Title

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TRANSITION-METAL-CATALYZED HYDROACYLATION

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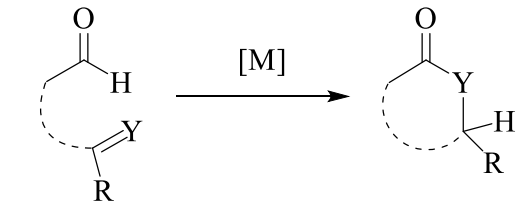
INTRODUCTION

Transition-metal catalysis has revolutionized the way natural products and medicinal targets are made. For example, asymmetric hydrogenation, olefin metathesis, and cross-coupling have evolved into indispensable tools for drug discovery. As a complement to these well-established strategies, the metal-catalyzed activation of C─H bonds is an increasingly valuable and attractive approach. In metal-catalyzed hydroacylation, an aldehyde C─H bond is oxidized to generate either a C─C bond or C─O bond, depending on the coupling partner used (e.g., alkene, alkyne, or carbonyl compound). This strategy represents an attractive, atom-economical approach for building both ketones and esters from aldehydes (Scheme 1).

(1)



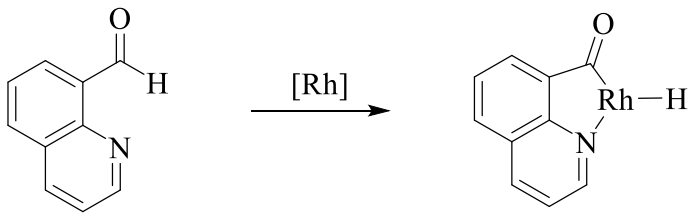
Y = CH_2 or O

Scheme 1. A general hydroacylation reaction.

To date, hydroacylation is most well-established for the preparation of five-membered rings, typically by rhodium catalysis. As the tether between the aldehyde and the unsaturated coupling partner becomes longer, decarbonylation becomes favored over hydroacylation. Similarly, the rate of decarbonylation is usually greater than the rate of hydroacylation in intermolecular reactions. The

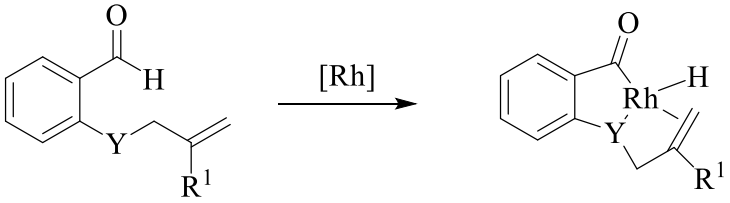
desired transformation is more favorable, however, when coodinating or directing groups are present on the substrate (Schemes 2 and 3). Lewis-basic coordinating groups, including sulfur,{Willis, 2004 #426}{Willis, 2005 #427}{González-Rodríguez, 2010 #260}{Pawley, 2010 #258}{González-Rodríguez, 2011 #256}{González-Rodríguez, 2011 #257}{Lenden, 2011 #254}{Chaplin, 2012 #253}{Coulter, 2009 #24}{Coulter, 2010 #16} oxygen, {Coulter, 2009 #24}{Coulter, 2010 #16}{Tanaka, 2003 #424}{Imai, 2004 #425}{Tanaka, 2005 #446}{Stemmler, 2007 #445}{Inui, 2009 #269}{Shen, 2008 #37}{Shen, 2009 #27}{Phan, 2010 #17}{Murphy, 2011 #5}{Murphy, 2012 #4}{von Delius, 2012 #2}{Kokubo, 1997 #422}{Kokubo, 1999 #423} and phosphorus{Murphy, 2011 #5}{Murphy, 2012 #4}{Lee, 1995 #385} were designed to saturate the coordination sphere about the metal center during key steps of the catalytic cycle (Figure 1).

(2)



Scheme 2

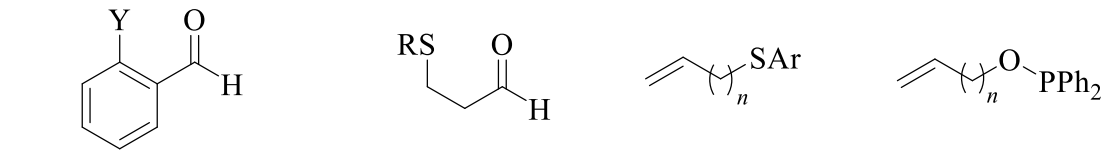
(3)



Y = O, S, NR^2

Scheme 3

(4)



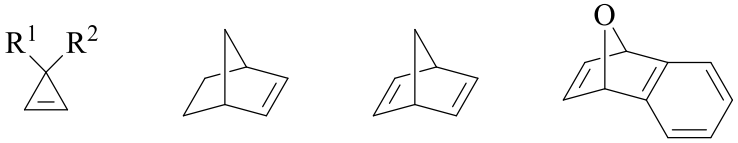
Y = OH, SMe, N(alkyl)$_2$ R = Me, Et *n* = 1,2 *n* = 1,2

Figure 1. Select substrates containing directing groups.

In addition to directing groups, strained{Kokubo, 1999 #423} or electronically activated substrates{Randell-Sly, 2009 #429} have also been used to achieve productive intermolecular reactivity Figure 2).

(5)

Strained olefins



Electronically-activated olefins

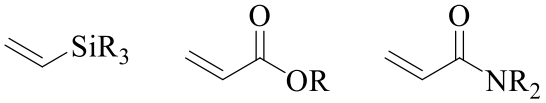
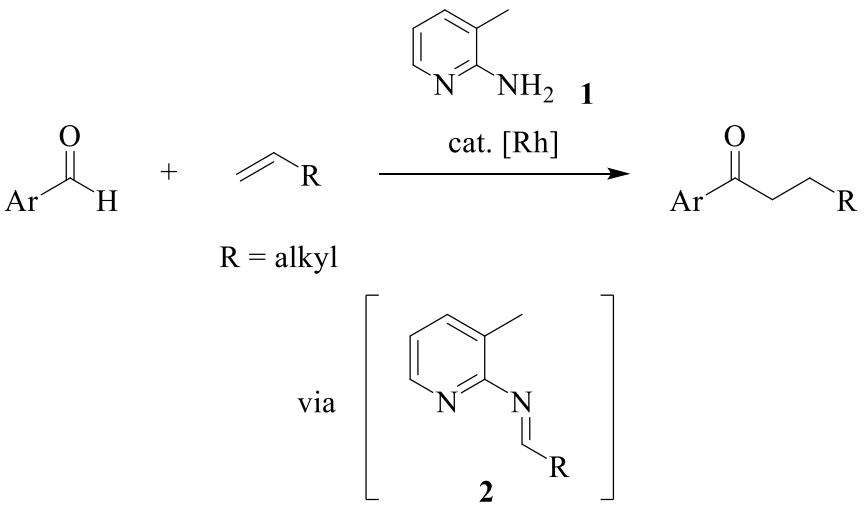


Figure 2. Strained and electronically-activated olefins that promote intermolecular hydroacylation.

Directing groups provide a basis for examining reactivity and selectivity, but limit the types of product structures possible. By using a co-catalyst such as 2-amino-3-picoline **(1)**, hydroacylation proceeds without the need for Lewis-basic functional groups in the substrates (Scheme 4). This strategy works by generating aldimine **2**, which binds the metal catalyst. Although high temperatures

(130−150˚) are typically required, this approach has been successful for the hydroacylation of unactivated alkenes such as 1-octene with unfunctionalized, non-chelating aldehydes.

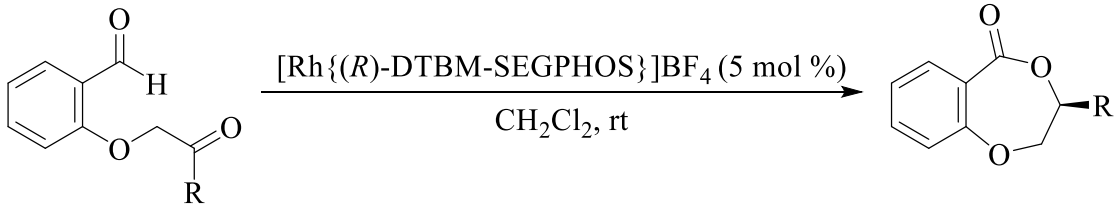
(6)



Scheme 4

In contrast to the large number of successful alkene and alkyne hydroacylations, transition-metal-catalyzed ketone hydroacylations are rare, with a single example reported in 1990{Bergens, 1990 #349} and the first enantioselective cases reported in 2008 (Scheme 5).{Shen, 2008 #37} Tethering the two reactive components is often necessary to achieve the desired transformation. Because of the higher reactivity of aldehydes over ketones, aldehyde dimerization is a competitive process.{Seki, 2006 #755},{Törmäkangas, 2001 #756}

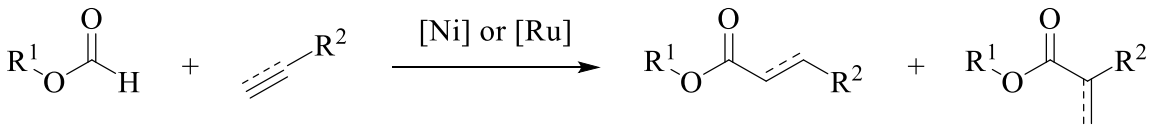
(7)



Scheme 5

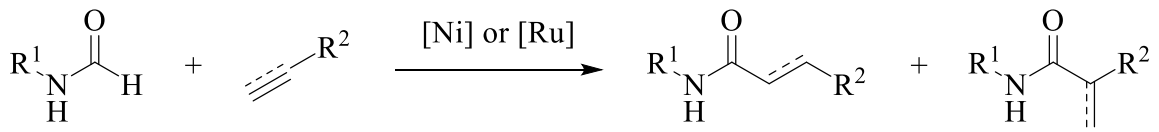
Although the majority of hydroacylation methods use rhodium catalysis, there have been recent reports using ruthenium{Kondo, 1987 #352}{Shibahara, 2008 #442}{Patman, 2009 #474}{Williams, 2009 #359}{Leung, 2012 #263}{Murphy, 2013 #1} and the more abundant and inexpensive cobalt{Vinogradov, 1985 #351}{Vinogradov, 1988 #223}{Lenges, 1997 #238}{Lenges, 1998 #444} {Chen, 2014 #508} and nickel{Tsuda, 1990 #469}{Ogoshi, 2008 #491}{Ogoshi, 2010 #244}{Hoshimoto, 2011 #243}{Hoshimoto, 2012 #489} complexes to achieve this transformation. These metals proceed through alternative mechanisms distinct from rhodium, often times allowing the system to bypass the decarbonylation pathway. Moreover, unique transformations such as hydroesterification{Kondo, 1989 #438}{Yang, 1998 #495}{Ko, 2002 #492}{Konishi, 2012 #488}{Armanino, 2013 #493} and hydrocarbamoylation{Nakao, 2009 #496}{Miyazaki, 2012 #265}{Armanino, 2013 #494}{Li, 2014 #497} (Schemes 6 and 7) using formate and *N*-formamide C─H bonds, respectively, are enabled with these different metal catalysts.

(8)



Scheme 6

(9)



Scheme 7

This chapter provides a comprehensive survey of intra- and intermolecular alkene, alkyne, and carbonyl hydroacylations, including hydroesterifications and hydrocarbamoylations, using transition-metal-catalysis. The use of directing groups to achieve reactivity and selectivity will be emphasized, and strategies that have been implemented to minimize directing groups will be discussed. The literature through 2014 is covered. Four reviews exist that discuss the development of alkene and alkyne hydroacylation{Jun, 1999 #418}{Willis, 2009 #46}{Jun, 2007 #267}{Willis, 2014 #533} as well as a short minireview on directing-group-free methods.{Leung, 2012 #263} Although carbonyl hydroacylation has not been thoroughly reviewed, some aspects of rhodium-catalyzed ketone hydroacylation have appeared in recent reviews on modern esterification chemistry.{Coulter, 2012 #757}{Tsakos, 2015 #752}{Yang, 2015 #753}{Liu, 2015 #754} To date, hydroesterification and hydrocarbamoylation reactions have not been reviewed.

MECHANISM AND STEREOCHEMISTRY

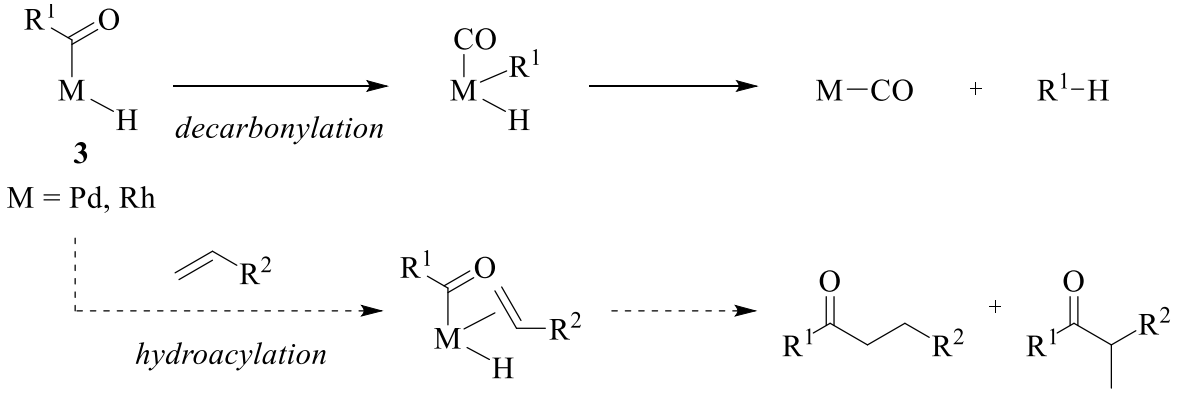
Alkene Hydroacylation

Rhodium(I) Catalysis.

Hydroacylation originated from Tsuji's early examination of aldehyde decarbonylation in 1965.{Tsuji, 1965 #345}{Tsuji, 1965 #483} The mechanism was postulated to involve the intermediacy of an acylmetal hydride **3**, which could then be intercepted with a suitable acceptor (Scheme 8). This hypothesis was validated in 1977 when Sakai and coworkers discovered that a series of 4-pentenals **4**

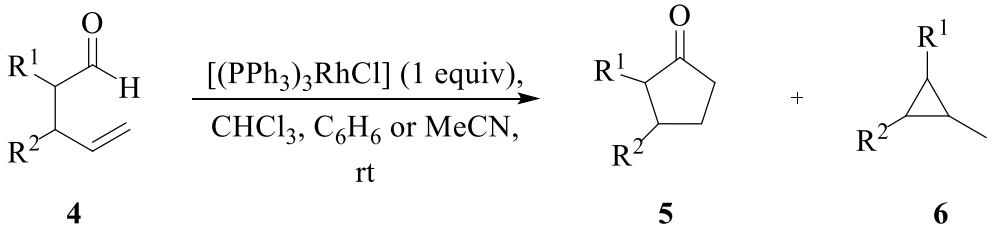
could be cyclized using stoichiometric amounts of Wilkinson's complex {[$(PPh_3)_3RhCl$]} to afford cyclopentanone products **5** en route to the synthesis of prostaglandin derivatives (Scheme 9).{Sakai, 1972 #216} Under these reaction conditions, a significant amount of decarbonylation also occurs to give cyclopropanes **6.** To date, decarbonylation remains a primary impediment to hydroacylation, and recent efforts have focused on developing methods to suppress this undesired pathway.

(10)



Scheme 8

(11)

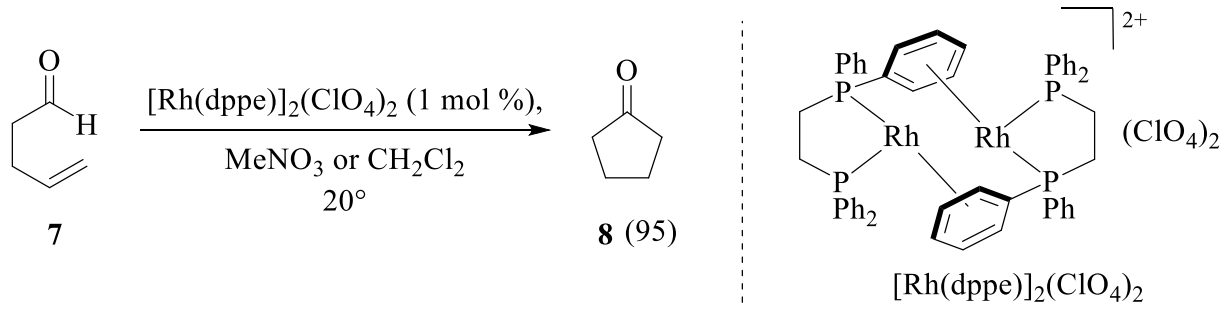


		Yield (%)	
R^1	R^2	**4**	**5**
n-$C_6H_{12}CO_2Me$	*n*-C_8H_{15}	30	30
n-Bu	*n*-Pr	29	35
n-$C_6H_{12}CO_2Me$	H	26	23

Scheme 9

Bosnich and coworkers developed cationic rhodium(I) complexes {*i.e.*, [Rh(diphosphine)]$^{+}$} as highly reactive catalysts for hydroacylation.{Fairlie, 1988 #224}{Fairlie, 1988 #225} In the presence of 1 mol % of [Rh(dppe)]BF_4, 4-pentenal (**7**) is transformed into cyclopentanone (**8**) in 95% yield (Scheme 10). In these cases, catalytic turnover is achieved and no decarbonylation is observed. These cationic rhodium(I) catalysts have had considerable impact on modern hydroacylation methods.

(12)



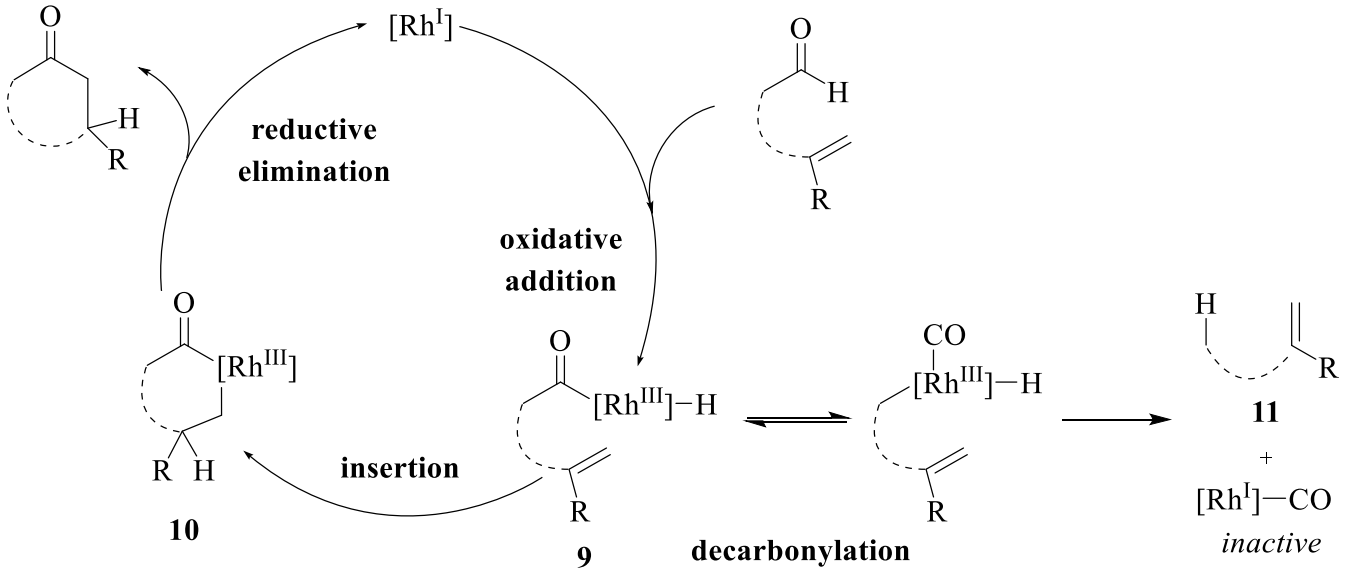
7 **8** (95) [Rh(dppe)]$_2$(ClO$_4$)$_2$

Scheme 10

The general mechanism for rhodium(I) catalyzed hydroacylation involves oxidative addition of the aldehydic C─H bond into rhodium(1) to generate acylrhodium hydride **9** (Scheme 11). Insertion of the C=C bond into the Rh─H bond produces Rh(III)-intermediate **10**, which subsequently undergoes reductive elimination to give the ester or ketone product, while regenerating the rhodium(I) catalyst. Intermediate **9**, however, can undergo reductive decarbonylation to give a defunctionalized product **11** and a Rh-carbonyl species that is generally inactive toward hydroacylation. This mechanism is often referred to as a "black box" because of the difficulties in detecting the proposed intermediates in the catalytic cycle.{Fairlie, 1988 #225} Attempts to identify reaction intermediates involved monitoring the reaction progress by low-temperature ^{1}H and ^{13}C NMR spectroscopy. At −30˚ and using up to 1:1 catalyst/substrate mixtures in the cyclization of 4-pentenal (Scheme 10), no catalysis is observed. At 0˚, product formation is observed, but with no evidence of putative reaction intermediates. As a

consequence, mechanistic information is often probed using a variety of deuterium labeling and kinetics experiments as well as density functional theory (DFT) calculations. Detailed mechanistic studies have been reported for this process, providing insights to resting states, catalyst decomposition, selectivity, and the turnover-limiting step.{Fairlie, 1988 #225}{Hyatt, 2007 #476} {Roy, 2007 #434}{Coulter, 2010 #16}{von Delius, 2012 #2} Although catalytically active

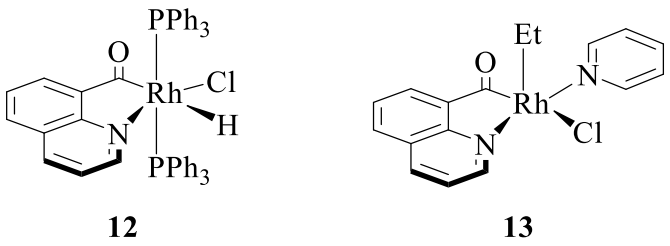
(13)



Scheme 11

intermediates have not been directly observed in these reactions, acylrhodium hydride **12** and acylrhodium alkyl complex **13** have been successfully prepared stoichiometrically when a suitably positioned nitrogen atom is incorporated to stabilize the rhodium species (Figure 3).{Suggs, 1978 #382}{Suggs, 1985 #383} Complex **13** undergoes reductive elimination upon addition of Ph_3P to generate the ketone product.

(14)

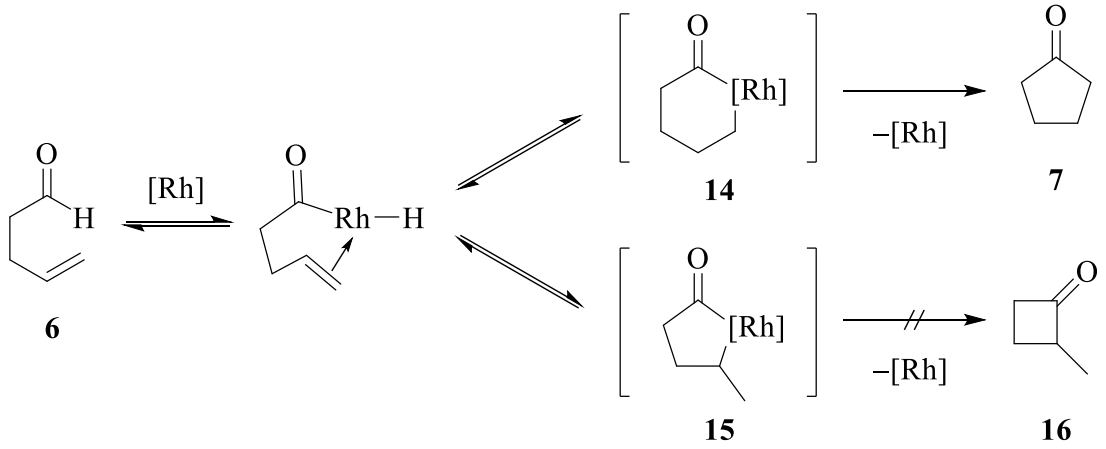


12 **13**

Figure 3. Stable acylrhodium hydride and alkyl complexes prepared via stoichiometric synthesis.

Regioselectivity. *Intramolecular Hydroacylation.* Although intramolecular hydroacylation has traditionally been limited to the formation of 5-membered ring products, current advances in catalyst development, ligand design and availability, as well as substrate engineering, have allowed access to larger rings such as 7 and 8-membered ones that are otherwise difficult to prepare.{Illuminati, 1981 #747} This transformation results in either Markovnikov or anti-Markovnikov addition to the alkene, depending on the substrate and catalyst, and can often be predicted by examining the possible rhodacycle intermediates or products (Scheme 12). In the case of 4-pentenal (**6**) and related derivatives,

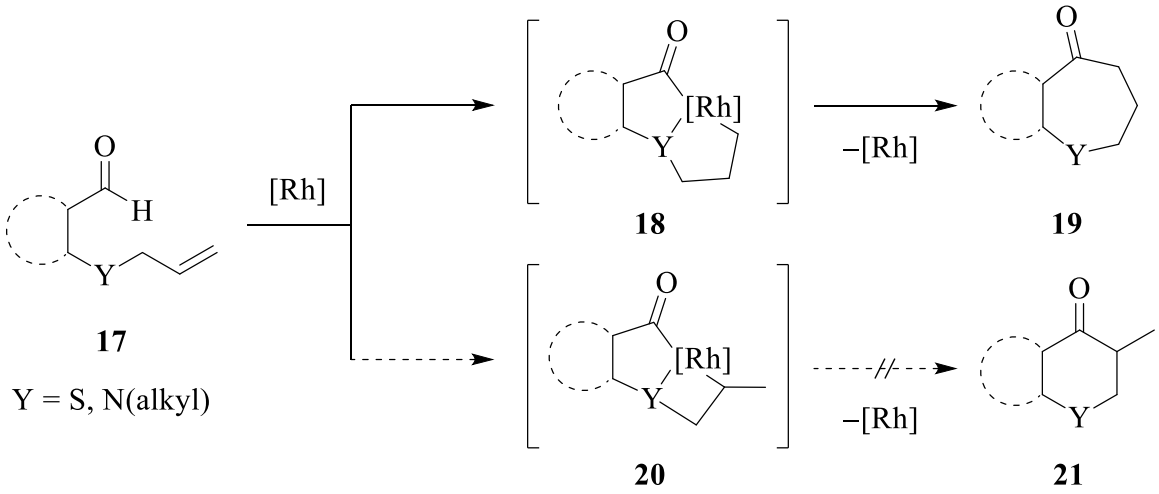
(15)



Scheme 12

rhodacycles **14** and **15** are formed reversibly following oxidative addition and insertion.{Fairlie, 1988 #225}. Turnover-limiting reductive elimination from the 6-membered rhodacycle **14** occurs exclusively to give cyclopentanone **7**. Cyclobutanone **16** does not form, and this may be attributed to substantial ring strain in the transition state of reductive elimination. With the exception of a sulfur-directed intramolecular hydroacylation{Coulter, 2009 #24} (Scheme 14) and a [Rh((*R*)-SIPHOS-PE)]-catalyzed intermolecular hydroacylation,{von Delius, 2012 #2} carbon─carbon bond reductive elimination is generally found to be turnover-limiting.{Campbell, 1980 #220}{Fairlie, 1988 #225}{Barnhart, 1995 #357}{Lenges, 1998 #444}{Roy, 2007 #434}{Hyatt, 2007 #476}

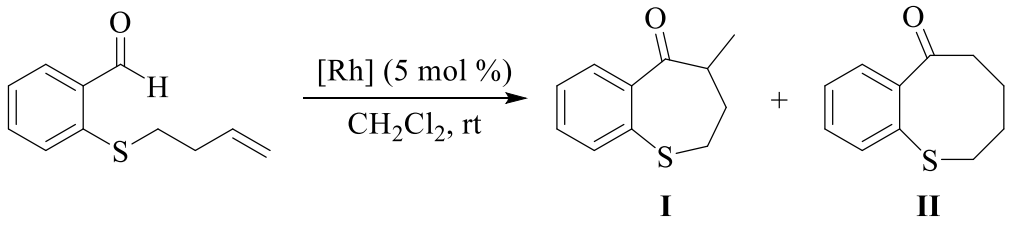
Examples of generating larger cyclic ketones via Rh(I)-catalyzed hydroacylation are limited, {Gable, 1991 #234} with only one report of cyclohexanone synthesis,{Beletskiy, 2012 #482} likely owing to the poor stability of the larger rhodacycle intermediates. To synthesize these larger ring products, Lewis-basic directing groups are incorporated to help stabilize the transient metallacycles and suppress decarbonylation (Scheme 13).{Bendorf, 2002 #237}{Coulter, 2009 #24}{Bendorf, 2012 #353}{Beletskiy, 2012 #482}{Arnold, 2014 #498} Alkenals **17** undergo hydroacylation to give cycloheptanones **19** in >20:1 diastereoselectivity through [3.3.0]-rhodabicyclic intermediates **18**. Cyclohexanones **21**, which would likely arise from energetically unfavorable [3.2.0]-rhodabicyclic intermediates **20**, are not formed in any appreciable amount. When the heteroatom is substituted for a methylene unit (Y = CH_2), only the decarbonylation product is formed, and no heterocycle is detected.{Bendorf, 2002 #237} Successful cyclizations using ether and sulfoxide directing groups



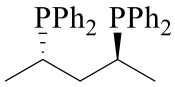
Scheme 13

have also been reported.{Coulter, 2009 #24} The position of the directing heteroatom dictates the regiochemical outcome of the reaction, in which 5-membered rhodacycles are preferred over the 4- or 6-membered analogues. Five-membered metallacycles are reactive, and labile intermediates and their significance and applications have been reviewed.{Omae, 2007 #519} However, if the position of the directing functional group does not allow the intermediacy of a 5-membered rhodacycle, then the reaction can proceed through a 6-membered rhodacycle. Although this trend holds true for all reports that use achiral catalysts, the regioselectivity can be reversed through the use of chiral catalysts (Scheme 14).{Bendorf, 2002 #237}{Coulter, 2009 #24}

(17)



I **II**



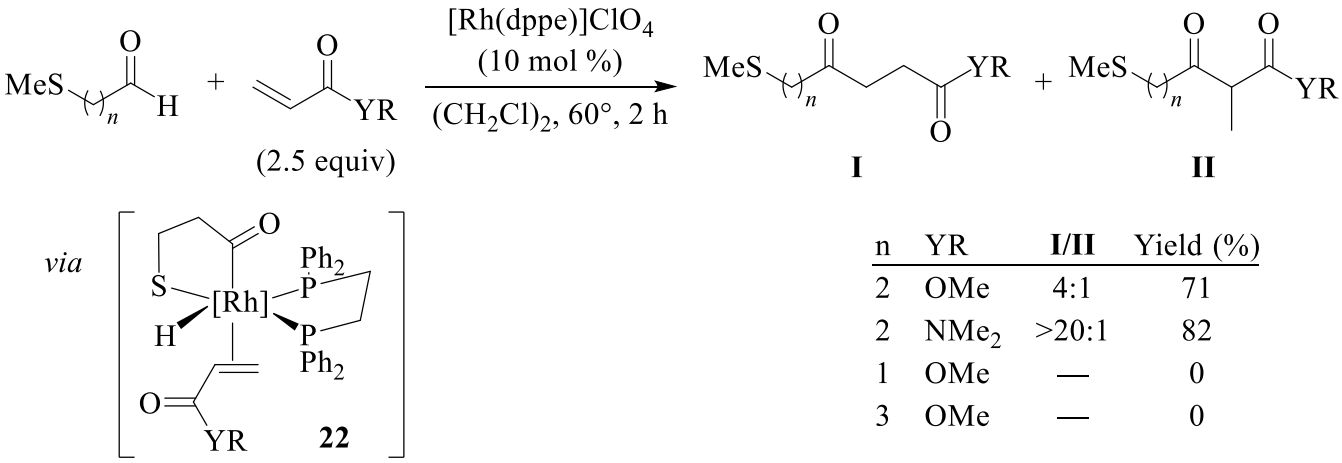
(*S*,*S*)-BDPP

	Yield (%)	
[Rh]	**I**	**II**
$[(PPh_3)_3RhCl]$	92	0
$[Rh(S,S)\text{-BDPP}]BF_4$	(0	91

Scheme 14

Intermolecular Hydroacylation. Early success in achieving intermolecular hydroacylation relied on the use of chelating aldehydes and activated alkenes. In most cases, the linear ketone product is observed ─ the hydride adds to the α-position, followed by C─C bond formation at the less hindered β-carbon atom (Scheme 15Willis, 2004 #426}{Moxham, 2006 #430}{Willis, 2006 #428} A sulfide directing group on the aldehyde is found to be necessary to effect the reaction. Importantly, 5-membered rhodacycle intermediate **22** is invoked as an active intermediate. Homologating or dehomologating the sulfur tether renders the system unreactive.

