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Review

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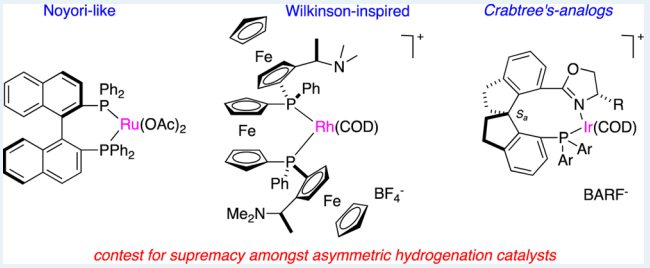
Comparison of Asymmetric Hydrogenations of Unsaturated Carboxylic Acids and Esters

Sakunchai Khumsubdee and Kevin Burgess*

Department of Chemistry, Box 30012, Texas A & M University, College Station, Texas 77841-3012, United States

ABSTRACT: As methodology development matures, it can be difficult to discern the most effective ways of performing certain transformations from the rest. This review summarizes the most important contributions leading to asymmetric hydrogenations of simple unsaturated acid and ester substrates, with the objective of highlighting at least the best types of catalysts for each. Achievements in the area are described, and these reveal situations where further efforts should be worthwhile and ones where more research is only likely to give diminishing returns. In general, our conclusions are that the most useful types of catalysts for unsaturated acids and esters tend to be somewhat different, simple substrates have been studied extensively, and the field is poised to address more complex reactions. These could be ones involving alternative (particularly cyclic) structures, chemoselectivity issues, and more complex substrate stereochemistries.



KEYWORDS: *stereoselective, hydrogenations, homogeneous, alkene esters, alkene acids*

A. INTRODUCTION

Most alkene substrates for asymmetric hydrogenations are relatively hindered tri- and tetrasubstituted ones. These are shielded to hydrogenation catalysts unless they bear coordinating functional groups (CFGs) for the metals typically involved, that is, Rh(1+)/Rh(3+), Ir(1+)/Ir(3+). Two important effects arise from substrates having strong CFGs in catalytic hydrogenation reactions. First, the substrate is drawn into the proximity of the metal, lowering the activation energies for hydrogenations. Second, binding of CFGs in catalytic transition states will synergize with chiral ligands tending to give relatively rigid, diastereomeric forms that lead to stereocontrol. For instance, enamides contain strong CFGs because they can give unstrained stable chelates (Figure 1).

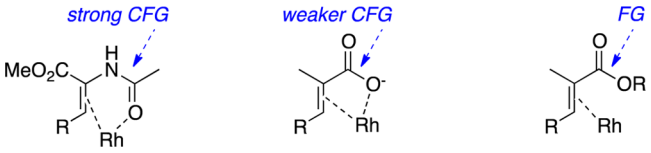


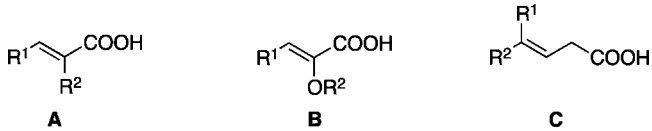
Figure 1. Coordinating functional groups (CFGs) and FGs in asymmetric hydrogenations.

Four-membered ring chelates from α,β-unsaturated carboxylic acids are presumably less stable because of ring strain. Esters that are α,β-unsaturated are not widely regarded as coordinating for Rh(1+)/Rh(3+); these are seen as simply functional groups. However, there is a "grey zone" between CFGs and FGs in asymmetric hydrogenations, and esters can sometimes fall in this area.

This review compares asymmetric hydrogenations of alkenyl carboxylic acids and esters that do not have other CFGs. Hydrogenations of 1,1-disubstituted alkenes[1,2] are excluded because these are relatively unhindered and amenable to hydrogenations by a range of catalyst systems. Thus, we attempt to identify the best catalysts known for asymmetric hydrogenations of simple tri- and tetrasubstituted alkenyl carboxylic acids and esters. Our goal is to compare catalysts that are used for each substrate type, then to look for similarities and differences for the two.

B. CARBOXYLIC ACIDS

Categories. Most of the alkenyl carboxylic acids reported as substrates for asymmetric hydrogenations are represented by one of the generic structures **A**–**C**. Alkenes **A**, where R^1 and R^2 are alkyl substituents (e.g., tiglic acid, $R^1 = R^2 = Me$) are relatively difficult to hydrogenate with high enantiocontrol, but the task is markedly easier if one or both R-groups is aryl. Alkenes **B** are more electron-rich and have steric features that are highly variable according to the substituents involved. Competing double bond migration processes could complicate attempts to achieve high enantioface selectivities for the β,γ-unsaturated systems **C**.



Ruthenium-Mediated (Noyori-type) Hydrogenations. Noyori's first report of asymmetric hydrogenations of type **A** alkenes[3] featured a range of different substituents and gave

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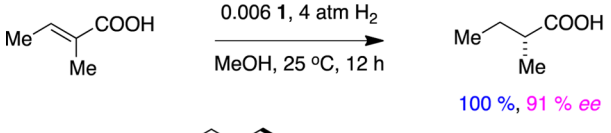
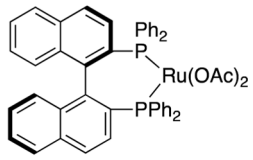
products with enantiomeric excesses in the 83−95% range. For tiglic acid (reaction 1) it was necessary to use hydrogen pressures of only 4 atm, but substrates with slightly bulkier substituents required around 100 atm. Throughout, the catalyst loadings used were very low.



100 %, 91 % *ee*



1 *reaction 1*

Halpern[4] and Takaya[5] considered kinetic and stereochemical aspects of illustrative reactions in this class. They concluded dihydrogen is split by oxidative addition to the metal, giving a ruthenium hydride **I** and protons (Figure 2);[6] this process tends

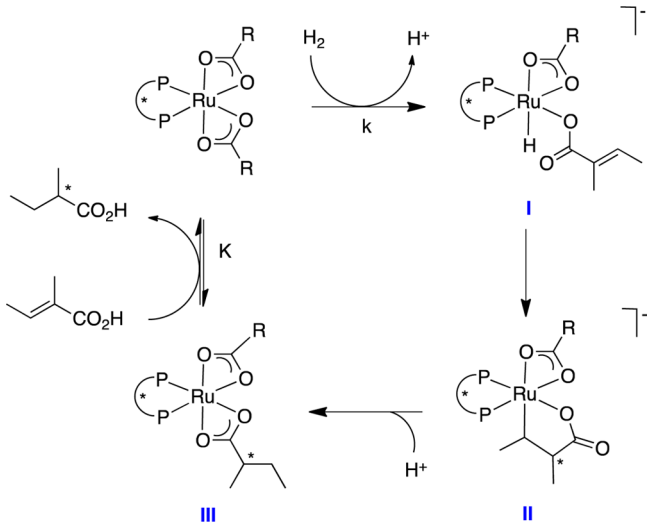
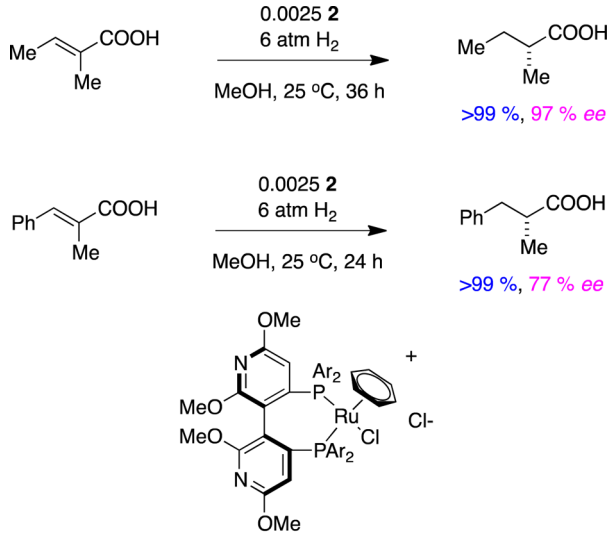


Figure 2. Halpern's postulate for hydrogenations of unsaturated carboxylic acids with Ru(2+)bisphosphine complexes.

not to be perturbed by addition of bases, but it is suppressed when the medium is made acidic. It was postulated that the reaction then proceeds via insertion of the coordinated alkene into the Ru−H bond to give a metallocyclopentane **II**; alternative pathways involving conjugate additions of hydride to form enolates were ruled out via labeling experiments. Protonation of species **II** to give the penultimate intermediate in the catalytic cycle, the product-containing dicarboxylate **III**, precedes exchange with starting-material carboxylates to close the catalytic cycle.

The studies cited above did not comment on the stereochemistry of the protonation step, except that the addition to the alkene was cis overall. We postulate that protonation of the anionic intermediates **II** *on the metal* would explain the cis-addition and how hydrogen atoms from the methanol solvent were incorporated into this position.

An example of other atropisomeric ligands applied in ways that follow Noyori's work on unsaturated acids comes from Albert Chan's lab.[7] Somewhat exceptionally in this type of transformation, higher enantioselectivities for the tiglic acid system were obtained relative to the analogous phenyl-substituted alkenes (Figure 3).



>99 %, 97 % *ee*

>99 %, 77 % *ee*

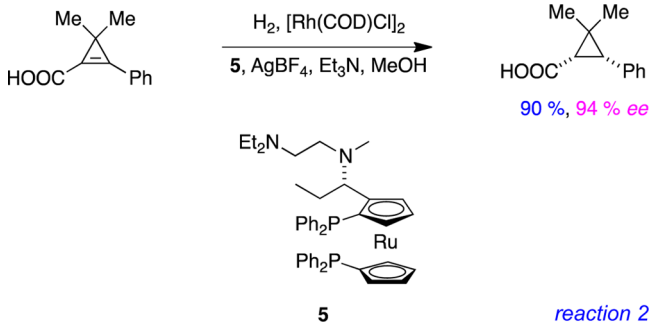
2

Figure 3. Hydrogenations of *α,β*-unsaturated alkenes mediated by a dipyridyl phosphine ligand.

