Discovery, Applications, and Catalytic Mechanisms of Shvo's Catalyst

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1. Introduction and Scope

Shvo's catalyst is a cyclopentadienone-ligated ruthenium complex, $\{[Ph_4(\eta^5\text{-}C_4CO)]_2H]\}Ru_2(CO)_4(\mu\text{-}H)$ (**1**, Scheme 1), that is a generally useful catalyst for transfer hydrogenation to alkenes, alkynes, carbonyl groups, and imines from alcohols, amines, dihydrogen, and several dihydrogen surrogates. The mechanism of hydrogenation and dehydrogenation reactions catalyzed by Shvo's catalyst is unique among transition-metal catalysts that affect similar transformations because it involves simultaneous transfer of separate hydrogen atoms from (or to) the metal center and the ligand. Thus, Shvo's catalyst is an example of a ligand−metal bifunctional catalyst wherein redox activity is distributed between the metal center and a cyclopentadienone ligand.

Many applications of Shvo's catalyst have been reported since its discovery in the mid 1980s, and some of these were reviewed as recently as 2005.[1] Since then a number of synthetic applications have appeared, most notably involving the use of alcohols and amines directly as alkylating agents via an oxidation−condensation−reduction sequence. These recent advances are well reviewed in the *Encyclopedia of Reagents for Organic Synthesis*.[2] Equally prolific as the recent developments in applications of this catalyst are contributions to understanding its reactivity mechanisms and designing analogous catalytic systems based on related ligand−metal bifunctional catalysis motifs. Some of the mechanistic studies were summarized in a review discussing metal-catalyzed transfer hydrogenation in 2006;[3] we will thoroughly review the details of those studies and discuss additional, more recent contributions. Most notable among these include recent extensive computational studies and extensions of the Shvo mechanism to lower cost, more benign iron congeners.

Our observation of the recent exciting new results, the obvious intrigue and utility of this catalyst motif, and the need for a concise summary of the mechanistic work in the area motivated us to prepare a comprehensive review. Thus, this review describes the discovery, structure, synthetic application, and reactivity mechanisms of Shvo's catalyst and related cyclopentadienone-ligated metal complexes.

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Brian Conley grew up in Dunbar, WV. He obtained his B.S. degree in Chemistry in 2004 from Elon Univeristy in North Carolina, where he conducted undergraduate research on the electrochemical properties of dipyridylketone-ligated platinum complexes. In December 2008 he obtained his Ph.D. degree from the University of Southern California, working with Roy Periana on oxygen-atom insertion into metal−carbon bonds and C−H activation of hydrocarbons. He is currently a postdoctoral fellow whose primary interests are in transition-metal-catalyzed bond functionalization.

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2. Nature of Shvo's Catalyst and the Cyclopentadienone Ligand

2.1. Reactivity

Shvo's catalyst (**1**)[4] is an air- and water-stable crystalline solid that is commercially available from several sources. Its discoverer, Youval Shvo, and colleagues introduced this versatile ruthenium catalyst that utilizes noninnocent[5] cyclopentadienone ligands to stabilize the metal in low oxidation states. This complex and its analogs have been studied extensively for reactions such as hydrogenation of aldehydes, ketones, alkynes, and alkenes, transfer hydrogenation, disproportionation of aldehydes to esters, isomerization of allylic alcohols, dynamic kinetic resolution (DKR), amine−amine coupling, and hydroboration reactions.

Complex **1** is a dimeric precatalyst that forms monomeric oxidizing (**2**) and reducing (**3**) forms upon dissociation in solution (Scheme 1). The concentrations of these active forms are governed by equilibrium effects; compounds **2** and **3** are interconverted through the gain or loss of "H_2" from donors and acceptors as shown. Although there is no crystal structure for either **2** or **3**, solution NMR data, mechanistic probes,

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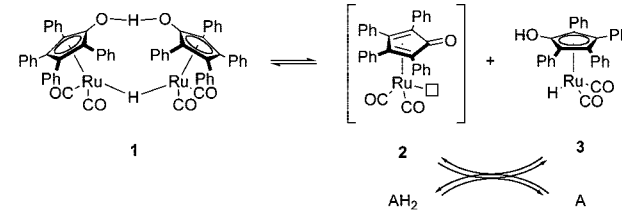
Travis Williams was an undergraduate at the University of North Texas and Caltech (B.S., 1998) and went on to graduate studies in the Paul Wender group at Stanford (Ph.D., 2005). He then returned to Caltech as an NIH postdoctoral fellow with John Bercaw and Jay Labinger. He joined the faculty of the Loker Hydrocarbon Research Institute at USC as an assistant professor in 2007.

and trapping experiments have been utilized to establish their structures. The structure of **3** is well characterized by NMR, while the structure of **2** is proposed to be a coordinatively unsaturated intermediate based on the characterization of trapped derivatives.

Scheme 1. Shvo's Catalyst (1): Heterodimer of Oxidizing (2) and Reducing (3) Complexes[a]



[a] **2** and **3** are interconverted in the presence of a hydrogen acceptor (A) or donor (AH_2). □ = vacant coordination site.

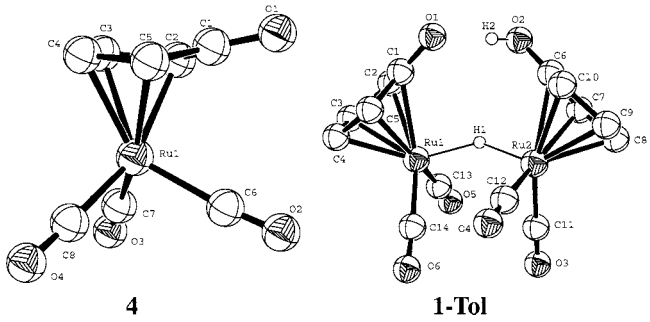


Figure 1. ORTEP diagrams of the molecular structures of $[Ph_4(\eta^4\text{-}C_4CO)]Ru(CO)_3$ (**4**, left) and $\{[2,5\text{-}Ph_2\text{-}3,4\text{-}Tol_2(\eta^5\text{-}C_4CO)H]\}\text{-}Ru_2(CO)_4(\mu\text{-}H)$ (**1-Tol**, right). Aromatic groups are omitted for clarity. (Left) Ru1−C1 (2.509 Å), Ru1−C2 (2.217 Å), Ru1−C5 (2.240 Å). (Right) Ru1−C1 (2.399 Å), Ru1−C2 (2.269 Å), Ru1−C5 (2.250 Å).

2.2. Structure

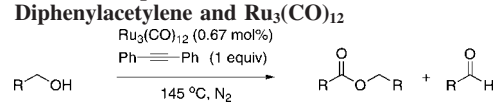
The dissociated monomeric forms of **1** are a ruthenium hydride (**3**) and a coordinatively unsaturated dicarbonyl species (**2**). Coordinatively unsaturated complex **2** rapidly (and usually reversibly) adds a dative ligand to its open site. Notably, both bridging hydrogen atoms are associated with the same monomer upon dissociation. Thus, upon dissociation one ruthenium is in the 2+ oxidation state (**3**) while the other is formally in the zero oxidation state (**2**). Ironically, it is the ruthenium(0) center, the formally more reduced monomeric form, that oxidizes alcohols by the concerted abstraction of H^+ and H^-. The formally more oxidized monomeric form possessing the two hydrogen atoms is the reducing complement. This creates for an interesting situation in which the species of higher formal oxidation state (Ru^{II}) is the reducing agent, and the formal ruthenium(0) species is the oxidizing complement. It is a conundrum created by the conversion of a formally neutral cyclopentadienone ligand to a formally anionic hydroxycyclopentadienone ligand by addition of a formal cation, H^+. It might be more reasonable to think of these species as two ruthenium(II) species, with the oxidizing form bearing a dianionic η^5-alkoxycyclopentadiene. However, such a view is inconsistent with the X-ray structure of $[Ph_4(\eta^4\text{-}C_4CO)]Ru(CO)_3$ (**4**, Figure 1). In this case, the cyclopentadienone ligand is puckered so that the Ru−C distance to C1 (2.509 Å) is larger than C2 (2.217 Å) or C5 (2.240 Å) as seen in Figure 1. This structure can be understood as an η^4-diene with a pendant carbonyl that has little (if any) interaction with the metal. By contrast, the Shvo homologue **1-Tol** (bearing *p*-tolyl groups) has similar Ru−C distances to C1, C2, and C5 (2.399, 2.269, and 2.250 Å, respectively).

Mechanistic studies by Casey, Bäckvall, and others have established that the catalyst transfers dihydrogen through a hydride on the transition metal (Ru−H in **3**) and a proton on the hydroxy cyclopentadienyl ligand (O−H in **3**) and is thereby a ligand−metal bifunctional catalyst. (Regarding ligand−metal bifunctional hydrogenation catalysts, see ref 3.) The mechanism of hydrogen transfer with Shvo's catalyst is further discussed in sections 6 and 7.

3. Discovery of Shvo's Catalyst

The discovery of **1** and its catalytic reactivity stemmed from the observation that triruthenium dodecacarbonyl, $Ru_3(CO)_{12}$, catalyzes the transfer dehydrogenation of alcohols in the presence of hydrogen acceptors such as diphenylacetylene, alkenes, and ketones. Aldehyde products from these reactions undergo subsequent Tishchenko-style oxidative coupling to the corresponding esters (vide infra, Table 1).[6] In these studies, Shvo found that diphenylacetylene greatly enhanced the activity of the parent ruthenium carbonyl, allowing for both increased rate and turnover number relative to a reaction in which diphenylacetylene is absent. Also, reactions run in the presence of diphenylacetylene maintain their homogeneity, while some of those that are run with other acceptors precipitate metallic material and lose reactivity. These observations were initially unexplained, but a series of insightful experiments indicated that a cyclopentadienone-ligated ruthenium complex was involved. Specifically, when cyclohexanone was used alone as the hydrogen acceptor, a ruthenium mirror formed on the side of the reactors, apparently from loss of carbon monoxide from ruthenium and aggregation of ruthenium metal, resulting in only ca. 25% conversion of alcohol.[6b] When a catalytic amount of diphenylacetylene is present the solution maintains its yellow color and homogeneity throughout the reaction. Further, even when a stoichiometric amount of diphenylacetylene is present in bulk ketone, ketone is the predominant H_2 acceptor (as opposed to the alkyne). These observations imply that diphenylacetylene forms a derivative of $Ru_3(CO)_{12}$ that remains soluble under the reaction conditions. At the time it was not clear why added phosphines did not have the same stabilizing effect on the system.

Table 1. Scope of Esterification of Alcohols with Diphenylacetylene and $Ru_3(CO)_{12}$



entry	alcohol	time (h)	conversion (%)	ester (%)	aldehyde (%)
1	propanol	4	93	91	2
2	octanol	4	98	97	1
3	isobutanol	4	95	94	1
4	neopentanol	4	76	73	3
5	2-ethoxyethanol	4	56	56	0
6	benzyl alcohol	4	96	93	3
7	benzyl alcohol[a]	9	83	71	2
8	4-chlorobenzyl alcohol	4	63	53	10
9	4-methylbenzyl alcohol	4	99	86	13
10	4-methoxybenzyl alcohol[b]	4	75	52	19
11	1,4-butanediol[c]	6	95	95	0

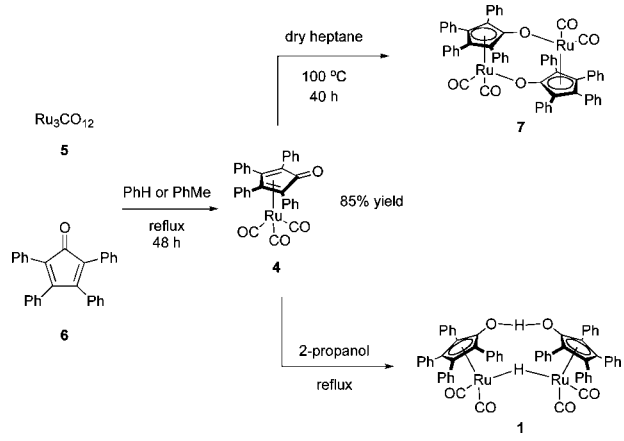
[a] Acetone (22.5 mmol) and diphenylacetylene (0.75 mmol) were used as acceptors. A small quantity of isopropyl benzoate was detected. [b] Bis(4-methoxybenzyl) ether was detected. [c] The product is γ-butyrolactone. Adapted from ref 6b.

It was shown in 1967 that refluxing $Ru_3(CO)_{12}$ in aromatic solvents in the presence of an alkyne results in the synthesis of cyclopentadienone-ligated transition-metal complexes via a [2 + 2 + 1] cycloaddition among two equivalents of diphenylacetylene and one metal-bound CO.[7] Along these lines, $[Ph_4(\eta^4\text{-}C_4CO)]Ru(CO)_3$ (**4**), $\{[Ph_4(\eta^5\text{-}C_4CO)]_2H\}\text{-}Ru_2(CO)_4(\mu\text{-}H)$ (**1**),[8] and free tetracyclone (**6**) were present in Shvo's reaction solutions. Shvo isolated **1** and **4**, used them directly in catalysis,[6c,9] and observed that they both have higher activity than a catalyst generated in situ.

