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Rational Design of Aldol Reactions That Proceed via Kinetic Resolution with Switchable Enantioselectivity

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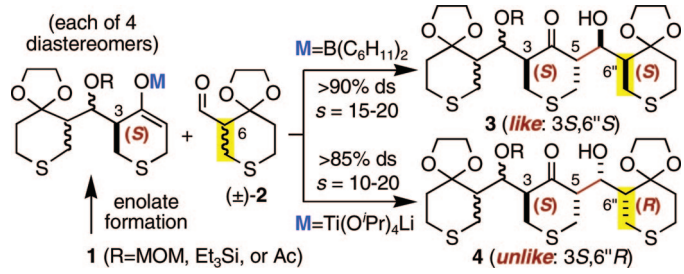

The stereoselectivity of aldol reactions of chiral reactants can be factorized into to three stereocontrol elements: the diastereoface selectivities of the ketone enol(ate) and aldehyde and the relative topicity of the coupling. Application of the multiplicativity rule to these elements leads to the prediction that kinetic resolution (KR) should be possible if all three stereocontrol elements are strongly biased. As a corollary, the enantioselectivity of the kinetic resolution should be switchable by a change in the sense of selectivity of any of the stereocontrol elements. This hypothesis was tested using aldehyde and ketone reactants with high diastereoface selectivities and developing reaction conditions that strongly favor either *syn* or *anti* relative topicity. The aldehyde **2** undergoes aldol reactions with near-exclusive Felkin diastereoface selectivity, and hydroxy-protected derivatives of ketone **1** (R = MOM, Et_3Si, or Ac) undergo aldol reactions with high diastereoface selectivity to give 3,5-*trans* adducts. High levels of *anti* and *syn* relative topicity were obtained with dicyclohexylboron enolates and $Ti(O^iPr)_4Li$ "ate" enolates, respectively. Using these enolates, aldol reactions of (±)-**2** with (±)-**1** gave two of the eight possible diastereomeric adducts (**3** from a diastereoselective *like* combination of reactant enantiomers and **4** from a diastereoselective *unlike* combination) predominantly (>95% of the adducts) in ratios of 0.05−20:1; boron enolates favored the *like* reaction (**3**:**4**, 15−20:1) and Ti "ate" enolates favored the *unlike* reaction (**3**:**4**, 1:10−20). Under these conditions, the ratio of *like* and *unlike* products is a measure of the mutual kinetic enantioselection (MKE) and reflects the ratio of the rate constants for the competing *like* and *unlike* reactions. For each of the four diastereomers of **1**, the reactions with the highest MKEs in favor of the *like* (**3**) or *unlike* products (**4**) were repeated using highly enantioenriched ketone. These reactions occurred with the expected KR (s = 10−20) allowing selective access to enantioenriched diastereomers of **3** or **4** from (±)-**2**. These adducts are useful for polypropionate synthesis, and this design strategy for KR should be applicable to related processes.

Introduction

Asymmetric syntheses of stereochemically complex targets typically follow a convergent path involving the coupling of chiral (nonracemic) fragments. When such couplings generate new stereogenic elements, the reactions are complicated by double stereodifferentiation (DS);[1] i.e., the unequal diastereoselectivities in the reactions of enantiomers with a chiral reactant. Nonetheless,

(1) Reviews: (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–30. (b) Kolodiazhnyi, O. I. *Tetrahedron* **2003**, *59*, 5953–6018.

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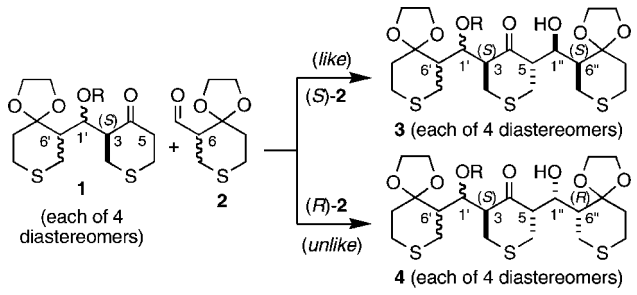
SCHEME 1



with judicious planning this strategy can benefit from the enhanced diastereoselectivities obtainable in "matched" cases.[1] In principle, the same outcome might be achieved by coupling enantiopure and racemic fragments via kinetic resolution (KR);[2] i.e., the unequal rates of reactions of enantiomers with a chiral reactant. Although KR is a very well-known phenomenon,[2] synthetic applications to the stereoselective coupling of chiral fragments are virtually unknown.[3] A major impediment to the development of such applications is the lack of suitable design elements. In this paper, we report the rational design and development of highly stereoselective aldol reactions of racemic **2** with any of the four enantioenriched diastereomers **1** that proceed with kinetic resolution ($s = 10-20$) to give one of the eight possible adduct stereoisomers (>85% diastereoselectivity). The fast and slow reactions are easily inverted by changing the reaction conditions allowing selective access to either **3** or **4** from the same reactants (Scheme 1). These adducts are hexapropionate synthons and are useful for polypropionate synthesis.[4]

The aldol reaction of an enantiopure ketone with an enantiopure aldehyde can produce up to four diastereomeric adducts (Figure 1).[5] However, if one or both reactants are racemic (or simply not enantiopure), up to eight adducts are possible: four each from the *like* and *unlike* combinations[6] of reactant enantiomers (Figure 1).[5] These reactions can occur with KR (one racemic reactant)[7] or with mutual kinetic enantioselection[8] (MKE; both reactants racemic).[9] Both KR and MKE are a consequence of different rate constants for the *like* and *unlike* reactions. The kinetically controlled stereoselectivities of these reactions can be factorized into three stereocontrol elements:[10]

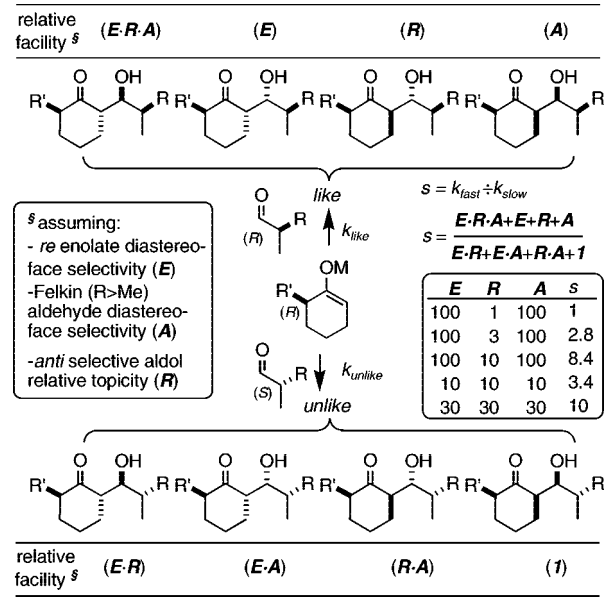


FIGURE 1. Multiplicativity rule applied to an aldol coupling of chiral reactants and the corresponding kinetic resolution selectivities ($s = k_{fast}/k_{slow}$) estimated according to the derived equation at various arbitrary values of ***E***, ***A***, and ***R***. Depending on the senses of the selectivities, any one of the eight possible adducts can be favored (i.e., "satisfy" the three selectivities and have relative facility = ***E*·*R*·*A***) and either the *like* or *unlike* combination can be the "fast" reaction. With the indicated assumed selectivities, the *like* reaction is "fast" (i.e., $k_{fast}=k_{like}$) and the major adduct (i.e., from addition of the *re* face of the enolate to the Felkin face of the aldehyde with *anti* relative topicity) is formed with an estimated diastereoselectivity (major adduct/others) of (***E*·*R*·*A***)/(***E*** + ***R*** + ***A***).

the diastereoface selectivities of the ketone enol(ate) (***E***) and aldehyde (***A***) and the relative topicity (***R***) of the coupling.[11] The *like* and *unlike* reactions typically have different diastereoselectivities (i.e., DS; cf. "matched" and "mismatched")[1] and the "multiplicativity rule"[1a,12] has previously been applied to predict and rationalize DS and MKE in aldol couplings[13] (and other reactions)[14] using the diastereoface selectivities of the two reactants (i.e., assuming perfect relative topicity).[15] By extending the multiplicativity rule to include relative topicity, the selectivity of the KR or related MKE (i.e., $s = k_{fast}/k_{slow}$) can be estimated[11] as illustrated in Figure 1.[15] This analysis indicates that the KR selectivity is limited by the least selective of the three stereocontrol elements and that useful selectivity (e.g., $s > 10$) requires each of those elements to be highly biased. A large body of previous work has clearly established that all three stereocontrol elements in aldol reactions of chiral reactants can be modulated, often predictably, by the choice of protecting groups, enolate type and ligands, and additives.[16] Thus, using these tools it should be possible to design aldol reactions that proceed with KR, and an example of that approach is illustrated here.

