# Transition Metal Catalyzed Alkene and Alkyne Hydroacylation

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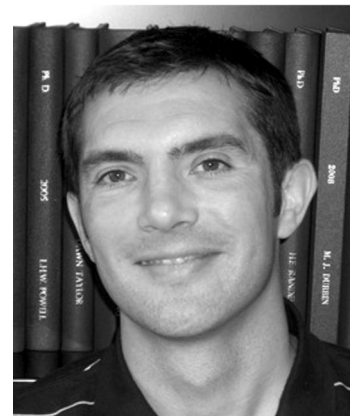
## *1. Introduction and Scope of the Review*

The catalytic activation and subsequent functionalization of C−H bonds is an attractive goal for synthetic chemists, with reactions that employ low catalyst loadings and result in the formation of C−C bonds being of particular interest.[1] The hydroacylation of alkenes and alkynes are transformations that fulfill these requirements; in addition these processes are inherently atom-economic[2] and can be catalyzed by a variety of transition metals. Hydroacylation formally involves the addition of an acyl unit and a hydrogen atom across a C−C multiple bond; intra- and intermolecular variants of the reactions are known (Scheme 1).

Intramolecular alkene hydroacylation using a stoichiometric amount of a rhodium catalyst and resulting in the formation of a cyclopentanone was first reported by Sakai and co-workers in 1972.[3] Since this first report, significant advances have been achieved. Intramolecular alkene hydroacylation can now be performed using low catalyst loadings under mild reaction conditions. A variety of ring sizes can be prepared. In addition, for cyclopentanone syntheses, the use of enantiomerically pure catalysts allows highly enantioselective reactions to be performed. The combination of these developments has resulted in intramolecular alkene hydroacylation being applied to a number of target syntheses. Intermolecular alkene hydroacylation is a less advanced reaction although a number of systems that employ low catalyst loadings and mild conditions have been developed, and the first examples of enantioselective reactions are beginning to appear. Both intra- and intermolecular alkyne hydroacylations are similarly less studied than their alkene counterparts, although recent reports have demonstrated that highly efficient enantioselective intramolecular reactions are now possible.

A number of mechanistic studies have been reported, and these will be discussed collectively in section 6; however, a brief mention of the reaction mechanism is warranted here. A basic, generally accepted, catalytic cycle for an intramolecular alkene hydroacylation reaction is shown in Scheme 2; the key steps involve oxidative addition of the metal catalyst across the aldehyde C−H bond to generate an acyl metal hydride **1**, subsequent addition across the alkene (**1** → **2**), followed by reductive elimination to generate a ketone product and regenerate the catalyst. The main limitation of hydroacylation as a synthetically useful reaction stems from the general propensity of acyl metal species such as **1** to undergo reductive decarbonylation. This produces reduced substrates and poorly active carbonylated catalysts. This type of decarbonylation is such a facile process that a number of



Michael Willis received his undergraduate education at Imperial College London and his Ph.D. from the University of Cambridge working with Prof. Steven V. Ley. After a postdoctoral stint with Prof. David A. Evans at Harvard University, as a NATO/Royal Society Research Fellow, he was appointed to a lectureship at the University of Bath. In January 2007, he moved to the University of Oxford, where he is a University Lecturer and Fellow of Lincoln College. He was awarded an EPSRC Advanced Research Fellowship in 2005 and the 2008 AstraZeneca Research Award for Organic Chemistry. His groups research interests are based on the development and application of new catalytic processes for organic synthesis.

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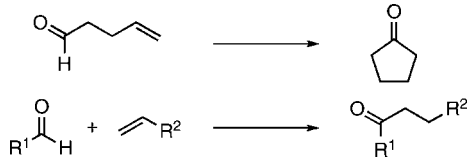
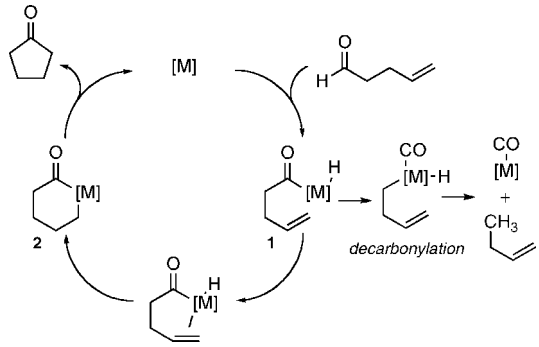
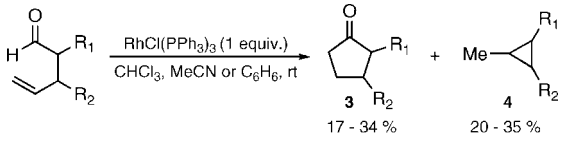
**Scheme 1**



**Scheme 2**




**Scheme 3**




synthetically useful methods based on this reaction are known.[4] In general, the most significant advances in hydroacylation chemistry have involved developing strategies, or methods, to limit this undesired decarbonylation pathway.

The review is divided according to the transformation being considered, that is, intramolecular alkene hydroacylation, intermolecular alkene hydroacylation, etc., and when needed also by catalyst type. During these sections, detailed mechanistic arguments relevant to the key hydroacylation step will not be presented; rather, these are collected together in section 6. The scope of this review is comprehensive from the first report in 1972 through June 2009. A number of reviews that deal with C−H activation cover some aspects of hydroacylation,[1] as do several metal-specific reviews;[5] however, a comprehensive treatment that covers all substrate types and all catalyst systems has yet to appear.[6] Reactions that generate acyl metal intermediates similar to **1** indirectly via simple carbonylation or carbonylation-type reactions are not considered.[7]

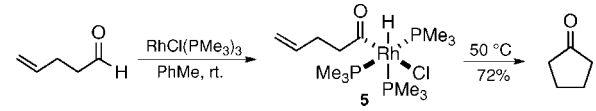
## 2. Intramolecular Alkene Hydroacylation

### 2.1. Stoichiometric Systems

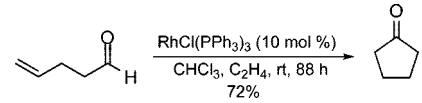
Sakai disclosed the first example of a metal-mediated hydroacylation reaction in a study on prostanoid synthesis.[3] The reactions involved treatment of a range of 4-enals with stoichiometric amounts of Wilkinson's complex at room temperature and delivered cyclopentanones **3** in up to 34% yield together with similar amounts of cyclopropane products **4** originating from decarbonylation pathways (Scheme 3).

Variation of the metal complex allowed Milstein to use a similar reaction to isolate and characterize an acyl rhodium(III) hydride intermediate; treatment of 4-pentenal with $RhCl(PMe_3)_3$ at room temperature delivered complex **5** in

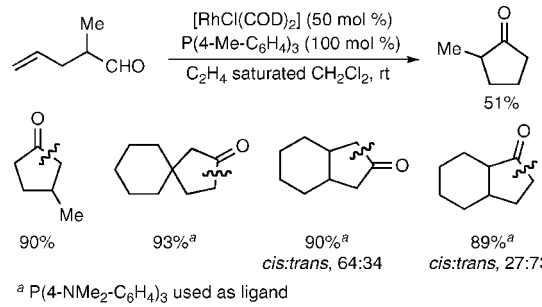
**Scheme 4**




**Scheme 5**




**Scheme 6**




which the acyl unit is positioned *trans* to the chloride ligand (Scheme 4).[8] The stability of complex **5** is due to the slow dissociation of the trimethylphosphine ligands.[9] Heating complex **5** to 50 °C resulted in intramolecular hydroacylation to provide cyclopentanone in 72% yield. An experiment using a catalytic amount of complex **5** achieved three turnovers; although only a low number of turnovers were achieved, this represented the first example of catalysis that did not rely on the presence of ethylene (for example, see Scheme 5).

### 2.2. Catalytic Systems

#### 2.2.1. Cyclopentanone Synthesis

Miller and co-workers demonstrated that intramolecular alkene hydroacylation could be performed using substoichiometric amounts of rhodium complexes if ethylene-saturated solvent was employed. 4-Pentenal could be cyclized to provide cyclopentanone in 72% yield using only 10 mol % Wilkinson's complex in ethylene saturated chloroform (Scheme 5).[10] Several products originating from intermolecular reaction of ethylene and pentenal were isolated in low yield (see Scheme 32).[11,12]

Larock observed a similar improvement in the efficiency of a range of intramolecular hydroacylation reactions upon the use of ethylene saturated solvent. In a departure from the Miller system, he found that catalysts generated in situ from $[Rh(COD)Cl]_2$ and $P(4\text{-}MeC_6H_4)_3$, $P(4\text{-}MeOC_6H_4)_3$, or $P(4\text{-}Me_2NC_6H_4)_3$ were most efficient.[13] With the relatively high catalyst loadings of 50 mol % in methylene chloride at room temperature, the method could be used for the synthesis of a range of substituted, spirocyclic, and fused cyclopentanone products (Scheme 6). No other olefin or acetylene additive proved as effective. It was also reported that adding water had no effect on the reaction yield although the catalyst was destroyed by the presence of oxygen. For the most reactive, generally unsubstituted, substrates, catalyst loadings of 10 mol % could be used. For 4-enals, substituents in either the 2- or 5-position significantly lowered the reaction efficiency. Efforts to extend the methodology to the synthesis of alternative ring sizes were unsuccessful.

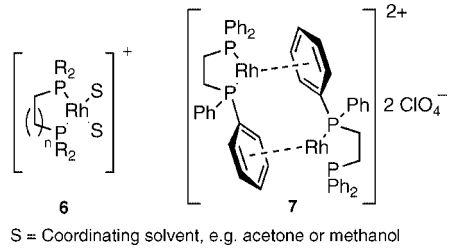



**Figure 1.**

The cyclization of 4-pentenal has been achieved using only 3 mol % of the complex $Co(dppe)(PPh_3)_2$ (dppe = 1,2-bis(diphenylphosphino)ethane) as a catalyst.[14−16] The authors propose the intermediacy of a cobalt(II) acyl hydride in analogy to the related rhodium(III) intermediates. This appears to be a potentially useful system although its application to other substrates has been limited.

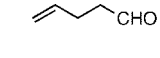
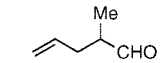
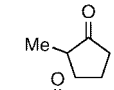
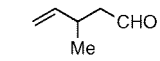
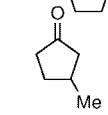
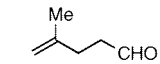
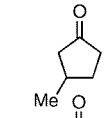
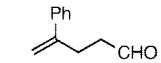
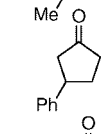
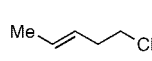
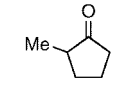
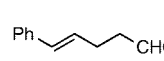
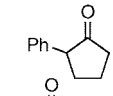
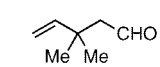
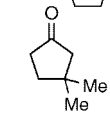
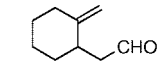
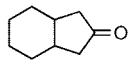
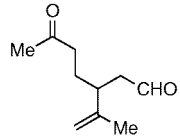
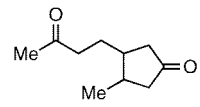
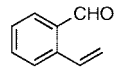
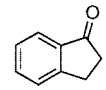
The development of cationic rhodium complexes as intermolecular hydroacylation catalysts by Bosnich represented a significant breakthrough in alkene hydroacylation chemistry because it allowed low catalyst loadings to be routinely employed.[17,18] Bosnich evaluated a number of catalyst systems, based on generic structure **6**, that combined bidentate phosphine ligands with a cationic rhodium center (Figure 1). The optimal system was found to be $[Rh(dppe)]ClO_4$, which could be isolated as the arene-bridged dimer **7** or generated in situ as a disolvated species corresponding to **6**.[19]

These complexes were applied to the cyclization of 4-pentenals; the catalyst $[Rh(dppe)]ClO_4$ was effective for the hydroacylation of a variety of differently substituted 4-pentenals (Table 1).[17] As can be seen, substituents in the 2-, 3-, 4-, and 5-positions were all possible although cyclizations with the 5-substituted substrates were significantly slower and generally required a higher catalyst loading. For the majority of substrates, a 1 mol % catalyst loading provided rapid reactions at room temperature. The use of ionic liquids as the reaction media for similar cyclizations has been reported.[20]

The majority of recent reports featuring intramolecular hydroacylation have employed the cationic Rh complexes popularized by Bosnich and originally developed by Osborne and Schrock[21] as the catalysts of choice (see section 2.4 for applications). Peters has shown that zwitterionic Rh complexes can also be used as effective complexes in hydroacylation reactions leading to cyclopentanones.[22] For example, neutral rhodium complex **8**, featuring an anionic borate ligand, was shown to be an effective catalyst in the conversion of enal **9** into cyclopentanone **10** (Scheme 7). Direct comparison with $[Rh(dppe)(NCMe)_2][PF_6]$ (**11**) showed that the zwitterionic complex **8** delivered 40 times the turnover frequency. The zwitterionic complexes also displayed greater tolerance to coordinating solvents, with effective reactions still being achieved in benzene, THF, or acetonitrile. The cationic complex **11** was poorly active in these solvents. Enal **9** was the only substrate evaluated.

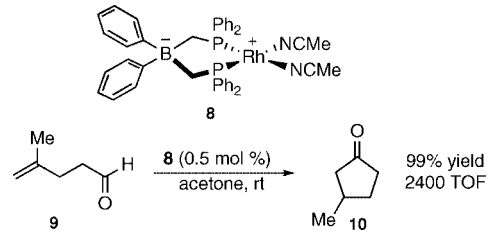
Morgan and Kundu have reported the preparation and application of a neutral bimetallic rhodium/titanium complex for intramolecular hydroacylation.[23] Complex **12** (Figure 2) was readily prepared in situ from the corresponding hydroxyphosphine, $Ti(OiPr)_4$, and $[Rh(COD)Cl]_2$ and was shown to promote the cyclization of two enals to the corresponding cyclopentanones. Control experiments, relative to Bosnich-type cationic Rh systems, showed that the new complex

**Table 1. Scope of Bosnich's Cationic Rh(I) Cyclizations**[a]

| entry | aldehyde | catalyst mol % | product | yield (%)[b] |
|---|---|---|---|---|
| 1 |  | 1 |  | 95 |
| 2 |  | 1 |  | 88 |
| 3 |  | 1 |  | 98 |
| 4 |  | 1 |  | 98 |
| 5 |  | 2 |  | 92 |
| 6 |  | 4 |  | 89 |
| 7[c] |  | 10 |  | 70 |
| 8 |  | 1 |  | 100 |
| 9 |  | 1 |  | 90<br>35 : 65<br>*cis : trans* |
| 10 |  | 2 |  | 94<br>42 : 58<br>*cis : trans* |
| 11 |  | 2 |  | 30 |

[a] $[Rh(dppe)]_2(ClO_4)_2$, $CD_3NO_2$, 20 °C. [b] Determined by GC and $^1H$ NMR methods. [c] 65 °C.

**Scheme 7**




delivered the target compounds with fewer side products but with slower rates and poorer yields.

The majority of substituted 4-pentenals used in the Bosnich study were prepared via Claisen rearrangements of the

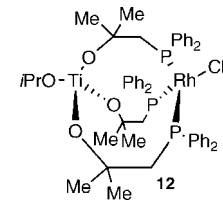
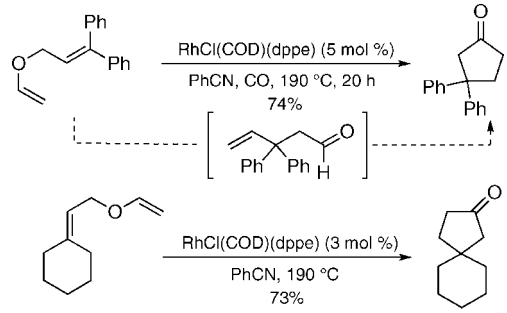
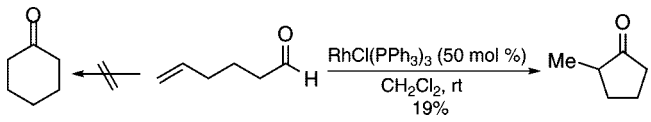



**Figure 2.**

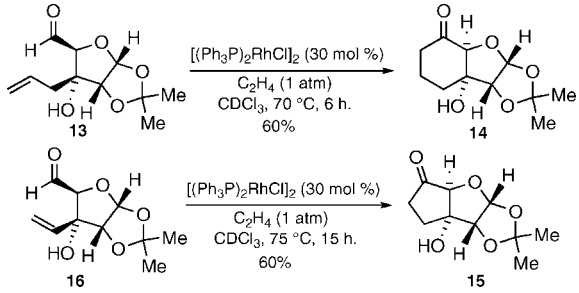
**Scheme 8**




**Scheme 9**




**Scheme 10**




appropriate allyl vinyl ethers. Eilbracht has established that with the use of a suitable catalyst, it is possible to couple hydroacylation with a Claisen rearrangement to achieve a one-pot conversion of allyl vinyl ethers to cyclopentanones, thus avoiding the isolation of potentially sensitive aldehydes.[24] Scheme 8 gives two examples; the use of RhCl(COD)(dppe) as a catalyst and a CO atmosphere was found to be optimal. The use of alternative catalysts such as $RuCl_2(PPh_3)_3$ required the use of higher pressures of CO (50 bar) to achieve similar conversions. A polystyrene-supported $\eta^5$-cyclopentadienyl rhodium catalyst has also been used in related transformations.[25]

### 2.2.2. Larger Ring Systems

The formation of ring systems larger than cyclopentanones using intramolecular hydroacylation is not a trivial exercise. Ring closure of these larger rings is generally slower than for five-ring formation and decarbonylation can become problematic. In addition, if a five-membered closure is possible, then this pathway will usually be followed. For example, reaction of 5-hexenal does not provide the cyclohexanone but delivers the cyclopentanone as the sole product (Scheme 9).[12]

Six-membered ring formation has been achieved using a rigid carbohydrate-derived scaffold (Scheme 10).[26] The authors had anticipated that treatment of enal **13** with the catalyst $[RhCl(PPh_3)_2]_2$ would provide a cyclopentanone; however, cyclohexanone **14** was obtained as the exclusive product. The authors reasoned that cyclopentanone formation is disfavored due to the ring strain that would be present in the resulting 5,5,5-tricyclic product. This was reinforced by the much slower formation of cyclopentanone **15** from enal **16**. This was not a general process and was only applicable to a limited range of substrates.

