ACCOUNTS
of chemical research

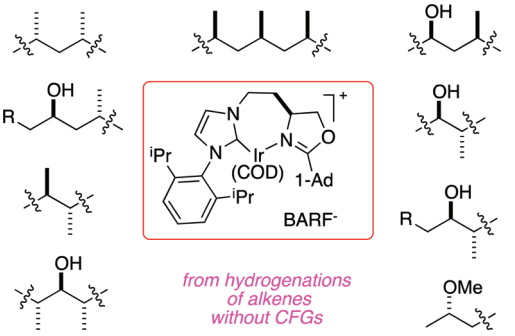
Filling Gaps in Asymmetric Hydrogenation Methods for Acyclic Stereocontrol: Application to Chirons for Polyketide-Derived Natural Products

YE ZHU AND KEVIN BURGESS*

Department of Chemistry, Texas A & M University, Box 30012, College Station, Texas 77841, United States

RECEIVED ON MAY 25, 2011

CONSPECTUS



The large volume of research studying hydrogenation catalysis might suggest that stereoselective hydrogenation of alkenes is a solved problem, but we believe the most important parts of asymmetric hydrogenation methodology remain unmastered. The most popular chiral catalysts, Rh- and Ir-diphosphine complexes, do not hydrogenate the largest categories of prochiral alkenes, hindered tri- and tetra-substituted ones, at useful rates unless the substrate has a "classical" coordinating functional group (CFG), for example, amides or homoallylic alcohols, to anchor the substrate to the metal. Therefore, while many methods are available for the asymmetric hydrogenation of alkenes with appropriate CFGs, synthetic chemistry would benefit from chiral hydrogenations of substrates with functional groups that typically do not coordinate in Rh- and Ir-diphosphine complexes.

In this Account, we demonstrate the application of chiral analogues of Crabtree's catalyst to asymmetric hydrogenations of coordinating unfunctionalized, trisubstituted alkenes. Crabtree's catalyst, a complex of iridium with 1,5-cyclooctadiene, tris-cyclohexylphosphine, and pyridine, differs from Rh- and Ir-diphosphine complexes, which we broadly refer to as "chiral analogues of Wilkinson's catalyst." Crabtree's catalyst analogues hydrogenate substrates that do not contain functionalities generally recognized as CFGs, and we propose reasons for this chemistry based on the catalytic mechanisms. Thus, chiral analogues of Crabtree's catalyst facilitate many hydrogenations that would *not* be possible using Rh- or Ir-diphosphine complexes. Directed hydrogenations have been used in acyclic stereocontrol for decades, but the realization that these catalysts can be used for acyclic stereocontrol *without* the types of directing groups that are necessary for other hydrogenations significantly broadens the scope of hydrogenations for this purpose. Recently, we have prepared chirons for polyketide-derived natural products using an *N,carbene*-Ir complex (1). This approach has led to catalytic syntheses of several important chirons to facilitate preparations of these ubiquitous natural products.

1. Introduction

Research on hydrogenation catalysts[1−4] is so ubiquitous that casual observers develop the impression that stereoselective hydrogenation of alkenes is a solved problem. Contrary to this, we believe the most important parts of asymmetric hydrogenation methodology have yet to be mastered.

Justification for the somewhat controversial assertion above is based on several observations. First, the largest categories of prochiral substrates for asymmetric hydrogenations are tri- and tetra-substituted alkenes; these are hindered. The most popular metal diphosphine complexes do not hydrogenate tri- or tetra-substituted alkenes at useful rates unless the substrate has a "classical"[a] coordinating functional group (CFGs) to anchor the substrate to the metal (Figure 1a).[1] *Asymmetric hydrogenations mediated by Rh-, Ir-diphosphine complexes are largely restricted to substrates with CFGs* (typically amides, homoallylic alcohols, e.g., **A** and **B**). Broadening the discussion to include Ru-diphosphine complexes reveals that some simple unsaturated carboxylic acids and

Published on the Web 10/05/2012 www.pubs.acs.org/accounts
10.1021/ar200145q © 2012 American Chemical Society

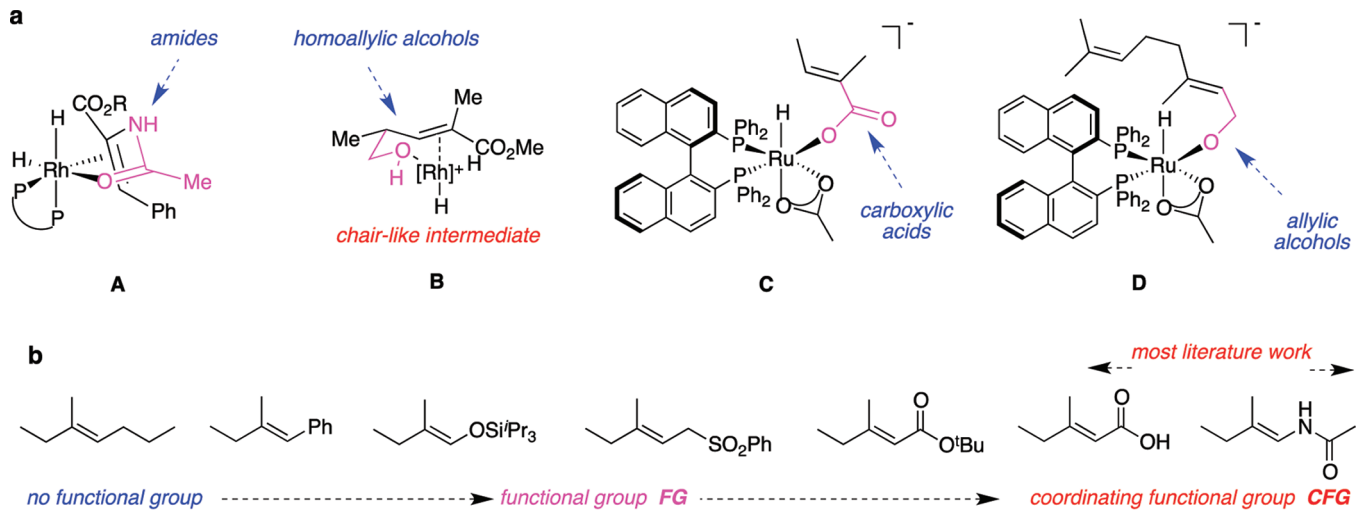
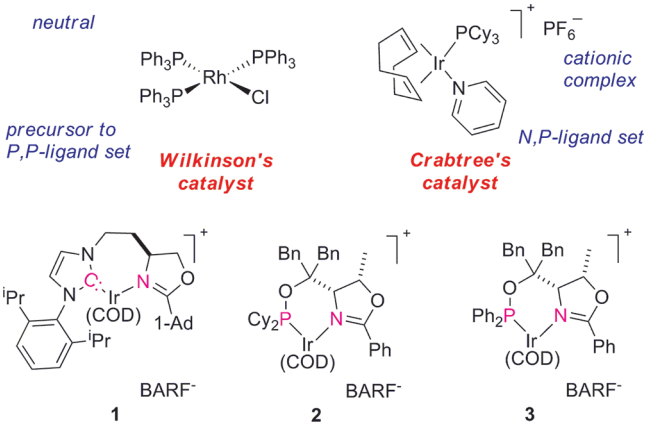


FIGURE 1. Asymmetric hydrogenations of substrates with functional groups, but not CFGs, are relatively unexplored.

alcohols can be reduced using this catalyst.[5] Thus, for the ruthenium complexes, carboxylic acids and allylic alcohols (e.g., **C** and **D**) might serve as CFGs, but the corresponding esters and ethers would not.[5] Asymmetric hydrogenation of alkenes with appropriate CFGs may well be mostly solved, but synthetic chemistry would benefit from asymmetric hydrogenations of substrates with functional groups that typically do not coordinate in Rh- and Ir-diphosphine complexes. There are wide gaps in hydrogenation methodologies corresponding to a broad range of substrates types, many of which are functionalized but not with the types of groups that are strongly coordinating, that is, CFGs (Figure 1b).

Broadly speaking, many Rh- and Ir-diphosphine complexes are chiral analogues of Wilkinson's catalyst. It takes different homogeneous catalysts to hydrogenate alkenes that do *not* have CFGs,[6,7] and the most useful are the ones based on Crabtree's catalyst,[8] specifically complexes of iridium(+1) that also have an *N*,*P*-ligand set.

All chiral analogues of Crabtree's catalyst (e.g., **2** and **3**) have an *N*,*P*-ligand except for the related *N*,*carbene* systems where the carbene ligand is a phosphine equivalent. The first of these iridocarbene analogues was **1** designed in our group,[9,10] and Andersson,[11] Bolm,[12] and Pfaltz's laboratory[13] have made others. Substitution of a *P*- with a carbene has interesting consequences (described later) but the key is that chiral analogues of Wilkinson's catalysts, that is, M-P_2 systems (where M = Rh, Ru, even Ir), do not tend to hydrogenate hindered alkenes without a CFG, but chiral analogues of Crabtree's catalyst, that is, Ir–*N*,*P* or Ir–*N*, carbene systems do. This begs the question: why are



analogues of Wilkinson's and Crabtree's catalyst fundamentally different?

2. Differences between Wilkinson's and Crabtree's Catalyst

Hydrogenation by Wilkinson's catalyst and similar complexes proceed via Rh(1+) and Rh(3+) intermediates related by oxidative addition of a single molecule of dihydrogen, and reductive elimination of σ-alkyl and hydride ligands. To elucidate why Crabtree's catalyst mediates hydrogenation of hindered alkenes without *CFGs*, our group[14,15] and others[16] first collected kinetic and NMR data, but spectroscopic studies are limited by the challenges associated with identifying and distinguishing multiple highly fluxional intermediates in a catalytic cycle that turns over rapidly. Consequently, we[14,17–19] and others[20–22] used DFT calculations coupled with kinetic studies and reached similar conclusions (Figure 2; "*C*" denotes carbene ligand). Loss of the COD ligand, complexation with the alkene,

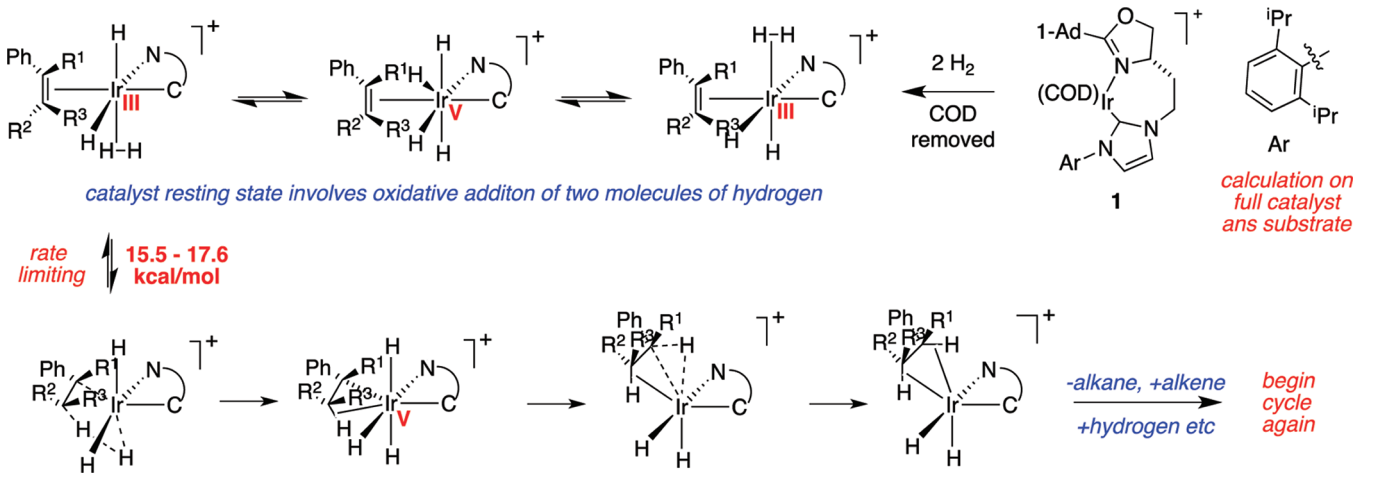


FIGURE 2. Iridium catalyzed hydrogenation with complex **1** deduced via DFT calculations.

and oxidative addition of *two* molecules of dihydrogen was implicated in those studies. Since two oxidative additions of hydrogen are involved, the Ir(1+) catalyst precursor is oxidized to an Ir(5+) intermediate before transfer of hydrogen to the coordinated alkene. Those calculations also show the Ir(5+) complex is in equilibrium with two Ir(3+) dihydrogen dihydride complexes of almost the same energy. Delivery of hydrogen to the coordinated alkene is rate-limiting; it may occur via a dihydrogen metathesis step for complex **1**, but that pathway is calculated to be only marginally more favorable than the expected migratory insertion of the alkene into Ir−H bond. Overall, this mechanism involving high oxidation state Ir intermediates is consistent with the observation that hydrogenations with these Ir-complexes are not particularly sensitive to oxygen.