4. Synthesis of Shvo's Catalyst

The first discrete synthesis of Shvo's catalyst is a two-step procedure in which monomeric tricarbonyl complex **4** is prepared and isolated and then converted to dimer **1** as illustrated in Scheme 2. In the first step $Ru_3(CO)_{12}$ is heated

Scheme 2. Two-Step Synthesis of Shvo's Catalyst 1 (bottom) and Dimer 7 (top)



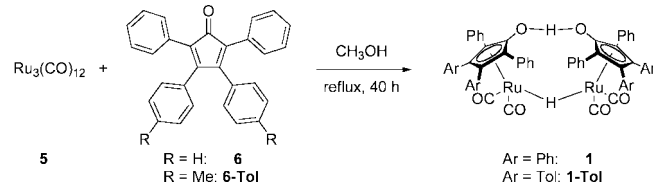
to reflux for an extended time (≥48 h) under inert atmosphere in a dry, aromatic solvent such as benzene,[7c] toluene, or mesitylene.[10] In net, tetracyclone (**6**) cleaves the ruthenium dimer and displaces one equivalent of carbon monoxide per metal. $[Ph_4(\eta^4\text{-}C_4CO)]Ru(CO)_3$ (**4**) is isolated as an orange, crystalline solid by this preparation. The η^4-binding mode of the cyclopentadienone ligand was confirmed by X-ray diffraction (Figure 1, left). Dimer **1** was reported in the same paper; it was prepared by refluxing **4** in 2-propanol.

Dimer **1** was originally identified as $\{[Ph_4(\eta^4\text{-}C_4CO)]Ru(CO)_2\}_2$ (**7**),[11] apparently by analogy to an iron-centered system, $[(\eta^4\text{-}C_4H_4CO)Fe(CO)_2]_2$, reported by Weiss.[12] However, Shvo soon discovered an upfield proton resonance in the ^{1}H NMR spectrum at −18 ppm in C_6D_6 that integrated 1:40 with respect to the aromatic protons.[1] This indicated that a bridging hydride formed from oxidation of the refluxing 2-propanol solvent. The position of such a bridging hydride between the two ruthenium centers is consistent with X-ray diffraction data for the chloro-substituted $[2,5\text{-}Ph_2\text{-}3,4\text{-}(p\text{-}ClC_6H_4)_2(\eta^5\text{-}C_4CO)_2H(CO)_4Ru_2](\mu\text{-}H)$[4] and **1-Tol** (Figure 1, right). Additionally, as indicated by the structural formula, another hydrogen was proposed to bridge the carbonyl oxygen atoms of the tetracyclone ligands. Thus, the formal oxidation state of each metal is 1+, resulting from the net two-electron oxidation of one molar equivalent of 2-propanol to acetone for every two ruthenium atoms. This forms one equivalent of $[Ph_4(\eta^5\text{-}C_4COH)]Ru(CO)_2(H)$ (**3**), which heterodimerizes with **2** to form **1**.

Many subsequent papers have reported use of the above two-step process for synthesis of **1**. Additionally, Bäckvall reported an alternative procedure that involves first refluxing tetracyclone and $Ru_3(CO)_{12}$ in mesitylene, followed by purification on silica gel to isolate **4**.[10] Compound **4** was then treated with an alkaline, aqueous acetone solution. Product **1** was extracted with CH_2Cl_2.

Casey's group reported a more concise synthesis of the ditolyl derivative of Shvo's catalyst, $\{[2,5\text{-}Ph_2\text{-}3,4\text{-}tol_2(\eta^5\text{-}C_4CO)H\}Ru_2(CO)_4(\mu\text{-}H)$, **1-Tol** (tol = 4-methylphenyl). In this procedure diphenylditolylcyclopentadienone (**6-Tol**, Scheme 3) is simply refluxed with $Ru_3(CO)_{12}$ for 40 h in methanol to form the target complex in one operation in 59% yield.[13] In our hands this procedure yields 60% of **1** under analogous conditions.[14] This procedure is far more convenient than the two-step procedure (Scheme 2) as the final product is isolated in analytical purity after filtering, washing with water, and drying under vacuum (Scheme 3). The ruthenium(0) dimer **7**, $\{[Ph_4(\eta^4\text{-}C_4CO)]Ru(CO)_2\}_2$, was isolated

Scheme 3. Efficient Route to Shvo's Catalyst (1) and Analogues



and characterized by refluxing **4** in neat, distilled heptane (Scheme 2).[15] This complex also serves as a precatalyst to the same reactions as **1**.

5. Synthetic Applications of Shvo's Catalyst

Many of the synthetic applications of Shvo's catalyst were well reviewed in 2005,[1] so these topics are given only cursory treatment in this presentation. Further, a concise summary of the organic reactivity of **1** has recently been published.[2] Since those publications, significant advancements have appeared, most notably amine coupling and hydroboration. This section of the review will give special emphasis to historical development and recent contributions to the area.

5.1. Oxidative Coupling of Primary Alcohols to Esters

Shvo's catalyst, generated in situ from $Ru_3(CO)_{12}$ and diphenylacetylene, catalyzes the transfer dehydrogenation of alcohols in the presence of hydrogen acceptors, such as diphenylacetylene, alkenes, and ketones.[6b] Aldehyde products from these reactions then undergo a Tishchenko-type disproportionation[16] to give the corresponding esters.[6a,c] When diphenylacetylene is employed as the hydrogen acceptor, the reaction is quite broad and general, as seen in Table 1.

The next important advance with this motif was acceptorless dehydrogenation of alcohols using **1** and **4** as catalysts with direct release of H_2 from open reactors.[7c] As above, these reactions oxidatively couple simple alcohols to form esters with the intermediacy of an aldehyde. This was quickly extended to the reverse reaction, hydrogenation of aldehydes, ketones, alkenes, and alkynes in the presence of pressurized hydrogen gas.[11]

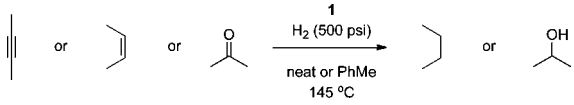
5.2. Oxidation of Alcohols to Form Ketones

Shvo's catalyst is useful for the oxidation of secondary alcohols to ketones; examples of these reactions are reviewed elsewhere.[1] Along these lines, several effective stoichiometric oxidants have been reported, including alkenes, alkynes, carbonyl groups,[17] and even chloroform.[18] Notably, an intramolecular acceptor can be used; this concept enables isomerization of allylic alcohols (and other alkene−alcohols) to the corresponding ketones.[19] Aerobic oxidation is also possible through the use of quinone and cobalt cofactors.[20,21]

5.3. Hydrogenation of Ketones and Alkenes

Shvo used **1** directly in hydrogenation of alkenes, alkynes, and carbonyl compounds (Table 2).[6c,11,22] Although a catalyst generated in situ from a mixture of $Ru_3(CO)_{12}$ and diphenylacetylene was effective in reactions of this type, **1** and **4** afforded higher activity than the in-situ-generated catalyst. Remarkably, these reactions can be conducted on large scales with reasonable catalyst loadings and minimal (if any)

Table 2. Hydrogenation Reactions of Shvo's Catalyst (1)



entry	starting material (mmol)	cat. (μmol, mol %)	solvent (mL)	time (min)	conv. (%) (TON)
1	1-octene (17.2)	10, 0.06	bulk	10	100 (1720)
2	2-pentene (46.5)	25, 0.05	bulk	15	100 (1860)
3	cyclohexene (49.4)	25, 0.05	bulk	15	100 (1976)
4	cyclohexene (49.4)[a]	25, 0.05	bulk	60	100 (1976)
5	1-methylcyclohexene (16.9)	10, 0.06	bulk	20	100 (1690)
6	styrene (52.4)	19, 0.04	bulk	720	67 (2760)
7	trans-stilbene (10)	50, 0.05	toluene (5)	180	93 (186)
8	1-hexyne (10)	50, 0.05	toluene (10)	35	100 (200)
9	4-octyne (10)	50, 0.05	toluene (10)	35	100 (200)
10	diphenylacetylene (10)	50, 0.05	toluene (10)	135	100 (326)
11	anthracene (10)	50, 0.05	toluene (10)	135	100 (520)
12	diethyl ketone (95)	47, 0.05	bulk	45	97 (1940)
13	cyclohexanone (100)[a]	50, 0.005	bulk	300	98 (1960)
14	diisopropyl ketone (50)	25, 0.005	bulk	180	88 (1760)
15	dibenzyl ketone (25)	25, 0.1	toluene (5)	180	100 (1000)
16	acetophenone (50)	25, 0.005	bulk	255	94 (1880)
17	benzophenone (10)	50, 0.05	toluene (10)	20	49 (96)
18	benzaldehyde (10)	50, 0.05	toluene (10)	10	81 (162)
19	pentanal (10)[a]	50, 0.05	toluene (10)	60	100 (200)

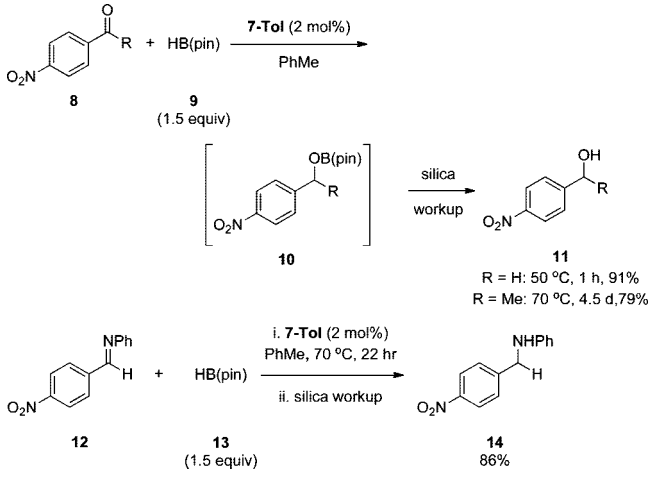
[a] At 100 °C. Adapted from ref 6c.

solvent. Transfer hydrogenation with formic acid as the reducing agent is also known.[23]

5.4. Aldehyde, Ketone, and Imine Hydroboration

Clark and Casey recently introduced conditions for hydroboration of aldehydes and aldimines with Shvo derivative **7-Tol** (Scheme 4).[24] In these reactions the H−B(pin) bond is added to a carbonyl (or imine) system by a mechanism wherein boron apparently takes on the role played by a proton in the reduction reactions above. Near quantitative hydroboration of benzaldehyde is observed by NMR, and high-yielding preparative-scale reduction reactions can be realized by hydrolyzing the resulting boronic ester (or amide) upon completion of the catalysis. Importantly, crossover experiments indicate that this reaction is not reversible. These data are significant to the mechanistic story of the Shvo system because they provide the first example of the use of a Lewis acid in the place of H^+ in the Shvo transition state. Moreover, they show that although this works well for reduction reactions, it is not effective in the complementary oxidation process; we similarly observed the latter.

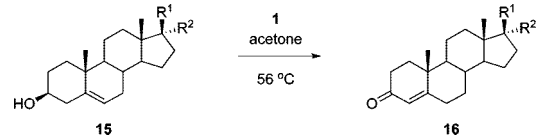
Scheme 4. Aldehyde and Aldimine Hydroboration



5.5. Oxidation of 3-β Steroidal Alcohols

Shvo's catalyst and its relatives have been used to affect a number of transformations of secondary alcohols. For example, catalyst **1** and $(PPh_3)_3RuCl_2$ were used (separately) for the catalytic oxidation of steroidal 5-en-3β-ols (**15**) to the corresponding 4-en-3-ones (**16**) (Table 3), which are biologically important substrates that are otherwise difficult to generate under mild conditions in high purity.[25] In some specific cases, one catalyst outperformed the other, but generally both catalysts were effective for a variety of steroids and showed excellent functional group tolerance (olefin, ketone, ester); the major difference between the two catalyst systems is the necessity of a base cocatalyst (K_2CO_3) and a small amount of water in the case of $(PPh_3)_3RuCl_2$. With either catalyst system, the reaction was run in refluxing acetone (56 °C), which served as both a solvent and a hydrogen acceptor. Concurrent with alcohol oxidation, the (6, 7) olefin is isomerized selectively to the (4, 5) position, presumably through an intermediate enol. This catalytic, selective, and mild transformation showed great improvement over previously employed methods in that no D-homosteroid rearrangement[26] was observed.