**Scheme 11**

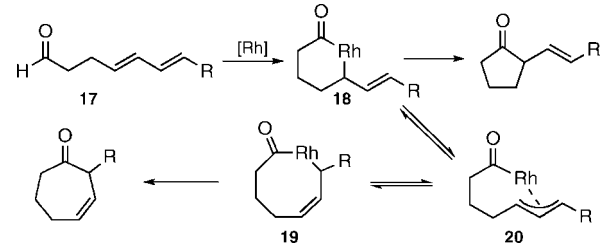
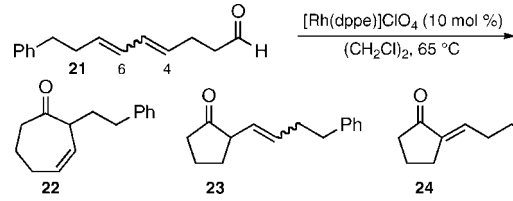


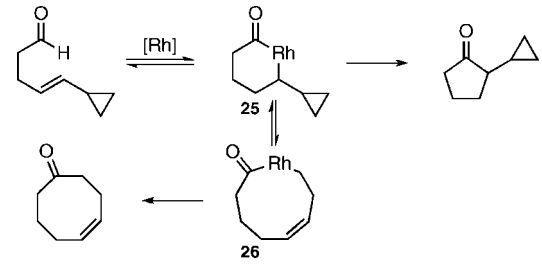

**Table 2. Effect of Diene Geometry on Cycloheptanone Synthesis**




| substrate | **22** (%) | **23** (%) | **24** (%) | starting material (%) |
|---|---|---|---|---|
| (4*E*,6*E*) | 62 | 13[a] | 6 | |
| (4*Z*,6*E*) | 65 | 11[a] | 5 | |
| (4*E*,6*Z*) | trace | 49[b] | trace | 38 |

[a] *E*-alkene. [b] *Z*-alkene.

**Scheme 12**

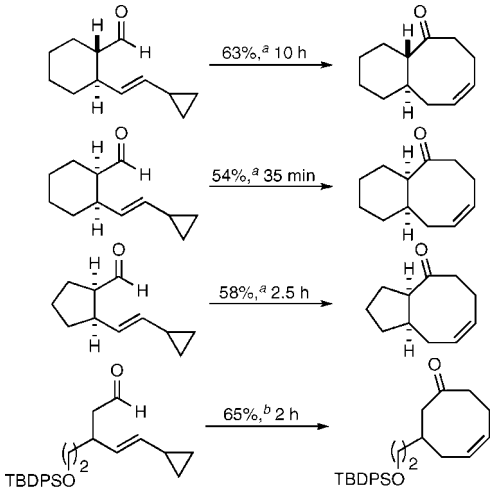



It is possible to access larger ring systems using hydroacylation if suitable additional functionality is incorporated into the substrate. Mori has developed the use of dienal substrates to allow access to cycloheptanone products (Scheme 11).[27,28] Treatment of dienal **17** with a rhodium(I) catalyst formed metallocyclohexane **18** as expected; from here the reaction could either proceed to the usual cyclopentanone product or isomerize to rhodacycle **19** by way of $\pi$-allylrhodium species **20**. Reductive elimination from **19** would then provide a cycloheptanone product.

The authors observed that diene geometry in substrate **21** had a significant effect on the product distribution (Table 2); if the diene contained an *E* alkene at C-6 then the required cycloheptanones were obtained; however, a *Z* alkene at C-6 produced the cyclopentanone product. Cyclopentanone formation was rationalized on the basis that formation of a $\pi$-allyl intermediate similar to **20** would be unfavorable for the *Z*-alkene due to steric repulsion. Provided dienes with *E*-geometry at C-6 were employed, the preparation of cycloheptanones was efficient for a number of substrates. The cationic rhodium systems favored by Bosnich were used throughout. For an application of this methodology to natural product synthesis, see Scheme 31.

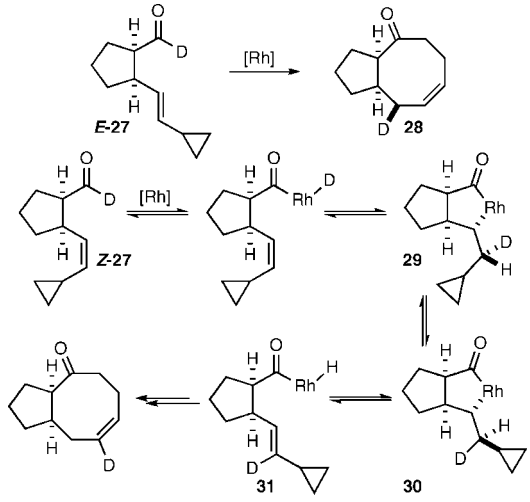
Shair and co-workers have developed an elegant method for the synthesis of cyclooctenones using intramolecular hydroacylation.[29] Eight-membered ring formation was achieved by the incorporation of a cyclopropane ring in the substrate. The proposed mechanism is shown in Scheme 12. The key step is the fragmentation and isomerization of rhodacycle

**Scheme 13**




[a] [Rh(dppe)]OTf (20 mol %), $C_2H_4$, $(CH_2Cl)_2$, 65 °C. [b] [Rh(dppe)]$ClO_4$ (20 mol %) employed.

**Scheme 14**



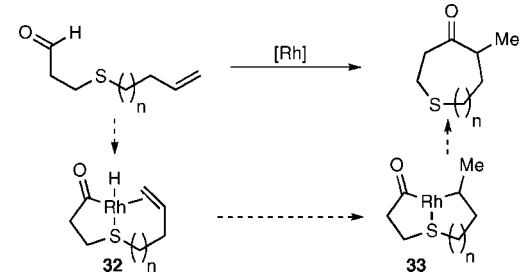

**25** into ring-expanded rhodacycle **26**. Reductive elimination from **26** would provide the required cyclooctanone.

Treatment of the relevant cyclopropane-containing substrates with cationic rhodium catalysts under an ethylene atmosphere delivered cyclooctenones in good to moderate yields (Scheme 13). Wilkinson's complex was ineffective as a catalyst.

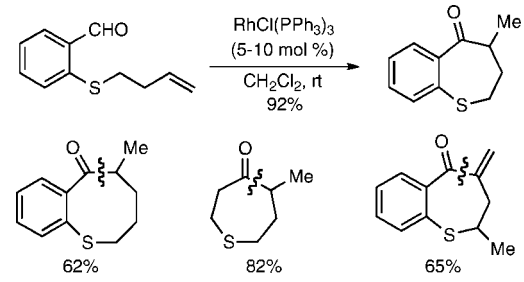
To explore the mechanism in operation, the authors studied the reactions of both the *E* and *Z* isomers of a deuterium-labeled substrate. The experiments led to two D-containing products in a ratio that exactly matched the *E*/*Z* ratio of the substrates. The authors proposed that the *E* isomer generated the expected cyclooctenone directly, via the mechanism in Scheme 12 (***E*-27** → **28**, Scheme 14). However, to account for the unexpected scrambling of the D-label, they proposed isomerization of the *Z* alkene in ***Z*-27** via five-membered rhodacycles **29** and **30** leading to intermediate **31**, featuring an *E*-configured alkene.

Bendorf and co-workers have prepared a series of medium-ring sulfur heterocycles using intramolecular hydroacylation.[30] Their strategy was based on the formation of chelation-stabilized intermediates such as **32** and **33** (Scheme 15). Reductive elimination from rhodacycles such as **33** would deliver the required medium-ring systems.

**Scheme 15**




**Scheme 16**




The hydroacylations were all performed using Wilkinson's complex as catalyst at room temperature in methylene chloride. The method allowed a variety of seven- and eight-membered rings to be prepared (Scheme 16). Alkyne as well as alkene containing substrates could be employed although the use of allyl sulfides was unsuccessful and was attributed to competitive cleavage of the allyl C−S bond. Control experiments conducted using substrates in which the sulfur atom was replaced by an oxygen or carbon atom confirmed that S-chelation was a requirement for cyclization. A recent report from Dong, concerned with the enantioselective synthesis of medium-ring ethers and sulfides, has demonstrated that it is possible to employ ether-linked substrates similar to those shown in Scheme 16 in hydroacylation chemistry (see Scheme 29, section 2.4).[31]

The Brookhart group have reported a single example of Co(I)-catalyzed intramolecular hydroacylation of a vinylsilane leading to the synthesis of a seven-membered ketone (see Scheme 57 for intermolecular examples).[32]

## 2.3. Stereoselective Reactions

### *2.3.1. Diastereoselective Systems*

The abundance of defined stereochemical motifs in natural products and designed bioactive molecules has driven the development of diastereoselective and enantioselective reactions. Sakai and co-workers were the first to explore diastereoselective intramolecular hydroacylation reactions.[33] They extended their early study (section 2.1) to include the cyclization of 3,4-disubstituted 4-pentenals (Scheme 17). The reactions proceeded with good levels of diastereoselectivity to deliver *cis*-3,4-disubstituted cyclopentanones. The origin of the selectivity is attributed to allylic strain, with transition state **34** being favored over **35**.

The use of a relatively high loading of Wilkinson's complex allowed a variety of synthetically useful substituents to be tolerated, including keto-, chloro-, and hydroxyl groups (Table 3). Aldehydes masked as lactol units could also be used successfully (entry 4). In all cases, the *cis* diastereomers were obtained as the sole products.

It was subsequently demonstrated that the use of chiral Rh(I) catalysts in cyclizations analogous to those shown in

**Scheme 17**

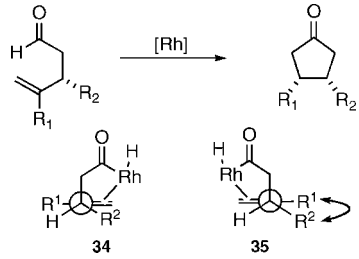
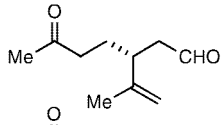
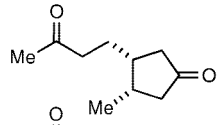
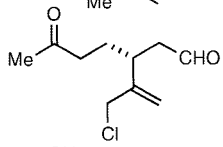
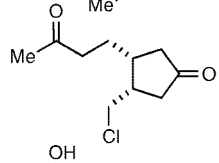
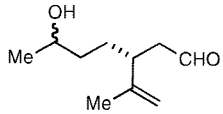
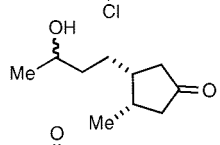
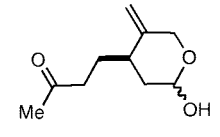
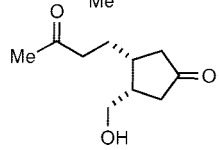
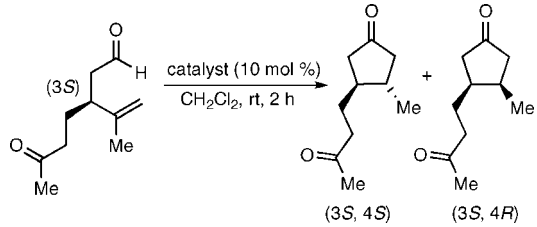



**Table 3. *Cis*-Selective Cyclopentanone Synthesis[a]**

| entry | substrate | product | yield (%) |
|---|---|---|---|
| 1 |  |  | 84 |
| 2 |  |  | 73 |
| 3 |  |  | 62 |
| 4 |  |  | 49 |

[a] $RhCl(PPh_3)_3$ (30 mol %), $CH_2Cl_2$, rt.

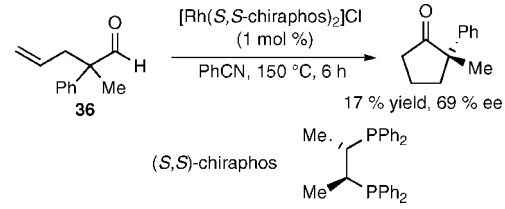
**Table 4. Stereoselective Synthesis of 3,4-Disubstituted Cyclopentanones**



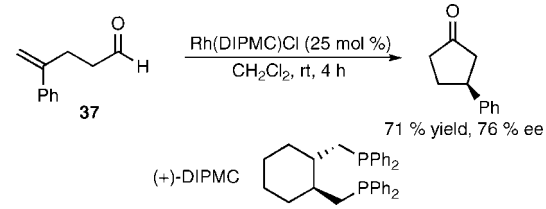

| entry | substrate | catalyst | time (h) | yield (%) | *cis*/*trans* |
|---|---|---|---|---|---|
| 1 | 3*R* | Rh[(*S*)-BINAP]$ClO_4$ | 1.5 | 85 | <1:>99 |
| 2 | 3*R* | Rh[(*R*)-BINAP]$ClO_4$ | 4 | 74 | 97:3 |
| 3 | 3*S* | Rh[(*R*)-BINAP]$ClO_4$ | 2 | 86 | <1:>99 |
| 4 | 3*S* | Rh[(*S*)-BINAP]$ClO_4$ | 5 | 82 | 96:4 |

Table 3 allowed double diastereoselection to be explored, employing first neutral and then cationic rhodium complexes.[34−36] Sakai found that the use of the cationic complex Rh(BINAP)$ClO_4$ allowed the selective synthesis of all four possible stereoisomers of 3,4-disubstituted cyclopentanones (Table 4).[36] For example, reaction of the (3*R*)-substrate with 5 mol % of the catalyst employing (*S*)-BINAP delivered the *trans* configured product with >99:1 selectivity. Conversely, cyclization of the same substrate with the (*R*)-catalyst provided the *cis* product with 97:3 selectivity. The situation was reversed for the (3*S*)-configured substrate. A similar pattern of selectivity was obtained with the neutral complexes Rh(BINAP)Cl; however, significantly higher catalyst loadings (50 mol %) were needed, and the levels of selectivity were inferior. Importantly, the matched and mismatched catalyst and substrate pairings were reversed when the neutral complexes were employed.

**Scheme 18**




**Scheme 19**



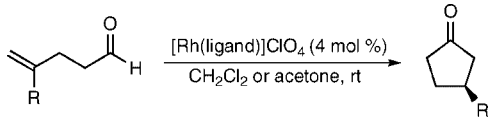

### 2.3.2. Enantioselective Systems

While investigating aldehyde decarbonylation using chiral rhodium catalysts, James and Young observed the first example of enantioselective intramolecular hydroacylation via kinetic resolution.[37,38] Reaction of racemic pentenal **36** with a catalyst incorporating enantiomerically pure (*S*,*S*)-chiraphos yielded the corresponding cyclopentanone with up to 69% ee (Scheme 18). This level of selectivity was only achieved at low conversions (17%); at conversions of 50−60%, the enantioselectivity was reduced to ~40%. The reactions were conducted using only 1 mol % of catalyst, although a temperature of 150 °C was needed to achieve reasonable conversions. One reason for this low reactivity was the presence of the quaternary center at C-2.

Sakai and co-workers were the first to report the cyclization of achiral 4-pentenals using enantiomerically pure catalysts.[34,35] Several ligand systems were investigated with *trans*-1,2-bis-[(diphenylphosphino)methyl]cyclohexane (DIPMC) delivering the highest selectivities. For example, cyclization of phenyl-substituted pentenal **37** furnished the cyclopentanone product in 71% yield and 76% ee (Scheme 19).[35] Relatively high catalyst loadings of 25 mol % were employed, and the reactions were conducted at room temperature.

