Asymmetric Catalysis

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α,ω-Functionalized 2,4-Dimethylpentane Dyads and 2,4,6-Trimethylheptane Triads through Asymmetric Hydrogenation**

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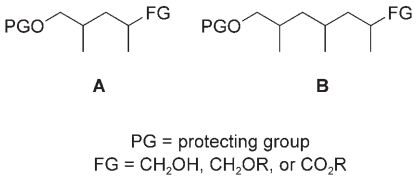
In memory of Vorawit Banphavichit (Bee)

Chiral analogues of the Crabtree catalysts,[1] [Ir(cod)(py)-(PR_3)PF_6] (that is, [M(*N*,*P*)*] systems; cod = cycloocta-1,5-diene, py = pyridine) are excellent enantioselective catalysts for hydrogenation reactions of trisubstituted alkenes,[2] and have been used extensively to reduce alkenes that are largely unfunctionalized insofar as they do not contain strongly coordinating groups.[3,4] Consequently, asymmetric hydrogenations are potentially possible for a broad range of substrates for which most other chiral catalysts are not effective.

Nearly all the substrates studied so far in hydrogenation reactions mediated by chiral analogues of the Crabtree catalyst give relatively simple products. To access more sophisticated chirons we launched a program to study hydrogenations of dienes and polyenes,[5–7] and Pfaltz and co-workers recently described the reduction of a 1,5,9-triene to give (*R*,*R*,*R*)-tocopherol.[8] This latter study stands out as the most synthetically useful application of the chiral Crabtree catalysts to date. Although formally a diastereoselective synthesis, the preexisting chiral center in the substrate was too far away from the nearest alkene to affect face selectivity. In fact, none of the research on chiral analogues of the Crabtree catalysts has systematically studied chiral substrates in which the chiral center is close enough to influence the stereochemical outcome. Herein we describe the first such study.

Our goal was to use the carbene oxazoline complex **1**[9,10] to prepare the α,ω-functionalized 2,4-dimethyl and 2,4,6-trimethyl stereochemical dyads and triads **A** and **B**



Scheme 1. α,ω-Functionalized 2,4-dimethyl and 2,4,6-trimethyl stereochemical dyads and triads.

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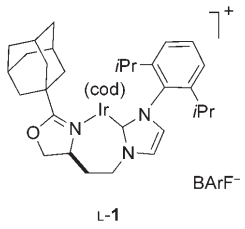
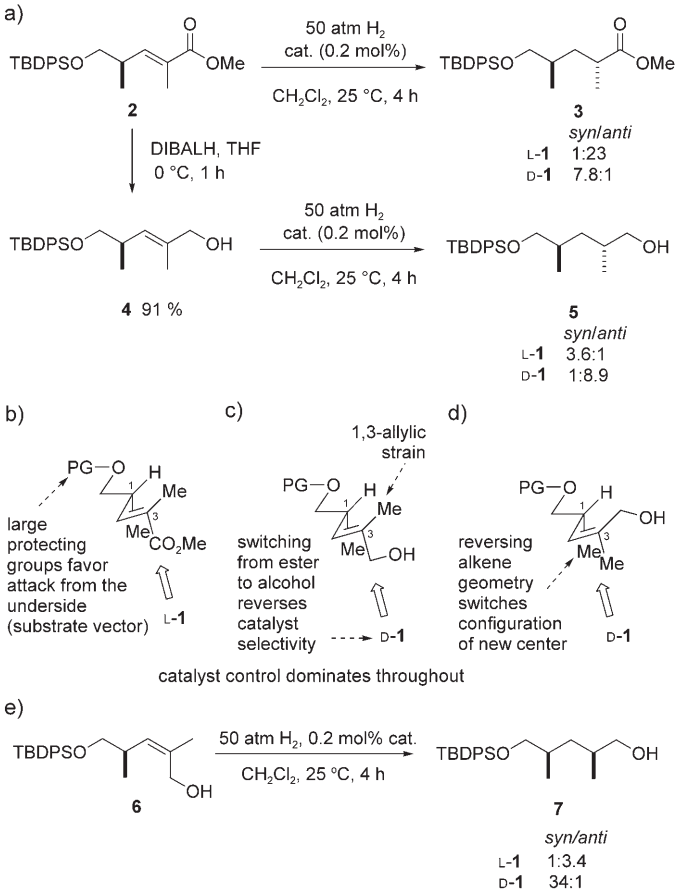
(Scheme 1). These chirons are found in a large family of natural products: the deoxypolyketides.

