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Asymmetric Hydrogenation Approaches to Valuable, Acyclic 1,3-Hydroxymethyl Chirons

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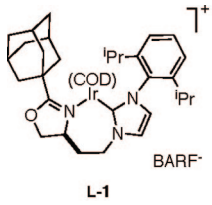
Research into directed hydrogenations for acyclic stereocontrol peaked in the 1980s.[1] Much of that work involved 1,1-disubstituted alkenes that are sterically noncongested and easy to hydrogenate. Examples involving trisubstituted alkenes are rarer and tend to feature homoallylic alcohols.[2] In these cases, high diastereoselectivities are possible because simultaneous coordination of the metal to the hydroxyl and alkene gives rigid, chairlike intermediates. However, there are relatively few examples of useful acyclic stereocontrol in hydrogenations of trisubstituted alkenes that are allylic alcohols, or where no alcohol at all is present. There is a good reason for this. Most of the work on directed hydrogenations has featured rhodium and iridium catalysts of the type MP_2 where P_2 is a chelating diphosphine ligand, and these do not hydrogenate trisubstituted alkenes at a significant rate if a directing group is not present. This is not so, however, for Crabtree's catalyst[3–6] and analogues of the IrN,P type (N,P = sp^2-N ligand and phosphine); they can hydrogenate trisubstituted and even tetrasubstituted alkenes where there are no apparent directing groups.[7] Few investigations of acyclic stereocontrol, however, have focused on Crabtree's catalyst,[8,9] and in those, the stereoselectivities obtained were poor. No studies on acyclic stereocontrol have featured optically active analogues of this catalyst; indeed, the first of these complexes was not reported until 1998.[10] This is a significant gap in the literature because chiral catalysts can constructively couple with substrate biases (matching effects),[11] and these catalysts, unlike diphosphine systems for the same substrates, can exert strong influences.[12–14] This communication describes applications of these concepts in hydrogenations mediated by complex **1** to afford the "internal" and "terminal" chirons **A** and **B** found in many natural products and useful derivatives.



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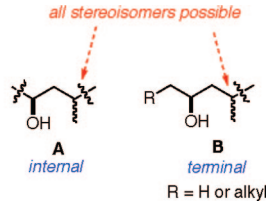

Syntheses of substrates to prepare the internal fragments **A** began with glycidol acetonide (conveniently available as either enantiomer).[15] Hence compounds **2**, **4**, and some other esters and allylic alcohols were prepared. Several of these were hydrogenated; only the best data are shown here. The substrate that corresponds to **2** but with the alcohol and silyl ether groups juxtaposed did not give high selectivities (not shown), but excellent data were obtained for **2** and **4** (Figure 1).

Formation of the *syn* product **3** is an excellent reaction because this lactone is crystalline and it can be recrystallized from the crude material without column chromatography. In both reactions, the diastereoselectivity is extremely high. A chairlike intermediate can

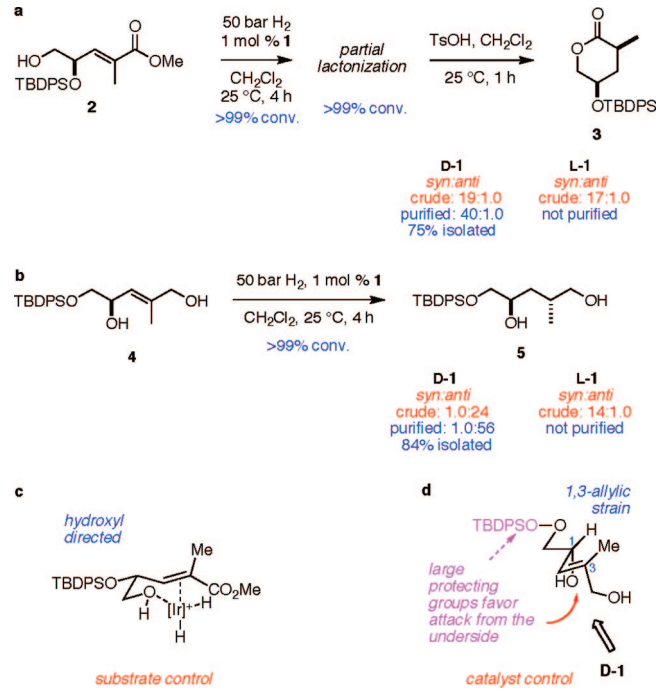

Figure 1. Preparation of (a) a *syn*-type **A** chiron, and (b) an *anti*-type **A** chiron. All ratios quoted are from GC. (c) Directed hydrogenation model gives substrate control, and (d) catalyst control dominates where the substrate conformation is only held by 1,3-allylic strain.

