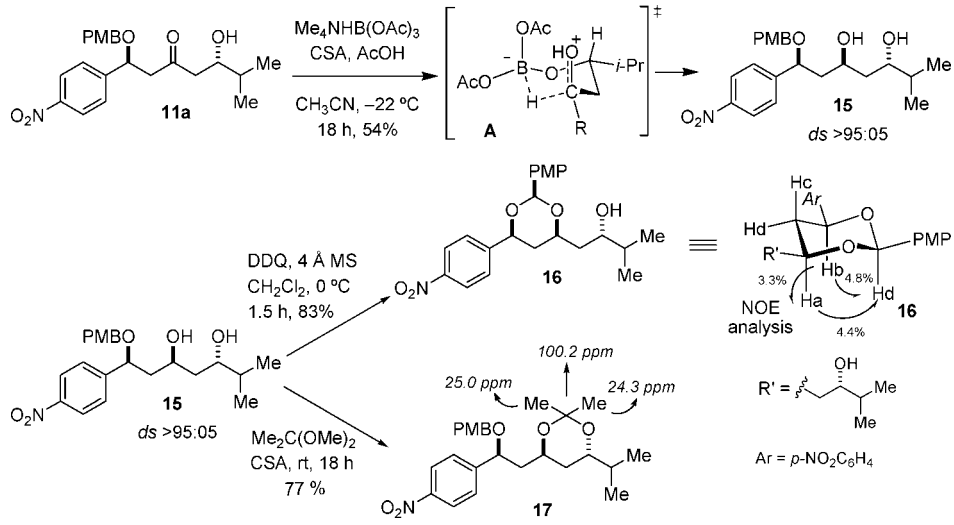
In order to assign the stereochemistry for aldol adducts obtained from methylketone **9** (R = TBS), we first treated aldol **20a** (R = PMB), of known stereochemistry, with DDQ, H$_2$O in CH$_2$Cl$_2$, to give diol 1,5-*anti*-**26** in 38% nonoptimized yield (Scheme 8).

The 32:68 mixture of *anti*- and *syn*-aldol adducts **22a** and **23a** (entry 10, Table 2) was separated by flash column chromatography, and the aldol products were independently treated with TBAF and AcOH in THF to give diols **26** and **27**, respectively, in good yields (Scheme 8).[18] After comparison of their ^{1}H and ^{13}C NMR spectra, we observed that the diol **26**, prepared from the minor aldol adduct **22a**, was identical in all respects with the 1,5-*anti*-diol prepared from PMB removal of **20a**. Again, this proved that the 1,5-*syn*-isomer is the major product in the aldol reactions of methylketone **9**, with a TBS protecting group (Scheme 5).

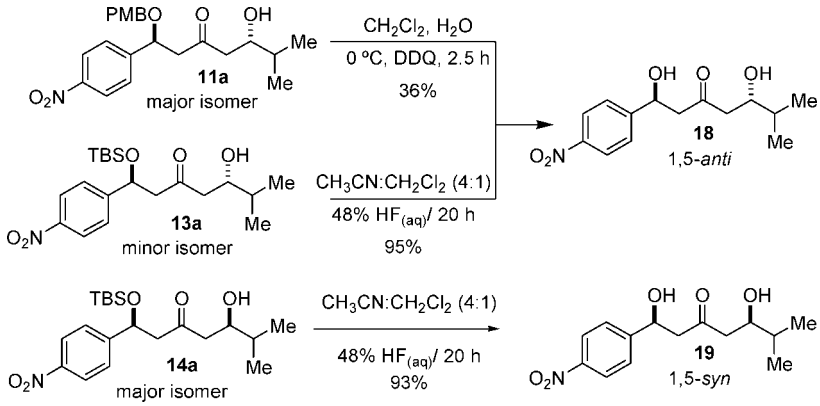
At this point, we decided to prepare methylketone **28** (R = *t*-Bu) in order to evaluate the stereoelectronic impact of the *tert*-butyl group at the β-oxygen (Scheme 9). Our intention was to compare the aldol addition of the boron enolate of this methylketone with that of methylketone **6** (R = TBS). To the best of our knowledge, there are no examples of aldol reactions of β-O*t*-Bu methylketones described in the literature. Treatment of methylketone **4** with *t*-Bu-acetimidate in the presence of catalytic amounts of CSA gave methylketone **28** in 23% yield (nonoptimized), together with α,β-unsaturated ketone **29**.[19,20]

Addition of aldehydes **10a**, **10b**, and **10e** to the boron enolate generated from methylketone **28** led to a mixture of the corresponding 1,5-*anti*- and 1,5-*syn*-aldol adducts in good yields with low levels of diastereoselectivity favoring the 1,5-*syn*-aldol products (Scheme 10).

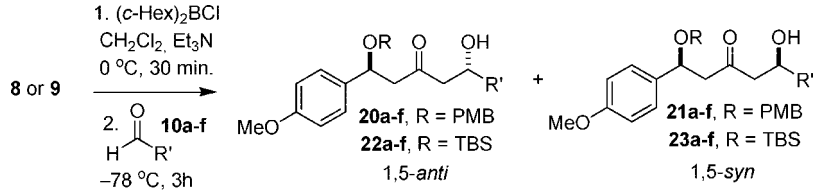
SCHEME 4. Proof of Stereochemistry for Aldol Adduct 11a



SCHEME 5. Proof of Stereochemistry for Aldol Adducts 13a and 14a



SCHEME 6. Aldol Reactions of β-Alkoxy Methylketones 8 and 9



The relative stereochemistry for the major product from the aldol reactions of methylketone **28** was confirmed after treatment of the 37:63 mixture of *anti*- and *syn*-aldol adducts **30a** and **31a** with $TiCl_4$ in CH_2Cl_2 to remove the *t*-Bu protecting group, leading to diols **18** and **19** in 63% combined yield (Scheme 11).[19,21] After comparison of their ^1H and ^{13}C NMR spectra, we have observed that the 1,5-*anti*-diol **18**, prepared from PMB removal of **11a** (Scheme 5), was identical in all respects with the minor isomer prepared from the mixture of aldol adducts **30a** and **31a**. This proved that the 1,5-*syn*-isomer is the major product in the aldol reactions of methylketone **28** with a *t*-Bu protecting group.

TABLE 2. Aldol Reactions of 8 and 9 with R′CHO

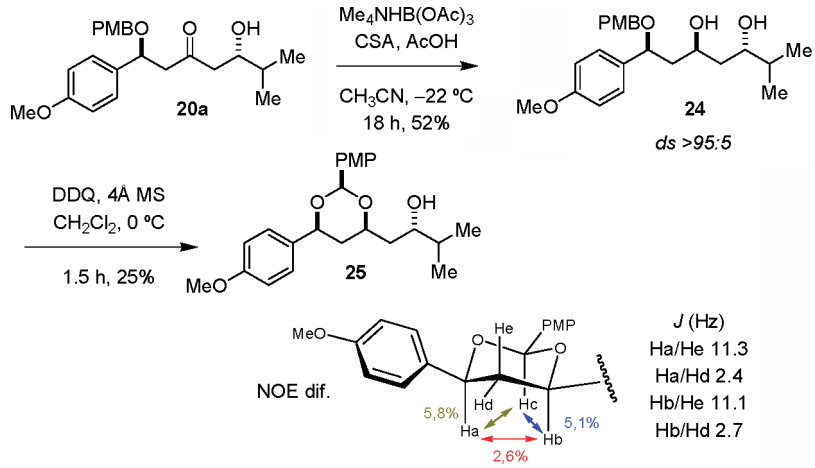
entry	R (ketone)	aldehyde (R′)	ds[a] (1,5-*anti*:1,5-*syn*)	yield (%)[b]
1	PMB (**8**)	**10a**, ^{i}-Pr	>95:05 (**20a**:**21a**)	84
2	TBS (**9**)		32:68 (**22a**:**23a**)	88
2	PMB (**8**)	**10b**, Ph	>95:05 (**20b**:**21b**)	89
3	TBS (**9**)		33:67 (**22b**:**23b**)	74
5	PMB (**8**)	**10c**, Et	94:06 (**20c**:**21c**)	60
6	TBS (**9**)		29:71 (**22c**:**23c**)	65
7	PMB (**8**)	**10d**, C(Me)=CH_2	>95:05 (**20d**:**21d**)	75
8	TBS (**9**)		32:68 (**22d**:**23d**)	81
9	PMB (**8**)	**10e**, p-C_6H_4OMe	>95:05 (**20e**:**21e**)	79
10	TBS (**9**)		33:67 (**22e**:**23e**)	50
11	PMB (**8**)	**10f**, p-$C_6H_4NO_2$	>95:05 (**20f**:**21f**)	85
12	TBS (**9**)		35:65 (**22f**:**23f**)	78

[a] Ratio was determined by ^1H NMR analysis of the diastereoisomeric mixture of adducts. [b] Isolated yields of both *syn* and *anti* isomers after SiO_2 flash chromatography.