Figure 2 reveals why Crabtree's catalyst derivatives, and *not* those of Wilkinson's catalyst, should hydrogenate tri- and tetra-substituted alkenes at a significant rate. First, in Crabtree-derivatives, the metal center is unipositive, not neutral, and it rises to a higher oxidation state [Ir(5+) vs Rh(3+)], so it is more electrophilic. Second, the Ir-center in the tetrahydride intermediate is less hindered than XRh(alkene)(phosphine)$_2$H$_2$ intermediates because the iridium is seven-coordinate, and because its four-hydride ligands are relatively small.

3. Differences between *N,P*- and *N,Carbene*-Iridium Catalysts

Studies on asymmetric hydrogenation of enol ethers led us to suspect that more protons were produced when *N,P*-Ir-catalyst precursors were used relative to the corresponding carbene ones. Specifically, while Andersson et al. had noted[23] that alkyl enol ethers gave complex mixtures when hydrogenated using one of their *N,P*-iridium catalysts, we observed only the expected hydrogenation products when our *N,carbene*-iridium catalyst **1** was used.[24]

Figure 3a contrasts formation of protons from Ir(5+)-phosphine and -carbene intermediates via formation of Ir(3+) species. The metal is reduced in these processes because its electron density increases. We proposed that this dissociation is easier with a *P*-ligand than a carbene because *P*-ligands are (i) inferior σ-donors and hence are less able to stabilize Ir(5+); and, (ii) superior π-acceptors and thus better able to stabilize Ir(3+). If this proposal is correct, Crabtree's catalyst and other *P*-ligated derivatives should be more acidic than the corresponding carbenes.

Using DFT, we calculated acidity differences for the key metal hydride complexes involved in hydrogenations with Crabtree's catalyst analogues (Figure 3b).[17] Hydrides **F** and **G** were predicted to be 7.6 to 5.9 pK_a units *more* acidic than the carbene intermediate **H**, consistent with Figure 3a. These calculations also indicated catalyst precursors **1**−**3** would give progressively more acidic intermediates in hydrogenations. This assertion was based on the fact that the carbene ligand is a better σ-donor than either of the *P*-ligands, and that the PCy$_2$ system has the best σ-donating properties of these two *P*-ligands. The degree of backbonding to these ligands is likely to follow the opposite trend.

Several experiments from our laboratory provided evidence that all the assertions outlined above are correct.[17] For instance, hydrogenations of acid-sensitive alkenes, like enol ethers, gave less byproduct with the carbene complex **1** than with *N,P*-complexes consistent with the supposition that **1** produces less protons in hydrogenation reactions.

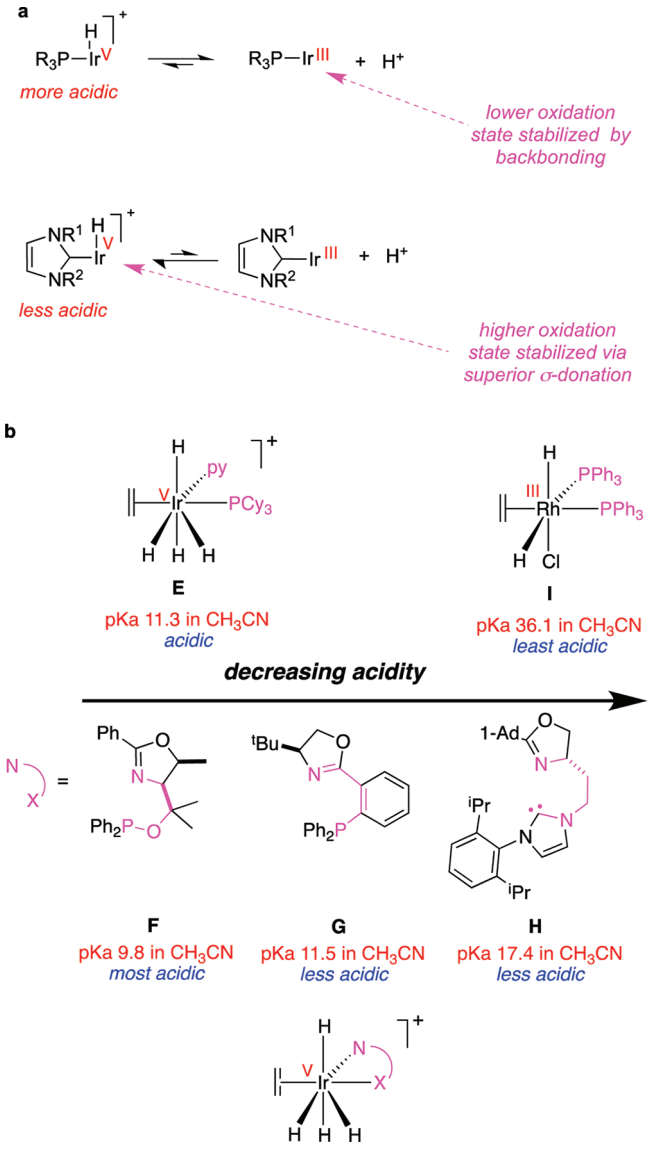


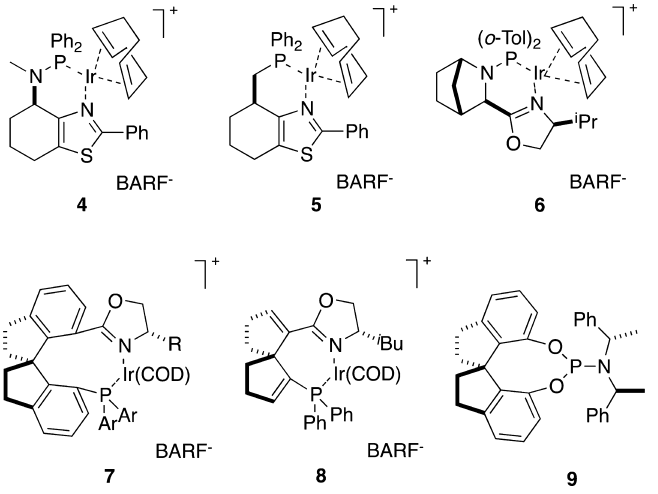
FIGURE 3. (a) Postulate for acidities of the *N,P*–Ir-H complexes relative to *N,carbene*–Ir-H systems; (b) relative acidities of putative intermediates in hydrogenations.

4. Enantioselective Hydrogenation of Largely Unfunctionalized Alkenes

In 2005, we reviewed enantioselective hydrogenations of largely unfunctionalized alkenes and reached several conclusions.[6] One of the most important was that there had been much work on ligand development for the generation of chiral analogues of Crabtree's catalyst, so much that literally hundreds of complexes had been formed, but the substrates that had been tested were almost without exception *uninteresting* in synthesis. At that time, only about 20 alkenes had been tested, and most of them were styrene and stilbene derivatives. The prevailing wisdom was that hydrogenation of alkenes with no functional groups (only alkyl substituents) was a "holy grail" but we decided that while hydrogenations of alkyl-substituted alkenes were certainly difficult, mainly due to difficulties determining the ee's of the products, they were not exceptionally useful.

Our 2005 *Chem. Rev.* also presented our interpretation of the most valuable application of chiral analogues of Crabtree's catalyst: hydrogenation of substrates with functional groups. This is because hydrogenation products are most useful if they can be used as chiral building blocks, chirons, and this requires at least one functional group (FG) for modification. We suggested alkene substrates with functional groups that were not strongly coordinating in hydrogenation reactions are particularly interesting since these could not be tackled using chiral analogues of Wilkinson's catalyst.

Andersson arrived at conclusions similar to those outlined above; since 2005, his group has published on chiral analogues of Crabtree's catalyst in hydrogenations of alkenes with functional groups that are not usually considered to be coordinating. Substrates studied (by Andersson and others) include vinyl phosphonates,[25−28] vinyl fluorides,[29,30] CF_3-substituted olefins,[31] vinyl silanes,[32] vinyl boronates,[33] enol phosphinate esters,[23,34] enol ethers (using catalysts **1** and **7**, reactions not shown here, but discussed later in the review),[24,35] enamines,[36−38] imines,[39] heterocyclic alkenes,[40] and even heteroaromatic rings.[2] Excellent yields and enantioselectivities were observed in many of these reactions (Figure 4). These hydrogenation products have intrinsic value, or can be transformed into high-value materials. Our focus has been different: acyclic stereocontrol in syntheses of chirons for polyketide derived natural products, as described in the next section.



5. Acyclic Diastereocontrol in Homogeneous Hydrogenations

Enantioselective hydrogenations achieve stereochemical control via preferred diastereomeric intermediates from

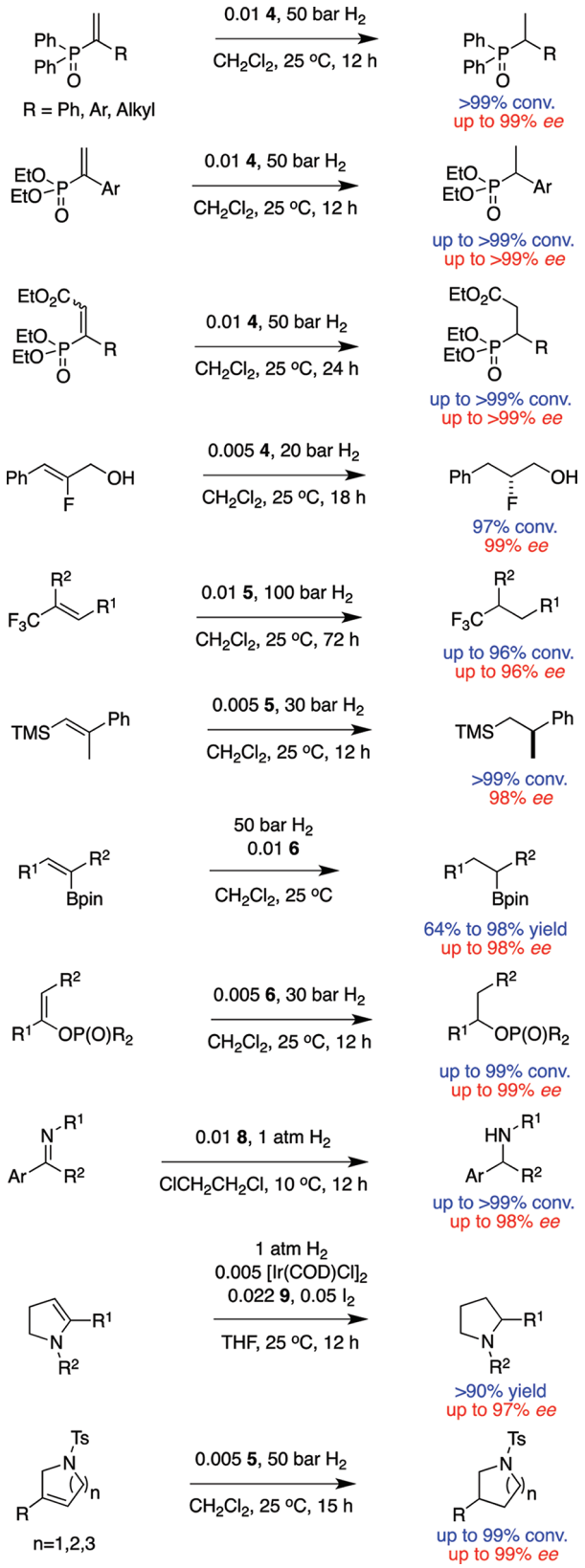


FIGURE 4. Some enantioselective hydrogenation of functionalized alkenes without CFGs, excluding those to make chirons for polyketide-derived natural products.