Table 3. Oxidation of a Steroidal Hydroxy Group to an Enone[a]



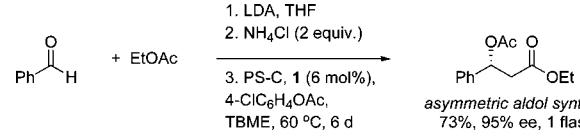
entry (compound)	R^1	R^2	catalyst	time (h)	yield (%)
1 (**a**)	OBz	H	**1** (0.5 mol %)	20	87
2 (**b**)		=O	**1** (0.25 mol %)	24	81
3 (**c**)		=O	$(PPh_3)_3RuCl_2$ (0.5 mol %), K_2CO_3 (10 mol %)	24	75
4 (**d**)	OH	Me	**1** (0.5 mol %)	18	93
5 (**e**)	OH	Me	$(PPh_3)_3RuCl_2$ (1 mol %), K_2CO_3 (40 mol %)	18	72

[a] Adapted from ref 25.

5.6. Dynamic Kinetic Resolution of Secondary Alcohols and Amines

Catalyst **1** has further been applied to the dynamic kinetic resolution (DKR) of secondary alcohols via conversion to the enantiopure acetate form in the presence of enzymes.[10,27] A DKR reaction is a kinetic resolution reaction in which the two or more compounds that are being resolved are also continuously interconverting throughout the resolution. Thus, as one compound is converted to an inert, resolved product, its concentration is replenished by equilibration of the other starting materials. Unlike a classical kinetic resolution, the resolved product can be obtained in up to 100% yield.[28] By contrast, the maximum resolved yield of a conventional kinetic resolution is the initial concentration of the desired product, 50% in a racemic mixture. Novozym 435 (*Candida antarctica* lipase B) and **1** transform a variety of secondary alcohol substrates to the enantiomerically pure acetate esters in >99% ee and good yield (Table 4). Whereas racemization reactions with $(PPh_3)_3RuCl_2$ generally proceeded faster than those catalyzed by **1**, attempts at DKR using $(PPh_3)_3RuCl_2$, Novozym 435, and base exhibited decreased enzyme activity. This is the result of the strong base required for catalysis with $(PPh_3)_3RuCl_2$; because Shvo's does not require added base, it is uniquely suited for use in conjunction with enzymes. Thus, Shvo's catalyst (**1**) performed better, and optimum conditions were found using toluene as a solvent at 70 °C with 4-chlorophenyl acetate as the acyl donor. A strategically similar reaction involving tandem reduction enables preparation of asymmetric acetates from ketones and vinyl acetates.[29,30] In these reactions, H_2 (1 atm) or an alcohol is introduced into the DKR reaction conditions so that chiral acetates can be prepared directly from oxidized precursors. Moreover, this DKR strategy can be used in tandem with aldol coupling to afford an asymmetric aldol.[31,32] The asymmetric aldol is produced via a two-step, one-pot synthesis: formation of the racemic aldol product followed by neutralization of the base and addition of **1** and *Pseudomonas cepacia* lipase (PS-C lipase) to generate the asymmetric product (Scheme 5).

Scheme 5. Two-Step Aldol Coupling and DKR



The substrate scope for the DKR process has been evaluated for 1-phenylethanol derivatives and aliphatic alcohols (Table 4). Aliphatic substrates also give high enantioselectivities and yields. This has special importance in cases where it is difficult to obtain selectivity by asymmetric ketone reduction. For example, Table 4 entry 3 illustrates dynamic resolution in the presence of an alkyl chloride functionality that might be sensitive to nucleophilic hydride reagents. Entry 4 illustrates differentiation of *n*-hexyl and methyl groups. This strategy can be applied to double-resolution cases. Particularly, a mixture of four diols (**17f**) can be converted to a single enantiomer diacetate (**18f**, Table 4, entry 6). The reaction is not limited to 4-chlorophenyl acetate as an acyl donor: simple alkyl esters are successful in certain cases,[33,34] and these are less expensive and more environmentally benign.

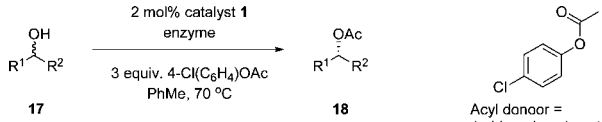
A further use of DKR with Shvo's catalyst is the conversion of racemic α-hydroxy acid esters to the corresponding enantiomerically pure acetates, as seen in Table 4, entries 7 and 8.[35] In these cases, Shvo's catalyst was used in the presence of PS-C lipase and 4-chlorophenylacetate in cyclohexane. The scope of this reaction is quite broad and is not restricted to aromatic hydroxy acids. The same methodology has also been used for the synthesis of δ-hydroxy esters as a route to chiral δ-lactones.[36]

Lastly, Bäckvall expanded this system for the dynamic kinetic resolution of amines by using an analogue of Shvo catalyst (**21**) and Novozym 435.[37] When using isopropyl acetate as the acylating agent, this system is able selectively to acylate amines. The reaction requires sodium carbonate, but it produces products in high yield and with high enantiopurity (Table 5). Further discussion of the reversible oxidation of amines is included in the following section.

5.7. Oxidation of Amines to Imines

Amine oxidation with Shvo's catalyst was first reported by Bäckvall's group in 2002 using either MnO_2 or 2,6-dimethoxybenzoquinone (**23**) as the oxidant, Scheme 6A.[38] Mild conditions were used to afford very selective, high-yielding conversion of aromatic amines to the corresponding imines (Table 6). In 2005 Bäckvall expanded this system to

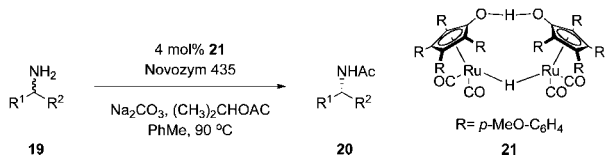
Table 4. Dynamic Kinetic Resolution of Secondary Alcohols[a]



entry (compound)	R^1	R^2	conditions	time (h)	yield (%)	ee (%)
1 (**a**)	Ph—	—Me	novozym 435, PhMe, 70 °C	46	80	>99 (*R*)
2 (**b**)	$PhOCH_2$—	—Me	novozym 435, PhMe, 70 °C	46	88	>99 (*R*)
3 (**c**)	$PhOCH_2$—	$—CH_2Cl$	novozym 435, PhMe, 70 °C	68	68	79 (*S*)
4 (**d**)	n-C_6H_{13}—	—Me	novozym 435, PhMe, 70 °C	68	80	>97 (*R*)
5 (**e**)			novozym 435, PhMe, 70 °C	48	65	>99 (*R*)
6 (**f**)			novozym 435, PhMe, 70 °C	48	63	>99 (*R*, *R*)
7 (**g**)	n-C_4H_9—	$—CO_2Me$	PS-C, cyclohexene, 60 °C	24	60	80 (*S*)
8 (**h**)	Ph—	$—CO_2Me$	PS-C, 60 °C cyclohexene,	48	80	94 (*S*)

[a] Adapted from references 10 and 35.

Table 5. Dynamic Kinetic Resolution of Primary Amines[a]

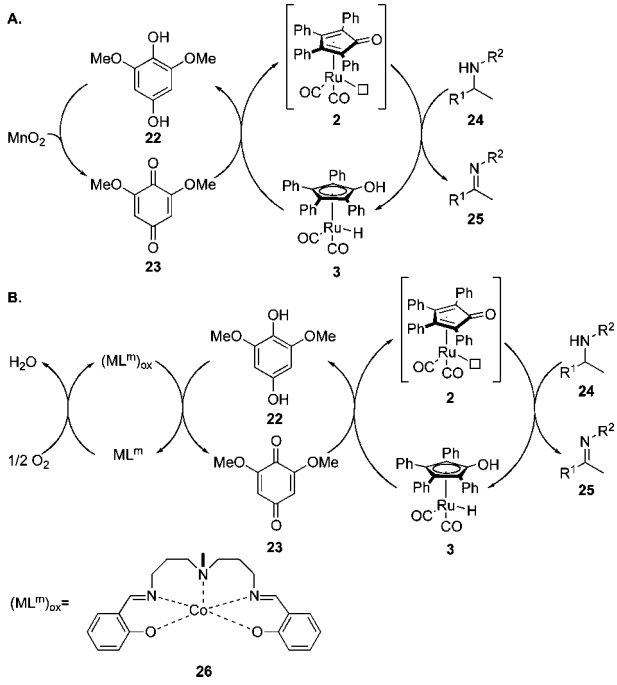


19 20 21

entry (compound)	R¹ / R²	yield (%)	ee (%)
1 (**a**)	Ph / Me	90	98
2 (**b**)	3-Me-C_6H_4 / Me	69	98
3 (**c**)	4-F-C_6H_4 / Me	83	99
4 (**d**)	4-Br-C_6H_4 / Me	78	99
5 (**e**)	4-OMe-C_6H_4 / Me	95	99
6 (**f**)	2-Naphthyl / Me	80	>99.5
7 (**g**)	Ph / Et	85	99
8 (**h**)		92	95
9 (**i**)	4-CF_3-C_6H_4 / Me	91	99
10 (**j**)	*n*-C_6H_{13} / Me	85	93
11 (**k**)	$PhCH_2CH_2$ / Me	78	95

[a] Adapted from ref 37.

Scheme 6. Oxidation of Amines with Terminal Oxidants

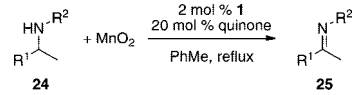


biomimetic aerobic oxidation by using cobalt cocatalyst **26** to reoxidize the quinone, Scheme 6B.[39]

5.8. Imine Hydrogenation

Reduction of imines by Shvo's catalyst was first reported for comparison of the rate of reduction of PhCH=NMe with benzaldehyde.[13] An imine is reduced ca. 26 times faster than the corresponding aldehyde in an analogous case (compare benzaldehyde versus benzaldehyde-*N*-methyl imine). Shortly after the original report, a preparative transfer hydrogenation of imines was reported with 2-propanol acting as the hydrogen donor in aromatic solvent (Table 7).[40] Several aromatic imines were reduced in high yields.

Table 6. Scope of Amine Oxidation with Shvo's Catalyst 1[a]



24 25

entry (compound)	R^1	R^2	time (h)	yield (%)
1 (**a**)	Ph−	Ph−	5	76
2 (**b**)	*p*-F-C_6H_4−	Ph−	5	70
3 (**c**)	*p*-Me-C_6H_4−	Ph−	5	83
4 (**d**)	*p*-MeO-C_6H_4−	Ph−	5	94
5 (**e**)	Ph−	*p*-MeO-C_6H_4−	5	91
6 (**f**)	Ph−	*o*-Me-C_6H_4−	5	90
7 (**g**)	*p*-MeO-C_6H_4−	*p*-MeO-C_6H_4−	4	94
8 (**h**)	Ph−	2,4,6-Me_3-C_6H_4−	4	90

[a] Adapted from ref 38.

5.9. Amination of Propargyl Alcohols

As an additional synthetic application of Shvo's catalyst[41] and analogous cyclopentadienone-ligated ruthenium species,[42] Haak demonstrated conversion of propargyl alcohols to aminated ketone derivatives (Scheme 7). In this work Shvo's catalyst mediates addition of aniline (and other amines) to a propargyl alcohol, such as **29**. The products apparently arise from ruthenium-catalyzed alcohol oxidation followed by aniline addition to the intermediate ynone to give **31** or **32**. Subsequent reduction to **33** is then possible. Other catalysts based on substituted cyclopentadienones gave significantly different product distributions, thus enabling selectivity among the products illustrated in Scheme 7.

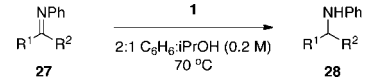
5.10. Alkylation of Amines with Alcohols

While Shvo's catalyst is not known to be highly efficient for the alkylation of amines using alcohols as alkyl donors, other catalysts have been used successfully. Scheme 8 illustrates early examples of this reaction.[43,44] Further examples involving both ruthenium and iridium catalysts have been reported subsequently. The ruthenium catalysts include $[(PPh_3)_3RuCl_2]$,[45] $[Ru(cod)(cot)]$,[45] $[Ru(p\text{-cymene})Cl_2]_2$ plus dppf,[46,47] $[(PPh_3)_2Ru(CH_3CN)_3Cl][BPh_4]$,[48] and $Ru_3(CO)_{12}$ with various phosphines,[49,50] while the iridium catalysts are $[Cp^*IrCl_2]_2$[51] and $[Ir(COD)Cl]_2$ plus dppf[52] or $Py_2NP(i\text{-}Pr)_2$.[53] The reaction can be very selective for monoalkylation; in fact, Milstein prepared primary amines from ammonia itself.[54] The oxidative process wherein an amine and alcohol are coupled to give the corresponding amide has also been reported.[55,56]

5.11. Alkylation of Amines with Amines

Beller's group recently extended the utility of **1** to include direct coupling of anilines and alkyl amines in high yield and selectivity. While investigating the reaction above (Scheme 8), they showed **1** to be only moderately effective for the alcohol−amine coupling but observed an amine homocoupling side product, presumably resulting from nucleophilic attack by free amine on an intermediate imine.[50] Thus, they developed **1** as a catalyst for the formation of *N*-substituted anilines using aliphatic amines as alkylating agents (Table 8).[57] Initial studies showed high yields above 140 °C, which were achieved with a variety of anilines and amino pyridines. Only 4-nitroaniline and 2,6-substituted anilines produced low yields. Further studies showed that in addition to primary amines, secondary, and tertiary amines

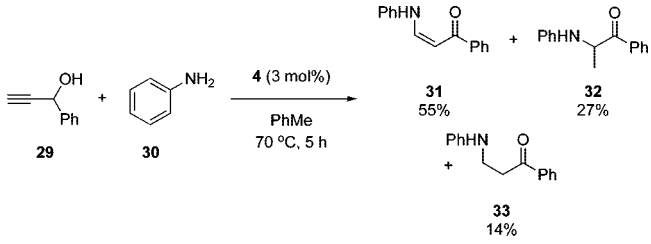
Table 7. Scope of Imine Hydrogenation with Shvo's Catalyst 1[a]



entry (compound)	R^1	R^2	catalyst loading (mol %)	time (h)	yield (%)
1 (**a**)	Ph—	—Me	0.3	1.5	97
2 (**b**)	Ph—	—H	0.3	5	98
3 (**c**)	Ph—	—Ph	1.0	4	94 (GC)
4 (**d**)	*i*-Pr—	—Me	0.3	4	94
5 (**e**)	*n*-C_5H_{11}—	—Me	0.5	6	94
6 (**f**)			0.5	6	94

[a] Adapted from ref 40.

