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Asymmetric Hydrogenation Routes to Deoxypolyketide Chirons

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Abstract: Asymmetric hydrogenations of monoenes and dienes were performed to obtain terminal deoxypolyketide fragments **A** and the corresponding internal chirons **B** and **C**. The chiral N-heterocyclic carbene catalyst **1** was used throughout. Modest selectivities for hydrogenations of simple monoenes relayed into high selectivities for preparations of the terminal deoxypolyketide fragments in which either two hydrogenations or one and an optically pure starting material were used. Curiously, the face selectivities for hydrogenation of α,β-unsaturated esters were consistently opposite to those that had been observed for styrene and stilbene derivatives in previous work, and to closely related allylic alcohol and ether derivatives in this work. Plausible mechanisms for this differing behavior were deduced by using DFT calculations. It appears that the origin of the unusual stereoselectivity for the ester derivatives is transient metal-coordination of the ester carbonyl whereas there is no evidence that the allylic alcohol or ethers coordinate. The routes developed to α,ω-functionalized internal deoxypolyketide fragments are extremely practical. These begin with the Roche ester being converted into alkene and, in one case, diene derivatives. Catalyst control prevails in the hydrogenations of these substrates, but there is a significant "substrate vector" (a term we used to describe the influence of the substrate on a catalyst-controlled reaction). This is determined by minimization of 1,3-allylic strain and, in some cases, *syn* pentane interactions. This substrate vector can be constructively paired with the (dominant) catalyst vector by use of the appropriate enantiomer of **1**. In the hydrogenation of a diene derivative, two chiral centers could be formed simultaneously with overall 11:1.0 selectivity; this is the first time this has been achieved in any asymmetric synthesis of a deoxypolyketide fragment. Throughout, diastereoselectivities of the crude material in the syntheses of α,ω-functionalized internal deoxypolyketide fragments were in excess of 11:1.0 and chromatographically purified samples could be isolated in high yields with dr (dr = diastereomeric ratio) values consistently in excess of 40:1.0.

Keywords: asymmetric catalysis · homogeneous catalysis · hydrogenation · iridium · polyketides

Introduction

Chirons **A**–**C** (Scheme 1a) are found in a large category of natural products, including deoxypolyketides.[1] Synthetic approaches to these materials (reviewed recently)[2] can be divided into those involving diastereoselective reactions featuring chiral auxiliaries and catalytic methods. The former are the more tried and tested, and our interpretation of these is that Myers' asymmetric alkylation methodology is the most practical.[3] Catalytic approaches, on the other hand, are gaining importance. Negishi has developed very elegant approaches centered around carboalumination of alkenes[4] and Feringa/Minnaard's asymmetric cuprate Michael additions[5] is an exciting development in the field. However, there is ample room for improvement in this area, with respect to safety of reagents, catalyst loadings, stereoselectivities, overall efficiency, and atom economy.[6] Further, the mechanisms of these reactions continue to yield surprises, as this work reveals.

Scheme 1b shows two conceptual approaches to deoxypolyketide fragments that feature asymmetric hydrogenation chemistry. The first, like all the existing methods, is basically an iterative process to build up extended chirons by a combination of alkene syntheses and hydrogenation steps. The second is an ideal, never before realized, in that two or even

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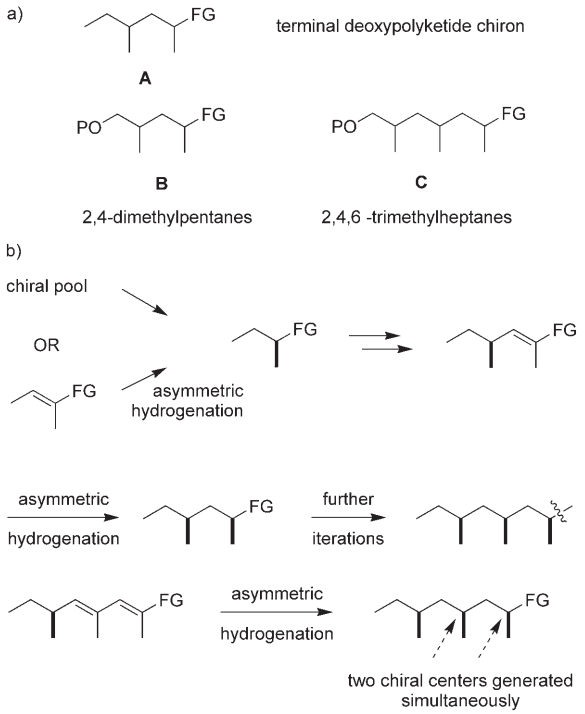
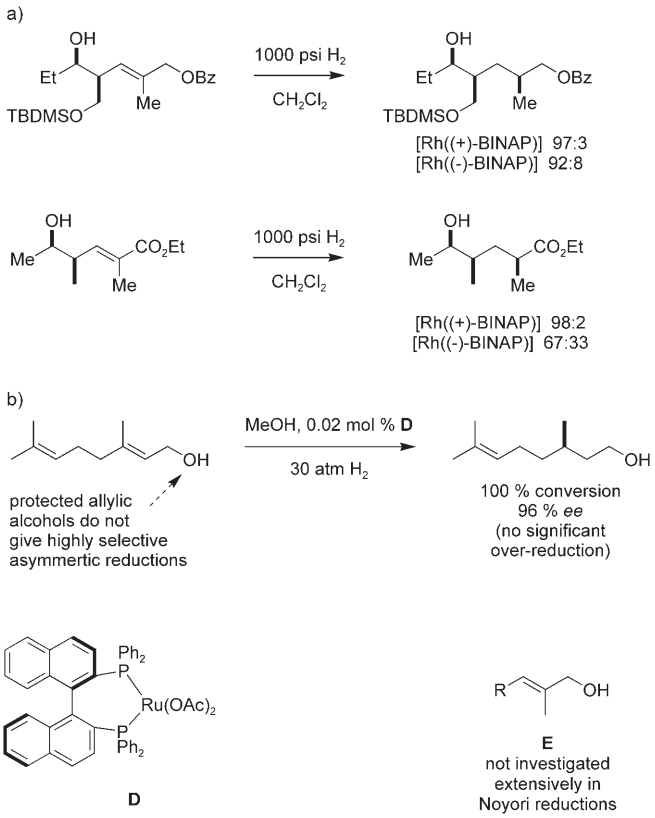