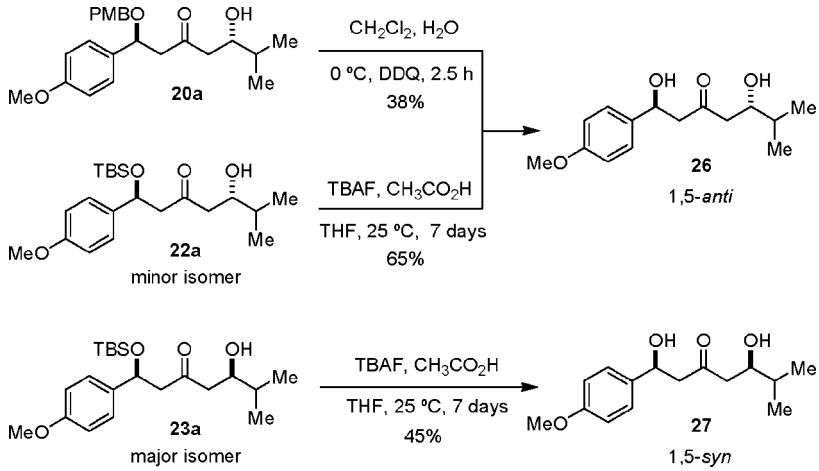
The observed results for methylketone **28** show that a steric effect is responsible for the formation of the 1,5-*syn*-isomer with

(18) Smith, A. B., III.; Ott, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 13095.
(19) (a) Wuts, P. G. M.; Greene, T. W. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley-Interscience: New York, 2007. (b) Dias, L. C.; Meira, P. R. R. *J. Org. Chem.* **2005**, *70*, 4762.
(20) Armstrong, A.; Brackenridge, I.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Lett.* **1988**, *29*, 2483.
(21) Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 1116.

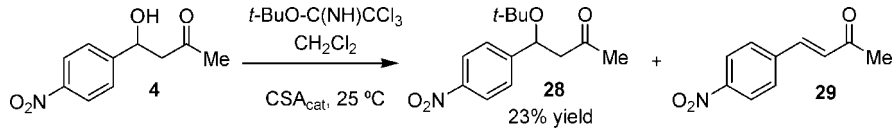
SCHEME 7. Proof of Stereochemistry for Aldol Adduct 20a



SCHEME 8. Proof of Stereochemistry for Aldol Adducts 22a and 23a



SCHEME 9. Preparation of β-Alkoxy Methylketone 28



a β-OTBS and a β-O*t*-Bu protecting groups. The lower basicity of the oxygen attached to the silicon may not be the only effect responsible for the observed lower selectivities as steric effects may play a very important role in controlling the observed sense of stereoinduction.[22,23]

Aldol Reactions of β-Methyl, β-Trichloromethyl, and β-Trifluoromethyl-β-alkoxy Methylketones. We then moved to investigate the stereochemical impact of β-methyl, β-trichloromethyl, and β-trifluoromethyl substituents on the β-alkoxy methylketones.[9]

We began with the preparation of β-trichloromethyl methylketone **36**, employing the directed aldol reaction of acetone with chloral hydrate in the presence of ammonium hydroxyde at room temperature (60% yield), as shown in Scheme 12.[12,24] Treatment of ketone **36** with BnBr, KI, and K_2CO_3 in acetone as solvent gave β-OBn methylketone **37** in 55% yield.[25] Attempts to protect the β-hydroxyl function of aldol adduct **36** as its TBS ether proved problematic under a variety of conditions. The usual procedures resulted in decomposition and low yields of the desired silyl ether **38**. The best conditions involved treatment of **36** with TBSCl, $AgNO_3$, and pyridine in DMF providing β-OTBS methylketone **38** in 89% yield (Scheme 12).[12] This supports the notion that the basic nature of the β-oxygen atom is significantly attenuated due to the strong electron-withdrawing capability of the trichloromethyl group.

The β-alkoxy methylketones **40** and **41** were prepared under similar conditions (Scheme 12). Aldol reaction of acetone with trifluoroacetaldehyde ethyl hemiacetal in the presence of pyrrolidine at room temperature provided hydroxyketone **39** in 88%

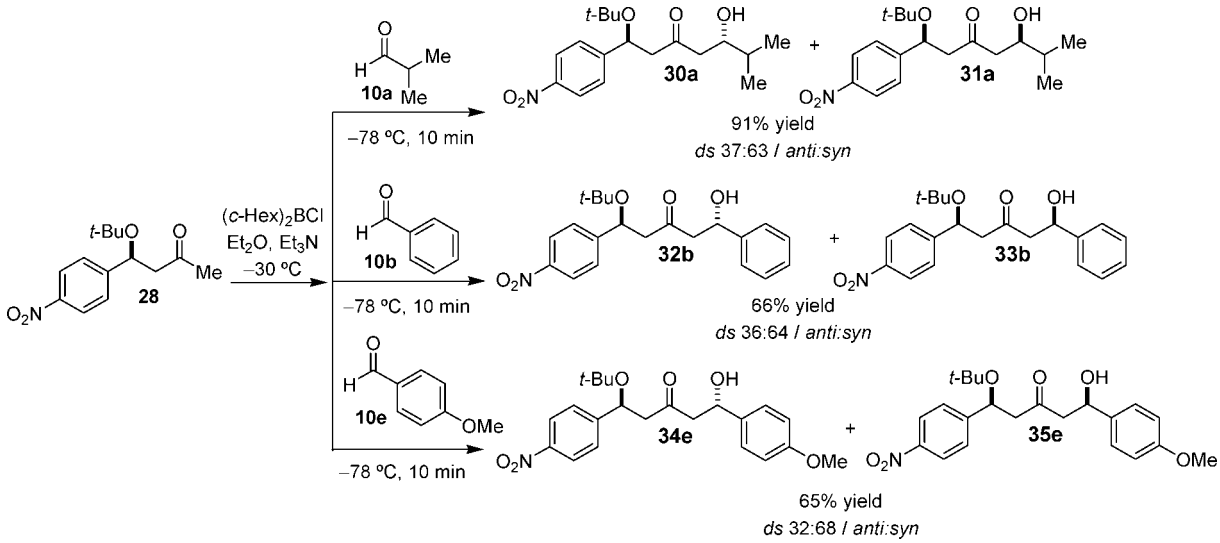
(22) (a) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462. (b) Chen, X. N.; Hortellano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 6130. (c) Mori, S.; Nakamura, M.; Nakamura, E.; Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1995**, *117*, 5055. (d) Schreiber, S. L.; Shambayati, S.; Blake, J. F.; Wierschke, S. G.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1990**, *112*, 697. (e) Beckmann, J.; Grabowsky, S. *J. Phys. Chem. A* **2007**, *111*, 2011.

(23) Dias, L. C.; Ferreira, M. A. B.; Tormena, C. F. *J. Phys. Chem. A* **2008**, *112*, 232.

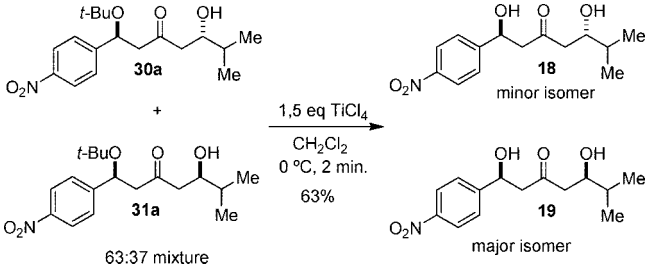
(24) Feng, L.; Xu, L.; Lam, K.; Zhou, Z.; Yip, C. W.; Chan, A. S. C. *Tetrahedron Lett.* **2005**, *46*, 8685.

(25) Witt, A.; Bergan, J. *J. Org. Chem.* **2001**, *66*, 2784.

SCHEME 10. Aldol Reactions of β-Alkoxy Methylketone 28



SCHEME 11. Proof of Stereochemistry for Aldols 30a and 31a



yield (Scheme 12).[26] Treatment of ketone **39** with BnBr, Ag_2O, and TBAI in CH_2Cl_2 as solvent gave β-OBn methylketone **40** in 45% yield. The best conditions for the preparation of methylketone **41** (R = TBS) involved treatment of **39** with TBSCl, $AgNO_3$, and pyridine in DMF (70% yield).[12]

At this point, we decided to prepare methylketones **44** and **46**, containing a β-methyl group in order to compare the corresponding aldol reactions with those using methylketones **37/38** and **40/41**. The methyl group is smaller in size compared to strongly electron-withdrawing CF_3 and CCl_3 groups. Monobenzylation of commercially available 1,3-diol **42** provided alcohol **43**, which was treated with PCC in CH_2Cl_2 to give β-OBn methylketone **44** in 64% yield for the two-step sequence (Scheme 13).[27,28]

Methylketone **46** was easily prepared by a sequence which involved treatment of diol **42** with TBSOTf and 2,6-lutidine in CH_2Cl_2 at −78 °C to provide alcohol **45**, followed by oxidation with PCC in the presence of anhydrous NaOAc (44%, two steps).[28]

Enolization of methylketones **37** (R = Bn) and **38** (R = TBS) with $(c\text{-Hex})_2BCl$ and Et_3N in CH_2Cl_2 at room temperature proceeded smoothly, providing the corresponding kinetic enol borinate, which was used in the aldol reactions with aldehydes **10a**−**g** (Scheme 14, Table 3). The reactions were studied at 0 °C as well as at −78 °C. We were delighted to find that these reactions led to the formation of 1,5-*syn*-products **47a**−**g** (R = Bn) and **49a**−**f** (R = TBS) as the major isomers (1,5-*syn*:1,5-*anti*-selectivities ranging from 78:22 to 92:08) in moderate to high yields (Scheme 14, Table 3). Usually, higher yields were obtained with aldol reactions at 0 °C, although higher levels of diastereoselectivities were observed at lower temperatures.

These studies showed a remarkable influence of the resident β-trichloromethyl group on the stereochemical course of these aldol reactions to give the 1,5-*syn*-isomer, independent of the nature of the β-alkoxy protecting group.