Rhodium Catalysts. Carboxylates coordinate to cationic rhodium complexes, and alkenyl groups in these substrates can be stereoselectively hydrogenated using chiral bisphosphine Rh complexes.[8] However, there are relatively few reports wherein high enantioselectivities have been achieved using rhodium-based catalysts in these types of reactions. For instance, a maximum of 82% ee was obtained for hydrogenation of a type **A** alkene (specifically, R^1 = Ph, R^2 = Me) using a typical Rh(1+) precursor, $Rh(NBD)_2BF_4$, and a series of ferrocenyl-based bisphosphines (Figure 4).[9]

An intriguing way to constrain intermediates in hydrogenations of unsaturated carboxylates is to ion-pair them with amines on the bisphosphine ligand.[10,11] Thus, when type **A** substrates (R = Ar) were hydrogenated with a bisferrocenyl ligand *containing appropriately oriented amine groups*, high enantioselectivities were obtained. Ion-paired intermediates such as **IV** were postulated to be involved in these transformations (Figure 4b).[11]

Reaction 2 shows another example of ion-paired catalysis in hydrogenations of *α,β*-unsaturated carboxylic acids when good enantioselectivities were obtained. This reaction is unusual because it is the only tetrasubstituted alkene substrate that we encountered for acid substrates; it is one in which hydrogenation is favored by strong factors relating to partial relief from strain in the cyclopropene system.[12]



90 %, 94 % *ee*

5 *reaction 2*

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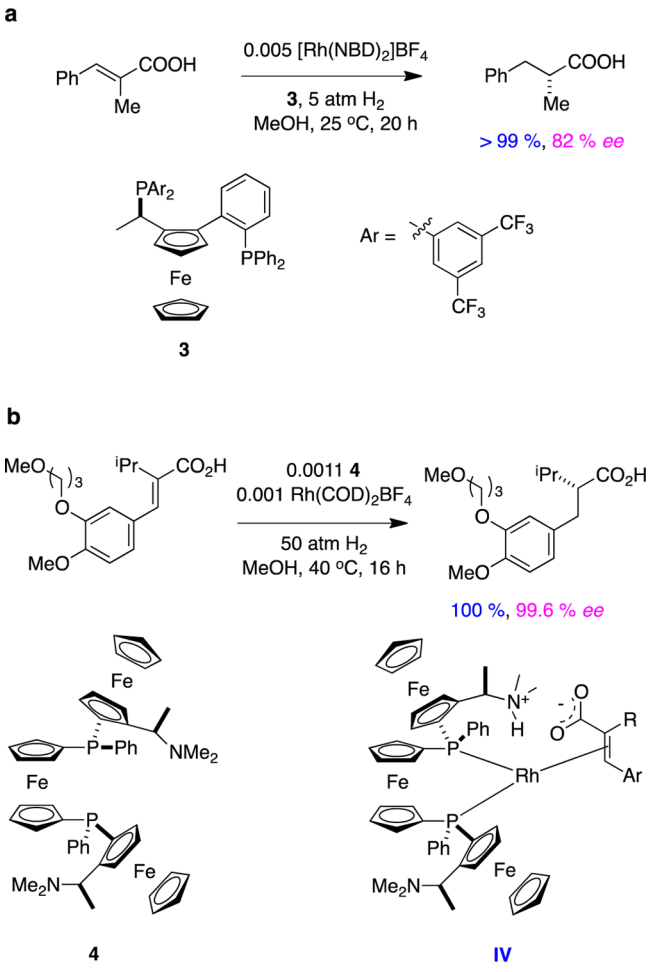
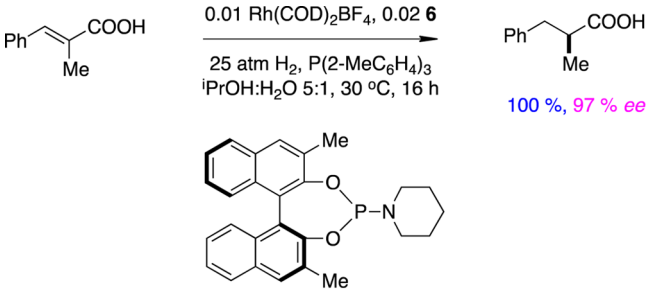


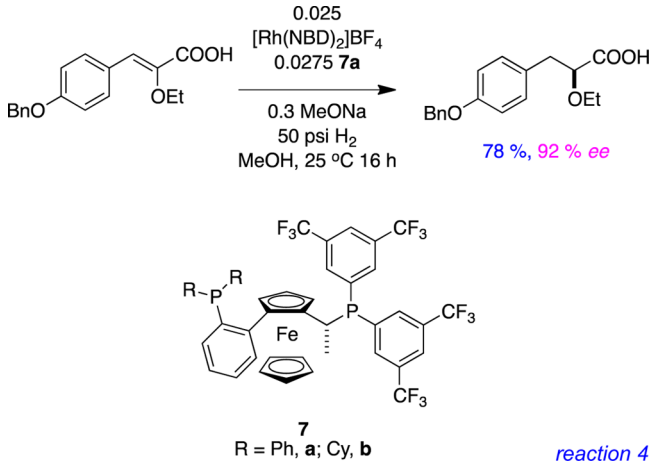
Figure 4. Hydrogenation of unsaturated carboxylic acids using ferrocenyl-based bisphosphines: (a) without and (b) with pendant amines.

Rapid optimization of stereoselectivities in asymmetric hydrogenations of α,β-unsaturated carboxylic acids has been achieved by testing combinations of chiral monodentate ligands.[13,14] This methodology works exceptionally well for these substrates, as shown in reaction 3.[15] Comparison of this transformation with those in Figure 4 and reaction 2 suggests there is at least the possibility that carboxylic acids in these substrates ion-pair via the nitrogen on the phosphoramidite ligands, but this possibility has not been discussed or explored in the literature.



6 *reaction 3*

An example of asymmetric hydrogenation of an alkoxy-substituted (type **B**) substrate was demonstrated in a process synthesis of a medicinally active compound. Reaction 4 shows the system developed after screening over 250 catalyst–ligand combinations; however, even after all that effort, a maximum of only 92% ee was obtained.[16] In the context of the previous discussion, it is interesting that these somewhat disappointing results correspond to a bisphosphine that does *not* contain amine groups to ion-pair.



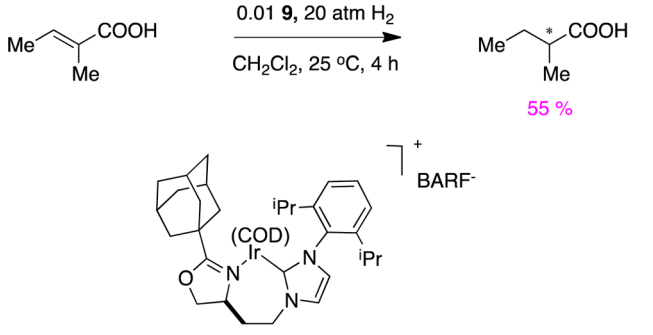
7
R = Ph, **a**; Cy, **b**

reaction 4

Chiral Analogs of Crabtree's Catalyst. Hydrogenations mediated by chiral analogs of Crabtree's catalyst have at least the potential to involve oxidative additions of *two* hydrogen molecules, giving Ir(5+) intermediates. Several groups have asserted this mechanism based on DFT calculations.[17−21] However, to the best of our knowledge these calculations have never been performed for unsaturated carboxylic acid substrates, so involvement of Ir(5+) in this particular case is unresolved (calculations on unsaturated esters[22] are discussed later).

Qi-Lin Zhou's spirocyclic ligands **8**[23] give impressive enantioselectivities in hydrogenations of some α,β-unsaturated carboxylic acids.[24] Figure 5 shows several reactions in which **8a** and **b** (benzyl and *iso*-propyl oxazoline substituents, respectively) shone in these transformations. Excellent ee's were achieved for aryl-substituted systems, tiglic acid, and substrates containing simple alkyl substituents.

The selectivities obtained by Zhou are excellent compared with most other catalysts for this transformation. For instance, the carbene oxazoline complex **9**[22] gave relatively modest enantiomeric excesses in hydrogenations of tiglic acid (reaction 5).



9 *reaction 5*

Recently, Zhou has shown the spirocyclic catalysts **10** are also effective for hydrogenation of the same types of α,β-unsaturated carboxylic acids with very high enantioselectivities (e.g., Figure 6).[25] These are perhaps the first examples of phosphine–amine ligands on iridium(1+) to be used in asymmetric hydrogenation reactions of any hindered alkene substrate.