Scheme 7. Amination of Propargyl Alcohols



are effective alkylating agents.[58] In fact, a mixture of mono-, di-, and trisubstituted amines was used to selectively produce monoalkylated anilines. In addition to anilines, amines bearing tertiary alkyl groups can also be coupled with primary, secondary, and tertiary amines (Table 8, entry 8).[59] These conditions can also be used with cyclic alkyl amines as the alkylating agents (Table 8, entry 9).[60] This apparently occurs via aminal formation and ring opening followed by dehydrogenation of the primary amine and ring closing as summarized in Scheme 9.

Ammonia forms a stable adduct with coordinatively unsaturated intermediate **2** and can be displaced by equilibria with coordinating alkyl and aryl amines.[61] The ammonia complex was isolated and characterized and can be used as a catalyst precursor. It is only slightly soluble in organic solvents in the absence of other coordinating amines, so it precipitates from solution when the reaction is complete. This is a potential means of catalyst recycling.

The mechanism of these coupling reactions was deemed a "hydrogen borrowing mechanism"[57] because an added hydrogen source or hydrogen transfer reagent is not needed. In these reactions, the "borrowed" hydrogen is stored as the reduced form of the catalyst until it is used at a later point

Scheme 8. Direct Coupling of an Alcohol and an Amine

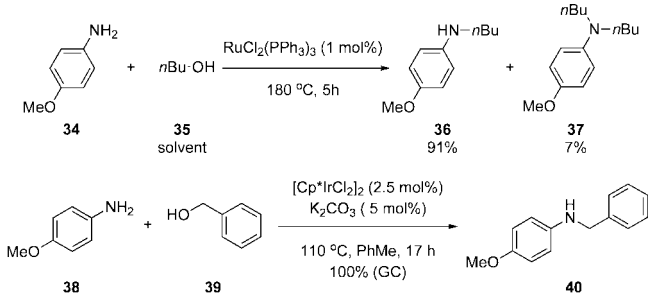
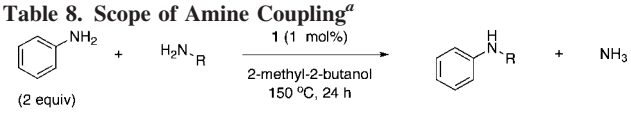
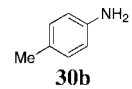
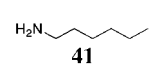
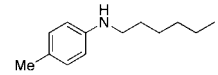
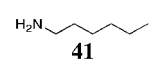
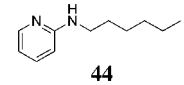
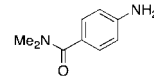
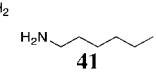
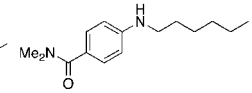
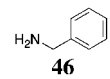
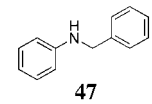
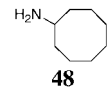
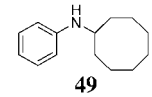
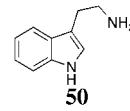
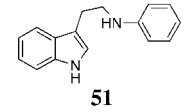
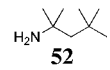
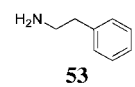
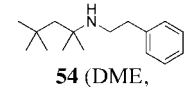
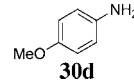
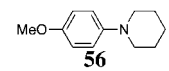


Table 8. Scope of Amine Coupling[a]

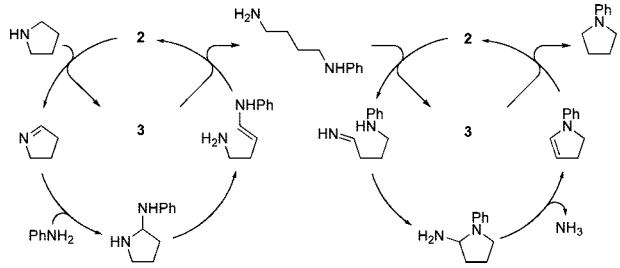


entry	amine	alkyl donor	product	yield (%)[b]
1	 **30b**	 **41**	 **42**	98
2	 **43**	 **41**	 **44**	96
4	 **30c**	 **41**	 **45**	83
5	 **30a**	 **46**	 **47**	94
6	 **30a**	 **48**	 **49**	99
7	 **30a**	 **50**	 **51**	93
8	 **52** (3 equiv)	 **53**	 **54** (DME, 170 °C)	75
9	 **30d**	 **55** (neat)	 **56**	68

[a] Adapted from references 57, 59, and 60. [b] Yields of isolated product are based on alkyl amine.

in the mechanism. A sample mechanistic proposal is outlined in Scheme 9 for a case of net arylation of pyrrolidine. Simply, pyrrolidine is dehydrogenated to the dihydropyrrole and the resulting H_2 is "borrowed" and stored as the reduced form of the catalyst until it is used later in the mechanism. The resulting imine then undergoes nucleophilic attack and

Scheme 9. Mechanism for *N*-Alkylation of Aryl Amines with Cyclic Alkyl Amines



subsequent ammonia elimination to form a new imine, which is hydrogenated by hydride **3**.

5.12. Condensation of Amines and 2-Aminophenols to Form Benzoxazoles

In addition to amine coupling reactions, Williams applied **1** to the coupling of primary amines and 2-aminophenols to form benzoxazoles in the presence of two equivalents of oxidant.[62] This reaction appears to proceed by **1**-catalyzed oxidation of the amine to an imine, which undergoes transimination with the aminophenol. This is followed by cyclization and oxidation by **1** to form the benzoxazole. This methodology is effective for a variety of substrates as shown in Table 9.

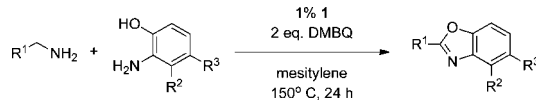
6. Mechanism of Oxidation of Alcohols and Reduction of Aldehydes and Ketones

The mechanism of hydrogenation and dehydrogenation by Shvo's catalyst has garnered intense interest. The mechanism of these reactions has unfolded in many papers. Remarkably, detailed kinetics, isotopic labeling, and structural characterizations have confirmed many original proposals about the catalytic cycle. This body of work has shown the Shvo mechanism to be an example of ligand−metal bifunctional catalysts that has similarities to Noyori's asymmetric transfer hydrogenation catalysts.[63,64] In the first detailed discussion about the reaction mechanism of alcohol oxidation with **1**, Shvo provided evidence for the formation of a 16-electron, coordinatively unsaturated species (**2**) by trapping it with triphenylphosphine (PPh_3).[6c] He also demonstrated that one molar equivalent of excess CO, delivered by starting from $[Ph_4(\eta^4\text{-}C_4CO)Ru(CO)_3]$, impedes the oxidation of alcohols.[6c] Since then, many mechanistic experiments have been applied to the Shvo system as described in this section.

6.1. Proposed Mechanisms

Two plausible mechanisms shown in Scheme 10 can explain the observed reactivity of Shvo's catalyst. Both are presented in the oxidation direction in this scheme; the reduction direction will be addressed more specifically

Table 9. Scope of Benzoxazole Formation[a]

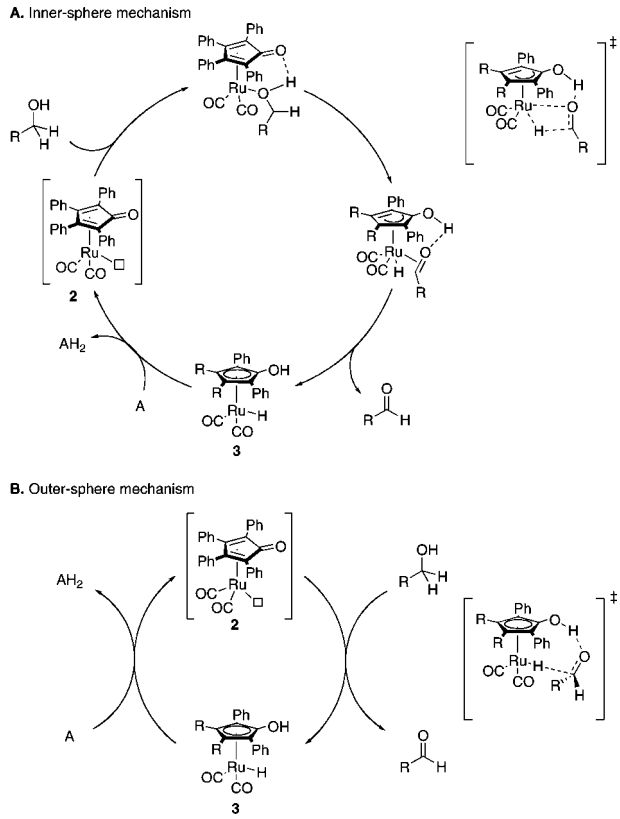


57 58 59

entry	amine	R^1	aminophenol	R^2, R^3	product	yield (%)
1	**57a**	Ph	**58a**	H, H	**59a**	43
2	Bn_2NH	Ph	**58a**	H, H	**59a**	66
3	**57b**	4-$MeOC_6H_4$	**58a**	H, H	**59b**	70
4	**57c**	4-MeC_6H_4	**58a**	H, H	**59c**	62
5	**57d**	4-ClC_6H_4	**58a**	H, H	**59d**	36
6	**57e**	2-thienyl	**58a**	H, H	**59e**	30
7	**57a**	Ph	**58b**	H, Me	**59f**	64
8	**57b**	4-$MeOC_6H_4$	**58c**	H, Cl	**59g**	50
9	**57a**	Ph	**58d**	Me, H	**59h**	52
10	**57f**	$ArCH_2$[b]	**58a**	H, H	**59i**	48

[a] Adapted from ref 62. [b] Ar = 3,4-$(MeO)_2C_6H_3$−.

Scheme 10. Proposed Catalytic Cycles for Alcohol Oxidation



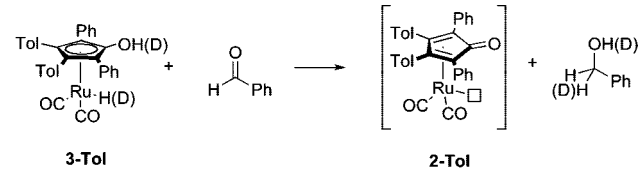
throughout the text. Bäckvall[35] and Shvo[6c] both argued that the mechanism could involve a pre-equilibrium coordination of alcohol to the metal center. Bäckvall proposed that this was followed by ($\eta^4-\eta^3$) ring slippage and concurrent β-hydride elimination and proton transfer, an inner-sphere mechanism as outlined in Scheme 10A. Casey proposed that the transfer could occur without precoordination of the alcohol and no ring slippage (Scheme 10B); this represents a rare example of a transition-metal-catalyzed process that does not require precoordination to activate the substrate.[13,65]

6.2. Kinetic Isotope Effect Studies

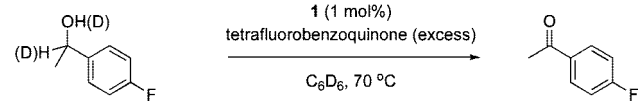
Casey[13] and Bäckvall[66] both provided compelling arguments for concerted hydrogen transfer in reactions interconverting alcohol and carbonyl compounds, predominantly based on measured kinetic isotope effects, Table 10. Casey used ruthenium hydride **3-Tol** to reduce benzaldehyde (Table 10, entries 1−5),[67] while Bäckvall studied the oxidation of 1-(4-fluorophenyl)ethanol by in-situ-generated **2** (entries 6−10). Casey's values for the reduction (top) include strong isotope effects at the ligand −OH (k_H/k_D = 2.2(1)) and at the ruthenium hydride (k_H/k_D = 1.5(2)), which multiply together to give a combined value of k_H/k_D = 3.3(2). This prediction agrees with the measured combined value of k_H/k_D = 3.6(3). These observations are most consistent with a mechanism in which both the proton and the hydride are transferred in a single, rate-determining step.

