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Enantioselective Direct Intermolecular Aldol Reactions with Enantiotopic Group Selectivity and Dynamic Kinetic Resolution

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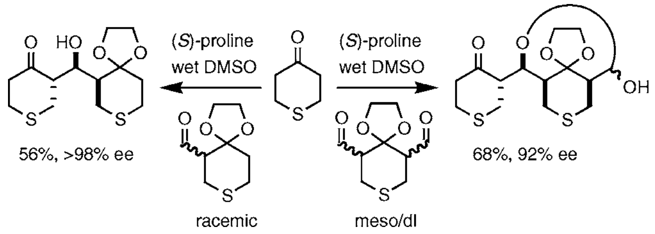
ABSTRACT



Proline-catalyzed aldol reactions of tetrahydro-4*H*-thipyranone with racemic 1,4-dioxa-8-thia-spiro[4.5]decane-6-carboxaldehyde and with *meso/dl* 1,4-dioxa-8-thiaspiro[4.5]decane-6,10-dicarboxaldehyde proceed with dynamic kinetic resolution and give single adducts in good yields with excellent ee's. The high enantiotopic group selectivity results from the high intrinsic diastereoface selectivity of the aldehydes. These reactions significantly extend the scope of the enantioselective direct aldol reaction and constitute simple and efficient syntheses of useful tetrapropionate synthons.

In a landmark paper in 2000, List, Lerner, and Barbas described the first examples of proline-catalyzed enantioselective direct intermolecular aldol reactions.[1] This report prompted an extensive investigation by several groups of the use of proline and its derivatives to catalyze aldol (and other) reactions.[2] Although very high stereoselectivity has been observed in several examples, a major limitation of this process has been the rather narrow substrate scope. The vast majority of examples to date have involved simple achiral reactants. In this contribution, we report that proline-catalyzed aldol reactions of **10** with the racemic aldehydes (±)-**9** or (±)-**19** and/or *meso*-**19** proceed with a combination of enantiotopic group selectivity[3] and dynamic kinetic resolution[4] to give adducts in good yields with excellent stereoselectivities. Conceptually, these reactions significantly extend the scope of the direct aldol reaction and constitute exceedingly simple and efficient syntheses of useful tetrapropionate synthons.

Proline-catalyzed enantioselective aldol reactions were first reported in the 1970s in the context of the Hajos−Parrish−Eder−Sauer−Wiechert reaction (i.e., **1** → **2**; Scheme 1).[5] Recent mechanistic studies have concluded that the reaction

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(1) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396.

(2) Reviews: (a) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481−2495. (b) List, B. *Tetrahedron* **2002**, *58*, 5573−5590. (c) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65−75. (d) List, B. *Acc. Chem. Res.* **2004**, *37*, 548−557. (e) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580−591. (f) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175. (g) List, B. In *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VGH: Weinheim, 2004; Vol. 1, Chapter 4, pp 161−200.

(3) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765−1784.

(4) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291−8327.

(5) (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615−1621. (b) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496−497. Reviews: (c) Cohen, N. *Acc. Chem. Res.* **1976**, *9*, 412−417. (d) Drauz, K.; Kleemann, A.; Martens, J. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 584−608. (e) Martens, J. *Top. Curr. Chem.* **1984**, *125*, 165−246. Also see ref 2a,b.

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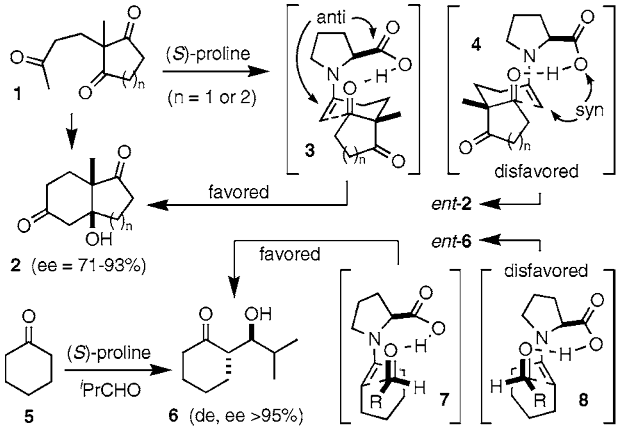
Scheme 1