Scheme 1. a) Internal deoxypolypropionate chirons and b) the asymmetric hydrogenation approaches to these chirons that are investigated here. P = protecting group, FG = CH_2OH, CH_2OR, or CO_2R.



Scheme 2. Neither a) optically active rhodium–bisphosphine catalysts (substrate control dominates in both cases shown) nor b) Noyori's ruthenium catalysts are known to be useful for allylic alcohols of the substitution pattern **E** (*ee* = enantiomeric excess).

more chiral centers can be formed simultaneously with high stereocontrol. This manuscript describes our efforts to reduce these hydrogenation tactics to practice. A preliminary communication of some of this work has appeared.[7]

Selection of an appropriate catalyst to realize the goal indicated in Scheme 1 is a major issue. An optically active catalyst that reduces such substrates with high levels of catalyst control would be necessary. Of particular interest are catalysts that will reduce such substrates in which the functional group (FG) is an alcohol or an ester. The literature indicates two catalyst types should be considered: rhodium– and iridium–bisphosphine systems[8] and Noyori-type ruthenium–BINAP catalysts (BINAP = 2,2-bis(diphenylphosphino)-1,1-binaphthyl).[9,10]

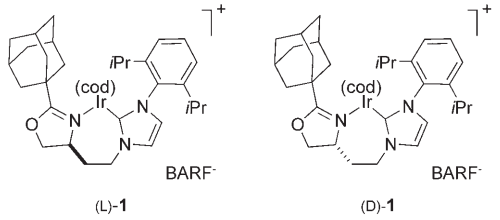
Rhodium bisphosphine catalysts do not reduce isolated double bonds at any significant rate readily unless there is a strongly coordinating group present, and even then the levels of catalyst control observed tend to be poor. Scheme 2a illustrates a relevant reaction from the literature to support this assertion. The reduction is only possible because of the homoallylic alcohol directing group, and the influence of the chiral catalyst on the stereochemical outcome is poor.[11] There are other limitations on these rhodium-catalyzed reactions. First, for acyclic stereocontrol in these Rh-mediated hydrogenations, allylic alcohols do not have any proven value. Second, less coordinating groups, such as esters, do not seem to be particularly advantageous.

Noyori-type ruthenium–BINAP derivatives are useful catalysts for hydrogenations of allylic alcohols, most famously for geraniol derivatives (Scheme 2b). They have been used to give high levels of enantioselectivity for prochiral substrates and to differentiate enantiomeric allylic alcohols in kinetic resolution processes.[12] However, there are some limitations to this chemistry: 1) High enantiomeric excesses are not uniformly obtained for all allylic alcohol substitution patterns,[13] the substrates **E** have not been investigated frequently; and, 2) the reaction does not work for α,β-unsaturated esters. Further, these types of reductions can be complicated by double-bond migration reactions.[14]

Another way to view the problem is to consider catalysts that do not require any peripheral coordinating groups to hydrogenate alkenes. There are very few of these and, of the limited pool,[15] chiral analogues of Crabtree's catalysts[16] stand out as the best choices. Crabtree's catalysts are based on N,P-ligation; these are very different to the bisphosphine complexes mentioned above and, crucially, these catalysts can reduce isolated "unfunctionalized" alkenes that only react very slowly in the presence of iridium– or rhodium–bisphosphine catalysts.

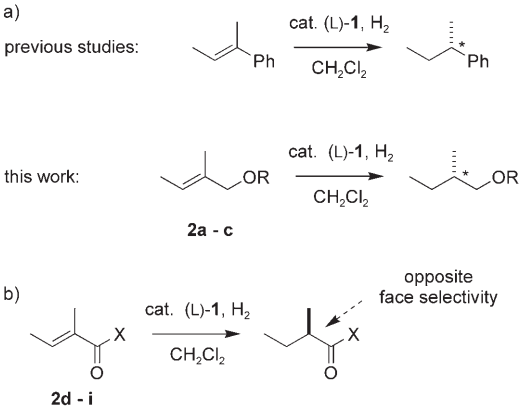
So far, research on chiral analogues of Crabtree's catalyst has been dominated by substrates that give relatively simple, uninteresting products. In response, we have begun to study dienes and polyenes.[17–19] Then, very recently, Pfaltz et al. reported reduction of a 1,5,9-triene to give (*R*,*R*,*R*)-to-

copherol[20] by a diastereoselective synthesis in which the pre-existing chiral center in the substrate was too far away from the nearest alkene to affect the face selectivity. Chiral analogues of Crabtree's catalysts had never been systematically applied to chiral substrates in which the stereogenic center is close enough to influence the stereochemical outcome. Here we report the genesis of our interest in this area, which features our chiral analogue of Crabtree's catalyst, the N-heterocyclic carbene complex **1** to prepare deoxypolyketide fragments.