Other groups, including Ding and Zhang, have also shown interest in hydrogenations of α,β-unsaturated carboxylic acids, and they also used a spirocyclic ligand.[26] Unlike Zhou's work however, they studied α-aryl systems, particularly ones related

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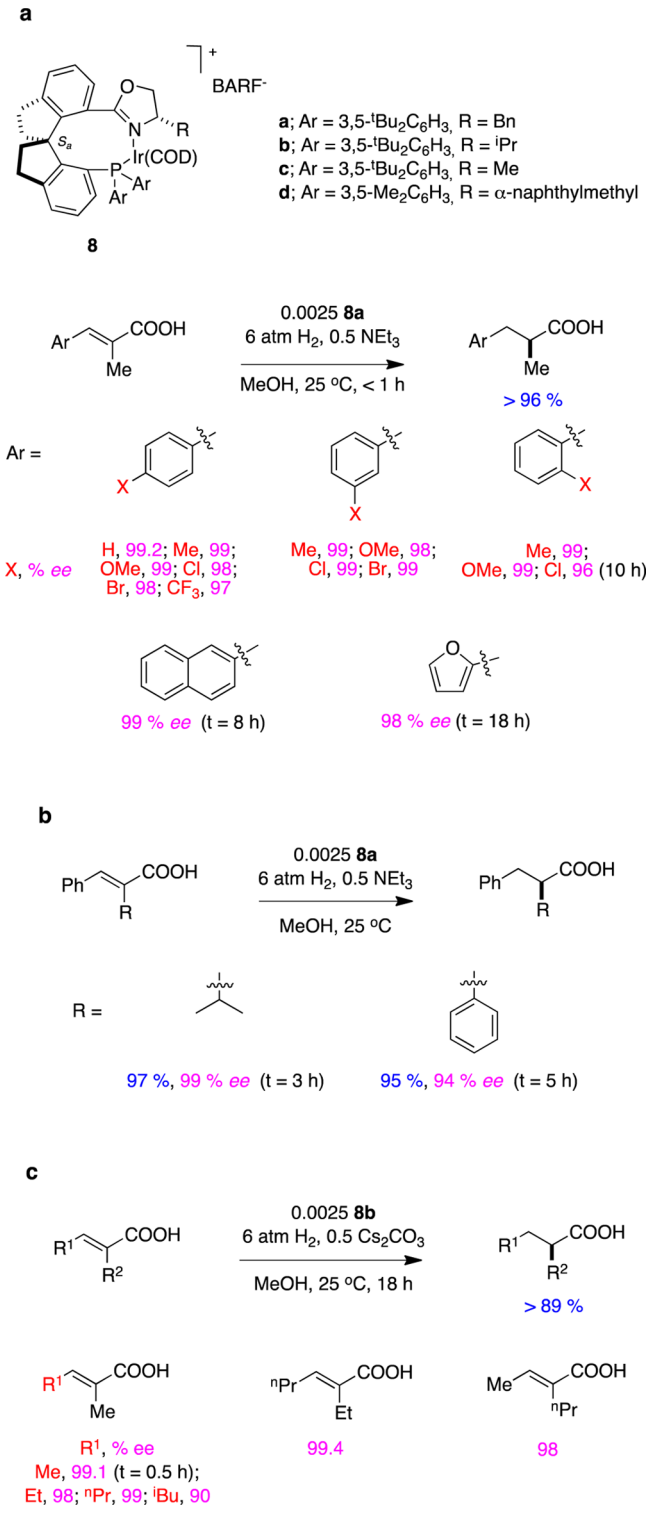

Figure 5. Spirocyclic ligands in asymmetric hydrogenations of alkyl-substituted α,β-unsaturated carboxylic acids: (a) α-methylcinnamate, (b), α-alkylcinnamate, and (c) dialkyl derivatives.

to an antidiabetic drug, and their spirocyclic ligand in **11** has a less extended structure than Zhou's. Very good enantiomeric excesses were obtained throughout, although the substrate diversity in this study was relatively narrow (Figure 7).

Andersson's group reported one example of hydrogenation of an unsaturated acid as part of a broader study on ester substrates (see below).[27] The enantioselectivity and conversion (100%) for

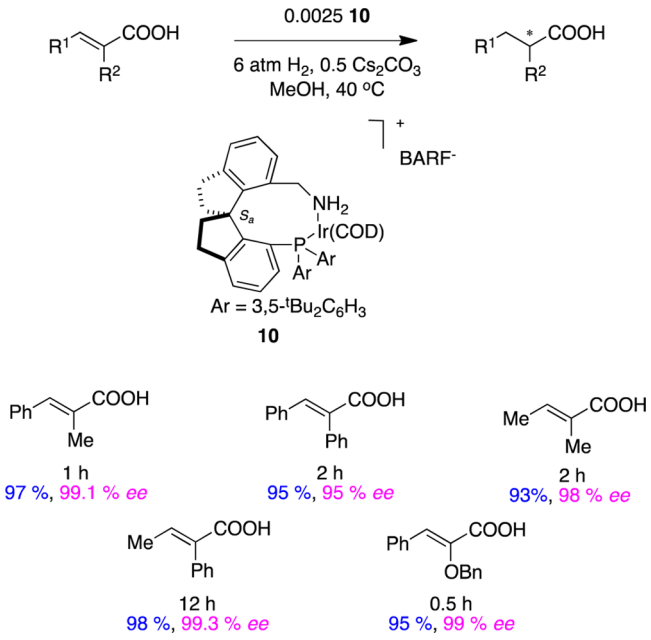

Figure 6. High enantioselectivities obtained for hydrogenations of diverse α,β-unsaturated carboxylic acids involving catalyst **10**.

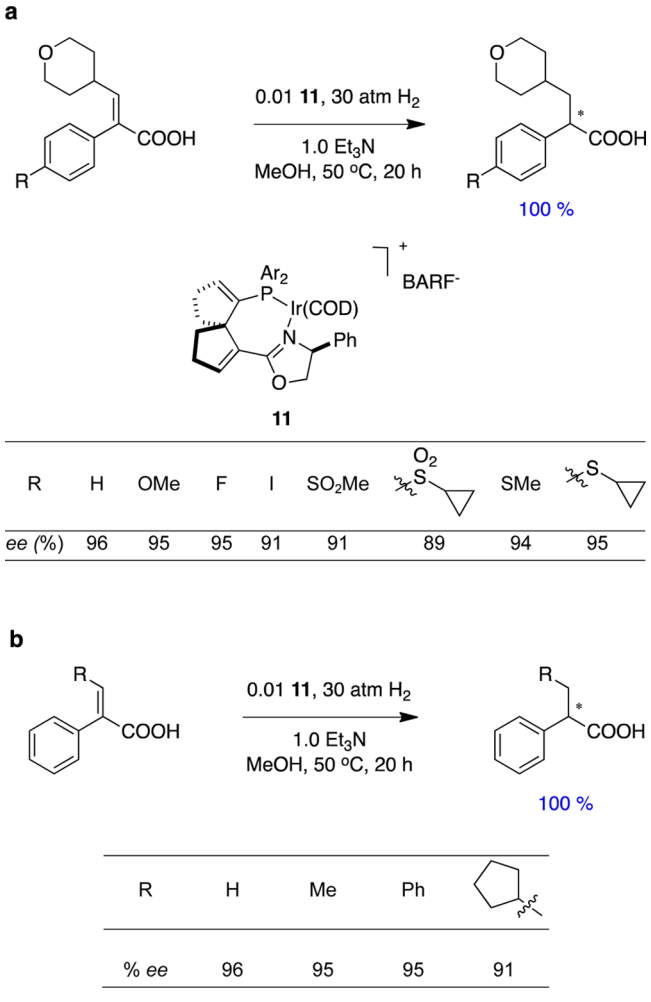

Figure 7. Use of spirocyclic complex **11** in asymmetric hydrogenations of α,β-unsaturated carboxylic acids.

that particular alkene was excellent using a low loading of the catalyst (reaction 6). Unlike many of the transformations

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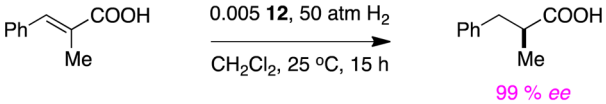
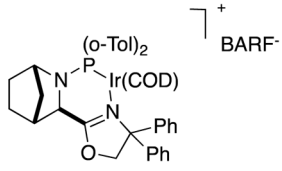
discussed above, there was no need for an additive in this reaction, and dichloromethane was used as a solvent, not methanol.



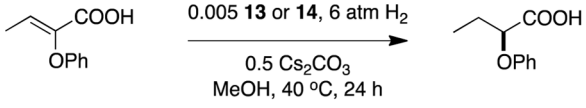


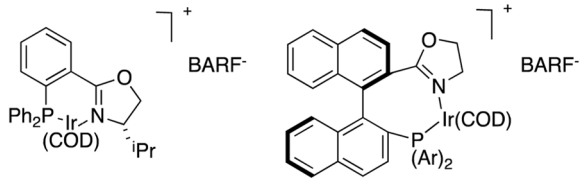
12 *reaction 6*

Zhou also applied his spirocyclic ligands to α-oxygenated-α,β-unsaturated carboxylic acids, and again, the results are highly impressive.[28] Several α-alkoxy derivatives were hydrogenated with high enantiomeric excesses, as illustrated in Figure 8.

Hydrogenations of the corresponding α-*aryl*-oxy substrates are shown in Figure 9.[29] It is impressive that such high enantiomeric excesses were obtained for the diverse set of substrates used in this study.

Zhou's group attempted to compare their catalysts with the PHOX-system **13**.[30] However, only the spirocyclic ligands gave a conversion; the PHOX system failed to generate product (reaction 7).





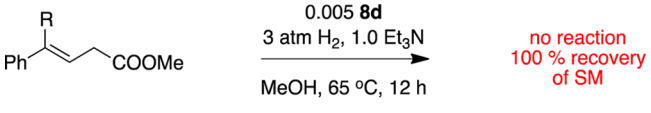
13
Ir-PHOX
0 %

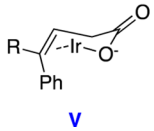
14
Ar = 3,5-^{t}Bu$_2$C$_6$H$_3$
15 %, 79 % *ee*

reaction 7

Zhou expanded his studies to include (*E*)-γ-aryl-γ-methyl-β,γ-unsaturated acids[31] and achieved uniformly high enantioselectivities for a range of compounds with different aryl substituents, a naphthyl alkene, and a thiophenyl system; however, diminished enantioselectivities were observed when the γ-methyl substituent was substituted with a bulkier one, ^{i}Pr. Isomerization of these substrates would conjugate the alkene; however, experiments with D_2 addition showed double bond migration did not precede the hydrogenation step in these reactions (Figure 10).