With methylketones **40** (R = Bn) and **41** (R = TBS), we observed the same trend, and the overall diastereoselection of the process was again controlled by the facial bias of the β-trifluoromethyl group of the boron enolate to give the 1,5-*syn*-products **51a**−**e** (R = Bn) and **53a**−**e** (R = TBS) as the major isomers (Scheme 15, Table 4).[11]

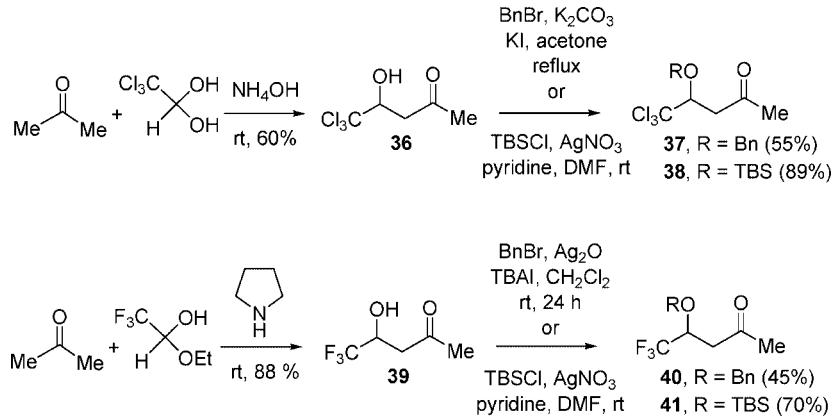
It is interesting that higher levels of 1,5-*syn*-diastereoselection were observed with β-CCl_3 methylketones **37** (R = Bn) and **38** (R = TBS), when compared with β-CF_3 methylketones **40** (R = Bn) and **41** (R = TBS). This may well be related to the larger size of the β-CCl_3 group.

The relative stereochemistries of the major aldol adducts **49a** and **53a** were determined by ^1H NMR and NOESY analysis of the bicyclic derivatives **59** and **60** (Scheme 16). Diastereoselective 1,3-*anti*-reduction[15] of **49a** and **53a** with $Me_4NBH(OAc)_3$ gave the corresponding diols **55** and **56**, respectively, in good yields, which, after removal of the TBS protecting group with HF in CH_3CN/CH_2Cl_2, provided triol derivatives **57** (92%) and **58** (72%) (Scheme 16).

Treatment of triols **57** (X = Cl) and **58** (X = F) with trimethylorthoacetate and catalytic amounts of CSA gave the bicyclic derivatives **59** and **60**, respectively, in good yields. Analysis of the ^1H NMR coupling constants for **59**, specifically $J_{Ha\text{-}Hc}$ = 6.5 Hz, $J_{Ha\text{-}Hb}$ = 10.0 Hz, $J_{Hd\text{-}He}$ = 4.0 Hz, $J_{Hd\text{-}Hf}$ = 11.0 Hz, and $J_{Hg\text{-}Hb} = J_{Hg-Hf}$ = 6.5 Hz, proved that Ha and Hd were both axial. This was also supported by the illustrated NOE interaction between Ha and Hd. Analysis of the ^1H NMR coupling constants for **60**, together with the illustrated NOE interaction between Ha and Hd, proved that Ha and Hd were both axial in **60**. These results confirmed the 1,5-*syn*-relationships for aldol adducts **49a** (X = Cl) and **53a** (X = F).

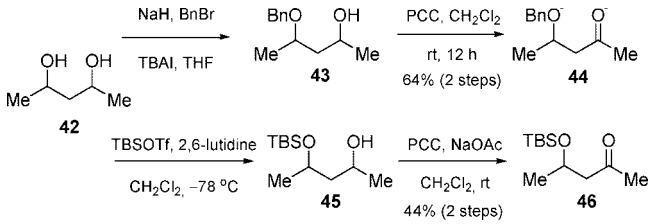
(26) Zhang, F.; Peng, Y.; Liao, S.; Gong, Y. *Tetrahedron* **2007**, *63*, 4636.
(27) Danishefsky, S.; Askin, D.; Angst, C. *J. Org. Chem.* **1987**, *52*, 622.
(28) Paquete, L. A. *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons Ltd.: Chichester, 1995; p 4356.
(29) (a) Debenham, J. S.; Rodebaugh, R.; Frader-Reis, B. *J. Org. Chem.* **1997**, *62*, 4591. (b) Park, M. H.; Takeda, R.; Nakanishi, K. *Tetrahedron Lett.* **1987**, *28*, 3823.

SCHEME 12. Preparation of β-Alkoxy Methylketones 37−41



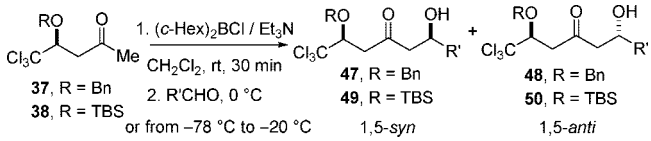
36 **39**

SCHEME 13. Preparation of β-Alkoxy Methylketones 44 and 46



42 **43** **44** **45** **46**

SCHEME 14. Aldol Reactions of β-Alkoxy Methylketones 37 and 38



In order to assign the relative stereochemistry for aldol adducts **47a** (R = Bn) and **51a** (R = Bn) obtained from methylketones **37** and **40** (R = Bn), respectively, we first treated aldol **49a** with HF in CH_3CN/CH_2Cl_2 to give *syn*-diol **61** in 56% yield (Scheme 17). The mixture of *syn*- and *anti*-aldol adducts **47a** and **48a** (R = Bn) was submitted to hydrogenolysis to give diol **61** as the major isomer. This diol was identical in all respects with the 1,5-*syn*-diol **61** prepared from TBS removal of **49a**. This proved that the 1,5-*syn*-isomer is the major product in the aldol reactions with both TBS and Bn protecting groups at the β-oxygen of β-trichloromethyl methylketones **37** and **38**.

Exactly the same strategy was applied for aldol adducts **53a** and **51a**. Removal of the TBS protecting group in **53a** and the benzyl protecting group in **51a** led to the same 1,5-*syn*-diol **62**. Again, this shows that the 1,5-*syn*-isomer is formed after aldol reactions of β-alkoxy β-trifluoromethyl methylketones **40** (R = Bn) and **41** (R = TBS).

The stereochemical outcome of these reactions with both TBS and Bn protecting groups at the β-position seems to be controlled mainly by the resident β-trichloromethyl and β-trifluoromethyl substituents of boron enolates and tends to give the 1,5-*syn*-isomer.

Finally, enolization of methylketones **44** (R = Bn) and **46** (R = TBS) with $(c\text{-Hex})_2BCl$ and Et_3N in CH_2Cl_2 at room temperature, followed by addition of aldehydes **10a**, **10b**, and **10f**, proceeded smoothly, providing the corresponding aldol adducts (Scheme 18, Table 5).

With methylketone **44** (R = Bn), high levels of diastereoselectivity favoring the 1,5-*anti*-aldol **63** were obtained. In the case of methylketone **46** (R = TBS), a 50:50 mixture of 1,5-*anti*-**65** and 1,5-*syn*-**66** aldol products was observed. These results are in accordance with a stereoelectronic effect of the β-alkoxy substituent playing a very important role in these aldol addition reactions.

The relative stereochemistry for aldol adducts **63** was ascertained after conversion of **63f** to bicyclic derivative **69**. Reduction of **63f** with $Me_4NBH(OAc)_3$ gave the corresponding 1,3-*anti*-diol **67** in 89% yield, which after removal of the Bn protecting group with $FeCl_3$ in CH_2Cl_2 provided triol **68** in 60% yield (Scheme 19).[29] Treatment of triol **68** with trimethylorthoacetate and catalytic amounts of CSA in CH_2Cl_2 gave the bicyclic derivative **69** in 63% yield.

Analysis of the ^1H NMR coupling constants for **69**, specifically $J_{Ha\text{-}Hd}$ = 12.0 Hz, $J_{Ha\text{-}Hf}$ = 4.0 Hz, $J_{Hd\text{-}Hb}$ = 5.0 Hz, $J_{Hc\text{-}Hg}$ = 12.0 Hz, and $J_{Hc\text{-}He}$ = 3.2 Hz, $J_{Hb\text{-}Hf}$ = 10.0 Hz, $J_{Hb\text{-}Hg}$ = 3.0 Hz, and $J_{Hb\text{-}He}$ = 1.5 Hz, together with the illustrated NOE interactions proved that Ha, Hc, Hd, and Hg are all axial (Scheme 19). These results confirmed the 1,5-*anti*-relationships for aldol adducts **63**.

Transition State for the 1,5-*anti*- and 1,5-*syn*-Aldol Reactions. Several computational studies indicate that chair-like and boat-like transition states in boron-mediated aldol reactions of methylketones are very close in energy.[30–32] Recently, Paton and Goodman proposed that the aldol reactions of boron enolates generated from β-alkoxy methylketones proceed via boat-like transition states.[30] They proposed also that a stabilizing formyl hydrogen bond favors the 1,5-*anti*-aldol adduct by minimizing steric interactions between the β-alkyloxy substituent and one of the ligands on boron, with the magnitude of this hydrogen bonding being determined by natural bond orbital (NBO) analysis. In our case, due to the lower intrinsic basicity of the oxygen with electron-withdrawing groups at the β-position, this formyl hydrogen bonding is prevented. In addition, the low levels of diastereoselectivity observed with a β-OTBS and a β-O*t*-Bu substituents led to the conclusion that steric effects are playing a very important role.

We believe that the main factor controlling the preference for the 1,5-*syn*-isomer is a combination of steric effects and

(30) Paton, R. S.; Goodman, J. M. *Org. Lett.* **2006**, *8*, 4299.

(31) (a) Paton, R. S.; Goodman, J. M. *J. Org. Chem.* **2008**, *73*, 1253. (b) Stocker, B. L.; Teesdale-Spittle, P.; Hoberg, J. O. *Eur. J. Org. Chem.* **2004**, 330.

(32) Several computational studies indicate that chair-like and boat-like transiton states in methylketone aldol reactions are close in energy: (a) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 1535. (b) Bernardi, F.; Robb, M. A.; Suzzi-Vall, G.; Tagliavini, E.; Trombin, C.; Umani-Ronchi, A. *J. Org. Chem.* **1991**, *56*, 6472.

