

Aldol-Type Chirons from Asymmetric
Hydrogenations of Trisubstituted
Alkenes

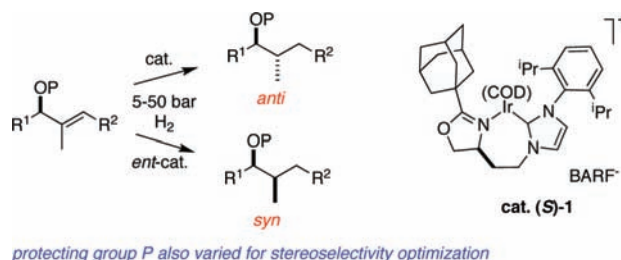
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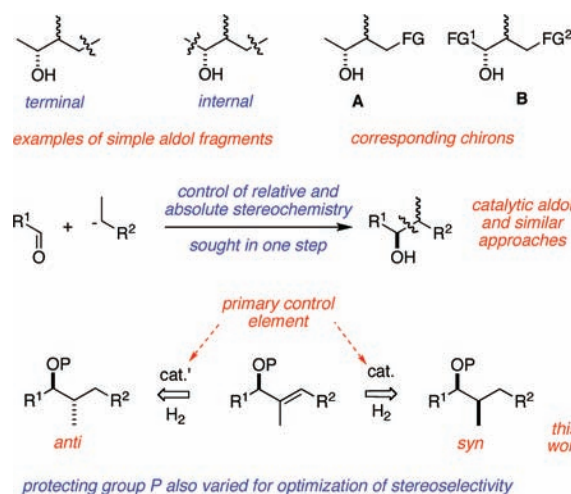
Received February 12, 2009

ABSTRACT



Catalyst control dominates in the asymmetric hydrogenations of largely unfunctionalized trisubstituted alkenes formed from lactic acid and glyceraldehyde, affording *syn*- and *anti*-aldol products of the type shown above.

Innumerable natural products synthesized over the past three decades contain polypropionate-derived fragments.¹ These entities can be situated at chain termini or internally, and many correspond to the generic chirons **A** and **B**, i.e., building blocks that can be elaborated in one or two directions, respectively. The state-of-the-art approach for preparation of chirons like these has shifted from diastereoselective aldol reactions involving chiral auxiliaries,² to catalytic enantioselective ones.^{3–6} However, the latter approach is challenging because both relative and absolute stereochemistries of *two* new chiral centers need to be controlled in a single, C–C bond-forming step.



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This paper describes an alternative to the strategy described above. It involves stepwise introduction of stereocenters: hydrogenation of chiral *trisubstituted* alkenes derived from readily available chiral starting materials. This approach is viable because excellent conversions and high levels of *catalyst*-control are possible using chiral analogs of Crab-

Table 1. Hydrogenation of Lactic Acid Derivatives **4**

| entry | | substrates 4 | | 1 | H ₂ (bar) | <i>syn/anti</i> ^a (crude material) |
|-------|----------|---------------------|------------------------|----------|----------------------|---|
| | | P | FG | | | |
| 1 | a | H | CO ₂ Et | R | 50 | 1.0:2.0 |
| 2 | | | | S | 50 | 61:1.0 |
| 3 | b | MOM | CO ₂ Et | R | 5 | 1.0:10 |
| 4 | | | | S | 5 | 27:1.0 |
| 5 | c | MOM | CH ₂ OH | R | 5 | 1.0:10 |
| 6 | | | | S | 5 | 16:1.0 |
| 7 | d | MOM | CH ₂ OTBDPS | R | 20 | 1.0:1.2 |
| 8 | | | | S | 20 | 14:1.0 |

^a Reactions run to >99% conversion. Conversions and enantiomeric excesses determined via GC on a chiral column.

tree's Ir-complexes^{7–12} like (*S*)-**1**.^{13,14} Stereoselective hydrogenations of chiral allylic alcohols were investigated extensively about two decades ago.^{15–} However, those reactions were all *substrate*-controlled, so it was not possible to obtain *syn*- and *anti*-aldol fragments by varying the catalyst chirality. Here it was possible to do that; hence, some important chirons were produced with high levels of catalyst control using 0.5 mol % of complex **1**; the syntheses are practical and potentially scalable with minimal optimization.

Before the current studies began, we had already reported moderate enantioselectivities for ethyl tiglate **C** and the corresponding alcohol **D**; both these substrates have an α-methyl group adjacent to the ester or hydroxymethylene group.¹⁸ In the current work, we discovered that much better enantioselectivities were obtained for substrates **2** and **3** where the methyl group is attached to the β-carbon of the alkene (100% conversion at 0.5 mol% (*S*)-**1**, 25 °C, 6 h; **2**, 5 bar H₂; **3**: 25 bar H₂), as outlined below.



Substrates **4a–d** were prepared to expand the scope of the discovery outlined above in the context of preparing chirons **A** (Table 1). Largely inconsequential changes were made to the protecting group “P” and the functional group

to optimize the diastereoselectivities in either direction, i.e., so that either the *syn* or the *anti* diastereomers could be obtained. Pressure can influence enantioselectivities in hydrogenations of some substrates with catalyst **1**, but that was not the case here; the main objective of varying it for substrates **4** was to achieve >99% conversion within 12 h.