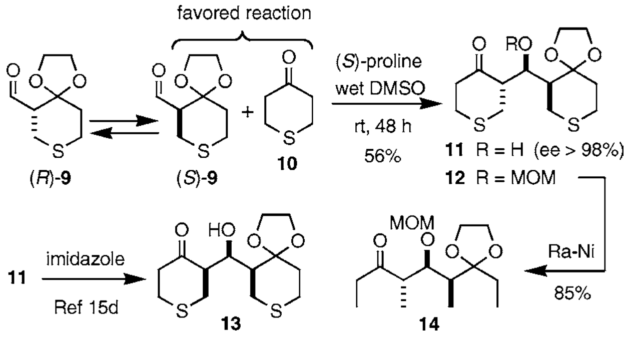


proceeds by intramolecular carboxylic acid catalyzed addition of a proline enamine to the carbonyl group.[6] The transition state structures **3** and **4** for additions to the two cyclic carbonyl groups differ by an *anti* vs *syn* orientation of the enamine, and the enantiotopic group selectivity derives from the greater stability of the *anti* orientation *combined* with the inherent preference for addition *trans* to the quaternary methyl group.[7] The reaction has been applied to acyclic C_S symmetric diketones[8] and dialdehydes,[9] but the stereoselectivity is lower in these cases presumably because of poor enantiotopic group selectivity in the enamine-forming step[10] and/or similar reactivity among the diastereomeric enamines.[7]

The transition state structures proposed for the proline-catalyzed intermolecular aldol reaction (e.g., **5** → **6**) are similar to those for the intramolecular reaction, in this case favoring addition from the *re* face of the β-carbon in an *anti*-oriented enamine to the *re* face of the aldehyde (cf. **7**).[11] It is convenient to consider that face selectivity for addition to the enamine is controlled by the absolute configuration of the proline catalyst and the face selectivity for addition to the aldehyde is dictated by the "closed" transition state. In a similar reaction with a chiral aldehyde, the intrinsic diastereoface selectivity can either reinforce or counteract the face selectivity preferred by this closed transition state (i.e., the influence of a chiral R fragment in TS **7**) resulting in double stereodifferentiation and/or kinetic resolution. Only modest levels of enantiotopic group selectivity have been observed among the scattered examples of proline-catalyzed aldol reactions with chiral aldehyde "acceptors" reported to date.[12,13] We speculated that these reactions might show significant enantiotopic group selectivity and double stereodifferentiation if the aldehyde possessed sufficient diastereoface selectivity.[14]

We have been developing stereoselective sequential two-directional aldol reactions of **9** and **10** as the foundation of a thiopyran-based synthetic route to polypropionates.[15] Aldehyde **9** emerged as a good candidate for enantiotopic group selective direct aldol reaction because additions to its carbonyl group show exclusive Felkin diastereoface selectivity.[15c] A preliminary study established that proline-catalyzed aldol reactions of **10** with simple achiral aldehydes are highly diastereo- and enantioselective.[16] In the event, proline-catalyzed aldol reaction of **10** with (±)-**9** under the previously established conditions[16] gave the expected[17] adduct **11**[18] as a single diastereomer (Scheme 2), albeit in poor yield (33%) and with disappointing enantioselectivity (ca. 50% ee) (Table 1, entry 1).

Scheme 2



The aldol reaction of **9** and **10** was dramatically improved in the presence of added water,[10b,16] and optimization of the conditions with respect to solvent, concentration, stoichi-

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[6] (a) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558−569. (b) List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5839−5842. (c) Clemente, F. R.; Houk, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 5766−5768.

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[9] (a) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785−2788. (b) Mans, D. M.; Pearson, W. H. *Org. Lett.* **2004**, *6*, 3305−3308. (c) Kurteva, V. B.; Afonso, C. A. M. *Tetrahedron* **2005**, *61*, 267−273.

[10] For examples of low stereoselectivity in proline enamine formation from C_S symmetric cyclohexanones, see: (a) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Hibino, K.; Shoji, M. *J. Org. Chem.* **2004**, *69*, 5966−5973. (b) Nyberg, A. I.; Usano, A.; Pihko, P. M. *Synlett* **2004**, 1891−1896.

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[13] Kinetic resolution of racemic substrates is equivalent to an enantiotopic group selective reaction; i.e., groups on enantiomeric substrates are enantiotopic by external comparison. See: Mislow, K.; Raban, M. *Top. Stereochem.* **1969**, *1*, 1−38.

[14] For a discussion of this design strategy, see: Ward, D. E.; Sales, M.; Hrapchak, M. J. *Can. J. Chem.* **2001**, *79*, 1775−1785.