Results and Discussion

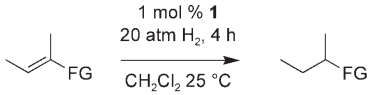
Pilot studies with simple alkenes: an intriguing face-selectivity reversal: Early in this study we found that hydrogenations of α,β-unsaturated esters and related derivatives mediated by catalyst **1** proceed with facial selectivities that are opposite to those observed for the same catalyst hydrogenating allylic alcohol derivatives and styrene/stilbenes (Scheme 3). Table 1 shows data supporting this assertion.



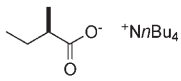
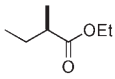
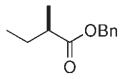
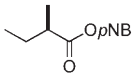
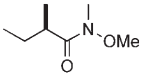
Scheme 3. a) Reduction of allylic alcohols and ethers (R = H, Bn, or TBS) studied in this work proceeds with the same face selectivity as styrene (and stilbene) derivatives; however, b) the face selectivity is reversed for the corresponding carboxylic acids, esters, and amides (X = O^-, OH, OEt, OBn, 4-$NO_2C_6H_4CH_2O$, or N(OMe)Me).

An allylic alcohol **2a**, two ether derivatives **2b–c**, the corresponding carboxylic acid **2d**, its carboxylate salt **2e**, three esters **2f–h**, and a Weinreb amide derivative **2i** were hydrogenated. The alcohol **2a** and the two ethers **2b** and **2c** gave the same facial selectivities that were previously observed for styrene and stilbene derivatives. However, all the carboxylic acid derivatives **2d–i** gave opposite stereoselectivities.

Table 1. Asymmetric hydrogenations of allylic alcohol and unsaturated ester derivatives.



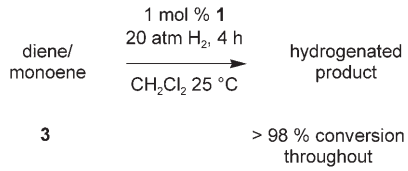
2 > 98 % conversion throughout

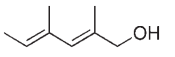
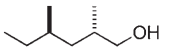
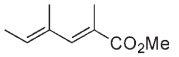
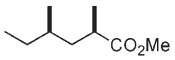
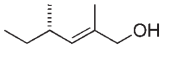
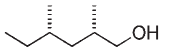
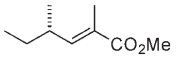
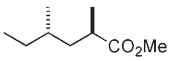
Compound	FG	Product	*ee* [%][a]
2a	CH_2OH		83
2b	CH_2OBn		59
2c	CH_2OTBS		49
2d	CO_2H		55
2e	CO_2NnBu_4		27
2f	CO_2Et		67
2g	CO_2Bn		73
2h	CO_2pNB[b]		42
2i	CO(NMe)OMe		46

[a] Determined by analysis on a chiral GC column. [b] *p*NB = 4-nitrobenzyl, only 22% conversion.

Modest enantioselectivities for single transformations, such as those shown in Table 1, can sometimes be useful when two are performed in tandem. In these cases, the enantiomeric excesses of the final products are higher than those obtained from a single, similarly selective process (Horeau's principle).[21] Thus, in hydrogenations of a diene, if the double bonds of a substrate were reduced with 9:1 and 8:1 facial selectivities (i.e. the same order of magnitude observed in Table 1), then the ratio of stereoisomers formed would be (9×8):(9×1):(8×1):(1×1). This corresponds to 97% *ee* for the major isomer formed with 73:17 dr relative to the minor diastereomer (5.9% *ee*). Hydrogenations of dienes **3a** and **3b** (Table 2) were investigated to explore this concept. Further, we sought to determine if the terminal allylic alcohol and α,β-unsaturated ester functionalities would lead to opposite facial selectivities on the proximal alkene. In that event, entries 1 and 2 in Table 2 show that hydrogenations of appropriate dienes can give two chiral centers simultaneously with moderate to good diastereoselectivities and high enantioselectivities. Moreover, the stereochemistry of the proximal hydrogenation was reversed as expected from Table 1.

Table 2. Asymmetric hydrogenations of substrates **3**.