All of the data in Table 1 indicate hydrogenation of **4** is catalyst controlled, but the substrate vector is also influential. Excellent *syn* selectivities could be obtained, with entry 2 being best of those studied. After flash chromatography of the material corresponding to entry 2, the *syn/anti* ratio was >99:1.0 (75% yield). The best crude selectivity for the *anti* isomer was 10:1.0 (entries 3 and 5); the material from the experiment represented by entry 3 was purified by flash chromatography giving 68% isolated yield of 1.0:31 *syn/anti* material.¹⁷

An interesting difference emerges when comparing the data for the “β-methyl” substrates in Table 1 (cf. Figure 1a) with similar “α-methyl” alkenes. Relatively many compounds of the latter type have been studied in our group,^{18–21} and two illustrative examples are given in Figure 1b. In all cases of the later type, carbonyl derivatives (like the ester shown) give opposite face selectivities relative to primary alcohol and ether compounds. This has been explained in terms of a catalyst vector (usually dominant) that involves

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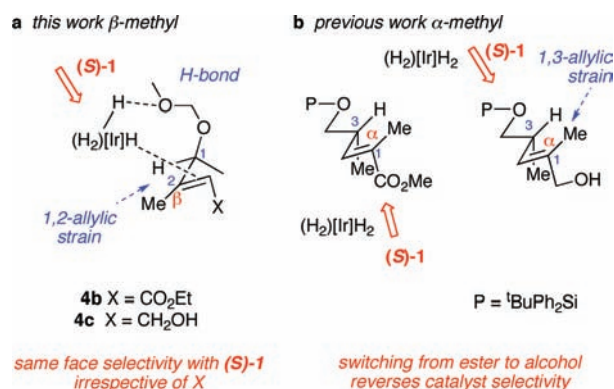


Figure 1. Substrates with an α -methyl group respond differently to the catalyst relative to those with a β -methyl group.

transient Ir coordination to the ester carbonyl in the catalytic cycle, and a substrate vector dictated by 1,3-allylic strain effects.¹⁸ The β -methyl of the alkenes in Table 1 may disfavor Ir coordination to the ester, changing the catalyst vector, while 1,2-strain effects govern the substrate one. The net effect of all these issues is that the selectivity for the β -methyl substrates is not affected by peripheral functional groups in the same way that the α -methyl substrates are.

Optically pure glycitol acetone was transformed into substrates **5a–c** for access to chirons **B** (Table 2). Again,

obtained from the *E*-alkene **5a** (entry 1; 40:1.0 *syn/anti* and 84% yield after chromatography). Excellent *anti*-selectivity was obtained from the same substrate simply by using the enantiomeric catalyst (entry 2; 1.0:53 *syn/anti* and 78% yield after chromatography), and even better control was achieved via the *Z*-alkene (entry 3) and the allylic alcohol (entry 6).

DIBAL-H reduction of the products obtained from entries 1 and 2, benzylation (BnBr, NaH), and removal of the acetonide (HOAc/H₂O) gave chirons **6a** and **6b**. Glycitol acetonide is available as both enantiomers, so the optical antipodes of these chirons are also accessible via this route. These chirons have been used in syntheses of pectenotoxins,^{22,23} azinotricins,²⁴ and halichorine.²⁵ Generally, they have been made via opening of Sharpless' epoxidation products²⁶ using trimethylaluminum. We believe the method shown here is safer, greener, more scalable, and equally practical; it should facilitate wider applications of these materials.



Looking forward, we are interested in developing hydrogenations of trisubstituted alkenes to access stereochemical triads and higher homologues based on aldol products. Toward that end, Scheme 1 outlines how manipulation of

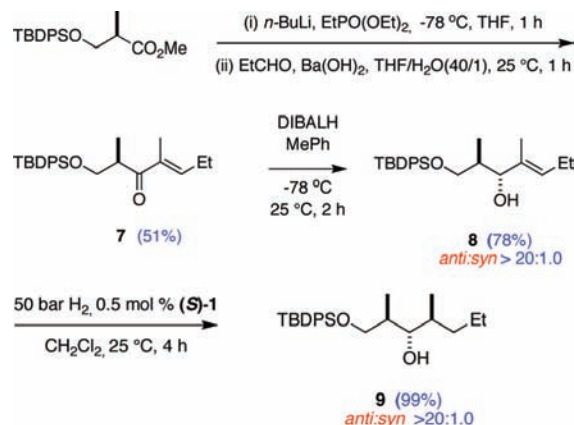
Table 2. Hydrogenation of Glycitol Derivatives **5**

| entry | alkenes 5 | I | H ₂ (bar) | <i>syn:anti</i> ^a (crude material) |
|-------|------------------|----------|----------------------|---|
| 1 | a | R | 5 | 25:1.0 |
| 2 | | S | 5 | 1.0:26 |
| 3 | b | R | 5 | 1.0:>99 |
| 4 | | S | 5 | 1.0:1.7 |
| 5 | c | R | 50 | 10.0:1.0 |
| 6 | | S | 50 | 1.0:40 |

^a Reactions run to >99% conversion. Conversions and enantiomeric excesses determined via GC on a chiral column.

elevated pressures were used in some cases to drive the reactions to completion. All the transformations were catalyst controlled except those shown in entries 3 and 4. 1,3-Allylic strain considerations apparently accentuated the substrate vector in the latter reactions. The best *syn*-selectivity was

Scheme 1. Preparation of the *anti,anti*-Chiron **9**



Roche ester derivatives can give substrates like **8** that can then be hydrogenated with very high diastereoselectivities to afford the valuable chiron **9**.²⁷

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The hydrogenations described here have several attributes. They are catalytic, high stereoselective, and afford chirons that should be valuable for preparations of many polyketide-derived natural products.

Acknowledgment. We acknowledge Dr. Jianguang Zhou for some preliminary experiments. Financial support for

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this work was provided by the National Science Foundation (CHE-0750193) and the Robert A. Welch Foundation.

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

OL900308W