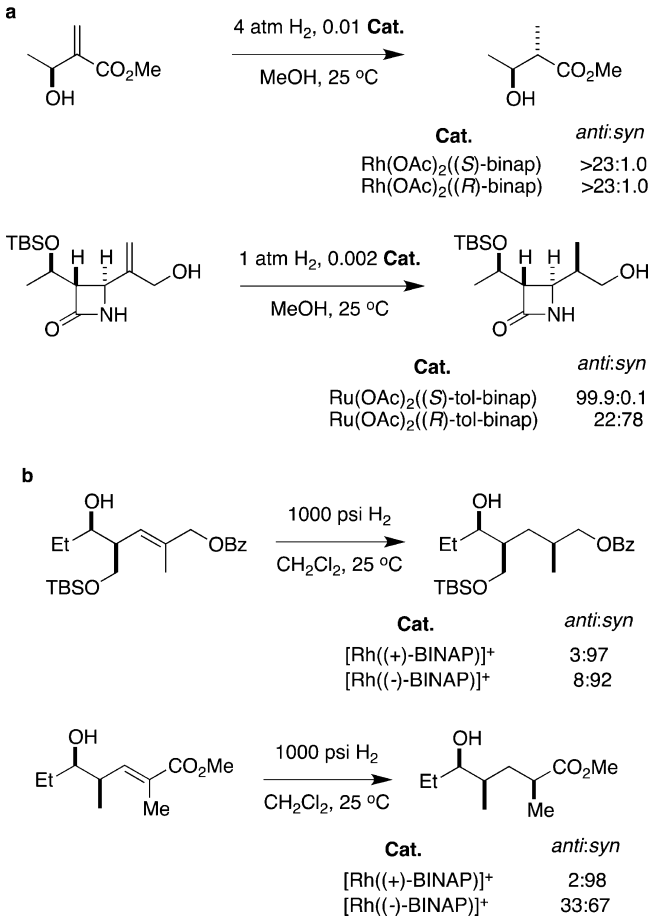


FIGURE 5. Chiral transition-metal catalyzed diastereoselective hydrogenations of (a) allylic alcohols; (b) homoallylic alcohols.

prochiral substrates and chiral metal complexes. A higher level of sophistication is involved when the substrate is also chiral because diastereoselectivities are achieved via double stereodifferentiation, that is, combining what we refer to as "stereochemical vectors" originating from the effects of the catalyst and of the substrate. In catalysis, stereochemically complex substrates provide stringent tests for the value of stereoselective catalysts, and require careful consideration of the possible effects of substrate modifications.

Research into directed hydrogenations for acyclic stereocontrol peaked in the 1980s,[41] and much of it featured 1,1-disubstituted alkenes that are relatively nonhindered and easy to hydrogenate. Those reactions were mostly substrate-controlled, so it was not possible to obtain both diastereomers of the hydrogenation product by varying the catalyst chirality alone (Figure 5a). Examples involving trisubstituted alkenes from that era are rarer, and tend to feature *homoallylic* alcohols.[42] In these cases, high diastereoselectivities are possible because simultaneous coordination of the metal to the hydroxy group and alkene gives

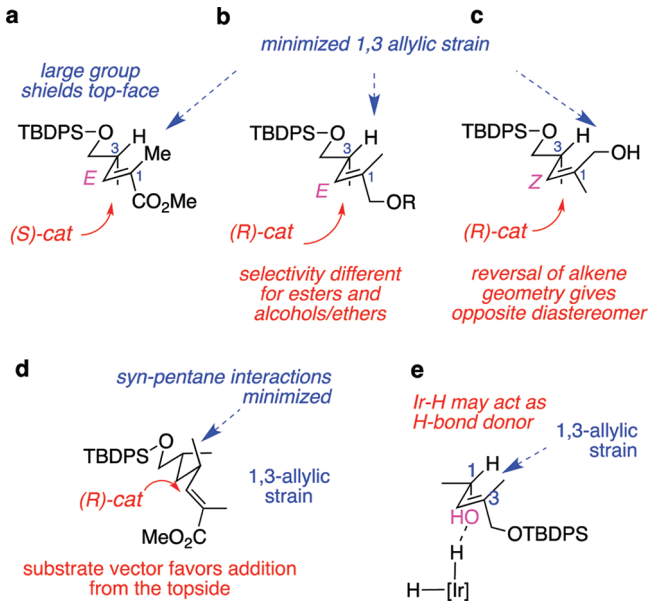


FIGURE 6. Acyclic stereocontrol via catalyst **1**: (a) Roche ester homologues; (b) corresponding allylic alcohols or ethers; (c) inverted alkene geometries; (d) effects of *syn*-pentane conformers; and, (e) putative *H*-bonding to allylic alcohols.

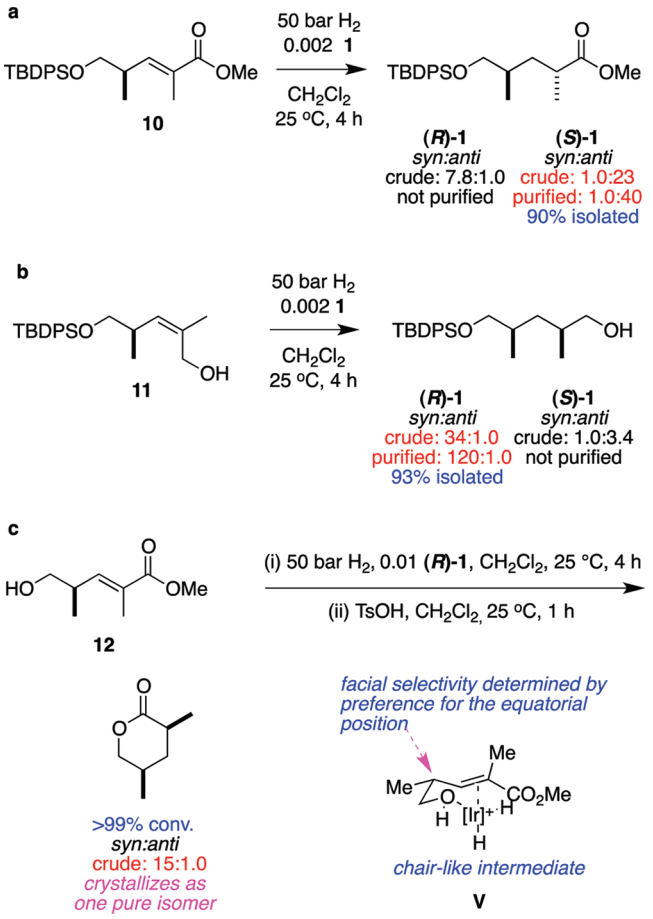


FIGURE 7. Preparation of (a) an *anti* type **J** chiron; (b) the *syn* type **J** chiron; (c) syn type **J** chiron via homoallylic alcohol directed hydrogenation (ratios from GC throughout).

rigid, chairlike intermediates **B** (Figure 5b).[42] Substrate controlled reactions require manipulation of variables besides the catalyst to obtain all stereoisomers in the series, and in the absence of a substantial *catalyst vector*, this can be impossible. Moreover, chiral analogues of Crabtree's catalyst were not available in the 1980s; the first chiral analogue of Crabtree's catalyst was not reported until Pfaltz's seminal paper in 1998.[43] Consequently, apart from the work described here, relatively few investigations of acyclic stereocontrol have focused on optically active analogues of Crabtree's catalyst,[44] but we think those catalysts can fill a significant gap in organic methodology: hydrogenations of substrates without CFGs for Ir- and Rh-diphosphine catalysts.

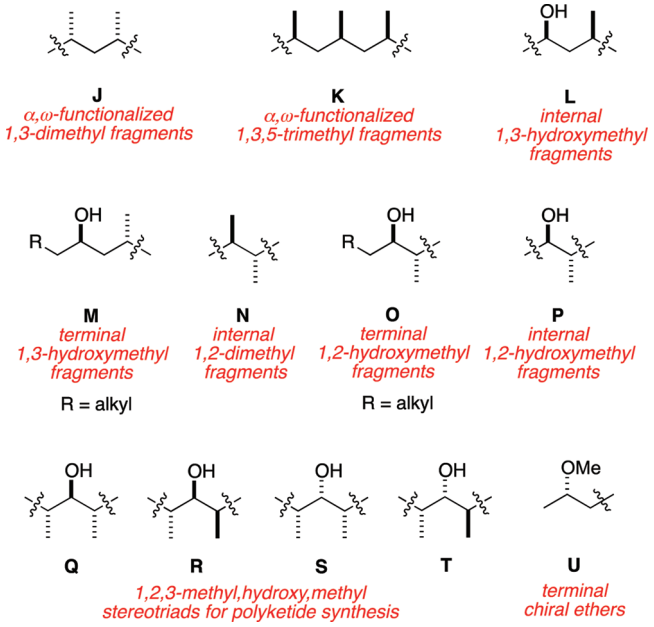
6. Significance of Chiral Crabtree'S Catalysts for Acyclic Stereocontrol

N,Carbene-catalyst **1** is able to mediate directed hydrogenations, just like chiral analogues of Wilkinson's catalyst, and with excellent diastereoselectivities. However, it can do much more because it mediates hydrogenation of trisubstituted alkenes without CFGs, and, second, it tends to do so with high levels of catalyst control. This is not simply a matter of pairing the stereochemical bias of the substrate and the catalyst, as the discussion below explains.