be used to rationalize preferential formation of the product **3**, so this is a typical directed hydrogenation of a homoallylic alcohol via *substrate* control (Figure 1c). Formation of **5**, however, is *catalyst*-controlled. In that case, there is a substrate vector based on conformers preferred by 1,3-allylic strain considerations and possibly some directing effect from the allylic alcohols; however, these two factors modulate, but do not overcome, the catalyst vector.

A similar approach was used to obtain optically pure *syn*- and *anti*-isomers corresponding to the terminal fragment **B**, except that lactic acid was the starting material. Seven relevant substrates were prepared and tested, but the discussion here is limited to hydrogenation of the two that gave the highest *syn* and *anti* selectivities, that is, **6** and **8** (Figure 2). Catalyst control dominated for substrate **6**, and the optimal stereoselectivity was obtained when the 1,3-allylic strain vector from the substrate matched with the preferred approach of the catalyst (Figure 2c). Hydrogenation of **8** was substrate controlled. In this example, the alkene is quite hindered. The simplest explanation for the observed selectivity is in terms of directed attack resulting from coordination to the allylic alcohol. This could occur via oxygen coordinating with iridium or via hydrogen bonding from an iridium hydride to the allylic alcohol oxygen.[16,17] The latter is possible since recent observations from our group indicate the iridium complex is slightly acidic.[18]

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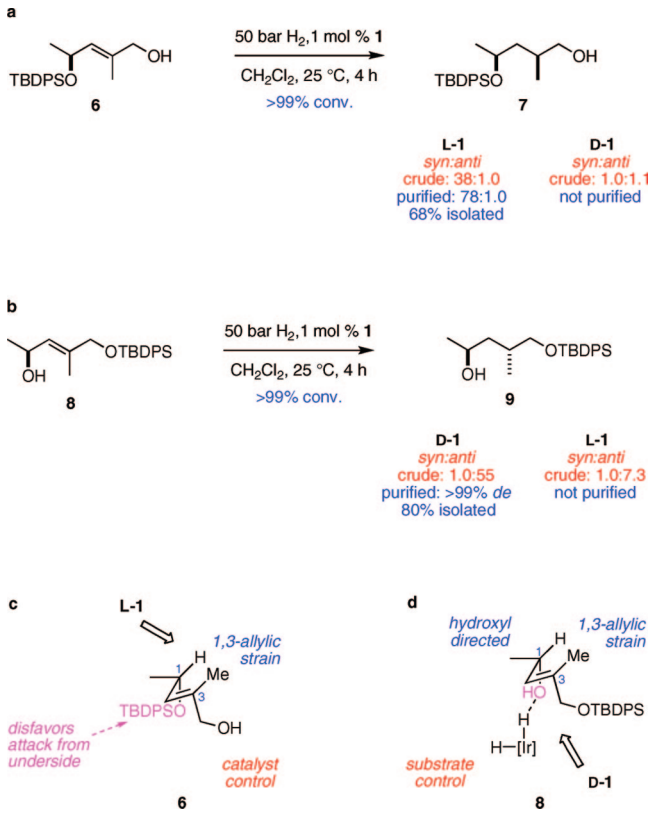
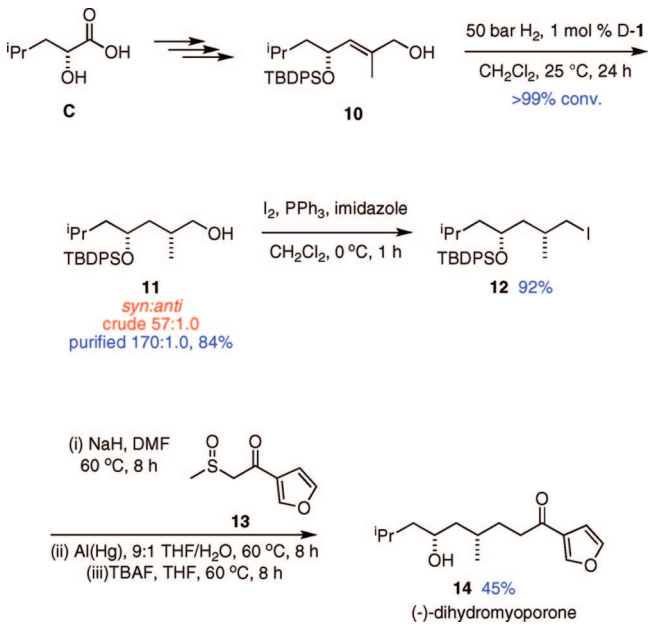