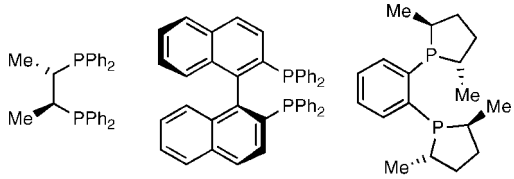
Both Sakai and Bosnich found that the use of cationic rhodium complexes incorporating chiral ligands allowed highly enantioselective cyclizations of achiral 4-pentenals using low catalyst loadings. In the first report, Sakai found that the use of the catalyst [Rh(BINAP)]$ClO_4$ allowed the cyclization of certain substrates to deliver enantioselectivities up to 99%.[36] Later, Bosnich and co-workers evaluated a range of bidentate chiral ligands and found that BINAP, chiraphos, and DuPhos all generated selective catalysts for certain substrates (Table 5).[39−41] An impressive range of substituents could be tolerated ranging from sterically demanding electron-donating groups such as $SiMe_3$ to much smaller electron-withdrawing groups such as C(O)Me. In all cases, conversions of >95% were achieved with enantioselectivities for the majority of substrates falling in the 94−99% range. Aryl-substituted products delivered the lowest selectivities (70−75% ee). To obtain the optimal levels of yield and enantioselectivity, it was crucial to match ligand selection to individual class of substrate. For example, BINAP was most effective

**Table 5. Enantioselective Reactions Using Cationic Catalysts**




| entry | R | ligand | ee (%) |
|---|---|---|---|
| 1[a,b] | Me | (*S,S*)-MeDuphos | 94 |
| 2[a,b] | *i*Pr | (*S,S*)-MeDuphos | 96 |
| 3[a,b] | cyclopentyl | (*S,S*)-MeDuphos | 96 |
| 4[c] | *t*Bu | (*S*)-BINAP | >99 |
| 5[c] | $SiMe_3$ | (*S*)-BINAP | >99 |
| 6[c] | Ph | (*S,S*)-chiraphos | 78 |
| 7[c] | 4-MeO-Ph | (*S,S*)-chiraphos | 75 |
| 8[c] | C(O)Me | (*S*)-BINAP | 87 |
| 9[c] | C(O)Ph | (*S*)-BINAP | 94 |
| 10[b] | $CO_2Et$ | (*S*)-BINAP | >99 |
| 11[b] | $CO_2iPr$ | (*S*)-BINAP | >99 |

[a] $PF_6^-$ salt (5 mol %) used. [b] Acetone. [c] $CH_2Cl_2$.




(*S,S*)-chiraphos (*S*)-BINAP (*S,S*)-MeDuphos

for substrates with tertiary alkyl or ester and ketone substituents, while DuPhos was superior for substrates containing primary or secondary alkyl groups.

The Sakai group further investigated the cyclization of the 4-aryl-substituted pentenals using BINAP-derived catalysts and discovered an unusual effect of *ortho*-halo substituents.[42] In general, cyclization of 4-aryl-susbtrates with (*R,R*)-configured catalyst delivered (*R*)-configured products. However, when substrates containing an *ortho*-halo substituent were employed the (*S*)-configured products were obtained. The highest selectivities obtained were 83% ee.

The Sakai and Suemune groups significantly extended the scope of these enantioselective cyclizations by adopting an enantioselective desymmetrization approach and employing substrates that led to the formation of two stereocenters (Table 6).[43,44] Cationic rhodium perchlorate BINAP complexes delivered *trans*-configured products in good yields with high enantioselectivity, while the corresponding neutral complexes provided the *cis*-cyclopentanones, again with good yields and selectivities. The neutral complexes required 50 mol % catalyst loadings compared with the 5 mol % employed with the cationic systems; however, by correct catalyst selection, it was possible to produce any of the four possible product stereoisomers. The method was further extended to deliver products containing a quaternary stereocenter; however, with these substrates the neutral complexes were no longer active catalysts. The cationic complexes delivered the *trans*-configured products with excellent enantioselectivities.

The same group also explored the kinetic resolution of nonsymmetric racemic diene-aldehydes (Scheme 20).[45] Reaction of aldehyde **38** with Rh[(*S*)-BINAP]$ClO_4$ delivered *trans*-substituted cyclopentanone in 46% yield and an excellent >95% ee. The use of the corresponding neutral complexes allowed access to the *cis*-configured products with good enantioselectivity although the regioselectivity between the Ph- and Me-substituted alkenes was poor, and high catalyst loadings were needed. These selectivities follow from the desymmetrization studies described above.

Bosnich has also explored kinetic resolution processes using cationic complexes and incorporated D-labeling studies to investigate the origin of the enantioselectivity in the cyclizations of 4-pentenals.[46] Reaction of racemic 3-phenylpentenal **39** with Rh[(*S*)-BINAP]$ClO_4$ delivered the expected cyclopentanone **40** in 51% yield along with 42% of 4-phenylpentenal **41** and 7% of the isomerized alkenes **42** (Scheme 21). The formation of 4-phenylpentenal is consistent with the mechanism proposed by Bosnich for achiral hydroacylation (see Scheme 77). The conclusion reached by Bosnich is that no single step is responsible for the stereoinduction, rather a number of reversible steps all contribute. Given the complexity of the mechanism, it was not possible to propose a simple model that accounts for the observed enantioselectivity.[47,48] The desymmetrization systems described by Sakai (Table 6) are less complex in that isomerization products corresponding to aldehydes **41** and **42** were not seen. Consequently the authors proposed a series of models based on the steric interactions between the BINAP ligand and the substrates and the corresponding rates of reaction.[49]

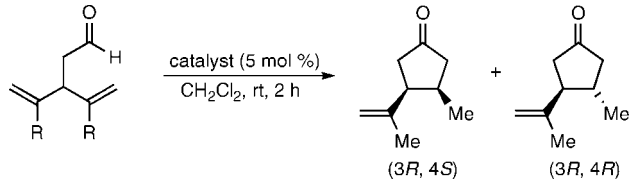
## 2.4. Applications of Intramolecular Alkene Hydroacylation

The majority of reports discussed in the preceding section have focused on either reaction or catalyst development. Given the success of a number of these systems, it is not surprising that these methods are starting to be employed as key reactions in synthetic schemes. For example, the ability to construct cyclopentanone systems efficiently using simple acyclic precursors and low catalyst loadings has resulted in a number of applications of the reactions to the synthesis of target systems. Sakai's discovery of the hydroacylation reaction was achieved during an investigation into the synthesis of prostanoid derivatives, and in a series of publications, he has continued these endeavors. In particular, he has exploited the availability of enantiomerically pure enals from terpenes such as limonene and limonen-10-ol in a number of syntheses. For example, (−)-limonen-10-ol was converted through a series of steps to provide enantiomerically pure enal **43** (Scheme 22).[50] Treatment of enal **43** with Wilkinson's complex provided ketone **44** in 88% yield as a single diastereomer. Ketone **44** was then advanced to a key intermediate in the synthesis of 11-deoxyprostaglandin. Similar sequences have been employed to prepare intermediates in routes toward iridomyrmecin, isoiridomyrmecin,[51] carbacyclin,[52] 8-isoprostanoic acid[53] and the nepetalactones.[54]

Eilbracht has utilized his tandem Claisen rearrangement/hydroacylation sequences in the synthesis of a number of key intermediates for natural product syntheses. For example, a potential intermediate (**45**) for the synthesis of solavetivone was prepared in a tandem sequence starting from vinyl ether **46** (Scheme 23). Treatment of ether **46** with RhCl(COD-)(dppe) in benzonitrile and 150 °C provided cyclopentanone **45** in 35% yield by way of aldehyde **47**.[55] The relatively low yield obtained for the tandem conversion was attributed to acid-promoted decomposition. The same group has used a similar strategy in the formal synthesis of erythrodiene and spirojatamol.[56]

Undheim and co-workers have utilized cyclopentanone-forming hydroacylation reactions in the synthesis of spirane-bridged bisarenes[57] and in the preparation of spirane-bridged indenes needed for the preparation of semititanocenes.[58] For

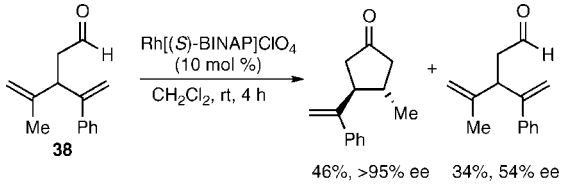
**Table 6**



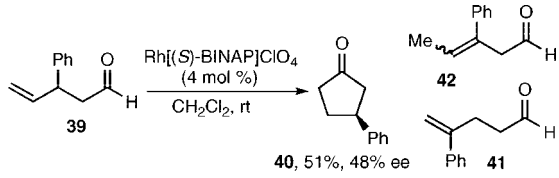

| entry | R | catalyst | time (h) | yield (%) | *cis*/*trans* | ee (%)[a] | config |
|---|---|---|---|---|---|---|---|
| 1[b] | Me | [Rh((*R*)-BINAP)]Cl | 72 | 25 | 97:3 | >95 | 3*S*,4*R* |
| 2[b] | Me | [Rh((*S*)-BINAP)]Cl | 72 | 31 | 97:3 | >95 | 3*R*,4*S* |
| 3 | Me | [Rh((*R*)-BINAP)]$ClO_4$ | 1 | 81 | 3:97 | >95 | 3*S*,4*S* |
| 4 | Me | [Rh((*S*)-BINAP)]$ClO_4$ | 1 | 84 | 4:96 | >95 | 3*R*,4*R* |
| 5 | Ph | [Rh((*S*)-BINAP)]$ClO_4$ | 2 | 70 | 18:82 | >95 | 3*S*,4*S* |
| 6 | Ph | [Rh((*R*)-BINAP)]$ClO_4$ | 2 | 76 | 17:83 | >95 | 3*R*,4*R* |
| 7 | *i*Bu | [Rh((*R*)-BINAP)]$ClO_4$ | 3 | 74 | 2:98 | >95 | 3*S*,4*S* |
| 8 | *i*Bu | [Rh((*S*)-BINAP)]$ClO_4$ | 4 | 77 | 2:98 | >95 | 3*R*,4*R* |

[a] Of major product. [b] Catalyst used at 50 mol %.

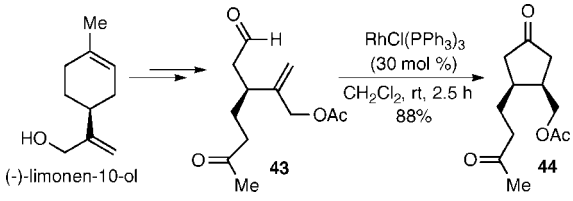
**Scheme 20**




**Scheme 21**



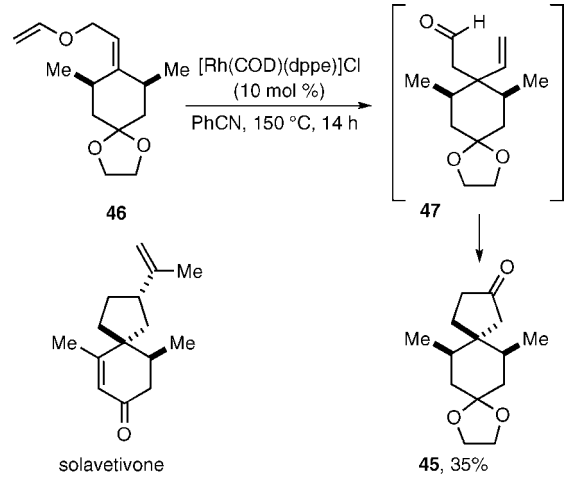

**Scheme 22**



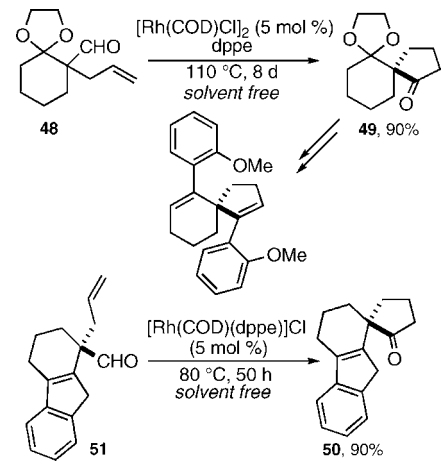

example, enal **48** was converted to ketone **49** using a dppe-derived catalyst (Scheme 24). Importantly, to achieve good yields the reactions needed to be performed under solvent-free conditions for eight days. The use of benzonitrile or nitromethane as solvent resulted in significant decarbonylation. The second example also employed solvent-free conditions and shows the preparation of ketone **50** from enal **51**, in 90% yield. In this second example, the use of benzonitrile as solvent lead to the formation of a significant byproduct. These two examples both employ complex enal substrates, featuring quaternary carbon centers, a ketal, and an indene ring system and, despite the relatively high temperatures and extended reaction times needed, illustrate the good functional group tolerance of the hydroacylation process.

A kinetic resolution using a cationic rhodium complex was employed by Rousseau and Mioskowski in a formal synthesis of brefeldin A (Scheme 25).[59] Reaction of racemic aldehyde **52** with Rh[(*S*)-BINAP]$ClO_4$ (0.9 mol %) triggered an intramolecular hydroacylation reaction to deliver a 1:1 mixture of cyclopentanones **53** and **54**; both were obtained with 96% enantiomeric enrichment. The *trans*-configured product was advanced through a short sequence to deliver

**Scheme 23**



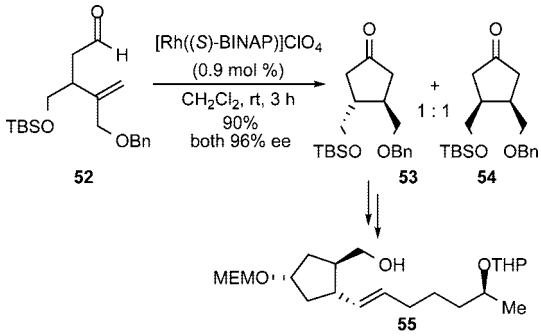

**Scheme 24**



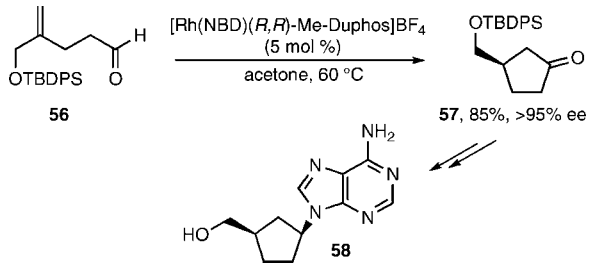

alcohol **55**, an intermediate in the synthesis of brefeldin A previously reported by Gais.[60]

Related enal systems were recently employed by Castillón in the enantioselective synthesis of carbocyclic nucleosides (Scheme 26).[61] For example, treatment of enal **56** with a cationic Me-DuPhos-containing catalyst, as described by Bosnich, delivered cyclopentanone **57** with >95% ee. Advancement of ketone **57** through reduction and a lipase-mediated dynamic kinetic resolution ultimately allowed access to carbocyclic nucleoside **58**.

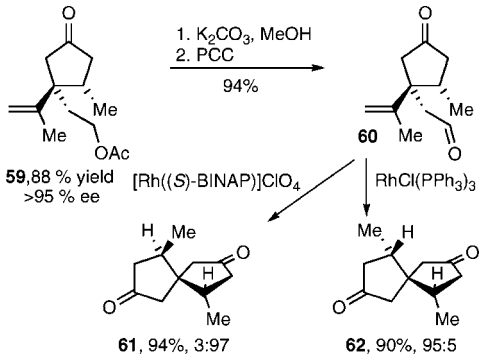
**Scheme 25**




**Scheme 26**




**Scheme 27**

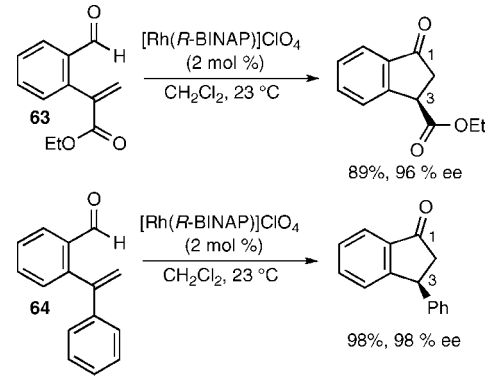



Two sequential hydroacylation reactions were employed by the Sakai group in the preparation of a enantiomerically enriched spiro[4.4]nonanedione derivatives (Scheme 27).[62,63] Cyclopentanone **59** was obtained with excellent enantioselectivity using the enantioselective desymmetrization method described in Table 6. Conversion of the acetate group to the aldehyde required for a second hydroacylation reaction provided enal **60**. Cyclization of enal **60** using the cationic complex Rh[(*S*)-BINAP]$ClO_4$ provided dione **61** in good yield and with excellent diastereoselectivity. Reaction of enal **60** with the enantiomeric complex resulted in no reaction; however, treatment with Wilkinson's complex delivered the diastereomeric dione **62** with similarly good selectivity.