Figure 6a illustrates how the catalyst dominates when a Roche-ester-derived substrate is hydrogenated, and how optimal stereoselectivity is obtained by matching this with the inherent bias caused by the substrate conformation (we call this the *substrate vector*, often based on 1,3-allylic strain effects). However, to obtain satisfactory stereoselectivities, the protecting group on the homoallylic-*O* was made large (here TBDPS) to enhance the substrate vector; overall, the reaction is still, in fact, catalyst controlled but that modification to the substrate is important to obtaining high stereoselectivities. Thus, this is a three-dimentional problem in which the catalyst and substrate vectors are matched, and peripheral features of the substrate may be modified to enhance that synergy (see Figure 7 for examples). Strategies based on these ideas are critical to elaborating optically active substrates with chiral catalysts. Surprises can emerge when considering the role of the substrate; for example, part (b) of Figure 6 illustrates that our catalyst approaches allylic alcohols (ethers, acetates, etc.) and α,β-unsaturated esters from different faces (for reasons that we have described[18]). Besides functional group interchanges between ester, alcohol, or ethers, alkene geometries may also be manipulated

to bring *substrate vectors* into alignment with the catalyst bias (part c); *E*-to-*Z* changes tend to reverse the configuration of one chiral center formed in a catalyst controlled reaction, and increase 1,3-allylic strain effects leading to enhanced matched stereoselectivities. *syn*-Pentane interactions should also be considered for extended systems with two chiral centers in the chain (d). Finally, part (e) outlines a hypothesis we developed invoking H-bonding to allylic alcohols, since the Ir−H ligands are acidic,[17] though we cannot exclude mechanisms that involve stereoselective double bond migration to an enol, then hydrogenation of the aldehyde; our catalyst does mediate hydrogenations of aldehydes (and, very slowly, ketones).

Important chirons **J**–**U** for syntheses of polyketide-derived natural products can be prepared by following the guidelines outlined in Figure 6. Approaches to these chirons are outlined in the following sections.



6.1. Deoxypolyketide Chirons. Chirons **J** and **K**, as in deoxypolyketides, are made via "diastereoselective reactions involving chiral auxiliaries" or "catalysis".[45] Of the diastereoselective group, Myers' asymmetric alkylation methodology is probably the most practical.[46] Catalytic approaches, on the other hand, are gaining importance.[47,48] In 2007, we found that allylic alcohols and enoates bearing a stereogenic center adjacent to the C=C bond can be converted to precursors for syntheses of deoxypolyketides. Hydrogenation of enoate **10** using (*S*)-**1** occurs with high diastereoselectivity. An *inverted* and smaller diastereoselectivity was observed for the antipode of the catalyst, hence this transformation is catalyst controlled

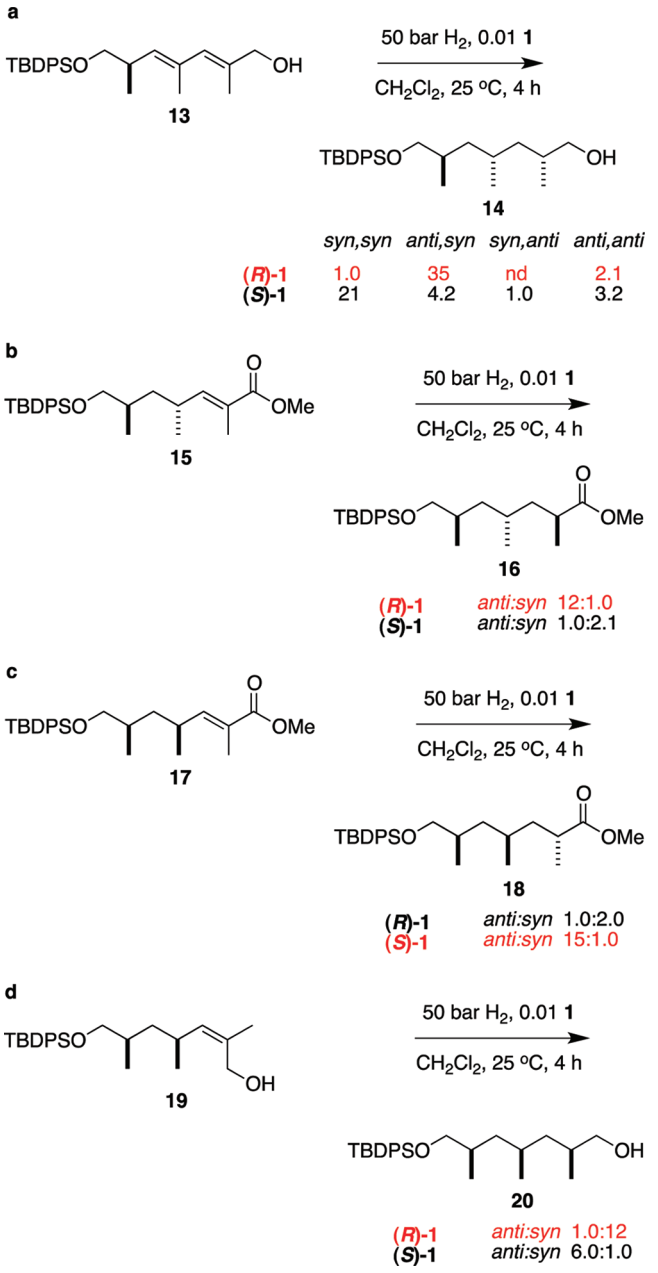


FIGURE 8. (a) *anti,syn* type **K** chiron: **14** was isolated in 83% yield and with a 51:1 *anti,syn/syn,syn* ratio after one chromatographic purification. (b) *anti,anti* type **K** chiron: **16** was reduced (DIBALH) to an isomer of alcohol **20** and isolated in 70% yield with a 120:1 *anti,anti/anti,syn* ratio after chromatography. (c) *syn,anti* type **K** chiron: **18** was reduced to an isomer of alcohol **20** and isolated in 82% yield, 89:1 *syn,anti/syn,syn*. (d) *syn,syn* type **K** chiron: **20** was isolated in 71% yield with >120:1 *syn,syn/syn,anti* ratio after one chromatographic purification.

(Figure 7a).[49] The corresponding *syn*-product was obtained with high selectivity when the *Z*-allylic alcohol **11**, was hydrogenated using (*R*)-**1** (Figure 7b).[50] Figure 7c shows a directed hydrogenation of the type discussed above, but using catalyst **1**.

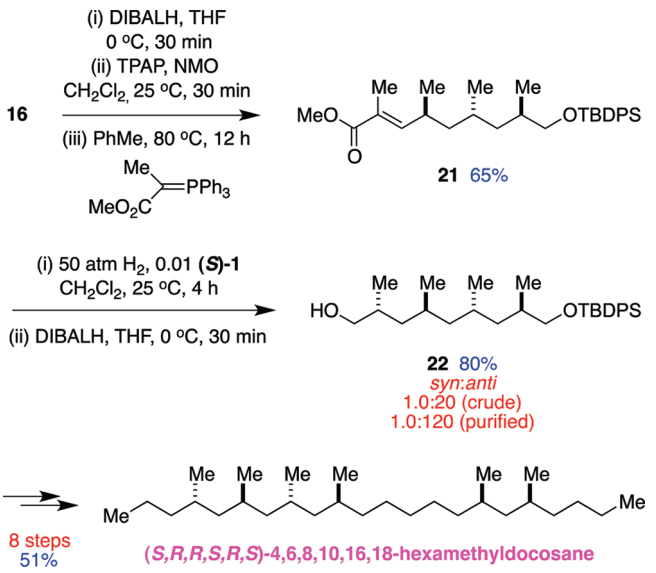


FIGURE 9. Total synthesis of (*S*,*R*,*R*,*S*,*R*,*S*)-4,6,8,10,16,18-hexamethyldocosane.

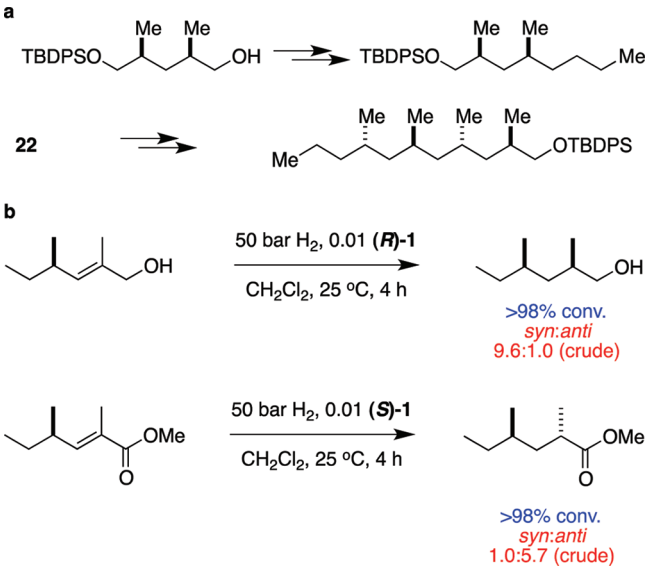


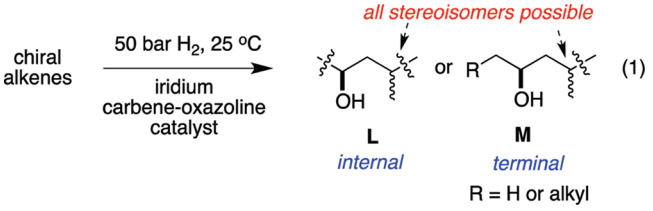
FIGURE 10. (a) α-Monofunctionalized chirons from α,ω-functionalized ones; (b) direct synthesis of α-monofunctionalized chirons via asymmetric hydrogenations.

A higher homologue of 1,3-dimethylated chirons, the *anti,syn*-1,3,5-trimethylated chiron **K**, was obtained from direct hydrogenation of a chiral diene (Figure 8a). This is a special transformation in which two chiral centers were generated simultaneously, and with good diastereoselectivity.[50] Other stereoisomers of this triad were prepared by homologating the product shown in Figure 7 to give the starting materials shown in Figure 8b−d; all these alkenes were hydrogenated with high stereoselectivities.

Asymmetric hydrogenation routes to deoxypolyketide fragments has been used in a preparation of (*S*,*R*,*R*,*S*,*R*,*S*)-4,6,8,10,16,18-hexamethyldocosane, a putative sex pheromone from an Australian beetle.[51] This synthesis involved a simple 1,3-dimethyl based chiron (not shown) and homologation of a 1,3,5-trimethyl system into the 1,3,5,7-tetramethyl chiron. Experience gained in syntheses of chirons **J** and **K** meant that this task was relatively easy (Figure 9).

In the synthesis of the natural product above, two α,ω-functionalized hydrogenation products were converted to a monofunctionalized chiron (Figure 10a) even though this is less direct hydrogenating to give two monofunctionalized chirons. Why was this approach used when we had already developed methods to prepare monofunctionalized 1,3-dimethyl chirons (Figure 10b)? The reasons are that stereoselectivities tend to be greater for hydrogenations of α,ω-functionalized alkenes than for similar α-monofunctionalized ones because there are more ways to optimize the substrate vector when *two* functional groups are available for manipulation. Second, α,ω-functionalized chirons can generally be transformed into α-monofunctionalized ones with any alkyl group at the terminus, and to do so is usually more efficient than trying to optimize asymmetric hydrogenations for new substrates. As is often the case in organic chemistry, it is not only the number of steps involved, but the practicality of each one that counts. Micalizio's group have used catalyst **1** in similar hydrogenations to form 1,3-dimethyl fragments. This step was part of their synthesis of dictyostatin.[52]

6.2. 1,3-Hydroxymethyl Chirons. All the substrates featured in the last section were derived from Roche's ester. However, several other readily available natural starting materials can be used to generate other valuable chirons in a similar way. This section features 1,3-hydroxymethyl fragments (eq 1) where the chiral alkenes are derived from glyceraldehyde or lactic acid.[53]



Allylic alcohols **23** and **24** can be synthesized from glyceraldehyde in a few steps with high enantiomeric purities. Hydrogenation of enoate **23** occurs with 19:1.0 diastereoselectivity (*syn*:*anti*) when using (*R*)-**1**. Substrate control was observed in this reaction presumably because the homoallylic alcohol directs the catalyst via a chair like intermediate **V** (Figure 7c) with the allylic substituent in an

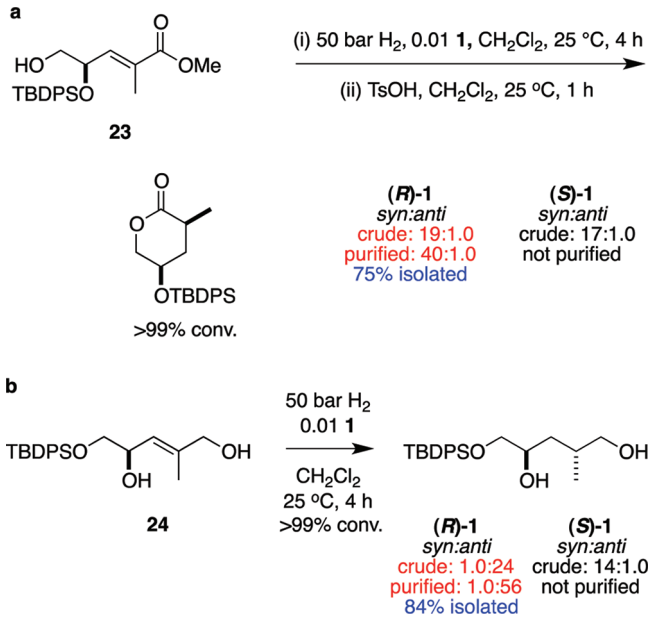


FIGURE 11. (a) *syn* type **L** chiron; (b) preparation of the *anti* type **L** chiron.