A direct comparison between ester and acid substrates under the conditions outlined above proved that the carboxylic acid is essential and the ester does *not* react. We postulate the carboxylate reactions could proceed via a chairlike intermediate, **V**, for which there is no direct parallel with esters.





V

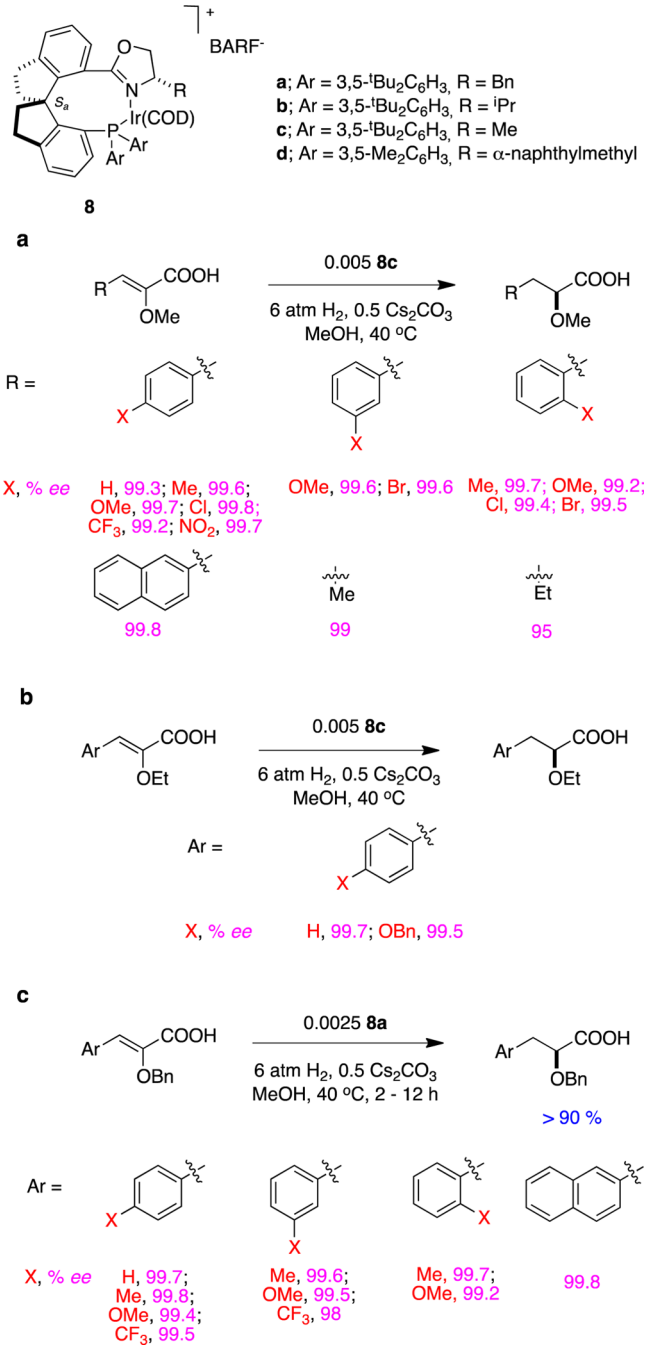


Figure 8. Hydrogenations of α-alkoxy substrates.

Summary for Hydrogenations of Alkenyl-Carboxylic Acids. Hydrogenations mediated by Ru(2+), Rh(1+)-bisphosphine, and Ir-*N,P*-ligands (chiral analogs of Crabtree's catalyst) probably follow three different reaction pathways. The ruthenium reactions are suppressed by acid, the rhodium ones proceed under neutral conditions, and the iridium ones are almost always performed in the presence of added base. A somewhat longer reaction time tends to be required for the Rh systems. Catalysts based on Ir-*spirocyclic-N,P* ligands give the best enantioselectivities obtained so far in the series. Exploratory work using those spirocyclic ligands must be relatively slow because the backbone chiralities have to be matched with the oxazoline, but once the ideal combination is established, then this process need not be repeated. It remains to be seen, however,

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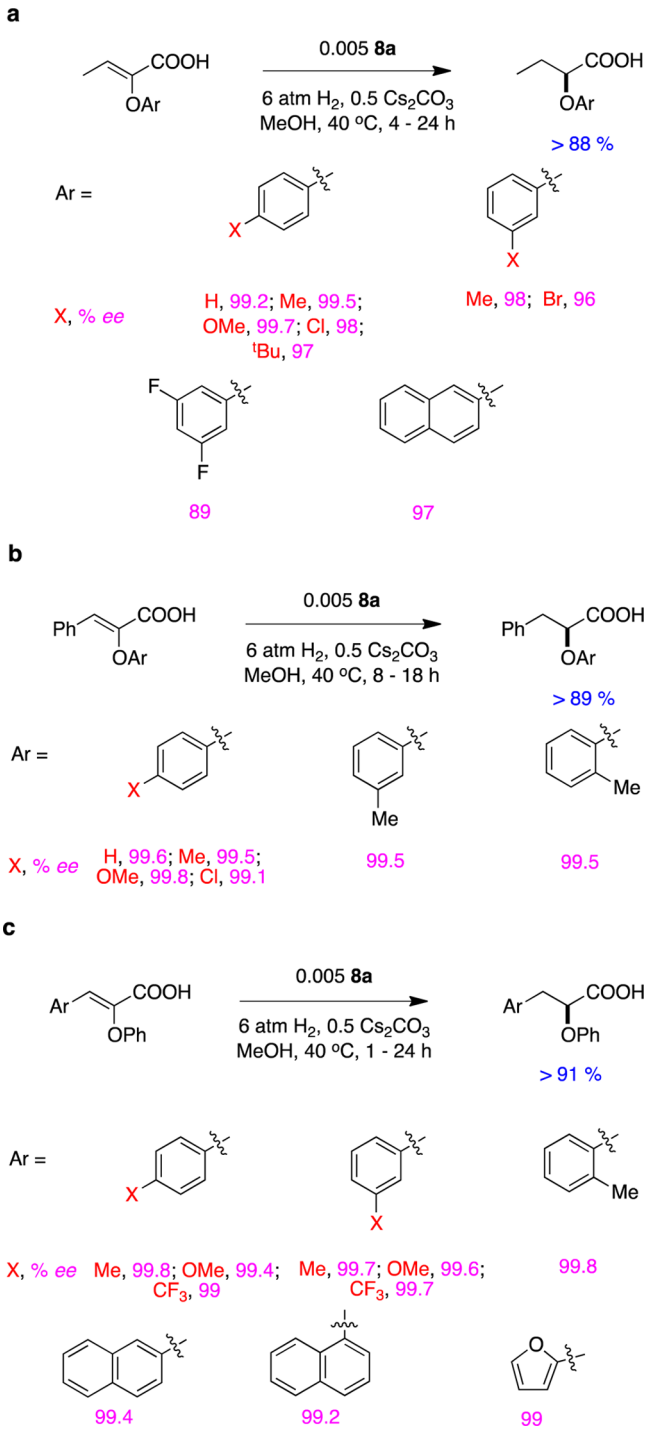


Figure 9. Hydrogenations of α-aryloxy substrates.

how these catalysts perform on more complicated substrates; they are relatively hindered, so conversion may be a problem in these cases.

There is enough data on asymmetric hydrogenations of carboxylic acids to make a limited catalyst/substrate comparison (Table 1). Within this data set, appropriate chiral analogs of Crabtree's catalysts give higher enantioselectivities. Less work has been reported on Ru and Rh systems, so this is not an even comparison, but it also could be indicative of a trend that will be reinforced as more examples are reported. Similar conditions were used for hydrogenations mediated by all three catalyst types.

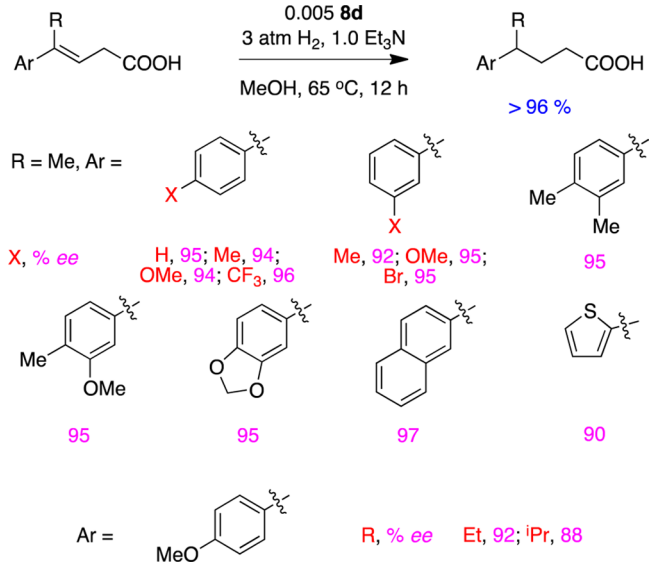
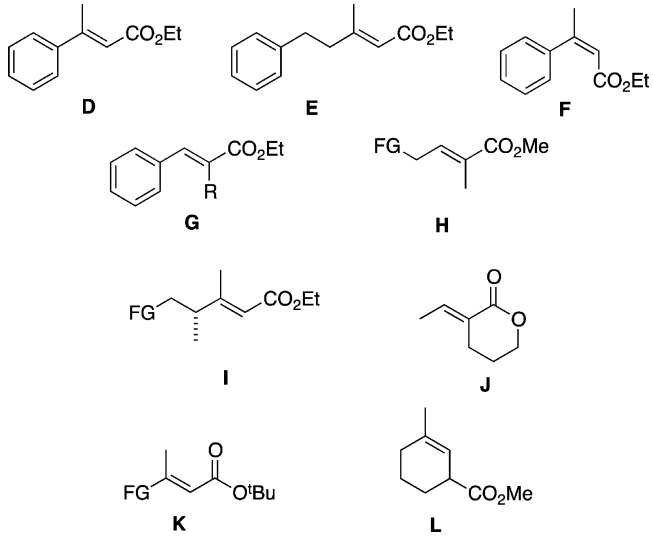


Figure 10. Asymmetric hydrogenations of nonconjugated alkene–carboxylic acids (type **C** substrates).