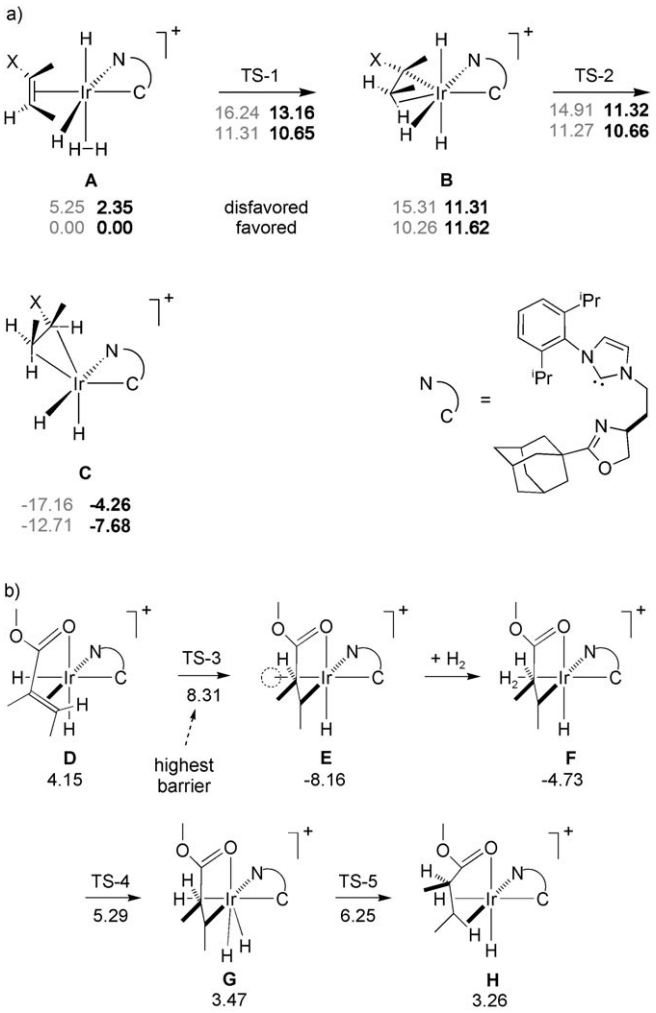
Compound	Substrate	Product	*ee* [%][a]	dr [%][a]
3a[b]			97	11:1.0
3b[b]			90	2.9:1.0
3c			>98	9.6:1.0
3d			97	5.1:1.0

[a] Determined by analysis on a chiral GC column; stereochemical assignments were made by comparison with authentic samples prepared by the Myers′ method.[3] [b] 12 h and 50 atm were used to obtain full conversion.

Origin of the face-selectivity reversal: The mechanisms by which chiral analogues of Crabtree's catalyst mediate hydrogenations of alkenes are interesting and have invoked experimental and theoretical studies from various groups.[18,22–25] Detailed theoretical studies from these laboratories have led us to conclude that hydrogenation of stilbene and styrene derivatives by catalyst **1** proceeds by a cycle involving a dihydride–dihydrogen iridium complex and cycling between Ir^{III} and Ir^{V} oxidation states.[26] These observations were broadly similar to those calculated by Brandt, Andersson and coworkers for a simplified phosphine–oxazoline iridium complex mediating hydrogenation of ethene.[22] They have also considered hydrogenations of α,β-unsaturated esters by using a chiral N,P-ligated iridium complex.[27]

A pivotal issue to be answered in this study was the origin of the face selectivity reversal for the α,β-unsaturated esters. To address this we turned towards calculation of possible mechanisms involved in these reactions by means of the DFT approach already described by us.[26] Briefly, different mechanisms were envisioned and the relative energies of the intermediates and transition states were calculated for approach to both enantiofaces. Complete catalyst and substrate structures were used throughout. Close correspondence of experimental and theoretical data had already validated these calculations for the stilbene/styrene substrates.[26]

The reaction pathway previously identified for stilbene and styrene substrates was used as a starting point to explore the possible mechanisms for the hydrogenation of (*E*)-2-methylbut-2-en-1-ol (**2a**) and (*E*)-methyl 2-methylbut-2-enoate (**2j**). The results are shown in Scheme 4a in which the bold numbers are indicative of the allylic alcohol **2a** and the gray ones represent the ester **2j** ($X=CO_2CH_3$). If this



Scheme 4. a) The reaction pathway previously deduced for (*E*)-1,2-diphenylpropene applied to predict enantioselectivities and absolute configurations by DFT-PBE calculations. ΔG values in kcal mol^{-1} listed for (*E*)-methyl 2-methylbut-2-enoate (gray, $X=CO_2CH_3$) and (*E*)-2-methylbut-2-en-1-ol (bold, $X=CH_2OH$), respectively. The terms favored and disfavored refer to the calculated pathways which have the lower and higher overall activation free energies; thus the pathway was favored for the allylic alcohol but not for the α,β-unsaturated ester. b) The alternative reaction pathway used to predict absolute configurations for hydrogenation of (*E*)-methyl 2-methylbut-2-enoate. Relative free energies shown are calibrated to structure **A** in Scheme 2; only a one-face selectivity pathway is represented because hydrogenation to give the enantiomer was not feasible by means of this mechanism.

mechanism were followed for both substrates, then the face selectivities would be the same for each; the preceding discussion makes it clear this not the case. In fact, this mechanism is consistent with the absolute configuration of the allylic alcohol observed, but not for the ester derivative.

An extensive study of other possible reaction pathways was undertaken to find a viable mechanism that would explain the observed face selectivities for the ester derivatives. Several alternative reaction pathways were explored (see the Supporting Information) and the most favorable identified is shown in Scheme 4b. Free energies calculated for the

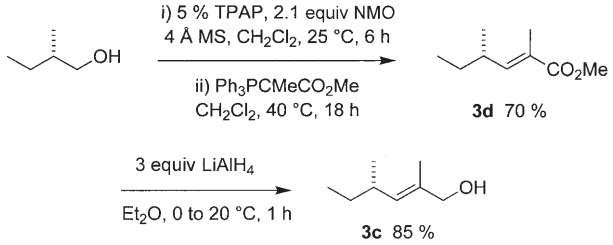
highest-energy transitions states in Scheme 4a (X = CO_2CH_3) and 4b indicate the latter is more favorable by 3.0 (i.e. 11.31 versus 8.31) kcal mol^{-1}.