TABLE 3. Aldol Reactions of 37 (R = Bn) and 38 (R = TBS) with R′CHO

entry	R (ketone)	aldehyde (R′)	temp (°C)	ds[a] (1,5-*syn*:1,5-*anti*)	yield (%)[b]
1	Bn (**37**)	**10a**, *i*-Pr	0	81:19 (**47a**:**48a**)	76
2			−78 to −20	92:08 (**47a**:**48a**)	80
3	TBS (**38**)		0	82:18 (**49a**:**50a**)	92
4			−78 to −20	82:18 (**49a**:**50a**)	91
5	Bn (**37**)	**10b**, Ph	0	78:22 (**47b**:**48b**)	85
6			−78 to −20	87:13 (**47b**:**48b**)	65
7	TBS (**38**)		0	83:17 (**49b**:**50b**)	82
8	Bn (**37**)	**10c**, Et	0	80:20 (**47c**:**48c**)	85
9			−78 to −20	88:12 (**47c**:**48c**)	61
10	TBS (**38**)		0	81:19 (**49c**:**50c**)	60
11			−78 to −20	81:19 (**49c**:**50c**)	70
12	Bn (1)	**10d**, H_2C=C(Me)	0	80:20 (**47d**:**48d**)	87
13			−78 to −20	87:13 (**47d**:**48d**)	72
14	TBS (**38**)		0	80:20 (**49d**:**50d**)	87
15			−78 to −20	82:18 (**49d**:**50d**)	69
16	TBS (**38**)	**10e**, *p*-PhOMe	0	80:20 (**49e**:**50e**)	53
17	Bn (**37**)	**10f**, *p*-PhNO$_2$	−78 to −20	82:18 (**47f**:**48f**)	54
18	TBS (**38**)		−78 to −20	82:18 (**49f**:**50f**)	57
19	Bn (**37**)	**10g**,	−78 to −20	90:10 (**47g**:**48g**)	65

[a] Ratio was determined by ^{1}H NMR analysis of the diastereoisomeric mixture of adducts. [b] Isolated yields of the mixture of *syn*- and *anti*-isomers after SiO_2 flash chromatography.

SCHEME 15. Aldol Reactions of β-Alkoxy Methylketones 40 and 41

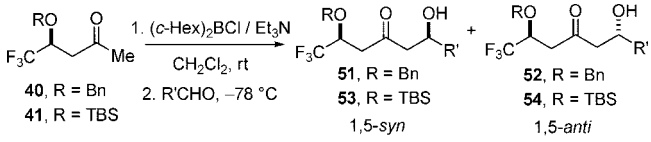


TABLE 4. Aldol Reactions of 40 and 41 with R′CHO

entry	R (ketone)	aldehyde (R′)	ds[a] 1,5-*syn*:1,5-*anti*	yield (%)[b]
1	Bn (**40**)	**10a**, *i*-Pr	66:34 (**51a**:**52a**)	70
2	TBS (**41**)		80:20 (**53a**:**54a**)	73
3	Bn (**40**)	**10b**, Ph	66:34 (**51b**:**52b**)	68
4	TBS (**41**)		90:10 (**53b**:**54b**)	75
5	Bn (**40**)	**10c**, Et	63:37 (**51c**:**52c**)	72
6	TBS (**41**)		80:20 (**53c**:**54c**)	64
7	Bn (**40**)	**10d**, H_2C=C(Me)	62:38 (**51d**:**52d**)	78
8	TBS (**41**)		77:23 (**53d**:**54d**)	61
9	Bn (**40**)	**10e**, *p*-PhOMe	65:35 (**51e**:**52e**)	58

[a] Ratio was determined by ^{1}H NMR analysis of the diastereoisomeric mixture of adducts. [b] Isolated yields of the mixture of *syn*- and *anti*-isomers after SiO_2 flash chromatography.

minimization of dipole moments in the corresponding boat-like transition states **A** and **B** (Scheme 20). Transition state **B** is favored for bulky substituents at the β-alkoxy oxygen, as well, because it keeps the β-CCl_3 and β-CF_3 groups *anti* to the C−O bond of the enolate and *anti* to the aldehyde C=O bond. In transition state **B**, the aldehyde approaches from the side opposite to the OR group (R = TBS, ^{t}Bu), leading to the 1,5-*syn*-isomer. Approach of the aldehyde from the same side of the OR group (R = TBS, ^{t}Bu) as in transition state **A** should be disfavored. Theoretical studies are underway in order to clarify these issues.

Conclusions

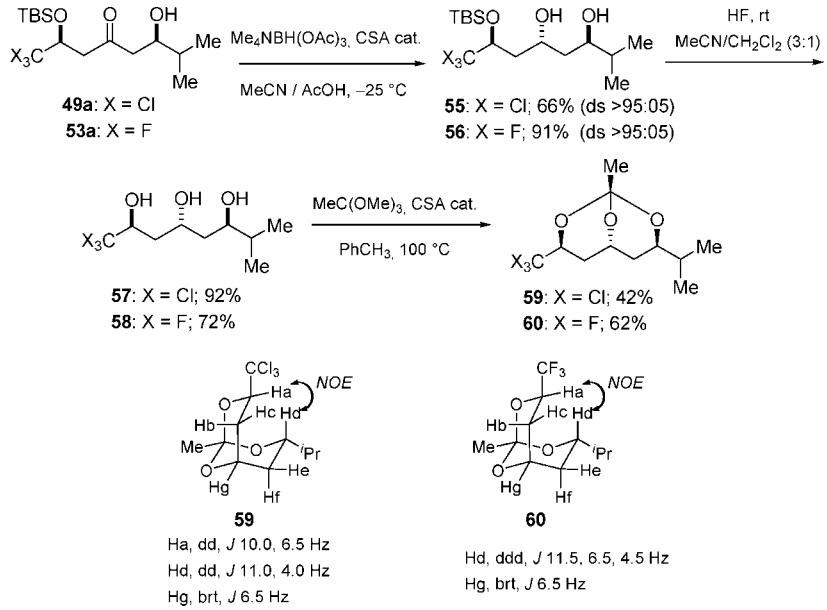
The use of boron enolates generated from β-aryl-β-alkoxy methylketones in aldol reactions with achiral aldehydes gives the corresponding 1,5-*anti*-products with high levels of diastereoselectivity when the β-alkoxy substituent is a β-OPMB group. In the case of β-OTBS and β-O*t*-Bu susbtituents, the 1,5-*syn*-isomer is obtained with low levels of diastereoselectivity. These results show that steric effects play a very important role in these aldol reactions. The nature of the substituent at the aromatic ring does not influence the stereochemical outcome as *p*-OMe and *p*-NO_2 lead to similar results.

Notably, we have observed that good levels of substrate-based 1,5-*syn*-stereocontrol could be achieved in the boron-mediated aldol reactions of β-trichloromethyl and β-trifluoromethyl methylketones with achiral aldehydes. Independent of the nature of the β-protecting group (TBS or Bn), the 1,5-*syn*-diastereoisomer was always isolated as the major product. This result is opposite to the 1,5-*anti*-stereoinduction observed for boron aldol reactions of simple β-alkoxy methylketones, indicating the overriding contribution in this special case from the substituent at the β-position, which is a very strong electron-withdrawing group. To the best of our knowledge, this is the first report of boron-mediated aldol reactions of methylketones leading to the 1,5-*syn*-isomer with useful levels of diastereoselection, even with a β-OBn substituent.[5] These stereoselective aldol reactions should prove valuable in polyketide syntheses, and we believe they will allow synthetic chemists to confidently pursue more aggressive convergent approaches toward assembling complex polyacetate arrays in the synthesis of natural products.

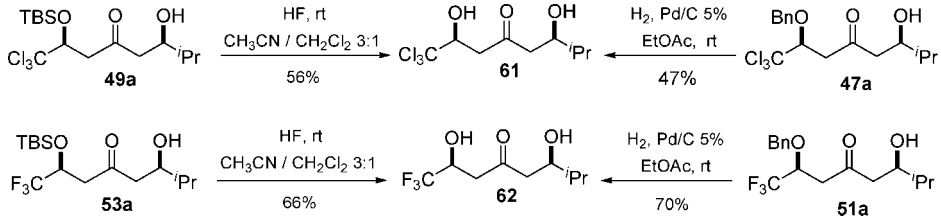
Experimental Section

Preparation of (4*RS*)-4-(4-Methoxybenzyloxy)-4-(4-nitrophenyl)butan-2-one (5): To a solution of **4** (1.00 g, 4.78 mmol) and 2,2,2-trichloroacetonitrile (2.02 g, 7.15 mmol) in Et_2O (30 mL), under argon atmosphere at 0 °C, was carefully added dropwise a solution of 0.14 M triflic acid in Et_2O (0.5 mL, 0.0683 mmol) and warmed to room temperature. After 10 h, the reaction was quenched with an aqueous solution 10% $NaHCO_3$, and the aqueous phase was extracted with Et_2O. The organic phase was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the resulting oil was purified by flash chromatography (silica gel 200−400 mesh, 40% EtOAc in hexane), giving methyl ketone **5** in 64% yield (1.01 g, 3.07 mmol): R_f 0.54 (40% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.63 (dd, *J* = 4.6, 16.5 Hz, 1H), 3.05 (dd, 1H, *J* = 8.5, 16.5 Hz, 1H), 3.80 (s, 3H), 4.27 (d, *J* = 11.0 Hz, 1H), 4.34 (d, *J* = 11.0 Hz, 1H), 4.99 (dd, *J* = 4.6, 8.5 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 2H), 8.23 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$)