C. CARBOXYLATE ESTERS

Categories. The story of asymmetric hydrogenations of unsaturated esters has an intriguing plot featuring a few main substrate-actors and a handful of others filling peripheral roles. Generic ester **D** is a prima donna on which, frankly, too much attention has been lavished. Meanwhile, homologues **E**, geometric isomers such as **F**, and constitutional isomers such as **G** have received much less attention; they seem to be harder substrates to hydrogenate with high enantioselectivities. Asymmetric hydrogenations of tiglic and angelic acid esters are conspicuously underexplored and have not been achieved with high stereoselectivities using *any* system. The α,ω-functionalized substrates **H** are also underexplored, even though these give chirons that are inherently useful because they can be homologated at either end. Hydrogenations of γ-chiral substrates **I** give stereochemically complex chirons that can be useful in particular cases, and these have been studied in more depth. Hydrogenations of cyclic substrates include lactones **J**, β,β-disubstituted **K**, and chiral cyclohexenyl esters **L**.



Comparisons between Rh and Ir catalysts in this area are informative. Overall, however, it is striking that so much time

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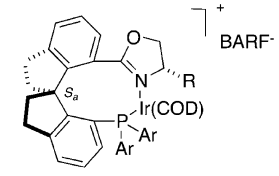
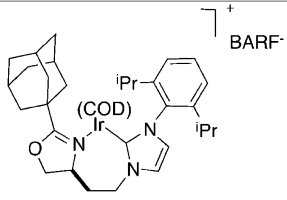
Table 1. Enantioselectivity Comparison for Substrate/Catalyst Combinations for Asymmetric Hydrogenations of Alkenyl Carboxylic Acids

alkenes	Analogs of Crabtree's Catalyst (% *ee*)							Ru (% *ee*)		Rh (% *ee*)	
	8a	**8b**	**9**	**10**	**11**	**12**	**14**	**1**	**2**	**3**	**6**
Ph, COOH, Me	99			99		99			77	82	97
Ph, COOH, Ph	94			95	95						
Me, COOH, Me		99	55	98				91	97		
Ph, COOH, OBn	99			99							
COOH, OPh	99						79				



8a, R = Bn; **8b**, R = ^{i}Pr



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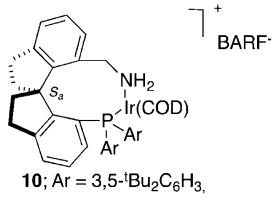
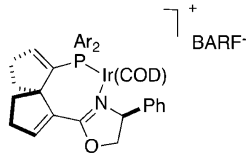


10; Ar = 3,5-^{t}Bu$_2$C$_6$H$_3$,



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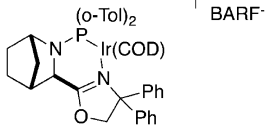

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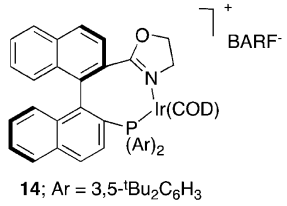
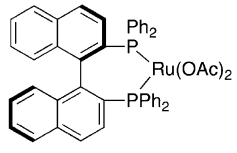
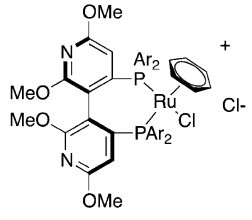


14; Ar = 3,5-^{t}Bu$_2$C$_6$H$_3$



1



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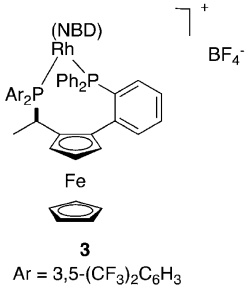
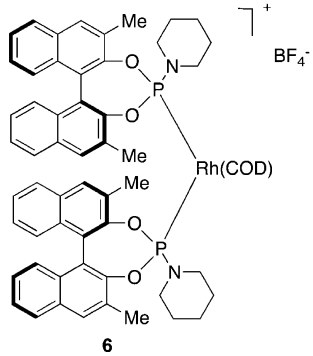


3
Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$



6

has been spent studying relatively small aspects of this area (e.g., **D** as a substrate), while some fundamental issues, such as

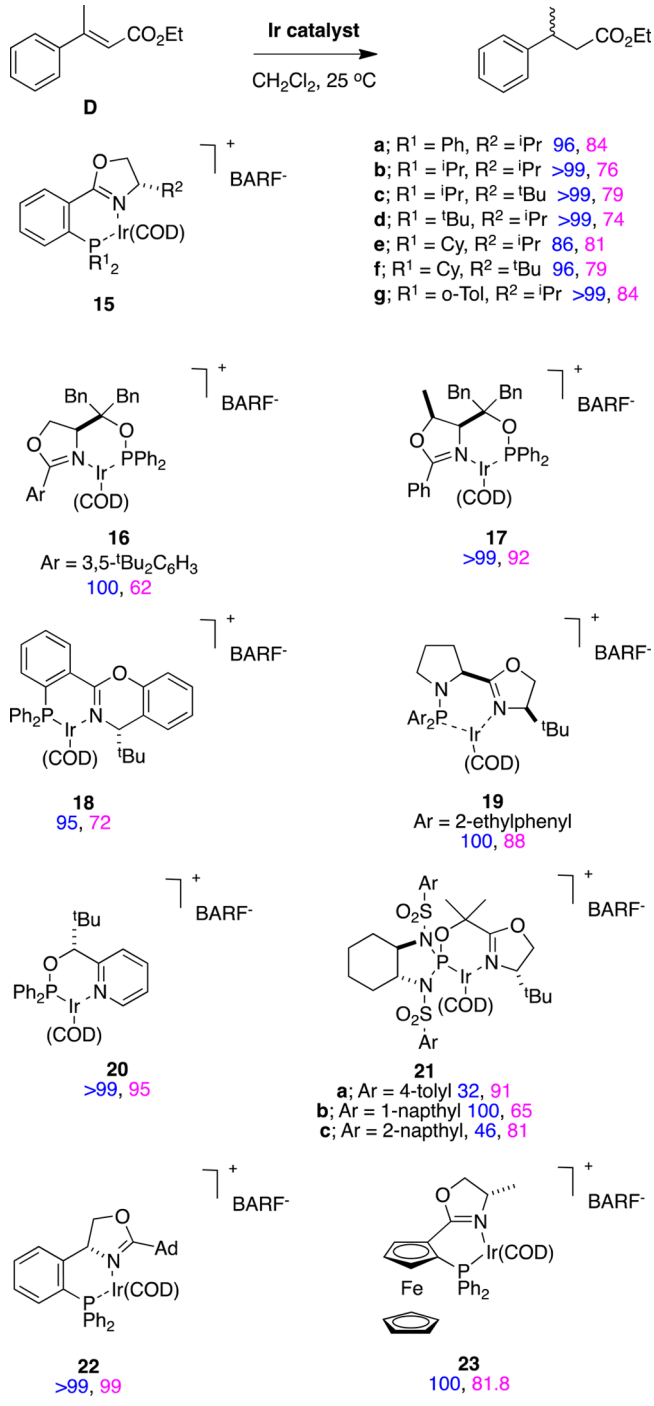


Figure 11. Conversions (shown in blue) and enantioselectivities (shown in purple) in Pfaltz's hydrogenations of substrates **D**.

isomerization preceding hydrogenations in these processes, remain unexplored.

Chiral Analogs of Crabtree's Catalyst. It is easy to hydrogenate substrates **D** with relatively high enantiomeric excesses using chiral analogs of Crabtree's catalyst. For instance, Pfaltz's group alone have published at least 18 research papers (excluding reviews) that feature hydrogenation of this particular substrate.[30,32−48] Figure 11 shows some of the ligands that have been used to do this, the particular ester involved, and the enantiomeric excesses obtained. Figure 12 shows ligands that Andersson's group have used in similar hydrogenations.[27,49−58] Stereoselectivities in these reactions are relatively tolerant of

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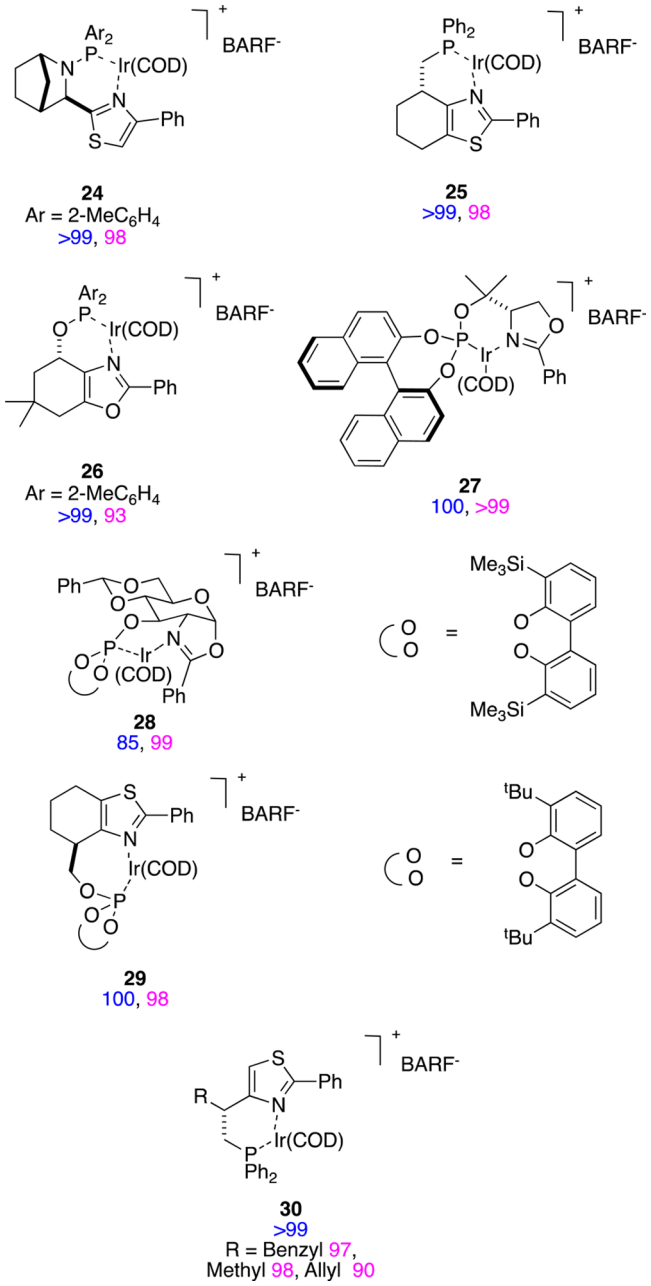

Figure 12. Conversions (shown in blue) and enantioselectivities (shown in purple) in Andersson's hydrogenations of substrates **D**.