Bäckvall's measurements for the oxidation direction also support concerted proton and hydride transfer. KIEs for alcoholic and carbinol positions (Table 10, bottom) are 1.9(2) and 2.6(3), respectively, and the combined KIE is 4.6(4). The theoretical value for the combined effect was 4.8(5),[68] which agrees with the experimental combined value.

Table 10. Kinetic Isotope Effects for Aldehyde Reduction (top) and Alcohol Oxidation (bottom)[a]



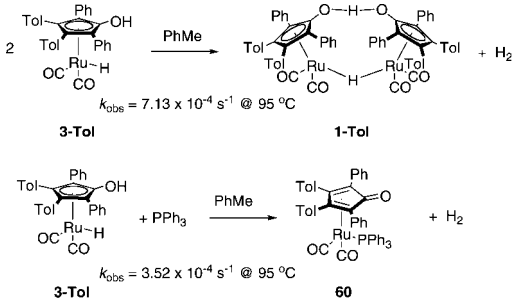
entry	KIE	studied value
1	k_{OHRuH}/k_{OHRuD}	1.5(2)
2	k_{ODRuH}/k_{ODRuD}	1.6(2)
3	k_{OHRuH}/k_{ODRuH}	2.2(1)
4	k_{OHRuD}/k_{ODRuD}	2.3(4)
5	$k_{OHRuH}/k_{OD/RuD}$	3.6(3)



entry	KIE	studied value
6	k_{OHCH}/k_{OHCD}	2.6(3)
7	k_{ODCH}/k_{ODCD}	2.5(2)
8	k_{OHCH}/k_{ODCH}	1.9(2)
9	k_{OHCD}/k_{ODCD}	1.8(2)
10	k_{OHCH}/k_{ODCD}	4.6(4)

[a] (Top) Adapted from ref 13. (Bottom) Adapted from ref 66.

Table 11. First-Order Kinetics of Loss of Dihydrogen from 3-Tol[a]



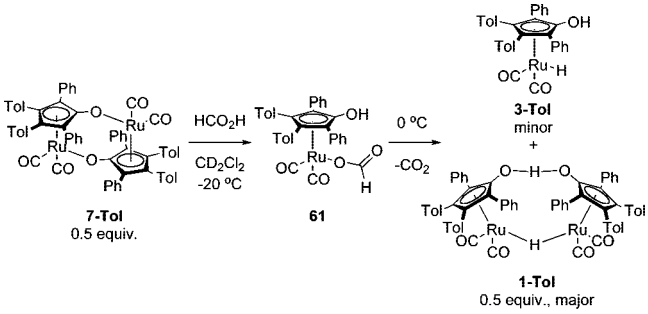
entry	KIE	value
1	k_{OHRuH}/k_{OHRuD}	1.3(1)
2	k_{ODRuH}/k_{ODRuD}	1.3(2)
3	k_{OHRuH}/k_{ODRuH}	1.7(2)
4	k_{OHRuD}/k_{ODRuD}	1.6(1)
5	k_{OHRuH}/k_{ODRuD}	2.1(2)

[a] k_{obs} was measured for disappearance of starting material. KIE values were determined in the presence of triphenylphosphine. [b] Adapted from ref 69.

6.3. Dihydrogen Activation

Because coordinatively unsaturated species **2** is nonisolable, it is impossible directly to study activation of dihydrogen with **2**. Instead, Casey studied this reaction by analyzing its microscopic reverse, conversion of **3** to **2** by loss of H_2. In a hydrogenation reaction involving Shvo's catalyst, the active reducing catalyst is hydride **3**. Shvo first provided evidence for the hydride species by converting **1** to **3** with H_2, though he incorrectly assigned the structure of **3** as the metal−dihydride instead of the hydroxycyclopentadienyl tautomer. Shvo further observed that hydride **3** loses H_2 under N_2 and reverts to **1**.[11] Casey's group later studied this reaction with **3-Tol** (Table 11).[69] They found that **3-Tol** loses one mole of H_2 and reverts to the dimer **1-Tol** and measured the rate constant. Disappearance of **3-Tol** corresponded to twice the rate of formation of H_2 as one

Scheme 11. Formation and Decarboxylation of a Hydroxycyclopentadienylruthenium Dicarbonyl Formate



equivalent lost H_2 and was trapped by a second equivalent of **3-Tol**. Employing triphenylphosphine as a trapping reagent for the unsaturated intermediate (**2**) formed from hydrogen loss, they showed that the process was first order in **3-Tol** and not accelerated by phosphine. Isotope effects for dihydrogen elimination were studied using isotopologs of **3-Tol**.[70] The reaction takes place in the absence of a strong base, so hydroxy group deprotonation is unlikely. This suggests the intermediacy of a dihydrogen adduct, probably formed by transfer of the acidic −OH proton to the ruthenium hydride. A ruthenium dihydride species is unlikely because if a dihydride were formed in the rate-limiting step, the nature of the pre-existing Ru−H bond would not have changed dramatically and would probably have an insignificant KIE (observed $k_H/k_D = 1.3$). The KIEs establish that both the O−H and Ru−H bonds were derivatized, and therefore, either a dihydrogen adduct intermediate or concerted dihydrogen loss mechanism is reasonable. The details of the mechanism for formation of the H−H bond warrant further discussion, which is presented in section 6.5.

6.4. Transfer Hydrogenation with Formic Acid

In 2001, Casey published the results of investigations into the hydroxycyclopentadienyl ruthenium dicarbonyl formate complex (**61**, Scheme 11),[71] which was proposed by Shvo to be formed in situ when using formic acid as a reducing agent in transfer hydrogenation.[23] Casey's group was able to form **61** at −20 °C by combining **7-Tol** and excess formic acid. They determined that **61** does not catalyze hydrogenation of benzaldehyde but instead decarboxylates to form **3-Tol**, which mediates reduction. The authors present a mechanism for decarboxylation of **61** involving reversible formation of **2-Tol** followed by concerted transfer of a hydride from the formate carbon and a proton from the oxygen of formic acid to produce **3-Tol** and CO_2. This transition state is analogous to alcohol oxidation (Scheme 10B). The authors note that this mechanism is not fully consistent with their observation of a negligible kinetic isotope effect in the formate C−H bond in the decarboxylation of **61**: $k_{61}/k_{61\text{-}d1} = 1.1(1)$. Participation of the ligand −OH group is verified by the observation that a methoxycyclopentadienyl ruthenium formate undergoes much slower decarboxylation.

6.5. Computational Studies

A 2007 DFT study provides further data discriminating the outer-sphere and ring-slippage mechanisms.[72,73] In this systematic calculation of possible coordination and slippage events, the precoordination, inner-sphere mechanism (Scheme 10A) was much higher in energy than the concerted outer-sphere mechanism (Scheme 10B), as shown by the comparison in Figure 2. The disparity in activation barriers for the two paths is large enough strongly to support the concerted, outer-sphere path. Interestingly, several ring-slippage pathways were studied, and the η^5 to η^2 pathway shown in Figure 2 (not the originally proposed η^5 to η^3 route) was of lowest energy in the reduction direction; the corresponding route ($\eta^4-\eta^2$) is optimal in the oxidation direction. KIEs for dehydrogenation in the outer-sphere mechanism were also calculated: the predicted combined KIE value (3.5, gas phase) is very close to experimental data (3.6(3)).[67]

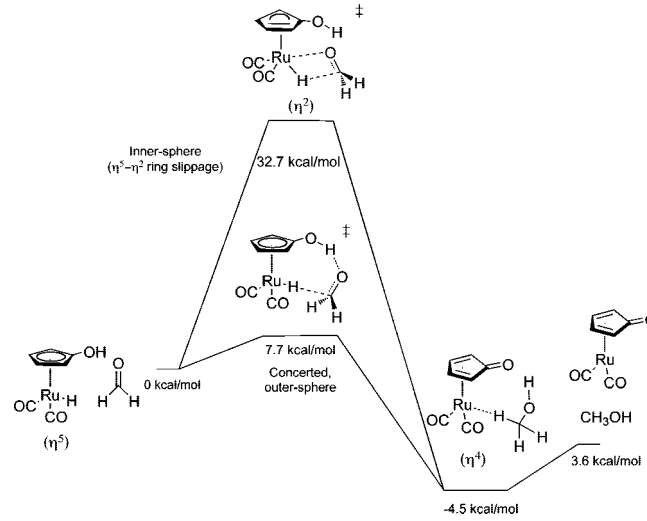


Figure 2. DFT study of reversible formaldehyde reduction with a homologue of **1**. DFT-calculated activation parameters for hydrogen transfer to ketones using Shvo's catalyst are consistent with a concerted, outer-sphere mechanism. See ref 72 for proper geometries and other calculated pathways.

This computational study also addresses the possibility of CO dissociation from the reduced form of the catalyst to enable ketone coordination prior to the reduction step. This is very endothermic (+51.2 kcal/mol), which is consistent with the experimental finding that ^{13}CO does not exchange with ruthenium-bound CO during reduction of aldehydes by **3-Tol**.[13] Thus, acetone displacement of CO is very unlikely.

Experimental measurements provide further insight into the mechanism of the conversion of **3-Tol** to **1-Tol** (Table 11). Arrhenius analysis indicates a barrier of 26.1 kcal/mol, which is far less than a theoretical value of 43.2 kcal/mol (B3LYP) for direct conversion of **3-Tol** to dihydrogen complex **62** (Figure 3A).[69] Moreover, ethanol catalyzes dihydrogen loss, and trace water impacts the rate in a complicated way. These observations are consistent with an important role for intermolecular proton transfer in the dihydrogen loss mechanism and raise the question of whether **3** is a catalyst for its own dehydrogenation through a proton transfer mechanism (Figure 3). Establishment of the effective size of **3** in solution provides an elegant strategy to find

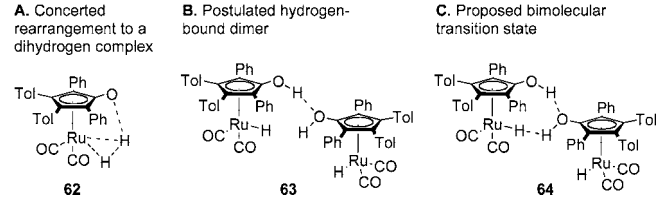


Figure 3. Dimeric nature of **3-Tol** in toluene has a role in H_2 loss.

evidence of its aggregation state (monomeric versus dimeric). To effect such a measurement, pulse gradient spin−echo measurements[74] of solutions of **3-Tol** in toluene were compared to known monomeric and dimeric species, 2,5-Ph_2-3,4-Tol_2(η^5-C_4COMe)Ru(CO)$_2$(H) and **1-Tol**, respectively. These measurements give diffusion properties of **3-Tol** that are consistent with an aggregate in solution that can be described by a dimeric structure as shown in Figure 3. These structural data provide anecdotal evidence of the role of **3** as a proton transfer catalyst in its own dehydrogenation. Thus, a mechanism in which 2 equivalents of **3** are involved in dehydrogenation best fits the observed kinetic order on [**3**] and its dimeric nature.

These data have been combined with spectroscopic data collected in a subsequent study[75] and used quantitatively to establish the catalytic scheme for hydrogenation of aldehydes and ketones. Impressively, kinetic modeling of the concentrations of aldehyde/ketone, **1-Tol**, and active reducing form **3-Tol** very well match the experimentally observed concentrations.