(2) Reviews: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249–330. (b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5–26. (c) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407–1446. (d) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974–4001.

(3) (a) Lee, C. B.; Wu, Z.; Zhang, F.; Chappell, M. D.; Stachel, S. J.; Chou, T.-C.; Guan, Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 5249–5259. (b) Tinsley, J. M.; Mertz, E.; Chong, P. Y.; Rarig, R.-A. F.; Roush, W. R. *Org. Lett.* **2005**, *7*, 4245–4248. (c) Ward, D. E.; Beye, G. E.; Sales, M.; Alarcon, I. Q.; Gillis, H. M.; Jheengut, V. *J. Org. Chem.* **2007**, *72*, 1667–1674.

(4) Jheengut, V.; Ward, D. E. *J. Org. Chem.* **2007**, *72*, 7805–7808.

(5) For each combination of reactant enantiomers, four diastereomeric aldol adducts are possible when two new stereocenters are formed in the reaction. When only one new stereocenter is created (e.g. aldol of a methyl ketone), two diastereomeric adducts are generally possible; nonetheless, four diastereotopic transition states are possible.

(6) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654–660.

(7) For examples of aldol reactions proceeding with significant KR see refs 3a,3c, and: Shinoyama, M.; Shirokawa, S.-i.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2009**, *11*, 1277–1280.

(8) Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *19*, 227–407.

(9) For examples of aldol reactions with significant MKE, see refs 3a, 3c, and: (a) Ward, D. E.; Guo, C.; Sasmal, P. K.; Man, C. C.; Sales, M. *Org. Lett.* **2000**, *2*, 1325–1328. (b) Delas, C.; Blacque, O.; Moise, C. *Tetrahedron Lett.* **2000**, *41*, 8269–8272. (c) Perkins, M. V.; Jahangiri, S.; Taylor, M. R. *Tetrahedron Lett.* **2006**, *47*, 2025–2028. (d) Perkins, M. V.; Sampson, R. A.; Joannou, J.; Taylor, M. R. *Tetrahedron Lett.* **2006**, *47*, 3791–3795.

(10) (a) Izumi, Y.; Tai, A. *Stereo-Differentiating Reactions -The Nature of Asymmetric Reactions*; Academic Press: New York, 1977.

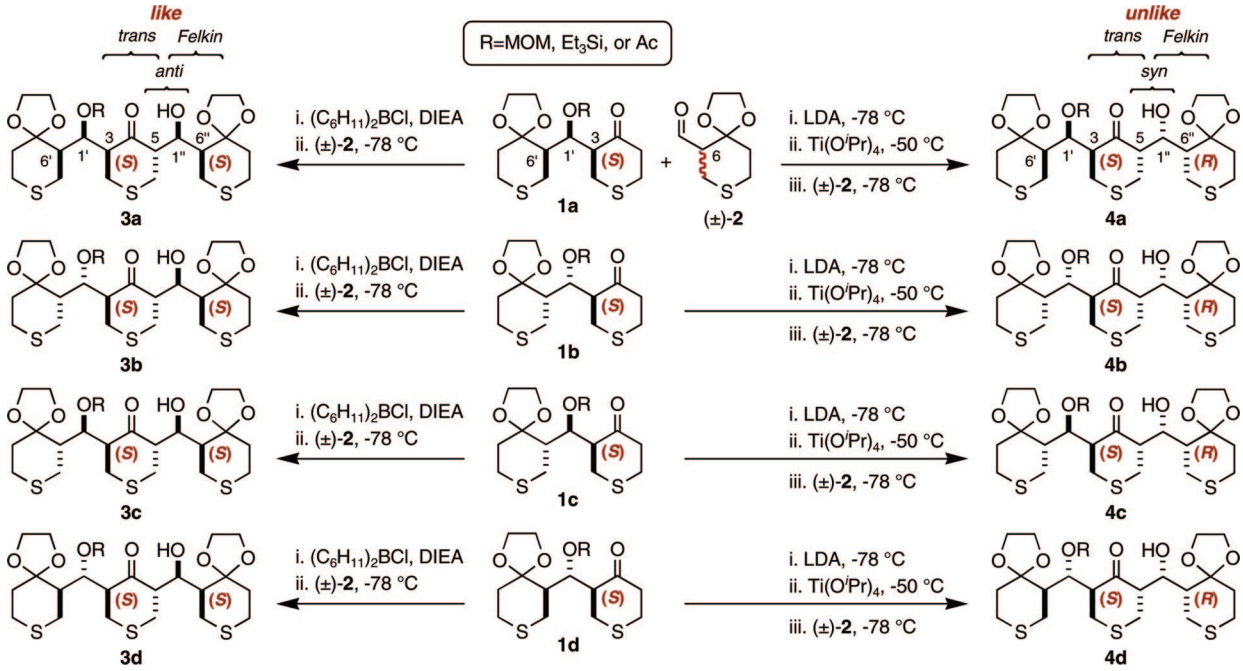
(11) As explained in ref 1a, this approach will necessarily be qualitative. The selectivities of the three stereocontrol elements (***E***, ***A***, and ***R***) are not fixed values but will vary depending on the other reactants. Moreover, they do not act independently but mutually interact in ways that are difficult to predict and are not necessarily the same in competing transition states. Nonetheless, this qualitative approach provides a simple paradigm to guide the design of reactions with desirable properties.

(12) For a derivation see: Nakayama, K. *J. Chem. Educ.* **1990**, *67*, 20–23.

(13) Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290–2300.

(14) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117–4126.

SCHEME 2



We previously reported a comprehensive study on the aldol reactions of (±)-**2** with each of the four diastereomers of (±)-**1** (R = MOM) via their Ti(IV) enolates (prepared by reaction with $Ti(O^iPr)Cl_3$ and $^iPr_2NEt$).[3c] Under optimized conditions, all four reactions gave two of the eight possible adducts predominantly (i.e., >95% of the aldol adducts): (±)-**3** (R = MOM) from the *like* reaction and (±)-**4** (R = MOM) from the *unlike* reaction (Scheme 1).[17] In each case, the *like* and *unlike* reactions occurred with comparable facility (i.e., **3**:**4**, 0.3−1.5:1), and both had the same sense of diastereoface selectivity with respect to both the enolate (3,5-*trans*) *and* the aldehyde (Felkin; 1″,6″-*syn*) but differed in aldol relative topicity (5,1″-*anti* in the *like* reaction vs 5,1″-*syn* in the *unlike* reaction).[17] By using enantiopure reactants under the same reaction conditions, either enantiopure **3** (R = MOM) or **4** (R = MOM) can be obtained selectively.[3c] Achieving the same outcome using the much more readily available (±)-**2** via KR would be a distinct advantage. Applying the multiplicativity rule, we reasoned that significant selectivity in KR (and MKE) should result under reaction conditions that strongly favored *syn* or *anti* relative topicity while maintaining high enolate and aldehyde diastereoface selectivities (see Figure 1).