The mechanism shown in Scheme 4b begins with formation of a complex **D** in which both the carbonyl oxygen and the alkene ligand are coordinating to the Ir center. Interestingly, the alkene and a hydride ligand in **D** are *trans*-oriented to the oxazoline and carbene ligands, respectively. These *trans* effects are suboptimal, as they destabilize **D** relative to **A** (Scheme 4b and a, respectively), but simultaneously lower the energy barrier for the next step. That next step, the migratory insertion process shown, is the highest barrier in this process. It vacates a coordination site in **E** that is then filled by a dihydrogen ligand to give the dihydrogen hydride complex **F**. The dihydrogen and hydride ligands in **F** are easily exchangeable, hence **G** can form. It is one of the hydrides *trans* to the carbonyl oxygen in the Ir^{V} intermediate **G** that undergoes the final, reductive elimination, step that completed reduction of the alkene. Facile ligand exchange steps then close the catalytic cycle. Simple modification of the mechanism shown in Scheme 4b to arrive at the opposite face selectivity, corresponding to the minor enantiomers, was not energetically accessible; consequently, the minor enantiomer is probably formed by a different pathway. In fact, the most favorable route to that enantiomer which was found corresponded to the mechanism in Scheme 4a (X = CO_2CH_3), that is, without C=O coordination.

Others have recently presented calculations on the hydrogenation of an α,β-unsaturated ester by using a chiral iridium P,N-ligand complex. They concluded that the hydrogenation proceeded without coordination of the carbonyl oxygen, but this possibility was not mentioned as one that was tested.[27] Instead, the researchers applied a very similar pathway to that originally deduced by them for their phosphine–oxazoline ligand system hydrogenating ethene without allowing for extensive modifications. The results presented here suggest further exploration of that particular reaction pathway, for unsaturated ester derivatives, is warranted.

In summary, the face selectivity observed for the allylic alcohols is consistent with the mechanism shown in Scheme 4a, and this is directly analogous to that previously deduced for (*E*)-1,2-diphenylpropene. The minor enantiomer formed by hydrogenation of (*E*)-methyl 2-methylbut-2-enoate may also be formed by a similar route. However, the major enantiomer from that α,β-unsaturated ester appears to be formed by the route depicted in Scheme 4b which involves transient coordination of the ester carbonyl group.

Enhanced enantioselectivities for diene substrates: terminal-deoxypolyketide fragments: We were intrigued by the possibility that all four stereoisomers of the useful natural product chirons,[2] deoxypolyketide dyads, might be accessible by using only one enantiomer of catalyst **1**. Stepwise approaches to augment the hydrogenations of dienes **3a** and **3b**, therefore, were considered to achieve this. (*S*)-2-Methylbutan-1-ol, which is commercially available at low cost, was converted to the substrates **3c** and **3d** by the route shown in Scheme 5. These were hydrogenated to give products with high optical purities and in moderate to good diastereoselectivities (Table 2).



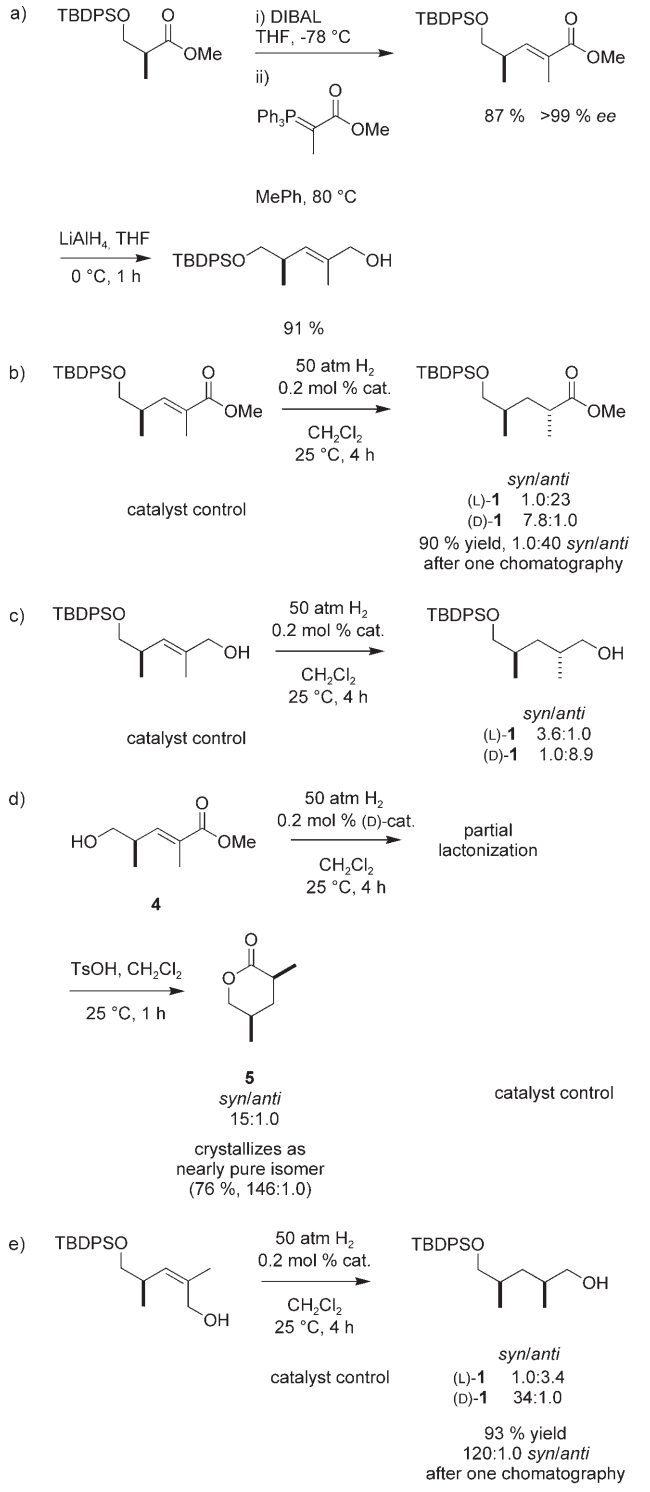
Scheme 5. Preparation of substrates **3c** and **3d**. NMO = *N*-Methylmorpholine *N*-oxide.

