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# A Tandem Organocatalytic α-Chlorination—Aldol Reaction That Proceeds with Dynamic Kinetic Resolution: A Powerful Tool for Carbohydrate Synthesis

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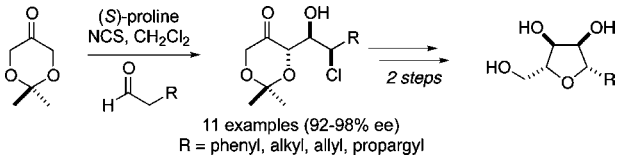
## ABSTRACT




**A tandem, proline-catalyzed α-chlorination/aldol reaction is described that involves a dynamic kinetic resolution of α-chloroaldehyde intermediates. The resulting *syn*-chlorohydrins are produced with good to excellent diastereoselectivity in high enantiopurity and provide new opportunities for the synthesis of carbohydrates.**

Carbohydrates play a vital role in regulating biological events that range from cell recognition to pathogen/host adhesion and are essential components of many biomolecules (e.g., DNA, RNA, and glycoproteins).[1] Not surprisingly, inhibitors of carbohydrate binding and cleaving processes have been identified as leads in various therapeutic areas, and several glycomimetic drugs have been approved for use.[2] Progress in glycomimetic research is often closely tied to advances in the *de novo* synthesis of unnatural carbohydrates, with much success being realized through the use of organocatalytic reactions.[3]

In particular, the pioneering work of List, Lerner, and Barbas III,[4,5] MacMillan,[6] Enders,[7] and others[8] have demonstrated that biomimetic transformations such as aldol reactions involving dihydroxy acetone derivatives can be catalyzed by chiral amines with excellent enantioselectivity (e.g., **1** → **3**,[7a] Scheme 1). These processes facilitate the rapid synthesis of carbohydrates and their analogues, but necessarily require the use of optically pure α-alkoxyaldehydes[7a] (e.g., **2**) or a subsequent aldol reaction (e.g., **6** → **8**).[6] Access to heterocyclic *C*-glycoconjugates, which continue to attract attention as drug leads and biological probes,[9] is also limited by the availability of suitably functionalized aldehydes. Our continued interest in the use of α-chloroaldehydes as building blocks for natural product synthesis[10] led us to probe their organocatalytic aldol reactions with the dioxanone **1**,[5c,7,11−13]

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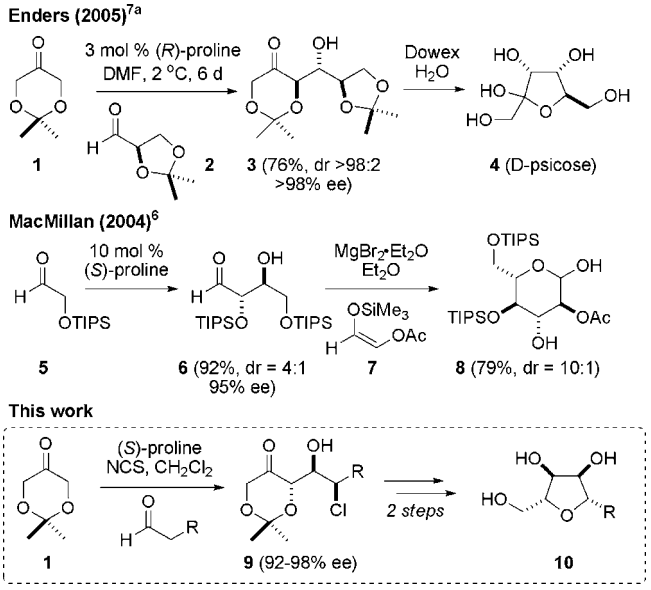
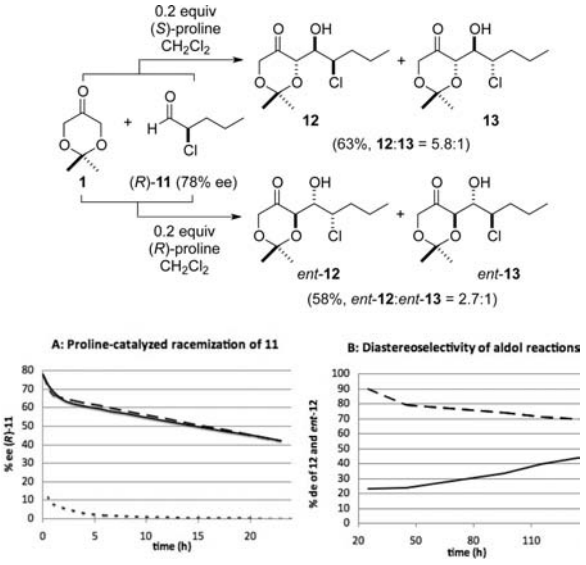
**Scheme 1.** *De Novo* Synthesis of Carbohydrates and a Tandem α-Chlorination–Aldol Reaction with Dynamic Kinetic Resolution