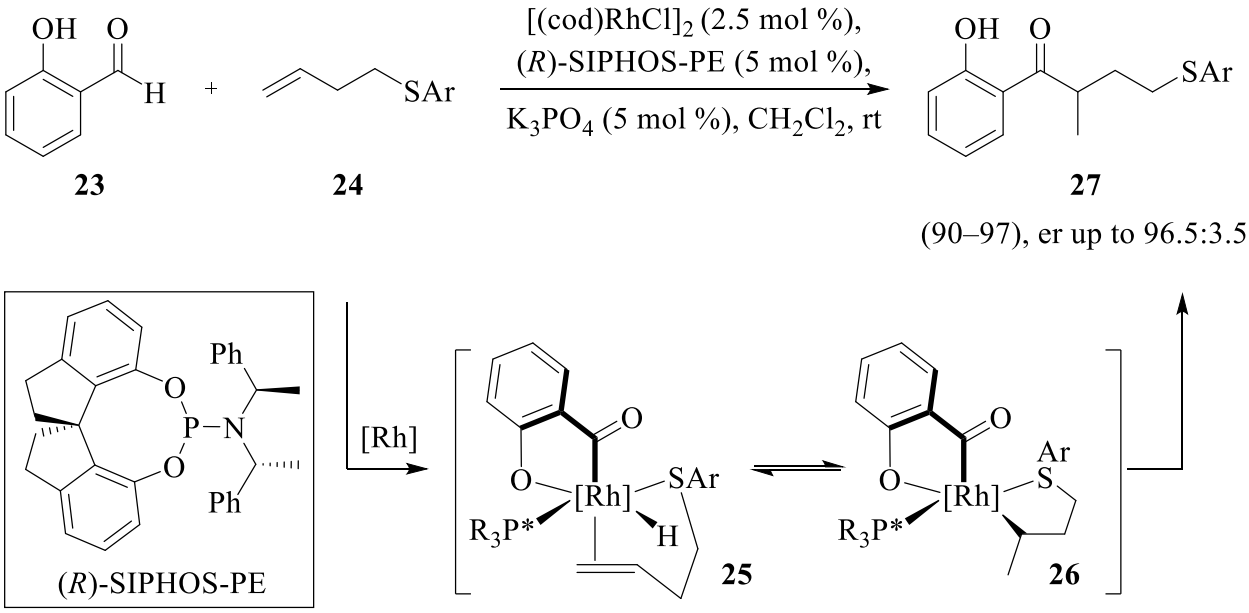
(18)



n	YR	I/II	Yield (%)
2	OMe	4:1	71
2	NMe_2	>20:1	82
1	OMe	—	0
3	OMe	—	0

Scheme 15

It is possible to favor branched-selectivity through the proper choice of catalyst and substrates.{Tanaka, 2003 #424}{Imai, 2004 #425}{Coulter, 2010 #16}{Zhang, 2011 #510}{Murphy, 2011 #5}{Murphy, 2012 #4}{Murphy, 2014 #513} A reaction in which both substrates **23** and **24** are capable of chelation, the use of a monodentate ligand such as (*R*)-SIPHOS-PE allows a chelation-assisted, branched insertion to give intermediate **26** consisting of two 5-membered rhodacycles (Scheme 16). Subsequent reductive elimination yields branched ketones **27** in >20:1



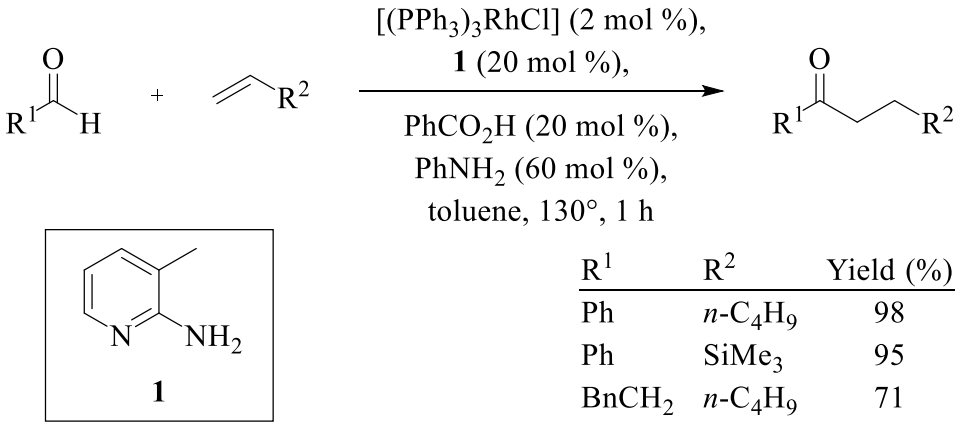
Scheme 16

regioselectivity. This method has been extended to encompass hydroacylation of a diverse range of alkenes that do not contain a sulfur directing group.{von Delius, 2012 #2} In the absence of the sulfur heteroatom, linear ketones are formed preferentially in >20:1 regioselectivity.

Developing directing motifs for highly regio- and enantioselective hydroacylation represents a modern frontier in transition-metal catalysis. However, the extensive use of directing groups that are embedded into the substrates is also a major drawback in the field. As a consequence, the use of catalytic scaffolding groups has emerged as an attractive strategy.{Bruch, 2008 #515}{Rousseau, 2011 #516}{Tan, 2011 #517}{Murphy, 2011 #5}{Murphy, 2012 #4} The most successful approach involves the use of 2-amino-3-picoline (**1**) as a co-catalyst with rhodium complexes. This metal-organic cooperative catalysis allows linear-selective hydroacylation of unactivated alkenes (without chelation-assistance and electronic or strain activation) with aldehydes that lack directing groups (Scheme 17). {Jun, 1997 #391} {Jun, 1999 #418} {Jun, 2000 #392} {Jun, 2001 #396} {Jun, 2002 #419} {Jun, 2004 #420} {Park, 2008 #421} {Jo, 2009 #398} The mechanism of this process begins with reversible

formation of aldimine **2**, which helps to activate the C─H bond toward oxidative addition by rhodium (Scheme 18). Although the oxidative addition process is generally believed to occur through a concerted 3-membered transition state, {Hyatt, 2007 #476}{Wang, 2008 #478}{Shen, 2009 #27}{von Delius, 2012 #2}, DFT calculations have suggested an alternative, lower energy, two-step pathway for the C─H

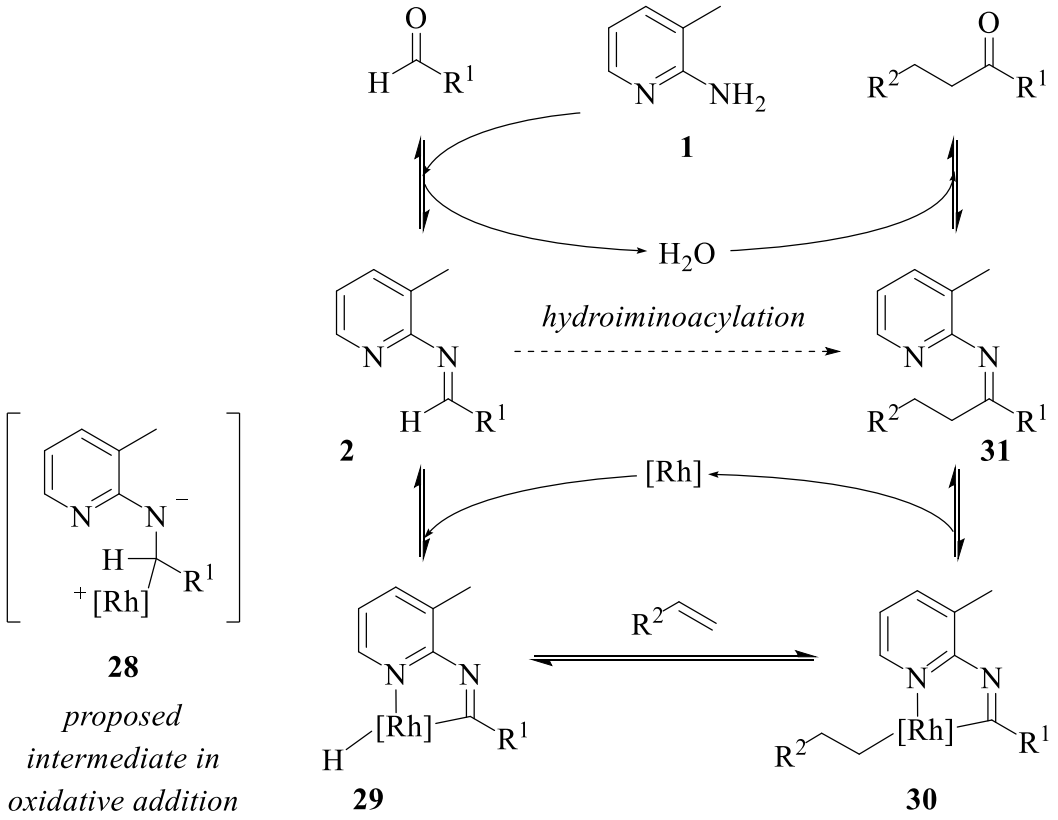
(20)



R^1	R^2	Yield (%)
Ph	*n*-C_4H_9	98
Ph	$SiMe_3$	95
$BnCH_2$	*n*-C_4H_9	71

Scheme 17

(21)



Scheme 18

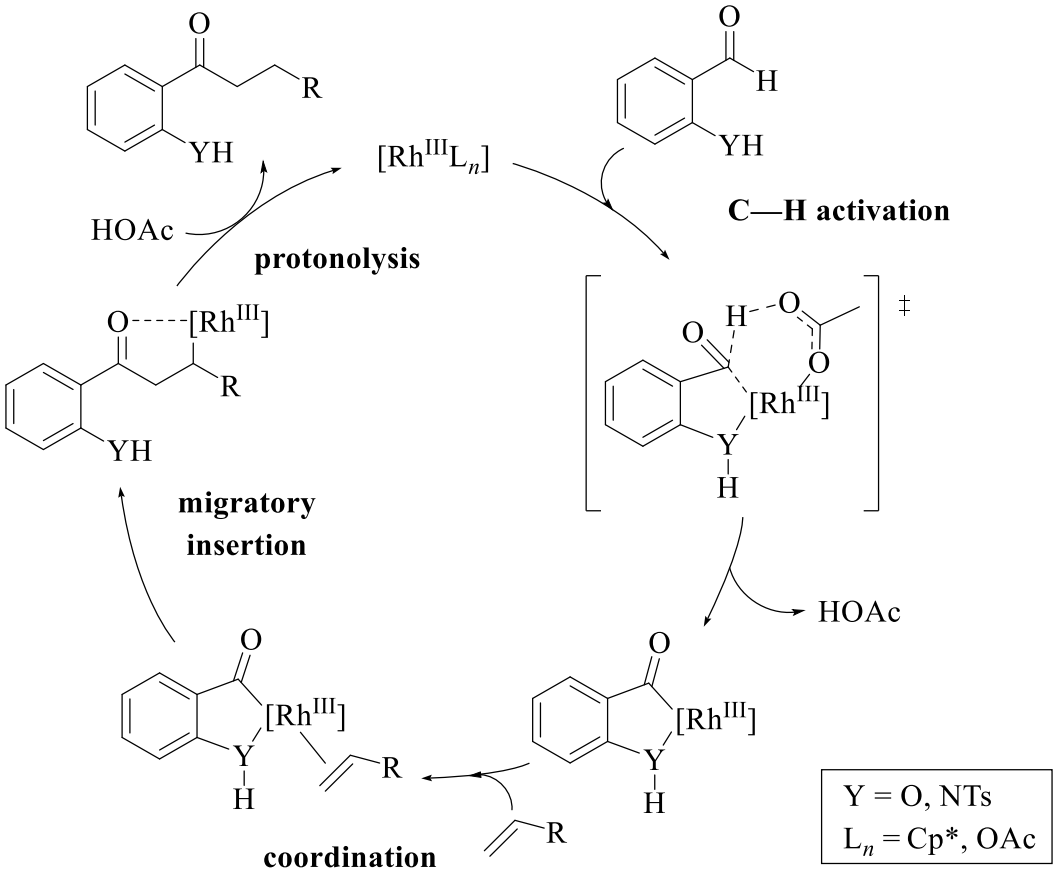
activation of aldimine **2**.{Yoo, 2008 #487} The rhodium(I) complex first adds into the aldimine **2** to give tetrahedral intermediate **28**, and subsequent [1,2]-hydride shift occurs to give iminoacylrhodium(III) hydride **29**. Coordination and insertion of the olefin into the Rh─H bond provides alkylrhodium(III) **30**, which undergoes reductive elimination to furnish imine **31**. Hydrolysis of imine **31** provides the hydroacylation product. This process is occasionally referred to as hydroiminoacylation or hydroimination.

Rhodium(III) Catalysis.

Rhodium(III) catalysis is commonly used to functionalize the C─H bonds of arenes and alkenes.{Satoh, 2010 #521}{Colby, 2011 #522}{Song, 2012 #520} Recent studies show that these catalysts can also activate aldehyde C─H bonds.{Shimizu, 2008 #523}{Shi, 2012 #524}{Zhou, 2013

#525}{Zhang, 2014 #509} In contrast to rhodium(I) catalysts which cycle between rhodium(I) and rhodium(III) oxidation states (Scheme 11), Rh(III) catalysts do not involve changes in oxidation state. Formyl C─H activation is proposed to occur by chelation assistance, potentially via a

(22)



Scheme 19

concerted-metalation-deprotonation mechanism (Scheme 19).{Guimond, 2011 #526} This type of C─H activation bypasses the need to occur through an acylrhodium hydride intermediate that is typical of rhodium(I) catalysis, thus preventing reductive decarbonylation of the aldehyde. Subsequent steps involve olefin coordination, migratory insertion, and protonolysis of the Rh─C bond to afford the ketone and turn over the rhodium(III) catalyst. In contrast to rhodium(I) catalysts, for which a large variety of

achiral and chiral phosphine ligands are available for optimizing catalyst activity and selectivity, the choice of ligands for rhodium(III) catalysts is currently limited to only a few cyclopentadienyl derivatives. Developing novel chiral ligands for rhodium(III) is currently an active area of research. {Hyster, 2012 #536}{Ye, 2012 #537}{Ye, 2013 #535}{Ye, 2014 #534}

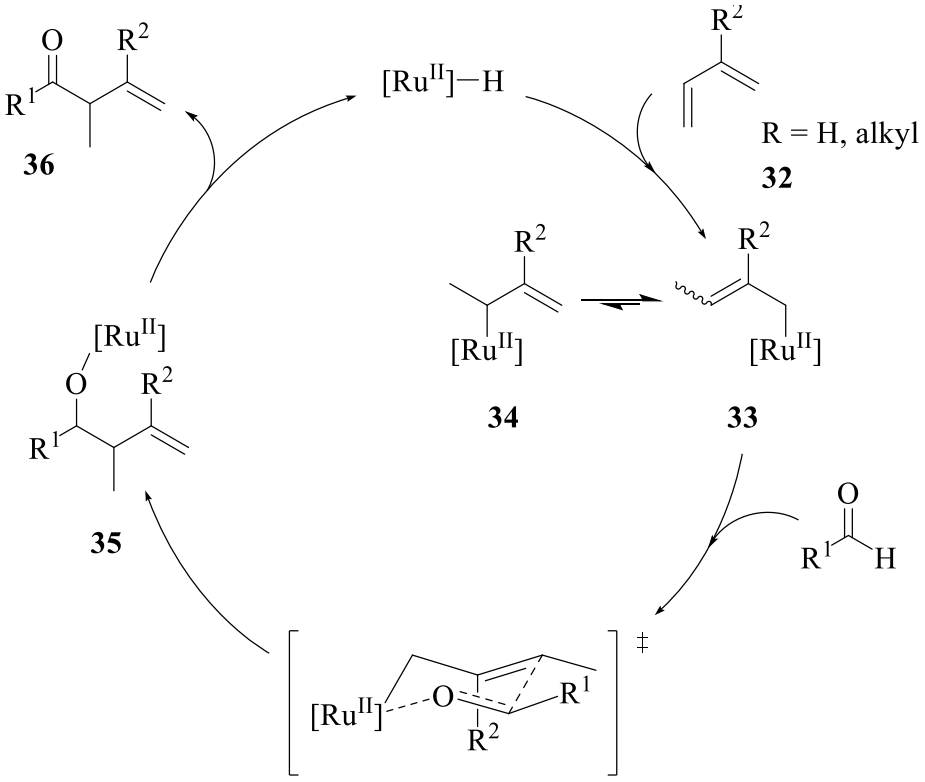
Ruthenium(I) Catalysis.

Low-valent ruthenium catalysts such as $Ru_3(CO)_{12}$ can activate the formyl C─H bonds of aldehydes,{Kondo, 1990 #439} *N*-substituted formamides,{Tsuji, 1987 #437}{Armanino, 2013 #494}{Li, 2013 #497} and formic esters,{Kondo, 1989 #438}{Kondo, 1989 #530}{Ko, 2002 #492}{Konishi, 2012 #488}{Armanino, 2013 #493}{Li, 2014 #518} and can catalyze addition of these units across unsaturated carbon-carbon bonds. The mechanism of these transformations entails direct oxidative addition of the C─H bond to form an acylruthenium hydride, followed by migratory insertion and reductive elimination to forge the hydroacylation product. The carbonyl deinsertion pathway is energetically accessible in these systems, and thus a carbon monoxide atmosphere is occasionally introduced to stabilize the active catalytic species and suppress aldehyde decarbonylation.{Kondo, 1990 #439}

Research in ruthenium(I) hydride reactivity has shown that hydroacylation of 1,3-dienes can be achieved without the need for directing groups.{Omura, 2008 #441}{Shibahara, 2008 #442}{Leung, 2012 #263} This unique system starts with addition of the ruthenium(II) hydride into the 1,3-diene **32** to generate equilibrating primary and secondary σ-allyl complexes **33** and **34**, respectively (Scheme 20). The more stable primary σ-allyl complex **33** undergoes addition into the aldehyde via a 6-membered transition state to provide ruthenium(II)-alkoxide **35**. Subsequent β-hydride elimination yields the branched β,γ-unsaturated ketone **36** with concomitant regeneration of the ruthenium(I) hydride catalyst.

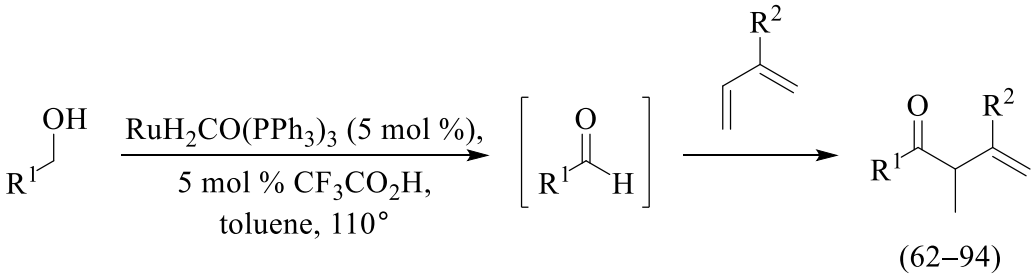
Avoiding an acylruthenium hydride intermediate is a key feature of this catalytic cycle. This process can also be performed under transfer hydrogenation conditions, which allows the use of alcohol substrates as surrogates for aldehydes (Scheme 21). This attractive method enables the use of sensitive aldehydes in hydroacylation by generating the aldehyde in situ from the alcohol oxidation state.

(23)



Scheme 20

(24)



Scheme 21

Regioselectivity. Contrary to rhodium-catalyzed, intermolecular hydroacylations, which generally give rise to linear ketone products in the absence of directing groups, ruthenium(II) hydride catalysis provides branched products with excellent diastereoselectivities in substrates with no directing groups. The greater stability of primary σ-allyl species **33** over secondary σ-allyl species **34** is invoked to rationalize the selectivity (Scheme 20).{Shibahara, 2008 #442}

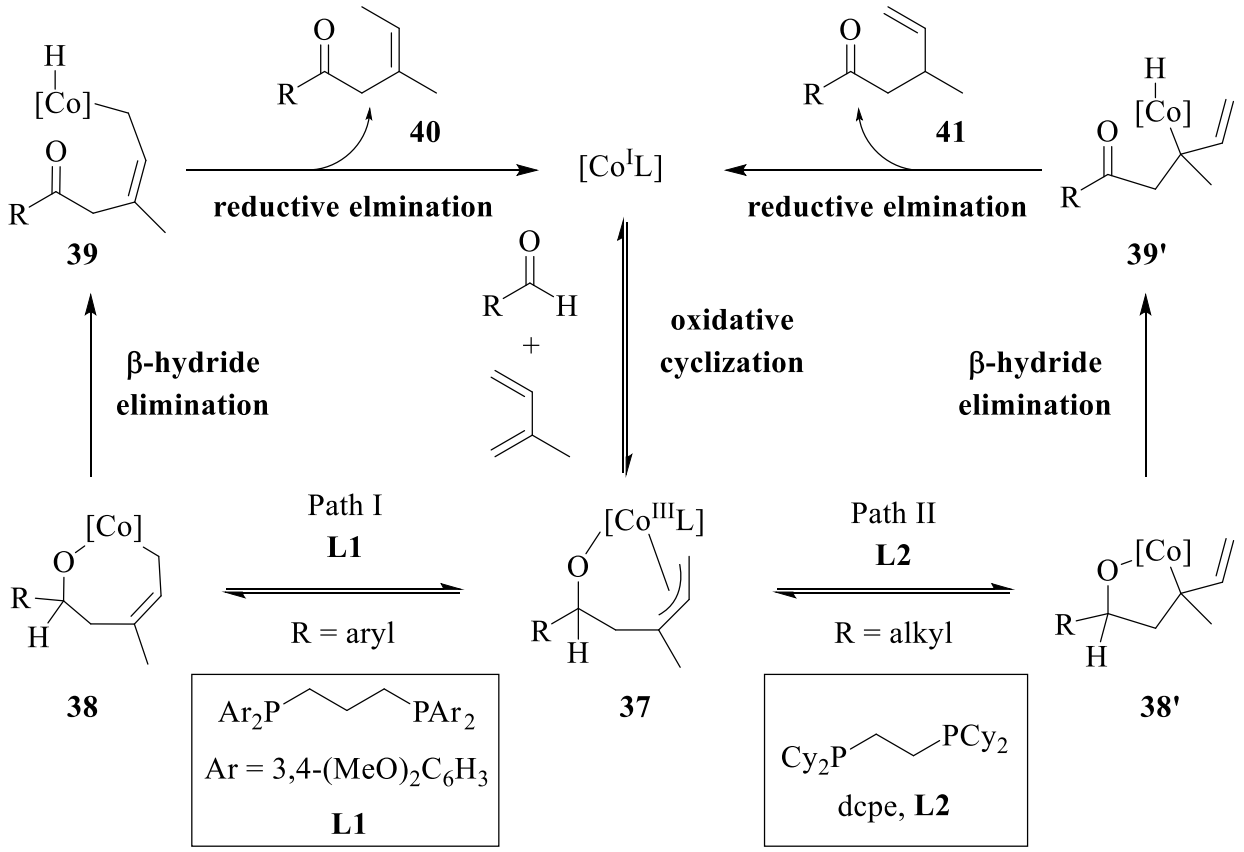
Cobalt(I) Catalysis.

The use of abundant and inexpensive first-row metals to achieve catalysis is an active area of research.{Bullock, 2010 #527} Hydroacylation with cobalt is known to proceed by a mechanism similar to that of rhodium(I) catalysis and is supported by detailed mechanistic investigations using well-defined cobalt(I) complexes.{Lenges, 1998 #444} An analogous mechanism that occurs through cobalt(0)/cobalt(II) oxidation states has also been documented for an intramolecular hydroacylation of 4-pentenal.{Vinogradov, 1988 #223}

A recent advance in this area takes advantage of Co(I)-diphosphine complexes to hydroacylate 1,3-dienes with various aldehydes in a 1,4-addition fashion to produce β,γ- and γ,δ-unsaturated ketones.{Chen, 2014 #508} On the basis of related hydrovinylation reports{Moreau, 2008 #529}{Hilt, 2012 #528} and preliminary mechanistic studies, a mechanism in which cobalt undergoes oxidative cyclization with the aldehyde and diene to generate π-allyl cobalt complex **37** is believed to take place (Scheme 22). The π-allyl intermediate equilibrates between 7-membered and 5-membered cobaltacycles **38** and **38'**, respectively, followed by rate-limiting β-hydride elimination to afford cobalt(III) hydride intermediates **39** and **39'**. Reductive elimination yields unsaturated ketones **40** (1,4-hydroacylation product) and **41** (1,2-hydroacylation product). It is observed empirically that the use of Co(**L1**) with aryl

aldehydes yields 1,4-hydroacylation products (Path I), whereas the use of Co(**L2**) with aliphatic aldehydes furnishes 1,2-hydroacylation products (Path II). Similar to the rhodium(III)- and ruthenium(II)-based methods described above, an advantage to the oxidative cyclization pathway over the oxidative addition pathway is that an acylmetal species is never formed. This aspect allows the system to bypass the decarbonylation pathway, thus minimizing catalyst deactivation.

(25)

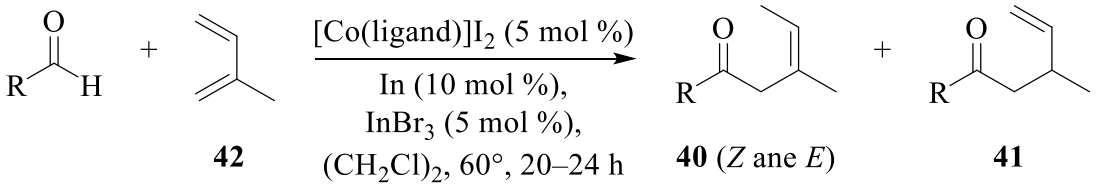


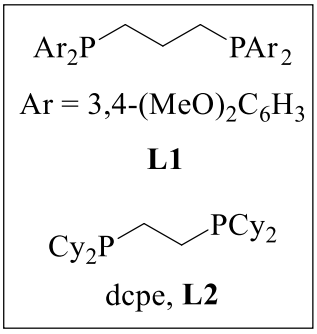
Scheme 22

The stereostructure of the products obtained via cobalt(I)-catalyzed hydroacylation of 1,3-dienes lends support to the proposed mechanism. When benzaldehyde derivatives and isoprene (**42**) are subjected to cobalt(I) conditions, trisubstituted *Z*-alkenes **40** are formed in high selectivity (Scheme 23). The *Z*-olefin geometry can be rationalized by considering the substrate-chelated cobaltacycle **38** (Scheme 22), which

ultimately dictates the olefin configuration (Path I). The level of *Z*/*E* selectivity decreases with electron-rich substituents on the aryl aldehyde because of competitive olefin isomerization under the reaction conditions. For reasons that are unclear, the regioselectivity begins to favor the terminal olefin **41** (via cobaltacycle **38'**) when aliphatic aldehydes are used (Path II). The regioselectivity is reversed to synthetically useful levels by using a cobalt catalyst ligated with dcpe (**L2**).{Chen, 2014 #508} The linear products obtained by this method complements the branched products obtained via ruthenium(II) hydride catalysis. No enantioselective methods have been reported using cobalt catalysis.

(26)





Ligand	R	Yield(%)	*Z*/*E* (**40**)	**40/41**
L1	Ph	87	19:1	>20:1
L1	4-BrC_6H_4	92	>20:1	>20:1
L1	4-$MeO_2CC_6H_4$	88	>20:1	>20:1
L1	4-$MeOC_6H_4$	97	2:1	>20:1
L1	Cy	17	—	2:1
L2	Cy	82	—	1:8

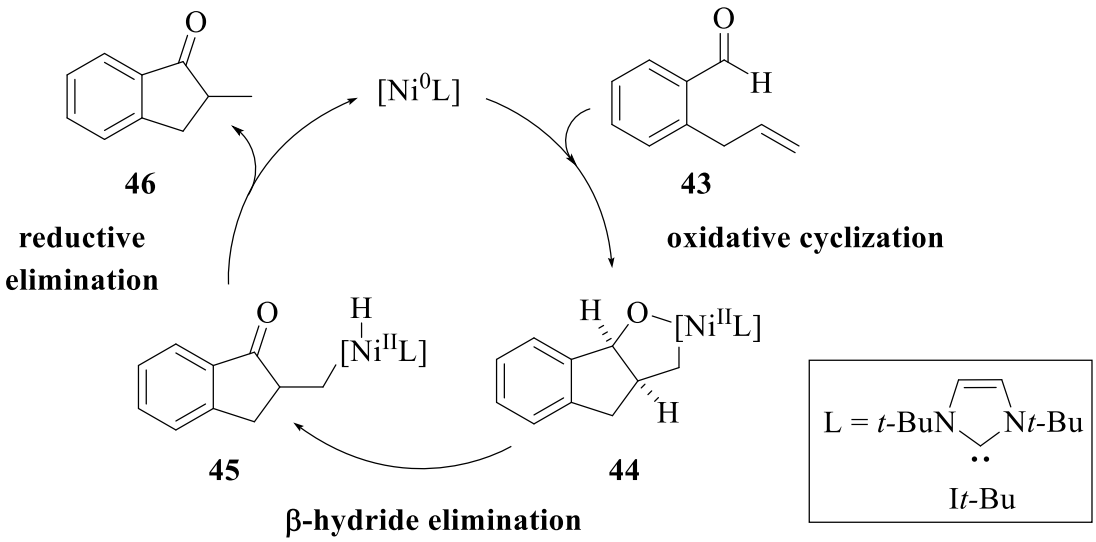
Scheme 23

Nickel(0) Catalysis.