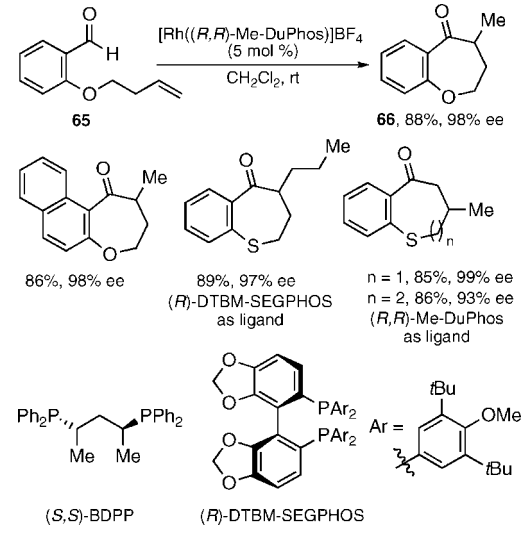
Morehead and co-workers have applied Rh-catalyzed hydroacylation reactions to the synthesis of 3-substituted indanones.[64] After establishing that α-substituted 2-vinyl benzaldehydes such as **63** and **64** were good substrates in reactions employing achiral catalysts, they moved on to investigate the use of enantiomerically pure catalysts (Scheme 28). Using BINAP-derived complexes delivered the indanone products in excellent yield and ee, using only 2 mol % of catalyst. Although substituents could only be tolerated at the C-3 position, a variety of electron-donating and electron-withdrawing groups could be incorporated.

Recently, the Dong group has used an enantioselective intramolecular hydroacylation process to access benzo-fused

**Scheme 28**




**Scheme 29**

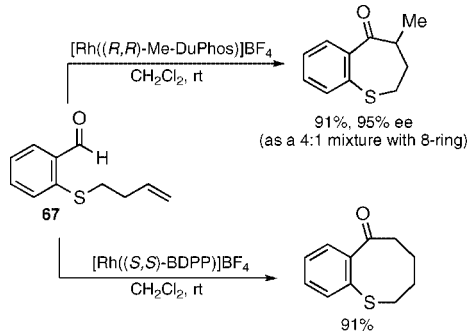



medium-ring heterocycles.[31] The group employed chelation control to access seven- and eight-membered rings. For example, treatment of ether-linked enal **65** with [Rh(Me-DuPhos)]$BF_4$ delivered seven-membered ketone **66** in 88% yield with 98% ee (Scheme 29). Sulfide-linked enals were also explored, and with some variation of ligand choice, it was possible to prepare ketones with alkyl substituents positioned either α or $\beta$ to the carbonyl. Interestingly, a substrate similar to ether **65** was earlier shown to be unreactive to Wilkinson's complex (see Scheme 16, section 2.2.2).[30]

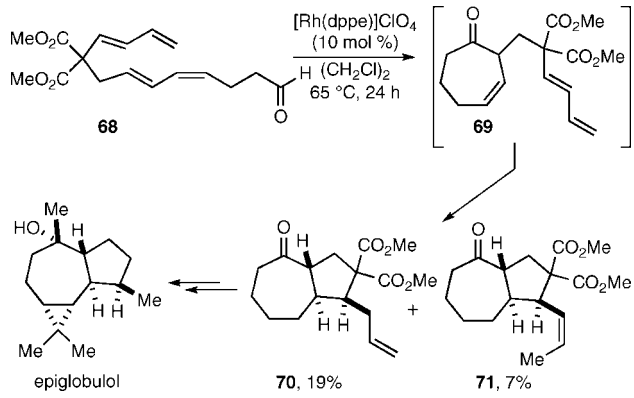
The Dong group was also able to demonstrate that with certain substrates the choice of ligand determined the ring size of the product formed; for example, when sulfide **67** was treated with a Me-DuPhos catalyst, the corresponding seven-membered ketone was formed as the major product as a 4:1 mixture together with the eight-membered ketone (Scheme 30). However, if the same substrate was treated with a catalyst featuring the ligand (2*S*,4*S*)-2,4-bis-(diphenylphosphino) pentane (BDPP), then the eight-membered ketone was formed as the exclusive product. The same group has also explored the use of related substrates in rhodium-catalyzed intramolecular ketone hydroacylation.[65,66]

The Sato group has reported a synthesis of epiglobulol, exploiting their intramolecular diene hydroacylation chemistry to access the key seven-membered ring (Scheme 31).[67] Their synthesis was based on a cascade process featuring an initial rhodium-catalyzed hydroacylation followed by a rhodium-catalyzed cycloisomerization process, allowing ac-

**Scheme 30**




**Scheme 31**



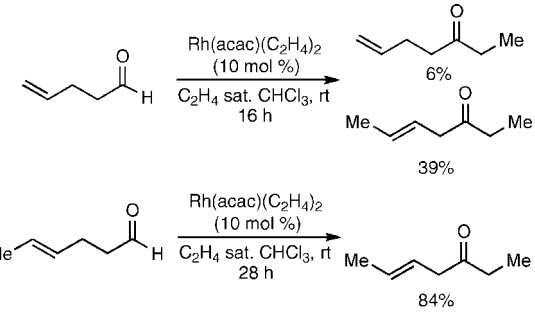

cess to the required fused-ring system. In order to achieve the second of these two stages, it was necessary to include a quaternary center in the tether. For example, treatment of tetraene **68** with [Rh(dppe)]$ClO_4$ at 65 °C resulted in initial hydroacylation to generate ketone **69**, followed by cycloisomerization to deliver the isomeric ketones **70** and **71** in 19% and 7% yield, respectively. When a substrate lacking the quaternary center was employed, the initial hydroacylation proceeded as expected; however the cycloisomerization failed. Performing the cascade process at reflux temperature allowed ketone **70** to be obtained as the exclusive product in 44% yield. Ketone **70** was advanced through an 11-step sequence to deliver epiglobulol.

## 3. Intermolecular Alkene Hydroacylation

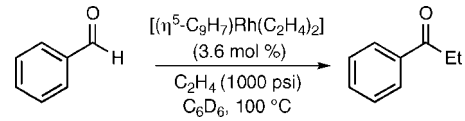
### 3.1. Rhodium Catalysis

Extending hydroacylation chemistry to intermolecular systems has proven to be challenging, with the main difficulty remaining the prevention of decarbonylation pathways. During Miller's intramolecular study using pentenal substrates (see Scheme 5), he observed that exchanging the catalyst from Wilkinson's complex to Rh(acac)$(C_2H_4)_2$ allowed products from the intermolecular reaction with ethylene to be isolated (Scheme 32).[10,68] For example, reaction of pentenal with Rh(acac)$(C_2H_4)_2$ in ethylene-saturated chloroform provided a mixture of heptenones, with the *E*-hept-5-en-2-one as the major component in 39% yield. Cyclopentanone was detected in only 1% yield. Reactions with saturated aldehydes provided no hydroacylation adducts; however, 4-hexenals were successfully employed. Subsequently, Vora showed that *Z*-4-heptenal could also be combined with ethylene, using identical conditions, to deliver 6-nonen-3-one in a 26% yield.[69] The requirement for the

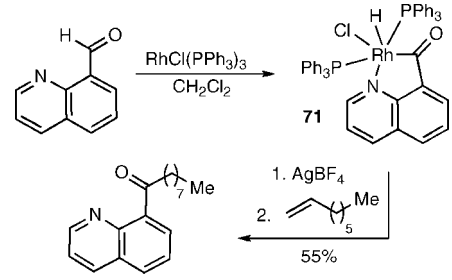
**Scheme 32**




**Scheme 33**




**Scheme 34**



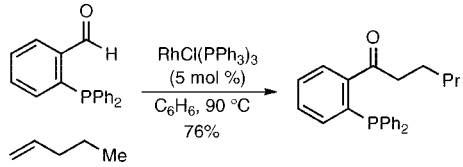

aldehydes to contain an alkene unit suggested that internal alkene coordination was a prerequisite for reactivity.

Marder and Millstein extended the utility of intermolecular hydroacylation reactions with the discovery that the indenylrhodium complex [Rh($\eta^5$-$C_9H_7$)$(C_2H_4)_2$] catalyzed the addition of a range of aromatic aldehydes to ethylene; a single example is shown in Scheme 33.[70] Provided relatively high pressures of ethylene (1000 psi at 25 °C) were employed, turnover numbers of ca. 4 $h^{-1}$ were observed with no decomposition of the catalyst to metallic rhodium. A range of simple aromatic aldehydes were employed, and methyl formate was also shown to produce hydroacylation adducts, although at a much slower rate (2−3 turnovers in 24 h).

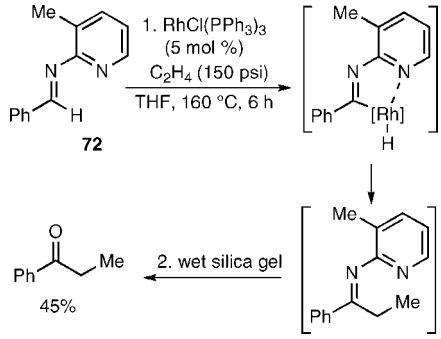
The first intermolecular hydroacylation systems, described by Miller,[68] employed enals as the aldehyde component (see Scheme 32), and their success was attributed to intramolecular coordination of the alkene to aid in catalyst stabilization. The use of heteroatom chelation has emerged as a successful strategy for intermolecular hydroacylation and a number of systems have been reported. Suggs first isolated acyl rhodium(III) complex **71** from the reaction of quinoline-8-carboxaldehyde and Wilkinson's complex, and found that after treatment with $AgBF_4$ and octene, the hydroacylation adduct could be isolated (Scheme 34).[71,72] Later, modification of the method to employ [RhCl$(COE)_2]_2$ as the catalyst followed by treatment with trimethylphosphite allowed this stoichiometric process to be applied to a range of electronically varied alkenes, delivering hydroacylation adducts in yields up to 75%.[73] Attempts to use substoichiometric amounts of Wilkinson's complex resulted in significantly reduced yields.

A related protocol, catalytic in rhodium, employed the chelating ability of a phosphine group to allow intermolecular hydroacylation; *o*-diphenylphosphino benzaldehyde could be

**Scheme 35**




**Scheme 36**




combined with a range of neutral alkenes using 5 mol % of Wilkinson's complex as catalyst in benzene as 90 °C.[74] An example reaction is shown in Scheme 35.

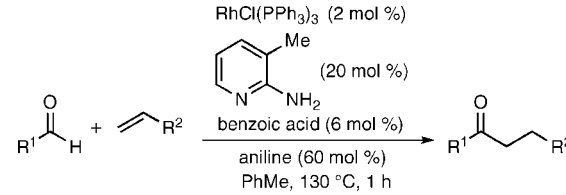
While providing insight into the requirements for stabilization of the key rhodium-acyl units, the use of quinoline- and phosphine-substituted aldehydes were limiting in that the products necessarily incorporated these large coordinating groups. The Jun group significantly advanced chelation-stabilized hydroacylation methods with the realization that picolyl imines, formed in situ, could serve as chelating-aldehyde equivalents. Suggs[75] had previously shown that imines such as **72** formed stable rhodium-iminoacyl complexes and exploited these in intermolecular hydroacylation reactions (Scheme 36). Treatment of the imines with Wilkinson's complex (5 mol %) and an alkene in THF at elevated temperature, delivered, after hydrolysis, the hydroacylation adducts. Isolated picolyl imines have been utilized in hydroacylation-based syntheses of acylferrocene derivatives[76−78] and, when enoates were employed as the alkene components, in the synthesis of 1,4-dicarbonyl systems.[79]

The Jun group was able to demonstrate that it was possible to generate suitable picolyl imines in situ from the corresponding aldehydes and amines.[80] The optimized catalyst system involved treating a mixture of the aldehyde and the alkene with Wilkinson's complex (2 mol %), picolyl amine (20 mol %), benzoic acid (6 mol %), and aniline (60 mol %) in toluene at 130 °C (Table 7).[81] By this method, a varied range of alkenes and aldehydes could be combined in good to excellent yields. Heteroaromatic aldehydes[82] and enoates[83] could also be employed as substrates.

Experimentation had established that the formation of the picolyl imine was the slow step of the original process. The described multicomponent catalyst mixture was needed to promote the facile transimination mechanism, described in Scheme 37, which provided more rapid access to the required picolyl imines. The overall system is noteworthy for the relatively low amounts of rhodium complex employed and the excellent yields obtained. Recently, the use of montmorillonite K10 clay as a cocatalyst to aid in imine formation has been reported,[84] as has the use of microwave heating under solvent-free conditions.[85,86]

The final example in Table 7 employed an alkyl aldehyde as the substrate and is notable because an aldol-derived

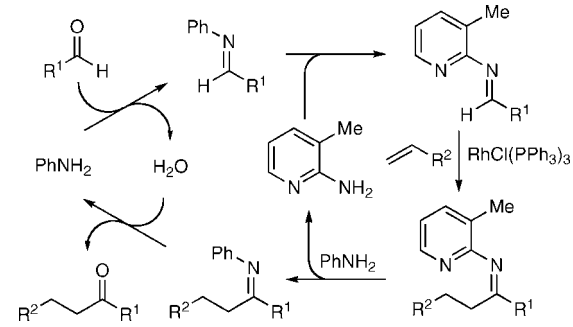
**Table 7.**



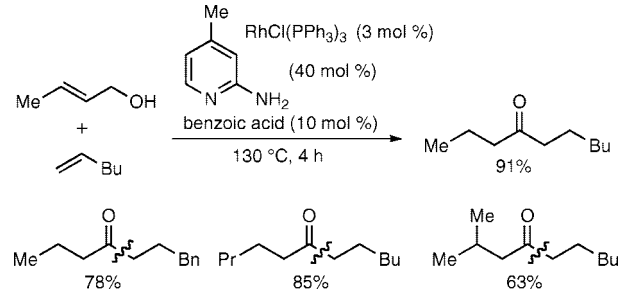

| entry[a] | $R^1$ | $R^2$ | yield (%) |
|---|---|---|---|
| 1 | Ph | Bu | 98 |
| 2 | Ph | Pr | 83 |
| 3 | Ph | Hex | 99 |
| 4 | Ph | *t*Bu | 84 |
| 5 | Ph | $SiMe_3$ | 95 |
| 6 | Ph | $C_6F_5$ | 98 |
| 7 | Ph | $PhOCH_2$ | 95 |
| 8 | 4-MeO-$C_6H_4$ | Bu | 79 |
| 9 | 4-$CF_3$−$OC_6H_4$ | Bu | 71 |
| 10 | 4-$Me_2N$−$C_6H_4$ | Bu | 60 |
| 11 | 4-Ph−$C_6H_4$ | Bu | 95 |
| 12 | $PhCH_2CH_2$ | Bu | 71[b] |

[a] Five equivalents of alkene used. [b] Ten percent of an aldol product also isolated.

**Scheme 37**



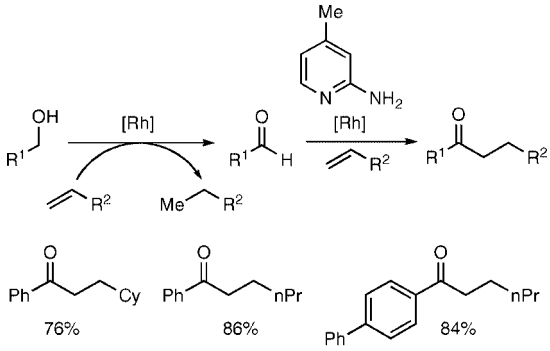

**Scheme 38**




byproduct was also isolated together with the expected product. This byproduct formation is typical when alkyl aldehydes are used as substrates with the conditions shown in Table 7. To address this issue, the Jun group has recently reported a modified procedure, employing cyclohexylamine and *p*-trifluoromethylbenzoic acid in place of aniline and benzoic acid, respectively.[87] These modified conditions allowed the efficient use of alkyl aldehydes by limiting the formation of aldol side products.