Commercially available (*S*)-methyl-3-hydroxyisobutyrate ((*S*)-Roche ester) was converted into several alcohol and ester derivatives, including **2** (>99% *ee*, Scheme 2), which contains a very bulky silyl protecting group. Catalyst L-**1** ($BArF^-$ = tetrakis-(3,5-bis(trifluoromethyl)phenyl)borate) was derived from L-





Scheme 2. a) Preparation of an *anti* type **A** chiron: **3** was isolated in 90% yield with a 40:1 *anti*/*syn* ratio after one chromatographic purification; b) model for substrate **2**; c) a similar model for substrate **4**; d) model for substrate **6**; and, e) preparation of the *syn* type **A** chiron: **7** was isolated in 93% yield after one chromatographic purification (*syn*/*anti* >120:1). Conversions were quantitative throughout. All ratios quoted were calculated from GC analysis. TBDPS = *tert*-butyldiphenylsilyl, DIBALH = diisobutylaluminum hydride.

aspartic acid, and D-**1** from the corresponding enantiomer. Hydrogenation of substrate **2** using catalyst L-**1** revealed that the chirality of the substrate matched that of the L-catalyst[11] and excellent diastereoselectivity was obtained. Interestingly, catalyst D-**1** gave an appreciable selectivity in the opposite direction, which illustrated that catalyst control is operative in this reaction. In fact, catalyst control applies in all the examples reported here. However, the substrates also have an intrinsic bias and, though less influential, it can be significant for optimizing selectivities. For brevity, we refer to this contribution as "the substrate vector"; this is different from "substrate control", which implies the overall stereoselectivity is governed by the substrate.

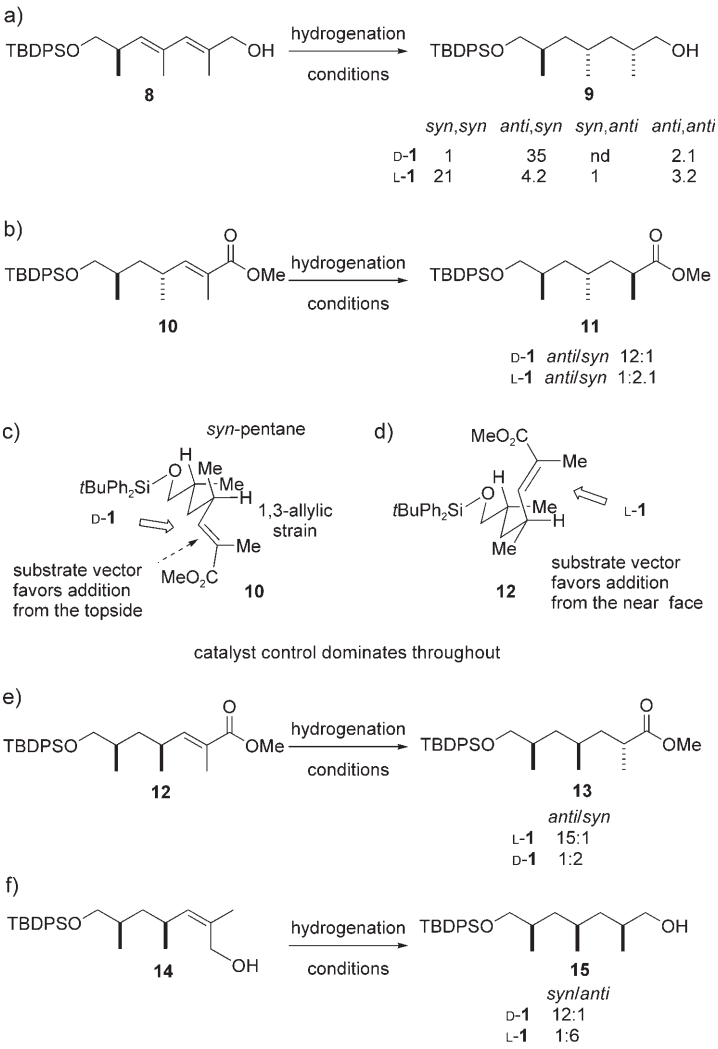
A rationale for the substrate vector in the hydrogenation of **2** is shown in Scheme 2b. This model predicts that the preferred conformation minimizes 1,3-allylic strain;[12] thus hydrogenation is favored on the alkene face which is least hindered. This subordinate effect corresponds with the effect of L-**1** to enhance the catalyst vector. However, when D-**1** is used, the substrate and catalyst vectors are mismatched and, since the later is dominant, the stereoselectivity is reversed and also diminished.