Nickel catalysts promote intramolecular cyclization of alkenals to yield cyclopentanones and cyclohexanones.{Hoshimoto, 2012 #489} A mechanism based on oxidative cyclization between alkenal **43** and nickel(0) to form a 5-membered oxanickelacycle **44** is proposed (Scheme 24). This step is

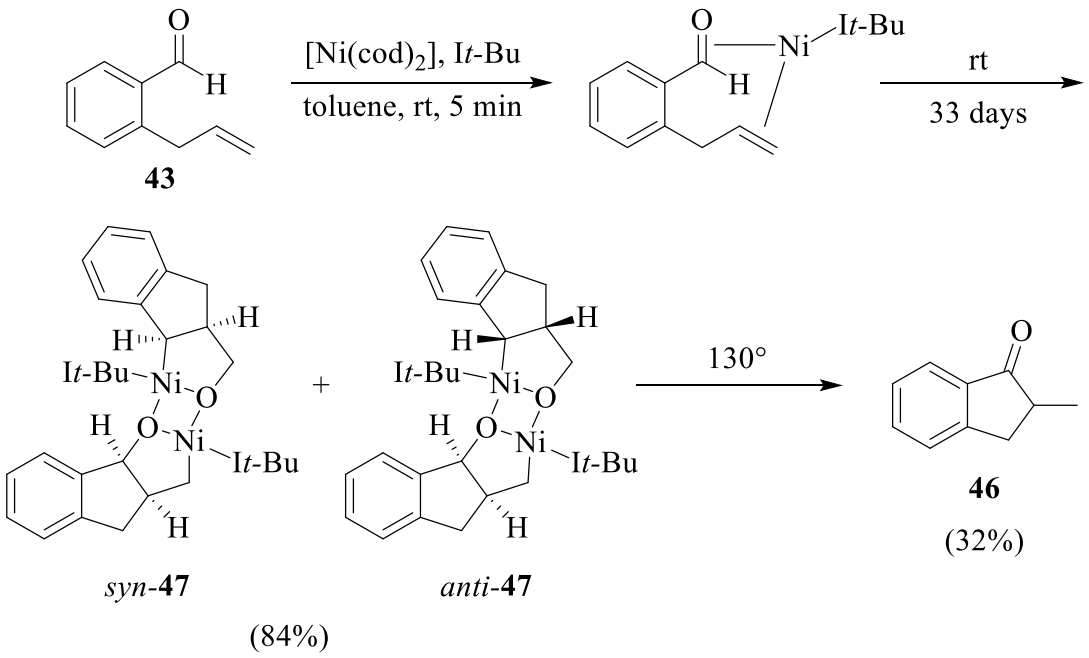
followed by β-hydride elimination to form alkylnickel(II) hydride **45**. A final C─H reductive elimination occurs to give the cyclic ketone **46** and regenerate the active Ni(0) catalyst. This pathway is supported by the results of stoichiometric experiments whereby an equimolar mixture of alkenal **43** and [Ni(cod)$_2$]/I*t*-Bu complex at room temperature results in formation and isolation of dimeric oxanickelacycles *syn*- and *anti*-**47** (Scheme 25). This complex is converted to ketone **46** in 32% yield upon heating to 130˚ for 24 hours. {Hoshimoto, 2012 #489} A similar oxanickelacycle is formed when using monodentate Cy_3P and Ph_3P ligands; however, no further transformation to the hydroacylation product takes place.{Ogoshi, 2004 #490}

(27)



Scheme 24

(28)



Scheme 25

Although the oxidative cyclization mechanism discussed above is generally favored for nickel(0)-catalyzed activation of aldehydes, there is some evidence for a mechanism involving direct oxidative addition into the formyl C─H bond to form an acylnickel(II) hydride.{Yu, 2012 #261} The oxidative addition mechanism is also invoked in nickel(0)-catalyzed hydrocarbamoylation reactions.{Nakao, 2009 #496}{Donets, 2013 #531}

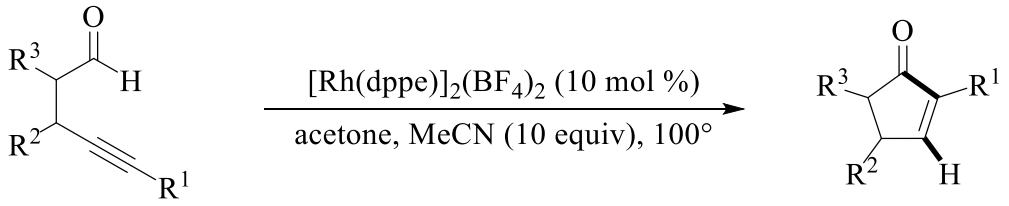
Alkyne Hydroacylation

Rhodium(I) Catalysis.

The mechanism of alkyne hydroacylation bears close resemblance to that of rhodium(I)-catalyzed alkene hydroacylation. It is noteworthy that the intramolecular hydroacylation of 4-alkynals **48** yields cyclopentenones **49** (Scheme 26).{Tanaka, 2001 #448}{Tanaka, 2002 #467}{Tanaka, 2003 #468} To obtain this product, the metal hydride must add *trans* across the alkyne. This unusual *trans*-

addition process has been studied computationally (Scheme 27).{Chung, 2008 #465} According to this analysis, the reaction proceeds with rate-limiting oxidative addition into the aldehyde

(29)



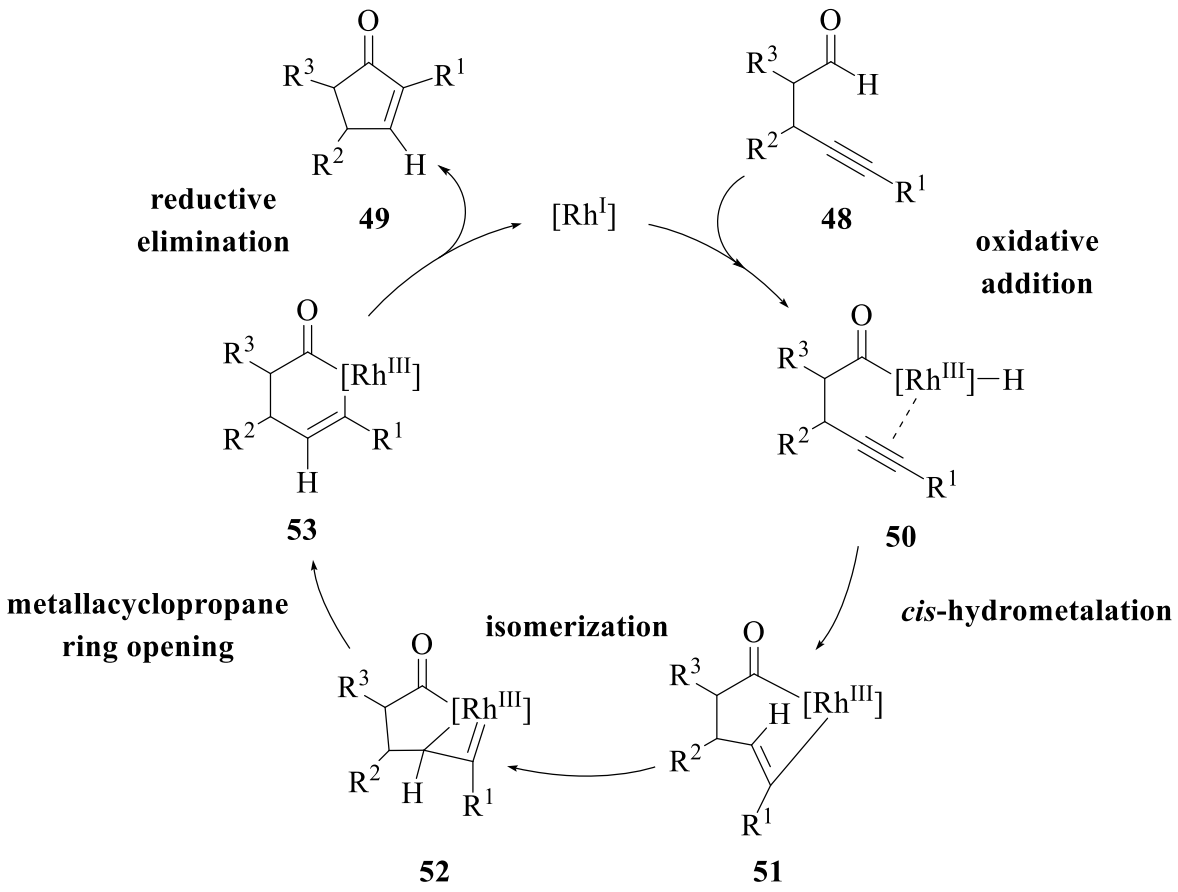
48 **49**

R^1	R^2	R^3	Yield (%)
n-$C_{10}H_{21}$	H	H	67
Ph	Me	H	88

Scheme 26

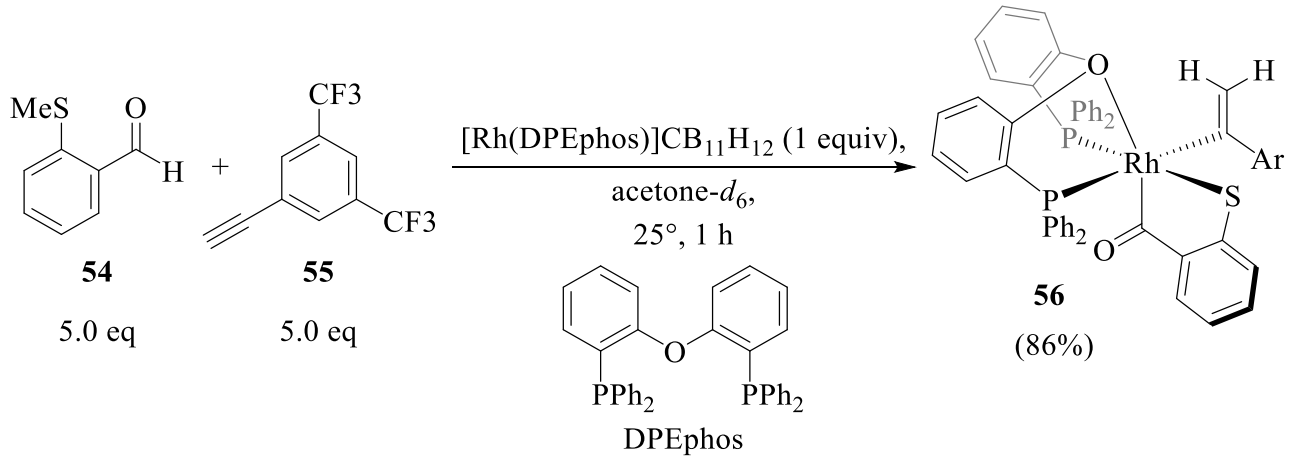
C─H bond, which is assisted by the alkyne functional group. The resulting acylmetal hydride **50** participates in *cis*-hydrometalation to give a strained and unstable acylmetal alkenyl species **51**, which rapidly isomerizes to metallacyclopropene **52** and subsequently ring opens to give 6-membered rhodacycle **53**. Reductive elimination from this relatively stable intermediate affords cyclopentenone **49**. In essence, the rather unusual *trans*-addition of the alkyne occurs through a common *cis*-hydrometalation, followed by a series of exergonic isomerization steps involving high-energy, transient intermediates. This pathway is supported by deuterium labeling experiments.{Tanaka, 2001 #448}{Pawley, 2012 #251}

(30)



Scheme 27

Organometallic intermediates in the *intermolecular* alkyne hydroacylation pathway have been successfully prepared and isolated when β-chelating aldehyde **54** and electron-deficient alkyne **55** are used as substrates and hemilabile DPEphos is used as the ligand (Scheme 28).{Pawley, 2012 #251} The direct observation of complex **56** suggests that, in fact, hydride migration onto the olefin occurs preferentially over acyl migration, an aspect of hydroacylation that had previously been explored only computationally.{Wu, 2005 #477}{Hyatt, 2007 #476}{Chung, 2008 #465}{Wang, 2008 #478}{Gao, 2009 #479} Deuterium labeling experiments reveal that metallacyclopropene (cf. **52**) formation is operative even in intermolecular reactions.



Scheme 28

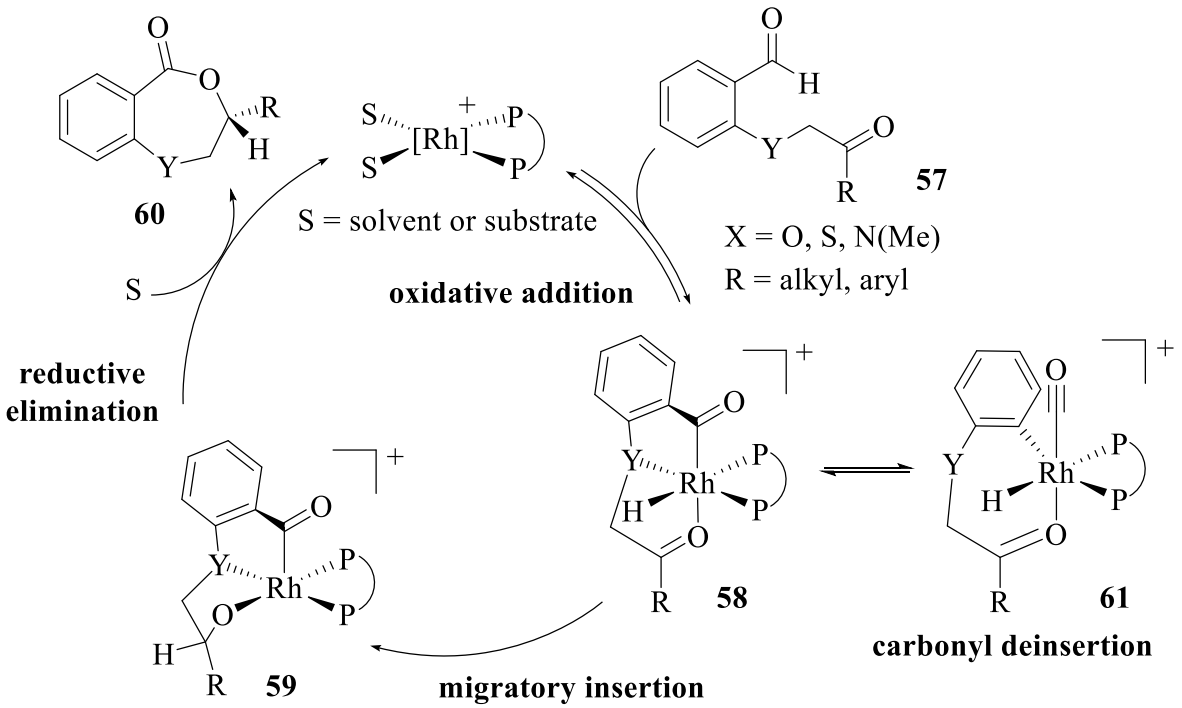
Carbonyl Hydroacylation

Rhodium(I) Catalysis.

A combination of experimental mechanistic studies and DFT calculations have been exploited to study carbonyl hydroacylations. One of the most thoroughly studied cases is the intramolecular ketone hydroacylation to generate 7-membered lactones.{Shen, 2008 #37}{Shen, 2009 #27} In this reaction, a diphosphine-ligated rhodium complex oxidatively adds into ketoaldehyde **57** to generate the coordinatively saturated acylrhodium(III) hydride **58**. The ligand arrangement resulting from oxidative addition (and partially imparted by the directing group and ligand) situates the rhodium─hydride bond and the ketone in close proximity and allows migratory insertion to occur via a 4-membered transition-state to form acylrhodium(III) alkoxide **59**. In contrast to alkene hydroacylation, in which reductive elimination is typically implicated as the turnover-limiting step, DFT, kinetic isotope effect (KIE = 1.79 ± 0.06), and Hammett studies point to ketone insertion as turnover-limiting. A final carbon─oxygen bond reductive elimination then furnishes the product and turns over the rhodium(I) catalyst. DFT calculations suggest that the oxygen is bound to the rhodium center throughout the hydroacylation pathway. However, carbonyl deinsertion can occur to generate complex **61** when the directing group (Y)

dissociates from the metal center. This decarbonylative pathway, which is found to be 3.0 kcal/mol higher in energy than the hydroacylation pathway, leads to both substrate and catalyst decomposition (Scheme 29). The very subtle energy difference between the barriers for hydroacylation and decarbonylation shows how the choice of ligand can significantly impact the reactivity and selectivity of the catalyst.

(32)

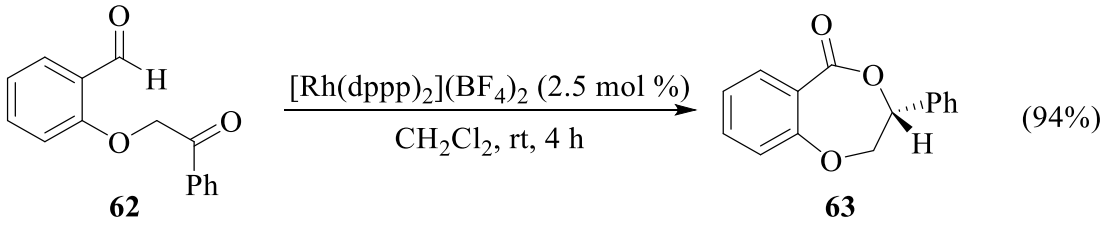


Scheme 29

The nature of the Y group is critical for reactivity. When keto-aldehyde **62**, containing the ether directing group, is subjected to the cationic complex $[Rh(dppp)_2]^+$ at room temperature for 4 hours, lactone **63** is formed in 94% yield (Scheme 30). However, when the oxygen atom is replaced with a methylene unit, no hydroacylation product is observed. Instead, only 4% of the decarbonylation product

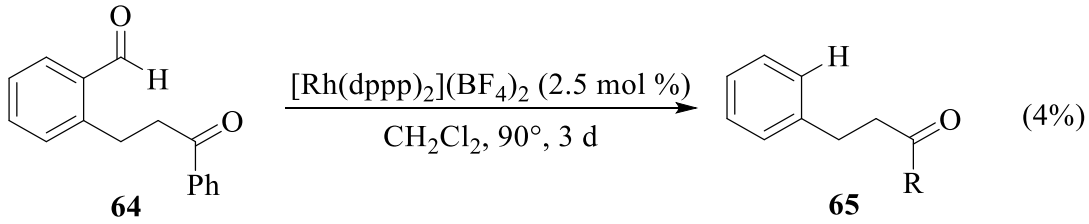
65 is formed after 3 days at 90˚ (Scheme 31). Under these conditions, no further activity occurs following the first turnover, and reductive decarbonylation is not catalytic.{Shen, 2009 #27}

(33)



Scheme 30

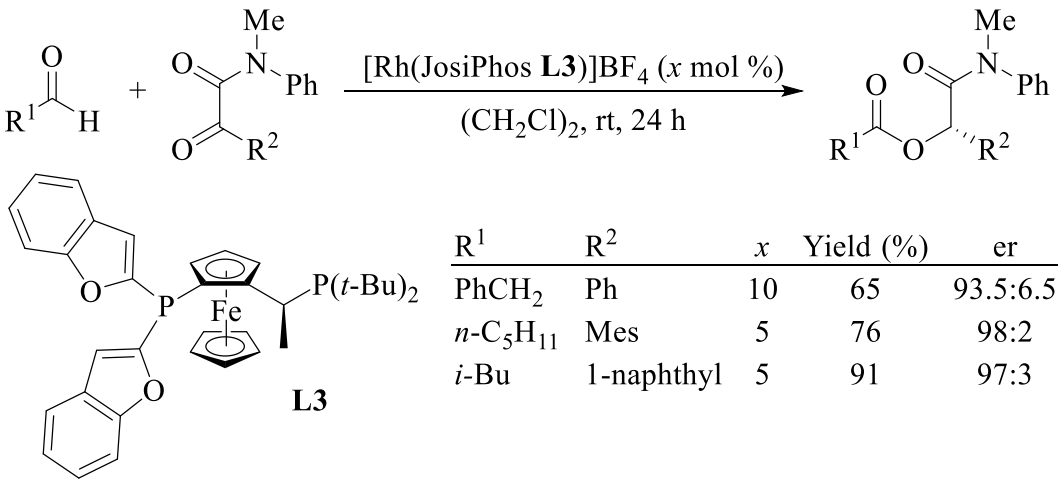
(34)



Scheme 31

Contrary to intramolecular ketone hydroacylation, the analogous intermolecular reaction is considerably more challenging because of competing decarbonylation, Tishchenko dimerization, and aldol pathways. To achieve chemoselectivity for aldehyde-ketone cross-coupling over aldehyde-aldehyde homocoupling, α-keto amides are used (Scheme 32).{Kou, 2014 #553} The amide directing group favors ketone binding to the metal center and effectively promotes aldehyde-ketone cross-coupling while disfavoring undesired pathways. This approach allows the use of non-chelating aliphatic aldehydes as substrates, a rare feature for rhodium(I) catalysis.

(35)

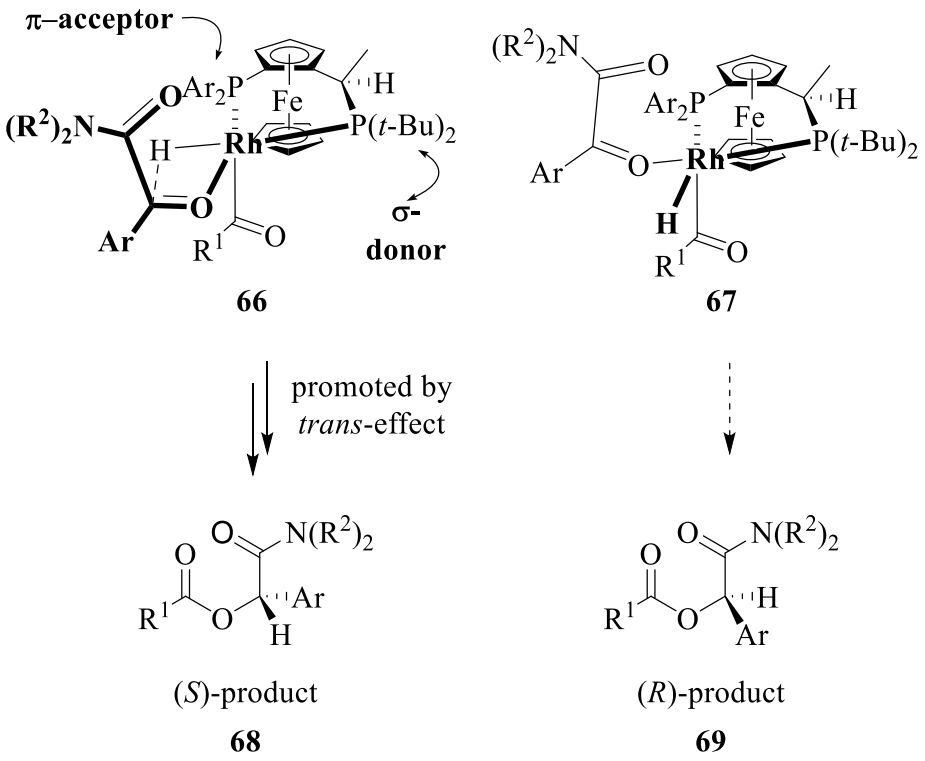


R^1	R^2	*x*	Yield (%)	er
$PhCH_2$	Ph	10	65	93.5:6.5
n-C_5H_{11}	Mes	5	76	98:2
i-Bu	1-naphthyl	5	91	97:3

Scheme 32

The asymmetric ligand **L3** containing a bulky σ-donating di-*tert*-butylphosphine and a π-accepting dibenzofurylphosphine is essential for obtaining reactivity and stereoselectivity for the current transformation.{Hasanayn, 2012 #246} Following oxidative addition of the aldehyde to form acylrhodium hydride **66**, the hydride *trans* to the σ-donating di-*tert*-butylphosphine is rendered more hydridic via the *trans*-effect, whereas the ketone *trans* to the π-accepting dibenzofurylphosphine becomes more electrophilic (Scheme 33).{Tu, 2003 #539} This phenomenon lowers the barrier for ketone insertion and ultimately leads to products of (*S*)-configuration. Conversely, intermediate **67** is stabilized by the *trans* effect, which results in an increased barrier to ketone insertion. This stereochemical model correctly rationalizes the absolute sense of the enantioinduction observed.

(36)



66 **67**

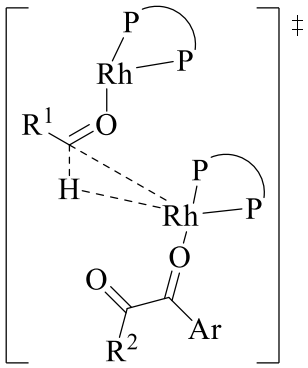
68 **69**

Scheme 33

Kinetic analysis of this intermolecular process reveals a first-order dependence of rate on both the aldehyde and the α-keto amide components. More striking is the observed second-order dependence of rate in the rhodium complex, suggesting that two rhodium species are involved in the turnover-limiting step. Together with KIE and nonlinear effect experiments, a mechanism invoking homobimetallic activation of the aldehyde is proposed (Figure 4), in which one rhodium species activates the aldehyde and a second rhodium species participates in turnover-limiting C─H activation. Most aldehydes that are used in hydroacylation contain a Lewis basic directing element that facilitates oxidative addition. The use of non-activated aldehydes (*i.e.*, no directing groups) likely contributes to an increased barrier for oxidative addition, and this conclusion is supported by some DFT studies.{Chung, 2008 #465}{Wang, 2008 #478} The use of mild Lewis acids in conjunction with transition-metal

catalysts could potentially offer a general solution for future applications in hydroacylation using non-chelating aldehydes.

(37)



rate = k[aldehyde]^1[α-keto amide]^1[catalyst]^2

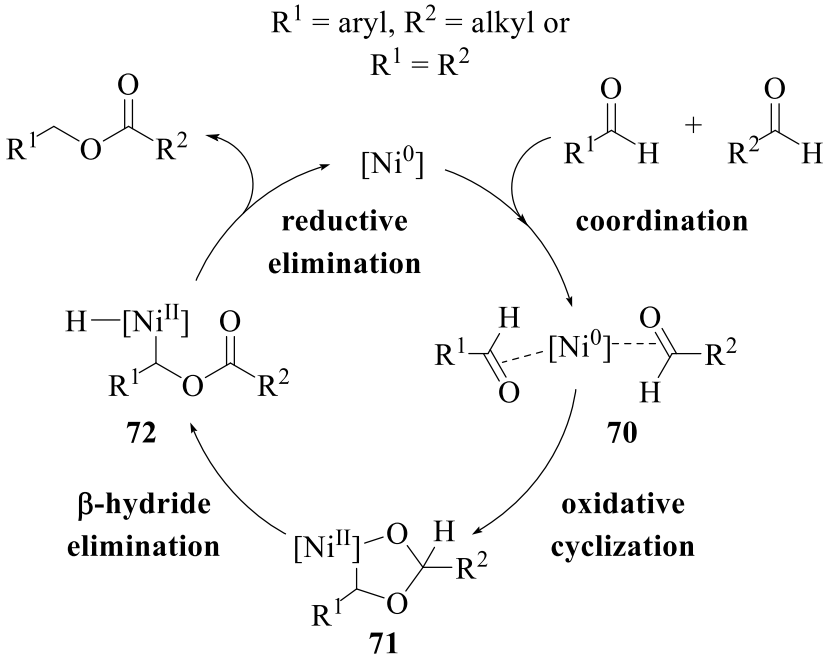
Figure 4. Proposed turnover-limiting homobimetallic oxidative addition.

Nickel(0) Catalysis.

Electron-rich nickel(0) complexes catalyze both homo- and cross-coupling of aldehydes (aldehyde hydroacylation).{Ogoshi, 2010 #244}{Hoshimoto, 2011 #243} Two mechanisms involving either oxidative cyclization or oxidative addition have been proposed in the recent literature.{Ogoshi, 2010 #244},{Hoshimoto, 2011 #243}{Yu, 2012 #261} The more commonly invoked pathway commences with coordination of the aldehydes to the metal center, followed by oxidative cyclization to afford dioxanickelacycle **71** (Scheme 34). β-Hydride elimination leads to alkylnickel(II) hydride **72**, and a final reductive elimination gives rise to product. This mechanism, however, does not explain the high selectivity observed for cross-coupling between aryl aldehydes and aliphatic aldehydes. Using the Ni(cod)$_2$/SIPr catalyst system, an equimolar mixture of cyclohexanecarboxaldehyde (**73**) and benzaldehyde (**74**) provides mixed ester **75** in 84% yield in which the alkyl aldehyde is oxidized and the

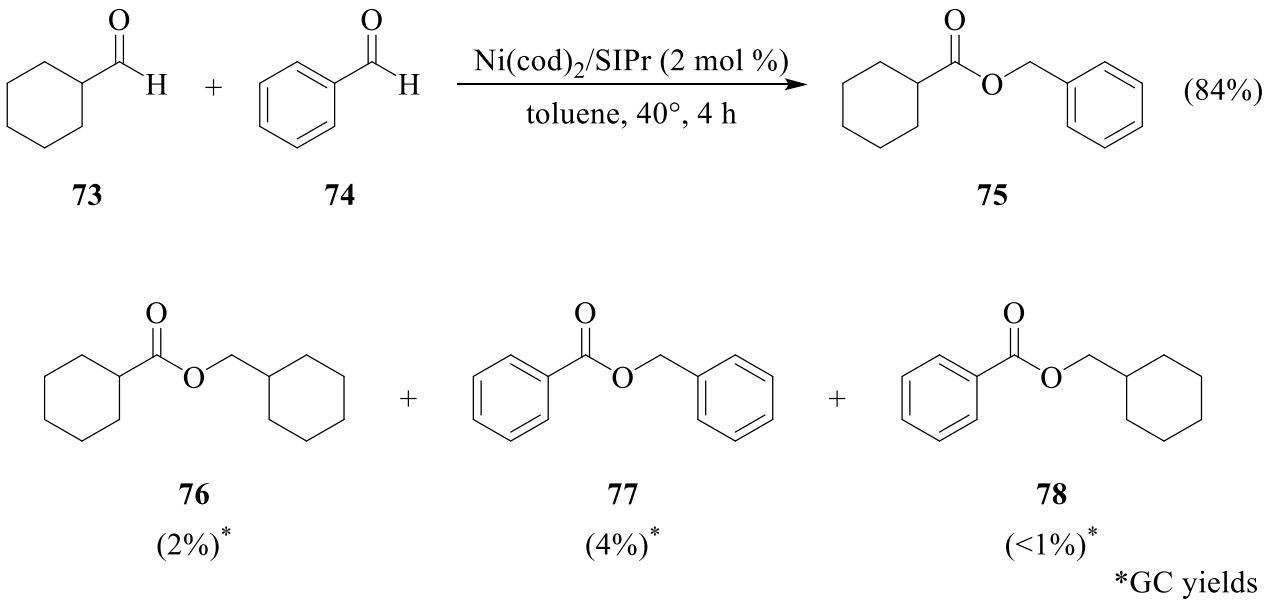
aromatic aldehyde is reduced (Scheme 35). The minor products are formed in a combined <7% yield by GC analysis.

(38)



Scheme 34

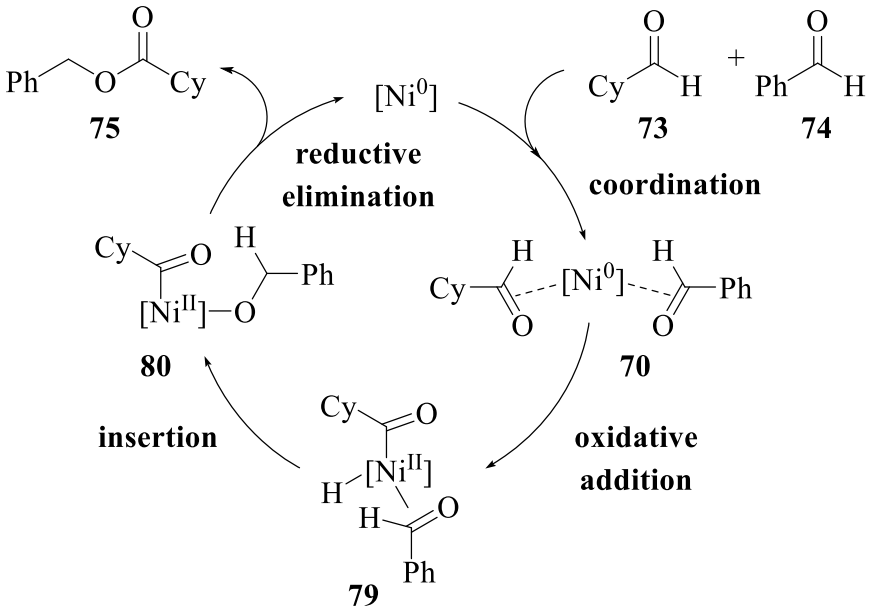
(39)



Scheme 35

Rigorous DFT calculations on this reaction system suggest that the oxidative cyclization pathway is energetically unfeasible, with a turnover-limiting β-hydride elimination barrier of approximately 50 kcal/mol.{Yu, 2012 #261} Instead, computational studies support a mechanism involving turnover-limiting C─H activation of the aliphatic aldehyde **73** to provide acylnickel(II) hydride **79** (Scheme 36). The energy barrier to this step is only approximately 20 kcal/mol. Subsequent addition of the nickel hydride bond across the benzaldehyde C=O bond affords complex **80**, and reductive elimination furnishes hydroacylation product **75**.