The hydrogenation approach to deoxypolyketide chirons in Table 2 has some attributes and interesting features. First, all four stereoisomers can be obtained by using one enantiomer of catalyst **1**, the one that is prepared from L-aspartic acid. Preparation of **3c** and **3d** uses the least expensive optically active form of 2-methylbutan-1-ol. Diastereomers of the 2,4-dimethylpenten-1-ol products can be separated by using flash chromatography[4] so pure products can be obtained. However, that separation is difficult and requires conversion of the esters to the alcohols so it was not performed carefully to give isolated yields in this study. The syntheses of α,ω-functionalized deoxypolyketide chirons described in the next section is more practical.

Internal deoxypolyketide fragments 1: **α,ω-functionalized 2,4-dimethylpentane dyads**: Esters and allylic alcohol substrates in this work are both readily accessible. Our work, described above, indicates that the hydrogenation catalyst preferentially approaches opposite faces of these alkenes; this provides a convenient element of control.

The *anti* isomer was relatively easy to produce, as shown in Scheme 6b. Of course, throughout this study, there is a compromise between isolated yields and *syn*/*anti* purity (depending on how finely the fractions were cut), but it was uniformly possible to isolate the desired isomer in high yield and diastereomeric purity.

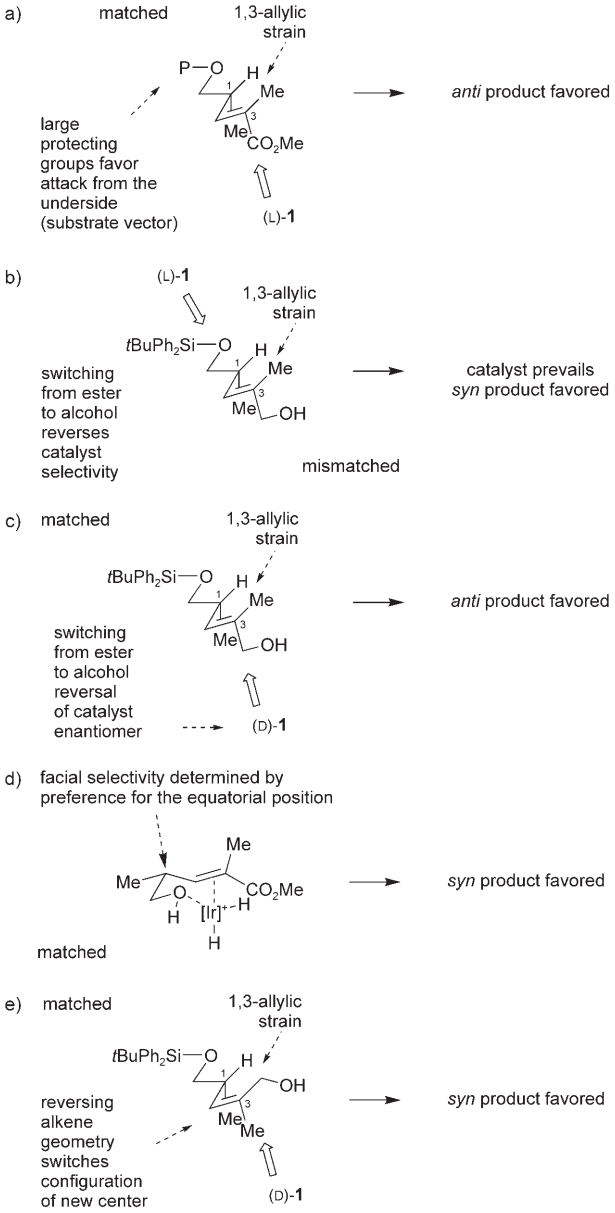
Preparation of the *syn* diastereomer was less straightforward and, in the event, three solutions were devised. Simply changing the ester to an alcohol group gave a modest (3.6:1.0) *syn* selectivity (Scheme 6c). Alternatively, the silyl protection of the homoallylic alcohol was removed for the ester substrate shown in Scheme 6d, then the hydrogenation gave the lactone indicated with high *syn* selectivity. This is a highly practical route because that lactone is crystalline and can be purified efficiently by recrystallization.[28] Finally, Scheme 6e shows how inverting the alkene stereochemistry of the allylic alcohol also gave the same *syn* product, with high diastereoselectivity. Catalyst control prevails in all the reactions shown in Scheme 6b–e.