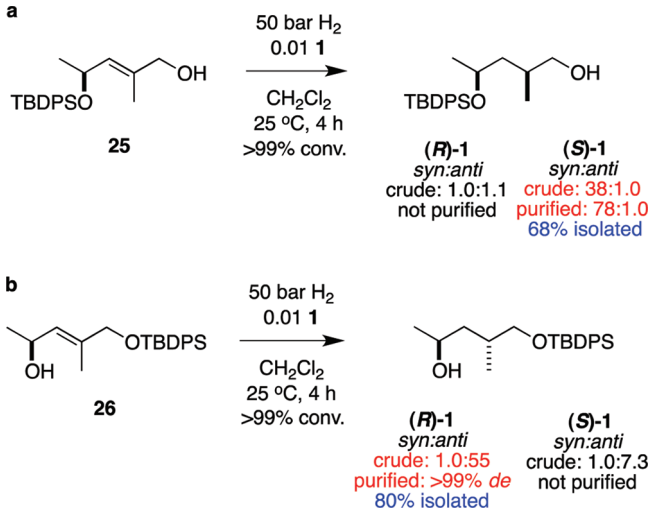


FIGURE 12. Preparation of (a) a *syn* type **M** chiron; (b) the *anti* type **M** chiron.

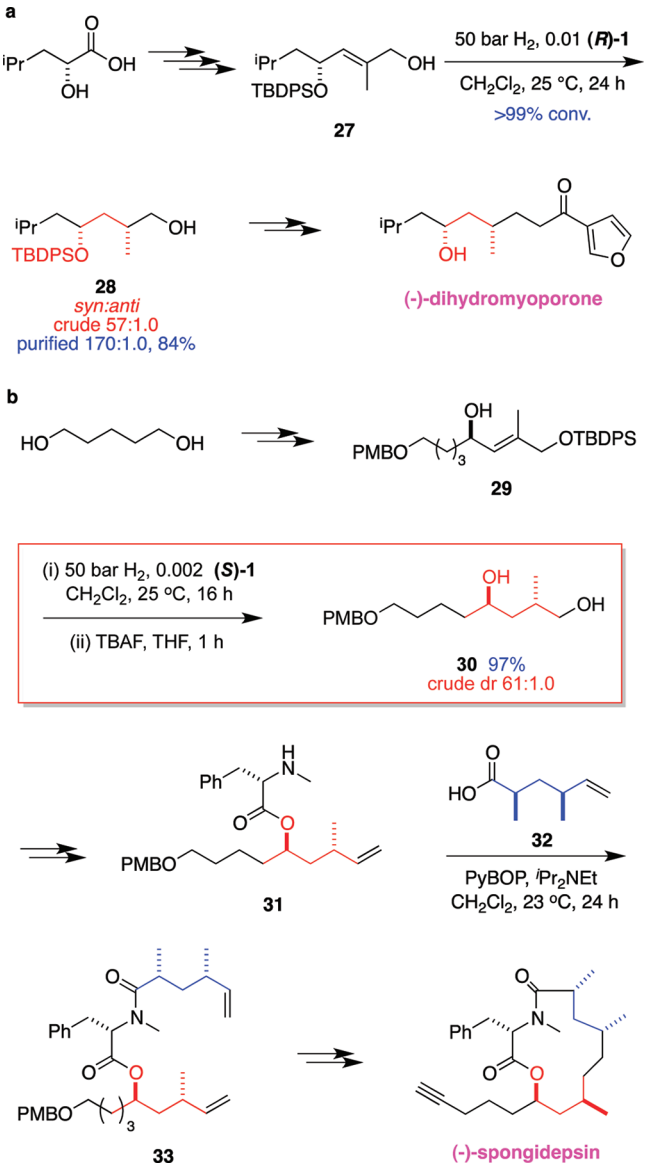


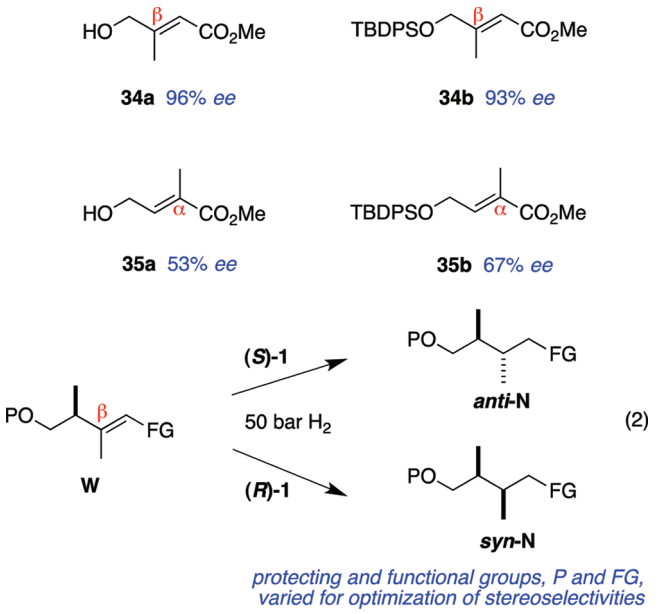
FIGURE 13. Total synthesis of (a) (−)-dihydromyoporone; (b) (−)-spongidepsin.

equatorial position.[42] After hydrogenation, the crude mixture was treated with catalytic acid to give the lactone shown, which can be purified via recrystallization to 40:1.0 *dr*; chromatography is thus avoided. To access the *anti*-stereoisomer of **L**, allylic alcohol **24** was hydrogenated using (*R*)-**1** to give the product with a crude *syn*:*anti* ratio of 1.0:24 (Figure 11).

A similar approach to that shown above, but using lactic acid as the alkene precursor, was used to obtain optically pure *syn*- and *anti*-isomers corresponding to the terminal fragment **M**. Both isomers could be obtained with excellent diastereoselectivities and high yields by optimizing the substrate protection. Hydrogenation of **25** was only marginally catalyst controlled, and substrate control dominated for **26** (Figure 12); this is unusual for complex **1** for which *catalyst* control is the norm.

A synthesis of (−)-dihydromyoporone (Figure 13a) was performed to illustrate hydrogenation of the α-hydroxy acid derived from diazotization of leucine rather than lactic acid; hydrogenation of the substrate derived from this proceeded with even higher stereoselectivity. A more complex natural product (−)-spongidepsin was also prepared; the latter compound contains both 1,3-dimethyl- and 1,3-hydroxymethyl fragments (Figure 13b).[54]

6.3. 1,2-Dimethyl Chirons. Carbon chains bearing adjacent methyl groups are observed in some natural products; access to these chirons tend to be difficult.[55] Hydrogenations of relatively simple substrates with catalyst **1**, however, had shown better enantioselectivities for the β-methyl esters **34** than the α-methyl systems **35** implying substrates **W** might be suited for syntheses of 1,2-dimethyl chirons **N**. We hypothesized both the *syn*- and *anti*-isomers of this system could be obtained by varying the protection and functional groups as implied in eq 2.



The idea outlined above was validated by experiment: the *anti*-isomer of **N** was obtained from enoate **36**, while allylic ether **37** was used to prepare the *syn*-form. Both of the reactions were *catalyst controlled*, but substrate vectors were significant. This methodology was subsequently used to obtain (−)-lasiol and the central fragment of (+)-kalkitoxin (Figure 14).[56] Hydrogenations to give both 1,3- and 1,2-dimethyl fragments were involved in the latter synthesis.

6.4. 1,2-Hydroxymethyl Chirons. Asymmetric hydrogenations of chiral α-oxy alkenes generate chirons that are typically made via aldol reactions. Stereoselective hydrogenations of chiral allylic alcohols, where the alkene fragments are 1,1-disubstituted, were extensively investigated about two decades ago;[41,57] metal *diphosphine* complexes were useful because the alkenes are relatively unhindered. However, most of those reactions were *substrate*-controlled (e.g., Figure 5); hence, it was impossible to obtain *both* the *syn* and *anti* aldol fragments by varying the chirality of the Rh- or Ir-diphosphine complexes. Use of

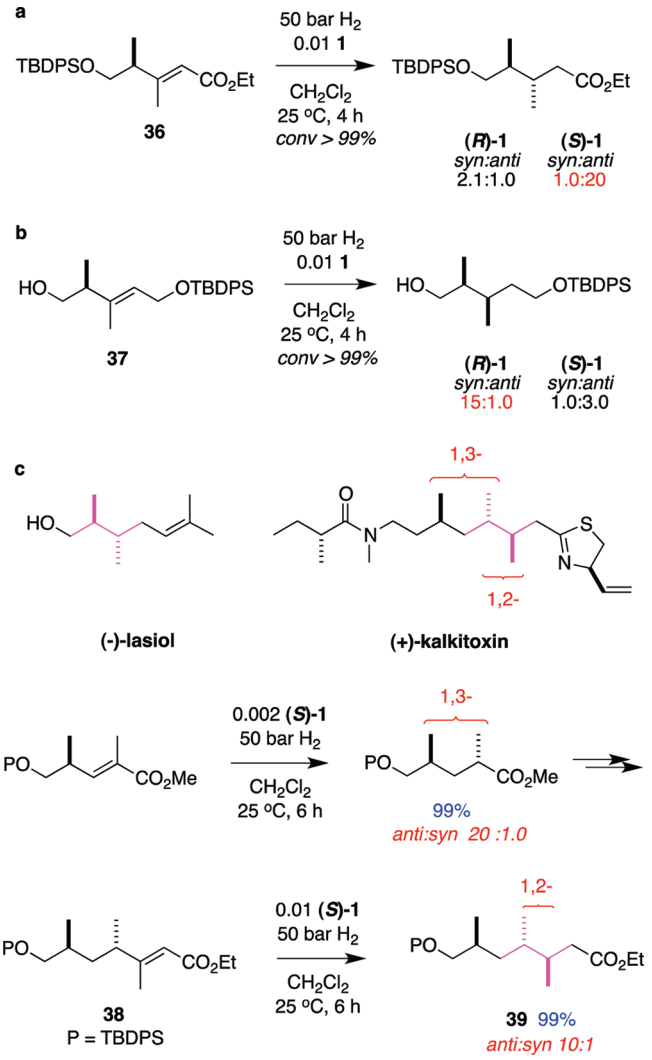
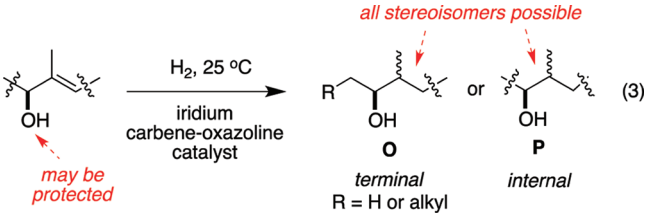


FIGURE 14. (a) *anti* type **N** chiron; (b) preparation of the *syn* type **N** chiron; (c) two natural products which were synthesized through the iridium catalyzed hydrogenations (ratios from GC analyses).

chiral analogues of Crabtree's catalysts like **1** expanded the methodology because the more hindered trisubstituted allylic alcohols *can* be used, and with high levels of catalyst control, allowing both the *syn*- and *anti*-isomers to be obtained (eq 3).[58]



Optically pure lactic acid was transformed into substrates **40** and **41** for access to generic type **P** chirons via hydrogenations. The best *syn*-selectivity was obtained from the allylic alcohol **40** (*syn*:*anti* 61:1.0; Figure 15a).