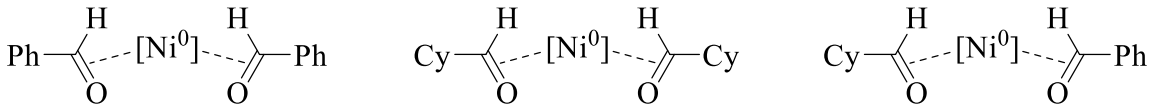
(40)



Scheme 36

The origin of chemoselectivity arises from the more electron rich aliphatic aldehydes being much more susceptible to oxidative addition by nickel than the less electron rich aromatic aldehydes. However, aromatic aldehydes are better π-acceptors and are thus better able to coordinate to the metal center. Hence, complex **81** with two benzaldehyde molecules coordinated to nickel is the only experimentally observed species by ^{1}H NMR spectroscopy (Figure 5).{Hoshimoto, 2011 #243} Complex **82** with two coordinated aliphatic aldehydes is predicted to be 6.0 kcal/mol higher in energy than complex **81** owing to weak metal-binding ability and is therefore present in negligible concentrations in the reaction mixture. Overall, the cross-selectivity is governed by a combination of effects: the relative ease of oxidative addition of aliphatic aldehydes and the stronger coordinating ability of aromatic aldehydes.

oxidative addition slow *negligible* *oxidative addition fast*



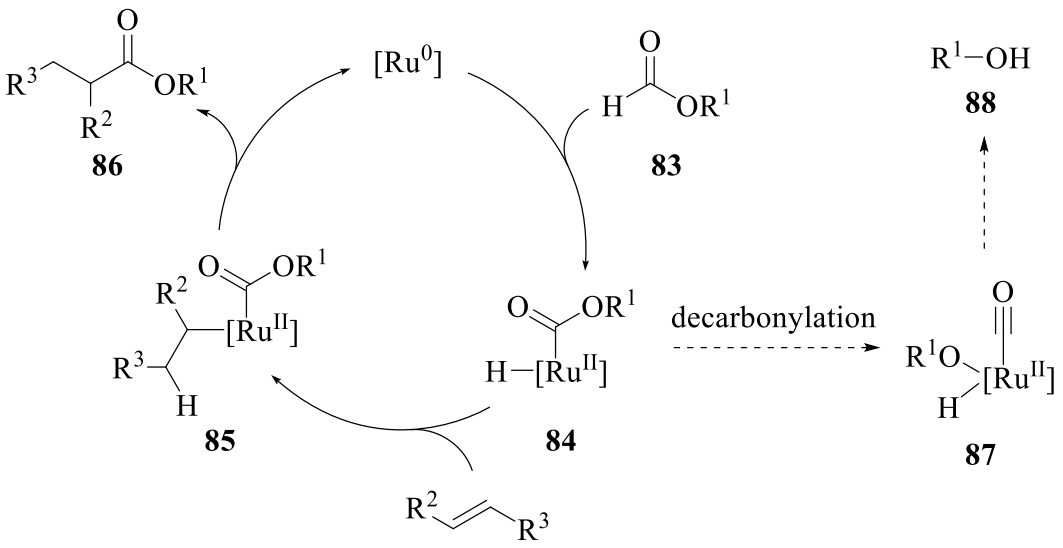
81 (0 kcal/mol) **82** (6.0 kcal/mol) **70** (2.6 kcal/mol)

Figure 5

Alkene Hydroesterification

Triruthenium dodecacarbonyl [$Ru_3(CO)_{12}$] can activate the formyl C─H bond of formate esters and catalyze hydroesterification of alkenes to generate new homologated esters.{Isnard, 1983 #436}{Kondo, 1989 #438}{Keim, 1989 #726} One proposed reaction mechanism involves oxidative addition of the formyl C─H bond of **83** into the ruthenium(0) complex to generate acylruthenium hydride **84** (Scheme 37).{Kondo, 1989 #438}{Ko, 2002 #492} Coordination and hydrometalation of the alkene affords acylruthenium alkyl species **85**, which undergoes C─C bond reductive elimination to yield ester **86** and turns over the ruthenium catalyst. Consistent with a formyl C─H activation mechanism is the observation of alcohol **88** as a side product, which arises from a decarbonylation pathway, presumably through the intermediacy of ruthenium carbonyl complex **87**. Early studies take advantage of high CO pressures to help stabilize the catalyst and prevent substrate decomposition; however, modern methods that employ a removable directing group,{Ko, 2002 #492}{Na, 2003 #737}{Park, 2006 #736}{Armanino, 2013 #493} no longer require the use of this hazardous gas (Figure 6).

(42)



Scheme 37

(43)

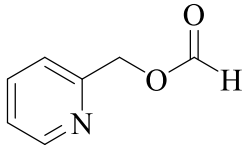
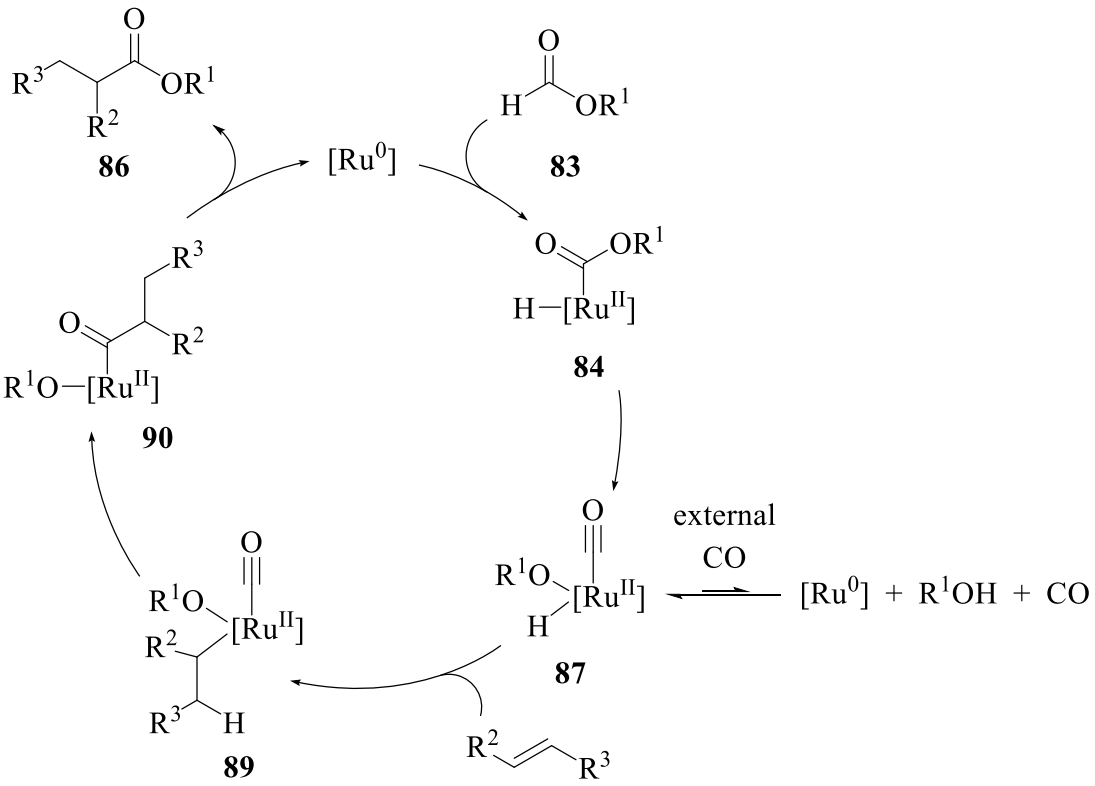


Figure 6. 2-Pyridyl methylformate containing a removable 2-pyridyl carbinol moiety.

Because $Ru_3(CO)_{12}$ catalyzes the same transformation starting from either the alcohol or formate ester{Kondo, 1989 #438} (Scheme 38), an alternative mechanism invoking reversible decarbonylation and carbonylation has also been proposed. Accumulation of CO pressure and alcohol over the course of the reaction has been observed and lends support to this proposal.{Profir, 2014 #734}{Konishi, 2014 #735} In this pathway, acylruthenium hydride **84** undergoes carbonyl deinsertion to give ruthenium-carbonyl complex **87**. This species can lose CO and form the alcohol byproduct; however, under an external pressure of CO, the equilibrium favors complex **87**. The alkene inserts into ruthenium hydride **87** to form complex **89**, which then undergoes migratory insertion to give acylruthenium alkoxide **90**. A

final C─O bond reductive elimination furnishes the desired product and regenerates the active ruthenium(0) catalyst.

(44)



Scheme 38

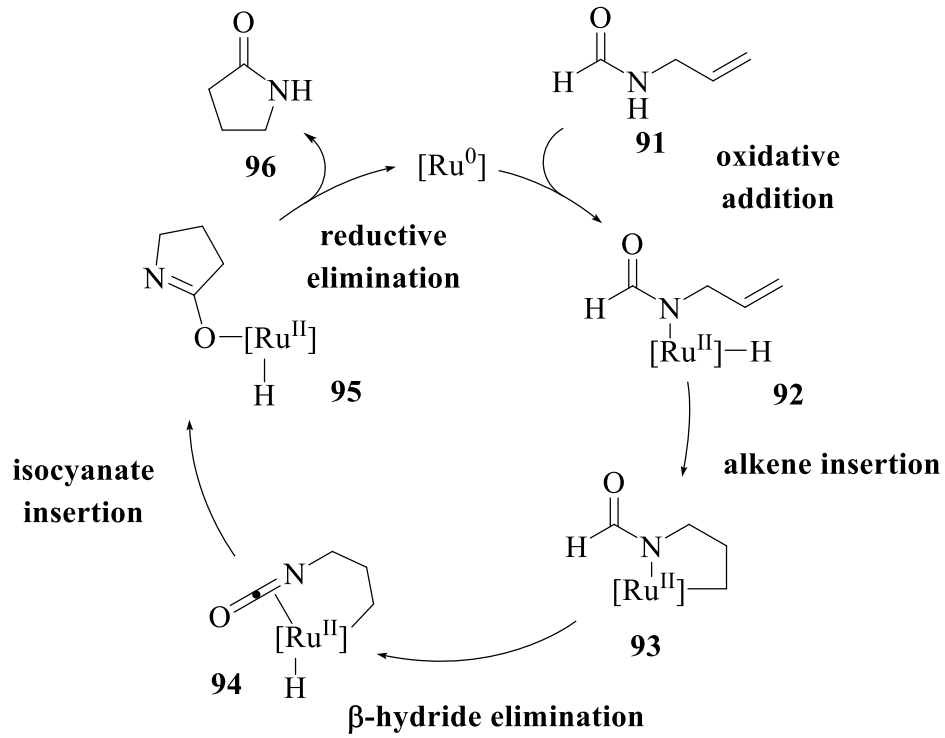
Alkene Hydrocarbamoylation

Ruthenium(0) Catalysis

Two distinct mechanistic pathways have been proposed for alkene hydrocarbamoylation. Ruthenium catalysts derived from $[Ru_3(CO)_{12}]$ and Bu_4NI tend to proceed through a mechanism involving N─H activation instead of initial C─H activation (Scheme 39).{Armanino, 2013 #494} Substrates lacking a free N—H bond are unreactive under these reaction conditions. Thus, oxidative addition of the metal into allylic formamide **91** generates amidoruthenium hydride **92**. The pendant

olefin inserts into the ruthenium-hydride bond, providing ruthenacycle **93**, which subsequently undergoes β-hydride elimination to form isocyanate-bound ruthenium hydride **94**. A second migratory insertion step takes place to form complex **95**. Reductive elimination then affords the new lactam **96** and turns over the catalyst.

(45)



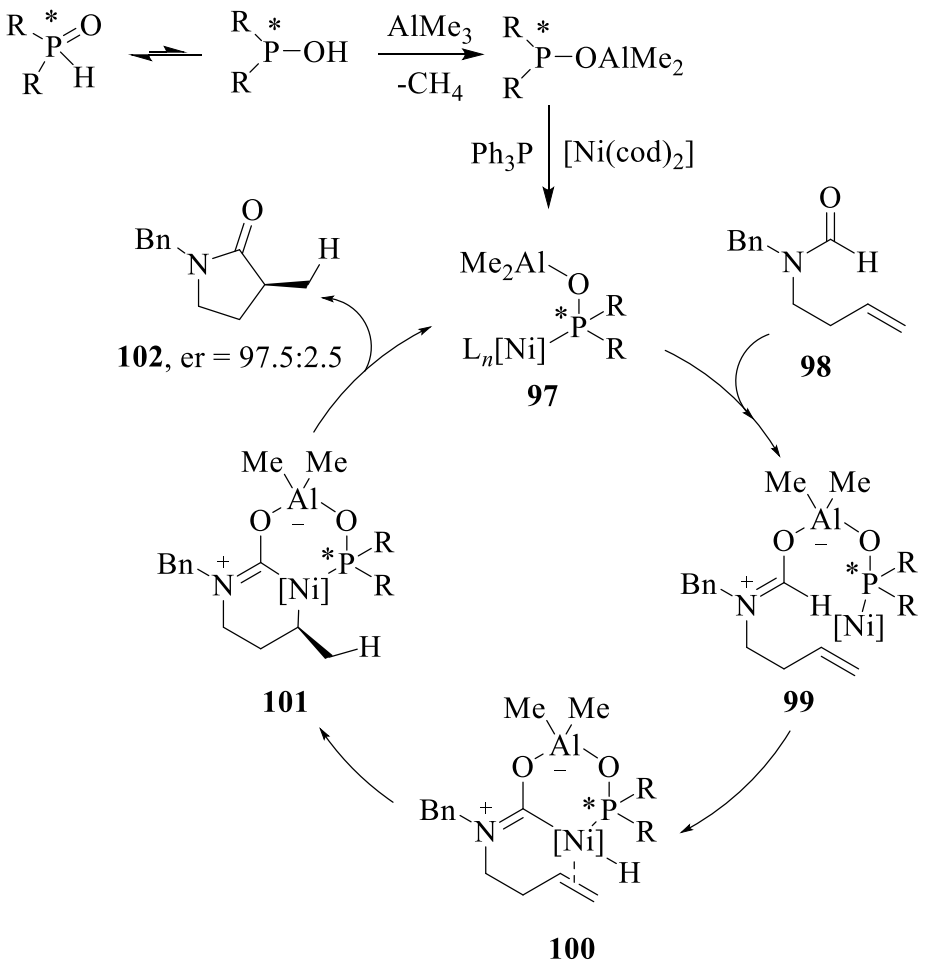
Scheme 39

The direct C─H activation mechanism is found to be operative under conditions in which halide additives are not used.{Li, 2014 #497} In this case the reaction pathway is proposed to occur in a fashion analogous to that illustrated in Scheme 38. The role of the added halide ion is generally believed to promote formation of an active halide-bridged ruthenium cluster, and not to dissociate the ruthenium cluster into its monomeric components.{Park, 2006 #736},{Li, 2014 #497}

Nickel(0) / Lewis Acid Co-Catalysis

The activation of formyl C─H bonds by nickel requires the addition of a Lewis acid co-catalyst. Using a Ni(0)/$AlMe_3$ bimetallic system, intramolecular hydrocarbamoylation can occur to form pyrrolidinones with high enantioselectivity. For example, a chiral secondary phosphine oxide ligand tautomerizes to its phosphinic acid form and coordinates $AlMe_3$ (Scheme 40).{Donets, 2013 #531} This results in the release of a molecule of methane to afford a Lewis acid-Lewis base adduct. The phosphorus atom then binds [$Ni(cod)_2$] to furnish bifunctional complex **97**. The aluminum atom simultaneously coordinates the carbonyl oxygen of formamide **98** to form adduct **99**, which brings the two reacting partners into close proximity and activates the formyl C─H bond for metal-mediated cleavage. Oxidative addition, migratory insertion, and reductive elimination yields pyrrolidinone **102**.

(46)



Scheme 40

SCOPE AND LIMITATIONS

Hydroacylation can be performed in both intra- and intermolecular settings, and both types of reactions can be rendered regio- and/or enantioselective in the presence of a chiral metal catalyst. Whereas early studies focused on intramolecular cyclizations of alkenals to furnish cyclopentenones using rhodium catalysts, recent efforts are targeted toward developing alternative catalysts that offer higher selectivity for hydroacylation over competing pathways, achieve intermolecular reactivity, and

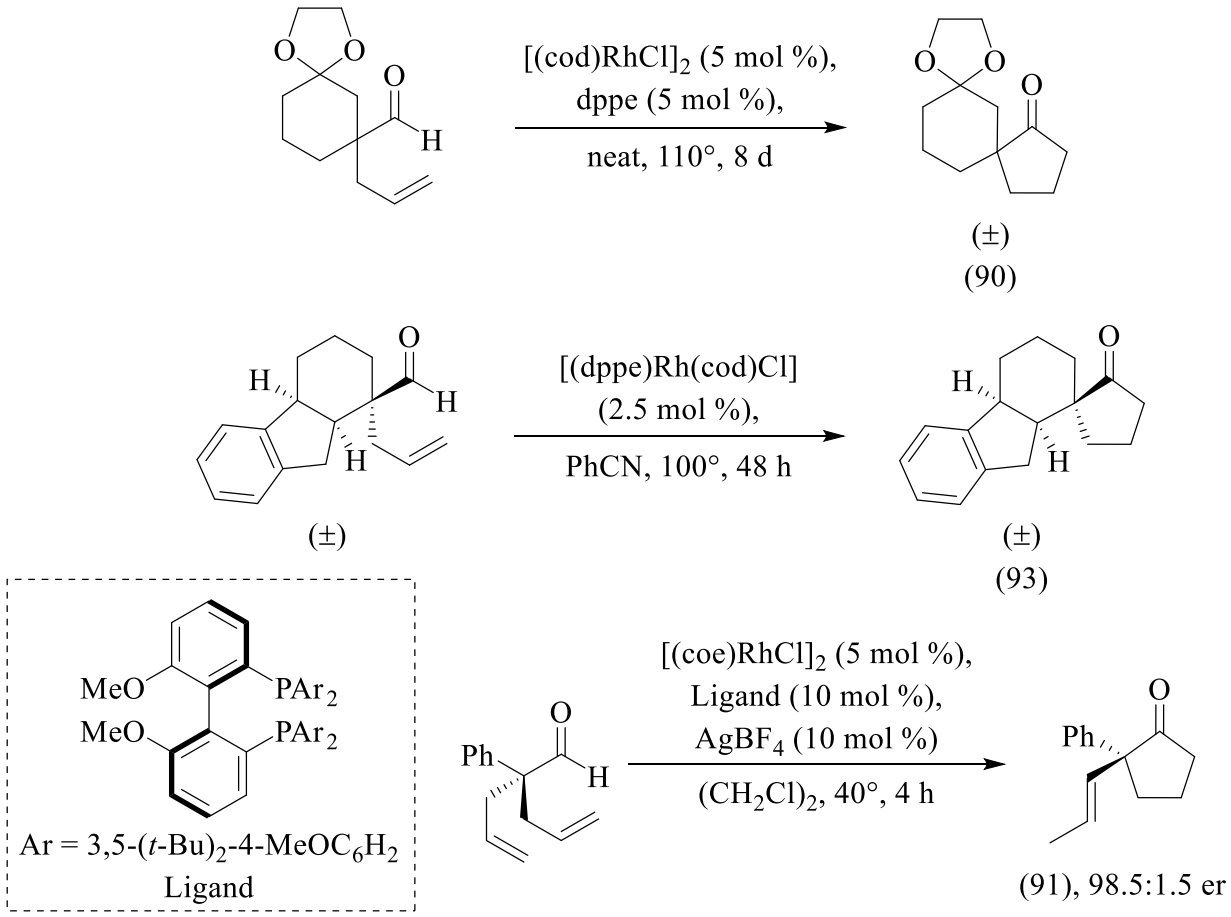
provide enantioenriched products. Because alkenes, alkynes, and carbonyl units all undergo hydroacylation, each of these classes of functional groups will be examined separately in this section.

Intramolecular Alkene Hydroacylation

Synthesis of Five-Membered Cyclic Ketones

The rhodium(I)-catalyzed cyclization of 4-alkenals **4** is one of the most thoroughly studied processes in hydroacylation. Substrates containing various substitution patterns, including 1,1- and 1,2-disubstituted alkenes, readily cyclize to form cyclopentenones.{Vautravers, 2011 #262} Cyclopentenones that are part of spirocyclic and fused-ring scaffolds are also readily accessed via hydroacylation.{Larock, 1980 #222}{Fairlie, 1988 #224}{Sattelkau, 1998 #367}{Sattelkau, 1998 #368}{Takahashi, 2000 #374}{Tanaka, 2001 #375}{Rolandsgard, 2005 #369} Currently, there are no examples of hydroacylating tri- and tetrasubstituted alkenes. Examples of activating formyl C─H bonds adjacent to quaternary carbon centers are rare, but reactivity is possible at elevated temperatures{James, 1983 #355}{Rolandsgard, 2005 #369}{Bjørnstad, 2008 #370} or with specialized substrates that bear an additional alkene that acts as a directing group{Park, 2015 #751} (Scheme 41). The versatility of this approach, and the low catalyst loadings required make this an attractive method for the construction of substituted 5-membered carbo- and heterocycles.

(47)

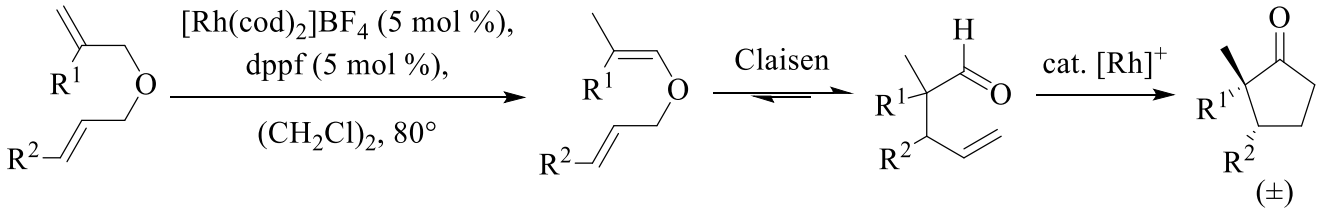


Scheme 41

The synthesis of substituted 4-pentenal substrates is often challenging. The precursors to this hydroacylation are generally air-sensitive and of low molecular weight, which renders them difficult to isolate and purify. One solution is to generate the 4-alkenal which would undergo a subsequent hydroacylation in one pot.{Eilbracht, 1995 #232}{Dygutsch, 1996 #233}{Sattelkau, 1998 #367} {Sattelkau, 1998 #368}{Okamoto, 2013 #231} A recently reported approach involves a cascade reaction starting from unsymmetric diallyl ether **103** (Scheme 42).{Okamoto, 2013 #231} The cationic catalyst $[Rh/dppf]^+$ chemoselectively isomerizes the terminal 2,2-disubstituted alkene to alkenyl ether **104**, which undergoes a thermal Claisen rearrangement. The same rhodium complex then catalyzes

hydroacylation of alkenal **105** to arrive at cyclopentanone **106**. Modest to good yields are obtained when the 2,2-disubstituted alkene contains an aryl group (R^1 = aryl). The yield is considerably lower when a 2,2-dialkyl-substituted alkene is used, presumably because of non-selective isomerization of the diallyl ether in the first step.

(48)



103 **104** **105** **106**

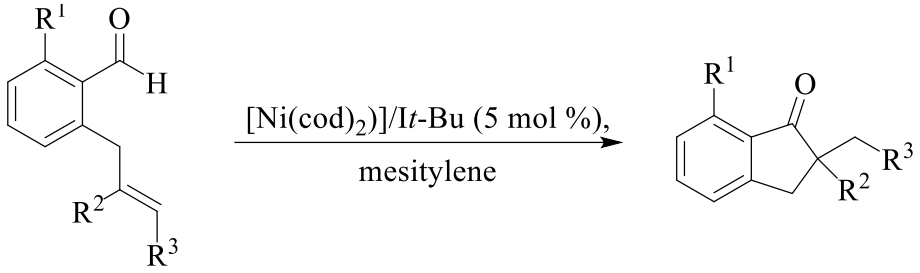
R^1	R^2	Time (h)	Yield (%)	dr	
Ph	Me	16	83	—	
4-$MeOC_6H_4$	Me	16	69	—	
4-BrC_6H_4	Me	16	60	—	
2-furyl	Me	16	58	—	
n-Bu	Ph	16	30	60:40	R^1 and R^2 *cis* (major)
Ph	H	72	37	97:3	R^1 and R^2 *cis* (major)

Scheme 42

Intramolecular hydroacylation is dominated by the use of rhodium catalysis with only two examples of cobalt catalysis involving the cyclizations of 4-pentenal **7**{Vinogradov, 1985 #351}{Vinogradov, 1988 #223} and vinylbenzaldehydes **114** (Scheme 45).{Yang, 2014 #750} Despite the interest in using catalysts that are derived from cheap and abundant metal sources, there is only one other report that uses nickel to cyclize *ortho*-allylbenzaldehyde derivatives **107** to generate 5-membered carbocycles **108** (Scheme 43).{Hoshimoto, 2012 #489} Of note, the regioselectivity of this nickel-catalyzed process is reversed as a consequence of the different mechanism with respect to rhodium, and

Markovnikov addition of the formyl group is observed. Yields are generally high; however, reaction temperatures up to 130˚ are required.

(49)



107 **108**

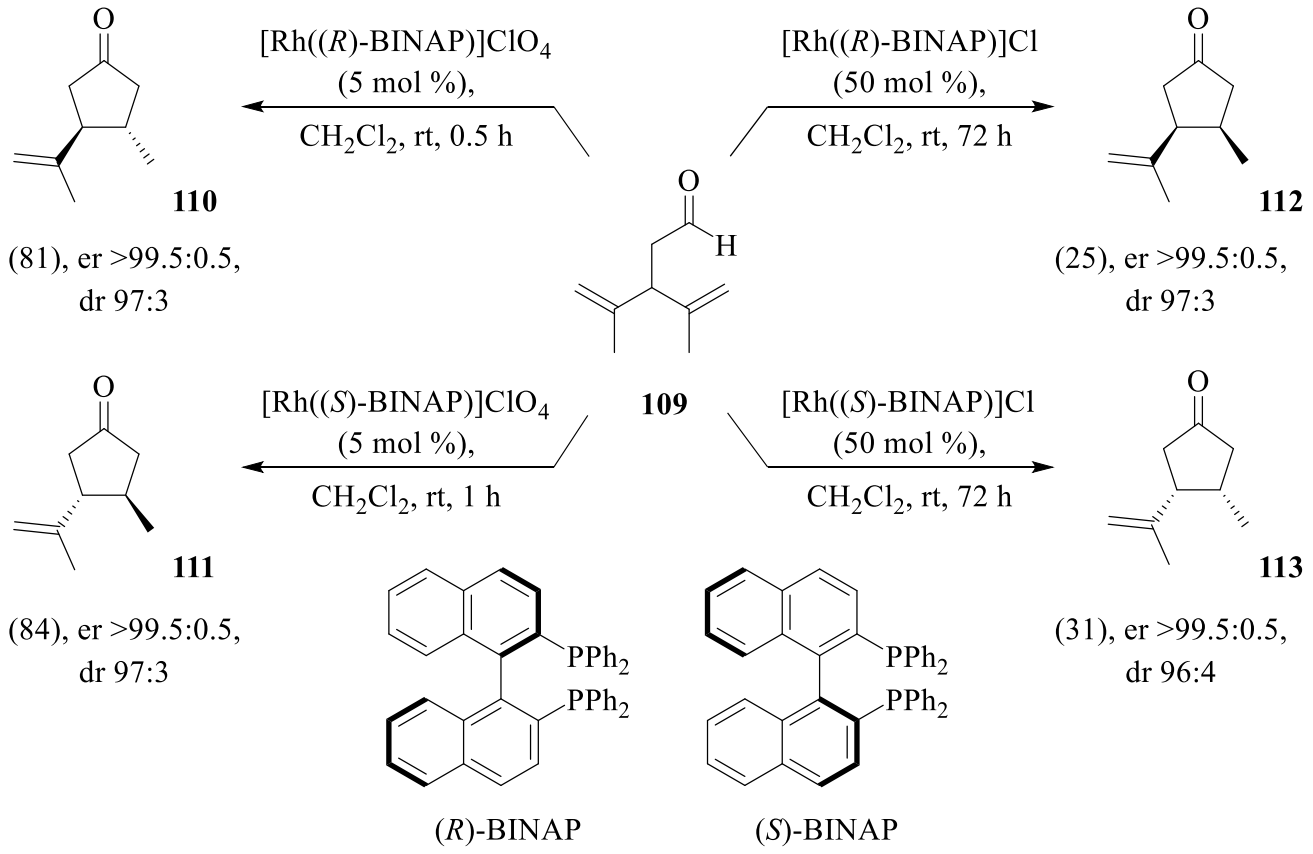
R^1	R^2	R^3	Temp (°)	Time (h)	Yield (%)
H	H	H	130	5	98
Bn	H	H	130	1	99
$SiEt_3$	H	H	130	2	99
allyl	H	H	90	5	93
H	Me	H	130	6	84
H	H	Ph	130	24	54

Scheme 43

Asymmetric Catalysis. Although a number of chiral ligands have been reported for enantioselective synthesis of cyclopentanones, high selectivities are achieved through the use of the chiral [Rh(BINAP)] and [Rh(Me-Duphos)] complexes.{Taura, 1989 #240}{Taura, 1991 #241}{Wu, 1992 #242}{Wu, 1993 #504}{Barnhart, 1994 #358}{Barnhart, 1994 #501}{Barnhart, 1995 #357}{Barnhart, 1997 #499}{Barnhart, 1997 #500} In fact, [Rh(BINAP)] exerts both remarkable enantio- and diastereocontrol by varying the metal counterion and the configuration of the ligand (Scheme 44).{Wu, 1992 #242}{Wu, 1993 #504} In the desymmetrization of dienal **109** using cationic comlex $[Rh(BINAP)]^+$ with the weakly coordinating ClO_4^- counterion, *trans*-cyclization products **110** and **111** are formed in high yields and selectivities. In contrast, the neutral [Rh(BINAP)Cl] with the

strongly coordinating Cl^- counterion is considerably less reactive, but still catalyzes a highly diastereo- and enantioselective transformation to yield *cis*-disubstituted cyclopentanones **112** and **113**. The precise role of the counterion in dictating diastereocontrol remains unclear.

(50)

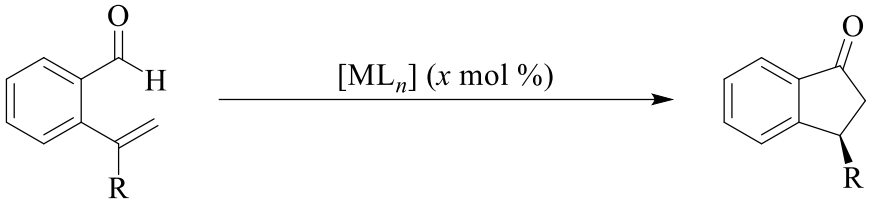


Scheme 44

Enantioselective hydroacylation of 2-vinylbenzaldehydes **114** offers a mild method for the synthesis of chiral 3-substituted indanones.{Kundu, 2005 #376}{Hyatt, 2007 #476}{Yang, 2014 #750} Compared to aliphatic alkenals discussed previously, 2-vinylbenzaldehydes are relatively easy to prepare. At present, this substrate is the only class that can undergo catalysis by both chiral rhodium and cobalt complexes. In the case of rhodium catalysis, slow addition of these substrates to 2 mol % of

[Rh((*R*)-BINAP)]ClO_4 provides the desired indanones **115** in excellent yields and er's with the exception of a vinylsilane (Scheme 45). The slow addition protocol keeps the concentration of 2-vinylbenzaldehyde in the reaction mixture low, which is necessary in this case to avoid an undesirable dimerization pathway.

(51)



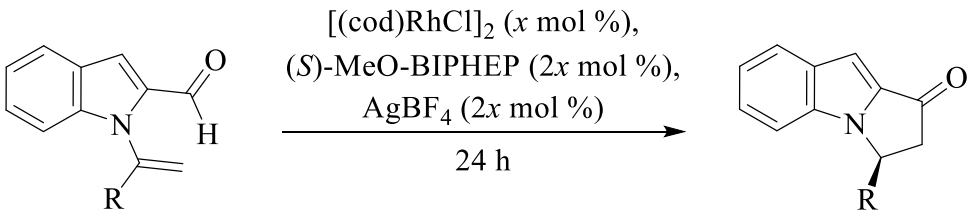
114 **115**

R	[ML$_n$]	*x*	Solvent	Temp (°)	Time (h)	Yield (%)	er
Me	[Rh((*R*)-BINAP)]ClO_4	2	CH_2Cl_2	23	2	97	99.5:0.5
Me	[Co((*R*,*R*)-BDPP)]Cl	10	MeCN	25	12	94	98.5:1.5
Ph	[Rh((*R*)-BINAP)]ClO_4	2	CH_2Cl_2	23	2	98	99:1
Ph	[Co((*R*,*R*)-BDPP)]Cl	10	MeCN	25	12	95	98.5:1.5
$SiMe_3$	[Rh((*R*)-BINAP)]ClO_4	2	CH_2Cl_2	23	2	93	85:15
CF_3	[Rh((*R*)-BINAP)]ClO_4	2	CH_2Cl_2	23	2	90	99.5:0.5
4-FC_6H_4	[Co((*R*,*R*)-BDPP)]Cl	10	MeCN	80	12	87	95:5

Scheme 45

Guided by studies on the hydroacylation of 2-vinylbenzaldehydes **114** (Scheme 45),{Kundu, 2005 #376}{Hyatt, 2007 #476} nitrogen-containing analogues **116** with electron-rich 2,2-disubstituted olefins are found to be reactive under rhodium catalysis to give non-racemic dihydroindolones **117** (Scheme 46).{Ghosh, 2014 #511} The reaction proceeds under mild conditions for various substituents on the internal carbon of the alkene with the exception of a larger cyclohexyl group, in which case a higher temperature and a higher-boiling solvent 1,4-dioxane are necessary.