6.6. Hammett Studies

Our group has studied the electronic character of the hydride transfer by conducting a linear free energy plot and determining the Hammett parameter (Figure 4) for oxidation with **1**.[76] We concluded, based on a ρ value of $-0.89(5)$, that the transition state features electrophilic character of the hydride abstraction event. A Hammett reaction parameter of $\rho = -0.89(5)$ is larger than expected for a transition state involving β-hydride elimination or free-radical hydrogen-atom transfer: Kaneda reports $\rho = -0.43$ for oxidation of *p*-substituted benzyl alcohols with a ruthenium catalyst immobilized on hydroxyapatite and proposes a β-hydride elimination mechanism.[77] Kuriacose reports $\rho = -0.3$ for the same reaction with ruthenium trichloride catalyst in the presence of *N*-methylmorpholine-*N*-oxide. These authors propose a hydrogen-atom (radical) abstraction by a ruthenium(V) oxo intermediate.[78] Thus, with catalyst **1** we interpret that significant cationic character is evolved at carbon in the rate-determining transition state; this is only slightly compensated by electron donation from concurrent deprotonation of the O−H bond. Complementary positive Hammett parameters have been measured for benzaldehyde reduction reactions mediated by homologues of **1**. Casey found $\rho = +1.77(8)$ for reduction with **104**, which has been shown to also proceed through a concerted, outer-sphere mechanism.[98] The Hammett parameter for benzaldehyde hydroboration with **7-Tol** is $\rho = +0.91$.[24]

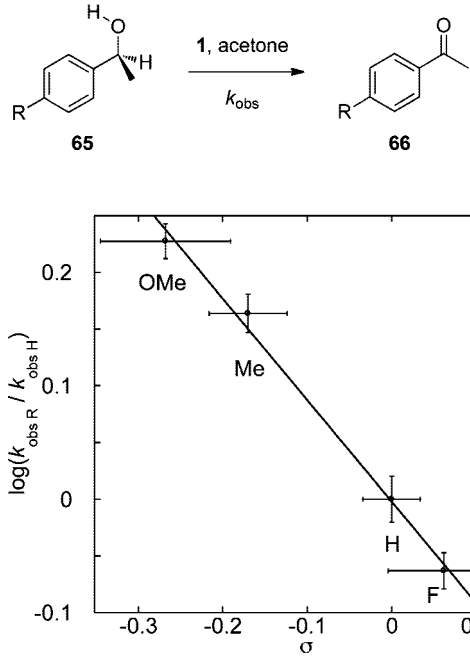


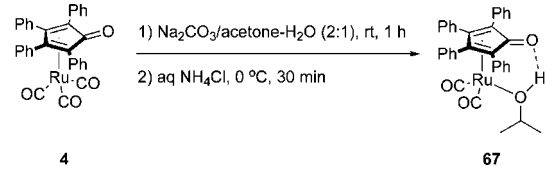
Figure 4. Hammett plot for oxidation reaction with *p*-RPh-CH(OH)Me.

6.7. Independent Synthesis of Proposed Intermediates

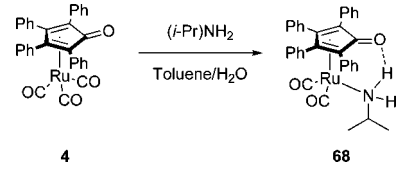
In 2001 Park et al. reported the formation of a stable, isolable 2-propanol complex, **67**,[79] that they were able to prepare by addition of Na_2CO_3 and acetone to **4** followed by low-temperature protonation with NH_4Cl (Scheme 12). They were able to acquire NMR, mass, elemental analysis, IR, and even X-ray diffraction data, which all appeared to support the proposed structure. However, the complex was shown to be stable to 90 °C in toluene and did not exhibit proton exchange with D_2O. This lack of expected behavior led Casey, Bäckvall, and Park to investigate the results in more detail.[80] Casey's group synthesized **67-Tol**, while Bäckvall worked with the same complex synthesized by Park (**67**). Careful examination of the characterization data and reactivity of the proposed alcohol complexes led the authors to conclude that it was, in fact, the isopropylamine complex, **68**. Independent synthesis and characterization of the isopropylamine complexes confirmed this assessment (Scheme 13). It is suspected that under the conditions used the acetone imine was produced and then reduced by a ruthenium hydride to form the amine complex.

Casey was later able to form hydroxycyclopentadienyl-ruthenium alcohol complexes by reacting hydroxycyclopentadienyl ruthenium dicarbonyl chloride (**69**) with silver tetrafluoroborate in the presence of an alcohol (Scheme 14).[81] The rate of alcohol exchange of the hydroxycyclopentadienyl ruthenium benzyl alcohol complex (**70**) with 2-propanol was measured to be similar to that of the rate of formation of

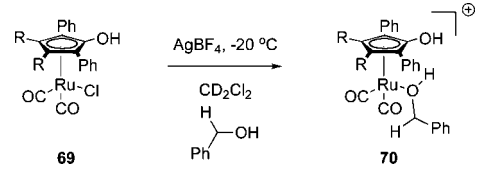
Scheme 12. Proposed Synthesis of an Alcohol Complex of 2



Scheme 13. Direct Synthesis of an Isopropylamine Complex of 2



Scheme 14. Successful Synthesis of an Isopropanol Complex of 2



benzyl alcohol from reduction of benzaldehyde by **3-Tol**. As the complex here reported is the protonated form of the proposed alcohol complex intermediate, alcohol dissociation from the deprotonated form is expected to be substantially faster.

7. Mechanism of Oxidation of Amines and Reduction of Imines

7.1. Proposed Mechanisms

Much like the corresponding reactions of carbonyl compounds and alcohols, the mechanism of reduction of imines and oxidation of amines has inspired debate.[82] Two viable mechanisms have been presented. The first, proposed by Bäckvall,[83] is an inner-sphere scheme that involves η^5 to η^3 ring slippage and coordination of free imine. This is followed by a fast hydrogen transfer reaction (Scheme 15A). The second, proposed by Casey,[84] is an outer-sphere process analogous to the reactions of alcohols that involves concerted transfer of proton and hydride followed by fast coordination of the newly formed amine (Scheme 15B). It is convenient in this reaction to study the reduction, as opposed to the oxidation reaction, because the amine product of reduction forms stable ruthenium complexes. This fact allowed for several of the key experiments that helped to elucidate the mechanism.

7.2. Kinetic Isotope Effect Studies

Bäckvall[85] reported a negligible double kinetic isotope effect for the reduction of *N*-[1-(4-methoxyphenyl)ethylidene]aniline, which indicates that hydrogen transfer is not involved in the rate-determining step. This evidence is consistent with the proposed inner-sphere mechanism (Scheme 15A). A separate study by Bäckvall[86] on the dehydrogenation of amines revealed a large KIE for the C−H bond ($k_{CHNH}/k_{CDNH} = 3.24$) and a negligible KIE for the N−H bond

Scheme 15. Proposed Mechanisms for Imine Reduction

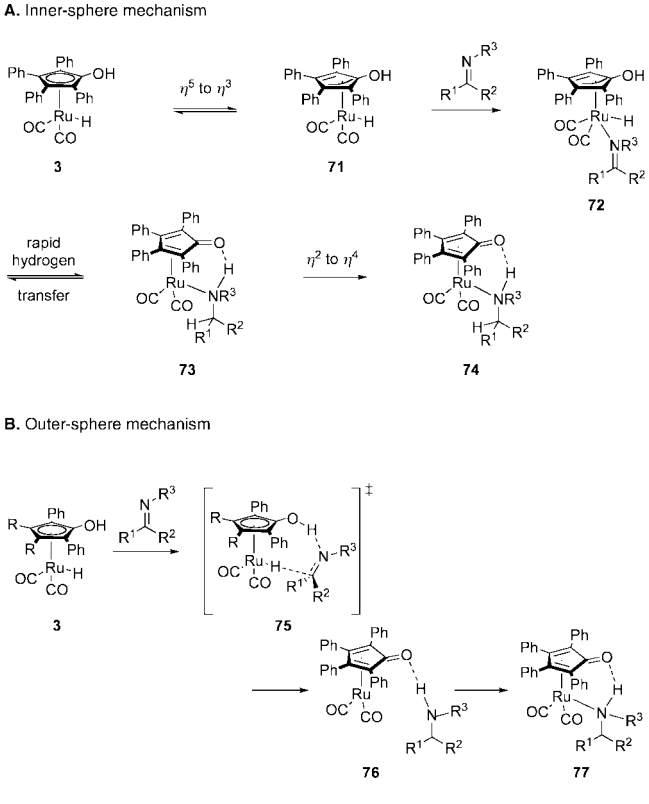
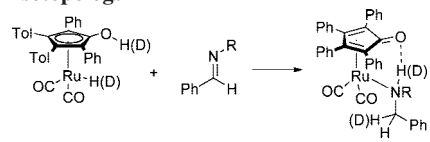


Table 12. Isotope Effects for Reduction of Imines with 3-Tol Isotopologs[a]



3-Tol 78 79

R	**78a**: C_6F_5	**78b**: Ph	**78c**: *i*-Pr	**78d**: *t*-Bu	**78e**: Bn
k_{RuHOH}/k_{RuHOD}	1.57(7)	1.30(13)	0.92(9)	0.90(7)	
k_{RuDOH}/k_{RuDOD}	1.66(8)	1.31(12)	0.91(7)	0.88(6)	
k_{RuHOH}/k_{RuDOH}	1.99(13)	1.23(12)	1.03(8)	0.64(5)	
k_{RuHOD}/k_{RuDOD}	2.11(4)	1.24(12)	1.02(7)	0.63(4)	
k_{RuHOH}/k_{RuDOD}	3.32(4)	1.60(17)	0.94(8)	0.56(5)	1.05(5)

[a] Adapted from ref 84.

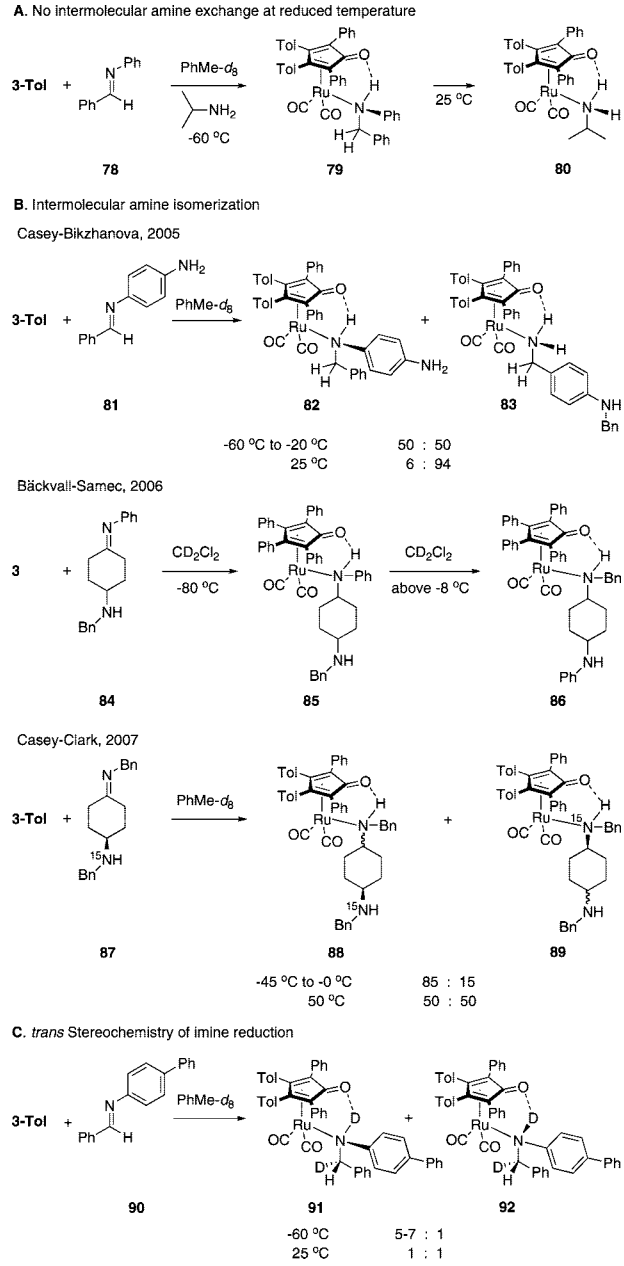
(overall $k_{CHNH}/k_{CDND} = 3.26$), which also support a stepwise mechanism such as the reverse of the proposed inner-sphere hydrogenation mechanism. Casey conducted a subsequent study[84] that examined a range of imines with varying electron density (Table 12). Remarkably, this study found strong KIEs on both O−*H* and Ru−*H* in the case of an electron-deficient imine (**78a**) and smaller KIEs for more electron-rich imines (**78b**−**e**), a situation that can obscure important mechanistic details when studying only a single substrate. Electron-deficient imine **78a** has a similar KIE profile to its oxygen homologue, benzaldehyde (Table 10), while more electron-rich imines **78c** and **78d** have inverse isotope effects. These data indicate that the rate-determining step is concerted hydrogen transfer in some cases but not others.