Having shown that the reduction of ester **2** is a good route to the *anti* isomer of chiron **A**, we then focused on the *syn* epimer. The mismatched pair in the reduction of **2** gave a 7.8:1 selectivity for the *syn* ester **3** (Scheme 2a). We sought to improve on this selectivity by converting the substrate into the corresponding allylic alcohol. We have previously found that the catalyst approaches such α,β-unsaturated esters and alcohols from opposite faces.[13] Thus, the substrate vector for alcohol **4** matched with D-**1**, whereas the corresponding ester **2** matched with L-**1**. Thus, for the reduction of **4** to **5** (Scheme 2a), the (matched) D-**1** catalyst favored the *anti* product, whereas *syn* selectivity was only 3.6:1 when the (mismatched) L-**1** was used. However, favorable *syn* selectivity was obtained by hydrogenation of the *Z* allylic alcohol **6** (>99% *ee*) using D-**1** (Scheme 2e). The model shown in Scheme 2d rationalizes this result.

Both antipodes of the Roche ester are commercially available, so the two enantiomers of the *syn* and *anti* chirons are accessible by using the methodology outlined above. The first milestone in this study was therefore reached, and attention was turned to chirons **B** (Scheme 1).

A direct route to the chirons **B** is to hydrogenate suitable diene substrates. We have been able to achieve this transformation with high stereoselectivity for one substrate, **8**. This reaction (Scheme 3a) gives a 35:3.1 (that is ca. 11:1) selectivity in favor of the *anti*,*syn* isomer relative to the other three isomers combined. Furthermore, this diastereoisomer is separable from the others through column chromatography. This transformation is unique insofar as no published method to deoxypolyketide chirons has reported the simultaneous production of two chiral centers. Experiments in which the reaction was terminated before completion indicate that the rates of reduction for the two double bonds are competitive.

Other stereoisomers of the triad **B** were obtained by the homologation of *anti*-**3** and *syn*-**7** (Scheme 2) into the corresponding alkenes, and subsequent hydrogenation. The *anti*,*anti* diastereomer was produced as depicted in Scheme 3b. Again, this reaction is catalyst controlled, but a high stereoselectivity was obtained by matching the catalyst and substrate vectors. Our model for the substrate vector (Scheme 3c) features a conformation that results from the relief of 1,3-allylic strain and *syn*-pentane interactions[14] which exposes one face of the alkene preferentially. Similarly,