(52)



116 **117**

R	Solvent	*x*	Temp (°)	Yield (%)	er
Ph	THF	2.5	60	90	99.5:0.5
4-$MeOC_6H_4$	THF	2.5	60	99	99.5:0.5
4-$CF_3C_6H_4$	THF	5	60	70	99.5:0.5
Me	THF	2.5	60	99	99.5:0.5
Cy	1,4-dioxane	2.5	100	45	97.5:2.5

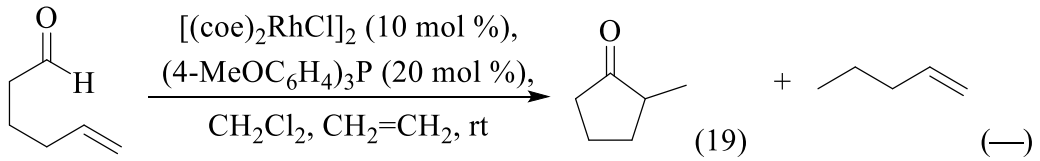
Scheme 46

Synthesis of Cyclohexanones

Developing hydroacylation strategies to afford 6-membered carbocycles and heteroatom-containing analogues is an ongoing challenge with few reported successes. Whereas rhodium(I) catalyzed hydroacylation of 4-alkenals is effective at producing cyclopentanones exclusively, subjecting 5-hexenal (**118**) to rhodium catalysis yields only a small amount of 2-methylcyclopentanone (**119**) with no trace of cyclohexanone formation (Scheme 47). In this case, a significant amount of aldehyde decarbonylation to 1-pentene (**120**) is observed (the reaction time was not reported).{Larock, 1980 #222} The desired reactivity of 5-alkenals does occur under special circumstances. For example, 3-allylribodialdose **121** is selectively transformed into cyclohexanone **122** in 60 % yield (Scheme 48).{Gable, 1991 #234} The 2-methylcyclopentanone isomer **123** is not formed under these conditions, presumably because of a potential build-up of strain in the 5,5,5-tricyclic structure. The added steric bulk in the 2,2-disubstituted alkene of 3-methallylribodialdose **124** effectively increases the barrier to hydroacylation. Instead, a rhodium-accelerated ene reaction occurs at 35˚ to generate cyclic,

homoallyllic alcohol **125** after 4 hours (yield of isolated product not reported). However, the use of *ortho*-methallyl benzaldehydes **126** with 2,2-disubstituted olefins coupled with 2-amino-3-picoline (**1**) as additive does favor cyclization to 6-membered carbocycles in modest yields (Scheme 49).{Beletskiy, 2012 #482}

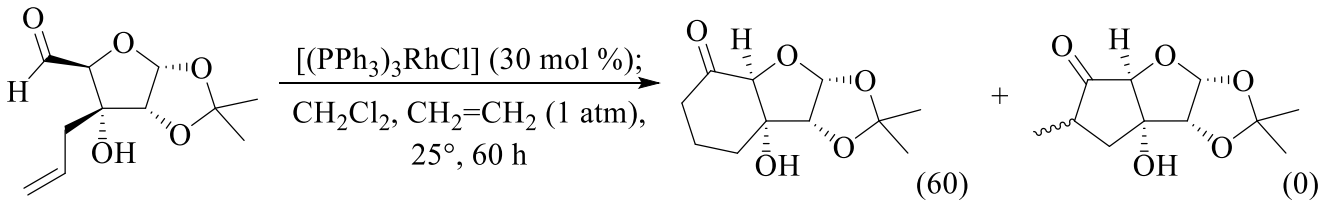
(53)



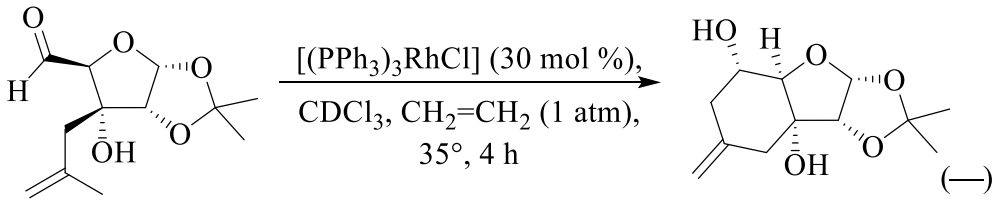
118 **119** **120**

Scheme 47

(54)



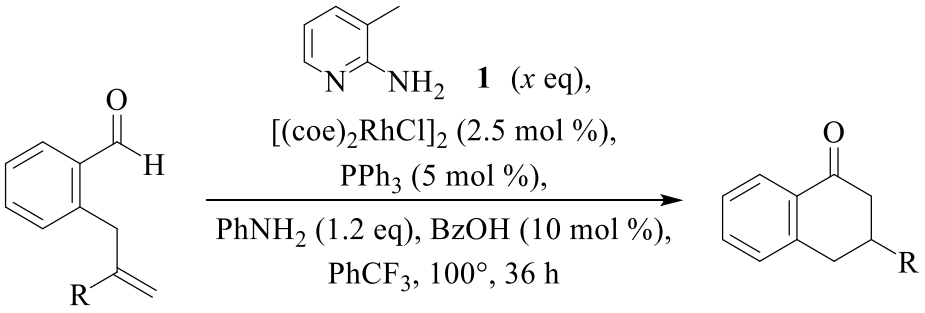
121 **122** **123**



124 **125**

Scheme 48

(55)



126 **127**

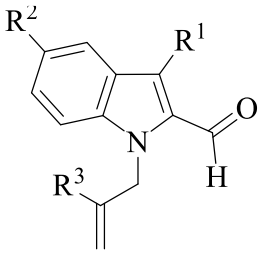
R	*x*	Yield (%)
Me	0.9	65
Ph	1	58

Scheme 49

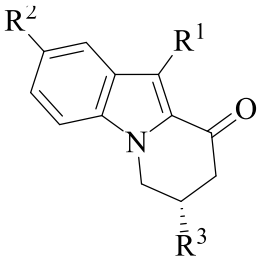
Cyclization to the 6-membered ring can be facilitated by incorporating a nitrogen atom into the system{Du, 2014 #764} *N*-Allylindole carboxaldehydes **128** are transformed into dihydropyridoindoles **129** under enantioselective rhodium catalysis (Scheme 50). The nitrogen atom in this circumstance does not act as a directing group. The high regioselectivity observed in this system may be attributed in part to the 2,2-disubstituted olefin, which would sterically favor anti-Markovnikov addition. The [Rh((*R*)-Tol-BINAP)]$^+$ catalyst developed for this method exhibits high reactivity for substrates containing a methyl-substituted alkene (R^3 = Me); however, the reactivity drops as the alkene is substituted with larger aliphatic or aromatic groups. When $R^3 \neq$ Me, both higher catalyst loading and higher reaction temperatures are necessary. In addition, the optimal catalyst for the more hindered substrates is derived from $AgSbF_6$ instead of $AgBF_4$. The SbF_6^- counterion is slightly less coordinating than BF_4^-, and presumably gives rise to a more active rhodium catalyst.{Diaz-Torres, 2011 #545} The same catalyst system promotes the transformation of *N*-allylpyrrolecarboxaldehydes **130** to enantioenriched dihydroindolizinones **131** (Scheme 51). In contrast to the hydroacylation of *N*-

allylindolecarboxaldehydes **128**, the hydroacylation of *N*-allylpyrrolecarboxaldehydes **130** is more tolerant of varying substituents on the central carbon of the allyl unit.

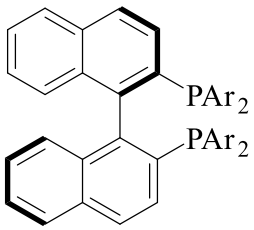
(56)



[(cod)RhCl]$_2$ (*x* mol %),
(*R*)-Tol-BINAP (2*x* mol %),
AgY (2*x* mol %),
1,4-dioxane, 24 h



128 **129**

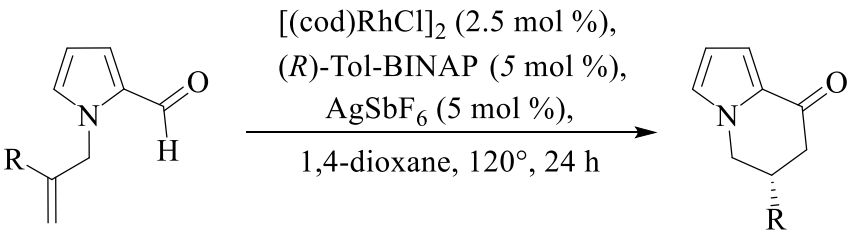


Ar = 4-MeC$_6$H$_4$
(*R*)-Tol-BINAP

R^1	R^2	R^3	*x*	Y	Temp (°)	Yield (%)	er
H	5-MeO	Me	2.5	BF_4	100	95	99.5:0.5
H	5-Cl	Me	2.5	BF_4	100	92	99:1
H	5-NO_2	Me	2.5	BF_4	100	89	98:2
Et	H	Me	2.5	BF_4	100	93	96.5:3.5
H	H	Et	5	SbF_6	120	53	98.5:1.5
H	H	*n*-C_6H_{13}	5	SbF_6	120	42	98:2
H	H	Ph	5	SbF_6	120	37	98.5:1.5
H	H	CO_2Et	5	SbF_6	120	23	98:2

Scheme 50

(57)



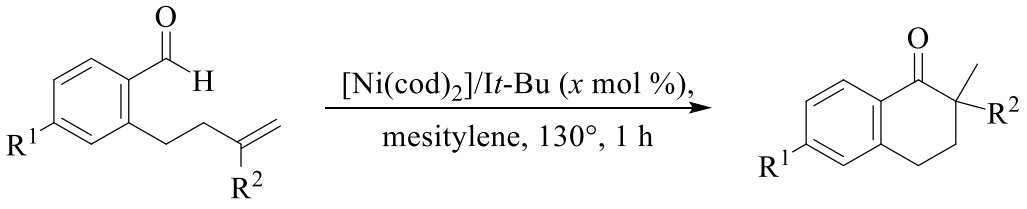
130 **131**

R	Yield (%)	er
Me	79	98.5:1.5
n-C_6H_{13}	(51	97:3
Ph	96	98.5:1.5
CO_2Et	98	99:1

Scheme 51

Examples of using rhodium catalysts to cyclize alkenals to 6-membered rings are limited, and the reported yields for carbocycle formation are only modest. Nickel catalysis offers a promising solution to this problem. Starting from *ortho*-homoallyl benzaldehyde derivatives **132**, 2-substituted-3,4-dihydronaphthalenones **133** are obtained in high yields and in short reaction times (Scheme 52).{Hoshimoto, 2012 #489} The high temperature required to achieve reactivity is a disadvantage to this method and would have a consequence on the substrate scope if more complex substrates were considered. However, further ligand and catalyst development should pave the way for milder reaction conditions and enantioselective protocols.

(58)



132 **133**

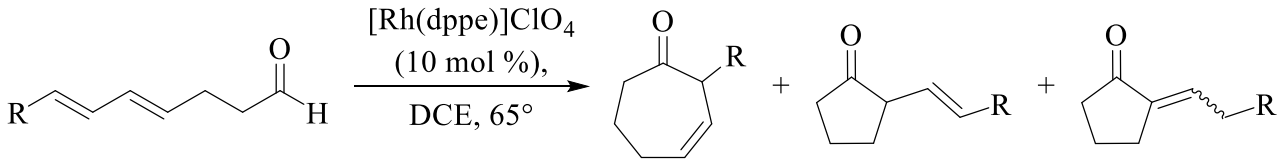
R^1	R^2	*x*	Yield (%)
H	H	5	92
OMe	H	5	99
F	H	5	70
H	Me	10	75

Scheme 52

Synthesis of Seven- and Eight-Membered Rings

Isomerization and Fragmentation Strategies. Seven- and eight-membered rings are among the most difficult ring sizes to prepare.{Illuminati, 1981 #747} Intramolecular alkene hydroacylation to generate rings that are larger than cyclopentanones is kinetically unfavorable and thus suffer from competing decarbonylation (for rhodium-catalyzed reactions). Strategies involving kinetically favorable hydride addition to a proximal double bond, followed by isomerization, and the use of directing groups have emerged for the catalytic syntheses of seven- and eight-membered carbocycles. For example, 4,6-dienals **134** provide an entry point into cycloheptenones **135**, although cyclopentanones **136** and **137** are also formed to some extent (Scheme 53).{Oonishi, 2007 #236}{Oonishi, 2007 #227} An electron-donating substituent at C7 is required for cycloheptenone formation, and when R = H, cyclopentanone **137** is formed as the major product.

(59)



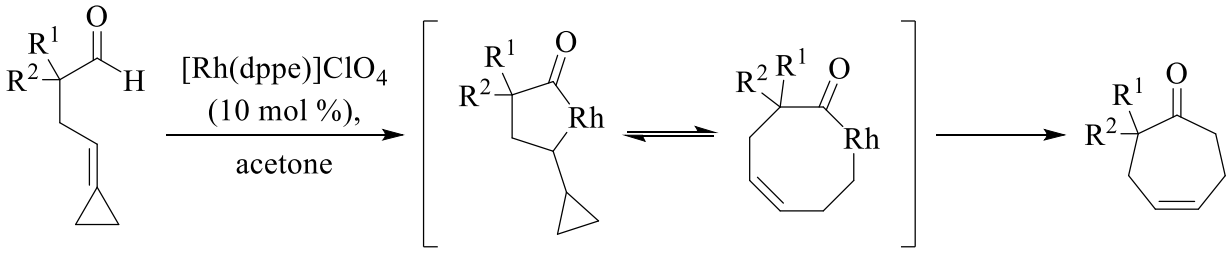
134 **135** **136** **137**

		Yield (%)			
R	Time (h)	**135**	**136**	**137**	*E*/*Z* (**137**)
CH_2CH_2Ph	18	6	13	62	*E* only
CH_2CH_2Cy	24	9	—	66	*E* only
H	17	45	—	7	*E*/Z = 1:2.5

Scheme 53

Seven-membered ring formation is also favored over five-membered ring formation with α-substituted 4-cyclopropylidenebutanal derivatives **138** (Scheme 54).{Crepin, 2011 #541} In contrast to the diene hydroacylation above, the reaction proceeds by hydride addition followed by ring opening of the strained cyclopropane by β-carbon elimination. α,α-Disubstitution gives rise to products with α-quaternary centers. In addition, this method exhibits high chemoselectivity for the cyclopropylidene functional unit and has little effect on other pendant alkenes or alkynes. Substituting the cyclopropylidene for a strained cyclobutylidene gives rise to cyclooctenone products (Scheme 55).{Crépin, 2010 #542}{Aïssa, 2013 #543} Azetidines exhibit a similarly high strain energy (26.2 kcal/mol) with respect to cyclobutane (26.3 kcal/mol) and also undergo ring-opening hydroacylation to generate 8-membered, nitrogen-containing heterocycles. In this study, $AgBF_4$ is used to abstract the chloride counterions from the rhodium precursor to generate more active cationic catalysts which also causes less decarbonylation.{Fairlie, 1988 #224}{Fairlie, 1988 #225} In one case, a neutral rhodium catalyst (chloride counterion) is more effective, but ethylene is necessary to achieve reactivity. In the absence of ethylene, no conversion of the starting materials occurs.

(60)

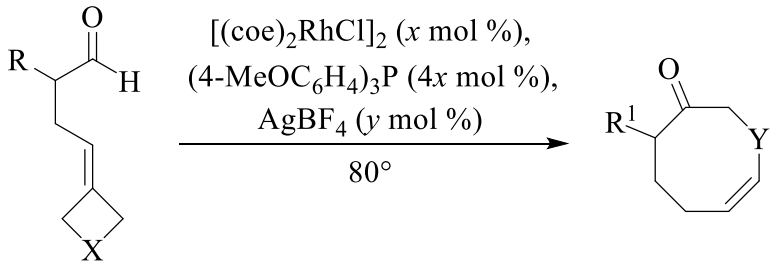


138 **139**

R^1	R^2	Temp (°)	Time (h)	Yield (%)
Ph	Me	21	2	85
CH_2OTBS	CH_2Ph	60	3	93
Ph	allyl	21	4	75
Ph	$CH_2CH{=}C(Me)_2$	21	12	75
Ph	$CH_2C{\equiv}CSi(Me)_3$	21	12	58

Scheme 54

(61)

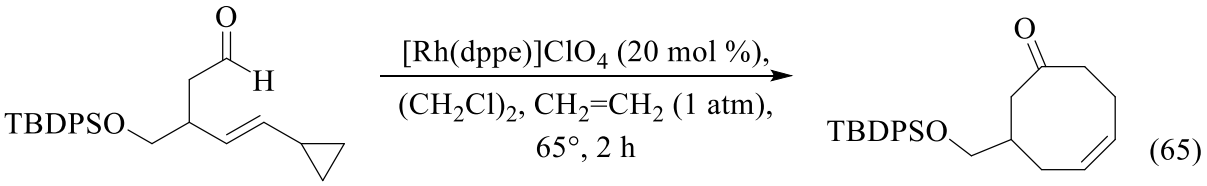


R	Y	Solvent	*x*	*y*	Time (h)	Yield (%)
H	$CHCH_2OBn$	$(CH_2Cl)_2$	2.5	5	16	69
H	CPh_2	$(CH_2Cl)_2$	5	10	22	79
Me	$CHCH_2OBn$	$(CH_2Cl)_2$ ($CH_2{=}CH_2$ saturated)	7.5	0	86	75
H	NTs	$(CH_2Cl)_2$ ($CH_2{=}CH_2$ saturated)	5	0	86	85

Scheme 55

4-Alkenal **140** containing a cyclopropyl moiety substituted at the 5-position undergoes fragmentation and is selectively transformed into cyclooctenone **141** using the [Rh(dppe)]ClO_4 catalyst (Scheme 56).{Aloise, 2000 #215} Compared to perchlorate, the less coordinating triflate counterion is more effective for the preparation of fused [3.6.0] and [4.6.0] bicycles (Scheme 57). Although this method offers a promising approach to 8-membered carbocycles, a limitation is the low catalyst turnover number — high catalyst loadings are required and the product yields are modest.

(62)

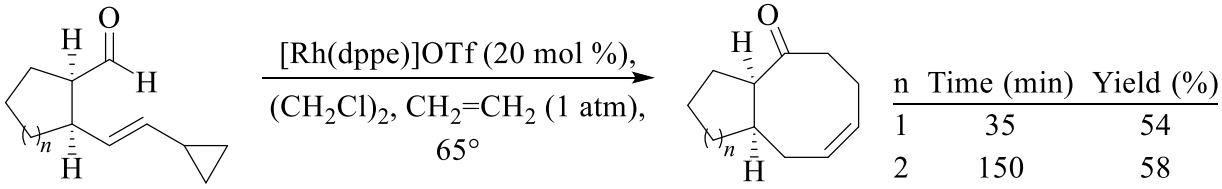


(65)

140 **141**

Scheme 56

(63)



n	Time (min)	Yield (%)
1	35	54
2	150	58

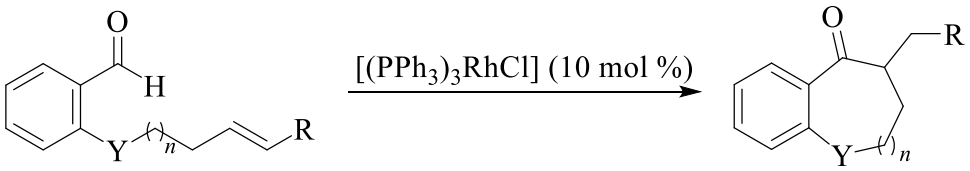
(±) (±)

Scheme 57

In general, the isomerization/fragmentation strategy to hydroacylation allows the synthesis of medium-sized rings without the use of directing groups. The alkene that is present in the product also provides a handle for further chemical manipulations. However, the synthesis of some of the hydroacylation precursors presented in this section is not always straightforward and often requires between five to eight synthetic steps. Nonetheless, compared to traditional ring closing methods, these

transition-metal-catalyzed processes do not give rise to oligomerization and polymerization byproducts and thus do not require high-dilution conditions. The preparation of non-racemic, medium-ring carbocycles via isomerization-hydroacylation has not been reported to date.

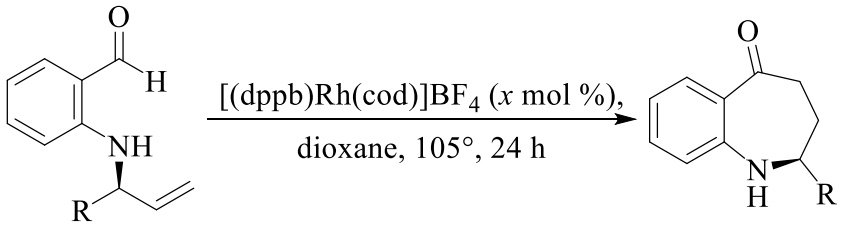
Directing Group Strategies. Lewis-basic heteroatoms are excellent at directing metal-catalyzed hydroacylations and have been exploited in the syntheses of medium-ring heterocycles. Substituted aniline,{Bendorf, 2012 #353} ether,{Coulter, 2009 #24} thioether,{Bendorf, 2002 #237}{Coulter, 2009 #24} and sulfoxide{Coulter, 2009 #24} functional groups effectively promote rhodium-catalyzed cyclization of alkenals to furnish seven- and eight-membered rings. Wilkinson's complex catalyzes nitrogen{Bendorf, 2012 #353} and sulfur{Bendorf, 2002 #237} directed hydroacylations (Scheme 58), but is inactive when oxygen-based directing groups are incorporated into the substrate. When the heteroatom is substituted with a homoallyl group (n = 1), seven-membered cyclic ketones are formed regioselectively. Chelation assistance with nitrogen allows both mono- and 1,2-disubstituted alkenes to participate in intramolecular hydroacylation (R = Ph). Although the allyl substituent on nitrogen is not transformed in the reaction, it exhibits a positive effect on reactivity (compared to other alkyl substituents such as methyl and benzyl) and can be removed by standard deprotection protocols when necessary. Homologating the alkyl chain by an additional methylene unit (n = 2) shuts down reactivity. The use of sulfur as the coordinating heteroatom allows the reaction to proceed at room temperature. In contrast to the use of nitrogen-based coordinating groups, only monosubstituted alkenes (R = H) undergo regioselective hydroacylation. Both homoallyl (n = 1) and bis-homoallyl (n = 2) units are compatible, thus providing the seven- and eight-membered cyclic ketones, respectively. However, when the sulfur atom is substituted with a tris-homoallyl (n = 3) group, no reaction takes place.



Y	*n*	R	Solvent	Temp	Yield (%)
N(allyl)	1	H	MeCN	reflux	84
N(allyl)	1	Ph	MeCN	reflux	77
N(allyl)	2	H	MeCN	reflux	0
S	1	H	CH_2Cl_2	rt	92
S	2	H	CH_2Cl_2	rt	62
S	3	H	CH_2Cl_2	rt	0

Scheme 58

Although Wilkinson's catalyst does not transform the alkene that is part of the *N*-allyl functional unit, [(dppb)Rh(cod)]BF_4 catalyzes the hydroacylation of allylic amine **142** into aza-ketone **143** (Scheme 59).{Arnold, 2014 #498} The stereogenic center in the enantioenriched starting material is not epimerized over the course of the reaction, despite the high temperature required. This method is particularly attractive because the complex [(dppb)Rh(cod)]BF_4 is commercially available and can be used to catalyze hydroacylation directly without pre-activation (see Experimental Procedures). This is an advantage because it greatly simplifies the procedure for rhodium-catalyzed hydroacylation. If the catalyst precursor involves the use of a rhodium source that is ligated with two bidentate diene ligands {*e.g.*., $[Rh(cod)_2]BF_4$ and $[Rh(nbd)_2]BF_4$}, a hydrogenation step is normally required to remove these non-spectator ligands, which compete for substrate binding.



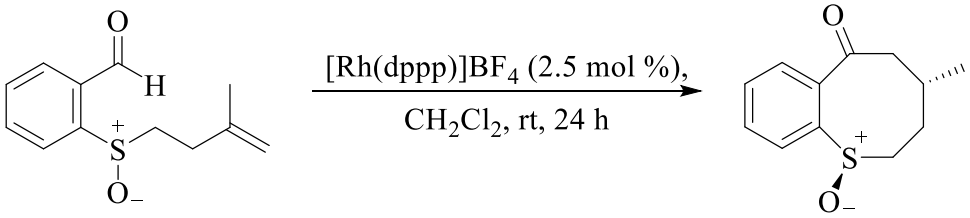
142 **143**

R	*x*	Yield (%)	er (**142**)	er (**143**)
Cy	7.5	(99)	90:10	90:10
i-Bu	7.5	(96)	90:10	89:11
CH_2Ph	5	(99)	96:4	96:4
CH_2OBn	5	(92)	93:7	93:7

Scheme 59

A rhodium complex supported by the bidentate dppp ligand catalyzes oxygen- and sulfur-directed intramolecular hydroacylations.{Coulter, 2009 #24} In addition, this catalyst promotes a sulfoxide-directed hydroacylation (Scheme 60). In contrast to hydroacylations catalyzed by Wilkinson's catalyst, which selectively gives branched products (Scheme 58), [Rh(dppp)]BF_4 catalysis generates an eight-membered ring heterocycle **145** by anti-Markovnikov addition to the sulfoxide-bearing alkenal **144**. Because the sulfoxide unit is chiral, the rhodium catalyst induces a highly diastereoselective process, providing the product in >20:1 dr.

(66)

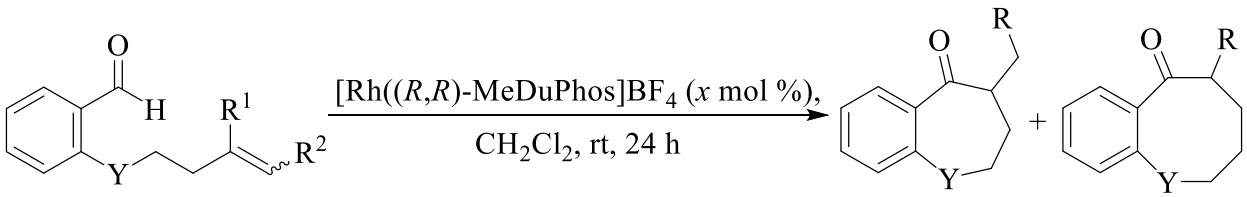


(±)-**144** (±)-**145**
(87), dr >20:1

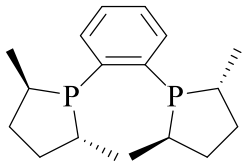
Scheme 60

Enantioselective Catalysis. Intramolecular hydroacylation via chelation-assistance can be rendered enantioselective by the use of chiral bidentate phosphine ligands.{Coulter, 2009 #24} Treatment of oxygen- and sulfur-containing alkenals **146** to catalytic amounts of [Rh((*R*,*R*)-MeDuPhos)]BF_4 resulted in formation of branched seven-membered cyclic ketones **147** regioselectively and in high er's (Scheme 61). However, the absolute configurations of the products are not determined. In the case of the sulfur-containing analogue, the eight-membered benzothiocinone **148** is formed as a minor constitutional isomer. The regioselectivity can be reversed to produce benzothiocinone **149** as the sole constitutional isomer by switching the ligand to (*S*,*S*)-BDPP (Scheme 62). In general, the sulfur atom appears to be more versatile than oxygen and can promote hydroacylation of disubstituted alkenes.

(67)



146 **147** **148**

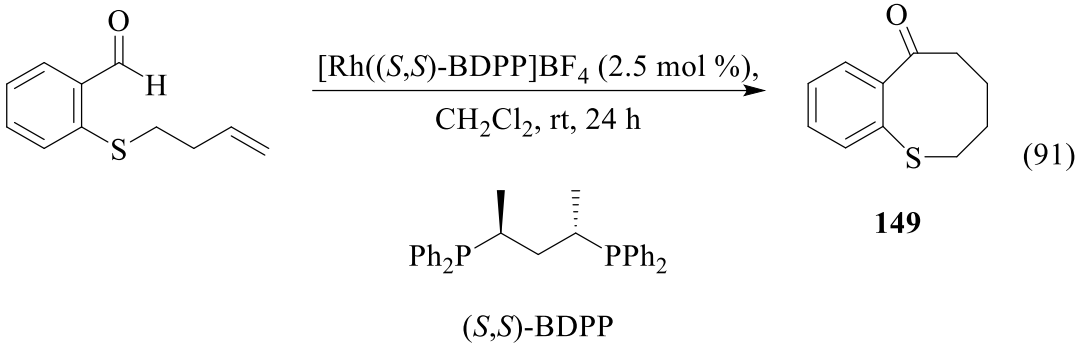


(*R*,*R*)-MeDuPhos

Y	R	*x*	Yield (%)	**147/148**	**er (147)**
O	H	5	88	>20:1	99:1
S	H	2.5	91	4:1	97.5:2.5
S	Et (*E*)	2.5	89	>20:1	98.5:1.5
S	Et (*Z*)	2.5	97	>20:1	96.5:3.5

Scheme 61

(68)



Scheme 62

Intramolecular hydroacylation allows access to a variety of five- to eight-membered cyclic systems. The ability to tune the rhodium catalyst by varying the ligand offers opportunities to control regioselectivity by catalyst control. Application to larger rings remains to be explored.

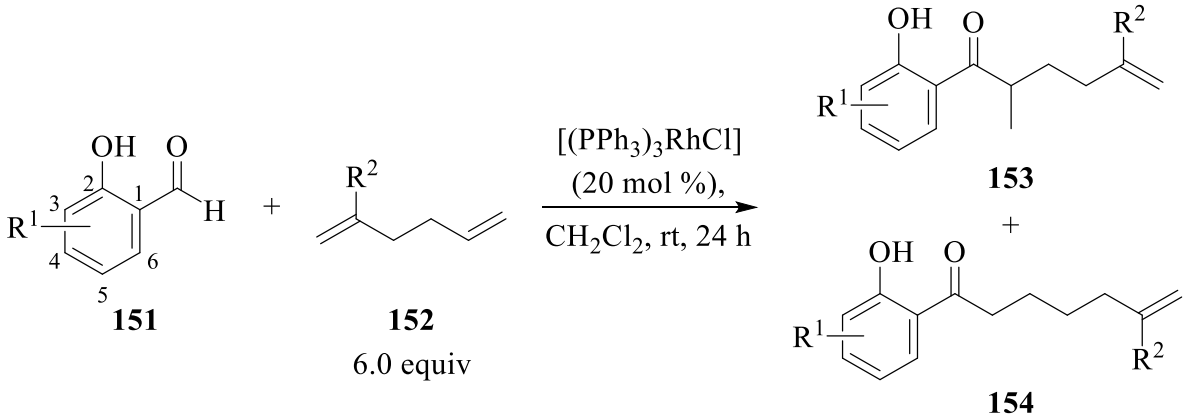
Intermolecular Alkene Hydroacylation

Rhodium-Catalyzed Reactions

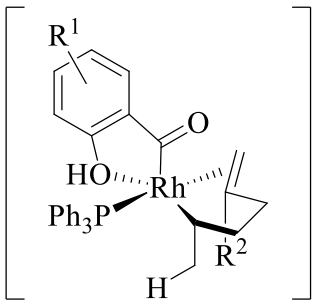
Aldehydes and alkenes are common and readily available reagents, and their intermolecular cross-coupling provides an atom-economical strategy for the preparation of ketones. However, rhodium-catalyzed, intermolecular alkene hydroacylation has proven especially challenging, owing to a lack of reactivity and the additional capacity of rhodium to catalyze aldehyde decarbonylation. To this end, chelation-control has been applied to accomplish intermolecular cross-couplings. In a double-chelation strategy where both the aldehyde and alkene can participate in two-point binding to the catalyst, 1,5-hexadienes **152** are hydroacylated with salicylaldehyde derivatives **151** to give branched ketones **153** in moderate selectivity (Scheme 63).{Tanaka, 2003 #424}{Imai, 2004 #425} Not only does chelation help suppress side-reactions, it also helps to favor branched selectivity in this system. When unsymmetrical

1,5-hexadienes containing a mono- and 2,2-disubstituted alkene are subjected to rhodium-catalysis, the monosubstituted alkene is selectively transformed. In contrast, substrates containing a monosubstituted and a 1,2-disubstituted alkene are considerably less reactive. The use of a catalytic amount of sodium acetate accelerates reactivity by deprotonating the phenolic hydroxyl group to promote chelation. Under these conditions, diene **155** has a slight preference to undergo hydroacylation at the internal alkene to give branched ketone **158** (Scheme 64). Ketone **159**, arising from linear-selective hydroacylation of the 1,2-disubstituted olefin, is not formed to any appreciable extent. However, both the linear and branched hydroacylations of the monosubstituted alkene to ketones **156** and **157** are observed.