In efforts to expand the utility of the process the Jun group has extended their methodology to allow the direct use of allyl alcohols as substrates.[88] In this new system, the same rhodium catalyst was employed and mediates an initial allyl alcohol to aldehyde isomerization, before hydroacylation takes place. As can be seen from Scheme 38, a good selection of substituted allyl alcohols could be combined with a range of alkyl aldehydes. Similar reaction conditions and catalyst

**Scheme 39**




[a] $RhCl_3.H_2O$ (3.3 mol %), $PPh_3$ (16.5 mol %), 2-amino-4-picoline (100 mol %), PhMe, 130 °C.

loadings to those in the basic process (Table 7) were employed, with 2-amino-4-picoline taking the place of 2-amino-3-picoline. A related process employing allylic pyridyl amines as substrates has also been reported.[89]

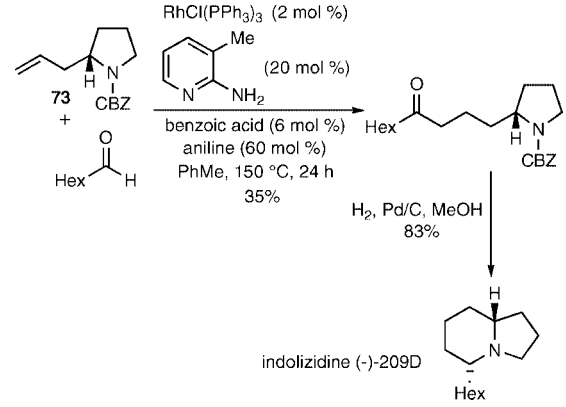
A further simplification of the process was to allow simple alcohols to be employed as the aldehyde precursors (Scheme 39).[90] The rhodium complex first catalyzes the oxidation of the alcohol to the aldehyde, using an equivalent of alkene as the oxidant, before promoting the hydroacylation reaction as described previously. The most efficient catalyst was found to be $RhCl_3 \cdot H_2O$ (3.3 mol %), used in combination with triphenylphosphine and a stoichiometric amount of 2-amino-4-picoline. Slight modification of the system allowed primary amines to be employed as aldehyde equivalents.[91] Methanol could also be employed as a substrate, generating formaldehyde in situ, and then undergoing double hydroacylation.[92]

The Jun group has exploited the excellent metal-directing effect of picolyl imines to develop a range of cascade process involving C−H and C−C bond activation; hydroacylation/*ortho*-alkylation,[93] ring-opening of cycloalkenones,[94] and the conversion of dienes to cycloalkanones[95] are some notable examples.

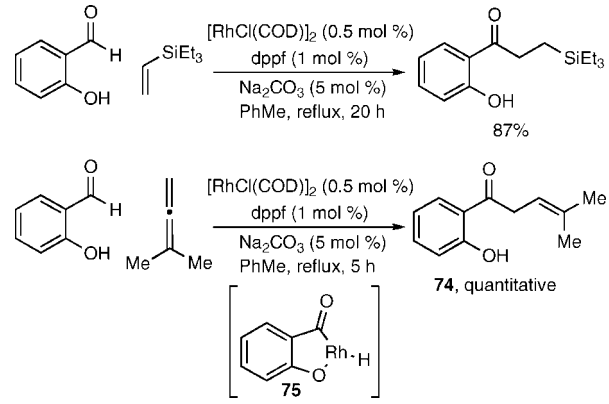
Efforts to aid catalyst recovery have also been reported. For example, polystyrene-supported diphenylphosphine was used in combination with $RhCl_3 \cdot H_2O$ as a tandem alcohol oxidation/hydroacylation catalyst.[96] The catalyst could be recovered and used four times before deactivation. More recently, the Jun group has described the use of a H-bonding solvent system to allow catalyst recycling in primary alcohol hydroacylation systems. A 4,4′-bipyridyl/phenol solvent combination generated a homogeneous system at elevated temperatures; however, upon cooling, two immiscible phases were generated, allowing easy catalyst and product separation. This approach allowed up to eight cycles of catalysis with minimal loss of activity.[97] A similar concept has been used to develop a H-bonding catalyst system;[98,99] the high temperatures needed for reaction disrupt a H-bonding network between 2,6-diamino pyridine and a barbiturate-bound rhodium, allowing efficient hydroacylation reactions. Cooling the reactions to room temperature allows the H-bonds to reform and generates two immiscible phases. Efficient catalyst recycling was again possible.

The Kim group has utilized the Jun methodology in the syntheses of indolizidines (−)-167B and (−)-209D.[100] The Jun conditions were translated directly and applied to the union of enantiomerically pure alkene **73** and heptanal to deliver the corresponding ketone in 35% yield (Scheme 40). Reductive conditions ($H_2$, Pd/C) allowed CBZ cleavage and

**Scheme 40**




**Scheme 41**



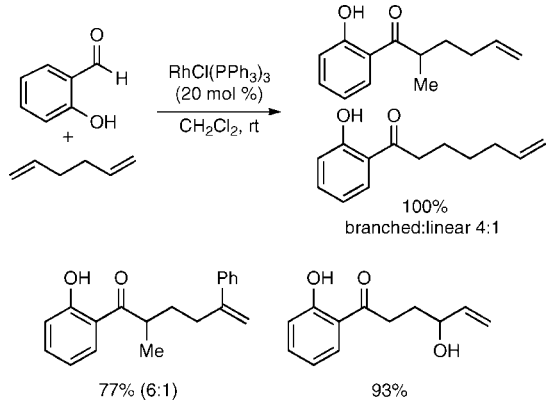

cyclization to generate the natural product. Despite the relatively low yield obtained for the hydroacylation step of the synthesis, no epimerization was reported, and the methodology allowed the use of commercial aldehydes. The Jun methodology has also been applied to the synthesis of $^{18}$F-labeled ketones[101] and to the functionalization of polymers.[102,103]

Several account and review articles documenting the development and application of picolyl imine intermediates in hydroacylation and related reactions are available.[6,104−107]

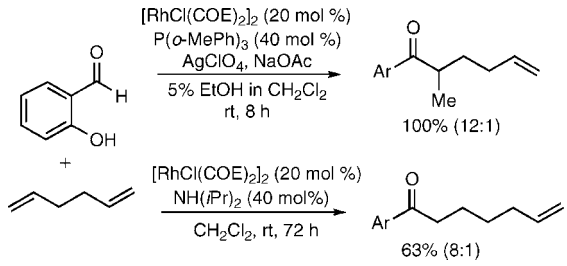
The Miura group has undertaken detailed studies on the use of salicylaldehyde as a chelating substrate for alkyne hydroacylation (see Scheme 71).[108,109] However, reactions of the same aldehyde with the majority of alkenes were poor.[109] The exception was reaction with vinyltriethylsilylane, which, when combined with salicylaldehyde and a catalyst generated from $[RhCl(COD)]_2$ and the ligand 1,1′-bis(diphenylphosphino)ferrocene (dppf), provided the hydroacylation adduct in good yield (Scheme 41). Simple allenes were also shown to be competent substrates, as illustrated by the formation of $\beta,\gamma$-enone **74**. The use of refluxing toluene was needed in order to achieve full conversion for both types of reaction. The authors proposed the intermediacy of a chelate such as **75** to account for the minimal decarbonylation observed.

More recently the Suemune group has investigated the use of salicylaldehydes in combination with diene substrates.[110,111] As can be seen from the examples presented in Scheme 42, it was possible to use very mild conditions to achieve excellent yields for the addition of salicylaldehydes to a variety of 1,4- and 1,5-dienes. The use of Wilkinson's complex (20 mol %) allowed the reactions to be performed at ambient temperature. Employing these conditions allowed

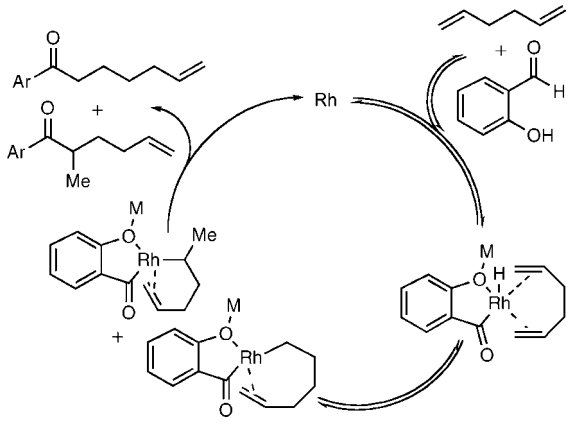
**Scheme 42**




**Scheme 43**



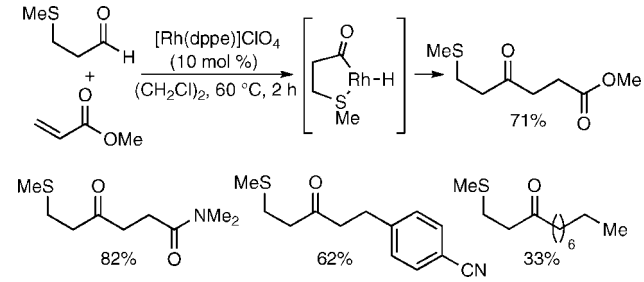

**Scheme 44**



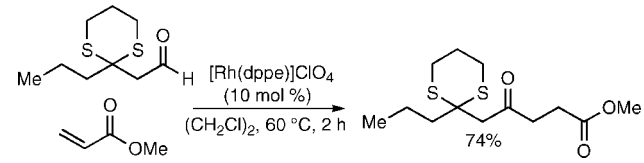

good yields to be realized; however mixtures of linear and branched isomers were obtained. The use of 1,6-dienes produced extremely low yields of adducts. A variety of 2-hydroxy aldehydes could be employed successfully; however, the absence of a free hydroxyl group in this position resulted in no reaction.

Modification of the catalyst allowed the selective production of either regioisomer; the use of $[RhCl(COE)_2]_2$, P(*o*-MePh)$_3$, $AgClO_4$, and NaOAc delivered the linear isomer, while the use of $[RhCl(COE)_2]_2$ in combination with NH(*i*Pr)$_2$ as base delivered the branched isomer (Scheme 43). The authors also undertook labeling studies using 1-deuterated aldehydes and observed considerable scrambling, with deuterium incorporation seen separately in the α-methyl group and $\beta$-methylene position of the products shown in Scheme 43. A proposed mechanism is shown in Scheme 44; double chelation involving two-point interactions of the rhodium with both the aldehyde and the diene and a series of reversible steps leading to an irreversible reductive elimination are proposed to account for the high reactivity and deuterium incorporation seen with this system.

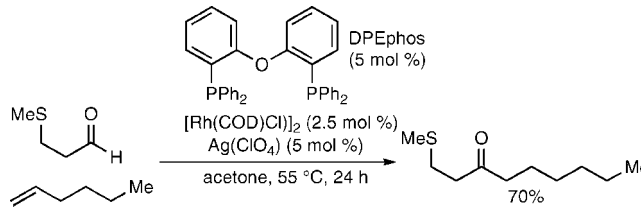
**Scheme 45**




**Scheme 46**




**Scheme 47**

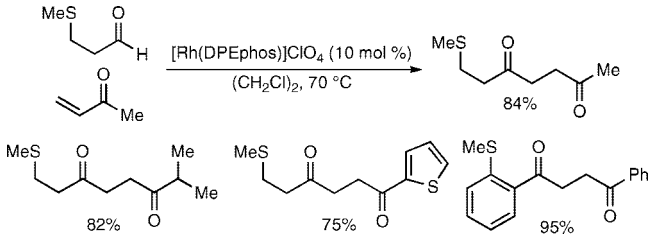



In section 2.2.2, an example of S-chelation to facilitate the preparation of a variety of cyclic ketones was described (Scheme 16). The Willis group has exploited S-chelation to develop intermolecular reactivity. $\beta$-Methylsulfide-substituted propanal could be combined with a range of functionalized electron-poor alkenes to generate hydroacylation adducts in good yields (Scheme 45).[112] The authors proposed the formation of a five-membered S-chelate-stabilized acyl rhodium species to account for the observed reactivity. The use of $[Rh(dppe)]ClO_4$ allowed reactions to be performed at 50 °C. The use of simple electron-neutral alkenes, such as 1-octene, resulted in reduced yields.

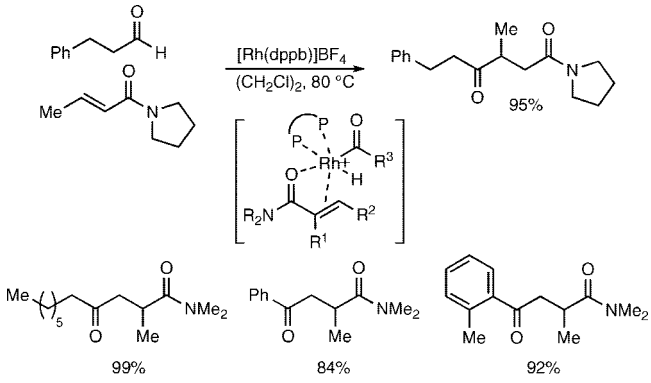
The same group has extended the concept of S-chelate stabilization and introduced $\beta$-thioacetal-substituted aldehydes as effective hydroacylation substrates (Scheme 46).[113,114] The complex $[Rh(dppe)]ClO_4$ was again used as catalyst to promote reaction with electron-poor alkenes. It was demonstrated that the thioacetals present in the hydroacylation adducts could be derivatized by hydrolysis to reveal the corresponding carbonyl or reduced with Raney nickel to deliver the methylene derivatives. Both the sulfide- and thioacetal-substituted aldehydes have also been combined successfully with 1,2- and 1,3-disubstituted allenes to deliver $\beta,\gamma$-enones as products.[115]

Weller and Willis have recently reported an improved catalyst system that allows poorly reactive neutral alkenes to be combined with $\beta$-*S*-aldehydes in good yields (Scheme 47).[116] For example, reaction between $\beta$-MeS-propanal and hexene, employing a catalyst incorporating the ligand DPEphos, delivered the hydroacylation adduct in 70% yield. The authors propose that the flexible, hemilabile nature of the DPEphos ligand allows it to adopt a number of coordination modes and geometries and ultimately provides a longer-lived catalyst, resulting in increased activity. In addition to the greater activity achieved with the DPEphos catalyst system, the ability to generate an active catalyst from the simple

**Scheme 48**




**Scheme 49**

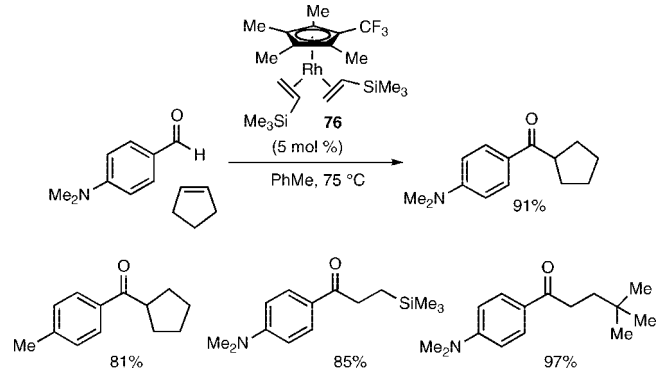



combination of $[Rh(COD)Cl]_2$, DPEphos, and $Ag(ClO_4)$, thus avoiding a hydrogenation step, is also highlighted by the authors as a significant advantage. X-ray crystal structures confirming the proposed S-chelation of the substrate and O-coordination of the ligand were also reported.[117]

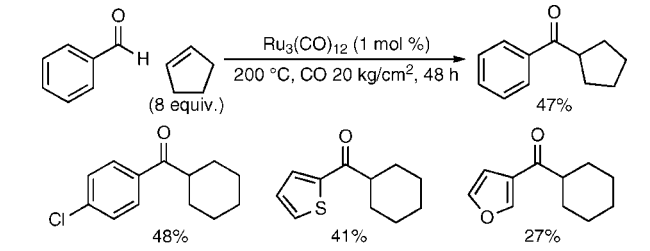
The Willis group has recently shown a divergence of reactivity in hydroacylation reactions employing enones as substrates in combination with $\beta$-*S*-aldehydes, dependent on the choice of catalyst.[118] The same group had previously shown that reactions between simple enones and $\beta$-S-substituted aldehydes using dppe-derived catalysts delivered reductive-aldol products at the expense of hydroacylation.[119] However, the use of a DPEphos-containing catalyst allowed enones to be effectively combined with $\beta$-S-substituted aldehydes to deliver 1,4-dicarbonyl products in good yields; a number of examples are shown in Scheme 48. The observed difference in reactivity of the dppe- and DPEphos-containing catalysts is again attributed to the ability of the DPEphos system to adopt variable coordination modes involving the O-atom.

The majority of the preceding examples have invoked stabilization of the acyl rhodium species by chelation from the aldehyde. The Tanaka group has adopted an alternative form of stabilization of the acyl rhodium species, invoking bidentate binding of the alkene substrate as the key interaction.[120] Using *N*,*N*-dialkyl acrylamides as the alkene components, they were able to achieve effective intermolecular hydroacylation reactions with a range of aldehydes, including alkyl and aryl variants. A number of examples are shown in Scheme 49, along with the proposed stabilized acyl rhodium hydride species. A cationic Rh-bidentate phosphine complex was again employed as the catalyst, although the most effective system was shown to incorporate the 1,4-bis(diphenylphosphino)butane (dppb) ligand, as opposed to the more commonly employed dppe. A single example, demonstrating extension of the method to include methyl acrylate as a substrate was also reported, although in this case it was necessary to employ the acrylate as solvent to obtain a 55% yield of the desired hydroacylation adduct.