Scheme 3. a) Preparation of an *anti*,*syn* type **B** chiron: **9** was isolated in 83% yield and with a 51:1 *anti*,*syn*/*syn*,*syn* ratio after one chromatographic purification; b) preparation of an *anti*,*anti* type **B** chiron: **11** was reduced (DIBALH) to an isomer of alcohol **9** and was isolated in 70% yield with a 120:1 *anti*,*anti*/*anti*,*syn* ratio after chromatography; c) 1,3-allylic strain/*syn*-pentane model for the hydrogenation of **10**; d) similar model for **12**; e) preparation of a *syn*,*anti* type **B** chiron: **13** was reduced to an isomer of alcohol **9** and was isolated in 82% yield with a 89:1 *syn*,*anti*/*syn*,*syn* ratio after chromatography; f) preparation of *syn*,*syn* type **B** chiron: **15** was isolated in 71% yield with >120:1 *syn*,*syn*/*syn*,*anti* ratio after one chromatographic purification. Hydrogenation conditions as in Scheme 2, although higher catalyst loadings (1 mol% versus 0.2 mol%) were used because the scale of the reaction was smaller. nd = not detected.

we believe that hydrogenation of substrate **12** gave a high selectivity for the *syn,anti* isomer because the substrate vector matches with L-**1** (Scheme 3d and e). By analogy with the reaction shown in Scheme 2d, the all-*syn* isomer **15** was obtained from the *Z* allylic alcohol **14** as shown in Scheme 3f.

Interchange of the functional groups at the termini of chirons **9**, **11**, **13**, and **15** would give the enantiomeric building blocks for deoxypolyketide syntheses. Alternatively, these enantiomers could be obtained from the (*R*)-Roche ester. Thus, we had met the second objective of this study.

Routes to chirons **A** and **B** can be segregated into either diastereoselective reactions involving chiral auxiliaries or catalytic methods.[15] The former are the more tried and tested, and we believe that, of these, the asymmetric alkylation methodology reported by Myers et al. is the most practical.[16] Nevertheless, catalytic approaches are gaining importance. The carboalumination of alkenes by Negishi et al.,[17] and the asymmetric cuprate Michael additions of Feringa and co-workers[18] are exciting developments in this field. However, the data collected herein show that routes to deoxypolyketide fragments using asymmetric hydrogenation can compete with the state-of-the-art methods in terms of catalyst loading, stereoselectivities, and atom economy.[19]

The approach described herein is fundamentally different from acyclic stereocontrol through directed hydrogenations of chiral homoallylic alcohols.[20] These reactions have been studied by using almost exclusively Rh or Ir catalysts of the type where the metal is coordinated to a chelating chiral bisphosphine (that is, not chiral Crabtree catalysts) and they are almost invariably substrate controlled. Furthermore, these systems are poor catalysts for the hydrogenation of trisubstituted alkenes when the substrate does not contain a homoallylic alcohol,[3,21] so they would not prove useful in the reactions described here. However, other chiral analogues of the Crabtree catalyst could be used, and some may give higher stereoselectivities. The prospects for further refinements to this method are therefore good, and the approach may evolve into one that equals or supersedes the classical directed approaches for acyclic stereocontrol through hydrogenation.

Experimental Section

General catalytic hydrogenation conditions: The corresponding alkene was dissolved in CH_2Cl_2 (1M solution) and the iridium catalyst L-**1** or D-**1** (1.0 mol% for small-scale, 0.2 mol% for gram-scale reactions, unless otherwise stated) was then added. The resulting solution was degassed by three cycles of freeze–pump–thaw and then transferred to a Parr bomb. The bomb was flushed with hydrogen for 1 min without stirring. The reaction mixture was then stirred at 700 rpm at 50 atm. After 4 h, the bomb was vented and the solvent evaporated. The crude product was passed through a small plug of silica gel (EtOAc/hexanes 3:7). The enantiomeric and diastereomeric ratios of the crude material were then determined by capillary GC analysis on a chiral β- or γ-cyclodextrin (CD) stationary phase (carrier gas: helium; column pressure: 29.71 psi; gas-flow rate: 2.1 mL min^{-1}; gradient temperature: 5 °C min^{-1}: starting temperature: 90 °C hold time: 30 min, 200 °C, 5 min, 90 °C.

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