Results and Discussion

***anti*-selective Relative Topicity with Boron Enolates.** Aldol reactions of six-membered cyclic ketones (including tetrahydro-4*H*-thiopyran-4-one)[18] via their boron enolates are known to proceed with high *anti* relative topicity.[19] Thus, we anticipated that aldol reactions of (±)-**2** with the enol dicyclohexylborinate of (±)-**1** would have high MKE in favor of the *like* reaction to give (±)-**3** selectively. To test this hypothesis, we initially examined the boron-mediated aldol reaction of (±)-**1a** (R = MOM) with (±)-**2**, and under optimized conditions,[20] (±)-**3a** (R = MOM) was indeed obtained in excellent yield and stereoselectivity (Scheme 2) (Table 1, entry 1). Interestingly, the Et_3Si- and Ac-protected derivatives (±)-**1a** gave much lower conversions under the same reaction conditions (entries 2 and 3). Similar reactions of the diastereomers (±)-**1b**−**d** (R = MOM, Et_3Si, or Ac) were also examined. The three derivatives of (±)-**1b** gave poor conversions under the conditions optimized for (±)-**1a** (R = MOM);[21] however, the most reactive of these, (±)-**1b** (R = Et_3Si), was also highly stereoselective, and the major adduct (±)-**3b** (R = Et_3Si) could be obtained in good yield by extending the reaction time (entry 6). Among the

(15) The *like* and *unlike* descriptors specify the relationship between the absolute configurations of the reactant enantiomers (see Scheme 12 in ref 6). Matched and mismatched are terms widely used to describe double stereodifferentiation in reactions of chiral reactants; that is, where the matched pair of reactant enantiomers gives enhanced diastereoselectivity relative to the mismatched pair (ref 1a). Alternatively, these terms are defined according to the diastereoselectivities of the individual reactants (for example, as determined in an analogous reaction with an achiral reactant) that can be either reinforcing (matched) or counteracting (mismatched). In the present context, matched and mismatched can become ambiguous, especially in cases where both combinations of reactant enantiomers lead to highly diastereoselective reactions (ref 3c). Moreover, these terms are specifically defined without reference to kinetics (see footnote ** in ref 1a). Thus, because *like* vs *unlike* and fast vs slow are unambiguously defined based on the structures of the reactant enantiomers and their relative facility for reaction, respectively, we have used these descriptors in preference to matched and mismatched. Nonetheless, application of the multiplicativity rule suggests that reaction of the matched pair of enantiomers will be more facile than reaction of the mismatched pair (ref 1a).

(16) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VGH: Weinheim, 2004; Vols. 1 and 2.

(17) The *like* (same configuration) and *unlike* (opposite configuration) reactions are defined here with respect to the stereochemical configurations at C-3 of **1** and C-6 of **2**; see ref 6. Each reaction can produce four unique diastereomers (i.e., *R* or *S* at C-5 and C-1″). For each diastereomer of **1**, the aldol adducts **3** and **4** have the same configurations at C-1′, C-3, and C-6′ as those in **1**.

(18) (a) Ward, D. E.; Sales, M.; Man, C. C.; Shen, J.; Sasmal, P. K.; Guo, C. *J. Org. Chem.* **2002**, *67*, 1618–1629. (b) Hayashi, T. *Tetrahedron Lett.* **1991**, *32*, 5369–5372.

(19) (a) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111. (b) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 2716–2721.

(20) Similar stereoselectivities but lower conversions were obtained with less $ClB(C_6H_{12})_2$ (e.g., 55% with 1.5 equiv) or shorter reaction times. Enolization at 0 °C for 20 min was equally effective in most cases. The quality of the $ClB(C_6H_{12})_2$ reagent was calibrated with the reaction of cyclohexanone with benzaldehyde which gave >90% of aldol adduct using 1 equiv of reagent; see ref 19b.

(21) Lower reactivity of the enolates was implicated as good conversions were obtained using propanal in place of (±)-**2** under the same conditions.

TABLE 1. Aldol Reactions of (±)-2 with Boron Enolates of 1a−d (R = MOM, Et_3Si, or Ac)[a]

entry	ketone	R	equiv of (±)-**2**	aldol adducts (ratio);[b] conversion[b,c] (%)	yield[d] (%)
1	(±)-**1a**	MOM	2	(±)-**3a**, (±)-**4a** (15:1); >90	86
2	(±)-**1a**	Et_3Si	2	(±)-**3a**, (±)-**4a**; 15	
3	(±)-**1a**	Ac	2	(±)-**3a**, (±)-**4a** (15:1); 45	
4	(±)-**1b**	MOM	2	(±)-**3b**, (±)-**4b** (7:1); 25	
5	(±)-**1b**	Et_3Si	2	(±)-**3b**, (±)-**4b** (20:1); 50	
6	(±)-**1b**	Et_3Si	2[e]	(±)-**3b**, (±)-**4b** (20:1); 80	71
7	(±)-**1b**	Ac	2	(±)-**3b**, (±)-**4b**; 20	
8	(±)-**1c**	MOM	2	(±)-**3c**, (±)-**4c** (5:1); 90	
9	(±)-**1c**	Et_3Si	2	(±)-**3c**, (±)-**4c** (7:1); 65	52
10	(±)-**1c**	Ac	2	(±)-**3c**, (±)-**4c** (18:1); 90	85
11	(±)-**1d**	MOM	2	(±)-**3d**, (±)-**4d** (13:1); 90	80
12	(±)-**1d**	Et_3Si	2	(±)-**3d**, (±)-**4d** (10:1); 35	
13	(±)-**1d**	Ac	2	(±)-**3d**, (±)-**4d**[f] (18:1); 90	80
14	(-)-**1a**[g]	MOM	3	(−)-**3a**, (−)-**4a** (9:1); >90	77
15	(-)-**1b**[g]	Et_3Si	3[e]	(−)-**3b**, (−)-**4b** (15:1); >90	80
16	(+)-*ent*-**1c**[h]	Ac	3	(+)-*ent*-**3c**, *ent*-**4c** (14:1); >90	80
17	(+)-**1d**[i]	Ac	3	(−)-**3d**, **4d**[f] (14:1); 90	74

[a] Enolization with $ClB(C_6H_{12})_2$ (2 equiv) and Et_3N (2.1 equiv) at −78 °C in CH_2Cl_2 (ca. 0.06 M in ketone) for 2 h followed by addition of (±)-**2** and 3 h reaction time; see the Experimental Section for detailed procedures. [b] Determined by ^1H NMR of the crude reaction mixture. For entries 1−13, this ratio is a measure of the MKE for the reaction. [c] Estimated from the ratio of adducts and starting ketone present in the crude reaction mixture. [d] Isolated yield of the major aldol adduct. [e] 17 h reaction time. [f] Not characterized; structure inferred by analogy. [g] >98% ee. [h] 94% ee. [i] 91% ee.

derivatives of (±)-**1c** and (±)-**1d**, reactions of those with R = Et_3Si gave the lowest conversions and reactions of those with R = Ac gave the highest stereoselectivities, the latter providing (±)-**3c** (R = Ac) and (±)-**3d** (R = Ac) in excellent yields (entries 10 and 13).