Scheme 6. a) Synthesis of a typical substrate from the Roche ester, b)–e) three different methods for production of the chirons with two methyl substituents. All ratios were measured by GC analysis. DIBAL = diisobutylaluminum hydride.

Scheme 6 shows routes to one enantiomer of the *syn* and *anti* isomers of the desired stereochemical dyad. The optical antipodes could be obtained by starting with the enantiomeric form of the Roche ester or by inverting the functional groups at either end of the product.

Scheme 7 outlines the stereochemical models used to rationalize the findings shown in Scheme 6. Catalyst control



Scheme 7. a) The catalyst (L)-**1** preferentially attacks from the *Si* face, and that orientation of approach is favored by large protecting groups P that protect the *Re* face in the preferred conformation. b) Substituting the ester with the hydroxymethylene gives a mismatched situation for (L)-**1**. c) (D)-**1** is matched with the same substrate. d) chelation-controlled model for the homoallylic alcohol and e) the effects of using the (*Z*)-allylic alcohol.

prevails, as mentioned above, but the "substrate vector" (discussed in scheme) has a bearing on the magnitude of the selectivity. Throughout this paper, the intrinsic bias caused by the alkene conformation is referred to as "the substrate

vector" (a term we use to depict the bias of the substrate, even though all the reactions are catalyst controlled). In Scheme 7a we envisage that the substrate preferentially populates a conformer in which relief of 1,3-allylic strain means that the *Si* face of the alkene (underside as shown) is least hindered. In Figure 7a, the substrate vector that contributes to this selectivity is enhanced when the protecting group P is larger. Consistent with this, the corresponding benzyl ether, in which P is much smaller, had no significant substrate vector (*syn*/*anti* for (L)-**1**: 1.0:3.9, for (D)-**1**: 3.9:1.0, not shown).

As predicted, substitution of the ester with a hydroxymethylene group gave opposite facial selectivity. Thus, Scheme 7b and c show the mismatched and matched cases[29] corresponding to the two enantiomers of the catalyst; it is now (D)-**1** that constructively pairs with the substrate vector. Only a modest *syn* selectivity was observed when (L)-**1** was used (Scheme 6a–c).

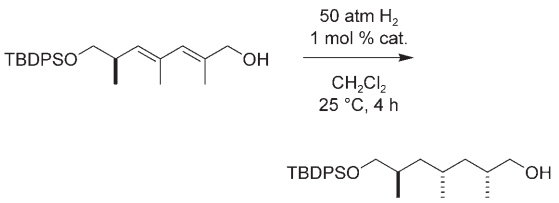
The chelation-controlled model in Scheme 7d accounts for the highly *syn*-selective hydrogenation shown in Scheme 6d. Here the homoallylic alcohol appears to be directing the hydrogenation through a chairlike transition state which preferentially folds to place the methyl group in the *pseudo*-equatorial position.

Finally, Scheme 7e gives the model for the *syn*-selective hydrogenation shown in Scheme 6e. Catalyst (D)-**1** matches with the substrate in the preferred conformation shown, as we predicted. Interestingly, the face selectivity of the catalyst is independent of the alkene geometry (compare Scheme 7c and e); this may be taken as circumstantial evidence that the allylic hydroxyl is not simultaneously coordinating to the metal and directing the hydrogenation to a preferred enantioface.

Having developed routes to the α,ω-functionalized 2,4-dimethylpentane dyads and rationales for the behavior of the catalyst in these reactions, we set about preparing chirons of the next higher homologue. These efforts are outlined in the next section.

Internal deoxypolyketide fragments 2: α,ω-functionalized 2,4,6-trimethylheptane triads: Throughout this section the catalyst loadings used were 1 mol%. This larger loading was used in this case rather than for the α,ω-functionalized 2,4-dimethylpentane dyads because the reactions were preformed on smaller scales than in the previous section. We suspect, but have not proved, that lower catalyst loadings could be used for larger scale reactions in the following series, provided the solvents and reagents are clean and dry.

The most direct route to deoxypolypropionate chirons would be to reduce dienes or oligoenes to produce several centers simultaneously. Such ambitious strategies will probably only be useful for the synthesis of one diastereomer at best. This was achieved in the course of this work (Scheme 8). Here the requisite diene was prepared from the Roche ester without any significant racemization. Hydrogenation of this substrate gave mixtures of diastereomers as shown; the best case was for (D)-**1** for which the *anti*,*syn*



	syn,syn	*anti,syn*	*syn,anti*	*anti,anti*
(D)-**1**	1.0	35	nd	2.1
(L)-**1**	21	4.2	1.0	3.2

Scheme 8. A diene prepared from the Roche ester without any significant racemization was hydrogenated to give mixtures of diastereomers as shown (nd = not detected).