which would provide a launching point for the preparation of various cabohydrates. These efforts resulted in the discovery of a one-pot α-chlorination/aldol reaction that involves the dynamic kinetic resolution of an *in situ* generated α-chloroaldehyde. As described below, this process provides direct access to novel, optically enriched building blocks (e.g., **9**) for the synthesis of carbohydrates and *C*-glycoconjugates.

As depicted in Scheme 2, we first investigated the (*S*)-proline catalyzed reaction of 2,2-dimethyl-1,3-dioxan-5-one (**1**) with (*R*)-2-chloropentanal (**11**) (78% ee), prepared following Jørgensen's α-chlorination protocol.[14b] We were delighted to find that this double diastereodifferentiating[15] aldol reaction produced a ca. 6:1 mixture of the chlorohydrins **12** and **13** (63% yield), respectively.[16] Surprisingly, when the reaction was repeated with (*R*)-proline catalysis,

**Scheme 2.** Proline-Catalyzed Aldol Reactions of 2-Chloropentanal




enantiomeric chlorohydrins were produced in similar yield and only slightly diminished diastereoselectivity, with the major product (*ent*-**12**) bearing the opposite configuration at the chloromethine stereocenter to that of the starting chloroaldehyde (*R*)-**11**. As we suspected the proline catalysts effected racemization of chloroaldehyde (*R*)-**11** during the course of these reactions,[14c] a sample of (*R*)-**11** was treated independently with (*S*)-proline (Scheme 2, Chart A, solid line) and (*R*)-proline (Chart A, long dash), and its enantiomeric excess was monitored over time. As depicted in Chart A, both antipodes of proline were equally efficient at promoting racemization of (*R*)-2-chloropentanal (**11**), with samples of the latter substance degrading to 40% ee over the course of one day. Likewise, a sample of (*R*)-**11** prepared by (*S*)-proline-catalyzed chlorination of pentanal (20% ee) was racemic after 10 h of stirring with (*S*)-proline (Chart A, short dash).

Based on the sense of diastereoselectivity in the aldol reactions depicted in Scheme 2, there is an inherent substrate bias for the reaction of the α-chloroaldehyde (*R*)-**11** with the chiral enamine derived from (*S*)-proline.[17,18] While it is well documented that proline-catalyzed aldol reactions involving dioxanone **1** are highly selective for *anti*-aldol products[7] as predicted by the Houk–List model,[7a,19] the observed *syn*-chlorohydrin selectivity is opposite to that expected from Evans–Cornforth models of stereoinduction.[20] A potential explanation for the preferential reaction of (*R*)-chloropentanal with the (*S*)-proline-derived

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(12) For cross aldol reactions involving α-chloroaldehydes where the chloromethine is directly reduced following the reaction, see: Kano, T.; Sugimoto, H.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 18130.

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(14) For the asymmetric α-chlorination of aldehydes, see: (a) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108. (b) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790. (c) Amatore, M.; Beeson, T. D.; Brown, S. P.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5121.

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(16) See Supporting Information for full details.

(17) For an example of kinetic resolution in the reaction of a racemic α-chloroaldehyde with a chiral enolate, see: Shinoyama, M.; Shirokawa, S.-i.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2009**, *11*, 1277.

(18) For examples of aldol reactions that proceed with kinetic resolution, see: Ward, D. E.; Becerril-Jimenez, F.; Zahedi, M. M. *J. Org. Chem.* **2009**, *74*, 4447 and references cited therein.