SCHEME 16. Proof of Stereochemistry for Aldols 49a and 53a



SCHEME 17. Proof of Stereochemistry for Aldols 47a and 51a



SCHEME 18. Aldol Reactions of *β*-Alkoxy Methylketones 44 and 46

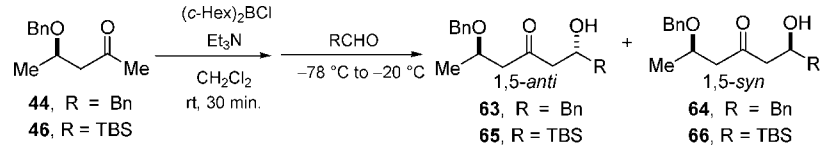


TABLE 5. Aldol Reactions of 44 and 46 with R′CHO

entry	R (ketone)	aldehyde (R′)	ds[a] (1,5-*anti*:1,5-*syn*)	Yield (%)[b]
1	Bn (**44**)	**10a**, *i*-Pr	>95:05 (**63a**:**64a**)	78
2[c]	Bn (**44**)		75:25 (**63a**:**64a**)	66
3[c,d]	TBS (**46**)		50:50 (**65a**:**66a**)	73
4	Bn (**44**)	**10b**, Ph	94:06 (**63b**:**64b**)	64
5	Bn (**44**)	**10f**, *p*-PhNO$_2$	>95:05 (**63f**:**64f**)	67

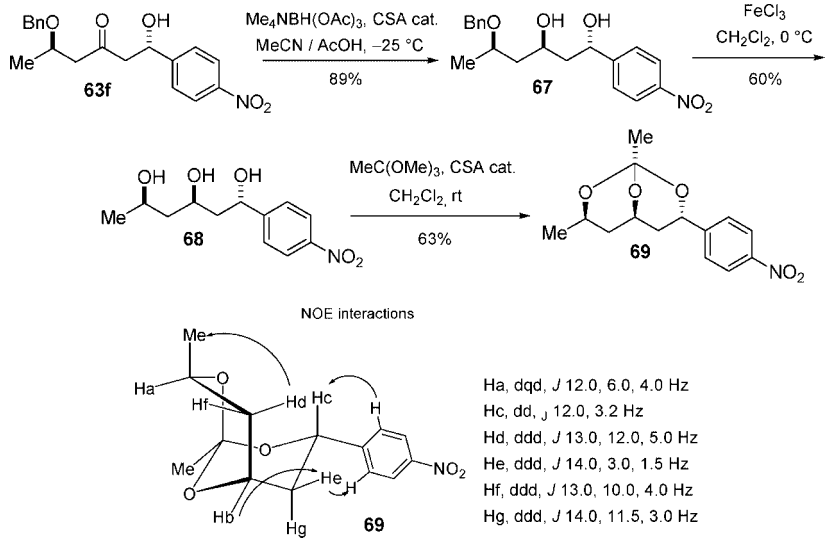
[a] Ratio was determined by ^{1}H NMR analysis of the diastereoisomeric mixture of adducts. [b] Isolated yields of the mixture of *syn*- and *anti*-isomers after SiO$_2$ flash chromatography. [c] Aldehyde addition was performed at 0 °C. [d] Aldehyde addition at −78 °C led to the same result.

δ 31.0, 51.6, 55.3, 71.2, 76.2, 113.8, 123.9, 127.4, 129.3, 129.5, 147.5, 149.0, 159.3, 205.2; IR ν_{max} (film) 3485, 3392, 3055, 2958, 2842, 1720, 1612, 1515, 1418, 1348, 1265, 1175, 1093, 1034, 856, 73; HRMS (ESI TOF-MS) calcd for $C_{18}H_{19}NO_5Na$ 352.1161; found 352.1196.

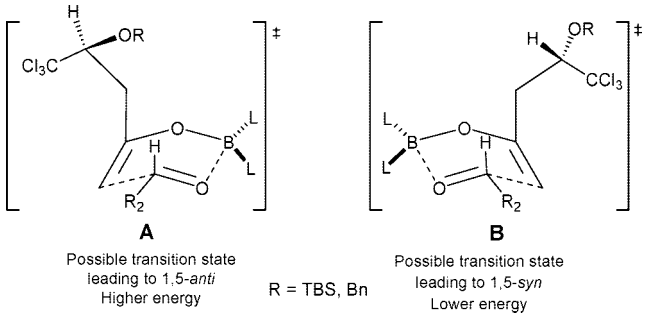
Preparation of (4*RS*)-4-(*tert*-Butyldimethylsilyloxy)-4-(4-nitrophenyl)butan-2-one (6): To a solution of **4** (1.00 g, 4.78 mmol) in DMF (15.4 mL), under argon atmosphere at room temperature, was added 3.85 mL of pyridine (47.8 mmol) followed by $AgNO_3$ (3.25 g, 19.1 mmol), waiting for the complete dissolution. Then, TBSCl (2.88 g, 19.1 mmol) was added, leading to the precipitation of a white solid (AgCl). The resulting mixture was stirred for 18 h. The solution was filtered and the precipitated was washed with Et_2O. The solution was diluted with water, and the aqueous phase was extracted with Et_2O. The organic phase was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the resulting oil was purified by flash chromatography (silica gel 200−400 mesh, 30% EtOAc in hexanes), providing methylketone **6** in 92% yield (1.43 g, 4,42 mmol): R_f 0.56 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.14 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 2.16 (s, 3H), 2.58 (dd, J = 4.4, 15.8 Hz, 1H), 2.95 (dd, J = 8.1, 15.8 Hz, 1H), 5.28 (dd, J = 4.4, 8.1 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 8.19 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, −4.7, 18.1, 25.7, 31.8, 53.9, 70.7, 123.6, 126.5, 147.2, 151.9, 205.9; IR ν_{max} (film) 3060, 2931, 1718, 1608, 1523, 1348, 1263, 1089, 838; HRMS (ESI TOF-MS) calcd for $C_{16}H_{26}NO_4Si$ 324.1631; found 324.1627.

(4*RS*)-4-(4-Methoxybenzyloxy)-4-(4-methoxyphenyl)butan-2-one (8): To a solution of **7** (1.60 g, 8.24 mmol) and 4-methoxybenzyl 2,2,2-trichloroacetimidate (4.66 g, 16.5 mmol) in CH_2Cl_2 (25 mL), under argon atmosphere at 25 °C, was added CSA (catalytic). After 7 h, the reaction was quenched by the addition of 10% aqueous $NaHCO_3$, and the aqueous phase was extracted with Et_2O. The organic phase was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the resulting oil was purified by flash chromatography (silica gel 200−400 mesh, 40% EtOAc in hexane), giving methylketone **8** in 57% yield (1.48 g, 4.70 mmol): R_f 0.55 (40% EtOAc in hexane); ^{1}H NMR (250 MHz, C_6D_6) δ

SCHEME 19. Proof of Stereochemistry for Aldol 63f



SCHEME 20. Possible Transition States



1.72 (s, 3H), 2.31 (dd, J = 4.6, 15.6 Hz, 1H), 2.83 (dd, 1H, J = 8.7, 15.6 Hz, 1H), 3.29 (s, 3H), 3.33 (s, 3H), 4.21 (d, J = 11.1 Hz, 1H), 4.37 (d, J = 11.1 Hz, 1H), 4.90 (dd, J = 4.6, 8.7 Hz, 1H), 6.85−6.75 (m, 4H), 7.26−7.14 (m, 4H); ^{13}C NMR (63 MHz, C_6D_6) δ 30.6, 52.1, 54.8, 70.4, 77.3, 114.0, 114.3, 128.3, 129.6, 131.0, 134.0, 159.7, 159.9, 204.5; IR ν_{max} (film) 3001, 2957, 2935, 2908, 2837, 1715, 1612, 1585, 1514, 1463, 1357, 1302, 1248, 1173, 1070, 1034, 835; HRMS (ESI TOF-MS) calcd for $C_{19}H_{22}O_4Na$ 337.1416; found 337.1228.

(4*RS*)-4-(*tert*-Butyldimethylsilyloxy)-4-(4-methoxyphenyl)butan-2-one (9): To a solution of **7** (1.16 g, 5.97 mmol) in CH_2Cl_2 (15 mL), under argon atmosphere at 25 °C, was added TBSCl (1.08 g, 7.16 mmol) followed by imidazole (0.569 g, 8.36 mmol), waiting for the complete dissolution. The resulting mixture was stirred for 24 h. The solution was diluted with water, and the aqueous phase was extracted with Et_2O. The organic phase was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the resulting oil was purified by flash chromatography (silica gel 200−400 mesh, 20% EtOAc in hexanes), providing methylketone **9** in 92% yield (1.69 g, 5.49 mmol): R_f 0.58 (20% EtOAc in hexane); ^{1}H NMR (250 MHz, C_6D_6) δ −0.06 (s, 3H), 0.14 (s, 3H), 0.96 (s, 9H), 1.72 (s, 3H), 2.24 (dd, J = 4.1, 15.4 Hz, 1H), 2.73 (dd, J = 8.7, 15.4 Hz, 1H), 3.29 (s, 3H), 5.24 (dd, J = 4.1, 8.7 Hz, 1H), 6.80 (d, J = 8.7 Hz, 2H), 7.19 (d, J = 8.7 Hz, 2H); ^{13}C NMR (63 MHz, C_6D_6) δ −4.93, −4.48, 18.4, 26.0, 31.2, 54.3, 54.7, 71.8, 114.0, 127.3, 128.3, 137.1, 159.5, 204.9; IR ν_{max} (film) 3001, 2957, 2932, 2897, 2856, 1719, 1612, 1514, 1472, 1362, 1304, 1250, 1173, 1084, 1038, 1005, 868, 837, 779; HRMS (ESI TOF-MS) calcd for $C_{17}H_{28}O_3SiNa$ 331.1705; found 331.1543.