Figure 2. Preparation of type **B** chirons: (a) a *syn*-form, and (b) an *anti*-form. All ratios quoted are from GC. (c) Catalyst control dominates where the substrate conformation is only held by 1,3-allylic strain, and (d) substrate control prevails for substrate **8**.

Scheme 1. Total Synthesis of (−)-Dihydromyoporone



A synthesis of (−)-dihydromyoporone **14**[19,20] was performed to illustrate that α-hydroxyacids other than lactic could be used to build terminal 1,3-hydroxymethyl chirons. Thus the allylic alcohol **10** was prepared from commercially available (*R*)-2-hydroxy-4-methylpentanoic acid **C** via a series of standard steps (see Supporting Information). Hydrogenation of this under our standard conditions gave the crude alcohol in excellent diastereoselectivity. The *iso*-butyl-for-methyl substitution that connects Figure 2c with the hydrogenation in Scheme 1 had no adverse effect on the stereoselectivity. After flash chromatography, the desired product was isolated in high yield, and the diastereomeric impurity was hardly perceptible by GC. Formation of the iodide **12**, homologation with sulfoxide **13**, reduction, then deprotection afforded the product **14**.

This communication attempts to convey several key points. First, constructive matching of chiral Crabtree's catalyst analogues with stereochemical vectors from substrates can afford high diastereoselectivities, even in cases where Ir− or Rh−*diphosphine* complexes would probably give poor conversions and/or selectivities. We have previously observed *catalyst* control dominating hydrogenation of some substrates leading to deoxypolyketides.[12–14] The fact that this is not uniformly so here enhances the scope of the approach; mechanistic complementarities enabled all stereoisomers of the ubiquitous chiral fragments **A** and **B** to be made. Reactions that gave lesser selectivities but led to the development of these highly stereoselective processes will be described in a full account of this work, along with other applications.

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Supporting Information Available: Experimental procedures for the preparation of compounds **2** to **14**, details of the determination of enantiomeric excesses, and assignments of absolute configurations. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Brown, J. M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 190–203.
(2) Evans, D. A.; Morrissey, M. M.; Dow, R. L. *Tetrahedron Lett.* **1985**, *26*, 6005–6008.
(3) Crabtree, R. H.; Felkin, H.; Morris, G. E. *Chem. Commun.* **1976**, 716–717.
(4) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *141*, 205–215.
(5) Crabtree, R. H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *135*, 395–403.
(6) Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331–337.
(7) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272–3296.
(8) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866–3868.
(9) Evans, D. A.; Morrissey, M. M. *Tetrahedron Lett.* **1984**, *25*, 4637–4640.
(10) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897–2899.
(11) Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–30.
(12) Zhou, J.; Burgess, K. *Org. Lett.* **2007**, *9*, 1391–1393.
(13) Zhou, J.; Ogle, J. W.; Fan, Y.; Banphavichit, V.; Zhu, Y.; Burgess, K. *Chem.—Eur. J.* **2007**, *13*, 7162–7170.
(14) Zhou, J.; Burgess, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1129–1131.
(15) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437.
(16) Crabtree, R. H. *Science* **1998**, *282*, 2000–2001.
(17) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*, *4*th ed.; Wiley: New York, 2005.
(18) Zhu, Y.; Burgess, K. *Adv. Synth. Catal.* **2008**, *350*, 979–983.
(19) Johnson, W. S.; Crackett, P. H.; Elliott, J. D.; Jagodzinski, J. J.; Lindell, S. D.; Natarajan, S. *Tetrahedron Lett.* **1984**, *25*, 3951–3954.
(20) Still, W. C.; Darst, K. P. *J. Am. Chem. Soc.* **1980**, *102*, 7385–7387.

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