All reactions in Table 1 favored the *like* combination of reactant enantiomers[17] and gave **3** as the major product that together with **4** (from the *unlike* reaction) comprised >95% of the aldol adducts. Thus, the diastereoselectivity of the *like* reaction is high (>20:1; only **3** was detected by ^1H NMR) in all cases. This is consistent with the finding that the configuration and nature of a β-alkoxy group has a minimal effect on the diastereoselectivity of aldol reactions of boron enolates of acyclic chiral ketones.[22] However, among the three derivatives (R = MOM, Et_3Si, or Ac) of the four diastereomers **1a**−**d**, the MKE for the reaction (i.e., the ratio of *like* and *unlike* products **3** and **4**, respectively) varies from 5 to 20:1. It is also noteworthy that the effects of the different protecting groups on the reactivity of the boron enolates and MKE of their reactions with (±)-**2** vary considerably among the four diastereomers. We assume that the reactions proceed via a "closed" transition state (i.e., coordination of the aldehyde C═O to the B-enolate) and that coordination of the aldehyde is easily reversible and not stereoselective (i.e., no significant preference for coordination of (+)-**2** vs (−)-**2**). In this case, the ratio of products **3** and **4** will be dependent on the relative rate constants for reaction of the *like* combination of **1** and **2** via a chairlike transition state (*anti* relative topicity) to give **3** vs reaction of the *unlike* combination via a twist boat-like transition state (*syn* relative topicity) to give **4**.[23,24] The underlying reasons for the observed effects of the protecting group and configurations at C-3 and C-6′ on the reactivities of the boron enolates of **1a**−**d** are uncertain but presumably relate to the nature of the intramolecular interaction of the different protecting groups with the boron enolate as modulated by the different conformational preferences of the diastereomers.[25]

As anticipated from the multiplicativity rule, each of the four diastereomers of (±)-**1** had at least one derivative whose boron enolate reacted with (±)-**2** with high MKE (>15:1) in favor of the *like* reaction[17] to give (±)-**3** in good yield and with high stereoselectivity. For reactions involving coupling of racemic reactants, it is well established[26] that the ratio of rate constants for the reactions of the *like* and *unlike* combinations of reactant enantiomers (i.e., k_{like}/k_{unlike} = MKE) is equal to the ratio of the total amounts of adducts from each reaction and that the analogous reaction where one reactant is enantiopure and the other is racemic should proceed via KR with the same selectivity (i.e., $s = k_{like}/k_{unlike}$) (see Figure 1).[17] To validate that opportunity, the most stereoselective of the reactions of (±)-**2** with (±)-**1** via the boron enolates were repeated using highly enantioenriched diastereomers of **1** (Table 1, entries 14−17).[27] In all cases, the KR behaved as predicted to give enantioenriched diastereomers of **3** in good yield and with high stereoselectivity. As expected from this type of KR, the ratio of *like* and *unlike* products was somewhat diminished compared to that obtained with (±)-**1** and the remaining (±)-**2** had moderate ee (ca. 25%).[28,29]

***syn*-Selective Relative Topicity with Titanium "Ate" Enolates.** Applying the same logic as above, aldol reactions of **1** with (±)-**2** under conditions that strongly favor *syn* relative topicity should facilitate the *unlike* combination of reactant enantiomers[17] and give adducts **4** selectively. Identifying

(22) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1–200.

(23) For an excellent discussion of the various transition states for aldol reactions, see: Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 2177–2194.

(24) Computational studies on aldol reactions of ethanal with simple acyclic (*E*)-enolborinates (e.g., from butanone) suggest that the major *anti* adduct is derived predominantly from a boatlike transition state (boat A) and the minor *syn* adduct from a different boatlike transition state (boat B). (a) Goodman, J. M.; Paton, R. S. *Chem Commun.* **2007**, 2124–2126. (b) Bernardi, F.; Robb, M. A.; Suzzi-Valli, G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1991**, *56*, 6472–6475. (c) Bernardi, A.; Capelli, A. M.; Gennari, C.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1990**, *55*, 3576–3581. (d) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481–493.

(25) Paton, R. S.; Goodman, J. M. *J. Org. Chem.* **2008**, *73*, 1253–1263. This DFT computational study on the diastereoselectivity of boron-mediated aldol reactions of β-alkoxy ketones suggests the importance of a formyl H-bond between the β-O and the aldehyde H. In the present context, this interaction would necessarily produce 3,5-*cis* products and can be neglected. .

(26) Horeau, A. *Tetrahedron* **1975**, *31*, 1307–1309.

(27) Structure labels with a (+) or (−) prefix refer to enantioenriched compounds with absolute configuration as illustrated for the structure with the same number without a prefix; labels with an *ent* prefix refer to enantioenriched compounds with absolute configuration opposite to that illustrated for the structure with that label. The (+) and (−) prefixes also indicate the sign of the $[\alpha]_D$ for the indicated absolute configuration.

TABLE 2. Aldol Reactions of (±)-2 with Ti(IV) "Ate" Enolates of 1a−d (R = MOM or Et_3Si)[a]

entry	ketone	R	equiv of (±)-**2** (rxn time, h)	aldol adducts (ratio);[b] conversion[b,c]	yield[d] (%)
1	(±)-**1a**	MOM	2 (0.5)	(±)-**3a**, (±)-**4a** (1:11); >90	79
2	(±)-**1a**	Et_3Si	2 (3)	(±)-**3a**, (±)-**4a** (1:1.6); >90	
3	(±)-**1b**	MOM	2 (3)	(±)-**3b**, (±)-**4b** (1:3); >90	
4	(±)-**1b**	Et_3Si	2 (3)	(±)-**3b**, (±)-**4b**, (±)-**5b**[e] (1:6:1.5); 75	
5	(±)-**1b**	Et_3Si	2 (9)	(±)-**3b**, (±)-**4b**, (±)-**5b**[e] (1:9:1); 90	61
6	(±)-**1b**	Et_3Si	2 (1)	(±)-**3b**, (±)-**4b**, (±)-**5b**[e] (1:4:3); 70	
7	(±)-**1b**	Et_3Si	2 (20)	(±)-**3b**, (±)-**4b**, (±)-**5b**[e] (1:7.5:0.5); >90%	
8	(±)-**1b**	Et_3Si	3 (9)	(±)-**3b**, (±)-**4b**, (±)-**5b**[e] (1:9:0.5); 90	63
9	(±)-**1c**	MOM	2 (2.5)	(±)-**3c**, (±)-**4c** (1:>20); >90	90
10	(±)-**1c**	Et_3Si	2 (2.5)	(±)-**3c**, (±)-**4c** (1:14); >90	76
11	(±)-**1d**	MOM	2 (2.5)	(±)-**3d**, (±)-**4d** (1:5); 85	
12	(±)-**1d**	Et_3Si	2 (2.5)	(±)-**3d**, (±)-**4d** (1:>20); >90	92
13	(−)-**1a**[f]	MOM	3 (0.5)	(−)-**3a**, (−)-**4a** (1:9); 85	67
14	(−)-**1b**[f]	Et_3Si	3 (9)	(−)-**3b**, (−)-**4b**, **5b**[e] (1:8:0.5); >90	66
15	(−)-*ent*-**1c**[g]	MOM	3 (2.5)	*ent*-**3c**, (+)-*ent*-**4c** (1:>20); >90	81
16	(−)-**1d**[h]	Et_3Si	3 (2.5)	**3d**, (−)-**4d** (1:16); 90	72

[a] Addition of LDA (0.17 M in THF; 1.1 equiv) to **1** (0.1 M in THF) at −78 °C, after 15 min addition of $Ti(O^iPr)_4$ (2.2 equiv), then −50 °C for 30 min followed by addition of (±)-**2** at −78 °C and indicated reaction time; see the Experimental Section for detailed procedures. [b] Determined by ^1H NMR of the crude reaction mixture. For entries 1−11, this ratio is a measure of the MKE for the reaction. [c] Estimated from the ratio of adducts and starting ketone present in the crude reaction mixture. [d] Isolated yield of the major aldol adduct. [e] **5b** is the C-5 epimer of **4b** and is an *unlike* adduct. [f] >98% ee. [g] 94% ee. [h] 91% ee.

appropriate reaction conditions proved difficult. We were unable to induce Mukaiyama-type aldol reactions of (±)-**2** with the trimethylsilyl enol ethers of (±)-**1a** or (±)-**1b** (R = MOM or $SiEt_3$) under a variety of conditions. Although reactions of the Sn(II) enolates of (±)-**1b** or (±)-**1c** (R = MOM) with propanal were highly 3,5-*trans*-5,1″-*syn* selective (as expected),[30] similar reactions with (±)-**2** were moderately *trans-anti* selective (**3**:**4**, 1.5−3.5:1). After extensive experimentation, we found that reactions of (±)-**2** with the putative Ti(IV) "ate" enolate[31] of (±)-**1a** (R = MOM) gave promising MKE in favor of the *unlike* combination of reactant enantiomers[17] presumably due to high *syn* relative topicity (Table 2). Under optimized conditions,[32] (±)-**4a** (R = MOM) was obtained in good yield and acceptable stereoselectivity (entry 1). In contrast, a similar reaction of (±)-**2** with (±)-**1a** (R = Et_3Si) gave (±)-**4a** (R = Et_3Si) with low selectivity (entry 2).