Representative Procedure for Methylketone Aldol Reactions. To a solution of the corresponding methylketone (0.296 mmol) in CH_2Cl_2 (3.7 mL), under argon atmosphere at −10 °C, was added dropwise (c-Hex)$_2$BCl (2.0 equiv, 0.592 mmol). After this, Et_3N (2.5 equiv, 0.740 mmol) was added dropwise. The resulting mixture was stirred for 30 min at 0 °C. The aldehyde (4.0 equiv, 1.18 mmol) was added dropwise to the enolate solution at −78 °C, and the resulting mixture was stirred for 3 h at −78 °C. The reaction was quenched by addition of 3.0 mL of MeOH and warmed to room temperature. The solvent was removed under reduced pressure, and the resulting oil was purified by flash chromatography (silica gel 200−400 mesh), providing the aldol adducts.

(1*SR*,5*SR*)-1-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-6-methyl-1-(4-nitrophenyl)heptan-3-one (13a): R_f 0.50 (hexane:EtOAc: CH_2Cl_2, 40:10:50); ^{1}H NMR (250 MHz, C_6D_6) δ −0.19 (s, 3H), 0.07 (s, 6H), 0.83 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 1.42−1.62 (m, 1H), 1.99 (dd, J = 3.5, 16.0 Hz, 1H), 2.17−2.25 (m, 2H), 2.51 (dd, J = 9.0, 16.0 Hz, 1H), 2.61 (d, J = 3.3 Hz, 1H), 3.75−3.87 (m, 1H), 5.11 (dd, J = 3.5, 9.0 Hz, 1H), 6.93 (d, J = 8.9 Hz, 2H), 7.85 (d, J = 8.9 Hz, 2H); ^{13}C NMR (62.5 MHz, C_6D_6) δ −5.1, −4.7, 17.7, 18.2, 18.5, 25.9, 33.4, 48.3, 53.7, 70.8, 71.9, 123.7, 126.4, 147.6, 151.5, 208.4; IR ν_{max} (film) 3446, 3082, 2956, 1714, 1608, 1523, 1348, 1261, 1081, 838, 700; HRMS (ESI TOF-MS) calcd for $C_{20}H_{34}NO_5Si$ 396.2206; found 396.2310.

(1*SR*,5*RS*)-1-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-6-methyl-1-(4-nitrophenyl)heptan-3-one (14a): R_f 0.63 (hexane:EtOAc: CH_2Cl_2, 40:10:50); ^{1}H NMR (250 MHz, C_6D_6) δ −0.19 (s, 3H), 0.07 (s, 6H), 0.83 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H), 0.91 (s, 9H), 1.40−1.60 (m, 1H), 2.02 (dd, J = 3.6, 16.0 Hz, 1H), 2.06 (dd, J = 2.5, 17.1 Hz, 1H), 2.28 (dd, J = 9.6, 17.1 Hz, 1H), 2.54 (dd, J = 8.8, 16.0 Hz, 1H), 2.72 (d, J = 3.5 Hz, 1H), 3.66−3.77 (m, 1H), 5.12 (dd, J = 3.6, 8.8 Hz, 1H), 6.96 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.9 Hz, 2H); ^{13}C NMR (62.5 MHz, C_6D_6) δ −5.1, −4.7, 17.6, 18.2, 18.6, 25.9, 33.4, 48.4, 53.5, 70.8, 72.1, 123.7, 126.5, 147.6, 151.6, 208.6; IR ν_{max} (film) 3465, 3077, 2958, 2858, 1708, 1608, 1523, 1348, 1253, 1081, 838; HRMS (ESI TOF-MS) calcd for $C_{20}H_{34}NO_5Si$ 396.2206; found 396.2310.

(1*SR*,3*SR*,5*SR*)-1-(4-Methoxybenzyloxy)-6-methyl-1-(4-nitrophenyl)heptan-3,5-diol (15): Acetic acid (1 mL) was added to a stirring suspension of $Me_4NHB(OAc)_3$ (0.758 g, 2.88 mmol) in acetonitrile (1 mL) at room temperature. The resulting mixture was stirred for 30 min and after was cooled to −40 °C. The aldol adduct **11a** (0.145 g, 0.360 mmol) in acetonitrile (1 mL) was added dropwise. After 1 min, a solution of CSA (0.041 g, 0.18 mmol), acetic acid (1 mL), and acetonitrile (1 mL) was added and the mixture was stirred for 18 h at −22 °C. The reaction was quenched by addition of a sodium bicarbonate aqueous solution (25 mL) followed by addition of potassium tartarate aqueous solution (25

mL) and Et_2O (50 mL), stirring vigorously at room temperature for 8 h. The organic phase was separated, and the aqueous phase was extracted four times with Et_2O. The organic phase was combinated and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the resulting oil was purified by flash column chromatography (silica gel 200−400 mesh, hexane:EtOAc:CH_2Cl_2, 20:5:75) giving **15** (54%, 0.0787 g, 0.195 mmol) as a yellow oil in >95:5 diastereoseletivity: R_f 0.41 (hexane:EtOAc:CH_2Cl_2, 5:20:75); ^{1}H NMR (300 MHz, C_6D_6) δ 0.87 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H), 1.33−1.46 (m, 2H), 1.50−1.66 (m, 2H), 1.97 (dt, J = 9.6, 14.4 Hz, 1H), 2.69 (brs, 1H), 3.31 (s, 3H), 3.65−3.75 (m, 1H), 3.81 (brs, 1H), 3.90 (d, J = 11.2 Hz, 1H), 4.01−4.11 (m, 1H), 4.13 (d, J = 11.2 Hz, 1H), 4.40 (dd, J = 4.2, 9.6 Hz, 1H), 6.80 (d, J = 8.5 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.8 Hz, 2H).

(*SR*)-1-((2*SR*,4*SR*,6*SR*)-2-(4-Methoxyphenyl)-6-(4-nitrophenyl)-1,3-dioxan-4-yl)-3-methylbutan-2-ol (16): Diol **15** (0.0580 g, 0.144 mmol) was dissolved in CH_2Cl_2 (2 mL), under argon atmosphere, followed by addition of powdered dry 4 Å molecular sieves (0.060 g). The solution was cooled to −10 °C, DDQ (0.0390 g, 0.173 mmol) was added, and the solution was stirred for 1.5 h at 0 °C. The resulting mixture was diluted with Et_2O and poured onto a pad of silica gel (200−400 mesh). The pad was washed repeatedly with CH_2Cl_2. The solvent was removed under reduced pressure, and the resulting oil was purified by flash chromatography (silica gel 200−400 mesh, hexane:EtOAc:CH_2Cl_2, 20:5:75), giving acetal **16** (83%, 0.0480 g, 0.120 mmol) as yellow oil: R_f 0.44 (hexane:EtOAc:CH_2Cl_2, 15:10:75); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H), 1.25 (dt, J = 2.6, 13.0 Hz, 1H), 1.34−1.66 (m, 5H), 3.28 (s, 3H), 3.70 (ddd, J = 2.0, 5.1, 9.9 Hz, 1H), 4.03 (ddt, J = 2.7, 8.4, 11.2 Hz, 1H), 4.40 (dd, J = 2.5, 11.2 Hz, 1H), 5.54 (s, 1H), 6.87 (d, J = 8.7 Hz, 2H), 7.04 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 18.7, 34.4, 39.1, 40.1, 54.8, 72.1, 74.4, 77.5, 101.4, 113.9, 123.6, 126.3, 127.7, 127.9, 131.6, 148.8, 160.7; IR ν_{max} (film) 3487, 3082, 2958, 1614, 1517, 1348, 1249, 1110, 1010, 831, 698; HRMS (ESI TOF-MS) calcd for $C_{22}H_{28}NO_6$ 402.1917; found 402.1845.

(4*SR*,6*SR*)-4-((*SR*)-2-(4-Methoxybenzyloxy)-2-(4-nitrophenyl-)ethyl)-6-isopropyl-2,2-dimethyl-1,3-dioxane (17): The diol **15** (0.0207 g, 0.0513 mmol) was dissolved in 2,2-dimethoxypropane (1 mL), followed by addition of CSA dissolved in 2,2-dimethoxypropane (1 mL) at room temperature and under argon atmosphere and was stirred for 18 h. The resulting mixture was diluted with Et_2O. The solvent was removed under reduced pressure, and the resulting oil was purified by flash chromatography (silica gel 200−400 mesh, hexane:EtOAc:CH_2Cl_2, 20:5:75) giving **17** (77%, 0.0175 g, 0.0395 mmol) as a colorless oil: R_f 0.80 (Hexane:EtOAc:CH_2Cl_2, 20:5:75); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (d, J = 6.6 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 1.23 (s, 3H), 1.31 (s, 3H), 1.40−1.57 (m, 3H), 1.74 (ddd, J = 4.8, 8.0, 12.8 Hz, 1H), 2.20 (ddd, J = 6.4, 8.7, 13.9 Hz, 1H), 3.37 (dt, J = 7.2, 14.4 Hz, 1H), 3.45−3.56 (m, 1H), 3.79 (s, 3H), 4.19 (d, J = 11.1 Hz, 1H), 4.30 (d, J = 11.1 Hz, 1H), 4.57 (d, J = 6.5, 7.8 Hz, 1H), 6.85 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 8.23 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 18.7, 24.3, 25.0, 32.9, 36.2, 44.0, 55.3, 63.3, 70.6, 71.4, 77.1, 100.2, 113.8, 123.7, 128.0, 129.5, 129.7, 147.6, 149.7, 159.3; IR ν_{max} (film) 3054, 2987, 1610, 1523, 1348, 1265, 1033, 740; HRMS (ESI TOF-MS) calcd for $C_{25}H_{33}NO_6Na$ 466.2206; found 466.2124.