**Scheme 50**




**Scheme 51**

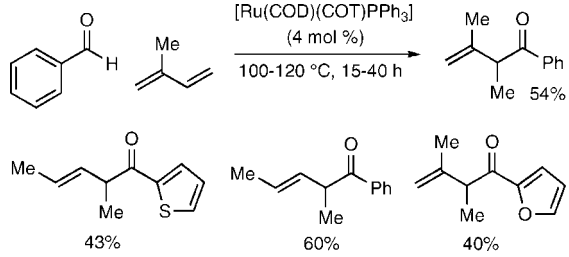



The Brookhart group has developed rhodium(I) bis-olefin complexes as effective alkene hydroacylation catalysts.[121] The same group had earlier established that related Co(I) systems also functioned as hydroacylation catalysts, although the reaction scope was limited to the use of vinylsilanes as the alkene components (see section 3.3). Rhodium complex **76**, featuring an electron-withdrawing $CF_3$ substituent on the Cp-ring, was found to be the most effective catalyst, allowing faster reaction rates than the corresponding penta-methyl variant (Scheme 50). Using complex **76** in toluene, at catalyst loadings of between 5 and 11 mol %, allowed a variety of aromatic aldehydes to be combined with a series of electron-rich alkenes; a selection of examples is shown in Scheme 50. The success of this system is particularly notable because it does not require coordinating groups on either the aldehyde or alkene substrate and also does not need an atmosphere of carbon monoxide to prevent decarbonylation. The group has also performed detailed mechanistic studies in order to establish the catalyst resting state and the turnover-limiting step of the catalytic cycle; these are presented in section 6.

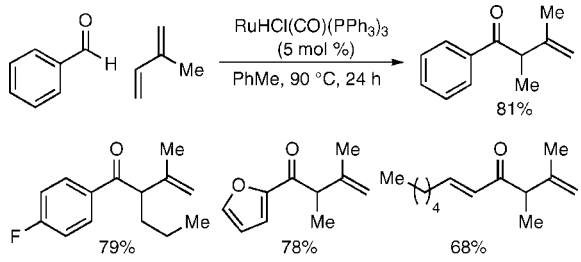
## 3.2. Ruthenium Catalysis

A report from Sneeden and Cognion in 1982 suggested that Ru(0) systems held promise as potential intermolecular hydroacylation catalysts.[122] In this initial report, only low yields of hydroacylation adducts were achieved for reactions between ethylene and propylene with simple alkyl aldehydes; significant quantities of Cannizzaro- and Tishchenko-type side products were also obtained. Despite a report of Ru catalysts effecting related alkyl formate−alkene coupling reactions subsequently appearing,[123−126] it was not until 1987 that a more successful Ru-catalyzed hydroacylation was described.[127,128] Watanabe and Kondo demonstrated that aromatic and heteroaromatic aldehydes could be combined with a range of alkenes using the complex $Ru_3(CO)_{12}$ (Scheme 51). Provided a relatively high CO pressure of 20 kg/cm$^2$ (284 psi) and a temperature of 200 °C were employed, it was possible to use catalyst loadings of only 1 mol %. Both simple acyclic and cyclic alkenes could be

**Scheme 52**




**Scheme 53**



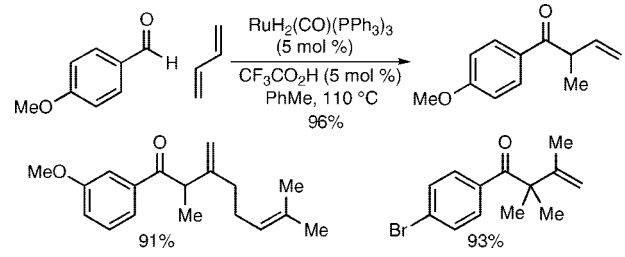

combined with aromatic aldehydes in moderate yields. Aliphatic aldehydes could not be employed and instead led to the formation of transformylation products. For example, the reaction of heptanal with cyclohexene provided cyclohexanecarboxaldehyde as the major product.

Several years later the same group explored the ruthenium-catalyzed hydroacylation of dienes.[129] If the catalysts were modified to [Ru(COD)(COT)PPh$_3$] then the addition of aromatic aldehydes to 1,3-dienes was possible (Scheme 52). In this system, it was not necessary to use a CO atmosphere although the dienes were employed as solvent; a range of aromatic and heteroaromatic aldehydes could be combined with dienes to generate $\beta,\gamma$-unsaturated ketones in moderate yields. The authors proposed that the key intermediates were (acyl)($\eta^3$-allyl)ruthenium complexes.

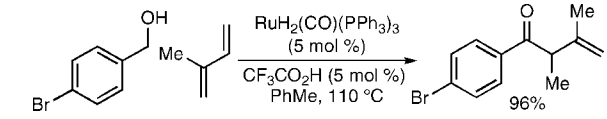
Recently both the Ryu and Krische groups have revisited the ruthenium-catalyzed addition of dienes to aldehydes. The Ryu group found that the ruthenium hydride catalyst, RuHCl(CO)(PPh$_3$)$_3$, used at a 5 mol % loading at 90 °C in toluene, promoted the coupling between a variety of 1,3-dienes and aryl and alkyl aldehydes (Scheme 53).[130] Branched $\beta,\gamma$-unsaturated ketones were obtained as the products in good to excellent yields.

The Krische group employed ruthenium-catalyzed transfer hydrogenation conditions to effect efficient coupling between 1,3-dienes and either aldehydes or alcohols to generate hydroacylation adducts.[131] They utilized the complex RuH$_2$(CO)(PPh$_3$)$_3$ at a 5 mol % catalyst loading, in combination with trifluoroacetic acid, to generate the required ruthenium hydride, which could be used to couple a wide range of substituted dienes with both aryl and alkyl aldehydes in excellent yields (Scheme 54). As with the Ryu chemistry, branched $\beta,\gamma$-unsaturated ketones were obtained as the major products. Using transfer hydrogenation conditions also allowed the Krische group to couple alcohols with 1,3-dienes to generate formal hydroacylation products. For example, Scheme 55 illustrates the coupling of *p*-Br-benzylalcohol with isoprene to deliver the hydroacylation product in 96% yield. Identical reaction conditions were used for both the aldehyde and alcohol coupling reactions. Both the Ryu and Krische reports are notable for the branched products that are obtained; these differ from the more usual linear selective

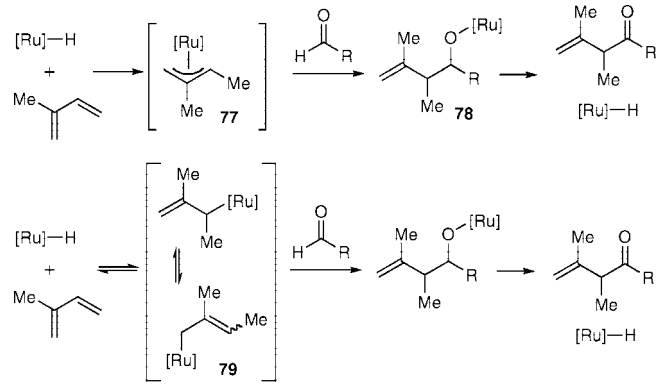
**Scheme 54**




**Scheme 55**




**Scheme 56**




reactions delivered by the majority of alternative intermolecular hydroacylation procedures.

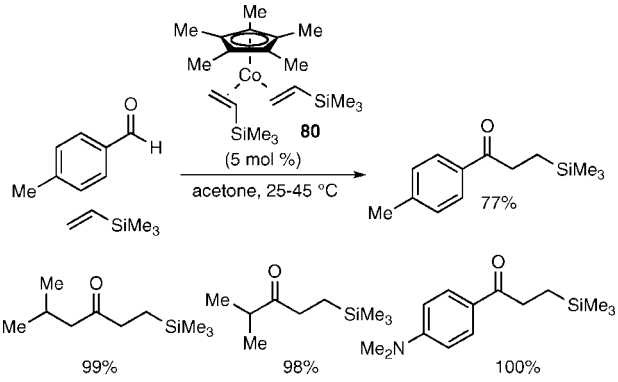
Similar mechanisms have been proposed for both the Ryu and Krische studies, and importantly, these differ from that put forward by Kondo and co-workers; both are briefly presented here, because they differ from conventional hydroacylation systems. The Ryu group proposes initial addition of a ruthenium hydride to the diene to generate a $\pi$-allylruthenium intermediate **77**. This then adds to the aldehyde via a six-membered transition state to deliver a ruthenium alkoxide (**78**), which then suffers $\beta$-hydride elimination to generate the formal hydroacylation products (Scheme 56). The Krische group propose a related mechanism but prefer to invoke initial formation of equilibrating $\sigma$-allyl ruthenium intermediates **79**, which then undergo addition to the relevant aldehydes. The important feature of both these mechanisms is that they do not involve the formation of acyl ruthenium intermediates.

The Krische group has also reported a reductive approach to hydrocylation products, in which acid anhydrides are combined with alkenes under rhodium catalysis.[132]

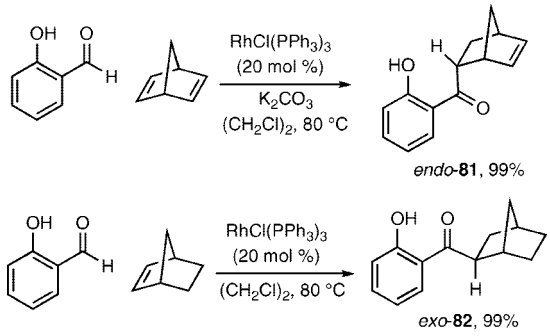
## 3.3. Cobalt Catalysis

The Brookhart group has developed a class of Co(I) complexes as effective hydroacylation catalysts.[32,133] Co(I) bis-olefin complex **80** was found to be an effective catalyst for the addition of aromatic and alkyl aldehydes to vinyltrialkylsilanes (Scheme 57). A broad range of aldehydes could be combined with vinyltrimethylsilane using 5 mol % catalyst at room temperature, and catalyst loadings as low as 0.5 mol % were possible with certain substrates. Vinyl silanes needed to be employed as substrates because they

**Scheme 57**




**Scheme 58**

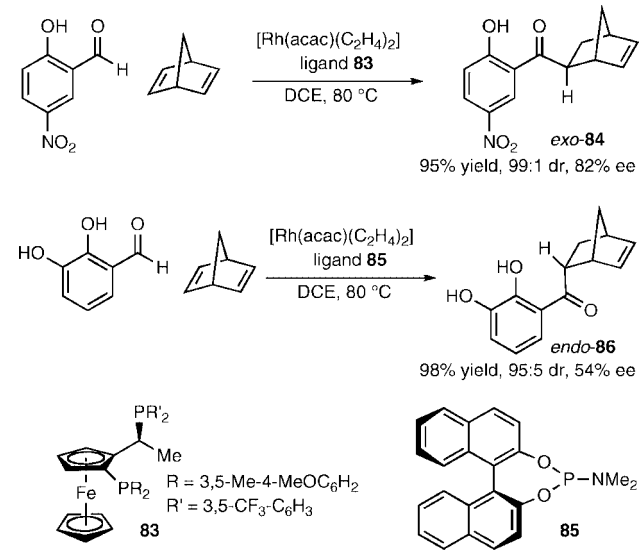



exhibited extremely facile dissociation from the Co center. Although the system is limited to the use of vinyltrialkylsilanes, the range of aldehydes employed, the low temperatures, the relatively low catalyst loadings, and the lack of the requirement of a CO atmosphere make this an attractive hydroacylation system. The same group has addressed some of the limitations with regard to alkene scope by employing related Rh(I) bis-olefin catalysts (see Scheme 50).[121]

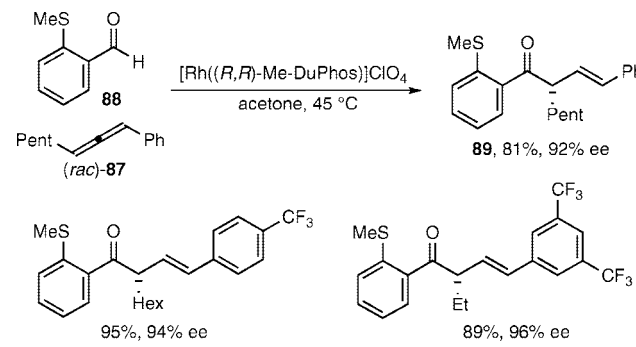
## 3.4. Stereoselective Reactions

Although the number of reports of successful intermolecular hydroacylation reactions is growing, there are still many more examples of successful intramolecular systems. This difference in numbers is also reflected in the development of stereoselective variants of the two processes, with many highly enantioselective hydroacylative cyclizations having been reported and only two examples of enantioselective intermolecular reactions being known. The Bolm group reported the first of these two systems in 2007.[134] They were able to show that salicylaldehyde derivatives could be combined with norbornene and norbornadiene using a number of enantiomerically pure catalysts. The Bolm study builds from an earlier report from Tanaka and Suemune who had demonstrated the $\pi$-facial selective intermolecular hydroacylation of norbornenes using salicylaldehydes.[135] Tanaka and Suemune were able to demonstrate endo-selective addition of salicylaldehyde to norbornadiene using Wilkinson's complex as the catalyst (Scheme 58). When norbornene was employed as the alkene component the exo-product was obtained selectively. The variation in selectivity was attributed to norbornadiene binding to the catalysts in a bidentate fashion, while the selectivity in the norbornene systems result from steric control. The reactions were generally performed at 80 °C; however, it was demonstrated that the addition of $AgClO_4$ to the reactions allowed the norbornene process to be performed at room temperature.

**Scheme 59**




**Scheme 60**

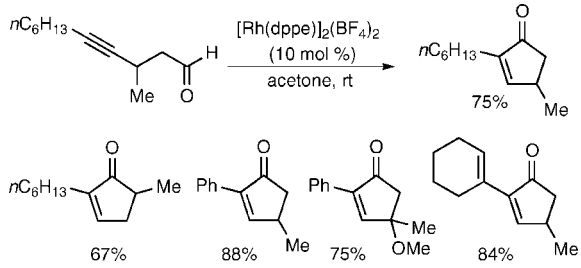



The authors also examined the use of 7-substituted norbornadienes and obtained the same endo-selectivity with the extra substituent position syn to the newly formed ketone carbonyl.

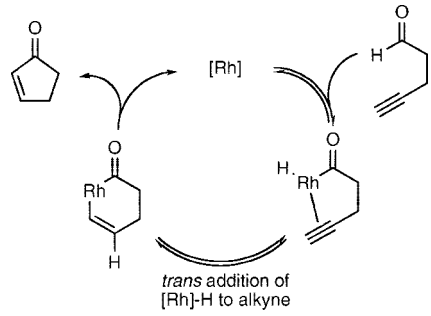
The Bolm group explored a wide range of both mono- and bidentate ligands in efforts to convert reactions similar to those shown in Scheme 58 into enantioselective processes. They found that the use of bidentate phosphine systems lead to the formation of exo-isomers with up to 82% ee. Scheme 59 shows an example in which ferrocene-derived diphosphine ligand **83** is employed to deliver the exo-isomer of ketone **84** in 95% yield with 82% ee. The exo-selectivity is explained by the bidentate diphosphine causing norbornadiene to bind in a monodentate manner. Scheme 59 also illustrates an endo-selective reaction, in which monodentate phosphoramidate ligand **85** is used to deliver the endo-isomer of ketone **86** in 98% yield with 54% ee. The minor exo-isomers obtained in these endo-selective reactions could be isolated with up to 92% ee, although in only poor yields.

The Willis group has recently reported an enantioselective variant of their intermolecular hydroacylation system employing $\beta$-S-substituted aldehydes (see Scheme 45).[136] In order to obtain sufficient reactivity in the alkene components, the authors employed 1,3-disubstitited allenes as substrates (for an earlier example of allene hydroacylation, see Scheme 41). For example, reaction between pentyl,phenyl-disubstituted allene **87** and aromatic $\beta$-*S*-aldehyde **88** employing a Me-DuPhos-derived cationic rhodium catalyst delivered $\beta,\gamma$-enone **89** in 81% yield and 92% ee (Scheme 60); several examples illustrating variation of the allene component are

**Scheme 61**




**Scheme 62**




also shown, confirming the high selectivity of the process. The group found that it was necessary to employ aromatic aldehyde **88** to obtain high enantioselectivity. The authors also established that the process was not a simple kinetic resolution of the starting racemic allene but rather proceeded by a dynamic kinetic asymmetric transformation, involving racemization of the allene during the course of the reaction.