The scope of the aldol reaction via the Ti(IV) "ate" enolate was investigated by applying the optimized conditions to the diastereomers (±)-**1b−d** (R = MOM or Et_3Si) (Table 2). For (±)-**1b**, reaction of the Et_3Si derivative (entry 4) had considerably higher MKE in favor of the *unlike* combination of reactant enantiomers than the MOM derivative (entry 3) but gave non-negligible amounts of a second *unlike* adduct, (±)-**5b** (R = Et_3Si), that was the C-5 epimer of (±)-**4b** (R = Et_3Si). Interestingly, extending the reaction time not only improved the conversion but also increased the ratio of the *unlike* adducts (**4b** and **5b**) in favor of (±)-**4b** (R = Et_3Si) (entry 5). Additional experiments confirmed the depletion of (±)-**5b** (R = Et_3Si) during the reaction (entries 6 and 7). It is noteworthy that in varying the reaction time over 1−20 h, the ratio of the amounts of *unlike* (**4b** and **5b**) to *like* (**3b**) adducts was relatively consistent (i.e., MKE = 7.5−10), while the ratio of the *unlike* adducts changed markedly (**4b**:**5b**, 1.3−15:1). The formation of relatively high amounts of **5b** early in the reaction might be due a change in the structure of the enolate (e.g., **5b** is the major product from the LDA-generated enolate in the absence of Ti(IV) additives); however, allowing more time for transmetalation (0.5−3 h) prior to addition of (±)-**2** had no effect on the product ratio obtained after a 3 h reaction time. The selective loss of (±)-**5b** (R = Et_3Si) with increased reaction time might be due to isomerization by enolization[33] and selective ketonization (i.e., to **4b**) or by retro-aldol[34] and re-aldol via an enolate that disfavors formation of **5b**. At present, we have insufficient data to distinguish among the possible mechanisms; however, regardless of the pathway, the desired (±)-**4b** (R = Et_3Si) can

(28) With a sufficient excess of (±)-**2**, the ratio and yield of products from the reaction of enantioenriched **1** should approach those obtained with (±)-**1** under the same conditions; however, the product ratio (and perhaps yield) will be diminished using less (±)-**2** due to depletion of the fast-reacting enantiomer (see ref 29 for a sample calculation of this effect). We found that 3 equiv of (±)-**2** gave a satisfactory compromise between selectivity and convenience. The moderate enantioenrichment of recovered **2** is consistent with that predicted from a kinetic resolution (see ref 29 for the calculated enrichment under various scenarios) indicating that racemization of **2** is slow under these conditions. The recovered enantioenriched **2** can be readily racemized for reuse. For the facile racemization of **2** in the presence of proline, see: Ward, D. E.; Jheengut, V.; Akinnusi, O. T. *Org. Lett.* **2005**, *7*, 1181–1184.

(29) For a reaction of an enantiopure substrate (**A**) with a racemic reactant ((±)-**B**) with $k_{fast}/k_{slow} = 15$, the ratio of products from the *fast* and *slow* reactions (at 90% conversion of **A**) as a function of the amount of (±)-**B** used is calculated to be: 7.9 (2 equiv of **B**; remaining **B**, 63% ee); 10.2 (3 equiv of **B**; remaining **B**, 35% ee); 11.8 (4 equiv of **B**; remaining **B**, 24% ee); 13.8 (10 equiv of **B**; remaining **B**, 8.5% ee). See ref 2a for the equations used for this computation.

(30) Aldol reaction of the Sn(II) enolate of cyclohexanone ($SnOTf_2$ and *N*-ethylpiperidine) with PhCHO is highly *syn*-selective: Mukaiyama, T.; Stevens, R. W.; Iwasawa, N. *Chem. Lett.* **1982**, 353–356.

(31) For aldol reactions of Ti(IV) "ate" enolates, see: (a) Reetz, M. T.; Peter, R. *Tetrahedron Lett.* **1981**, *22*, 4691–4694. (b) Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722–5728. (c) Yachi, K.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **1999**, *121*, 9465–9466. (d) Han, Z.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **2000**, *41*, 4415–4418. For other reactions of Ti(IV) "ate" enolates, see: (e) Bernardi, A.; Dotti, P.; Poli, G.; Scolastico, C. *Tetrahedron* **1992**, *48*, 5597–5606. (f) Bernardi, A.; Marchionni, C.; Pilati, T.; Scolastico, C. *Tetrahedron Lett.* **1994**, *35*, 6357–6360. (g) Viteva, L. Z.; Gospodova, T. S.; Stefanovsky, Y. N. *Tetrahedron* **1994**, *50*, 7193–7202. (h) Bernardi, A.; Marchionni, C.; Novo, B.; Karamfilova, K.; Potenza, D.; Scolastico, C.; Roversi, P. *Tetrahedron* **1996**, *52*, 3497–3508. (i) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 649–651. (j) Itoh, Y.; Houk, K. N.; Mikami, K. *J. Org. Chem.* **2006**, *71*, 8918–8925. For an NMR study on Ti(IV) "ate" enolates, see: (k) Bernardi, A.; Cavicchioli, M.; Marchionni, C.; Potenza, D.; Scolastico, C. *J. Org. Chem.* **1994**, *59*, 3690–3694. For the NMR and X-ray structure of $LiTi(O^iPr)_5$, see: (l) Hampden-Smith, M. J.; Williams, D. S.; Rheingold, A. L. *Inorg. Chem.* **1990**, *29*, 4076–4081.

(32) The enolate was prepared by reaction with LDA (1.1 equiv) followed by addition of $Ti(O^iPr)_4$ (2.2 equiv). Under analogous conditions, lower selectivities (i.e., **4a**:**3a** ratios) were obtained using the "amine free" Li enolates (refs 9a and 31e), $Ti(O^iPr)_3Cl$ (ref 31a, b), or $Ti(NEt_2)_3Cl$ (ref 31a), and in the absence of Ti(IV) additives, the reactions were moderately *anti*-slective.

(33) Ward, D. E.; Sales, M.; Sasmal, P. K. *J. Org. Chem.* **2004**, *69*, 4808–4815.

(34) For examples of retro-aldol/aldol in the presence of $Ti(O^iPr)_4$, see: Yang, W.; Digits, C. A.; Hatada, M.; Narula, S.; Rozamus, L. W.; Huestis, C. M.; Wong, J.; Dalgarno, D.; Holt, D. A. *Org. Lett.* **1999**, *1*, 2033–2035.

be obtained in acceptable yield and selectivity under these conditions (entry 8). Reactions of both the MOM and Et_3Si derivatives of (±)-**1c** were very selective and gave (±)-**4c** (R = MOM) and (±)-**4c** (R = Et_3Si), respectively, in high yields (entries 9 and 10). For (±)-**1d**, reaction of the Et_3Si derivative (entry 12) was much more selective than the MOM derivative (entry 11) and gave (±)-**4d** (R = Et_3Si) in excellent yield. In contrast to (±)-**1b** (R = Et_3Si) (entries 3−8), varying the reaction time had very little effect on the distributions of products from the reactions of (±)-**2** with (±)-**1a** (R = MOM), (±)-**1c** (R = MOM), or (±)-**1d** (R = Et_3Si).