Table 1. Proline-Catalyzed Aldol Reactions of **9** with **10**[a]

entry	[**9**](M)	**10** (equiv)	solvent (equiv of H_2O)	time (days)	yield[b] (%)	$[\alpha]_D$[c]
1	1	3	DMSO	2	33	−22
2	1	3	DMF	2	18	−19
3	1	3	DMF (2)	2	17	−29
4	1	3	DMSO (2)	2	39	−31
5	0.5	3	DMSO (2)	2	19	*d*
6	2	3	DMSO (2)	2	47	−20
7	1	3	DMSO (4)	2	32	−39
8	1	3	DMSO (8)	2	36	−43
9	1	3	DMSO (16)	2	19	−44
10	1	6	DMSO (8)	2	52	−46
11	1	12	DMSO (8)	2	52	−41
12	1	6	DMSO (8)	4	48	−46
13	1	6	DMSO (8)	8	47	−39
14[e]	1	6	DMSO (8)	2	38	−47
15[f]	1	6	DMSO (8)	2	37	−47
16[g]	**1**	**6**	**DMSO (8)**	**2**	**56**	**−47**[h]

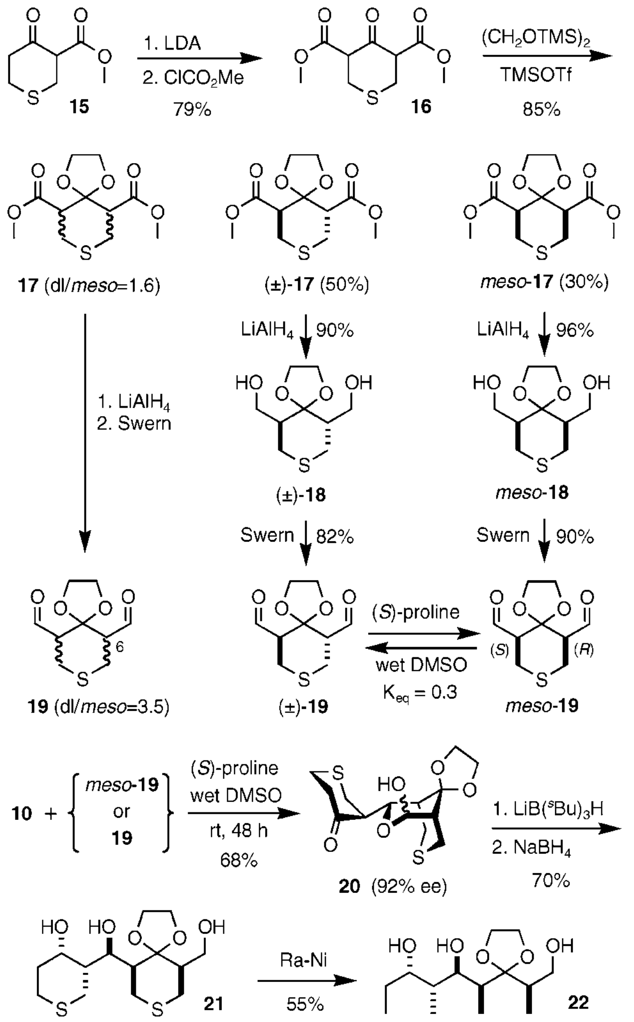
[a] Reactions at room temperature with 50 mg of **9** and 0.5 equiv of (*S*)-proline. [b] Isolated yield of **11**. [c] At ambient temperature (ca. 23°C); c = 1.0, $CHCl_3$; $[\alpha]_D$(max) for **11** = −47. [d] Not determined. [e] 0.25 equiv of (*S*)-proline. [f] 1.0 equiv of (*S*)-proline. [g] 1.0 g of **9**. [h] This sample was shown to be >98% ee by ^1H NMR of the derived **12** in the presence of (+)-Eu(hfc)$_3$.

ometry, and protocol allowed efficient preparation of **11** (56%, >98% ee) on a gram scale (Table 1). We conclude that the reaction is under kinetic control and proceeds with dynamic kinetic resolution rather than simple kinetic resolution because: (i) (−)-**11** (>98% ee) is re-isolated in >85% yield and >90% ee after exposure to (*S*)- or (*R*)-proline (48 h, wet DMSO); (ii) racemic **9** is recovered from the reaction; and (iii) (*S*)-**9**[18] readily racemizes under the reaction conditions. Previously reported examples of dynamic kinetic resolution[12g,h] and of isomerization of aldehydes[12c,f,g] during proline-catalyzed intermolecular aldol reactions have resulted in products with modest stereoselectivity.[19] Thus it is noteworthy that the reaction of (±)-**9** and **10** proceeds with high enantiotopic group selectivity and high aldol stereoselectivity to give the adduct **11** as a single diastereomer with excellent ee.

Aldol **11** is a versatile tetrapropionate synthon that can be utilized as a precursor for both *anti-syn* and *syn-anti* stereotriads because of its differentiated 1,5-dione functionality.[15] We have previously shown[15d] that **11** is readily isomerized to **13** allowing ready access to *syn-syn* stereotriads. Surprisingly,[16] Raney nickel desulfurization of **11** was somewhat capricious; however, reaction of the MOM ether derviative **12** gave **14** in good yield.