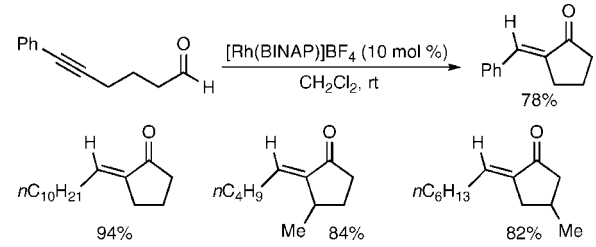
## 4. Intramolecular Alkyne Hydroacylation

### 4.1. Catalytic Achiral Systems

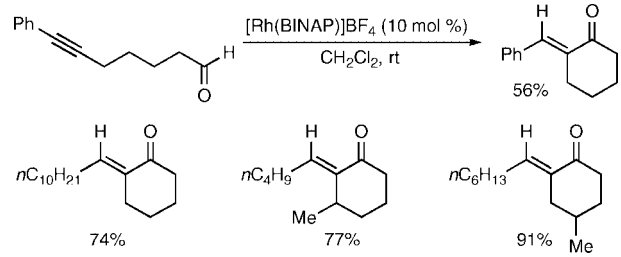
Perhaps due to the desire to generate organic molecules containing stereogenic centers, the study of alkynes in hydroacylation reactions has received significantly less attention than the alkene-based process. An early report from Larock noted that attempts to promote intramolecular hydroacylation of a range of ynals using Wilkinson's complex type catalysts were uniformly unsuccessful.[13] However, the Fu group has more recently reported the cyclization of 4-alkynals using cationic rhodium complexes.[137] Treatment of a range of 4-alkynals with $[Rh(dppe)]_2(BF_4)_2$ in acetone at room temperature provided good yields of the desired cyclopentenones (Scheme 61). An impressive range of substituents could be tolerated, including pendent alkene and alkyne functionalities. The choice of catalyst and solvent was found to be crucial to the success of these reactions. For example, the use of the equivalent BINAP-derived catalyst in combination with methylene chloride as solvent lead to alternative diene products, originating from an isomerization process.[138,139]

In order to achieve the 4-alkynal to cyclopentenone conversion, the hydroacylation mechanism must involve an unusual *trans* addition of the rhodium hydride across the alkyne (Scheme 62). Labeling and cross-over experiments support this hypothesis. A single example of a similar *trans* addition process has also been observed by the Nicolaou group; during their studies on the synthesis of dynemicin, an attempted aldehyde decarbonylation, employing stoichiometric amounts of Wilkinson's complex, resulted in the formation of an alkyne hydroacylation product.[140] The

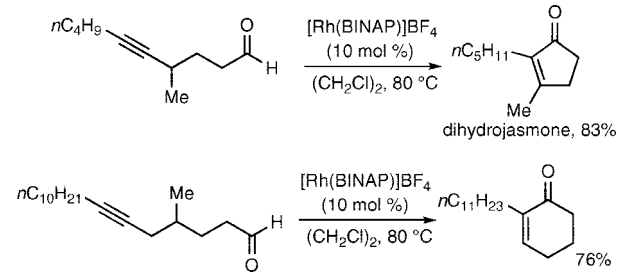
**Scheme 63**




**Scheme 64**




**Scheme 65**

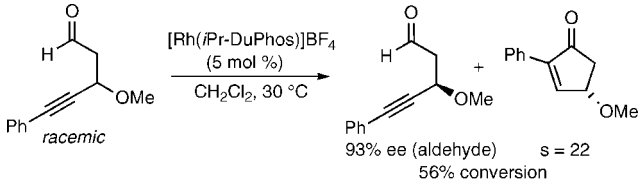



rhodium-catalyzed *trans* addition intramolecular hydroacylation of 4-alkynals has been the subject of a theoretical study.[141]

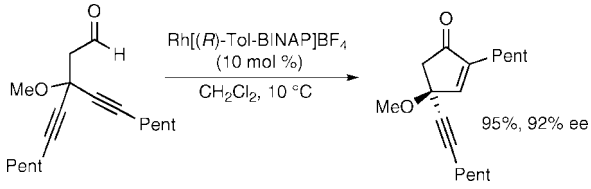
The Tanaka group has studied the cyclization of 5- and 6-alkynals and discovered complementary reactivity to the Fu chemistry described above;[142] they observed *cis* addition to alkynes to generate *exo*-methylene cycloakanones. For example, treatment of a range of 5-alkynals with $[Rh(BINAP)]BF_4$ generated α-alkylidenecyclopentanones in good yields (Scheme 63). The corresponding dppe-derived catalyst was significantly less efficient. The reactions were conducted at room temperature, and substitution at the 3-, 4-, and 6-positions was possible although the use of propargylic ether substituents (4-position) resulted in reduced yields. Reaction of corresponding 6-alkynals under identical conditions generated α-alkylidenecyclohexanone products (Scheme 64). This represented a significant advance because until this report the routine preparation of six-membered ketones using hydroacylation chemistry had relied upon conformational restrictions or chelation assistance (see section 2.2.2). Attempts to extend the methodology to the cyclization of a 7-alkynal, leading to the formation of a seven-membered ring, were unsuccessful and resulted in the return of starting material.

During these studies, the Tanaka group observed that when the 5- and 6-alkynal cyclizations were conducted at elevated temperatures, a double-bond migration occurred to deliver the corresponding cyclopentenones and cyclohexenones. The optimized procedure involved performing the whole process at 80 °C (Scheme 65). Experimentation established the double-bond migration was rhodium-mediated and not a simple thermal isomerization.

**Scheme 66**




**Scheme 67**



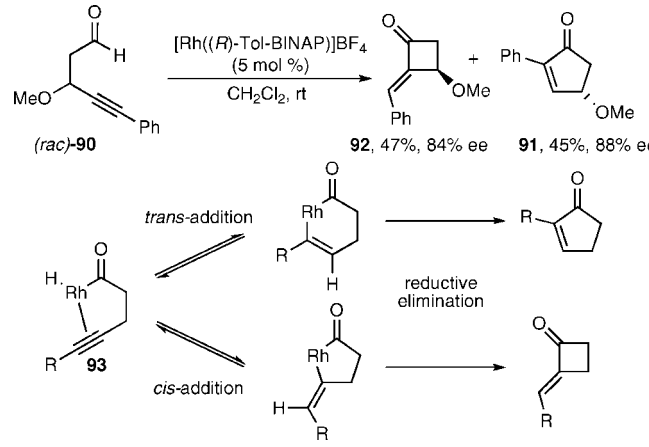

During their study of S-chelation-assisted intramolecular alkene hydroacylation reactions toward medium-ring systems (see Scheme 16), the Bendorf group also reported several examples of intramolecular alkyne hydroacylations.[30] Seven- and eight-membered α-alkylidenes arising from *cis* addition to the alkynes were obtained in moderate to good yields.

## 4.2. Enantioselective Processes

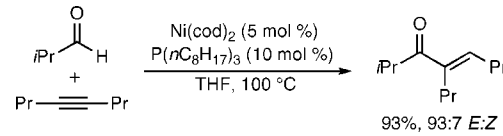
The Fu group has investigated the use of enantiomerically pure Rh catalysts in the cyclization of ynals.[143] Because no $sp^3$ centers are generated in these reactions, the group has investigated kinetic resolution and desymmetrization procedures. Racemic 4-alkynals bearing substituents in the 3-position underwent smooth kinetic resolution, providing enantiomerically enriched cyclopentenones with good selectivities; an example transformation is shown in Scheme 66. A methoxy substituent was employed to allow a two-point substrate−catalyst interaction. Catalysts incorporating the ligand *i*Pr-DuPhos were optimal for substrates incorporating tertiary centers, while those with a quaternary center gave highest selectivity using BINAP-derived catalysts. Selectivity factors (s) of 20−40 could be achieved, allowing either the unreacted starting material or cyclized product to be obtained with high levels of stereoinduction. Achiral substrates bearing a quaternary center were employed in desymmetrization reactions. The use of Tol-BINAP-derived catalysts allowed enantiomerically enriched cyclopentenones to be obtained with high levels of selectivity in good yield; an illustrative example is shown in Scheme 67.

During their investigation into the kinetic resolution chemistry described above, the Fu group discovered a rare example of a catalytic parallel kinetic resolution.[144] Treatment of racemic 4-alkynals such as **90** with a catalyst incorporating Tol-BINAP led to the formation of cyclopentenone **91** together with cyclobutenone **92** (Scheme 68). Both cycloalkanones were obtained with high ee. The two products were proposed to arise from differing modes of addition of rhodium hydride across the alkyne unit of intermediate **93**; *cis* addition leads ultimately to the cyclobutenone, while *trans* addition leads to the cyclopentenone product. The process could tolerate a variety of aryl, hetero aryl, and alkyl groups at the 5-position, while it was necessary to maintain a 3-methoxy group to achieve efficient parallel kinetic resolution.

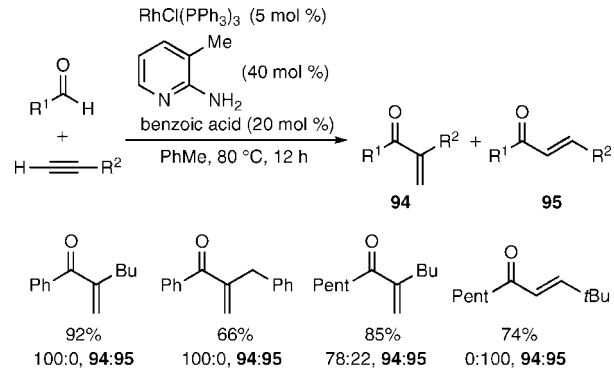
**Scheme 68**




**Scheme 69**




**Scheme 70**



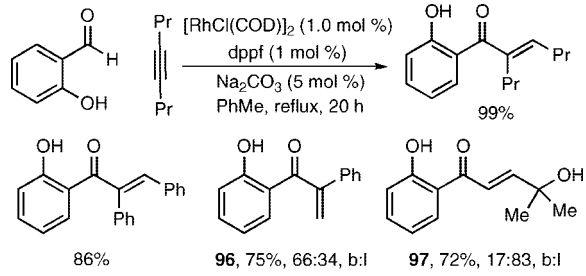

# 5. Intermolecular Alkyne Hydroacylation

## 5.1. Catalytic Achiral Processes

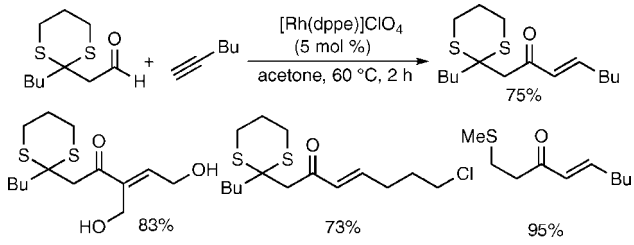
Although not employed in alkene hydroacylation reactions, Ni catalysts have been shown to be effective for intermolecular hydroacylation of alkynes. Tsuda demonstrated that Ni(0) complexes could be used to combine simple aryl and alkyl aldehydes with symmetrical internal alkynes (Scheme 69).[145] The use of *n*-alkyl phosphines as ligands allowed formation of the enone products with high *E*-selectivity. Aryl or bulky alkyl phosphines generated mixtures of enone and dienone products. Unsymmetrical alkynes led to regioisomeric product mixtures. Although no detailed mechanistic studies were undertaken, the authors propose a mechanism involving an acyl nickel hydride intermediate.

Jun has applied his rhodium-based methodology to the intermolecular hydroacylation of alkynes. The catalytic system generated from Wilkinson's complex, 2-amino-3-methylpicoline, and benzoic acid was effective for the combination of aryl and alkyl aldehydes with terminal alkynes (Scheme 70).[146] Interestingly, the major products in the majority of examples studied were the branched α,β-enones **94**. Selective formation of the linear isomers was only possible with the use of alkynes bearing sterically demanding substituents in combination with alkyl aldehydes. Achieving selectivity for formation of the branched enones across a

**Scheme 71**




**Scheme 72**



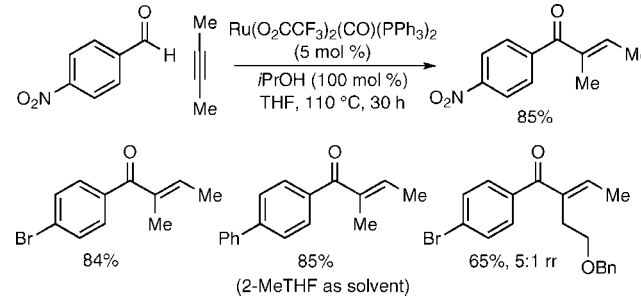

range of substrates is unique among the known intermolecular alkyne hydroacylation systems. Castillón has recently shown that greater quantities of the linear adducts can be obtained in the Jun system by the use of bulkier phosphine ligands.[147] Jun has also applied his Rh/picoline catalyst system to alkyne-cleavage/hydroacylation processes.[148,149]

The O-chelation available from the use of salicylaldehydes has been exploited by Miura in developing an effective alkyne hydroacylation protocol (see Schemes 41 and 42 for the use of a similar system with alkene substrates).[108,109] Reaction of salicylaldehyde with 4-octyne, using a catalyst generated from $[RhCl(COD)]_2$ and dppf with $Na_2CO_3$ as base, delivered the hydroacylation adduct in 99% yield (Scheme 71). When terminal alkynes were used in the process, mixtures of linear and branched isomers were obtained. For example, reaction of salicylaldehyde with 1-phenylacetylene provided the branched isomer **96** as the major product but with significant quantities of the linear isomer also being formed (l/b, 34:66). Greater selectivity for the linear isomer could be achieved if a propargylic O-substituent was introduced; with this approach, ketone **97** was prepared as an 83:17 mixture of linear/branched isomers.

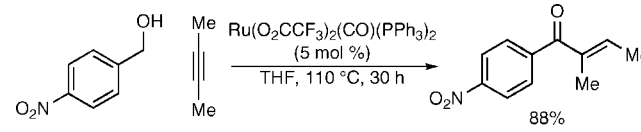
The S-chelating systems exploited by Willis in alkene hydroacylation have also been applied to alkyne hydroacylation reactions (Scheme 72).[112−114] Reactions of *β-S*-aldehydes with terminal alkynes, employing $[Rh(dppe)]ClO_4$ as catalyst, were selective for the formation of the linear hydroacylation adducts with good *E*-selectivity. Internal alkynes could also be employed, although longer reaction times were required. The authors also demonstrated that the process tolerated a variety of functional groups, including free hydroxyls, alkylchlorides and silyl ethers. More recently, the same group has used their modified catalyst system, featuring the ligand DPEphos, in a number of alkyne hydroacylation reactions.[116,117]

The Krische group has recently applied their ruthenium-catalyzed transfer hydrogenation-based chemistry to alkyne hydroacylation (Scheme 73, see Scheme 54 for diene hydroacylation).[150] For example, the combination of *p*-nitrobenzaldehyde and 2-butyne using $Ru(O_2CCF_3)_2(CO)(PPh_3)_2$ as the catalyst in the presence of an equivalent of isopropanol, delivered the expected hydroacylation adduct in 85% yield. Under these conditions, 2-butyne could be

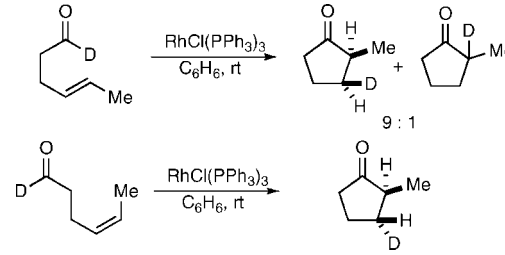
**Scheme 73**




**Scheme 74**




**Scheme 75**



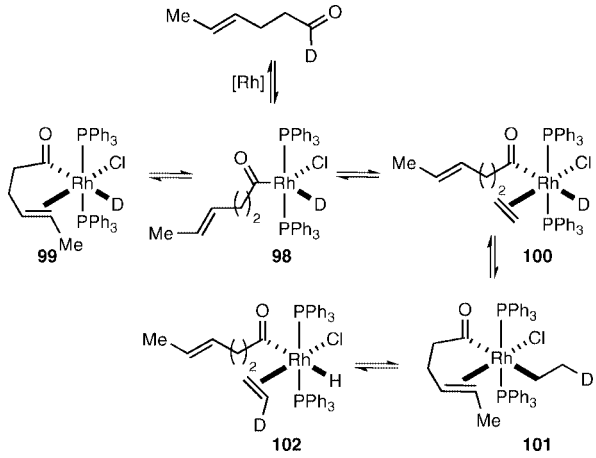

combined with a varied range of aryl aldehydes in good to excellent yields. A nonsymmetrical alkyne could also be coupled in good yield but provided a mixture of regioisomers. In analogy to their diene hydroacylation chemistry (see Scheme 55), the Krische group were also able to obtain hydroacylation adducts from the combination of appropriate alcohols and 2-butyne. Scheme 74 shows an example in which *p*-nitrobenzyl alcohol and 2-butyne are combined to deliver the expected hydroacylation adduct in 88% yield. The only difference in reaction conditions, relative to the aldehyde process, was the removal of isopropanol. Under these modified conditions, a varied range of alcohols were combined with 2-butyne in comparable yields to the aldehyde-based chemistry. This hydroacylation-focused study complements the group's earlier report of the ruthenium-catalyzed reductive coupling of aldehydes or alcohols with alkynes, leading to allylic alcohol products and illustrates how the methodology can be used to access all oxidation levels of substrates and products.[151]

## 6. Mechanistic Studies

Several groups have performed mechanistic investigations alongside their synthetic studies. This section collects these studies together with the aim of providing an overview of the current understanding of the mechanism of metal-catalyzed hydroacylation.