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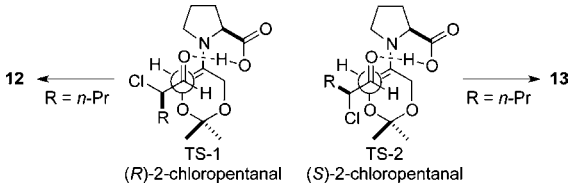
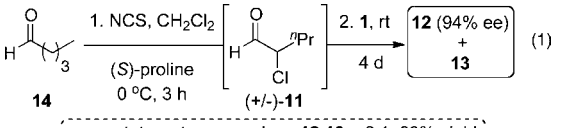



**Figure 1.** Potential Houk–List transition structures leading to aldol adducts **12** and **13**.

enamine (TS-1, Figure 1) involves avoidance of steric interactions as well as the destabilizing electrostatic interactions that exist between the Cl and O atoms in the merged Evans–Cornforth/Houk–List model (TS-2). The diastereomeric excess of both aldol adducts **12** and *ent*-**12** was also found to change considerably throughout the course of the reactions (Scheme 1, Chart B), further indicating that racemization of α-chloroaldehyde (*R*)-**11** is competitive with the desired aldol reaction. Importantly, these results confirm that the proline-catalyzed aldol reaction between dioxanone **1** and (*R*)-2-chloropentanal (**11**) proceeds via a dynamic kinetic resolution (DKR)[21] of the α-chloroaldehyde.

Based on the observations detailed above, we investigated one-pot variations of the reaction described in Scheme 2 (top) in which proline-catalyzed aldehyde chlorination is followed directly by a DKR proline-catalyzed aldol reaction. As depicted in eq 1, (*S*)-proline catalyzed chlorination of pentanal was complete in 3 h (ee ≈ 15%), after which time the dioxanone **1** was added directly to the reaction mixture. Alternatively, the experimental protocol could be further simplified by adding all reagents together at once. In both cases, this tandem process delivered the aldol adduct **12** in good yield, diastereoselectivity (dr = 5:1), and enantiopurity (94% ee).




As summarized in Table 1, we next surveyed reaction conditions in an effort to decrease the reaction time and probe the effect of solvent on both diastereoselectivity and yield of **12**. When the reaction depicted in eq 1 was repeated at −15 or 0 °C, very little product was formed, while increasing the temperature above 20 °C resulted in significant degradation of the α-chloroaldehyde (entries 1–4).

**Table 1.** Optimization of One-Pot α-Chlorination/Aldol Reaction[a]

| entry | solvent | (*S*)-proline (equiv) | temp (°C) | time (h) | yield (%)[b] | **12**:**13**[c] |
|---|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 0.2 | −15[d] | 72 | 0 | – |
| 2 | $CH_2Cl_2$ | 0.2 | 0 | 144 | 36 | 6:1 |
| 3 | $CH_2Cl_2$ | 0.2 | 20 | 144 | 55 | 5:1 |
| 4 | $CH_2Cl_2$ | 0.2 | 30 | 72 | 13 | nd[e] |
| 5 | $CH_2Cl_2$[f] | 0.2 | 20 | 48 | 49 | 6:1 |
| 6 | $CH_2Cl_2$ | 1.2 | 20 | 24 | 63 | 4:1 |
| 7 | $CH_2Cl_2$ | 0.8 | 20 | 24 | 72 | 6:1 |
| 8 | DCE | 0.8 | 20 | 24 | 51 | 2.6:1 |
| 9 | THF | 0.8 | 20 | 24 | 34 | 2.6:1 |
| 10 | $PhCH_3$ | 0.8 | 20 | 24 | 32 | 3.8:1 |
| 11 | MeCN | 0.8 | 20 | 24 | 63 | 1.5:1 |
| 12 | EtOAc | 0.8 | 20 | 24 | 49 | 2.2:1 |

[a] Reaction conditions: Pentanal (1 equiv), **1** (1.05 equiv), NCS (1.05 equiv), and (*S*)-proline (0.8 equiv) added to solvent (≈0.2 M) at 0 °C and allowed to warm gradually to designated temperature. [b] Combined isolated yield of **12** and **13**. [c] From analysis of $^1$H NMR spectra recorded on crude reaction mixtures. [d] Reaction maintained at −15 °C. [e] Not determined. [f] 0.5 equiv of $H_2O$ added.