All reactions in Table 2 favored the *unlike* combination of reactant enantiomers[17] and gave **4** as the major product. With the exception of the reaction of (±)-**1b** (R = Et_3Si), the diastereoselectivities of these *unlike* reactions are uniformly high (>20:1; only **4** was detected by ^{1}H NMR). There are few reports of aldol reactions of the putative Ti(IV) "ate" enolates formed from Li enolates in the presence of Ti(O^iPr)$_4$.[31a−d] Aldol reactions of various Ti(IV) enolates of cyclohexanone (i.e., cyclohexenyloxy-M with M = $TiCl_3$,[35] Ti(O^iPr)$_3$,[31a] and Ti(O^iPr)$_4$Li[31a]) with representative aldehydes have high *syn* relative topicity, and a "closed" twist-boatlike transition state has been proposed for the M = $TiCl_3$ enolate.[35,36] Alternatively, the lower Lewis acidity and higher nucleophilicity expected for the Ti(O^iPr)$_4$ "ate" enolate might facilitate a *syn*-selective aldol reaction via an "open" transition state. The reaction of (±)-**2** with the Ti(IV) "ate" enolate of tetrahydro-4*H*-thiopyran-4-one under the optimized conditions (cf. Table 2) was moderately *syn*-selective and gave a 4:1 mixture of **1a** (R = H) and **1b** (R = H), respectively (ca. 85% conversion); however, the same reactions via the Li (LDA or "amine" free) or Ti ($TiCl_4$, $^iPr_2NEt$) enolates gave **1b** (R = H) preferentially.[18a] It is noteworthy that in their reactions with (±)-**2**, the Ti(IV) "ate" enolates of (±)-**1** (LDA then Ti(O^iPr)$_4$) have much higher MKE in favor of the *unlike* adduct **4** (i.e., *syn* relative topicity) than the corresponding Li (LDA)[32] or Ti ($TiCl_4$, $^iPr_2NEt$)[3c] enolates. The effect of the MOM and Et_3Si protecting groups on the MKE of the reaction varies among the diastereomers **1a−d** (Table 2) with MOM being optimal for **1a** and **1c** and Et_3Si being optimal for **1b** and **1d**. We speculate that these differences relate to the combined effects of the nature of the protecting group and the configurations at C-1′ and C-6′ on the structure of the enolate.[37] For example, a greater propensity for intramolecular coordination of Ti with an *O*-MOM vs an *O*-$SiEt_3$ group is expected. For Ti(IV) "ate" enolates, such coordination would give octahedral geometry at Ti and possibly facilitate aldol reaction via an "open" transition state. By contrast, in the absence of intramolecular coordination an open coordination site is available for the aldehyde allowing for reaction via a "closed" transition state. In either case, MKE favoring the *unlike* reaction would be modulated by the effects of the different configurations at C-1′ and C-6′ in diastereomers **1a−d** on the competing transition states for the *like* vs *unlike* reactions.[37]

For each of the diastereomers (±)-**1a−d**, the Ti(IV) "ate" enolate of at least one derivative reacted with (±)-**2** with substantial MKE (>20−10:1) in favor of the *unlike* combination[17] of reactant enantiomers and gave **4** in good yield and with high diastereoselectivity. To verify the expected kinetic resolution,[26] those reactions were repeated using highly enantioenriched diastereomers **1a−d** (Table 2, entries 13−16).[27] In all cases, the KR behaved as predicted to give enantioenriched diastereomers of **4** in good yield and with high stereoselectivity. As expected from this type of KR, the ratio of *like* and *unlike* products was somewhat diminished compared to that obtained with (±)-**1** and the remaining (±)-**2** had moderate ee (ca. 30−40%).[28,29]

Summary and Conclusions

In summary, application of the multiplicativity rule to the three stereocontrol elements governing aldol couplings of chiral reactants (i.e., enol(ate) and aldehyde diastereoface selectivity and relative topicity) suggests that useful kinetic resolution (KR) should be attainable if all three are highly selective. This qualitative approach provides a simple paradigm to guide the design of useful reactions and the aldol reactions of **1** (R = Ac, MOM, or Et_3Si) with (±)-**2** were selected to illustrate this strategy. Previous work established that these reactants undergo aldol reactions with the required high levels of diastereoface selectivity.[3c] As anticipated,[19] high levels of *anti* relative topicity were obtained using the dicyclohexylboron enolates of (±)-**1**, and under optimized conditions, their reactions with (±)-**2** were remarkably stereoselective (Table 1). Of the eight possible adduct diastereomers, (±)-**3** was produced predominantly (>90% of the adducts). Thus, the *like* combinations of reactant enantiomers (e.g., (3*S*)-**1** with (*S*)-**2**) were strongly favored (>15:1 vs the *unlike* combination), and these reactions were highly diastereoselective (>20:1) in favor of **3**, the diastereomer that "satisfies" all three stereocontrol elements. Expectedly, the same reactions using highly enantioenriched **1** proceeded with KR to give enantioenriched **3** in good yields.

A corollary of this analysis is that the enantioselectivity of the kinetic resolution should be switchable by changing the sense of the selectivity in any of the stereocontrol elements. Toward that end, high levels of *syn* relative topicity were achieved in reactions of (±)-**2** with the Ti(IV) "ate" enolates[31] of (±)-**1** (R = MOM or Et_3Si) (Table 2). In the best cases, the *unlike* combinations of reactant enantiomers (e.g., (3*S*)-**1** with (*R*)-**2**) were strongly favored (>10:1 vs the *like* combination), and these reactions were highly diastereoselective (>15:1) in favor of **4**, the diastereomer that "satisfies" all three stereocontrol elements. Repeating these reactions using highly enantioenriched **1** gave **4** with good selectivity via the expected KR. It is remarkable that simply varying the nature of the enolate changes the relative rate constants for the competing *like* and *unlike* reactions by more than 2 orders of magnitude allowing selective access to either **3** or **4** from the same reactants.

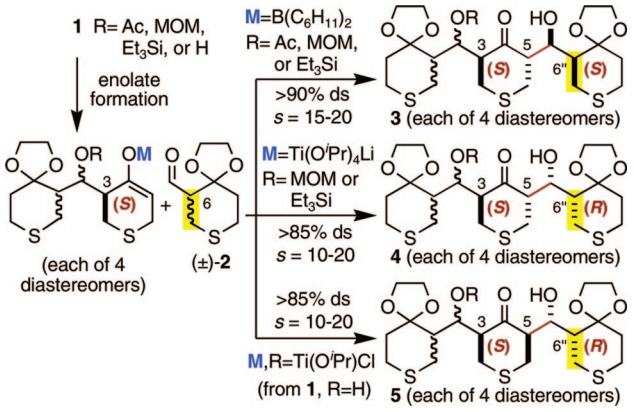
In principle, any of the eight possible diastereomeric adducts from aldol reaction of a given diastereomer of **1** with (±)-**2** might be selectively available by appropriate manipulation of the stereocontrol elements. Indeed, we previously discovered by serendipity that reactions of (±)-**2** with **1** (R = H) via the Ti(IV) enolates (Ti(O^iPr)Cl_3/$^iPr_2NEt$) also strongly favored the *unlike* combinations of reactant enantiomers (>10:1 vs the *like* combination).[3c] However, in contrast to the Ti(IV) "ate" enolates, these reactions showed *anti* relative topicity and 3,5-

(35) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3343–3346.

(36) In a case involving a (*Z*)-enolate, it was suggested (ref 31b) that excess Ti(O^iPr)$_4$ sequesters Li^iOPr from the "ate" enolate to give Ti(O^iPr)$_5$Li and the (^iPrO)$_3$Ti(IV) enolate that reacts via a closed chair-like transition state (*syn* relative topicity). Reactions of **1** via such a transition state would give *anti* relative topicity, contrary to our results.

(37) The structure and aggregation state of Ti "ate" enolates are uncertain (refs 31k,l) and it is not clear whether the competing transition states for the *like* and *unlike* reactions are the same type (e.g., "closed" chair vs twist-boat) or different types (e.g., "closed" vs "open"). Thus, differentiating among the various mechanistic possibilities (see ref 23) is not feasible at present.