Miller conducted a series of D-labeling studies to explore the mechanism of the intramolecular reactions he had reported (see Scheme 5).[11,12] The reactions presented in Scheme 75 were used to confirm the syn addition of the aldehyde C−D bond across the alkene. The reaction with *trans*-hex-4-enal-1-*d* showed significant deuterium scrambling. Miller had earlier noted the beneficial effects of added ethylene on general reaction efficiency; however, if the

**Scheme 76**



D-labeling reactions were performed in ethylene-saturated solvent then significant loss of deuterium to ethylene was also observed. The presence of deuterium in decarbonylation products was also reported.

A mechanism, proposed by Miller, that accounts for the beneficial effect of added ethylene is shown in Scheme 76. The main tenet of the mechanism is that the added ethylene results in the formation of a coordinatively saturated rhodium species that limits decarbonylation. Following initial oxidative addition to generate acylrhodium complex **98**, intramolecular alkene coordination to generate complex **99** is rapid. The geometry of **99** allows the observed syn addition. Slower intermolecular alkene coordination to generate complex **100** also occurs. From **100**, addition across the ethylene and intramolecular alkene coordination generates complex **101**, in which the ethyl ligand is *trans* to the acyl unit. This geometry disfavors carbon−carbon bond formation in octahedral complexes and accounts for the nonobservance of products originating from ethylene hydroacylation. Reductive elimination (**101** → **102**) leads to deuterium-labeled ethylene.

Bosnich has also reported mechanistic observations to accompany his extensive studies on Rh-catalyzed intramolecular hydrocylation systems. The success of the cationic rhodium catalysts is attributed to the coordinative unsaturation of both the Rh(I) and Rh(III) species. Upon addition of the enal substrates to the cationic complexes, coordination of the aldehyde should form intermediate **103** (Figure 3). Bosnich speculates that the coordinated alkene in **103** assists in the oxidative addition to the aldehyde C−H bond. Further, he suggests that decarbonylation is relatively disfavored compared with hydroacylation, based on the relative stabilities of metallocyclohexanone **104** and Rh−CO species **105**.[18]

Alongside their synthetic studies, the Bosnich group also reported an NMR-focused mechanistic investigation; extensive kinetic and deuterium labeling studies were performed.[18] No intermediates in the catalytic cycle could be isolated or observed spectroscopically, and the authors concluded that at any stage of catalysis the majority of material lies outside the catalytic cycle. Significant substrate inhibition was

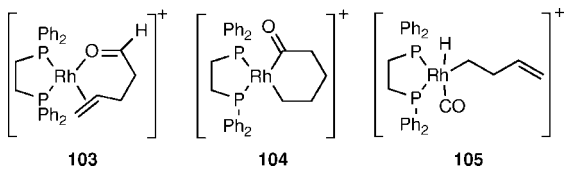


**Figure 3.**

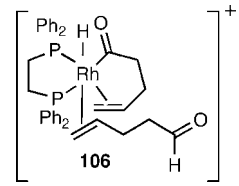


**Figure 4.**

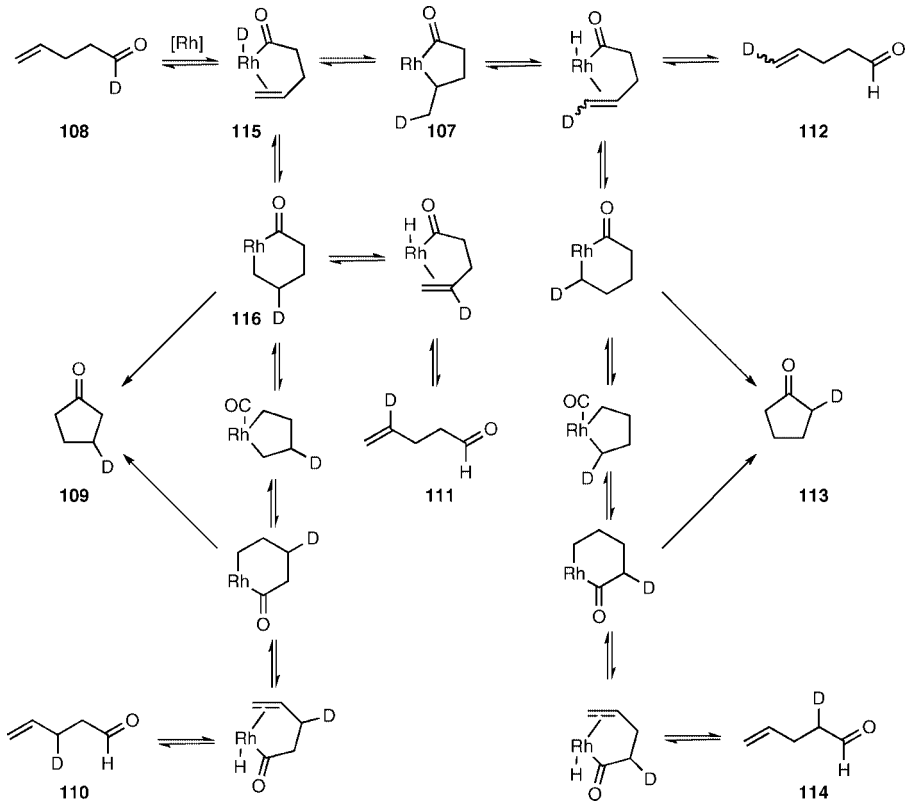
observed and was attributed to the formation of catalytically inactive species. As well as catalyst inhibition, higher substrate to catalyst ratios also resulted in a reduced rate of decarbonylation. Variation in catalyst concentration therefore allowed a balance between turnover rate and turnover number to be achieved. The reduced rate of decarbonylation is accounted for by the formation of intermediates such as **106** (Figure 4) in which a second molecule of substrate serves to stabilize the otherwise coordinatively unsaturated species; this is analogous to Miller's observation of ethylene stabilization of intermediates invoked using the $RhCl(PPh_3)_3$ catalyst system.[10−12] A recent computational study from Morehead and Sargent provides a slightly different view of the beneficial effect of excess substrate.[152] Although their calculations confirm the protective effect of binding a second molecule of substrate, this results not from slowing decarbonylation by blocking a vacant coordination site but by accelerating the productive reductive elimination step. Importantly, this coordination is through oxygen, rather than an alkene, as proposed by Miller and Bosnich.

Studies performed by Bosnich using 1-D-labeled 4-pentenal resulted in considerable scrambling; deuterium was found at positions 2 and 3 of the cyclopentanone product and at all of the carbons of unreacted pentenal. A mechanism in which every step apart from the final reductive eliminations are reversible was proposed; a pathway that accounts for the observed scrambling is shown in Scheme 77. In the mechanism proposed, metallocyclopentane **107** is the key intermediate that allows access to the two main pathways, that is, those leading to organic products **108**−**111** and those leading to products **112**−**114**. Bosnich concludes by suggesting that reductive elimination of the ketone products are the turnover-limiting steps.

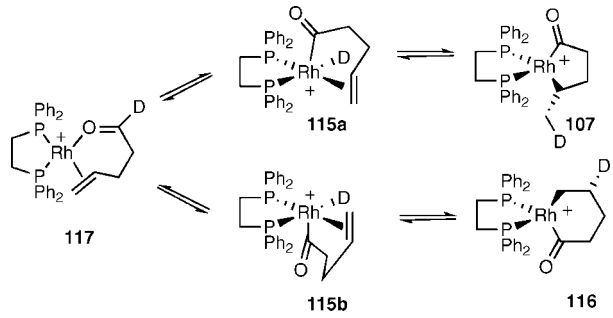
Based on their computational investigation, Morehead and Sargent produced a revised mechanism to account for the deuterium scrambling observed by Bosnich.[152] Key to the computational study was the finding that of the four possible diastereomers of oxidative addition product **115**, only the two isomers featuring apical acyl groups, **115a** and **115b**, were low enough in energy to be considered viable intermediates on the reaction pathway (Scheme 78). This stereochemical divergence at the oxidative addition step (i.e., **108** → **115**) demonstrated that metallocyclopentanone **107** and metallocyclohexanone **116** arise from different stereoisomers of **115**. The consequence of this is that metallocyclopentanone **107** can no longer function as the key intermediate that links the two major pathways. Rather, for metallocyclopentanone **107** and metallocyclohexanone **116** to interconvert they must revert to intermediate **117**. The Morehead and Sargent study supports Bosnich's suggestion of rate-limiting reductive elimination of ketone.

Weller and Willis have characterized a number of intermediates on, or close to, the catalytic cycle of their Rh(I)-catalyzed intermolecular hydroacylation system that employs S-chelating aldehydes and a DPEphos-derived catalyst system.[116,117] X-ray structure determination of several com-

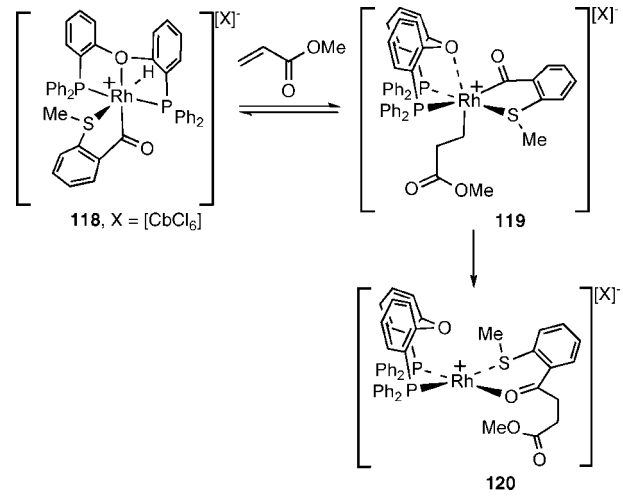
**Scheme 77**




**Scheme 78**



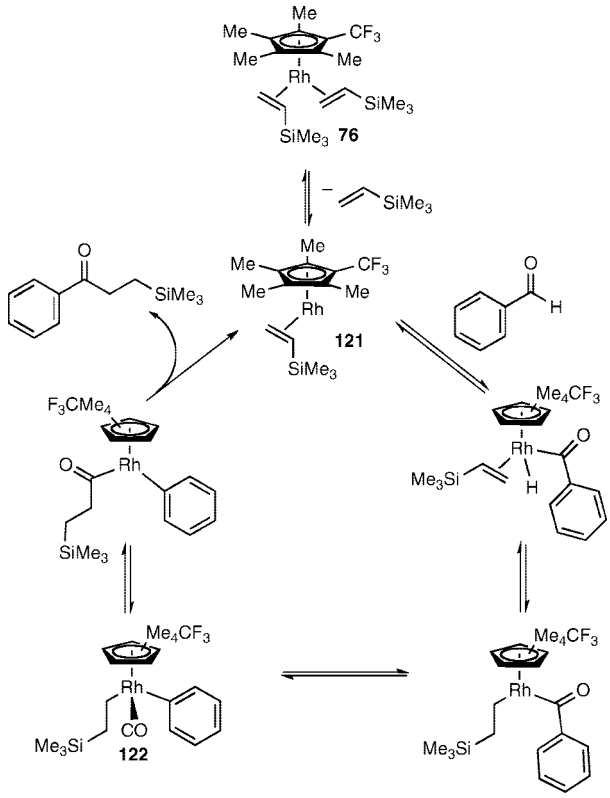

**Scheme 79**




plexes established the formation of the proposed chelated intermediates; for example, a structure of complex **118**, featuring *o*-MeS-benzaldehyde, was solved (Scheme 79). In a series of stoichiometric experiments they also employed NMR and ESI-MS/MS techniques to characterize several intermediates further along the catalytic cycle. For example, both complexes **119** and **120**, resulting from the addition of acyl rhodium hydride **118** to methyl acrylate and then the reductive elimination of the hydroacylation product, respectively, were characterized using these techniques. They were also able to show that addition of further aldehyde to complex **120** regenerated the initial oxidative addition complex **118**. An important conclusion from their mechanistic studies was that catalysts incorporating the ligand DPEphos suffered reductive decarbonylation at a significantly slower rate than the corresponding dppe-containing systems. They attribute this stability to the hemilabile nature of the tethering oxygen atom in the DPEphos ligand allowing stabilization of the key acyl rhodium intermediates, such as **118**.

Brookhart has performed extensive mechanistic investigations using his Rh(I)- and Co(I)-catalyzed intermolecular hydroacylation systems. Kinetic, spectroscopic, and crystallographic methods were used to determine a mechanistic explanation for the observed reactivity. An abbreviated mechanism for the hydroacylation of benzaldehyde with vinyltrimethylsilane using Rh complex **76** as the catalyst is shown in Scheme 80.[121] Intermediates **121**, resulting from the initial loss of alkene, and **122**, resulting from CO deinsertion, were established as the dual resting states of the cycle. It was also established that the final reductive elimination step was the turnover-limiting step of the catalytic cycle and that all the steps before this were reversible. Related schemes have also been proposed for the corresponding Co(I) system.[32,133] Computational studies exploring Rh(I)-catalyzed intermolecular hydroacylation processes employing ethene and ethyne with acetaldehyde[153−155] and formic acid and ethene[156] have been reported.

**Scheme 80**




The prevention of undesired decarbonylation pathways has been, and remains, a significant challenge in alkene and alkyne hydroacylation chemistry. However, both the Bosnich and Brookhart studies show that carbonyl deinsertion is reversible in certain hydroacylation systems and that it is *reductive decarbonylation* that leads to ultimate catalyst death.[18,121] The difficulty in preventing reductive decarbonylation arises from the requirements needed for it to take place, namely, deinsertion of the CO in an acyl hydride to generate an alkyl or aryl rhodium hydride, followed by reductive elimination. Both of these processes, together with product-forming reductive elimination and substrate binding, require coordinative unsaturation at the metal center; the challenge is to engineer product formation over reductive decarbonylation. Chelation control to temporarily block vacant coordination sites has been shown to be successful in both intra- and intermolecular systems. For example, early reports from Miller invoked intermediates such as **123** in which the pendent alkene on an intramolecular substrate is used as the coordinating group (Figure 5).[10−12] Stabilized intermediates featuring N-, O-, and S-chelation have all been proposed (**124**−**127**).[107,109,111,114] One argument for the control achieved in these systems is that decarbonylation would require the formation of strained four-membered intermediates. Stabilization can also be achieved by the temporary blocking of vacant sites with excess substrate, as shown in intermediates **128** and **129**, and more recently by the use of a hemilabile ligand, as in intermediate **130**.[116,117] Similar effects can also be achieved with coordinating solvent of atmospheres of ethylene.[60] An efficient intermolecular hydroacylation system has recently been developed where stabilization is achieved by the use of a chelating *alkene* substrate[120] to generate intermediates such as **131**. Taken together with the recent computational studies that suggest substrate binding can actually lower the barrier to productive reductive elimination,[152] these latter studies are encouraging for the development of a purely ligand stabilized system.

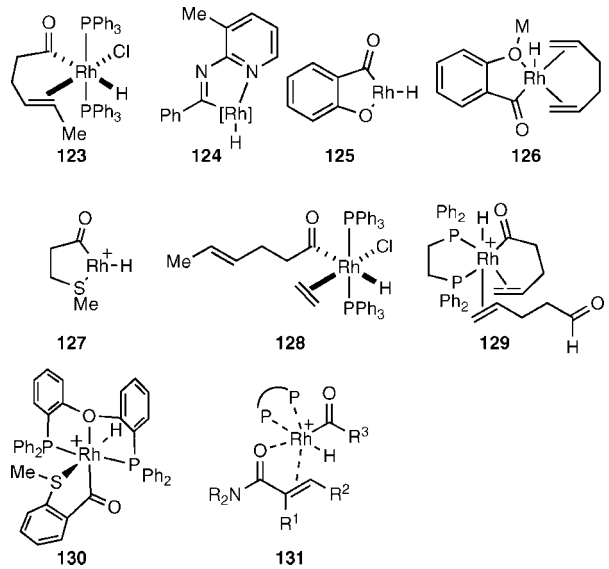



**Figure 5.**

## 7. Outlook

Since Sakai's initial report in 1972, alkene and alkyne hydroacylation has developed to be a useful synthetic tool. Low catalyst loadings, mild reaction conditions, and highly enantioselective processes have been developed for certain substrate classes. However, limitations still remain to the transformations that can be achieved; intramolecular reactions to generate rings other than five-membered systems are not trivial, and the development of an intermolecular process with wide substrate scope has still not been achieved. The development of regio- and enantio-control in intermolecular reactions is also in its infancy. Although these limitations exist, the wealth of information already amassed, together with the great potential of the process, bodes well for the development of truly general hydroacylation methods.

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