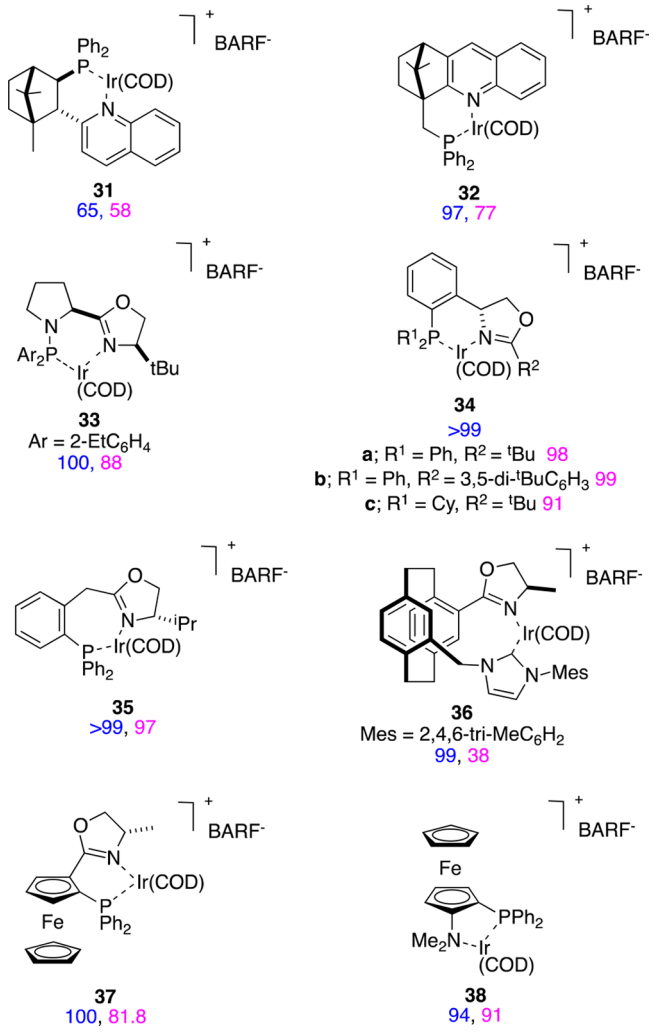

Figure 13. Asymmetric hydrogenation of substrate **D** from groups other than Pfaltz and Andersson.[59−67]

simple changes to the ester−alkyl functionality, and high conversions are the norm (Figure 13).

Substrate **D** has been hydrogenated by many groups, but the isomers and homologues **E**−**G** have not been studied so much. Catalysts **39**,[39,68] **40**,[57] **41**,[27] and **42**[37] (Figure 14) have been used for this series of substrates, and it appears that **41** and **42** are the most generally suitable. Relatively small changes to the substrate can significantly affect the conversions and enantioselectivities in these reactions. For instance, catalyst **40** is an excellent hydrogenation catalyst for substrate **D**, but a relatively poor one for **F** and **G**; this is also true for other catalysts that are not shown here.

The transformations shown in Figure 15a for tiglic acid derivatives illustrates how 1-methylpropyl- chiral centers could be generated if a good catalyst had been identified, but *none* has emerged so far. Intriguingly, the same catalyst **9** gives *opposite* enantiofacial selectivities for this ester relative to similar tiglic alcohol and α-methyl stilbene derivatives. DFT calculations reveal plausible explanations for these observations.[22] They indicated that one enantiomer of the product ester appears to be formed via a mechanistic pathway that parallels that for α-methyl stilbene hydrogenations by catalyst **9**. However, the other enantiomer of the product apparently results via a different mechanism that involves only Ir(3+) intermediates, and coordination of the ester carbonyl to the metal (Figure 15b). This pathway is possible only if there is a carbonyl group in this position; consequently, tiglic acid, the corresponding carboxylate salt, and the Weinreb amide derivative all give this "abnormal stereoface selectivity" but tiglic alcohol and its ether derivatives do not. This is a case in which two enantiomers of a product appear to be formed via different mechanisms because the diastereomeric intermediates in the catalytic cycle favor that pathway over a competing one for only one enantiomer. That favored pathway involves an ester as a CFG.

Hydrogenations of the dienes **43** and **44** have the potential to give useful chirons with two stereocenters in one step. These reactions involve sequential asymmetric hydrogenations (at similar rates); hence, high enantioselectivities are to be expected because diastereomers are the main stereochemical

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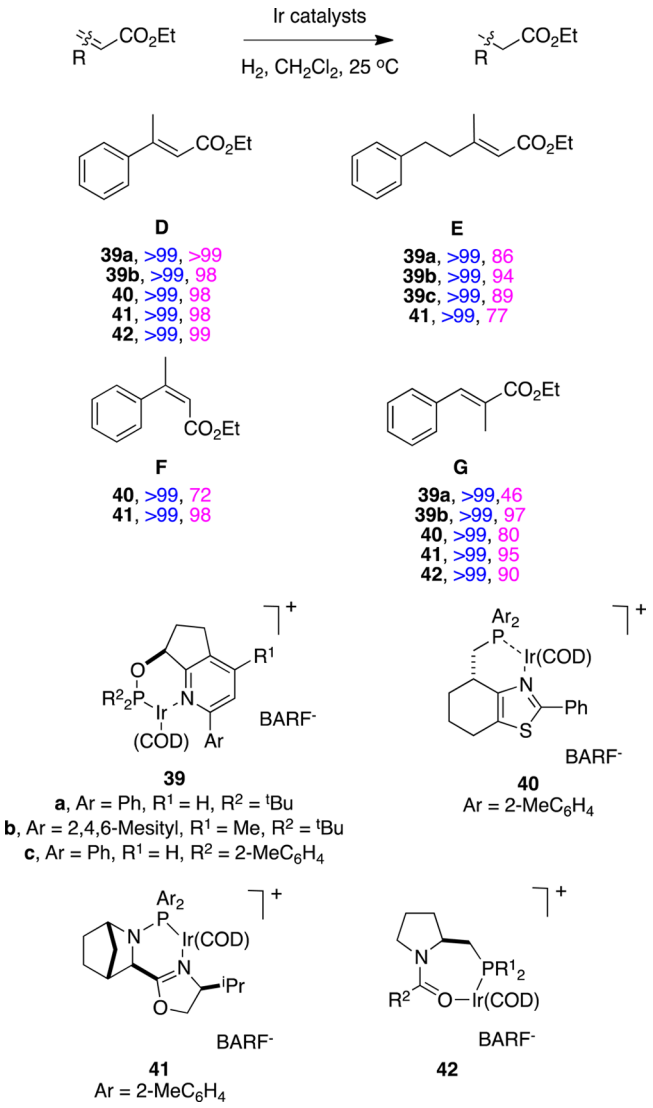


Figure 14. Comparison of asymmetric hydrogenations (conversions [shown in blue] and enantioselectivities [shown in purple]) of close analogs of substrate **D**.