SCHEME 3



cis enolate diastereoface selectivity to give the adducts **5** with high diastereoselectivity (>13:1) (Scheme 3). Thus, by simply varying the hydroxy protecting group and nature of enolate, each of the diastereomers of **1** undergoes aldol reaction with (±)-**2** via kinetic resolution to selectively give enantioenriched **3**, **4**, or **5** (Scheme 3). In this way, 11 of the 20 possible diastereomers from the reactions of the four diastereomers of **1** with **2** are selectively available.[38] These aldol adducts are useful for polypropionate synthesis[4] and this design strategy for kinetic resolution should be applicable to related processes.

Experimental Section[39]

General Procedure for KR Using Boron Enolates. A solution of **1** in CH_2Cl_2 (0.2 M; 1 equiv; typically 0.1−0.2 mmol) was added dropwise via syringe over 5 min to a stirred solution of $ClB(C_6H_{11})_2$ (1 M in hexanes; 2 equiv) and Et_3N (2.1 equiv) in CH_2Cl_2 (5 mL/mmol of **1**) at −78 °C under Ar. After 2 h, a solution of (±)-**2** in CH_2Cl_2 (0.6 M; 3 equiv) was added slowly via syringe (ca. 5 min). After the indicated reaction time, the reaction was quenched by sequential addition of phosphate buffer (pH 7; 2 mL), MeOH (2 mL), and 30% aqueous H_2O_2 (1.0 mL). The mixture was stirred at 0 °C for 10 min and then was diluted with ice−water and saturated aqueous Na_2SO_3 (ca. 5 mL) and extracted with CH_2Cl_2 (×3). The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product that was analyzed by ^{1}H NMR (the er of **2** was assessed[40] by adding (+)-Eu(hfc)$_3$). Fractionation of the crude by flash column chromatography (FCC) afforded recovered **1** and **2** and the aldol adduct **3**.

Aldol Adduct (−)-3a (R = MOM). Reaction of the boron enolate of (−)-**1a** (R = MOM) (48 mg, 0.14 mmol; >98% ee) with (±)-**2** (78 mg, 0.41 mmol) for 3 h according to the above general procedure gave a crude product that by ^{1}H NMR contained a 9:1 mixture of **3a** (R = MOM) and **4a** (R = MOM), respectively, and (*R*)-**2** (ca. 33% ee). Fractionation of the crude by FCC (20−50% ethyl acetate in hexane) afforded recovered (−)-**1a** (R = MOM) (1.8 mg, 3%), **2** (32 mg, 41%), **4a** (R = MOM) (11 mg; ca. 85% pure), and the title compound (57 mg, 77%) ($[\alpha]^{23}_D$ −80; *c* 0.8, $CHCl_3$). NMR data for (−)-**3a** (R = MOM) were consistent with those previously reported for (±)-**3a** (R = MOM).[3c]

Aldol Adduct (−)-3b (R = Et$_3$Si). The reaction of the boron enolate of (−)-**1b** (R = $SiEt_3$) (67 mg, 0.16 mmol; >98% ee) with (±)-**2** (90 mg, 0.48 mmol) for 17 h according to the above general procedure gave a crude product that by ^{1}H NMR contained a 15:1 mixture of (−)-**3b** (R = Et_3Si) and (−)-**4b** (R = Et_3Si), respectively, and (*R*)-**2** (ca. 20% ee). Fractionation of the crude by FCC (30% ethyl acetate in hexane) afforded recovered (−)-**1b** (R = Et_3Si) (4 mg, 6%) and **2** (29 mg, 32%), a 6:1:1 mixture of **2**, (−)-**3b** (R = Et_3Si), and (−)-**4b** (R = $SiEt_3$), respectively (22 mg), and the title compound (78 mg, 80%) ($[\alpha]^{26}_D$ −52; *c* 1.3, $CHCl_3$). ^{1}H NMR data (500 MHz, $CDCl_3$) for (−)-**3b** (R = Et_3Si) were consistent with those for (±)-**3b** (R = $SiEt_3$):[41] δ 4.71 (1H, br d, J = 4 Hz), 4.39 (1H, br s), 4.11−3.83 (8H, m), 3.17 (1H, dd, J = 12, 12 Hz), 3.07 (1H, d, J = 4.5 Hz), 3.04−2.89 (4H, m), 2.89−2.77 (4H, m), 2.77−2.59 (4H, m), 2.49 (1H, br d, J = 13 Hz), 2.15−2.04 (4H,), 1.68 (1H, ddd, J = 3.5, 13, 13 Hz), 1.63 (1H, m, J = 6, 7, 13 Hz), 0.95 (9H, t, J = 8 Hz), 0.67−0.60 (6H, ap q, J = 8 Hz).

Aldol Adduct (+)-*ent*-3c (R = Ac). The reaction of the boron enolate of (+)-*ent*-**1c** (R = Ac) (20 mg, 0.058 mmol; 94% ee) with (±)-**2** (33 mg, 0.17 mmol) for 3 h according to the above general procedure gave a crude product that by ^{1}H NMR contained a 14:1 mixture of (+)-*ent*-**3c** (R = Ac) and *ent*-**4c** (R = Ac), respectively, and (*S*)-**2** (ca. 33% ee). Fractionation of the crude by FCC (40% ethyl acetate in hexane) afforded recovered (+)-*ent*-**1c** (R = Ac) (1 mg, 5%) and the title compound (25 mg, 80%) ($[\alpha]^{25}_D$ +80; c 1.0, $CHCl_3$). ^{1}H NMR data (500 MHz, $CDCl_3$) for (+)-*ent*-**3c** (R = Ac) were consistent with those for reported for (±)-**3c** (R = Ac):[41] δ 5.81 (1H, dd, J = 4, 6 Hz), 4.87 (1H, ddd, J = 2.5, 3, 9.5 Hz), 4.15−3.85 (8H, m), 3.60 (1H, ddd, J = 6, 6, 10.5 Hz), 3.02 (1H, dd, J = 4, 14 Hz), 2.97 (1H, dd, J = 11, 14 Hz), 2.94 (1H, d, J = 3 Hz), 2.92−2.63 (10H, m), 2.55 (1H, bd, J = 13.5 Hz), 2.22−2.15 (3H, m), 2.04 (3H, s), 2.00 (1H, ddd, J = 2.5, 3.5, 11 Hz), 1.78−1.70 (2H, m).

Aldol Adduct (−)-3d (R = Ac). The reaction of the boron enolate of (+)-**1d** (R = Ac) (20 mg, 0.058 mmol; 91% ee) with (±)-**2** (33 mg, 0.17 mmol) for 3 h according to the above general procedure gave a crude product that by ^{1}H NMR contained a 14:1 mixture of (−)-**3d** (R = Ac) and **4d** (R = Ac), respectively, and (*R*)-**2** (ca. 20% ee). Fractionation of the crude by FCC (30% ethyl acetate in hexane) afforded recovered (+)-**1d** (R = Ac) (2 mg, 10%) and the title compound (23 mg, 74%) ($[\alpha]^{25}_D$ −29; *c* 3.0, $CHCl_3$). ^{1}H NMR data (500 MHz, $CDCl_3$) for (−)-**3d** (R = Ac) were consistent with those for (±)-**3d** (R = Ac):[41] δ 5.64 (1H, dd, J = 3.5, 8 Hz), 4.90 (1H, br d, J = 9.5 Hz), 4.14−3.87 (8H, m), 3.44 (1H, ap ddd, J = 4, 5, 10 Hz), 3.03−2.93 (4H, m), 2.90−2.80 (6H, m,), 2.72−2.55 (4H, m), 2.51 (1H, dddd, J = 2.5, 3.5, 4.5, 13.5 Hz), 2.24 (1H, ddd, J = 4, 10.5, 14 Hz), 2.17 (1H, ddd, J = 3, 3.5, 13.5 Hz), 2.03 (3H, s), 1.96 (1H, br dd, J = 2.5, 11.5 Hz), 1.76−1.70 (2H, m).