(69)



via

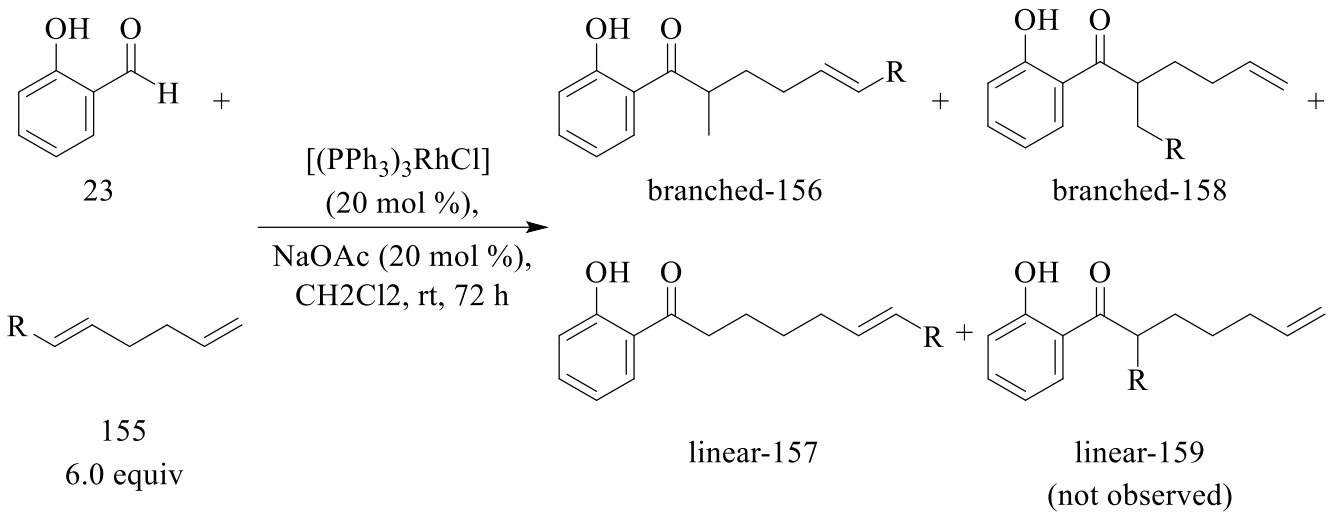


branched selective insertion

R^1	R^2	Time (h)	**153/154**	Yield (%)
H	H	24	4:1	100
3-OH	H	72	3:1	58
5-OH	H	72	3:1	90
5-Br	H	48	5:1	100
H	Me	24	20:1	100
H	Ph	72	6:1	77
H	$(CH_2)_2CH=CH_2$	72	5:1	74

Scheme 63

(70)



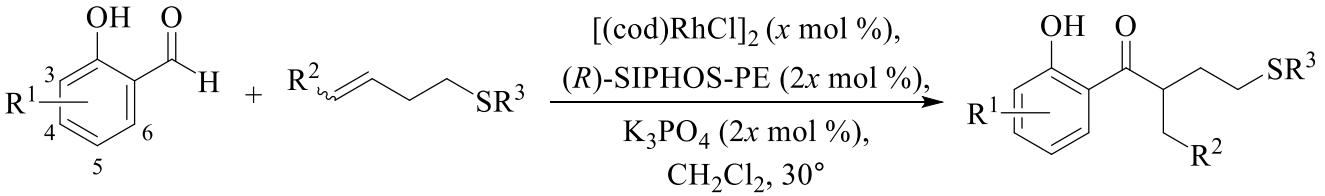
R	Yield (%)	**156/157/158**
Me	60	1:1:2
$(CH_2)_2CH=CH_2$	69	2.5:1:4.5

Scheme 64

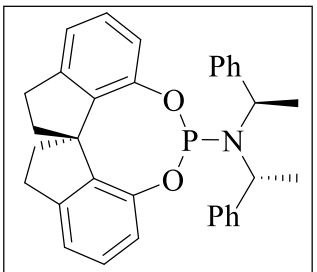
The reactivity and regioselectivity of the double-chelation approach can be substantially improved by substituting one of the double bonds in 1,5-hexadiene for sulfur. The sulfur heteroatom is an excellent ligand for rhodium, which makes it an excellent directing group for hydroacylation, and thereby allows the reaction to proceed with lower catalyst loadings and shorter reaction times. Salicylaldehyde derivatives **151** couple with homoallylic sulfides **160** to give chiral branched ketones **161** in >20:1 isomeric ratio (Scheme 65).{Coulter, 2010 #16} Good reactivity is observed for various substrates, including homoallylic sulfides containing a 1,2-disubstituted olefin; however, the er is affected by subtle steric and electronic influences. Introducing a sterically encumbering methyl substituent adjacent to the aldehyde (R^1 = 6-Me) results in a slightly diminished er. The electronic properties of the sulfur directing element also affect enantioselectivity. Increasing Lewis basicity correlates with decreasing er, with cyclohexyl sulfide (R^3 = Cy) directing the least enantioselective hydroacylation (77.5:22.5 er). Because this method involves two chelating substrates, monodentate

ligands are necessary which give rise to a coordinatively saturated rhodium complex **162** upon oxidative addition of the salicylaldehyde derivative **151** (Figure 7). Rhodium complexes ligated with bidentate phosphine ligands are not capable of accommodating both chelating substrates simultaneously and thus do not function as catalysts for these transformations.

(71)



151 **160** **161**

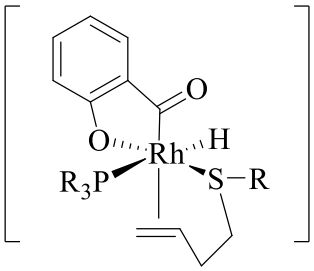


(*R*)-SIPHOS-PE

R^1	R^2	R^3	*x*	Time (h)	Yield (%)	er
H	H	Ph	2.5	18	97	96:4
5-CO_2Me	H	Ph	2.5	19	97	96:4
5-OMe	H	Ph	5	18	93	96.5:3.5
3-OMe	H	Ph	2.5	18	91	96:4
6-Me	H	Ph	5	18	94	92:8
H	H	2-MeO_2C-C_6H_4	5	24	92	98.5:1.5
H	H	4-ClC_6H_4	5	26	99	96:4
H	H	4-$MeOC_6H_4$	2.5	18	90	93.5:6.5
H	H	Cy	5	26	99	77.5:22.5
H	(*Z*)-Et	Ph	5	30	71	95:5
H	(*E*)-Et	Ph	5	30	84	95:5

Scheme 65

(72)

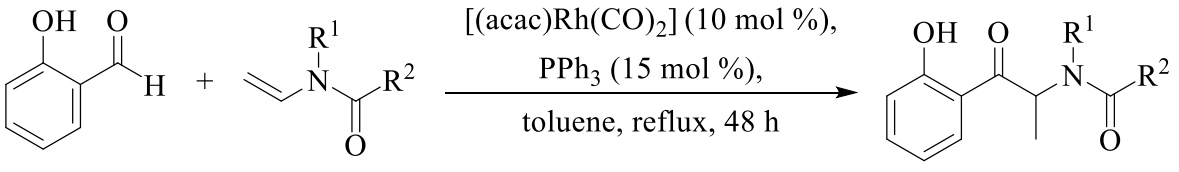


162

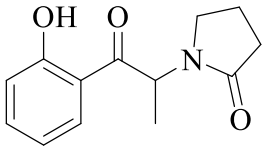
Figure 7. Monodentate ligand gives rise to coordinatively saturated rhodium complex.

Electron-rich enamides **163** react with salicylaldehyde **23** to generate α-amido ketones **164** (Scheme 66).{Zhang, 2011 #510} The reaction likely proceeds through a double-chelation pathway, which is consistent with the observation that rhodium-catalysts ligated with monodentate ligands afford the highest reactivity. In most cases, high regioselectivity for the α-branched ketone occurs and is directed by the amide functional group, despite the polarized nature of the olefin favoring the opposite linear selectivity. The resulting chiral, α-branched stereocenter is adjacent to both a carbonyl and a nitrogen functional group, which renders it susceptible to epimerization, especially in refluxing toluene conditions. Although some chiral catalysts are successful in promoting enamide hydroacylation, no er's for these reactions have been reported to date. Occasionally, acetonitrile is added to help reactivity, presumably by stabilizing some of the catalytic intermediates or resting states. Acetonitrile is not always beneficial, however, and can sometimes strongly bind to the metal and inhibit catalyst activity.

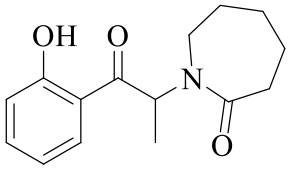
(73)



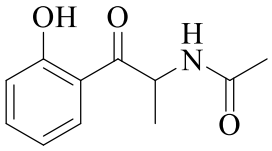
23 **163** **164**



(73)



(47)[a]

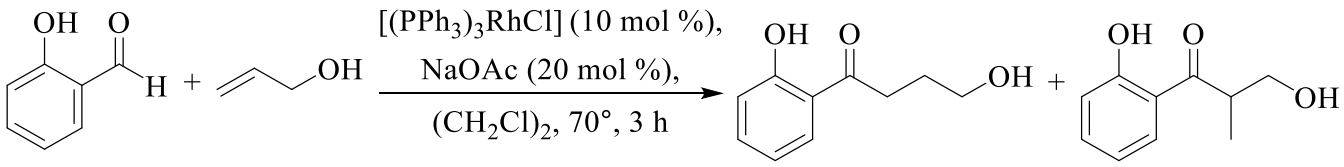


(75)[a]

[a] MeCN (6 equiv) as additive

Scheme 66

Although the phenolic OH group such as in salicylaldehyde **23**, amide carbonyl, and sulfur are good ligands for promoting catalysis, aliphatic alcohols and amines such as allylic alcohols and allylic amines are poor directing groups for intermolecular hydroacylation (Scheme 67).{Murphy, 2011 #5}{Murphy, 2012 #4} For example, hydroacylation of allylic alcohol **165** with salicylaldehyde **23** using Wilkinson's catalyst and a catalytic amount of NaOAc results in the formation of hydroxy ketones **166** and **167** in a combined yield of 4% in favor of the linear γ-hydroxy ketone **166**.{Murphy, 2012 #4} In view of the prevalence of oxygen and nitrogen in biologically-relevant molecules, developing hydroacylation methods that exploit and incorporate these functional groups into the end products would be especially valuable.

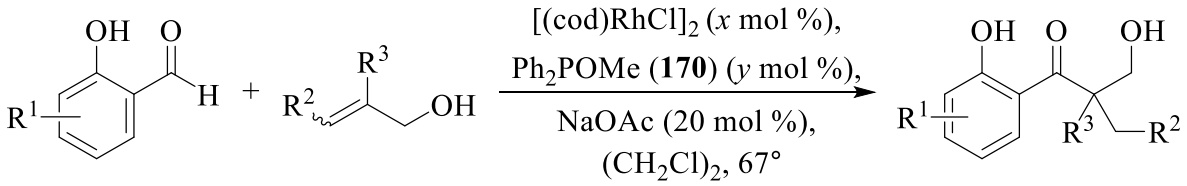


23 **165** **166** **167**

166 + **167** (4), **166**/**167** = 16:1

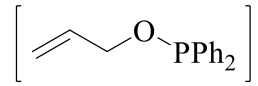
Scheme 67

To enhance the reactivity of allyllic alcohols, a cooperative catalytic system has been developed using rhodium and methyl diphenylphosphinite (**170**).{Murphy, 2012 #4} The latter exchanges the methoxy group with the allylic alcohol and the resulting allyl diphenylphosphinite intermediate (**171**) incorporates a phosphorus atom which is an excellent coordinating group (Scheme 68). Phosphinite **170** acts as both a ligand for rhodium and a substrate-bound directing element t promotes branched-selective hydroacylation in >20:1 isomeric ratio (*cf.* Scheme 67). In addition to various salicylaldehyde derivatives **151**, both 2,2- and 1,2-disubstituted alkenes **168** are transformed into β-hydroxy ketones **169** using this method.



151 **168** **169**

1.5 equiv

via 

171

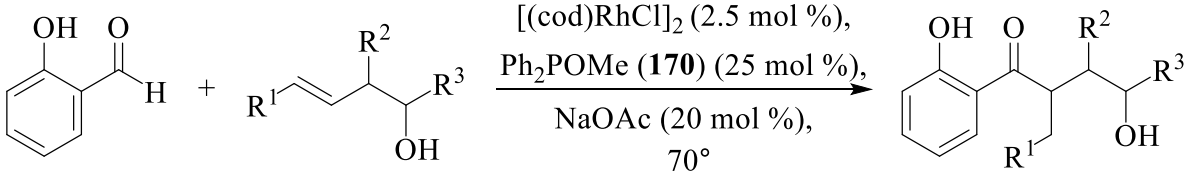
R^1	R^2	R^3	*x*	*y*	Time (h)	Yield (%)
H	H	H	2.5	25	3	74
H	(*Z*)-Et	H	2.5	25	3	88
H	(*E*)-Et	H	2.5	25	3	86
H	$(CH_2)_2CH{=}CH$	H	2.5	25	3	94
H	H	Me	1	10	16	93
5-OMe	H	Me	2.5	25	6	76
3-Me	H	Me	2.5	25	5	80
6-Me	H	Me	2.5	25	5	78

Scheme 68

Converting homoallyllic alcohols **172** (Scheme 69) and 2-hydroxystyrenes **173** (Scheme 70) into homoaldol products is also possible with the cooperative rhodium/phosphinite catalyst approach.{Murphy, 2011 #5} The major difference lies in the choice of solvent. Compared to the hydroacylation of allyllic alcohol **168** in which 1,2-dichloroethane is the optimal solvent, subjecting salicylaldehyde **23** and homoallyllic alcohol ($R^1 = R^2 = R^3 = H$) to hydroacylation conditions in 1,2-dichloroethane affords the branched ketone product in a modest 60% yield. A considerable amount of olefin isomerization byproduct is also formed, which presumably arises from a competing β-hydride elimination pathway prior to product-forming reductive elimination. The use of the more coordinating solvent THF suppresses undesired olefin isomerization by occupying vacant coordination sites, and thus favors hydroacylation. These conditions allow a number of differently substituted homoallyllic alcohols **172** to participate in cross-coupling, including substrates that contain a stereogenic center. Using chiral substrates, only modest dr's are observed in the resulting γ-hydroxy ketones. Further catalyst

development is necessary to address both enantio- and diastereocontrol. Additionally, similar transformations with allylic amines and homoallylic amines have not been reported, although the substrates should be able to take advantage of replacing the methoxy group of a diarylphosphinite.

(76)

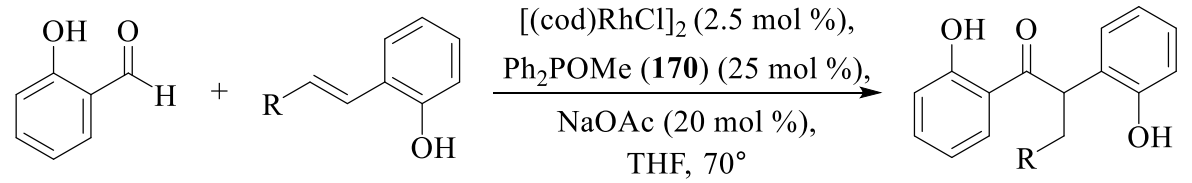


23 **172** 1.5 equiv

R^1	R^2	R^3	Solvent	Time (h)	Yield (%)	dr
H	H	H	$(CH_2Cl)_2$	18	60	—
H	H	H	THF	2.5	97	—
Et	H	H	THF	24	53	—
H	Me	H	THF	2.5	92	64:36
H	H	Ph	THF	16	98	71:29

Scheme 69

(77)



23 **173** 1.5 equiv

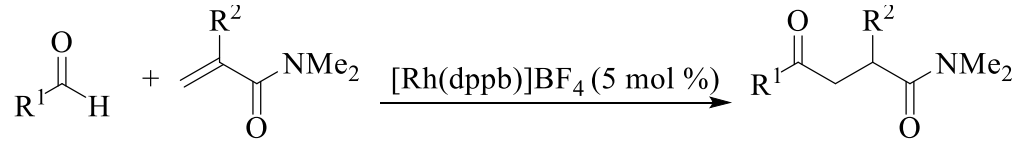
R	Time (h)	Yield (%)
H	4	88
Me	18	86

Scheme 70

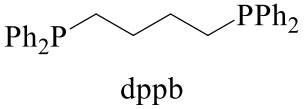
Much work on intermolecular hydroacylation has relied on the double chelation method to help suppress side reactions and bring the substrates and catalyst together in a termolecular fashion. However, given the proper ligand and the appropriate substrates, double chelation is not a requirement.

For example [(dppb)Rh]BF_4 catalyzes the reaction between aldehydes that lack coordinating atoms and acrylamides **174** to produce γ-keto amides **175** (Scheme 71).{Tanaka, 2007 #272} Because the aldehyde is devoid of a second Lewis basic element, a bidentate ligand is necessary to saturate the coordination sphere about the metal center (in contrast to double-chelation methods that involve monodentate ligands). Acrylamides **174** participate in two-point binding through the amide oxygen, which directs linear-selective hydroacylation. Aryl aldehydes tend to be harder to activate compared to aliphatic aldehydes, and require higher reaction temperatures and a higher-boiling solvent such as toluene.

(78)



1.1 equiv **174** **175**



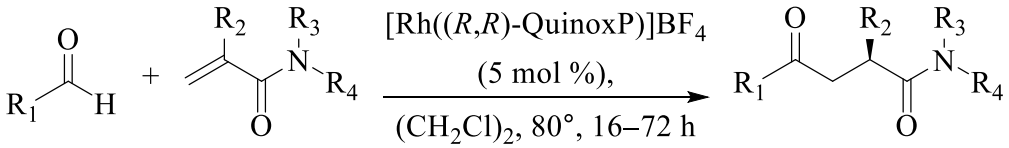
dppb

R^1	R^2	Solvent	Temp (°)	Time (h)	Yield (%)
$Ph(CH_2)_2$	H	$(CH_2Cl)_2$	80	42	67
n-C_7H_{15}	Me	$(CH_2Cl)_2$	80	5	99
Ph	Me	toluene	100	22	84

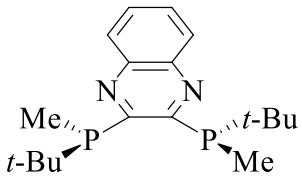
Scheme 71

An enantioselective variant is catalyzed by [Rh(*R*,*R*)-QuinoxP]BF_4.{Shibata, 2009 #271} Although the transformation is not branch-selective, the use of 2,2-disubstituted alkenes gives rise to enantioenriched products (Scheme 72). Primary and α-branched aldehydes (R^1 = Cy) are readily activated by the catalyst, however, α,α-disubstituted (R^1 = *t*-Bu) aldehydes are not suitable substrates for this reaction. Aryl aldehydes react slowly under the reaction conditions, and the enantioselectivity is only modest.

(79)



1.1 equiv



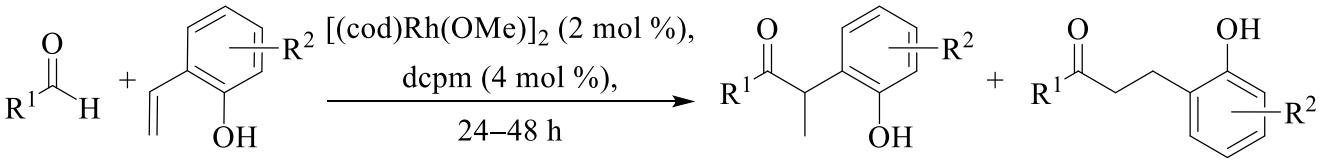
(*R*,*R*)-QuinoxP

R_1	R_2	R_3	R_4	Yield (%)	er
$Ph(CH_2)_2$	Me	Ph	Ph	87	99:1
$Ph(CH_2)_2$	Me	Bn	Bn	73	98.5:1.5
Cy	Me	Ph	Ph	76	99:1
t-Bu	Me	Ph	Ph	0	—
Ph	Me	Ph	Ph	12	79:21

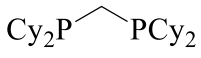
Scheme 72

When complexed to rhodium, small bite-angle ligands are effective for the hydroacylation of vinylphenols with non-chelating aldehydes (Scheme 73).{Murphy, 2014 #513} A neutral rhodium source is used as the catalyst, in which the methoxide anion acts as an internal base by deprotonating the vinylphenol. The electron-donating properties of the deprotonated vinylphenolate and the bis(phosphine) ligand renders the rhodium center electron-rich, which in turn facilitates aldehyde C─H activation. The phenolate also directs branched insertion of the olefin to generate ketone **177** as the major product. This anion-directed process is compatible with a wide range of aliphatic, alkenyl, and aryl aldehydes. Alkenyl and aryl aldehydes exhibit lower reactivity compared to alkyl aldehydes and thus require higher temperatures and a higher-boiling solvent to achieve good conversions.

(80)



176 branched-**177** linear-**178**



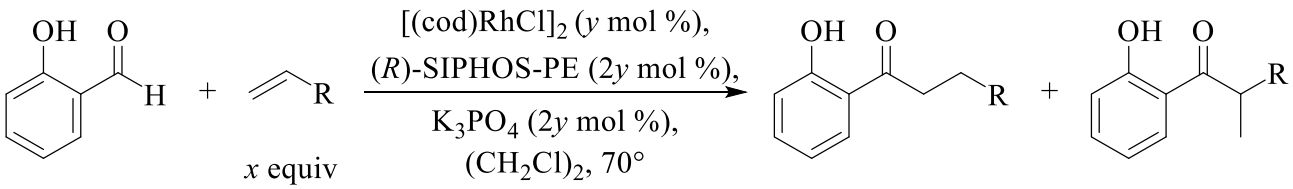
dcpm

R^1	R^2	Solvent	Temp (°)	Yield (%)	**177/178**
$Ph(CH_2)_2$	4-NO_2	THF	60	96	>20:1
cyclopropyl	4-NO_2	THF	60	94	>20:1
PhCH=CH	4-NO_2	1,4-dioxane	100	95	>20:1
Ph	4-NO_2	1,4-dioxane	100	78	16:1
Ph	4-OMe	1,4-dioxane	100	53	9:1

Scheme 73

Alternatively, the coordinating group may be positioned on the aldehyde component. Without a directing group on the alkene, hydroacylation tends to favor the linear constitutional isomer. Using [Rh((*R*)-SIPHOS-PE)]Cl as the catalyst, a broad range of alkenes are converted into ketones in a linear-selective fashion (Scheme 74).{von Delius, 2012 #2} Alkenes containing silylated and fluorinated alkyl chains are hydroacylated in high yields and regioselectivities. Whereas the majority of rhodium-catalyzed hydroacylation methods are air- and moisture-sensitive, the current reaction system is tolerant of oxygen and water. The use of a chiral ligand for non-asymmetric transformations is not conventional, however, this particular catalyst system is highly reactive and functional-group tolerant. It should be noted that the minor, branched products are formed with poor enantioselectivity.

(81)



23

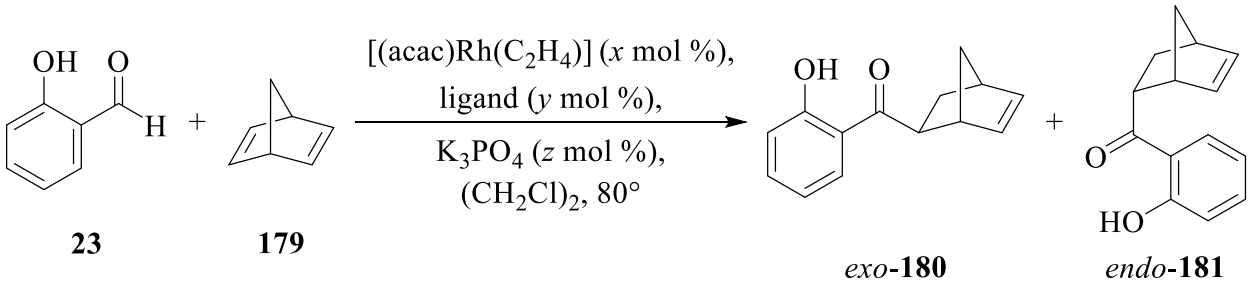
				Yield (%)		
R	*x*	*y*	Time (h)	*lin* + *br*	*lin*/*br*	er (*br*)
n-C_6H_{13}	3	1	72	60	>95:5	—
CH_2SiMe_3	2	2.5	70	63	>95:5	—
$(CH_2)_3Ph$	2	2.5	46	94	>95:5	—
n-C_6F_{13}	2	2.5	48	86	>95:5	—
Ph	2	2.5	36	98	89:11	<52.5:47.5

* major enantiomer not determined

Scheme 74

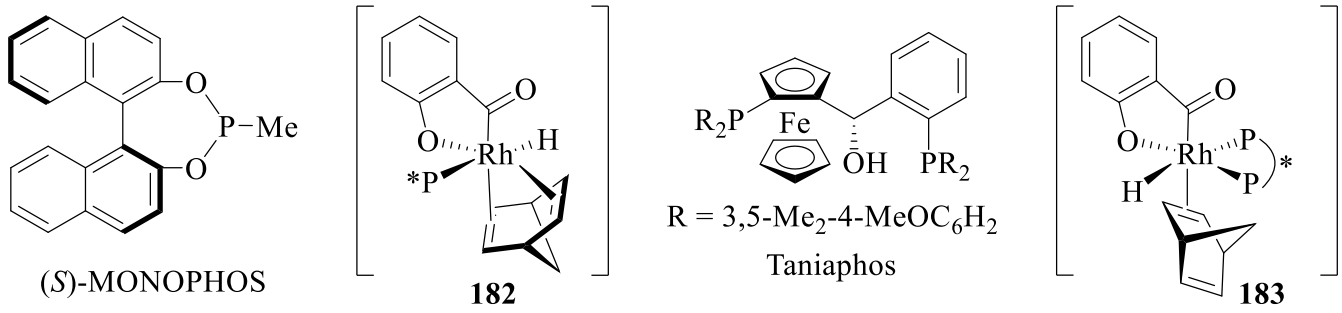
Strained alkenes such as norbornadiene (**179**) and cyclopropenes **184** are good ligands for rhodium, and their inherent strain favors insertion (hydroacylation) over decarbonylation. It is possible to control the *exo*/*endo* selectivity for norbornene and norbornadiene by the choice of mono- or bidentate ligands; however, controlling enantioselectivity remains a challenge.{Stemmler, 2007 #445} Norbornadiene possesses two alkenes that could potentially chelate rhodium (Scheme 75). Using the monodentate, (*S*)-MONOPHOS ligated rhodium catalyst, norbornadiene chelates rhodium at the *endo*-face (intermediate **182**) and is transformed into the *endo* adduct **181**. In contrast, when a bidentate ligand such as Taniaphos is use, norbornadiene is no longer able to chelate rhodium. Instead, the norbornadiene binds the metal via the more sterically-accessible *exo*-face in a monodentate fashion (intermediate **183**) and undergoes hydroacylation to form *exo*-adduct **180**. In both cases, the enantiomeric ratios of the products are low.

(82)



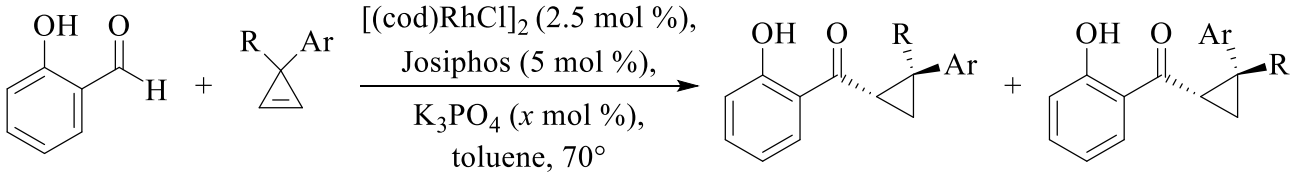
23 **179** *exo*-**180** *endo*-**181**

Ligand	*x*	*y*	*z*	Time (h)	Yield (%)	**180**/**181**	er (**180**)	er (**181**)
(*S*)-MONOPHOS	5	10	—	1	87	5:95	—	67.5:32.5
Taniaphos	5	5.5	20	18	99	>98:2	74:26	—



Scheme 75

Achiral cyclopropenes **184** are desymmetrized to enantioenriched cyclopropyl ketones **185** and **186** with vicinal tertiary and quaternary centers using a chiral [Rh(Josiphos)]Cl catalyst (Scheme 76).{Phan, 2010 #17} The *trans*-adduct **185** is formed as the major diastereomer, and enantiomeric ratios are generally high for both *trans*-**185** and *cis*-**186** diastereomers. A methoxymethyl-substituted cyclopropene requires more base and a longer reaction time to achieve full conversion. The additional Lewis basic methoxy functional group likely plays a role in competing for rhodium binding and hampering reactivity, hence, the addition of more base helps to favor coordination of salicylaldehyde **23**.

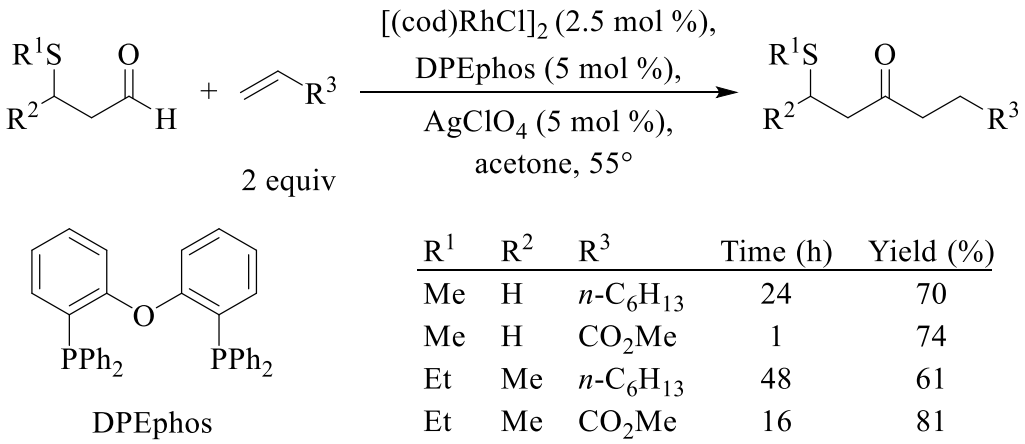


23 **184** *trans*-**185** *cis*-**186**

				Yield (%)				
R	Ar	*x*	Time (h)	**185**	**185**/**186**	er (**185**)	**186**	er (**186**)
Me	Ph	10	12	86	13:1	99:1	(8)	94:6
Me	3-BrC_6H_4	10	12	80	10:1	99.5:0.5	(13)	99.5:0.5
Me	2-furyl	10	12	81	>20:1	99.5:0.5	—	—
CH_2OMe	Ph	30	24	76	6.5:1	99:1	(13)	80:20

Scheme 76

Salicylaldehyde derivatives are good substrates for hydroacylation because the phenolic hydroxyl group is easily deprotonated with base. On the contrary, aliphatic aldehydes with a pendant hydroxyl group have not been successful in hydroacylation reactions to date. Part of the reason for this is the higher basicity of non-phenolic alcohols, which could potentially sequester the rhodium catalyst. Sulfur tends to be more versatile than oxygen or nitrogen in directing ability, and both β-thio alkyl and aryl aldehydes can participate in intermolecular hydroacylation.{Willis, 2004 #426}{Willis, 2005 #427}{Moxham, 2006 #430}{Willis, 2006 #428}{Moxham, 2008 #431}{Randell-Sly, 2009 #429} Although simple alkenes containing no directing groups can couple with β-sulfur aldehydes when treated with catalytic amounts of [Rh(DPEphos)]ClO_4, alkenes that are activated, such as methyl acrylate ($R^3 = CO_2Me$), are considerably more reactive (Scheme 77).{Willis, 2004 #426}{Moxham, 2006 #430}{Willis, 2006 #428} In most cases, the linear constitutional isomer is generated as the major product.