7.3. Amine Coordination and Exchange

One apparent inconsistency with a concerted outer-sphere mechanism (Scheme 15B) is the absence of crossover between the amine product and an external amine at reduced temperature. For example, when the reaction is run in the presence of isopropyl amine, an isopropylamine-ligated product is not observed at low temperature (Scheme 16A).[84] This is inconsistent with an outer-sphere mechanism leading initially to **2** and an uncoordinated amine. To explain this observation, Casey conducted an intramolecular trapping experiment wherein an imine and amine were tethered together in the same molecule (**81**, Scheme 16B, Casey−Bikzhanova).[87] Two different amine-bound ruthenium products were formed upon reduction (**82** and **83**), which indicates that unsaturated species **2-Tol** does form but that dissociation from the solvent sphere is slow compared to trapping. Hydrogen bonds between the product N−H and cyclopentadienone C═O help account for this phenomenon.[87]

Bäckvall responded to these results[83] by suggesting that the formation of the two distinct amine complexes is not the result of the formation of coordinatively unsaturated species **2** but rather the result of ruthenium migration along the face of the aromatic system of the linking benzene in **82** via an intermediate benzene π complex. To test this, Bäckvall conducted an intramolecular trapping experiment wherein the imine and amine were linked by a cyclohexyl group (Scheme 16B, Bäckvall−Samec). In this experiment only the complex resulting from the newly formed amine was observed.[83] Thus, Bäckvall suggested that an outer-sphere mechanism could explain the results only if amine coordination is faster than hydrogen bond breaking.[83]

Scheme 16. Amine Exchange and Stereochemistry in Imine Reduction



Casey followed the study above with a subsequent experiment showing exactly that relationship between hydrogen-bond cleavage and amine coordination.[88] Casey designed an electron-rich imine attached to a ^{15}N-labeled amine via a cyclohexyl group (**87**, Scheme 16B, Casey−Clark). Upon reduction with **3-Tol**, the resulting complex was proposed to form a weaker hydrogen bond than the amine used by Bäckvall. When the trapping experiments were run, two distinct amine complexes were formed, supporting the outer-sphere mechanism. Bäckvall recently added further data to the solvent cage debate by examining the solvent cage effect in the reduction of 4-aminocyclohexanone in CD_2Cl_2.[89] They concluded that there is no solvent cage effect based on the formation of both 4-aminocyclohexanone and 4-aminocyclohexanol complexes as well as **1**. They report that since oxygen forms stronger hydrogen bonds than nitrogen and an amine complex is formed at the end of the reaction, these results indicate that there is no solvent cage effect and that hydrogen bond breaking is faster than coordination.

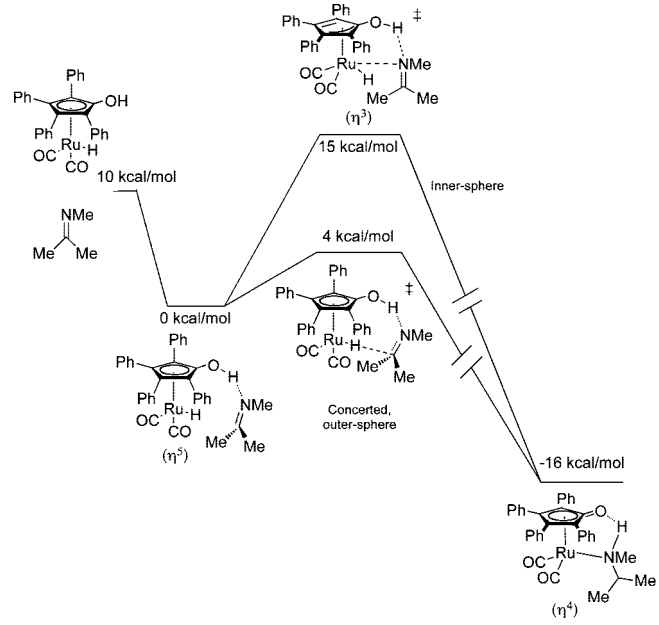


Figure 5. DFT studies of reversible imine reduction with **1**. DFT-calculated activation parameters for hydrogen transfer to imine using Shvo's catalyst is consistent with a concerted, outer-sphere mechanism. See refs 91 and 92 for proper geometries and other calculated pathways.

Therefore, the reaction appears to proceed through an inner-sphere mechanism because of the preference for formation of the new amine complex instead of an alcohol complex. However, the inability to observe an analogous alcohol complex under these conditions must be considered when comparing these systems (see section 6.7). In addition, it is important to note that the experiments conducted by Bäckvall were done in CD_2Cl_2 and those by Casey were done in toluene-d_8. Complementary experiments by Casey in CD_2Cl_2 showed less exchange than those conducted in toluene-d_8.

Of further interest to the imine reduction mechanism is that the stereochemistry of aryl imine reduction initially is trans, but the first-formed adduct (**91**) isomerizes quickly at room temperature (Scheme 16C).[90] Stereochemical analysis is more complicated in the case of *N*-alkyl imines.

7.4. Computational Studies

Both Bäckvall[91] and Casey[87] published DFT calculations to support their respective mechanisms. In 2008 a study was published[92] that thoroughly examined the proposed mechanisms for imine, alkene, and alkyne hydrogenation. This study confirmed the results presented by both Casey and Bäckvall but concluded that the barrier for the outer-sphere mechanism is more than 10 kcal/mol lower in energy than the lowest reported barrier[91] for the inner-sphere mechanism (Figure 5).[92] However, they also conceded that a stepwise mechanism was not unreasonable for electron-rich imines. These theoretical results are in agreement with the experimental data presented above.

7.5. Summary

Taken together the mechanistic details outlined in sections 6 and 7 provide a clear picture of a single, rate-determining transition state through which both the oxidation and the reduction reactions pass in most cases, although debate remains active. It differs in character from a traditional aluminum alkoxide-catalyzed Meerwein−Ponndorf−Verley

reduction (or Oppenauer oxidation) in that there is a persistent metal hydride intermediate. Moreover, the rates of transfer hydrogenation and dehydrogenation with **1** are generally acceptable for the oxidation/reduction of a wide range of substrates. The systems can be optimized for a desired outcome by substrate concentration, i.e., oxidizing alcohols in acetone drives the reaction to completion. In addition, the mechanism is of fundamental interest for studies of systems involving oxidative coupling of alcohols or amines and nucleophilic substrates. Importantly, the ability of the metal hydride in **3** to reduce unsaturated substrates such as alkynes, alkenes, and imines makes alcohols a practical reducing agent in several different cascade reactions.

8. Analogous Systems

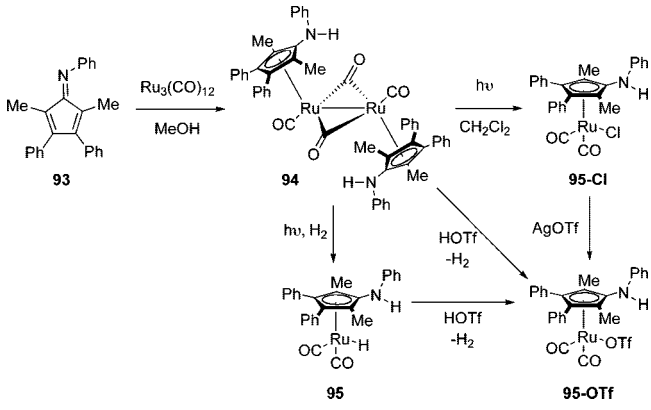
8.1. Structural Analogues

Several ruthenium-based catalysts have been designed starting from the Shvo scaffold. These include an aminocyclopentadienyl ruthenium hydride,[93] a dimer in which the bridging hydride is replaced with an iodide,[94] an immobilized catalyst secured to a silica matrix,[95] and a phosphine-ligated analog in which a CO ligand is exchanged.[96] These are reviewed here.

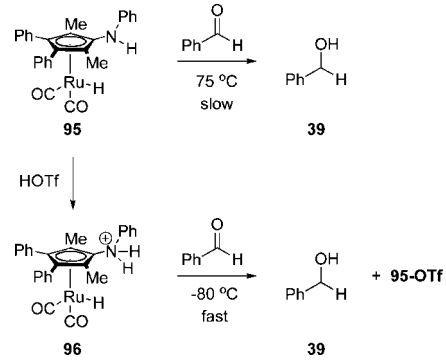
8.1.1. Cyclopentadienyl Amine Derivatives

Casey synthesized a phenylaminocyclopentadienyl dicarbonylruthenium complex **95** (Scheme 17).[93] The authors proposed that the bulky phenyl group and relatively weaker N−H−N hydrogen bond (versus O−H−O) would discourage the formation of a dimer analogous to **1**. Indeed, a hydride-bridged dimer is not observed, although prior to hydrogenation the complex exists as the carbonyl-bridged dimer, **94**. Catalyst **95** affords hydrogenation of benzaldehyde approximately 10 000 times slower than **3-Tol** (Scheme 18). The authors attribute this to the decreased acidity of the aniline N−*H* in **95** (pK_a ca. 30). To address this they prepared a protonated ammonium form of the catalyst with triflic acid. The resulting complex (**96**) hydrogenates benzaldehyde rapidly: the reaction is complete in less than 5 min at −80 °C (Scheme 18). The complex does not hydrogenate cyclohexene, however, and is unstable above −25 °C. After hydrogenation, the deprotonated triflate complex **95-OTf** is formed. The authors suggest that it is possible to reproduce the active species **96** by addition of H_2 to the triflate **95-OTf**, but no example of a functional catalytic cycle has been presented. In further exploration of this complex, Casey's

Scheme 17. Synthesis and Reactivity of Aminocyclopentadienyl Ruthenium Complex 95



Scheme 18. Reduction of Benzaldehyde with 95



Scheme 19. Synthesis of Aminocyclopentadienylruthenium Alcohol Complex 97

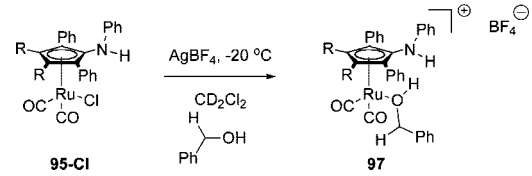
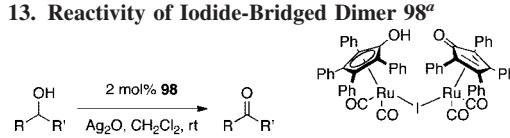


Table 13. Reactivity of Iodide-Bridged Dimer 98[a]



entry	product	time (h)	yield (%)[b]
1	**100a**	4.0	>99
2	**100b**	3.0	>99
3	**100c**	3.0	>99
4	**100d**	3.0	93
5	**100e**	3.0	90

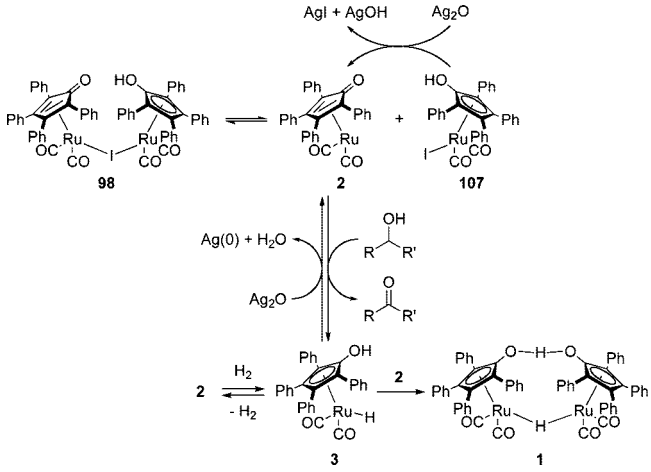
[a] Adapted from ref 94. [b] Determined by GC.

group generated aminocyclopentadienyl ruthenium dicarbonyl alcohol complex **97** (Scheme 19).[81] Dissociation of benzyl alcohol from this complex was shown to be slower than the rate of production of benzyl alcohol from benzaldehyde by **96**. Along these lines, Kim and Park reported that an isopropyliminocyclopentadienone-functionalized homologue of **1** is an efficient catalyst for the racemization of alcohols and can be combined with an enzyme for DKR similar to the reactions presented in Table 4.[97]

8.1.2. μ-Iodo Homologue

An iodide-bridged Shvo analogue (**98**) is reported to oxidize alcohols faster and at lower temperature than **1** (Table 13).[94] For example, in the presence of 1 equivalent of silver oxide, 2 mol % of **98** oxidizes 1-phenylethanol in 4 h at room temperature while the oxidation with **1** is not observed at room temperature. The complex is formed by combining $[Ph_4(\eta^5\text{-}C_4COH)](CO)_2RuI$ and **7** in dichloromethane under an argon atmosphere. The mechanism

Scheme 20. Proposed Mechanism for the Oxidation of Alcohols by Iodide-Bridged Dimer 98



proposed by the authors involves reversible splitting of dimer **98** into **2** and a ruthenium iodide, **101** (Scheme 20). Iodide **101** reacts with silver(I) oxide to form **3**, silver(I) hydroxide, and silver(I) iodide. **2** then reacts with the substrate alcohol to form the ketone product and **3**. Another equivalent of silver(I) oxide reacts with **3** to regenerate **2**. Alternatively, **3** can react with **2** to form **1**. Therefore, the active species is identical to that formed by **1**. This makes the observed rate enhancement difficult to understand because reoxidation of **3** is known not to be rate-determining in **1**-catalyzed alcohol oxidation.[76]

8.1.3. Silica-Supported Homologue

In 2004, Choi et al. successfully immobilized a Shvo-type complex on a silica support.[95] By replacing one phenyl group of the cyclopentadienone ligand in **102** with a (hydroxymethyl)phenyl, they were able to immobilize the catalyst on tetramethyl orthosilicate by a sol−gel process (Scheme 21). The heterogeneous catalyst shows excellent reactivity (Table 14), is recoverable by simple filtration, and retains over 90% of its reactivity through its the fourth use. This is the only example of repeated reuse of the Shvo catalyst, and it illustrates the robustness of the apparently labile cyclopentadienone ligand.