As $H_2O$ has been reported to accelerate organocatalytic aldol reactions,[3,22] the addition of 0.5 equiv of $H_2O$ was also examined (entry 5) and the reaction time was reduced without significantly impacting the overall yield or diastereoselectivity.[23] Increasing the amount of (*S*)-proline to 1.2 equiv further reduced the reaction time to 24 h, albeit with a slight decrease in diastereoselectivity. While the entire process can be promoted effectively by 0.2 equiv of (*S*)-proline (entry 3), optimally, the use of 0.8 equiv of (*S*)-proline delivered the aldol adducts **12** and **13** in a combined yield of 72% in 24 h (entry 7). Notably, following the conditions described in entry 7, this reaction could be run on multigram scale without a decrease in yield, diastereoselectvity, or product enantiopurity. As summarized in entries 8 to 12, a variety of solvents were also examined. Notably, access to significant quantities of the *anti*-chlorohydrin **13** could be gained by simply using MeCN (entry 11), in which near equal amounts of the diastereomeric aldol adducts were produced in 63% yield.

Having identified an optimal set of reaction conditions for the formation of the aldol adduct **12** (Table 1, entry 7), we next evaluated the scope of this one-pot reaction. As highlighted in Figure 2, 10 additional aldehydes were reacted with dioxanone **1** and NCS in the presence of (*S*)-proline, providing a range of enantiomerically enriched and functionally diverse chlorohydrins **16a**–**j**. The diastereoselectivity of these reactions ranged from modest to excellent depending on the electronic and steric features of the aldehyde. For example, in the series propanal → butanal → pentanal, the diastereomeric ratio of the resulting chlorohydrins increases from 2.5:1 (**16a**) to 3.8:1 (**16b**) to 6:1 (**12**). As exemplified by the reaction of

(20) (a) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112. (b) Cee, V. J.; Cramer, C. J.; Evans, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 2920.

(21) For examples of organocatalytic dynamic kinetic resolutions, see: (a) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 659. (b) Ward, D. E.; Jheengut, V.; Akinnusi, O. T. *Org. Lett.* **2005**, *7*, 1181. (c) Reyes, E.; Cordova, A. *Tetrahedron Lett.* **2005**, *46*, 6605. (d) Ward, D. E.; Jheengut, V.; Beye, G. E.; Gillis, H. M.; Karagiannis, A.; Becerril-Jimenez, F. *Synlett* **2011**, 508.

(22) Zotova, N.; Franzke, A.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2007**, *129*, 15100.

(23) Other additives that had little effect on the diastereoselectivity or yield of this process include $H_2O$, succinimide, and benzoic acid.

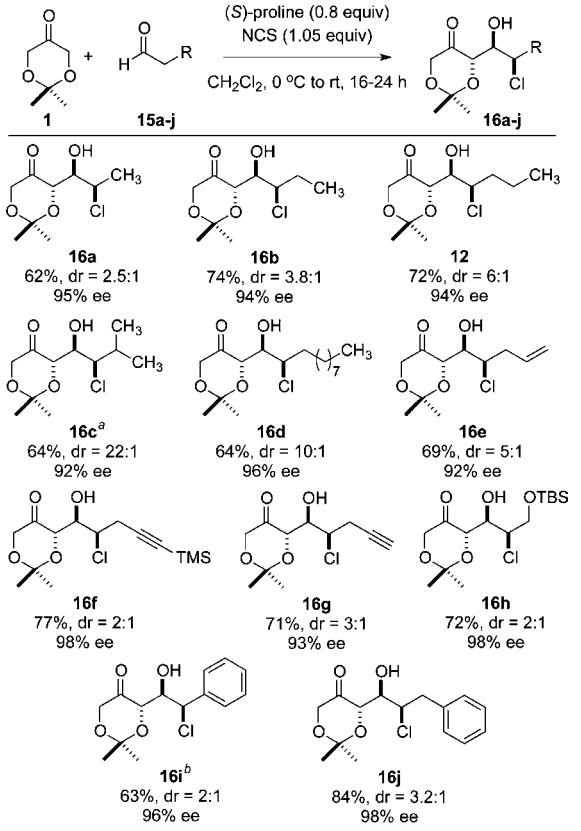
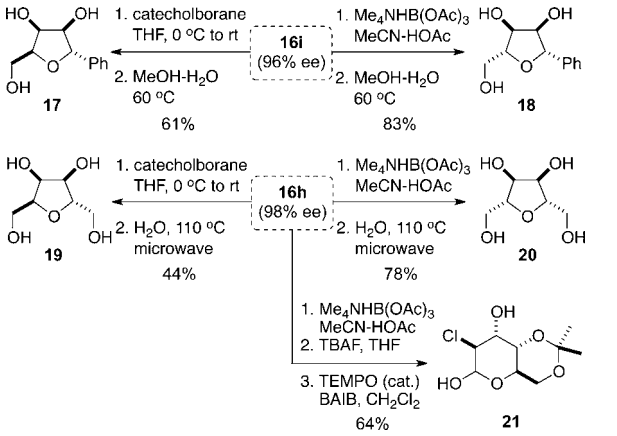