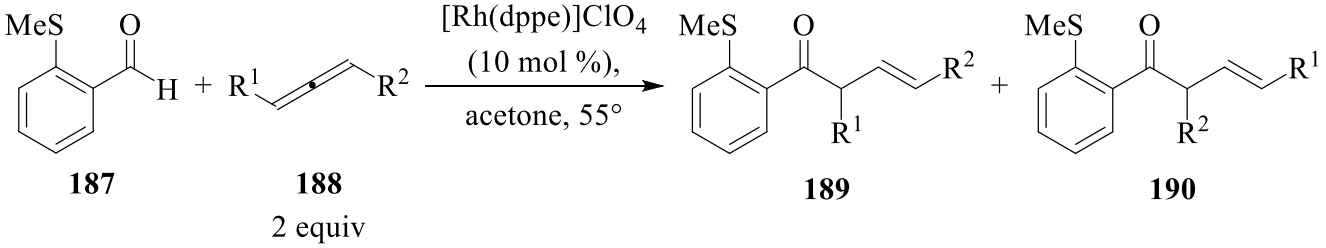


R^1	R^2	R^3	Time (h)	Yield (%)
Me	H	*n*-C_6H_{13}	24	70
Me	H	CO_2Me	1	74
Et	Me	*n*-C_6H_{13}	48	61
Et	Me	CO_2Me	16	81

Scheme 77

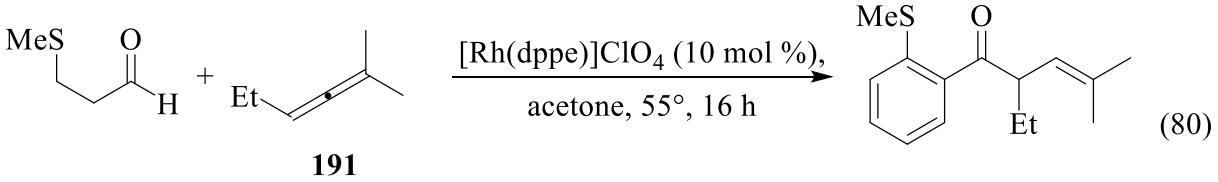
Allenes **188,** are in general, more reactive than alkenes and alkynes, and are excellent substrates for intermolecular hydroacylation (Scheme 78).{Kokubo, 1999 #423}{Randell-Sly, 2009 #429} When unsymmetrical alkyl, aryl-disubstituted allenes are used, hydroacylation occurs across the alkyl-substituted C=C bond to give the non-conjugated enone **189**. The high regioselectivity observed is attributed to the low reactivity of the phenyl-substituted C=C bond. Poor regioselectivity is observed for aryl, aryl-disubstituted allenes, albeit with a small preference for addition of the aldehyde across the less electron-rich C=C bond. For 1,1,3-trisubstituted- and 1,1-disubstituted allenes **191** and **192**, the regioselectivity is governed by steric factors. This method provides an alternative approach to the preparation of synthetically challenging β,γ-unsaturated ketones. If necessary, the thiomethyl directing group can be removed via a rhodium-catalyzed reductive cleavage.{Hooper, 2013 #249}

(85)

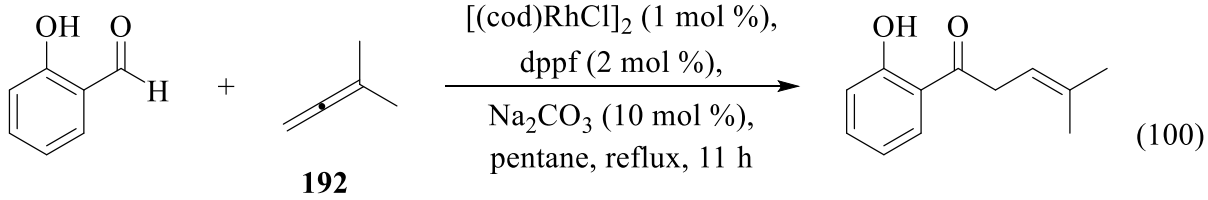


187 **188** 2 equiv **189** **190**

R^1	R^2	Time (h)	Yield (%)	**189/190**
n-C_6H_{13}	Ph	8	94	>20:1
4-$CF_3C_6H_4$	Ph	16	97	1.8:1
4-$MeOC_6H_4$	Ph	16	32	1:1.6



191 (80)

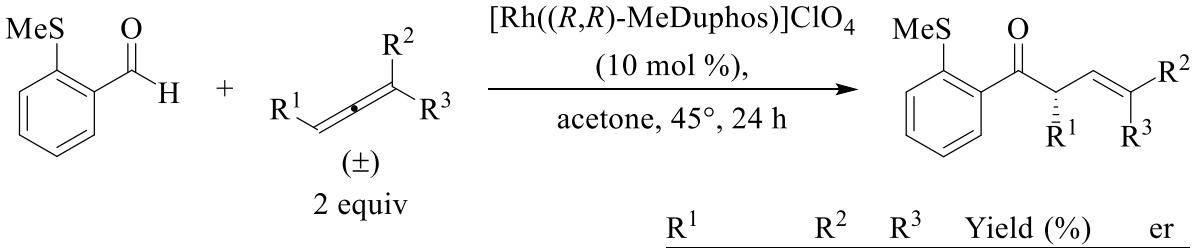


192 (100)

Scheme 78

Enantioenriched β,γ-unsaturated ketones can be obtained by coupling β-thio aryl aldehydes and 1,3-disubstituted allenes using the [Rh((*R*,*R*)-MeDuphos)]ClO_4 catalyst (Scheme 79).{Osborne, 2008 #447} Trisubstituted allenes, however, are not converted to product in synthetically useful yields. Even though two equivalents of racemic allene are used, mechanistic studies support a dynamic kinetic asymmetric transformation (DYKAT) pathway, rather than a kinetic resolution. The purpose of the excess allene is to increase the rate of reaction.

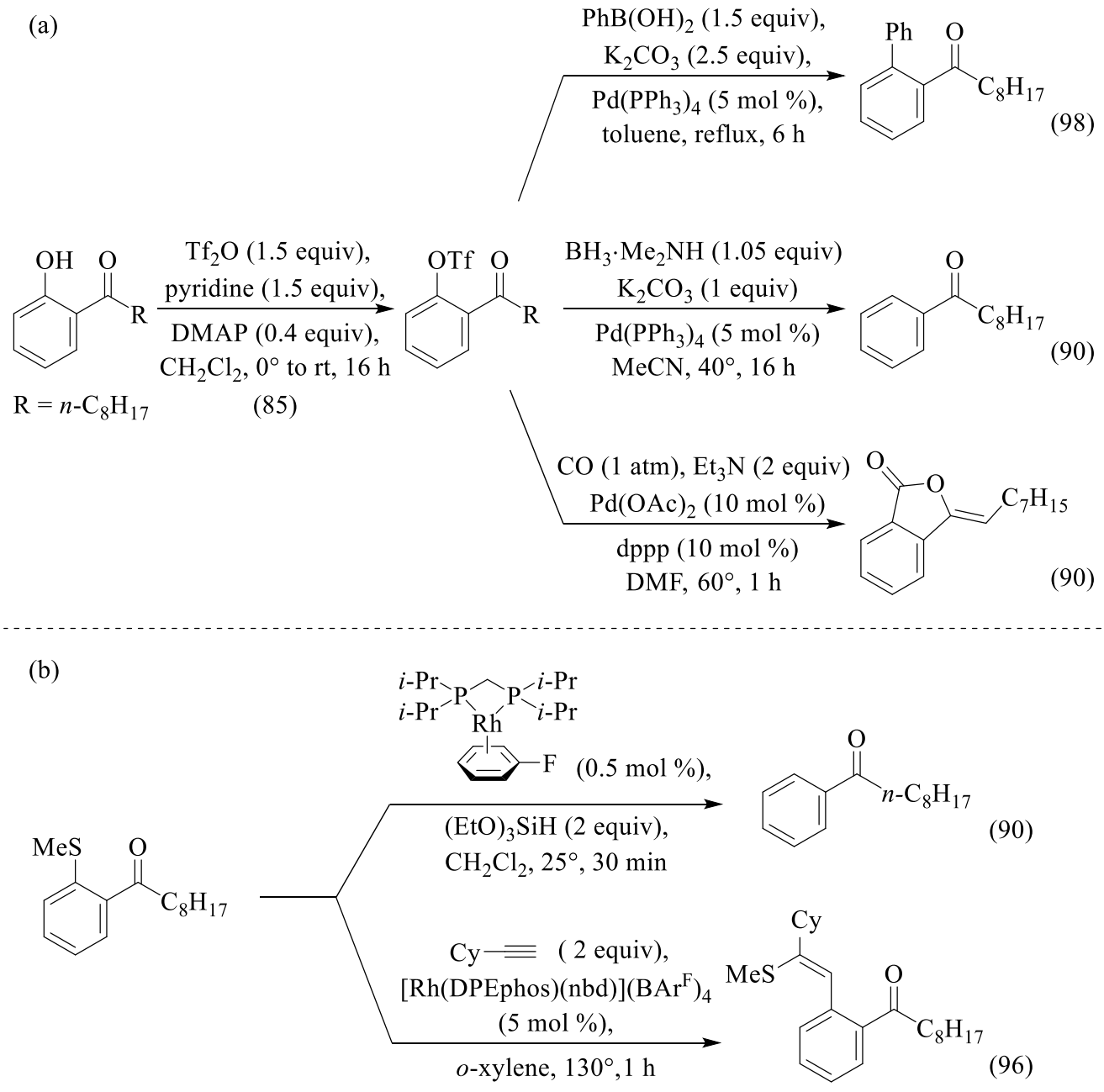
(86)



R^1	R^2	R^3	Yield (%)	er
n-C_6H_{13}	Ph	H	88	97:3
n-C_6H_{13}	Ph	Ph	25	97:3

Scheme 79

The directing groups presented thus far provide a means of achieving reactivity and selectivity in bimolecular reactions. To increase the applicability of directing-group-enabled hydroacylations, methods for further transforming or removing some of the directing groups such as the hydroxyl and methyl thioether groups have been developed. {Willis, 2004 #426}{Murphy, 2011 #5}{von Delius, 2012 #2}{Hooper, 2012 #546}{Hooper, 2013 #249}{Murphy, 2014 #513} The phenolic hydroxyl can be converted to the triflate and subsequently arylated, reduced, or cyclocarbonylated (Scheme 80a).{von Delius, 2012 #2} Similarly, the methyl thioether can be reduced or subjected to alkyne carbothiolation (Scheme 80b).{Hooper, 2012 #546}{Hooper, 2013 #249}

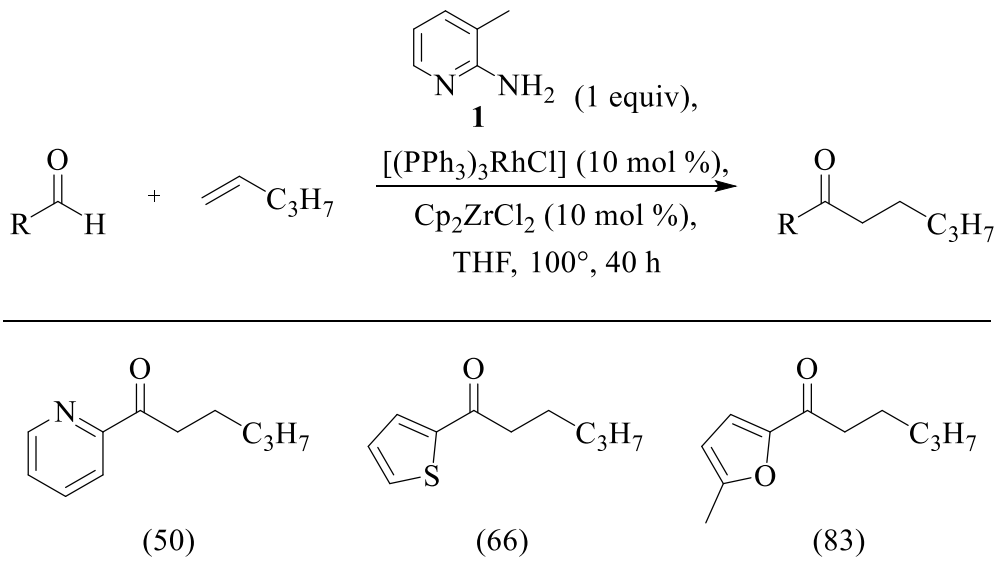


Scheme 80

One of the major goals of hydroacylation research is to be able to combine any aldehyde and alkene to produce a new ketone product in the absence of substrate-bound directing groups. This would allow a direct and atom-economical synthesis of ketones without the need to perform a post-

defunctionalizaton step to remove the unwanted coordinating motifs. One of the best solutions within the rhodium-catalyzed processes involves the use of 2-amino-3-picoline (**1**), which acts as a "catalytic directing group" in conjunction with rhodium(I) (Scheme 17).{Jun, 1997 #391}{Jun, 2000 #392}{Jun, 2007 #267}{Park, 2008 #421} Under standard conditions, aryl- and alkyl aldehydes are activated by the rhodium catalyst and added across the alkene in a linear-selective manner. However, heteroaromatic aldehydes tend to be poorly reactive. The use of catalytic amounts of Lewis-acidic additives such as Cp_2ZrCl_2 and Cp_2TiCl_2significantly accelerates reaction rates, with the former giving slightly better yields of the hydroacylation adduct (Scheme 81).{Jun, 1997 #393} Pyridinecarboxaldehyde, thiophenecarboxaldehyde, and furfural derivatives are all transformed into the corresponding ketones. Because similar rate accelerations are not observed for non-heteroaromatic aldehydes, the Lewis acid additive likely forms a Lewis acid-base pair with the heteroatom of the heteroaromatic system during the C─H activation step and prevents it from sequestering the rhodium catalyst.

(88)

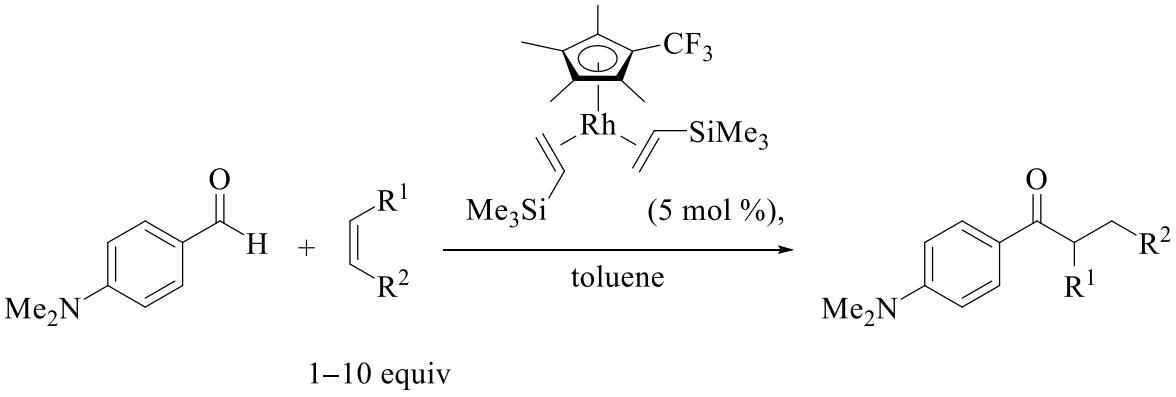


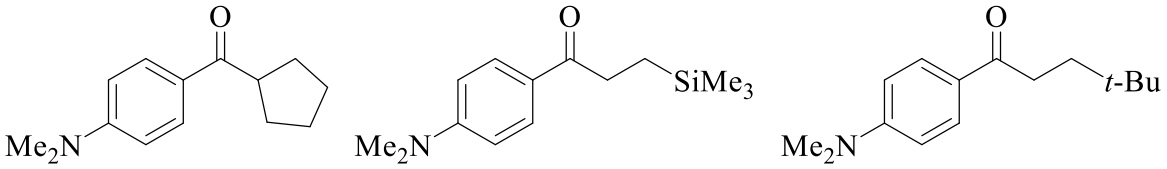
(50) (66) (83)

Scheme 81

Although metal-organic cooperative catalysis with the rhodium(I)/2-amino-3-picoline (**1**) system can cross-couple a range of aldehydes and alkenes that do not possess coordinating groups, only simple monosubstituted alkenes are hydroacylated. Being able to extend this system to include a broader range of alkenes, as well as to select for α-branched ketones, would be major advances in the field. This state-of-the-art cooperative approach is extremely versatile and has been applied to a variety of reactions, including C—C bond cleavage,{Lee, 2003 #748}{Ko, 2014 #547} and ketone α-alkylation;{Mo, 2014 #548} however, a key drawback is the high temperature that is required to achieve reactivity. Further developments to allow the reaction to operate under mild reaction conditions would not only render the reaction more practical, but would likely also allow a broader range of substrates to participate in hydroacylation.

Hydroacylation in the complete absence of directing groups is possible, but rare. Using a relatively electron-deficient rhodium(I) bis-olefin catalyst, electron-rich aldehydes are converted to ketones in a linear-selective manner (Scheme 82).{Roy, 2007 #434} Incorporating the electron-withdrawing CF_3 group into the Cp^* ligand increases the rate of turnover-limiting reductive elimination. In most cases (except for cyclopentene), a large excess of alkene is required to obtain high conversions. The high concentration of alkenes likely helps to promote hydroacylation and prevents undesired side reactions. The rate of reaction increases significantly as the aldehyde becomes more electron-rich in the order $CF_3 << Me < OMe < NMe_2$.





1 eq alkene, 75°, 3 h
(92)

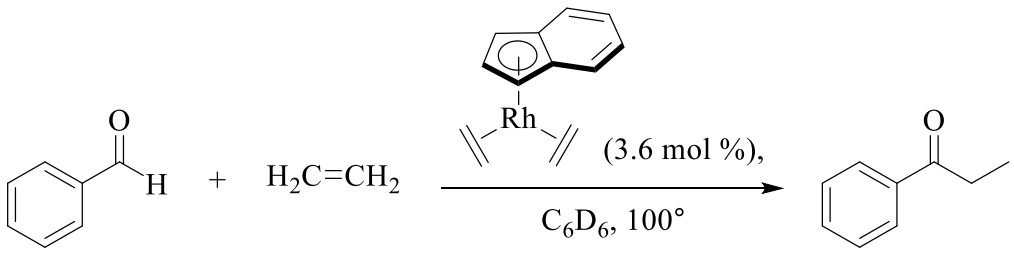
10 eq alkene, 100°, 12 h
(85)

10 eq alkene, 100°, 6 h
(97)

Scheme 82

Similarly, an η^5-indenyl-bound rhodium(I) bis-olefin complex catalyzes the addition of benzaldehyde derivatives to ethylene with a turnover frequency of 4 h^{-1} (Scheme 83).{Marder, 1988 #765} High pressures of ethylene and high temperatures are required to achieve good reactivity; however, under these reaction conditions, aldehyde decarbonylation is not a significant pathway.

(90)



1000 psi

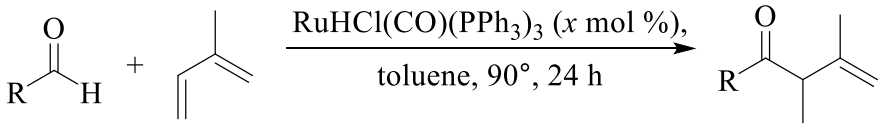
TOF = 4 h^{-1}

Scheme 83

Ruthenium-Catalyzed Processes

Ruthenium(II) hydride complexes catalyze branch-selective intermolecular hydroacylation of 1,3-dienes **42** in the absence of chelation-assistance. Aryl-, alkenyl-, and alkyl aldehydes add across the less substituted C=C bond of the 1,3-diene in a 1,2-fashion.{Omura, 2008 #441}{Shibahara, 2008 #442} Two related ruthenium systems have been developed: one involves the use of catalytic $RuHCl(CO)(PPh_3)_3$ (Scheme 84),{Omura, 2008 #441} and the other involves generating the active catalyst, $RuH(CF_3CO_2)(CO)(PPh_3)_3$ *in situ* by mixing $RuH_2CO(PPh_3)_3$ with CF_3CO_2H (Scheme 85).{Shibahara, 2008 #442} Both systems demonstrate similar substrate scope with the latter catalyst displaying better reactivity with an alkyl aldehyde.

(91)

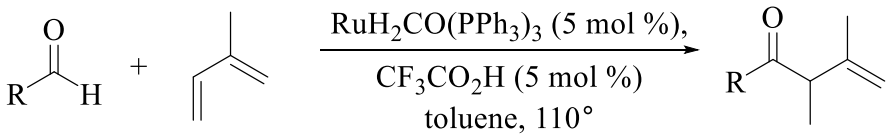


42
4 equiv

R	*x*	Yield (%)
Ph	5	81
4-$MeOC_6H_4$	5	70
n-C_7H_{15}	20	89

Scheme 84

(92)



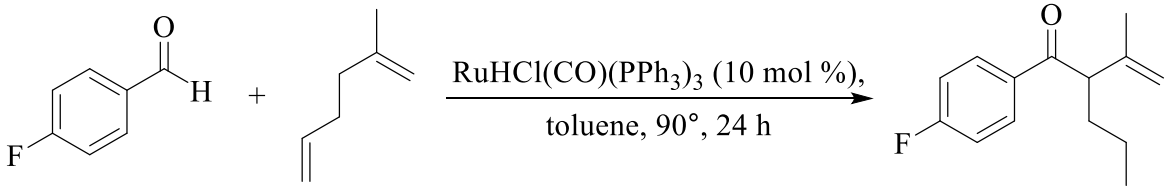
42
2.5 equiv

R	Time (h)	Yield (%)
2-$MeOC_6H_4$	48	98
4-$MeO_2CC_6H_4$	45	62
n-C_8H_{17}	45	84

Scheme 85

Because ruthenium(II) hydrides are efficient catalysts for isomerizing olefins, non-conjugated dienes can be subjected to hydroacylation (Scheme 86).{Omura, 2008 #441} Diene **194** isomerizes to the corresponding 1,3-diene and is subsequently functionalized with 4-fluorobenzaldehyde (**193**) to afford β,γ-unsaturated ketone **195**. Another nice feature of ruthenium catalysts lies in its ability to oxidize alcohols to aldehydes. Many aldehydes, especially alkyl aldehydes, are air-sensitive and readily decompose. Alcohols can thus serve as surrogates for aldehydes under ruthenium catalysis (Scheme 87).{Shibahara, 2008 #442} This tandem oxidation/hydroacylation protocol, starting from the alcohol oxidation state, provides yields that are comparable to those obtained starting from the aldehyde oxidation state.

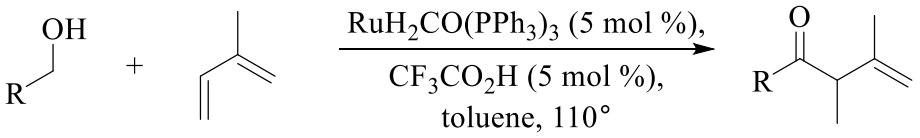
(93)



193 **194** **195**
(79)

Scheme 86

(94)



42
2.5 equiv

R	Time (h)	Yield (%)
2-$MeOC_6H_4$	45	98
4-$MeO_2CC_6H_4$	24	62
n-C_8H_{17}	24	84

Scheme 87

Cobalt-Catalyzed Hydroacylation

Only one report of a cobalt-catalyzed intermolecular hydroacylation of 1,3-dienes exists (Scheme 23).{Chen, 2014 #508}This method does not require the use of substrate-bound directing groups, and both aryl- and alkyl aldehydes can be used as substrates. Under optimized conditions, aryl aldehydes undergo regioselective 1,4-addition across the diene, and alkyl aldehydes undergo 1,2-addition across the more highly substituted double bond. No examples on enantioselective intermolecular reactions with cobalt catalysts are known.

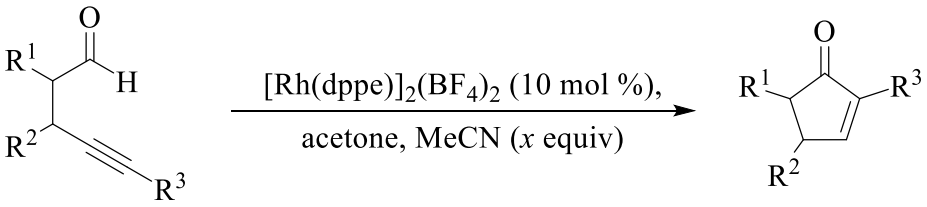
Intramolecular Alkyne Hydroacylation

Rhodium-Catalyzed Processes

Intramolecular cyclization of alkynals using cationic rhodium catalysts gives rise to cyclobutenones, cyclopentenones, and cyclohexenones. Unlike branch-selective alkene hydroacylations, which form a new stereogenic center, alkyne hydroacylation generates no new stereogenic centers. Cyclization of 4-alkynals **196** using $[Rh(dppe)]_2(BF_4)_2$ affords cyclopentenones **197** in good yields

(Scheme 88).{Tanaka, 2001 #448} Alkyl-substituted alkynes are more difficult to hydroacylate and require high temperatures and the addition of 10 equivalents of acetonitrile to achieve good conversion. In contrast, aryl-substituted alkynes cleanly cyclize to the desired products at room temperature. A diynal also undergoes hydroacylation at the proximal alkyne at 100˚ while leaving the distal alkyne intact.

(95)



196 **197**

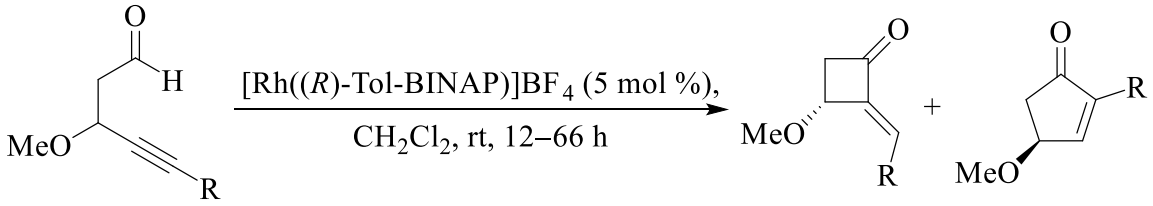
R^1	R^2	R^3	*x*	Temp (°)	Time (h)	Yield (%)
H	H	*n*-$C_{10}H_{21}$	10	100	72	67
Me	H	*n*-C_6H_{13}	10	100	72	67
H	Me	Ph	—	rt	48	88
H	H	C≡C*n*-$C_{10}H_{21}$	—	100	48	76

Scheme 88

A parallel kinetic resolution takes place to give enantioenriched cyclobutenones **199** and cyclopentenones **200** when racemic 3-methoxy-4-alkynals **198** are treated with [Rh((*R*)-Tol-BINAP)]BF_4 (Scheme 89).{Tanaka, 2003 #468} The methoxy substituent is postulated to coordinate rhodium during cyclization, and thus alleviates the need for a coordinating solvent. Cyclobutenones **199** are formed with excellent enantioselectivities, albeit in lower yields, whereas cyclopentenones **200** exhibit relatively lower enantioselectivities and higher yields. The degree of partitioning between cyclobutenone and cyclopentanone is governed by the matched/mismatched interactions between the absolute configuration of the substrate and the chiral catalyst (Scheme 90). When enantiopure alkynal

(*R*)-**198** is subjected to a rhodium catalyst derived from (*R*)-Tol-BINAP, cyclobutenone **199** is formed as the major product. Alternatively, treatment with the enantiomeric ligand gives rise to cyclopentenone **200** as the major product. This powerful method allows one to select the desired product by choice of ligand.

(96)

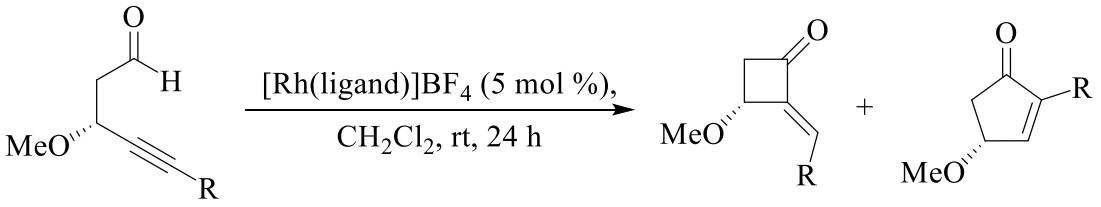


(±)-**198** **199** **200**

	Yield (%)		Yield (%)	
R	**199**	er (**199**)	**200**	er (**200**)
Ph	47	92:8	45	94:6
4-$CF_3C_6H_4$	32	>99.5:0.5	58	81:19
2-Me-C_6H_4	27	>99.5:0.5	41	92.5:7.5
2-furyl	26	99:1	66	73:27
Cy	25	>99.5:0.5	41	92:8

Scheme 89

(97)



(*R*)-**198**
er >99.5:0.5

199
er >99.5:0.5

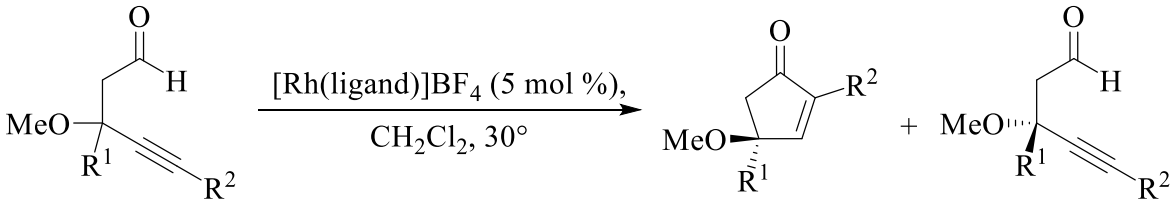
200
er >99.5:0.5

Ligand	**199**/**200**
(*R*)-Tol-BINAP	89:11
(*S*)-Tol-BINAP	2:98

Scheme 90

Racemic methoxy-substituted alkynals **201** bearing stereogenic tertiary center are kinetically resolved in the presence of chiral rhodium catalysts. This approach provides an entry into enantioenriched cyclopentenones **202** and 4-alkynals **201** (Scheme 91).{Tanaka, 2002 #467} The (*S*,*S*)-*i*-Pr-Duphos ligand performs best for 4-alkynals containing a secondary carbon center at the 3-position (R^1 = H), whereas the (*R*)-Tol-BINAP ligand performs best for those with a chiral tertiary carbon (R^1 = Me). The selectivity factors (*s* = rate of fast-reacting enantiomer/rate of slow-reacting enantiomer) are typically around 20 or higher, which allow cyclopentenones **202** and the unreacted 4-alkynals **201** to be isolated with high enantioselectivities. If highly enantioenriched cyclopentenones **202** are desired, the best approach is to run the kinetic resolution to a level of conversion such that 4-alkynal **201** can be isolated with high selectivity, and then resubjecting this material to intramolecular hydroacylation using the achiral catalyst $[Rh(dppe)]_2(BF_4)_2$.

(98)



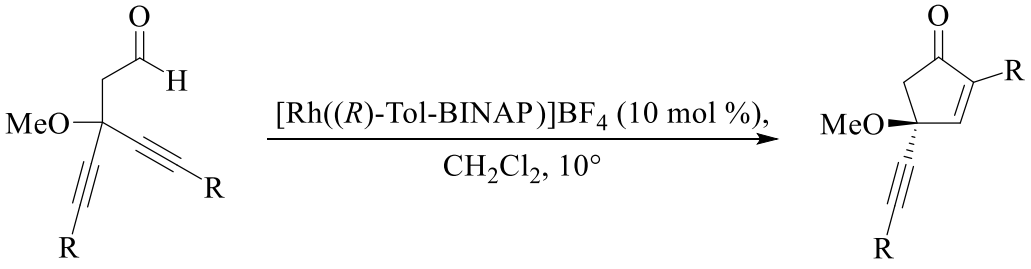
(±)-**201** **202** **201**

R^1	R^2	Ligand	Conversion (%)	er (**201**)	*s*
H	Ph	(*S*,*S*)-*i*-Pr-Duphos	56	96.5:3.5	22
H	$CHCMe_2$	(*S*,*S*)-*i*-Pr-Duphos	53	96.5:3.5	41
Me	Ph	(*R*)-Tol-BINAP	60	99.5:0.5	22
Me	1-cyclohexenyl	(*R*)-Tol-BINAP	63	99.5:0.5	18

Scheme 91

Desymmetrization of prochirial diynals **203** to enantioenriched cyclopentenones **204** is accomplished using [Rh((*R*)-Tol-BINAP)]BF_4 (Scheme 92).{Tanaka, 2002 #467} Alkynes substituted with various aliphatic groups are well tolerated. However, the enantioselectivity drops slightly when additional Lewis basic groups are present (R = CH_2OMe).