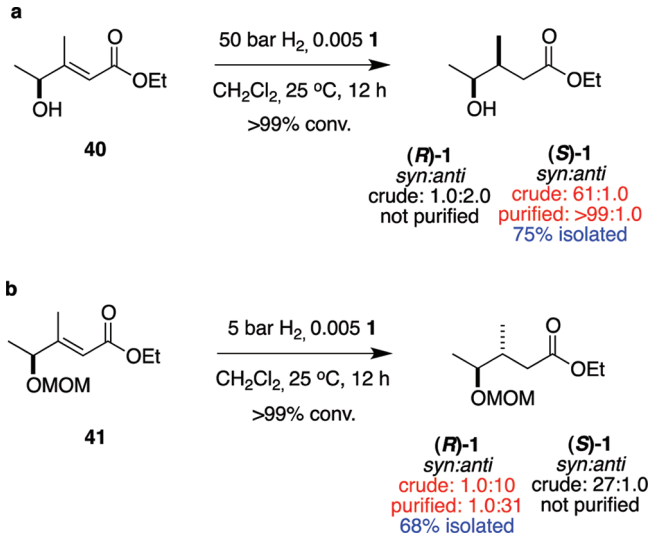
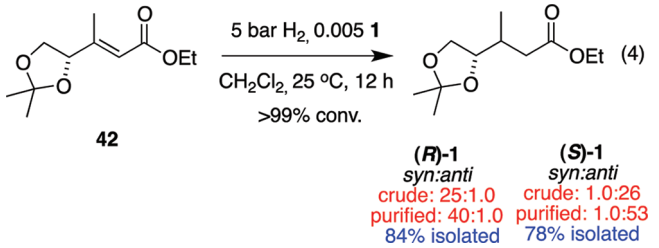


FIGURE 15. Preparation of the (a) *syn* type **O** chiron; and, (b) *anti* type **O** chiron (ratios from GC analyses).

Good *anti*-selectivity was derived by MOM-protecting the alcohol **40** to give the ether substrate **41** (*syn*:*anti* 1.0:10 in the hydrogenation; Figure 15b).

To obtain α,ω-difunctional chirons via hydrogenations, optically pure glycitol acetonide was transformed into alkene **42** to access chiron **P**. The best *syn*-selectivity was obtained from (*E*)-alkene **42** with (*R*)-**1**, and excellent *anti*-selectivity from the same substrate was observed using (*S*)-**1**, that is, the substrate vector was totally overwhelmed by the catalyst one (eq 4).



7. 1,2,3-*Me,OH,Me*-α,ω-Functionalized "Triad Chiron Cassettes"

Contiguous *Me,OH,Me* substituents, as in **Q**–**T**, are found in many polyketide-derived materials.[59] Much research effort has been expended on *de novo* construction of these triads as parts of linear synthetic strategies.[60] An alternative might involve practical syntheses of suitably functionalized and protected triad units on scale, enabling these fragments to be marketed as cassettes then used in convergent routes. Ideal methodologies to achieve this would encompass: (i) routes that are amenable to scale-up; (ii) access to *all* isomers in the series; and, (iii) α,ω-functional groups to enable homologation in either direction. In fact, there

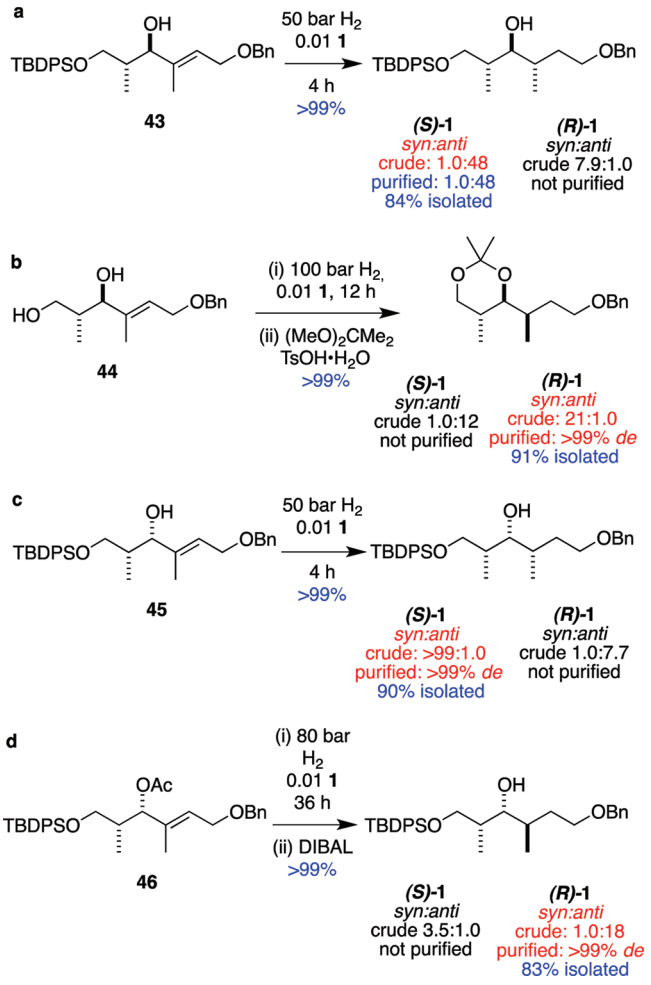
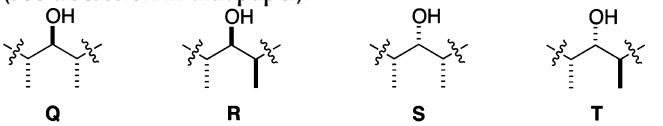


FIGURE 16. Chirons for α,ω-functionalized triads: (a) *anti,anti*-type **Q**; (b) *anti,syn*-type **R**; (c) *syn,syn*-type **S**; and, (d) *syn,anti*-type **T** (ratios from HPLC; all reactions in CH_2Cl_2 at 25 °C).

are only a few methods that can be used to obtain *all* four diastereomers (and their enantiomers) with high stereoselectivities by elaboration of the Roche ester. Methods that can do this include ones involving resolved allenyl-stannane,[61] -silyl,[62,63] or -zinc reagents,[64] or on optically pure crotylsilanes,[65] and a 2011 contribution by Leighton's group that is probably the best method for elaboration of Roche ester derivatives into the targeted triads (see discussion in that paper).[66]



To elaborate the Roche ester via hydrogenation methodology,[67] it was built out with high diastereoselectivity via a Felkin-Anh type reduction into the *anti*-alcohol **43**, then deprotection gave diol **44**. Another elaboration of the Roche's ester via a highly stereoselective chelation-controlled reduction afforded the *syn*-alkenes **45** and **46**.

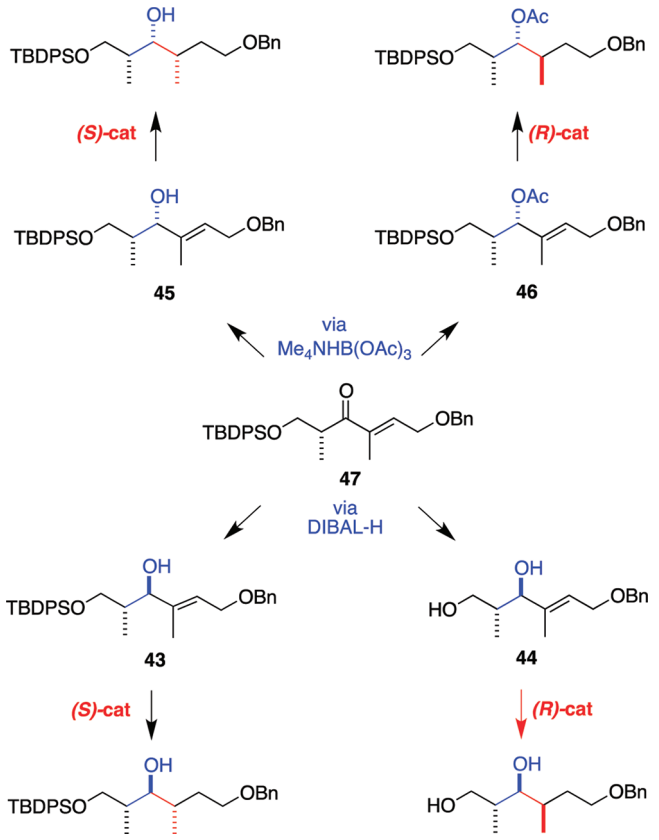


FIGURE 17. Key transformations in this paper diverge from the enone **47** via hydridic reductions of the ketone then asymmetric hydrogenations of the alkene fragment.

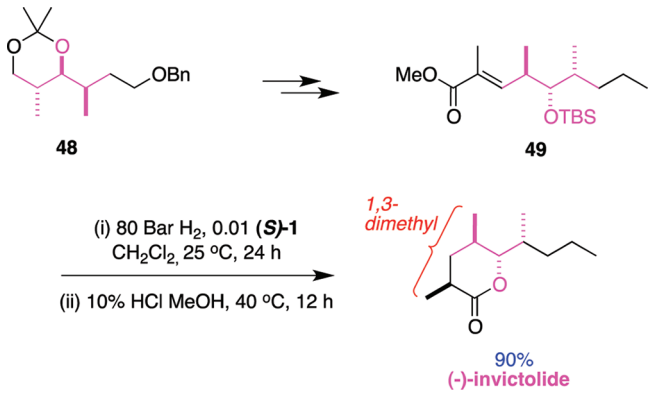


FIGURE 18. Total synthesis of (−)-invictolide.

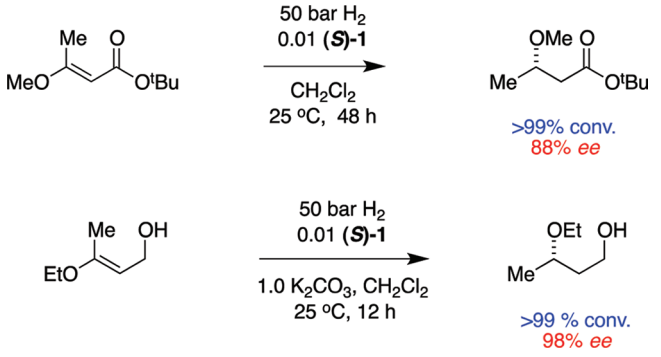


FIGURE 19. Hydrogenations of enol ether substrates using catalyst **1**.