**Figure 2.** Scope of proline-catalayzed chlorination/aldol reaction (combined isolated yield). [a] Reaction carried out at 5 °C for 16 h. [b] Reaction carried out at 0 °C for 48 h.

isovaleraldehyde, the incorporation of a branching position adjacent to the cholormethine stereocenter also led to increased diastereoselectivity (**16c**, dr = 22:1) without significantly impacting the overall yield of the process. Remarkably, reactions involving the silyl protected 3-hydroxypropanal or phenylacetaldehyde both afford the corresponding chlorohydrins **16h** and **16i** in excellent enantiopurity. These results are notable since we have not been able to effect the asymmetric α-chlorination[14] of either aldehyde. While the reactions depicted in Figure 2 generally proceed with excellent enantioselectivity at 20 °C, both that of isovaleraldehyde and phenylacetaldehyde provided the corresponding chlorohydrins **16c** and **16i** in 86% ee and 78% ee, respectively, at rt. In both cases, however, repetition of the reaction at lower temperatures (0 or 5 °C) significantly improved the enantiopurity of these products.

Finally, with direct access to the unique series of enantiomerically enriched chlorohydrins **16a**–**j** (Figure 2), several of these compounds were converted into carbohydrate analogues and *C*-glycoconjugates (Scheme 3). Building on our previous efforts in the preparation of tetrahydrofurans from ketochlorohydrins,[10e,f] each of the aldol adducts **16i**, **16h**, and **16g** were reduced in either a

**Scheme 3.** Conversion of Aldol Adducts **16i**, **16h**, and **16g** into Carbohydrate Analogues




1,3-*syn*- or 1,3-*anti*-selective manner and heated in a mixture of MeOH–$H_2O$ to effect cyclization to the corresponding D-ribose analogues **17**–**20** and **22**. Impressively, this methodology permits the *de novo* synthesis of these carbohydrates in excellent optical purity in only three steps from commercially or readily available aldehydes. Furthermore, the protected 2-chloro-2-deoxyaltrose **21** was produced from the 1,3-*syn* reduction product (not shown) of aldol adduct **16h** by simple deprotection and oxidation of the resulting primary alcohol function.

In summary, we have developed a robust, asymmetric organocatalytic aldehyde chlorination/aldol process that proceeds with dynamic kinetic resolution of *in situ* formed α-chloroaldehydes. This sequence of reactions proceeds with modest to excellent levels of diastereoselectivity, favoring the formation of *syn*-chlorohydrin products with high enantiopurity. Importantly, this process avoids the isolation and purification of α-chloroaldehydes and is sufficiently general to allow incorporation of branched alkyl, aryl, propargyl, and benzyl groups adjacent to the chloromethine stereocenter. The products of this reaction are excellent building blocks for the synthesis of carbohydrates and *C*-glycoconjugates as demonstrated by the formation of several derivatives of D-ribose and 2-deoxy-2-chloroaltrose. These aldol adducts should also find use in the preparation of other classes of natural products and glycomimetics, work that is ongoing in our laboratory.

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**Supporting Information Available.** Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.