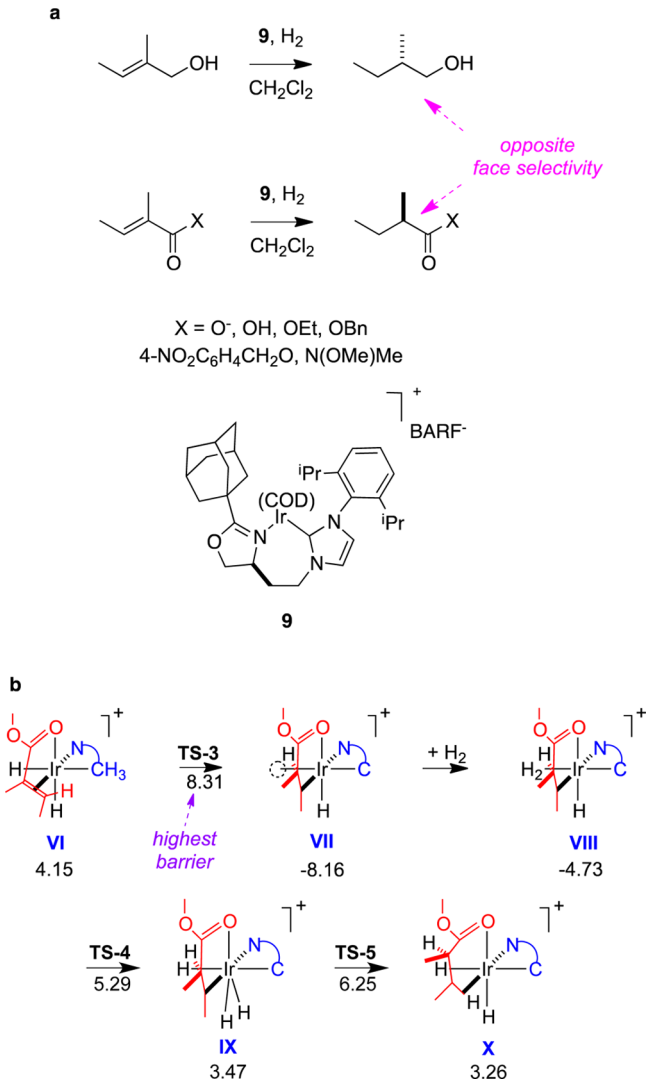
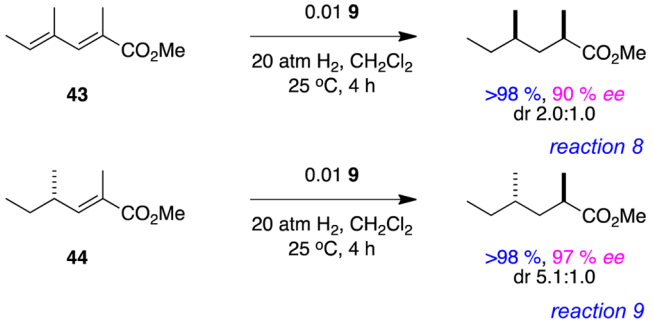
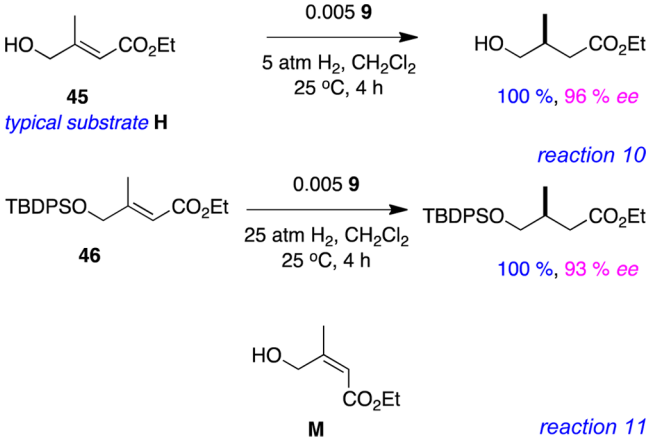


Figure 15. (a) Tiglic alcohol and acid derivatives give opposite face selectivities. (b) DFT calculations indicate formation of the favored enantiomer in the hydrogenations of tiglic ester derivatives occurs via coordination of the ester carbonyl.

impurities (Horeau's principle).[69] This interesting situation should not cloud the fact that the face selectivities of the hydrogenation steps involved cannot be high. If a more selective catalyst were identified for tiglic esters, then it would be worth probing stereoselectivities in reactions 8 and 9 using that. Indeed, it would be interesting now to investigate hydrogenations of the corresponding dienyl carboxylic acids using some of Zhou's complexes that have spirocyclic ligands since these do hydrogenate tiglic acid with high stereoselectivities (see above).



There are many potential applications of α,ω-functionalized substrates **H** (e.g., **45** and **46**) because the termini can be elaborated via chemoselective reactions that give orthogonal stereoselectivities. It is surprising that, to the best of our knowledge, these substrates have been investigated only in reactions 10 and 11.[70] The isomeric systems **M** have apparently not been investigated at all.



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Matching the influences of substrate and catalyst "vectors" for γ-chiral alkenes **I** (e.g., **47**−**49**) can afford a range of chirons that may be used to prepare, among other things, polyketide-derived natural products. Figure 16 gives some examples of

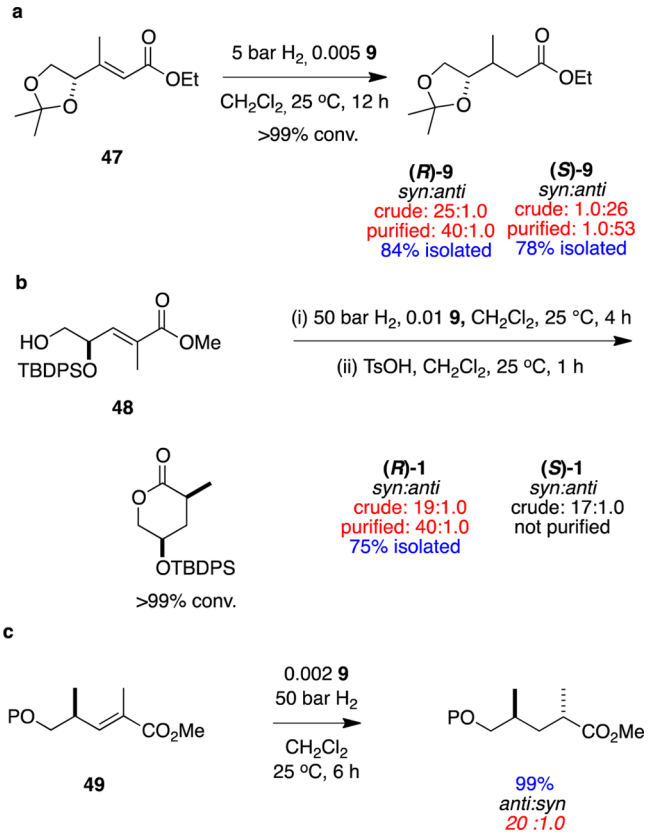
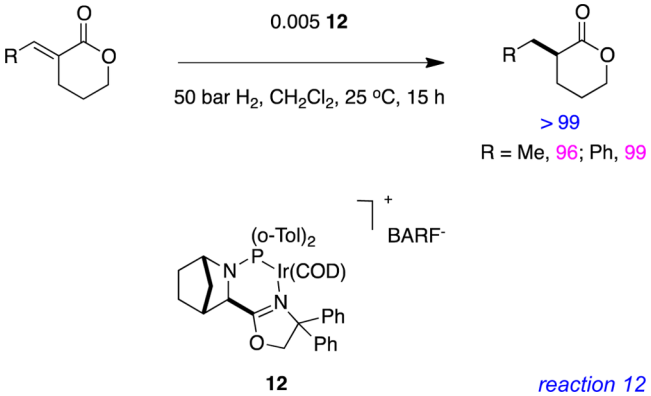


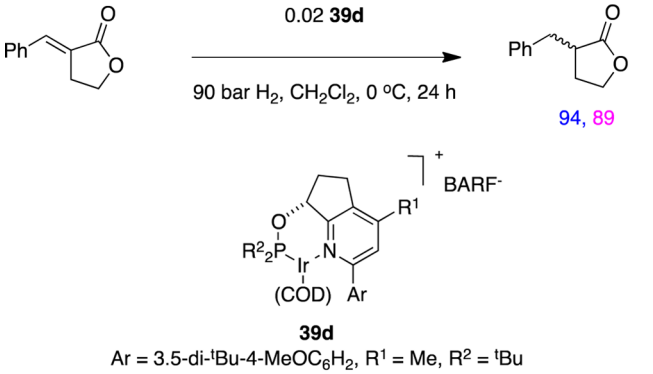
Figure 16. Hydrogenation of γ-chiral substrates to give (a) 1,2-hydroxylmethyl, (b) 1,3-hydroxylmethyl, and (c) 1,3-dimethyl chirons.

when these reactions have been used to give 1,2- and 1,3-hydroxylmethyl, and 1,3-dimethyl motifs.[22,70,71] Substrate vectors contribute to the overall stereoselectivities of these reactions; in most cases, the catalyst influence is dominant (e.g., Figure 16a and c), but not for the γ-chiral homoallylic alcohol in Figure 16b.

Relatively few lactones have been reported as asymmetric hydrogenation substrates. Reactions 12 and 13 show examples featuring chiral analogs of Crabtree's catalyst; high enantioselectivities were obtained in both cases.[27]

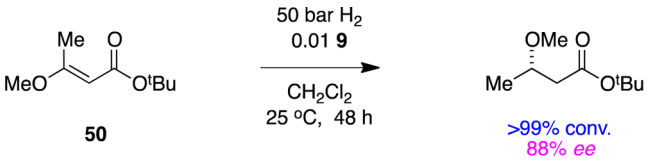


reaction 12



reaction 13

Asymmetric hydrogenations of β-alkoxy-α,β-unsaturated esters (e.g., **50**) have been studied in one paper.[72] Protons generated in hydrogenations with Crabtree's catalyst analogs[73] can lead to decomposition of enol ether substrates in competition with hydrogenation processes, but this does not happen with the carbene-oxazoline complex **9** when applied to these slightly less electron-rich alkenes.



reaction 14

Hydrogenations with Other Catalysts. We cannot find reports of Noyori-style ruthenium catalysts in hydrogenations of simple (no other functionality) α,β-unsaturated carboxylate esters. A possible explanation for this is evident by reference to Halpern's mechanism for hydrogenations of α,β-unsaturated carboxylic acids with these catalysts (Figure 2). This pathway features dissociation of saturated carboxylates and their replacement with α,β-unsaturated ones; esters simply cannot coordinate in the same way as carboxylates and give the same types of neutral Ru(2+) complexes. However, Takaya et al. have reported hydrogenation of unsaturated lactones using their ruthenium catalyst; only substrates with exocyclic alkenes gave high enantioselectivities, and the conversions were sometimes incomplete (Figure 17).[74]

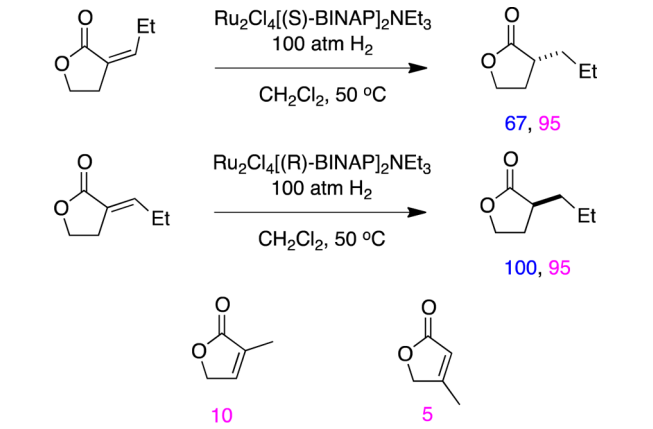


Figure 17. Conversions (shown in blue) and enantioselectivities (shown in purple) in hydrogenations of lactones using Ru-BINAP catalysts.