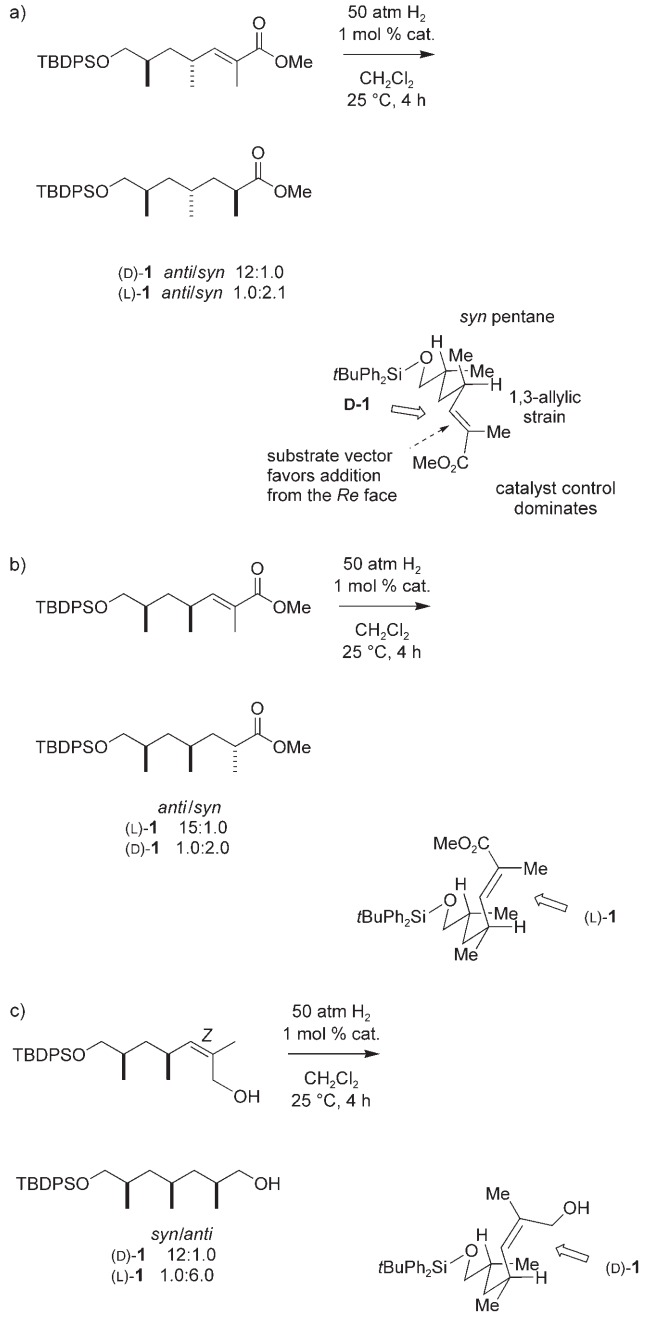
isomer prevailed over all the others with a selectivity of about 11:1.0 (*anti*,*syn*/others). When this reaction was stopped before completion, GC analyses indicated that hydrogenation of the two double bonds had occurred at a competitive rate. Hydrogenations of various other dienes were attempted but none gave usable selectivities.

The remainder of the isomers in the 2,4,6-trimethyl chiron series were formed from alkenes derived by homologating the dimethyl series described in the previous section. Thus the *anti* ester shown in Scheme 9a was hydrogenated to the *anti*,*anti* product. The reaction is catalyst controlled, and (D)-**1** preferentially approaches the α,β-unsaturated ester from the *Re* face, just as before. The only difference with the simpler series is that *syn* pentane interactions[30] have to be invoked to explain the preferred substrate conformation. Other isomers in the series were prepared by using exactly the same concepts as before; in every case, the desired products could be isolated in high purities. Just as for the lower homologues, enantiomers of the products in this series could be prepared by starting with the enantiomer of the Roche ester or by inverting the functional groups at the termini of the product shown in Scheme 9.

Conclusion

The methodology described here did not require that isolated alkene units in the substrates be hydrogenated with extremely high selectivities. This is because the face selectivities could be magnified by performing asymmetric hydrogenations in tandem. Alternatively, optically pure starting materials were used and the byproducts were removed as diastereomeric impurities. Almost certainly, other ligands could be found that would give improved stereoselectivities, but finding them is less important than developing the overall methodology.

Reversal of face selectivity for the ester and allylic alcohol substrates is an interesting facet of this research. It is somewhat surprising that no pathway involving coordination of the alcohol was found in the DFT calculations. We suspect that either the alcohol cannot coordinate and simultaneously deliver the hydrogen to the alkene or there is a mechanistic pathway available that we have not yet located.



Scheme 9. Routes to the a) *anti*,*anti*-, b) *syn*,*anti*-, and c) *syn*,*syn*-2,4,6-chiron isomers. The ester product in (a) was reduced to an alcohol and then chromatographed to give *anti*,*anti*/*anti*,*syn* 120:1.0 isolated in 70% yield. For (b) the product was reduced to an alcohol and then chromatographed (once) to give *syn*,*anti*/*syn*,*syn* 89:1.0 isolated in 82% yield. For (c) the alcohol was chromatographed (once) to give *syn*,*syn*/*syn*,*anti* 120:1.0 isolated in 71% yield. All ratios were measured by GC analysis.

In any event, it is clear that the face selectivity observed for the stilbene derivatives and for the allylic alcohols is the same, and that α,β-unsaturated esters are anomalous.

Research on chiral analogues of Crabtree's catalyst is moving into a new era. This is built on almost a decade of research that focused primarily on ligand development. The new emphasis will be on meaningful applications of these catalysts to produce chirons for syntheses of sophisticated organic molecules. Pfaltz's reduction of a 1,5,9-triene to give (*R*,*R*,*R*)-tocopherol[20] is a very specialized application, but one that perhaps has commercial potential. The work presented here is a broader-based piece of methodology designed to target an important set of chiral building blocks. Related efforts following this same theme are in progress in our laboratory.

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