(1*SR*,5*SR*)-1,5-Dihydroxy-6-methyl-1-(4-nitrophenyl)heptan-3-one (18): Method 1: To a stirred solution of PMB ether **11a** (36.1 mg, 0.0899 mmol) in CH_2Cl_2 (1 mL) and H_2O (0.10 mL) at 0 °C was added DDQ (20.1 mg, 0.0910 mmol). After 2.5 h at 0 °C, the solution was warmed to room temperature and stirred for an additional 30 min. The reaction mixture was partitioned with saturated aqueous $NaHCO_3$ (4 mL) and extracted with CH_2Cl_2 (3 × 8 mL). The combined organic extracts were dried over $MgSO_4$. Flash chromatography (silica gel 200−400 mesh, 50% EtOAc in hexane) gave **18** as a yellow oil (36%, 9.2 mg, 3.3 mmol): R_f 0.23 (hexane:EtOAc:CH_2Cl_2, 5:20:75); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.77 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H), 1.32−1.52 (m, 1H), 1.95 (dd, J = 2.5, 16.4 Hz, 1H), 2.07 (dd, J = 3.0, 17.2 Hz, 1H), 2.16 (dd, J = 8.1, 16.4 Hz, 1H), 2.26 (dd, J = 9.5, 17.2 Hz, 1H), 2.45 (d, J = 2.5 Hz, 1H), 3.24 (d, J = 3.0 Hz, 1H), 3.62−3.73 (m, 1H), 4.82−4.92 (m, 1H), 6.97 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 18.4, 33.6, 47.2, 51.7, 68.8, 72.2, 123.6, 126.3, 147.6, 150.3, 210.5; IR ν_{max} (film) 3425, 2962, 1704, 1606, 1519, 1348, 1064, 856, 750, 702; HRMS (ESI TOF-MS) calcd for $C_{14}H_{19}NO_5Na$ 304.1161; found 304.1218.

Method 2: 13a (24.1 mg, 0.0609 mmol) was dissolved in 1.5 mL of 4:1 CH_3CN:CH_2Cl_2 at room temperature, and four drops of 48% aqueous HF were added. After 20 h, 5 mL of saturated aqueous $NaHCO_3$ was added to quench and the mixture was extracted with four 10 mL portions of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (silica gel 200−400 mesh, 50% EtOAc in hexane) gave **15** as a yellow oil (95%, 16.3 mg, 0.0579 mmol).

(1*SR*,5*SR*)-1,5-Dihydroxy-6-methyl-1-(4-nitrophenyl)heptan-3-one (18) and (1*SR*,5*RS*)-1,5-Dihydroxy-6-methyl-1-(4-nitrophenyl)heptan-3-one (19): A solution of a mixture of **30a** and **31a** (0.0200 g, 0.0590 mmol) in anhydrous CH_2Cl_2 (0.5 mL) at 0 °C was treated with 1.5 equiv of $TiCl_4$ (0.01 mL, 0.09 mmol). After 2 min, 1 mL of saturated aqueous solution of NH_4Cl and 5 mL of Et_2O were added. The aqueous phase was extracted, and the organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (silica gel 200−400 mesh, hexane:EtOAc:CH_2Cl_2, 20:5:75) gave **18** (minor isomer) and **19** (major isomer) as colorless oils (63%, 0.0104 g, 0.0370 mmol): R_f 0.17 (hexane:EtOAc:CH_2Cl_2, 20:5:75).

(1*SR*,5*RS*)-1,5-Dihydroxy-6-methyl-1-(4-nitrophenyl)heptan-3-one (19): 14a (30.1 mg, 0.0761 mmol) was dissolved in 1.5 mL of 4:1 CH_3CN:CH_2Cl_2 at room temperature, and four drops of 48% aqueous HF were added. After 20 h, 5 mL of saturated aqueous $NaHCO_3$ was added to quench and the mixture was extracted with four 10 mL portions of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (silica gel 200−400 mesh, 50% EtOAc in hexane) gave **19** as a yellow oil (93%, 19.9 mg, 0.0708 mmol): R_f 0.15 (hexane:EtOAc:CH_2Cl_2, 5:20:75); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H), 1.35−1.54 (m, 1H), 1.96 (dd, J = 2.5, 16.5 Hz, 1H), 2.07 (dd, J = 2.9, 17.2 Hz, 1H), 2.20 (dd, J = 9.9, 16.5 Hz, 1H), 2.33 (dd, J = 9.6, 17.2 Hz, 1H), 2.59 (s, 1H), 3.38 (s, 1H), 3.68 (ddd, J = 2.5, 5.4, 9.7 Hz, 1H), 4.89 (dd, J = 2.5, 9.5 Hz, 1H), 6.99 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 18.4, 33.6, 47.4, 51.9, 69.0, 72.5, 123.6, 126.3, 147.6, 150.3, 210.7; IR ν_{max} (film) 3384, 3072, 2962, 1716, 1598, 1517, 1342, 1056, 854, 748; HRMS (ESI TOF-MS) calcd for $C_{14}H_{19}NO_5Na$ 304.1161; found 304.1218.

(1*SR*,3*SR*,5*SR*)-1-(4-Methoxybenzyloxy)-6-methyl-1-(4-methoxyphenyl)heptan-3,5-diol (24): Acetic acid (1 mL) was added to a stirring suspension of $Me_4NHB(OAc)_3$ (0.577 g, 2.19 mmol) in acetonitrile (1 mL) at room temperature. The resulting mixture was stirred for 30 min and was cooled to −40 °C. The aldol adduct **20a** (0.106 g, 0.274 mmol) in acetonitrile (1 mL) was added dropwise. After 1 min, a solution of CSA (0.031 g, 0.14 mmol), acetic acid (1 mL), and acetonitrile (1 mL) was added and the mixture was stirred for 18 h at −22 °C. The reaction was quenched by addition of a saturated aqueous solution of sodium bicarbonate (25 mL) followed by addition of a potassium tartarate aqueous solution (25 mL) and Et_2O (50 mL), stirring vigorously at room temperature for 8 h. The organic phase was separated, and the aqueous phase was extracted four times with Et_2O. The organic phase was combined and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the resulting oil was purified

by flash column chromatography (silica gel 200−400 mesh, hexane:EtOAc:CH_2Cl_2, 20:5:5) giving **24** (52%, 0.0556 g, 0.143 mmol) as a yellow oil in >95:5 diastereoseletivity: R_f 0.45 (hexane:EtOAc:CH_2Cl_2, 5:20:75); ^{1}H NMR (250 MHz, C_6D_6) δ 0.90 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H), 1.73−1.38 (m, 4H), 2.21 (dt, J = 10.0, 14.6 Hz, 1H), 3.11 (brs, 1H), 3.29 (s, 3H), 3.35 (s, 3H), 3.83−3.74 (m, 1H), 4.06 (d, J = 11.3 Hz, 1H), 4.30−4.15 (m, 2H), 4.32 (d, J = 11.3 Hz, 1H), 4.44 (dd, J = 3.2, 10.0 Hz, 1H), 6.77 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 7.19−7.10 (m, 4H); ^{13}C NMR (63 MHz, C_6D_6) δ 18.1, 18.9, 34.4, 40.4, 45.5, 54.75, 54.84, 70.0, 70.2, 73.3, 81.9, 114.3, 114.4, 128.3, 129.8, 130.2, 134.0, 159.9, 160.0; IR ν_{max} (film) 3449, 2955, 2872, 2837, 1614, 1585, 1514, 1464, 1302, 1248, 1173, 1072, 1034, 833, 737; HRMS (ESI TOF-MS) calcd for $C_{23}H_{32}O_5Na$ 411.2148; found 411.2113.

(*SR*)-1-((2*SR*,4*SR*,6*SR*)-2-(4-Methoxyphenyl)-6-(4-methoxyphenyl)-1,3-dioxan-4-yl)-3-methylbutan-2-ol (25): Diol **24** (0.0427 g, 0.109 mmol) was dissolved in CH_2Cl_2 (1.5 mL), under argon atmosphere, followed by addition of powdered dry 4 Å molecular sieves (0.046 g). The solution was cooled to −10 °C, DDQ (0.0290 g, 0.130 mmol) was added, and the solution was stirred for 1.5 h at 0 °C. The resulting mixture was diluted with Et_2O and poured onto a pad of silica gel (200−400 mesh). The pad was washed repeatedly with CH_2Cl_2. The solvent was removed under reduced pressure, and the resulting oil was purified by flash chromatography (silica gel 200−400 mesh, hexane:EtOAc:CH_2Cl_2, 20:5:75) giving acetal **25** (25%, 0.0106 g, 0.0274 mmol) as yellow oil: R_f 0.32 (Hexane:EtOAc:CH_2Cl_2, 15:10:75); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H), 1.43 (dt, J = 2.2, 13.1 Hz, 1H), 1.58−1.48 (m, 2H), 1.62 (ddd, J = 2.2, 8.2, 14.5 Hz, 1H), 1.82−1.73 (m, 2H) 3.26 (s, 3H), 3.33 (s, 3H), 3.77−3.72 (m, 1H), 4.07 (ddt, J = 2.7, 8.4, 11.1 Hz, 1H), 4.62 (dd, J = 2.5, 11.3 Hz, 1H), 5.64 (s, 1H), 6.83 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 7.67 (d, J = 8.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.6, 18.8, 34.4, 39.5, 40.1, 54.7, 54.8, 72.2, 74.7, 78.6, 101.5, 113.8, 114.0, 127.5, 128.3, 132.2, 159.7, 160.4; IR ν_{max} (film) 3530, 2959, 2874, 2837, 1614, 1516, 1466, 1302, 1250, 1173, 1101, 1034, 829; HRMS (ESI TOF-MS) calcd for $C_{23}H_{30}O_5Na$ 409.1991; found 409.1892.