These divergent linear syntheses can be used to produce *all four* key chiral alkene substrates in a highly efficient manner because two of them are intermediates in the syntheses of the other two. Thus substrates for the featured hydrogenations can be made efficiently from Roche esters via substrate-controlled reactions that do not require chiral auxiliaries, resolved reagents, or even asymmetric catalysis.

Hydrogenations of the pivotal substrates **43**−**46** in this methodology are shown in Figure 16. High levels of *catalyst control* dominate such that the *least* selective reaction (Figure 16d) gave an 18:1.0 bias in the crude reaction material, and the most (Figure 16c) gave only one diastereomer in our HPLC analysis (UV detection). In two cases (Figure 16b and d), it was advantageous to modify the hydrogenation products to facilitate removal of trace stereoisomers by chromatography.

Figure 17 summarizes this methodology in which two pairs of very similar substrates (**43** + **44**, and **45** + **46**) can be formed from a single enone (**47**) then elaborated into the targeted α,ω-functionalized *Me,OH,Me* chirons. Leighton's crotylation methodology appears to us to be the most practical way to obtain all the stereoisomers of the targeted triads, so it is informative to compare our method to that. After considering the steps involved, our analysis is that the two methods are of similar practicality for scalable syntheses of all four isomers of the products.

(−)-Invictolide was prepared to illustrate the practicality of our hydrogenation methodology (Figure 18). To do this, more than a gram of chiron **48** was prepared via the reactions indicated above, and classical reactions were used to transform this into alkene **49**. Another of our diastereoselective hydrogenations[18,50,51,54] was used to produce a 1,3-disposed dimethyl fragment, before the last step in the synthesis: deprotection and cyclization to the lactone target.

8. Missing Pieces

Some work remains to show hydrogenation reactions can be used to obtain all chirons to build polyketide-derived natural products; specifically, motifs including α,ω-functionalized 1,3-dihydroxy, 1,2,3-*OH,Me,OH* and 1,2,3,4-*Me,OH, Me,OH* fragments have yet to be made via alkene hydrogenations. Some of these chirons might be made via hydrogenation of acid-sensitive enol ethers, for which catalyst **1** is particularly well suited for the reasons discussed already. Figure 19 gives some illustrative reactions that indicate how such strategies might proceed.

9. Conclusion

Chiral analogus of Crabtree's catalyst are almost uniquely suitable for asymmetric hydrogenation of coordinating unfunctionalized, trisubstituted alkenes. These relatively hindered substrates typically would *not* be reduced at a significant rate using metal diphosphine complexes.

Complex **1** usually gives catalyst control for hydrogenations of chiral alkenes. Metal diphosphine complexes tend only to hydrogenate substrates with a coordinating functional group, in which case substrate control is usually observed. Consequently, we have been able to prepare chirons containing 1,3-dimethyl-,[18,50,51] 1,3-hydroxymethyl-,[53,54] 1,2-dimethyl-,[56] 1,2-hydroxymethyl-,[58] and 1,2,3-methyl,hydroxy,methyl fragments. Stereoselectivities in these reactions were enhanced by constructively coupling the substrate with the catalyst-vectors via first matching the catalyst enantiomer with the substrate bias, then changing the following substrate variables to optimize this synergy: (i) alcohol protecting groups; (ii) alkene geometries; and, (iii) functional group interconversion between ester and allylic alcohols (or protected allylic alcohols).

Catalyst **1** is of the *carbene,N*-type, and this makes it particularly suited for acid-sensitive substrates; however, it is clear that *N,P*-ligated chiral analogues of Crabtree's catalyst could be used for most of the other reactions presented here. Indeed, we have come to realize limitations of our catalyst. It appears not to hydrogenate endocyclic and tetrasubstituted alkenes well. Moreover, one of Zhou's chiral analogues of Crabtree's catalyst was reported to give higher enantioselectivities for hydrogenation of tiglic acid than **1**,[68] implying at least this catalyst, and maybe others, might outperform our *N,carbene* system in hydrogenations of more complex chirons with tiglic-acid-like fragments. Consequently, our work demonstrates the potential of hydrogenations with chiral analogues of Crabtree's catalyst to obtain chirons for polyketide syntheses, but upper limits for the stereoselectivities have probably yet to be reached.

We would like to thank all the co-workers at Texas A & M who contributed to the work for this review, and those who helped to provide a scholarly environment to talk about it. Generous support was provided by The National Science Foundation (CHE-0750193) and The Robert A. Welch Foundation (A-1121).

BIOGRAPHICAL INFORMATION

Ye Zhu received a bachelor degree (2002) in chemistry from Nanjing University, and his Ph.D. degree in chemistry (2011) under the supervision of Prof. Kevin Burgess from Texas A&M University. Currently he is carrying out postdoctoral research on functional electrolytes for lithium-ion batteries at Argonne National Laboratory, Chicago. He received the Chinese Government Award for Outstanding Self-financed Students Abroad (2010). His PhD research focuses on the asymmetric hydrogenations of chiral acyclic alkenes with a chiral *N,carbene*-Iridium catalyst for important chiron synthesis.

Kevin Burgess is Rachel Professor of Chemistry at Texas A & M University, where he has been since 1992. His research interests focuses on peptidomimetics for mimicking or disrupting protein–protein interactions, asymmetric organometallics catalysis, and fluorescent dyes for applications in biotechnology. He has been coauthor of the *Highlights* section in *Chemistry and Industry* for over 20 years, and has recently published a work-book for graduate students studying organic chemistry: *Organic Chemistry By Inquisition* (www.byinquisition.org).

FOOTNOTES

*To whom correspondence should be addressed. E-mail: burgess@tamu.edu.

The authors declare no competing financial interest.

[a]By *classical* we refer groups that most organometallic chemists recognize as being easily able to bind to a transition metal in standard hydrogenation methods. Actually, we believe that some groups that are *not* classically regarded as CFGs in hydrogenations *do* coordinate to high oxidation state iridium in the reactions featured here; for instance, these are not CFGs in rhodium catalyzed hydrogenations but they might be weakly ligate Ir(5+) intermediates in a catalytic cycle. We are not referring to CFGs in other reaction types.

REFERENCES

1 Zhang, W.; Chi, Y.; Zhang, X. Developing Chiral Ligands for Asymmetric Hydrogenation. *Acc. Chem. Res.* **2007**, *40*, 1278–1290.

2 Zhou, Y.-G. Asymmetric Hydrogenation of Heteroaromatic Compounds. *Acc. Chem. Res.* **2007**, *40*, 1357–1366.

3 Minnaard, A. J.; Feringa, B. L.; Lefort, L.; de Vries, J. G. Asymmetric Hydrogenation Using Monodentate Phosphoramidite Ligands. *Acc. Chem. Res.* **2007**, *40*, 1267–1277.

4 Tang, W.; Zhang, X. New Chiral Phosphorus Ligands for Enantioselective Hydrogenation. *Chem. Rev.* **2003**, *103*, 3029–3070.

5 Noyori, R. *Asymmetric Catalysis In Organic Synthesis*; John Wiley & Sons, Inc.: New York, 1994.

6 Cui, X.; Burgess, K. Catalytic Homogeneous Asymmetric Hydrogenations of Largely Unfunctionalized Alkenes. *Chem. Rev.* **2005**, *105*, 3272–3296.

7 Roseblade, S. J.; Pfaltz, A. Iridium-Catalyzed Asymmetric Hydrogenation of Olefins. *Acc. Chem. Res.* **2007**, *40*, 1402–1411.

8 Crabtree, R. H. Iridium Compounds in Catalysis. *Acc. Chem. Res.* **1979**, *12*, 331–337.

9 Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. Optically Active Iridium Imidazol-2-ylidene-oxazoline Complexes: Preparation and Use in Asymmetric Hydrogenation of Arylalkenes. *J. Am. Chem. Soc.* **2003**, *125*, 113–123.

10 Powell, M. T.; Hou, D.-R.; Perry, M. C.; Cui, X.; Burgess, K. Chiral Imidazolylidine Ligands for Asymmetric Hydrogenation of Aryl Alkenes. *J. Am. Chem. Soc.* **2001**, *123*, 8878–8879.

11 Kaellstroem, K.; Andersson, P. G. Asymmetric hydrogenation of trisubstituted alkenes with Ir-NHC-thiazole complexes. *Tetrahedron Lett.* **2006**, *47*, 7477–7480.

12 Bolm, C.; Focken, T.; Raabe, G. Synthesis of iridium complexes with novel planar chiral chelating imidazolylidenen ligands. *Tetrahedron Asymmetry* **2003**, *14*, 1733–1746.

13 Nanchen, S.; Pfaltz, A. Chiral phosphino- and (phosphinooxy)-substituted N-heterocyclic carbene ligands and their application in iridium-catalyzed asymmetric hydrogenation. *Helv. Chim. Acta* **2006**, *89*, 1559–1573.

14 Cui, X.; Fan, Y.; Hall, M. B.; Burgess, K. Mechanistic Insights into Iridium-Catalyzed Asymmetric Hydrogenations of Dienes. *Chem.—Eur. J.* **2005**, *11*, 6859–6868.

15 Cui, X.; Burgess, K. Iridium-Mediated Asymmetric Hydrogenation of 2,3-Diphenylbutadiene: A Revealing Kinetic Study. *J. Am. Chem. Soc.* **2003**, *125*, 14212–14213.

16 Mazet, C.; Smidt, S. P.; Meuwly, M.; Pfaltz, A. A Combined Experimental and Computational Study of Dihydrio(phosphinooxazoline)iridium Complexes. *J. Am. Chem. Soc.* **2004**, *126*, 14176–14181.

17 Zhu, Y.; Fan, Y.; Burgess, K. Carbene-Metal Hydrides Can Be Much Less Acidic Than Phosphine-Metal Hydrides: Significance in Hydrogenations. *J. Am. Chem. Soc.* **2010**, *132*, 6249–6253.

18 Zhou, J.; Ogle, J. W.; Fan, Y.; Banphavichit, V.; Zhu, Y.; Burgess, K. Asymmetric Hydrogenation Routes To Deoxypolyketide Chirons. *Chem.—Eur. J.* **2007**, *13*, 7162–7170.

19 Fan, Y.; Cui, X.; Burgess, K.; Hall, M. B. Electronic Effects Steer the Mechanism of Asymmetric Hydrogenations of Unfunctionalized Aryl-Substituted Alkenes. *J. Am. Chem. Soc.* **2004**, *126*, 16688–16689.

20 Brandt, P.; Hedberg, C.; Andersson, P. New Mechanistic Insights into the Iridium - Phosphanooxazoline-Catalyzed Hydrogenation of Unfunctionalized Olefins: A DFT and Kinetic Study. *Chem.—Eur. J.* **2003**, *9*, 339–347.

21 Church, T. L.; Rasmussen, T.; Andersson, P. G. Enantioselectivity in the Iridium-Catalyzed Hydrogenation of Unfunctionalized Olefins. *Organometallics* **2010**, *29*, 6769–6781.

22 Hopmann, K. H.; Bayer, A. On the mechanism of iridium-catalyzed asymmetric hydrogenation of imines and alkenes: a theoretical study. *Organometallics* **2011**, *30*, 2483–2497.

23 Cheruku, P.; Gohil, S.; Andersson, P. G. Asymmetric Hydrogenation of Enol Phosphinates by Iridium Catalysts Having N,P Ligands. *Org. Lett.* **2007**, *9*, 1659–1661.

24 Zhu, Y.; Burgess, K. Iridium-Catalyzed Asymmetric Hydrogenation of Vinyl Ether. *Adv. Synth. Catal.* **2008**, *350*, 979–983.