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Some of John Brown's early (1985) studies of alkenyl ester hydrogenations provide an excellent comparison of the relative importance of ester-coordinating effects for Crabtree's catalyst and Rh(1+)(diphosphine) complexes.[75] Specifically, his work on the achiral complexes **51** and **52** (Figure 18) show that

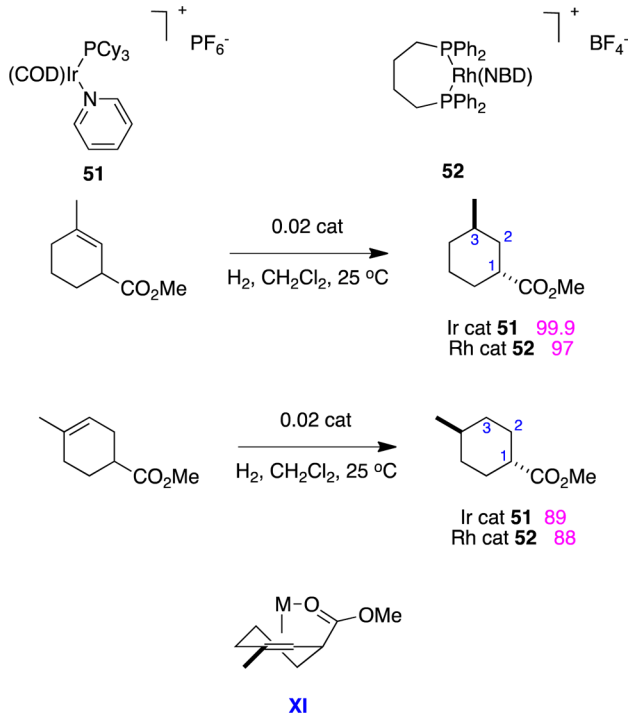
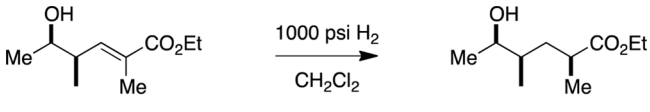


Figure 18. Crabtree's catalysts gives stronger directing effects than rhodium diphosphines (enantioselectivities in purple).

hydrogenations with the Ir(1+) catalysts are considerably faster and more syn-selective than the Rh(1+) species. Coordination to the ester via intermediates such as **XI** was implicated in both cases, but this effect was more significant for Crabtree's catalyst, presumably because of transient complexation to Ir(5+) intermediates.

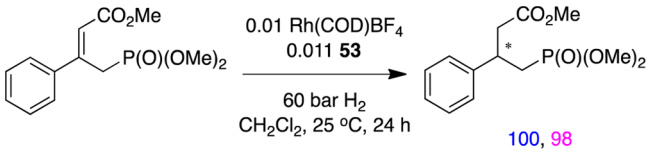
The studies outlined in Figure 18 also featured deuteration of the same substrates. Brown et al. found deuterium was incorporated onto the C^{1-3} positions, and only two deuterium atoms, on average, were incorporated into each molecule. This is indicative of double bond migration concurrent with the hydrogenation event.[76]

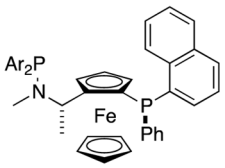
There are, in fact, few hydrogenations reported for α,β-unsaturated esters (no other FGs) that feature Rh(1+) catalysts. The examples that are in the literature tend to involve other functional groups that could be coordinating; for example, the homoallylic alcohols in reaction 15[22] and the allylic phosphonate in reaction 16.[77]



substrate control dominates in both cases

reaction 15

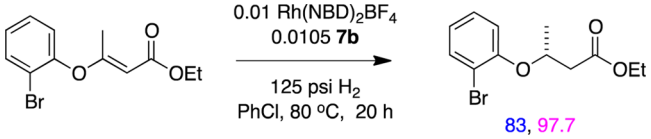


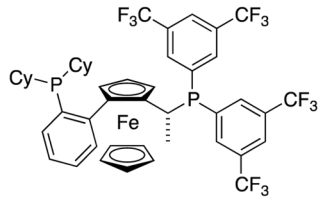


53
Ar = 4-$CF_3C_6H_4$

reaction 16

An exception to the observation that CFG groups tend to be required in Rh(1+)-mediated catalysis of enol ether substrates **K** is depicted in reaction 17.[78] In that transformation, there are no obvious CFGs for Rh(1+) or other ways for the substrate to form out-of-sphere association with the ligand. The in situ-generated catalyst involved in these reactions was probably identified from a broad screening effort.





7b

reaction 17

Summary for Hydrogenations of Carboxylic Esters. Brown's early work (Figure 18) and the stereochemical reversal for tiglic esters relative to similar substrates (Figure 15) indicate that esters *are* coordinating functional groups in hydrogenations mediated by chiral analogs of Crabtree's catalysts. These coordinating effects may not be as powerful as others (e.g., from homoallylic alcohols), but they are significant enough to promote asymmetric hydrogenations by chiral Ir-*N*,*P* catalysts, making them uniquely useful for this substrate class. Ruthenium and rhodium bisphosphine complexes do not hydrogenate unsaturated esters with comparable conversions and enantioselectivities. A reason for this difference is the possible involvement of higher oxidation-state iridium species for Crabtree catalyst analogs.

Future research in this area should feature substrates that give more useful products than **D** does; for example, the α,ω-functionalized ones **H** and **I**. Other studies should include deuteration reactions to monitor double bond migration.

D. CONCLUSIONS

Despite all the work that has been reported on hydrogenations of unsaturated acid and ester derivatives, it is hard to make direct comparisons for the same carbon backbones. In fact, we are able to present this for only three types of substrates (Table 2). Selected iridium complexes from Zhou, featuring spirocyclic ligands, and some Noyori-based systems are preferred for the

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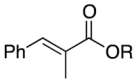
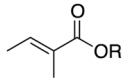
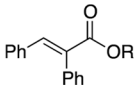
Table 2. Comparison of Hydrogenations of α-Methyl Cinnamate and Tiglic Acid Derivatives[a]

Substrates	R = H % conversion, % ee, **complex**	R = alkyl % conversion, % ee, **complex**
	>99, 77, **2 (Ru)** >99, 82, **3 (Rh)** 100, 97, **6 (Rh)** >96, 99, **8a (Ir)** 97, 99, **10 (Ir)** 100, 99, **12 (Ir)**	various >99, >93, **12 (Ir)** Et >99, 98, **25 (Ir)** Et >99, 32-50, **30 (Ir)** Et 88, 82, **38 (Ir)** Et >99, 97, **39c (Ir)** Et 90, 40, **40 (Ir)** various >86, >89, **42 (Ir)**
	100, 91, **1 (Ru)** >99, 97, **2 (Ru)** >89, 99, **8b (Ir)** 100, 55, **9 (Ir)** 93, 98, **10 (Ir)**	Et >98, 67, **9 (Ir)** various >99, >91, **12 (Ir)**
	95, 95, **10 (Ir)**	^{i}Pr 80, 97, **39b (Ir)** Et >63, >56, **42 (Ir)**

[a]Satisfactory system for each substrate shown in red.

carboxylic acids. Ruthenium- and rhodium-based diphosphine catalysts are significantly less useful for hydrogenations of carboxylic esters. For ester substrates, the preferred catalysts tend to be Ir-*N*,*P* complexes, notably from Pfaltz and Andersson; Zhou's spirocyclic systems are significantly less reactive for these substrates.

Researchers interested in hydrogenating the simple substrates shown in Table 2 can find catalysts that have already been shown to reduce them with high stereoselectivities and conversions; there are no pressing needs to search further for other catalysts, but arguments might be made in favor of new designs that are more accessible. It might also be useful in some cases if a catalyst could be found to reduce unsaturated esters and acids with high stereoselectivities and conversions; at present, Andersson's complex **12** comes the closest to meeting this aim.

The next phase in this research is hydrogenations of more complex substrates. These include alkenes with other functionalities to gauge chemoselectivity issues and the effects of potential CFGs on stereoselectivities. Endo cyclic alkene lactones and carbocyclic rings with peripheral acid groups also deserve more attention. More work on hydrogenation of chiral substrates to give stereochemically complex materials is warranted. Overall, it is time to identify and prioritize the most important substrates to hydrogenate.

Figure 15 and the discussion around it indicate esters are CGFs in asymmetric hydrogenations mediated by Crabtree's catalyst analogs. There has been a tendency to rationalize face selectivities for hydrogenations by these catalysts in terms of empirical "quadrant" models. These cannot be totally reliable in situations for which a supposedly innocuous group such as an ester can coordinate to the metal; consequently, models like this should be evaluated with care. It is even possible that phenyl groups and aliphatic C−H bonds have weak coordinating effects with Crabtree's catalyst analogs that go unnoticed in most reactions, and they may perturb facial selectivities.

Finally, Brown performed deuteration studies in his hydrogenation work over 30 years ago to test for competing double bond migration reactions. This type of experiment is rarely repeated in contemporary studies (though there are examples as outlined above), but these informative experiments could be used more in optimization reactions to distinguish alkenes that are being isomerized from those that are being hydrogenated directly.

AUTHOR INFORMATION

Corresponding Author

*E-mail: burgess@tamu.edu.

Notes

The authors declare no competing financial interest.

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