(1*SR*,5*SR*)-1,5-Dihydroxy-6-methyl-1-(4-methoxyphenyl)heptan-3-one (26): Method 1: To a stirred solution of PMB ether **20a** (0.128 g, 0.331 mmol) in CH_2Cl_2 (3.7 mL) and H_2O (0.5 mL) at 0 °C was added DDQ (0.0788 mg, 0.347 mmol). After 2.5 h at 0 °C, the solution was warmed to room temperature. The reaction mixture was partitioned with saturated aqueous $NaHCO_3$ (4 mL) and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$. Flash chromatography (silica gel 200−400 mesh, 50% EtOAc in hexane) gave **26** as a yellow oil (38%, 0.0335 g, 0.126 mmol).

Method 2: A solution of **22a** (0.0286 g, 0.165 mmol) in anhydrous THF (4.0 mL) at room temperature was treated with a solution of TBAF/AcOH (1:1, 1 M in THF, 0.75 mL, 0.752 mmol). After 7 days, 20 mL of saturated aqueous solution of $NaHCO_3$, 20 mL of saturated aqueous solution of potassium/sodium tartarate, and 100 mL of Et_2O were added. This solution was strongly stirred for 8 h. The organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (silica gel 200−400 mesh, 50% EtOAc in hexane) gave **26** as a yellow oil (65%, 0.0492 g, 0.0492 mmol): R_f 0.28 (hexane:EtOAc:CH_2Cl_2, 5:20:75); ^{1}H NMR (250 MHz, C_6D_6) δ 0.80 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H), 1.48 (octet, J = 6.7 Hz, 1H), 2.05 (ddd, J = 1.3, 2.7, 16.7 Hz, 1H), 2.21 (ddd, J = 1.6, 9.8, 16.7 Hz, 1H), 2.32 (ddd, J = 1.3, 3.0, 16.7 Hz, 1H), 2.60 (ddd, J = 1.9, 9.5, 16.7 Hz, 1H), 3.41−2.81 (brs, 2H), 3.33 (s, 3H), 3.74 (dddd, J = 1.2, 2.5, 5.4, 8.1 Hz, 1H), 5.09 (dd, J = 2.7, 9.5 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H); ^{13}C NMR (63 MHz, C_6D_6) δ 17.7, 18.6, 33.5, 47.5, 52.5, 54.8, 69.8, 72.1, 114.1, 127.2, 136.0, 159.6, 211.4; IR ν_{max} (film) 3329, 2961, 2916, 2849, 1705, 1612, 1514, 1464, 1385, 1302, 1248, 1177, 1034, 833.

(1*SR*,5*RS*)-1,5-Dihydroxy-6-methyl-1-(4-methoxyphenyl)heptan-3-one (27): A solution of **23a** (0.0626 g, 0.165 mmol) in anydrous THF (8.5 mL) at room temperature was treated with a solution of TBAF/AcOH (1:1, 1 M in THF, 1.65 mL, 1.65 mmol). After 7 days, 20 mL of saturated aqueous solution of $NaHCO_3$, 20 mL of saturated aqueous solution of potassium/sodium tartarate, and 100 mL of Et_2O were added. This solution was vigorously stirred for 8 h. The organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography (silica gel 200−400 mesh, 50% EtOAc in hexane) gave **27** as a yellow oil (45%, 0.0198 g, 0.0743 mmol): R_f 0.22 (hexane:EtOAc:CH_2Cl_2, 5:20:75); ^{1}H NMR (250 MHz, C_6D_6) δ 0.82 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H), 1.61−1.43 (m, 1H), 2.10−1.98 (m, 1H), 2.42−2.27 (m, 2H), 2.81−2.66 (m, 1H), 3.33 (s, 3H), 4.12−3.09 (br, 2H), 3.84−3.73 (m, 1H), 5.19−5.10 (m, 1H), 6.83 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H); ^{13}C NMR (63 MHz, C_6D_6) δ 17.7, 18.6, 33.6, 47.7, 52.9, 54.8, 69.9, 72.4, 114.1, 127.3, 136.2, 159.6, 211.5; IR ν_{max} (film) 3414, 2961, 2916, 1707, 1612, 1514, 1466, 1387, 1304, 1248, 1177, 1034, 833; HRMS (ESI TOF-MS) calcd for $C_{15}H_{22}O_4Na$ 289.1416; found 289.1276.

(4*RS*)-4-*tert*-Butoxy-4-(4-nitrophenyl)butan-2-one (28): To a solution of **4** (3.30 g, 15.8 mmol) and 4-*tert*-butoxy-2,2,2-trichloroacetimidate (6.90 g, 31.6 mmol) in CH_2Cl_2 (35 mL), under argon atmosphere at 25 °C, was added CSA (catalytic). After 15 h, the reaction was quenched with 10% NH_4Cl aqueous solution and the aqueous phase was extracted with Et_2O. The organic phase was dried over $MgSO_4$, the solvent was removed under reduced pressure, and the resulting oil was purified by flash chromatography (silica gel 200−400 mesh, 40% EtOAc in hexane), giving methyl ketone **28** in 23% yield (0.964 g, 3.63 mmol): R_f 0.70 (40% EtOAc in hexane); ^{1}H NMR (250 MHz, C_6D_6) δ 0.95 (s, 9H), 1.68 (s, 3H), 1.90 (dd, J = 4.1, 15.7 Hz, 1H), 2.45 (dd, J = 8.7, 15.7 Hz, 1H), 4.89 (dd, J = 4.1, 8.5 Hz, 1H), 6.96 (d, J = 8.7 Hz, 2H), 7.83 (d, J = 8.7 Hz, 2H); ^{13}C NMR (63 MHz, C_6D_6) δ 28.5, 31.2, 52.3, 70.2, 74.9, 123.6, 126.7, 147.3, 153.2, 204.1; IR ν_{max} (film) 2974, 2931, 1705, 1599, 1518, 1346, 1190, 1163, 1065, 1011, 845, 750, 698.

(4*RS*)-4-(Benzyloxy)pentan-2-one (44): NaH, 60% in mineral oil (1.628 g, 40.7 mmol) was suspended in dry THF (50 mL) under argon atmosphere at room temperature. Diol **42** (2.0 mL, 18.5 mmol) was added dropwise, and the suspension was stirred for 30 min. After, BnBr (2.2 mL, 18.5 mmol) and a catalytic amount of TBAI (50 mg) were added, and the reaction was refluxed over 18 h. The mixture was poured into water (20 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), and the solvent removed in vacuo. Purification by flash column chromatography (30% EtOAc in hexane) afforded compound **43** (2.41 g) as a colorless oil. **43** (2.41 g, 12.4 mmol) was dissolved in CH_2Cl_2 (40 mL) under argon atmosphere, PCC (5.36 g, 24.9 mmol) was added, and the suspension was stirred at room temperature overnight. The solid was removed by filtration in silica, and the solution was concentrated in vacuo. Purification by flash chromatography (20% EtOAc in hexane) afforded the compound **44** (2.26 g) as colorless oil in 63% to two steps: ^{1}H NMR (250 MHz, C_6D_6) δ 7.33−7.20 (m, 5H), 4.51 (d, J = 11.5 Hz, 1H), 4.39 (d, J = 11.5 Hz, 1H), 4.04 (m, 1H), 2.74 (dd, J = 16.0, 7.3 Hz, 1H), 2.42 (dd, J = 16.0, 5.5 Hz, 1H), 2.10 (s, 3H), 1.18 (d, J = 6.3 Hz, 3H); ^{13}C NMR (62.5 MHz, C_6D_6) δ 207.4, 138.4, 128.3, 127.7, 127.5, 71.5, 70.8, 50.7, 31.0, 19.8; IR ν_{max} (film) 3066, 3031, 2972, 2930, 1714, 1450, 1373, 1171, 1135, 1092, 949.

(4*RS*)-4-(*tert*-Butyldimethylsilyloxy)pentan-2-one (46): A mixture of TBSOTf (2.71 mL, 11.75 mmol) and 2,6-lutidine (2.81 mL, 24.1 mmol) in CH_2Cl_2 was added dropwise to a cooled at −78 °C solution of diol **42** (1.2 g, 11.5 mmol) in CH_2Cl_2 (85 mL) under argon atmosphere. The reaction was stirred at −78 °C for 1 h. After this time, MeOH (0.5 mL) was added and the mixture was allowed to warm to room temperature. The mixture was washed with water

(30 mL) and brine (30 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. Purification by flash column chromatography (30% EtOAc in hexane) afforded compound **45** (1.26 g) as a colorless oil. **45** (1.26 g, 5.77 mmol) was dissolved in CH_2Cl_2 under argon atmosphere, PCC (3.12 g, 17.3 mmol) and anhydrous NaOAc (3.55 g, 43.25 mmol) were added, and the suspension was stirred at room temperature overnight. The solid was removed by filtration in silica, and the solution was concentrated in vacuo. Purification by flash chromatography (20% EtOAc in hexane) afforded the compound **44** (1.10 g) as colorless oil in 44% yield in two steps: ^{1}H NMR (250 MHz, C_6D_6) δ 4.27 (m, 1H), 2.64 (dd, J = 15.0, 7.3 Hz, 1H), 2.41 (dd, J = 15.0, 5.3 Hz, 1H), 2.15 (s, 3H), 1.16 (d, J = 6.3 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (62.5 MHz, C_6D_6) δ 208.1, 65.6, 53.1, 31.7, 25.8, 24.0, 17.9, −4.5, −5.0; IR ν_{max} (film) 2960, 2930, 2858, 1720, 1473, 1367, 1255, 1134, 1081, 1022, 902.

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Supporting Information Available: Product characterization for the compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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