25 Cheruku, P.; Paptchikhine, A.; Church, T. L.; Andersson, P. G. Iridium-N,P-Ligand-Catalyzed Enantioselective Hydrogenation of Diphenylvinylphosphine Oxides and Vinylphosphonates. *J. Am. Chem. Soc.* **2009**, *131*, 8285–8289.

26 Wang, D.-Y.; Hu, X.-P.; Deng, J.; Yu, S.-B.; Duan, Z.-C.; Zheng, Z. Enantioselective Synthesis of Chiral alpha -Aryl or alpha -Alkyl Substituted Ethylphosphonates via Rh-Catalyzed Asymmetric Hydrogenation with a P-Stereogenic BoPhoz-Type Ligand. *J. Org. Chem.* **2009**, *74*, 4408–4410.

27 Huang, Y.; Berthiol, F.; Stegink, B.; Pollard, M. M.; Minnaard, A. J. Asymmetric hydrogenation of alpha, beta -unsaturated ester-phosphonates. *Adv. Synth. Catal.* **2009**, *351*, 1423–1430.

28 Goulioukina, N. S.; Dolgina, T. y. M.; Bondarenko, G. N.; Beletskaya, I. P.; Ilyin, M. M.; Davankov, V. A.; Pfaltz, A. Highly enantioselective hydrogenation of a,b-unsaturated phosphonates with iridium-phosphinooxazoline complex: Synthesis of a phosphorus analogue of naproxen. *Tetrahedron Asymmetry* **2003**, *14*, 1397–1401.

29 Engman, M.; Diesen, J. S.; Paptchikhine, A.; Andersson, P. G. Iridium-Catalyzed Asymmetric Hydrogenation of Fluorinated Olefins Using N,P-Ligands: A Struggle with Hydrogenolysis and Selectivity. *J. Am. Chem. Soc.* **2007**, *129*, 4536–4537.

30 Kaukoranta, P.; Engman, M.; Hedberg, C.; Bergquist, J.; Andersson, P. G. Iridium catalysts with chiral imidazole-phosphine ligands for asymmetric hydrogenation of vinyl fluorides and other olefins. *Adv. Synth. Catal.* **2008**, *350*, 1168–1176.

31 Engman, M.; Cheruku, P.; Tolstoy, P.; Bergquist, J.; Voelker, S. F.; Andersson, P. G. Highly selective iridium-catalyzed asymmetric hydrogenation of trifluoromethyl olefins: a new route to trifluoromethyl-bearing stereocenters. *Adv. Synth. Catal.* **2009**, *351*, 375–378.

32 Kaellstroem, K.; Munslow, I. J.; Hedberg, C.; Andersson, P. G. Iridium-catalysed asymmetric hydrogenation of vinylsilanes as a route to optically active silanes. *Adv. Synth. Catal.* **2006**, *348*, 2575–2578.

33 Paptchikhine, A.; Cheruku, P.; Engman, M.; Andersson, P. G. Iridium-catalyzed enantioselective hydrogenation of vinyl boronates. *Chem. Commun.* **2009**, 5996–5998.

34 Cheruku, P.; Diesen, J.; Andersson, P. G. Asymmetric Hydrogenation of Di and Trisubstituted Enol Phosphinates with N,P-Ligated Iridium Complexes. *J. Am. Chem. Soc.* **2008**, *130*, 5595–5599.

35 Li, S.; Zhu, S.-F.; Xie, J.-H.; Song, S.; Zhang, C.-M.; Zhou, Q.-L. Enantioselective hydrogenation of alpha-aryloxy and alpha-alkoxy alpha,beta-unsaturated carboxylic acids catalyzed by chiral spiro iridium/phosphino-oxazoline complexes. *J. Am. Chem. Soc.* **2010**, *132*, 1172–1179.

36 Cheruku, P.; Church, T. L.; Trifonova, A.; Wartmann, T.; Andersson, P. G. Access to chiral tertiary amines via the iridium-catalyzed asymmetric hydrogenation of enamines. *Tetrahedron Lett.* **2008**, *49*, 7290–7293.

37 Hou, G.-H.; Xie, J.-H.; Yan, P.-C.; Zhou, Q.-L. Iridium-Catalyzed Asymmetric Hydrogenation of Cyclic Enamines. *J. Am. Chem. Soc.* **2009**, *131*, 1366–1367.

38 Baeza, A.; Pfaltz, A. Iridium-catalyzed asymmetric hydrogenation of unfunctionalized enamines. *Chem.—Eur. J.* **2009**, *15*, 2266–2269.

39 Han, Z.; Wang, Z.; Zhang, X.; Ding, K. Spiro[4,4]-1,6-nonadiene-Based Phosphine-Oxazoline Ligands for Iridium-Catalyzed Enantioselective Hydrogenation of Ketimines. *Angew. Chem., Int. Ed.* **2009**, *48*, 5345–5349.

40 Verendel, J. J.; Zhou, T.; Li, J.-Q.; Paptchikhine, A.; Lebedev, O.; Andersson, P. G. Highly Flexible Synthesis of Chiral Azacycles via Iridium-Catalyzed Hydrogenation. *J. Am. Chem. Soc.* **2010**, *132*, 8880–8881.

41 Brown, J. M. Directed Homogeneous Hydrogenation. *Angew. Chem., Int. Ed.* **1987**, *26*, 190–203.

42 Hoveyda, A. H.; Evans, D. A.; Fu, G. C. Substrate-Directable Chemical Reactions. *Chem. Rev.* **1993**, *93*, 1307–1370.

43 Lightfoot, A.; Schnider, P.; Pfaltz, A. Enantioselective Hydrogenation of Olefins with Iridium-Phosphanodihydrooxazole Catalysts. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897–2899.

44 Bell, S.; Wustenberg, B; Kaiser, S.; Menges, F.; Netscher, T.; Pfaltz, A. Asymmetric Hydrogenation of Unfunctionalized, Purely Alkyl-Substituted Olefins. *Science* **2006**, *311*, 642–644.

45 Hanessian, S.; Giroux, S.; Mascitti, V. The Iterative Synthesis of Acyclic Deoxypropionate Units and Their Implication in Polyketide-Derived Natural Products. *Synthesis* **2006**, *7*, 1057–1076.

46 Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. Pseudoephedrine as a Practical Chiral Auxiliary for the Synthesis of Highly Enantiomerically Enriched Carboxylic Acids, Alcohols, Aldehydes, and Ketones. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.

47 Negishi, E.; Tan, Z.; Liang, B.; Novak, T. An efficient and general route to reduced polypropionates via Zr-catalyzed asymmetric C-C bond formation. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5782–5787.

48 Horst, B. t.; Feringa, B. L.; Minnaard, A. J. Iterative strategies for the synthesis of deoxypropionates. *Chem. Commun.* **2010**, *46*, 2535–2547.

49 Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. R. Double Asymmetric Synthesis and a New Strategy for Stereochemical Control in Organic Synthesis. *Angew. Chem., Int. Ed.* **1985**, *24*, 1–30.

50 Zhou, J.; Burgess, K. α,ω Functionalized 2,4-Dimethylpentane Dyads and 2,4,6-Trimethylheptane Triads via Asymmetric Hydrogenation. *Angew. Chem., Int. Ed.* **2007**, *46*, 1129–1131.

51 Zhou, J.; Zhu, Y.; Burgess, K. Synthesis of (S,R,R,S,R,S)-4,6,8,10,16,18-Hexamythyldocosane from Antitrogus parvulus via Diastereoselective Hydrogenations. *Org. Lett.* **2007**, *9*, 1391–1393.

52 Shimp, H. L.; Micalizio, G. C. A formal total synthesis of dictyostatin. *Tetrahedron* **2009**, *65*, 5908–5915.

53 Zhu, Y.; Burgess, K. Asymmetric Hydrogenation Approaches to Valuable, Acyclic 1,3-Hydroxymethyl Chirons. *J. Am. Chem. Soc.* **2008**, *130*, 8894–8895.

54 Zhu, Y.; Loudet, A.; Burgess, K. An Asymmetric Hydrogenation Route To (−)-Spongidepsin. *Org. Lett.* **2010**, *12*, 4392–4395.

55 Dutheuil, G.; Webster, M. P.; Worthington, P. A.; Aggarwal, V. K. Stereocontrolled Synthesis of Carbon Chains Bearing Contiguous Methyl Groups by Iterative Boronic Ester Homologations: Application to the Total Synthesis of (+)-Faranal. *Angew. Chem., Int. Ed.* **2009**, *48*, 6317–6319.

56 Zhao, J.; Burgess, K. Synthesis of Vicinal Dimethyl Chirons by Asymmetric Hydrogenation of Trisubstituted Alkenes. *J. Am. Chem. Soc.* **2009**, *131*, 13236–13237.

57 Brown, J. M.; Cutting, I. Effective kinetic resolution in the asymmetric hydrogenation of α-(hydroxyalkyl)acrylate esters. *J. Chem. Soc., Chem. Commun.* **1985**, 578–579.

58 Zhao, J.; Burgess, K. Aldol-type Chirons From Asymmetric Hydrogenations of Trisubstituted Alkenes. *Org. Lett.* **2008**, *11*, 2053–2056.

59 Koskinen, A. M. P.; Karisalmi, K. Polyketide stereotetrads in natural products. *Chem. Soc. Rev.* **2005**, *34*, 677–690.

60 Li, J.; Menche, D. Direct methods for stereoselective polypropionate synthesis: a survey. *Synthesis* **2009**, 2293–2315.

61 Marshall, J. A.; Perkins, J. F.; Wolf, M. A. Synthesis of syn,syn; anti,syn; syn,anti; and anti, anti Stereotriads from a Single Pair of Enantiomeric Reagents. *J. Org. Chem.* **1995**, *60*, 5556–5559.

62 Perez, L. J.; Micalizio, G. C. Titanium-mediated fragment union processes in complex molecule synthesis: development of a branched reaction pathway of high step economy for the synthesis of complex and diverse polyketides. *Synthesis* **2008**, 627–648.

63 Bahadoor, A. B.; Flyer, A.; Micalizio, G. C. A Pentenyl Dianion-Based Strategy for Convergent Synthesis of Ene-1,5-diols. *J. Am. Chem. Soc.* **2005**, *127*, 3694–3695.

64 Marshall, J. A.; Schaaf, G. M. Synthesis of stereopentad analogs of the C14-C22 segment of callystatin A through additions of chiral allenylzinc reagents to stereotriads. *J. Org. Chem.* **2001**, *66*, 7825–7831.

65 Jain, N. F.; Takenaka, N.; Panek, J. S. Double-Stereodifferentiating Crotylation Reactions with Chiral (E)-Crotylsilanes. Evaluation of a New Approach for the Synthesis of Polypropionate-Derived Natural Products. *J. Am. Chem. Soc.* **1996**, *118*, 12475–12476.

66 Kim, H.; Ho, S.; Leighton, J. L. A More Comprehensive and Highly Practical Solution to Enantioselective Aldehyde Crotylation. *J. Am. Chem. Soc.* **2011**, *133*, 6517–6520.

67 Zhu, Y.; Burgess, K. Highly Selective 1,2,3-Me,OH,Me Stereochemical Triads via Asymmetric Hydrogenation Reactions. *Adv. Synth. Catal.* **2012**, in press.

68 Li, S.; Zhu, S.-F.; Zhang, C.-M.; Song, S.; Zhou, Q.-L. Iridium-Catalyzed Enantioselective Hydrogenation of α, β-Unsaturated Carboxylic Acids. *J. Am. Chem. Soc.* **2008**, *130*, 8584–8585.