Encouraged by these results, we attempted to extend the process to desymmetrization of a meso dialdehyde.[20] Carboxylation of **15**[15c] and protection of the resulting ketodiester **16** gave **17** as a readily separable 1.6:1 mixture of (±)-**17** and *meso*-**17**, respectively (Scheme 3). $LiAlH_4$ reduction of *meso*-**17** followed by careful Swern oxidation of the product diol *meso*-**18** gave *meso*-**19** in good yield. Reaction of **10** with *meso*-**19** under the optimized conditions gave **20** (a 3:1 mixture of anomers in C_6D_6) as the only aldol adduct in 68% yield and 92% ee. The adduct **20** exists exclusively in the

Scheme 3



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(16) Ward, D. E.; Jheengut, V. *Tetrahedron Lett.* **2004**, *45*, 8347−8350.

(17) The relative and absolute configurations of the product correspond to reaction of an (α*S*)-aldehyde via a TS analogous to **7**. The favored addition to the aldehyde *re* face (cf. **7**) corresponds to the favored Felkin selectivity for an (α*S*)-aldehyde but is anti-Felkin for an (α*R*)-aldehyde (e.g., **9** or **13**).

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

(19) For an example of a proline-catalyzed intramolecular aldol cyclization with dynamic kinetic resolution involving (in part) isomerization by aldehyde enolization, see: Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chênevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, S. R.; Ong, B. S.; Press: J. B.; RajanBabu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3210−3213.

hemiacetal form, suggesting that the stereocenter originating from C-6 in **19** could be set under thermodynamic control. Gratifyingly, reaction of **10** with the readily available 3.5:1 mixture of (±)-**19** and *meso*-**19**, respectively, produced **20** in the same yield and ee as when using *meso*-**13** alone.[21] Rapid proline-catalyzed isomerization of *meso*-**19** to give a 3.5:1 equilibrium mixture of (±)-**19** and *meso*-**19**, respectively, was established by ^{1}H NMR.

The selective formation of **20** from *meso*-**19** is readily explained by preferential aldol reaction of **10** with the (α*S*)-aldehyde group of *meso*-**19** (in analogy to the reaction with (±)-**9**).[17] However, **20** might also arise by preferential aldol reaction of **10** with (*S*,*S*)-**19** followed by rapid isomerization and hemiacetal formation. We are unable to distinguish these possibilities; however, in either scenario, the reaction of **10** with **19** occurs with an unusual combination of enantiotopic group selectivity together with dynamic kinetic and thermodynamic resolution. To the best of our knowledge, examples of such reactions have not been previously described. This remarkable process simultaneously generates four stereogenic centers with excellent diastereo- and enantioselectivity. The adduct **20** has versatile functionality and should be a useful tetrapropionate synthon.[22] To illustrate, the ketone and hemiacetal groups in **20** were sequentially reduced to give **21** which gave **22** on desulfurization (Scheme 3).

In summary, proline-catalyzed direct aldol reactions of **10** with the chiral aldehydes **9** and **19** are highly diastereo- and enantioselective. The aldol adducts **11** and **20** are useful tetrapropionate synthons.[15] The remarkable stereoselectivity in these reactions is attributable to combination of the high propensity for addition to the aldehyde *re* face imposed by the (*S*)-proline catalyst together with the high Felkin diastereoface selectivity intrinsic to these aldehydes that results in a strong kinetic preference for the “matched” reaction (i.e., high enantiotopic group selectivity).[14] Because the proline-catalyzed isomerization of the aldehydes is much faster than the aldol, the reactions proceed with dynamic kinetic resolution.[19] This design strategy should be applicable to other substrates in enantioselective direct aldol reactions and significantly expands the scope of this important process.

Acknowledgment. We thank J. Wilson Quail of the Saskatchewan Structural Sciences Center for determination of the X-ray structures of (±)-**20** and (+)-**21**. Financial support from the Natural Sciences and Engineering Research Council (Canada) and the University of Saskatchewan is gratefully acknowledged.

Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds synthesized and X-ray crystallographic data for **20** and **21** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) For examples of desymmetrization of *meso* dialdehydes by aldol reaction, see ref 9 and (a) Oppolzer, W.; De Brabander, J.; Walther, E.; Bernardinelli, G. *Tetrahedron Lett.* **1995**, *36*, 4413−4416. (b) Oppolzer, W.; Walther, E.; Balado, C. P.; De Brabander, J. *Tetrahedron Lett.* **1997**, *38*, 809−812. (c) De Brabander, J.; Oppolzer, W. *Tetrahedron* **1997**, *53*, 9169−9202. For examples using reactions other than aldol, see ref 3.

(21) For kinetic resolution of *meso*/*dl* mixtures, see: Ward, D. E.; How, D.; Liu, Y. *J. Am. Chem. Soc.* **1997**, *119*, 1884−1894.

(22) The stereochemical motif in **20** is present in several polypropionates (e.g., erythromycins, oleandomycin, rutamycin, etc.)