8.1.4. Phosphine-Substituted Homologue

In 2006 Casey reported the synthesis of the phosphine-substituted hydroxycyclopentadienyl ruthenium hydride [2,5-Ph_2-3,4-Tol_2(η^5-C_4COH)]Ru(CO)(PPh_3)H (**104**, Figure 6).[96] The phosphine-ligated complex does not form a hydride-bridged dimer like the dicarbonyl parent catalyst **1**. Moreover, the phosphine ligand increases the hydride donor ability of the Ru−H, which should accelerate reduction, and decreases the acidity of the CpOH proton, which should slow down reduction reactions. This complex reduces aldehydes stoichiometrically in the presence of a trapping ligand (such as pyridine) for the unsaturated intermediate but is slower than **1** as a result of the decreased acidity of the CpOH. By contrast, **104** catalytically reduces aldehydes at lower temperature and hydrogen pressure than **1**: compare with Table 2, 145 °C and 500 psi versus room temperature and 37 psi.[98] This increased activity is likely due to the fact that **104** exists as a monomer. Interestingly, the rate of alcohol oxidation with phosphine-substituted system **104** is less sensitive to temperature than reactions

Scheme 21. Synthesis of a Silica-Supported Homologue of 1

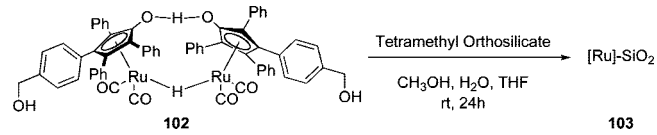
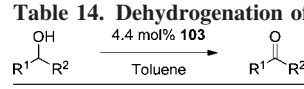


Table 14. Dehydrogenation of Alcohols with 103[a]



entry	substrate	time (h)	yield (%)[b]
1	1-phenylethanol	6	97
2	1-(4-chlorophenyl)ethanol	6	97
3	1-(4-methoxyphenyl)ethanol	6	97
4	1-cyclohexylethanol	8	97
5	2-octanol	6	97
6	cyclohexanol	20	100
7	benzyl alcohol	6	41

[a] Reactions were run in refluxing toluene (0.1 M) with 4.4 mol % **103**. [b] Determined by GC. Adapted from ref 95.

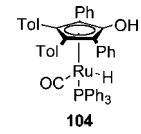


Figure 6. Phosphine-substituted homologue of **3**

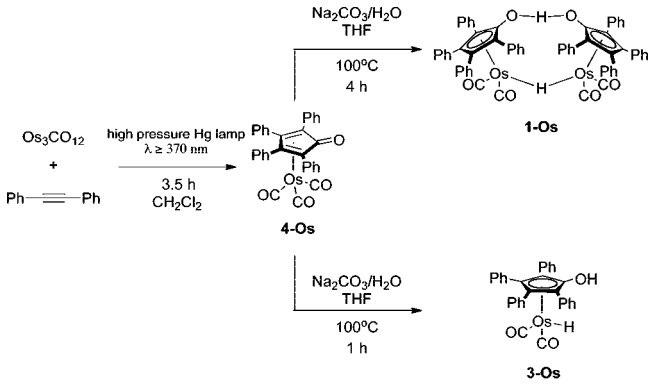
based on **1**. At 35 atm of hydrogen and 22 °C, **104** catalyzes the hydrogenation of benzaldehyde more than 8 times faster than **1**; at 60 °C, **1** catalyzes the hydrogenation approximately 1.5 times faster than **104**. Further, this phosphine complex shows a much greater selectivity for reducing aldehydes over ketones than **1**, most likely due to the steric bulk of the phosphine ligand. In an internal competition experiment using acetophenone and benzaldehyde, **104** reduced the aldehyde approximately 1200 times faster than the ketone; by comparison, **1** showed a chemoselectivity of 40:1.[98] This is a mechanistically important addition to the family of Shvo-type catalysts because it retains hydrogenation functionality while avoiding dimerization.

8.2. Osmium

The most closely related non-ruthenium homologues of Shvo's catalyst are [Ph_4(η^4-C_4CO)]$Os(CO)_3$, **4-Os**, and [Ph_4(η^4-C_4CO)]$Fe(CO)_3$, **4-Fe**. The osmium analogue was first prepared in 1994 by Takats.[99] Notably, the synthesis does not proceed through simple ligation of tetracyclone (**6**) to $Os_3(CO)_{12}$, as the dissociation kinetics at osmium in this case are predictably slow. Preparations in our lab and others' attempting this synthesis were unsuccessful, even at high temperature (refluxing toluene). Instead, it is imperative to use long-wavelength (>350 nm) photochemical activation of the carbonyl-ligated trimer first to generate, either in situ or in isolation, $Os(CO)_5$, which can be converted to **4-Os**. The most straightforward synthesis is shown in Scheme 22. Unlike the synthesis of Shvo's catalyst, this molecule can be easily converted to either monomeric hydride **3-Os** or the bimetallic hydrogen-bridged species **1-Os**, {[Ph_4(η^5-C_4CO)]$_2$H}$Os_2(CO)_4$(μ-H), as there is presumably a slow conversion from the former to the latter; the same conditions are used for synthesis of both, with bridging species isolated in higher yield at longer reaction times (Scheme 22).

Takats reports the very slow rates of reaction for these precursors for the hydrogenation of ketones.[100] By contrast,

Scheme 22. Synthesis of the Analogous Osmium-Centered Homologue of 1



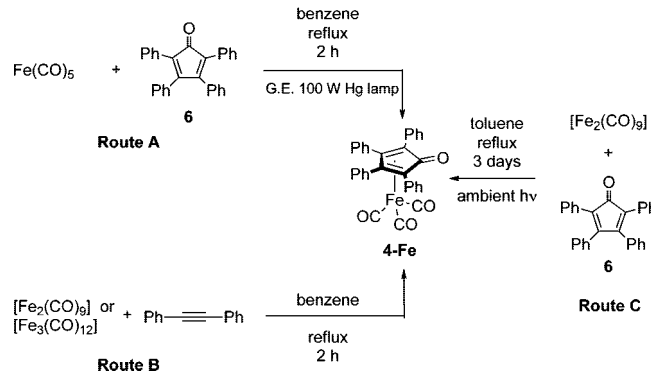
Shvo's catalyst was very efficient under the same conditions. For example, attempted hydrogenation of cyclohexanone with dihydrogen (47 atm) at 105 °C over a period of 4 h gave minimal conversion to the corresponding alcohol. Under these conditions, **1** catalyzes reduction very efficiently (Table 2, entry 13). Beyond these initial reports, the literature is devoid of reactivity data for osmium homologues of Shvo's catalyst. This is not surprising given its decreased reactivity (the hydride is stable indefinitely to air!) and the wealth of mechanistic data gleaned from studying Shvo's catalyst directly.

8.3. Iron

While osmium offers no great advantage to compensate for slow catalysis, a stable, active iron-based congener would be valuable because of iron's known low cost, toxicity, and high abundance. In fact, though $[Ph_4(\eta^4\text{-}C_4CO)]Fe(CO)_3$ (**4-Fe**) was well known as of 1958 (Scheme 23) before the advent of Shvo's catalyst in the 1980s,[101,102] it shows "very little catalytic activity and decomposes to give a heterogeneous mixture under the conditions used" when investigated for hydrogenation of ketones in aqueous THF.[103]

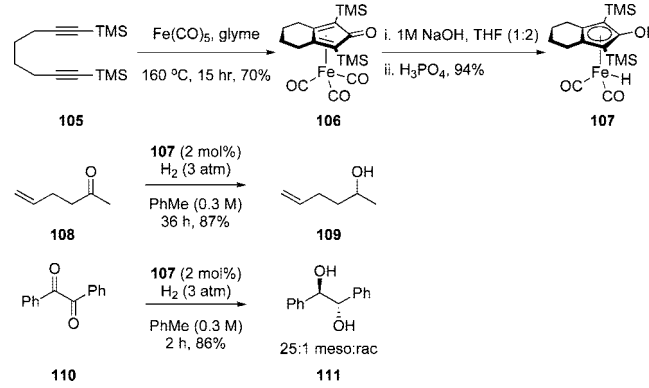
Casey recently demonstrated that iron species **107** is a very efficient catalyst for hydrogenation of aldehydes, ketones, and aldimines.[104] Knölker prepared the catalytically active complex (**107**)[105] through an iron-mediated [2 + 2 + 1] cycloaddition[106] of **105** followed by alkaline CO hydrolysis (Scheme 24).[107] This catalyst is then delivered as a solution. Scheme 24 also illustrates some indicative examples of the reactivity of **107**. Importantly, alkenes and alkynes are not readily reduced under these conditions. For example, unconjugated enone **108** is selectively converted to alkene−alcohol **109** without over-reduction; a conjugated enone is less selective. Moreover, dione **110** is converted selectively

Scheme 23. Synthesis of $[Ph_4(\eta^4\text{-}C_4CO)]Fe(CO)_3$[a]



[a] We reported the complex in ref 76 using Route C, a modification of procedures from ref 12.

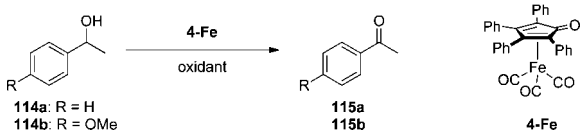
Scheme 24. Iron-Centered Homologue of 1 for Reduction Reactions



to meso compound **111** with excellent preference of the racemic diastereomers.[104]

The mechanism of reduction of carbonyl groups with **107** is analogous to reactions involving **2** and **3** except that dimerization of the iron species does not seem to play an important role. Stoichiometric reactions of **107** with benzaldehyde highlight some important features of the mechanism.[108] For example, benzaldehyde reduction with **107** occurs in minutes at −78 °C. With ruthenium hydride **3-Tol**, this reaction does not proceed below −40 °C. The first-formed product is the corresponding alcohol complex **112**. This undergoes ligand exchange in minutes at room temperature (Scheme 25). Moreover, an isotopic labeling experiment revealed that the reaction is reversible: benzaldehyde-d_1 is observed by ^2H NMR when benzaldehyde is mixed with **107**-d_2 and warmed above 10 °C.

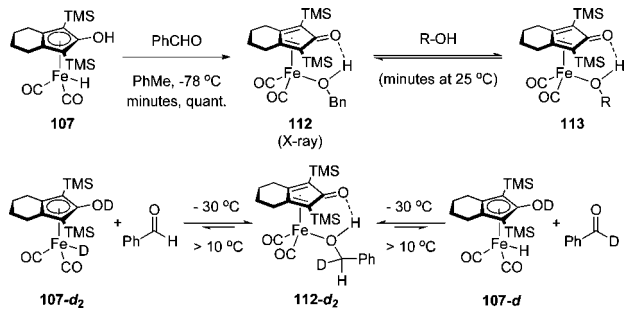
Table 15. Conversion of Alcohols to Ketones with 4-Fe[a]



entry	**4-Fe**, equiv	alcohol	oxidant	solvent	*T* (°C)	yield (%) (conv., %), time
1	0.1	**114a**	benzoquinone	C_6D_6	65	11 (14), 17 h 24 (26), 4 days
2	0.1	**114a**		$(CD_3)_2CO$	54	38 (44), 4 days
3	0.2	**114b**		$(CD_3)_2CO$	80	52 (79), 4 days
4	0.5	**114b**		$(CD_3)_2CO$	80	79 (97), 2 days

[a] Adapted from ref 76.

Scheme 25. Mechanism of Iron-Catalyzed Reduction



Preparative-scale oxidation chemistry with an iron homologue of **1** has been an elusive goal because of the oxidative instability of iron(0). We found success with $[Ph_4(\eta^4\text{-}C_4CO)]Fe(CO)_3$ in the conversion of aryl alcohols to ketones (in up to 79% yield) under the mildly oxidizing hydrogen transfer conditions in acetone solvent (Table 15).[76] This precatalyst, like the ruthenium homologue, must first undergo CO dissociation or hydrolysis (by trace water to give CO_2) in order to form a coordinatively unsaturated catalytic species. Though the catalysis was slower than the analogous ruthenium system, we believe that the demonstration of stable conditions that give high conversion and yields is a significant advance toward developing low-valent iron-based oxidation catalysts.

9. Outlook

In these pages we have offered the first comprehensive treatment of the chemistry of Shvo's catalyst starting from its discovery in the 1980s through the detailed mechanistic work that is being done with it and other cyclopentadienone-ligated metal complexes today. The mechanistic evidence and synthetic applications of Shvo's catalyst reported to date describe a versatile and general platform for reversible dihydrogen transfer among alcohol/carbonyl, amine/imine, and alkyne/alkene/alkane systems. Its structure and reactive mechanism are unique and well studied and thus offer an outstanding platform for development of further high-impact dihydrogen transfer reactions.

Significant opportunities that remain in this manifold of reactivity include the discovery of a similarly efficient and robust but inexpensive and less toxic homologue, such as one that might result from a first-row metal. Efficient access to oxidative cleavage of higher energy C−H bonds, such as hydrocarbons, also presents a formidable challenge and significant pay off.

10. Acknowledgments

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