General Procedure for KR Using Titanium "Ate" Enolates. A solution of freshly prepared LDA (0.17 M in THF; 1.1 equiv) at 0 °C was added via syringe to a stirred solution of **1** (70 mg, 0.20 mmol) in THF (0.1 M; 1 equiv; typically 0.1 mmol) at −78 °C under Ar. After 15 min, Ti(O^{i}Pr)$_4$ (2.2 equiv) was added. The reaction mixture was stirred for 10 min at −78 °C, 30 min at −50 °C (CH_3CN/dry ice bath), and finally 5 min at −78 °C. A solution of (±)-**2** (75 mg, 0.40 mmol) in THF (0.8 M; 3 equiv) was added via syringe. After the indicated time, the reaction was quenched by addition of saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic layers were passed over a short column layered with Na_2SO_4, SiO_2, and Na_2SO_4 and concentrated to give the crude product that was analyzed by ^{1}H NMR (the er of **2** was assessed by adding (+)-Eu(hfc)$_3$[40]). Fractionation of the crude by FCC or preparative thin-layer chromatography (PTLC) afforded recovered **2** and the aldol adduct **4**.

Aldol Adduct (−)-4a (R = MOM). The reaction of the Ti(IV) "ate" enolate of (−)-**1a** (R = MOM) (40 mg, 0.11 mmol; >98% ee) with (±)-**2** (64 mg, 0.34 mmol) for 0.5 h according to the above

(38) If R = H, 20 diastereomers are possible; if R ≠ H, 32 diastereomers are possible. From the perspective of diversity of relative configurations, here we are considering the 32 R≠H diastereomers to be "synthetically equivalent" to the 20 R = H diastereomers. Because one diastereomer is produced from two reactions (i.e, **3a** (R = H) ≡ **4b** (R = H)), 11 (rather than 12) unique diastereomers are generated.

(39) See the Supporting Information for general methods and procedures.

(40) Ward, D. E.; Akinnusi, O. T.; Alarcon, I. Q.; Jheengut, V.; Shen, J.; Quail, J. W. *Tetrahedron: Asymmetry* **2004**, *15*, 2425–2430.

(41) See the Supporting Information for the complete characterization data for this racemic adduct obtained via the same procedure but using (±)-**1**.

general procedure as a crude product whose ^{1}H NMR spectrum indicated the presence of an 9:1 mixture (−)-**4a** (R = MOM) and (−)-**3a** (R = MOM), respectively, and (*S*)-**2** (ca. 33% ee). Fractionation of the crude by FCC (30% ethyl acetate in hexane) gave recovered **2** (44 mg, 68%), (−)-**1a** (R = MOM) (5 mg, 13%), (−)-**3a** (R = MOM) (5 mg, 8%), and the title compound (41 mg, 67%) ($[\alpha]^{26}_D$ −93; *c* 1.2, $CHCl_3$). NMR data for (−)-**4a** (R = MOM) were essentially identical to those previously reported for (±)-**4a** (R = MOM).[3c]

Aldol Adduct (−)-4b (R = Et$_3$Si). The reaction of the Ti(IV) "ate" enolate of (−)-**1b** (R = Et_3Si) (50 mg, 0.12 mmol; >98% ee) with (±)-**2** (67 mg, 0.36 mmol) for 9 h according to the above general procedure gave a crude product that by ^{1}H NMR contained a 8:0.5:1 mixture of of (−)-**4b** (R = Et_3Si), **5b** (R = $EtSi_3$), and (−)-**3b** (R = Et_3Si), respectively, and (*S*)-**2** (ca. 40% ee). Fractionation of the crude by FCC (20% ethyl acetate in hexane) gave recovered **2** (44 mg, 65%), (−)-**1b** (R = Et_3Si) (3.7 mg, 7%), a 2.5:1 mixture of (−)-**3b** (R = Et_3Si), and **5b** (R = Et_3Si), respectively (9 mg, 12%), and the title compound (48 mg, 67%) ($[\alpha]^{25}_D$ −62; *c* 1.1, $CHCl_3$). ^{1}H NMR data (500 MHz, $CDCl_3$) for (−)-**4b** (R = $SiEt_3$) were consistent with those for (±)-**4b** (R = Et_3Si):[41] δ 4.80−4.70 (2H, m), 4.12−3.79 (8H, m), 3.21−3.08 (3H, m), 3.04−2.91 (3H, m), 2.91−2.70 (6H, m), 2.70−2.61 (2H, m), 2.57 (1H, br d, J = 13.5 Hz), 2.18−2.05 (3H, m), 2.00 (1H, ddd, J = 3, 3, 10 Hz), 1.69 (1H, ddd, J = 3, 11, 14 Hz), 1.65−1.57 (1H, m), 0.96 (9H, t, J = 8 Hz), 0.64 (6H, ap q).

Aldol Adduct (+)-*ent*-4c (R = MOM). The reaction of the Ti(IV) "ate" enolate of (−)-*ent*-**1c** (R = MOM) (20 mg, 0.058 mmol; 94% ee) with (±)-**2** (33 mg, 0.17 mmol) for 2.5 h according to the above general procedure gave a crude product that by ^{1}H NMR contained a >20:1 mixture of (+)-*ent*-**4c** (R = MOM) and *ent*-**3c** (R = MOM), respectively. Fractionation of the crude by PTLC (40% ethyl acetate in hexane) afforded the title compound (25 mg, 81%) ($[\alpha]^{25}_D$ +51; *c* 2.5, $CHCl_3$). NMR data for (+)-*ent*-**4c** (R = MOM) were consistent with those reported for (±)-**4c** (R = MOM).[3c]

Aldol Adduct (−)-4d (R = Et$_3$Si). The reaction of the Ti(IV) "ate" enolate of (−)-**1d** (R = Et_3Si) (20 mg, 0.048 mmol; 91% ee) with (±)-**2** (27 mg, 0.14 mmol) for 2.5 h according to the above general procedure gave a crude product that by ^{1}H NMR contained a 16:1 mixture of (−)-**4d** (R = Et_3Si) and **3d** (R = Et_3Si), respectively, and (*S*)-aldehyde (ca. 40% ee). Fractionation of the crude by PTLC (20% ethyl acetate in hexane) afforded the title compound (24 mg, 82%) ($[\alpha]^{25}_D$ −67; *c* 2.3, $CHCl_3$). ^{1}H NMR data (500 MHz, $CDCl_3$) for (−)-**4d** (R = Et_3Si) were consistent with those reported for (±)-**4d** (R = Et_3Si):[41] δ 4.84 (1H, br dd, J = 3, 66 Hz), 4.51 (1H, dd, J = 1.5, 6 Hz), 4.09−3.85 (8H, m), 3.19 (1H, br s), 3.12−2.82 (10H, m), 2.78−2.68 (3H, m), 2.63−2.56 (1H, m), 2.48 (1H, br d, J = 13.5 Hz), 2.26 (1H, ddd, J = 1.5, 2.5, 11.5 Hz), 2.11−2.06 (2H, m), 1.96 (1H, ddd, J = 3, 3.5, 9.5 Hz), 1.72 (1H, ddd, J = 3.5, 11, 13.5 Hz), 1.69 (1H, ddd, J = 3.5, 13, 13 Hz), 0.97 (9H, t, J = 8 Hz), 0.65 (6H, ap q, J = 8 Hz).

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Supporting Information Available: Experimental procedures for **1a**−**d** (R = Et_3Si and Ac), **3a**−**d** (R = Et_3Si and Ac), **4a**−**c** (R = Et_3Si and Ac), **4d** (R = Et_3Si), and **5b** (R = Et_3Si); full spectroscopic data and ^{1}H and ^{13}C NMR spectra for all new compounds; determination of the relative configurations for the aldol adducts in Tables 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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