(99)



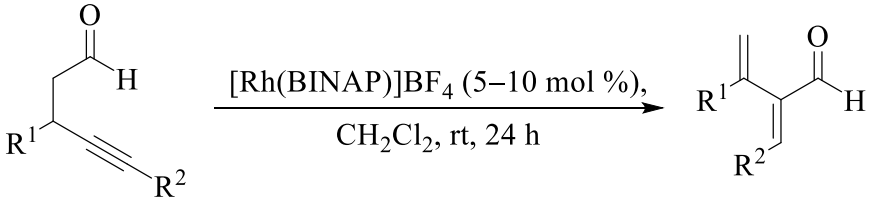
203 **204**

R	Yield (%)	er
Cy	94	97.5:2.5
$(CH_2)_3Cl$	91	95.5:4.5
CH_2OMe	93	91:9

Scheme 92

The choice of ligand plays an important role in determining regio- and enantioselectivity. In some instances, changing the ligand leads to completely different reactivity. 4-Alkynals **196**, which lack a coordinating group, normally undergoes intramolecular hydroacylation when treated with $[Rh(dppe)]_2(BF_4)_2$ in a coordinating solvent such as acetone (Scheme 88).{Tanaka, 2001 #448} However, a BINAP-modified rhodium catalyst promotes a novel alkyne isomerization with concomitant formyl group migration (Scheme 93).{Tanaka, 2002 #463} Compared to previous approaches, this decarbonylation/carbonylation method provides access to dienals **205** in higher regioselectivity, stereoselectivity and step-economy. The major byproduct of the reaction is cyclopentenone **197** (yields not reported), which arises from the traditional hydroacylation pathway. Substitution at the 3-position (R^1 = Me, Ph, etc.) is required for the isomerization process to occur. When R^1 = H, only cyclopentenones and other byproducts are observed.

(100)



196 **205**

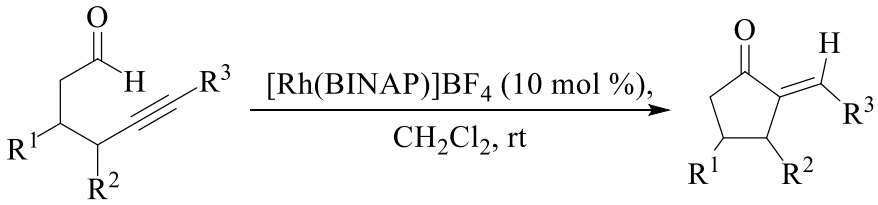
R^1	R^2	Solvent	Temp (°)	Yield (%)
Me	*n*-C_6H_{13}	CH_2Cl_2	rt	50
Me	1-cyclohexenyl	CH_2Cl_2	rt	72
Ph	TMS	acetone	60	87

Scheme 93

Highly substituted α-alkylidene cyclic ketones can be synthesized by hydroacylation of 5- and 6-alkynals **206** and **208**. In contrast to the intramolecular cyclization of 5-alkenals, which are deemed difficult (Scheme 43), intramolecular cyclization of 5-alkynals **206** takes place readily at room

temperature in the presence of [Rh(BINAP)]BF_4 to furnish α-alkylidenecyclopentanones **207** (Scheme 94).{Takeishi, 2004 #466} In all cases, the (*E*)-alkene is formed as a single geometric isomer. Substitutions along the carbon framework, including Lewis-basic coordinating elements, are compatible, but not required for the reaction to proceed. Similarly, 6-alkynals **208** are transformed into α-alkylidenecyclohexanones **209** (Scheme 95). No reaction occurs when 7-alkynals are subjected to hydroacylation conditions even at elevated temperatures.

(101)

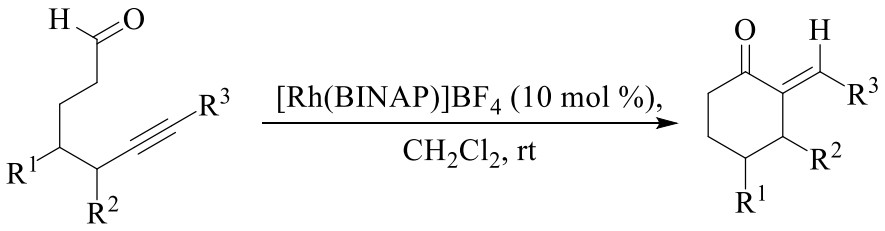


(±)-**206** (±)-**207**

R^1	R^2	R^3	Yield (%)
H	H	Ph	78
H	H	*n*-$C_{10}H_{21}$	94
H	OMe	Ph	57
Me	H	*n*-C_6H_{13}	82

Scheme 94

(102)



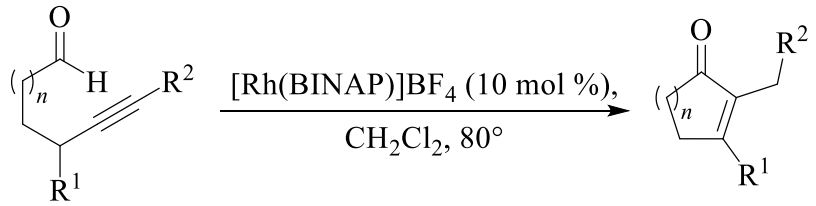
(±)-**208** (±)-**209**

R^1	R^2	R^3	Yield (%)
H	H	Ph	56
H	H	*n*-$C_{10}H_{21}$	74
H	Me	*n*-C_4H_9	77
Me	H	*n*-C_6H_{13}	91

Scheme 95

The exo-double bonds in cyclic ketones **207** and **209** are prone to isomerization. When the hydroacylation is performed at 80˚ instead of room temperature, endocyclic, unsaturated cyclopentenones and cyclohexenones are formed by tandem hydroacylation/isomerization (Scheme 96). 6-Alkynals containing substituents along the carbon framework do not undergo olefin isomerization.

(103)

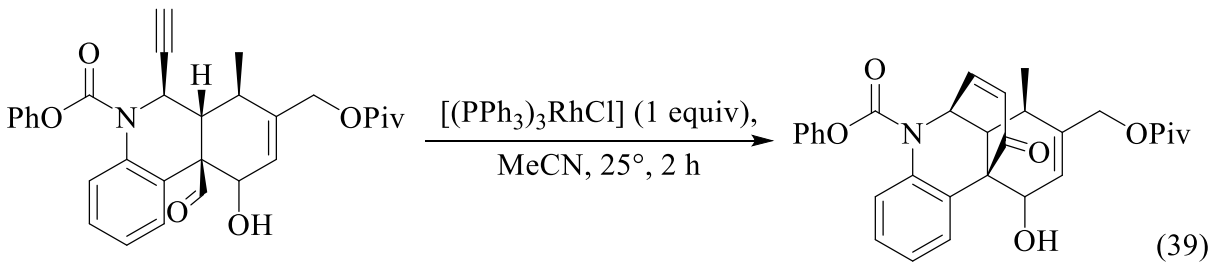


n	R^1	R^2	Yield (%)
1	H	Ph	60
1	Me	*n*-C_4H_9	83
2	H	Ph	41
2	Me	*n*-C_6H_{13}	0

Scheme 96

Cationic rhodium(I)-complexes have shown the most success for catalytic, intramolecular hydroacylation, whereas examples of hydroacylation with neutral rhodium species generally exhibit poor reactivity.{Larock, 1980 #222} One of the few examples of intramolecular hydroacylation involves the use of stoichiometric amounts of Wilkinson's catalyst (Scheme 97). While attempting to perform a defunctionalization via rhodium-catalyzed decarbonylation, an unexpected alkyne hydroacylation occurred to give the fused cyclohexenone **211** in 39% yield (78% based on 50% conversion).{Nicolaou, 1996 #464} Although the product yield is modest, the practical aspect of the method lies in its ability to achieve reactivity adjacent to a quaternary carbon center even in the presence of a variety of functional groups. Further development in catalyst design to improve reactivity would render this method very appealing for complex molecule synthesis.

(104)



(39)

210 **211**

Scheme 97

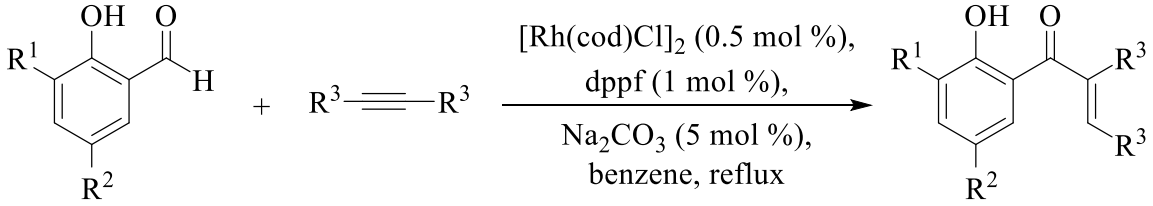
Intermolecular Alkyne Hydroacylation

Rhodium Catalyzed Processes

Exploiting directing groups is the most common approach to achieving intermolecular alkyne hydroacylation, and the majority of studies to date involve aldehydes that contain the directing element. For example, salicylaldehyde derivatives **151** add across symmetrical, disubstituted alkynes **213** to give enones **213** in high yields with low catalyst loadings (Scheme 98).{Kokubo, 1997 #422}{Kokubo, 1999

#423} Hydroacylation of terminal alkynes **214** with salicylaldehyde (**23**) affords a mixture of constitutional isomers **215** and **216** (Scheme 99). Alkyl- and aryl-substituted terminal alkynes slightly favor branched enones **216**, whereas a propargyl alcohol derivative favors the linear isomer **215** with moderate selectivity.

(105)

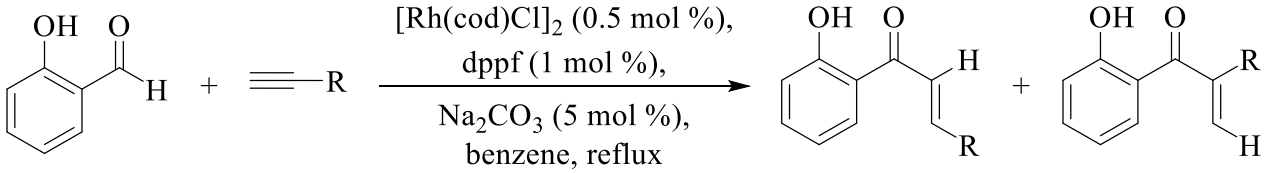


151 **212** **213**

R^1	R^2	R^3	Time (h)	Yield (%)
H	H	Pr	2.5	99
OMe	H	Pr	0.5	99
H	H	Ph	7	94

Scheme 98

(106)



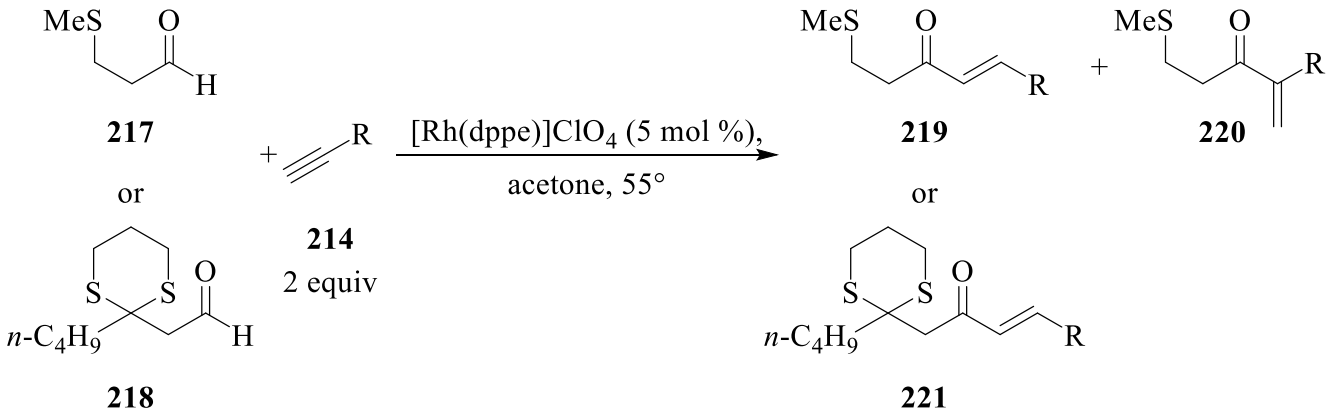
23 **214** **215** **216**

R	Time (h)	Yield (%)	**215/216**
n-C_6H_{13}	2	99	45:55
Ph	4	93	34:66
$C(OH)Me_2$	5.5	75	83:17

Scheme 99

β-Thio aldehydes **217** and **218** cross-couple with terminal alkynes **214** to generate linear adducts with high regioselectivity (Scheme 100).{Moxham, 2006 #430}{Willis, 2006 #428}{Moxham, 2008 #431} The type of sulfur-containing directing group has a noticeable effect on the rate of reaction, with β-thioacetal-containing aldehyde **218** requiring much longer reaction times compared to aldehyde **217**. The reaction accommodates a variety of functional groups, some of which include primary alcohols and primary alkyl chlorides. Surprisingly, an alkyl nitrile reverses the regioselectivity and completely favors the branched hydroacylation adduct **220**. This phenomenon is attributed to the nitrile acting as a directing group. Addition of an excess of acetonitrile to the reaction mixture restores linear selectivity, presumably by saturating the vacant sites of the catalyst and preventing substrate-bound nitriles from directing the reaction.

(107)

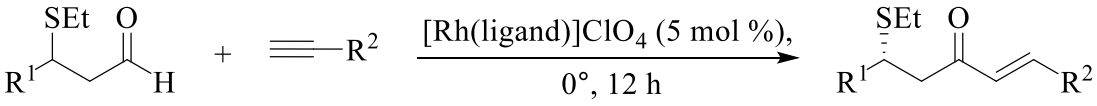


Aldehyde	R	Time (h)	Yield (%)	*linear/branched*
217	*n*-Bu	1	95	>20:1
217	$(CH_2)_3OH$	1	95	>20:1
217	$(CH_2)_3CN$	1	68	<1:20
218	*n*-Bu	16	75	>20:1
218	$(CH_2)_3Cl$	16	73	>20:1

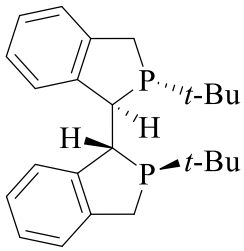
Scheme 100

Kinetic resolution of racemic β-thioalkoxy aldehydes **222** is accomplished by intermolecular hydroacylation of alkynes **214** using a chiral rhodium catalyst (Scheme 101).{González-Rodríguez, 2010 #260} The (*R*,*R*)-MeDuphos ligand provides the best results for β-aryl-β-thioalkoxyaldehydes (R^1 = Ar) whereas the (*R*,*R*,*S*,*S*)-Duanphos ligand is optimal for β-alkyl-β-thioalkoxyaldehydes (R^1 = alkyl). At 0˚, the reactions exhibit good levels of enantioselectivities and reasonable selectivity factors. Racemic α-branched-β-thioalkoxyaldehydes **224** are also competent substrates for kinetic resolution (Scheme 102). Variations of the aldehyde and alkyne components are possible; however, a low selectivity factor is observed for an α-*t*-Bu-substituted aldehyde.

(108)



(±)-**222** **214** **223**

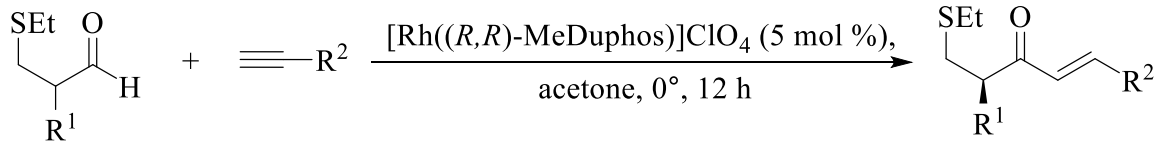


(*R*,*R*,*S*,*S*)-Duanphos

R^1	R^2	Ligand	Solvent	Yield (%)	er	*s*
4-$MeOC_6H_4$	Ph	(*R*,*R*)-Me-Duphos	$(CH_2Cl)_2$	42	87:13	12
Ph	Bu	(*R*,*R*)-Me-Duphos	$(CH_2Cl)_2$	48	92:8	30
Et	Ph	(*R*,*R*,*S*,*S*)-Duanphos	acetone	37	91:9	17

Scheme 101

(109)



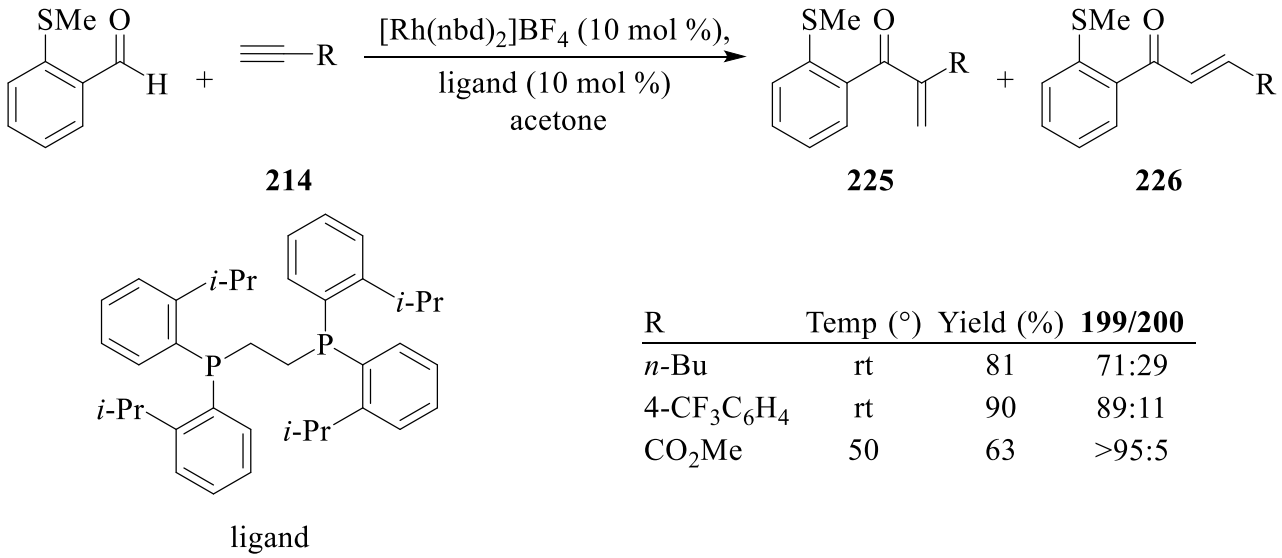
(±)-**224** **214**

R^1	R^2	Yield (%)	er	*s*
Ph	Ph	39	94:6	34
t-Bu	Ph	43	84:16	9
Ph	TMS	42	90:10	17

Scheme 102

Examples of alkyne hydroacylation using β-thioether-chelating aldehydes presented thus far are generally highly linear-selective, with the exception of a chelating alkyne (Scheme 100). However, the regioselectivity is reversed to favor the branched constitutional isomer **225** over the linear constitutional isomer **226** when a bulky bidentate phosphine ligand with *ortho*-substituted aryl groups is used to modify the rhodium catalyst (Scheme 103).{González-Rodríguez, 2011 #256} Electron-deficient alkynes give the best branched-to-linear selectivities. The success of this system results from an irreversible selectivity-determining reductive elimination step that is promoted by the bulky ligand and enforced by electron-deficient substrates.

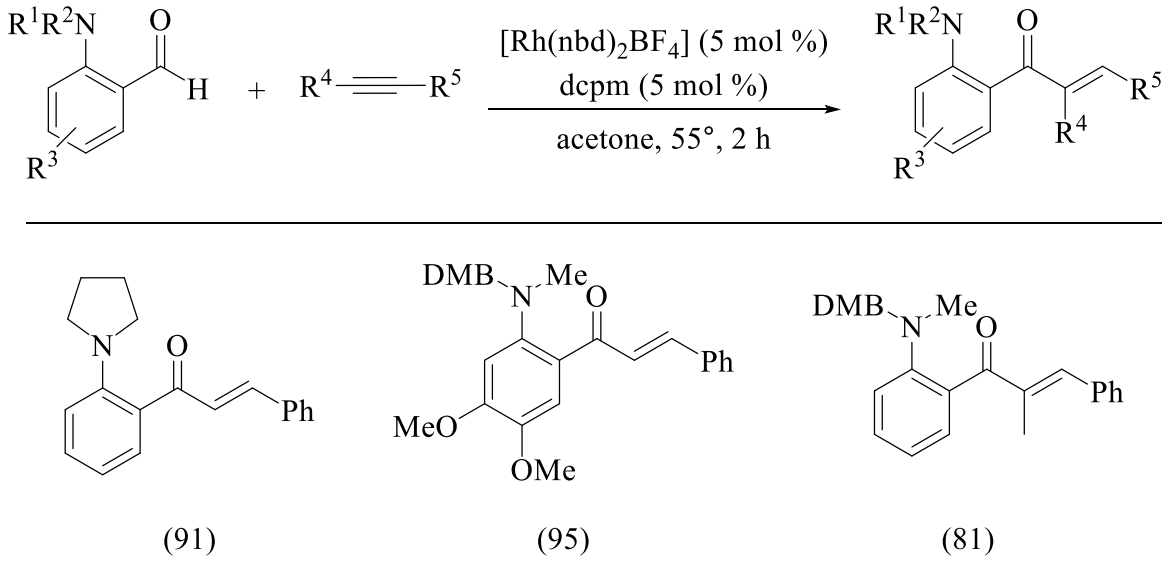
(110)



R	Temp (°)	Yield (%)	**199/200**
n-Bu	rt	81	71:29
4-$CF_3C_6H_4$	rt	90	89:11
CO_2Me	50	63	>95:5

Scheme 103

Apart from oxygen- and sulfur-based directing groups, amino groups also serve as suitable directing elements for intermolecular hydroacylation. Various 2-aminobenzaldehyde derivatives combine with terminal and internal alkynes in the presence of a rhodium catalyst to deliver enones in >20:1 linear-to-branched regioselectivities (Scheme 104).{Castaing, 2013 #248} A rhodium catalyst derived from bis(dicyclohexylphosphino)methane (dcpm), a small bite-angle ligand, is the most active catalyst for this transformation. Compared to a more typical rhodium catalyst such as $[Rh(nbd)_2]BF_4$/dppe, which converts all starting material to product in 16 hours with 10 mol % catalyst loading, the current small bite-angle catalyst system achieves full conversion in 30 minutes with 10 mol % catalyst loading. Decreasing the catalyst loadings to 2−5 mol % does not affect product yields. These small bite-angle ligands have been featured in several recent hydroacylation studies.{Pernik, 2012 #250}{Hooper, 2013 #249}{Murphy, 2014 #513} As is the case with intramolecular alkene hydroacylations (Schemes 58 and 59), only aniline derivatives are effective at directing hydroacylation.

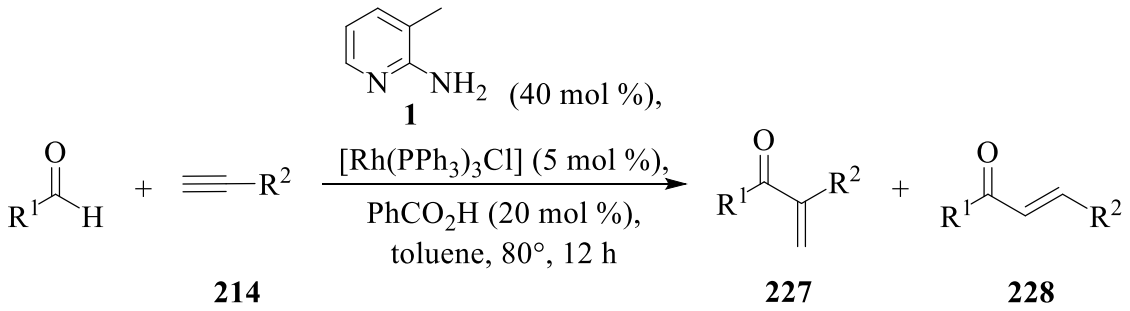


(91) (95) (81)

Scheme 100

Simple aldehydes and alkynes that lack coordinating groups can be combined using the metal-organic cooperative catalysis approach with Wilkinson's complex and 2-amino-3-picoline (**1**) (Scheme 105).{Jun, 2002 #470} This catalyst system favors branched enones **227** with complete regioselectivity with benzaldehyde derivatives. Mixtures of constitutional isomers are obtained when aliphatic aldehydes are used; however, high regioselectivity for linear (*E*)-α,β-enones **228** is observed when a sterically-encumbered alkyne (R^2 = *t*-Bu) is used.

(112)

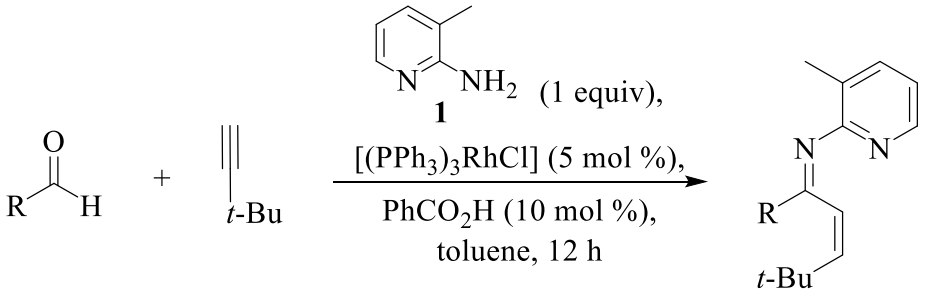


R^1	R^2	Yield (%)	**227**/**228**
Ph	*n*-Bu	92	100:0
4-pyridyl	*n*-Bu	78	100:0
n-C_5H_{11}	*n*-Bu	85	78:22
n-C_5H_{11}	*t*-Bu	74	0:100

Scheme 105

With aryl aldehydes and *tert*-butylacetylene (**229**), 2-amino-3-picoline (**1**) does not turn over, but instead is a stoichiometric reagent that is incorporated into ketimine product **230** with the (*Z*)-olefin geometry (Scheme 106).{Jun, 2002 #470} Reasons for selective formation of the (*Z*)-olefin isomer are unclear. Ketimine **230** is exceptionally stable, and an attempt to hydrolyze it to the corresponding enone using aqueous HCl (1 M) was unsuccessful.

(113)



229 **230**

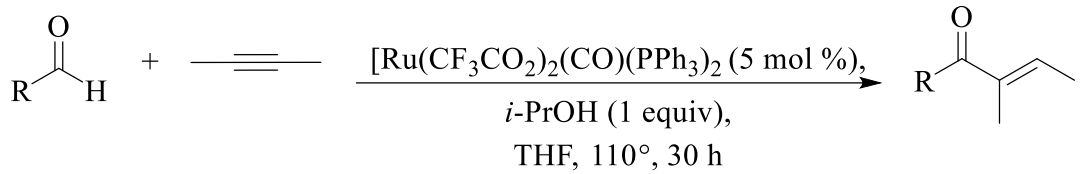
R	Temp (°)	Yield (%)
Ph	80	93
3-pyridyl	100	91

Scheme 106

Ruthenium Catalyzed Processes

Ruthenium(II) hydride complexes catalyze hydroacylation between aldehydes and 2-butyne (**231**) to generate enones **232** with complete (*E*)-geometrical selectivity in the absence of Lewis basic coordinating groups (Scheme 107).{Williams, 2009 #359} An equivalent of isopropyl alchohol is used to reduce the Ru(II)-catalyst precursor, $Ru(CF_3CO_2)_2(CO)(PPh_3)_2$, to the active Ru(II)-hydride catalyst. Alternatively, the reaction can be performed using the more stable alcohol precursor, and the alcohol itself can serve as a reducing agent to generate the active catalyst *in situ* (Scheme 108). Yields for the tandem oxidation/hydroacylation protocol are generally comparable or slightly higher than for the hydroacylation method starting from the aldehyde.

(114)

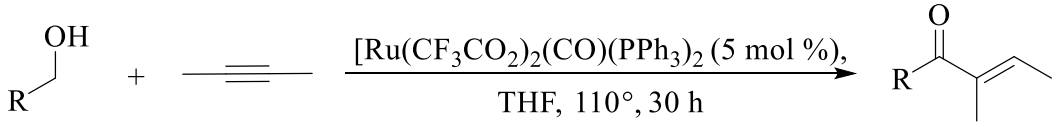


1.5 equiv **231** **232**

R	Yield (%)
4-O_2NPh	85
n-C_6H_{17}	69

Scheme 107

(115)



1.5 equiv **231** **232**

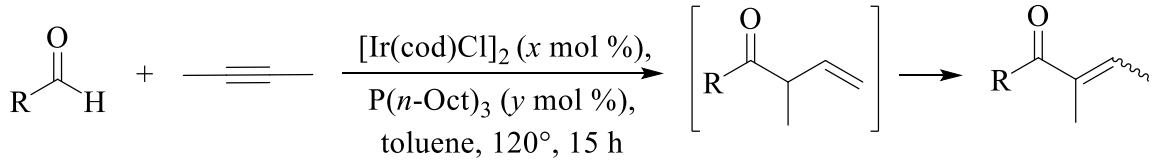
R	Yield (%)
4-O_2NPh	88
n-C_6H_{17}	70

Scheme 108

Iridium Catalyzed Processes

Similar to ruthenium(II) catalysis, iridium(I) complexes catalyze the hydroacylation of 2-butyne (**231**) with aryl- or alkenyl aldehydes (Scheme 109).{Hatanaka, 2010 #266} The resulting β,γ-enones **233** are isomerized to α,β-enones **232** as a mixture of *E*/*Z*-isomers at high temperatures. The reaction can also be performed starting from the alcohol oxidation state (Scheme 110). A limitation is that alkyl aldehydes perform poorly under the reaction conditions. The modest *E*/*Z* ratios obtained makes this method less appealing than the ruthenium-based methods.

(116)



231
4 equiv

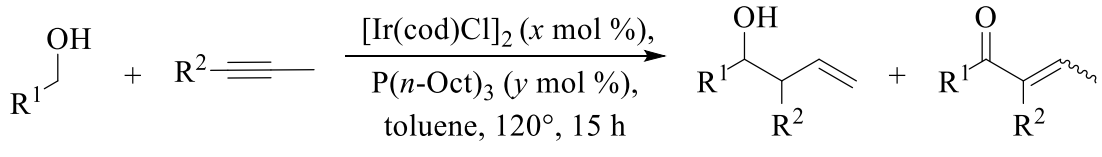
233

232

R	*x*	*y*	Yield (%)	*E*/*Z*
2-naphthyl	5	20	81	43:57
CH=CHPh	10	40	72	84:16

Scheme 109

(117)



2 equiv

234

235

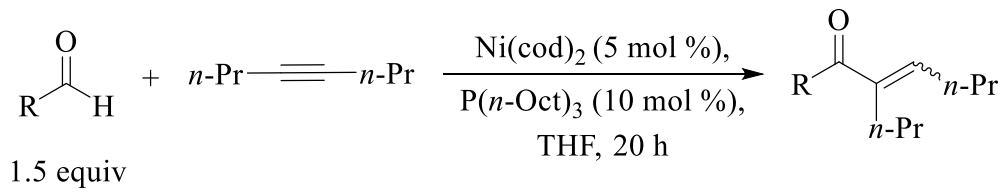
				Yield (%)		
R^1	R^2	*x*	*y*	**234**	**235**	*E*/*Z*
2-naphthyl	Me	5	20	(0)	(89)	57:43
Me	Ph	10	60	(12)	(34)	98:2

Scheme 110

Nickel Catalysis

In view of the low cost and high abundance of nickel, developing nickel catalysts for hydroacylation is highly desirable. Various alkyl- and aryl aldehydes are added across symmetrical alkynes using a phosphine-modified nickel catalyst at high temperatures (Scheme 111).{Tsuda, 1990 #469} Unsymmetrical internal alkynes also participate in hydroacylation, however, the regioselectivities are often low.

(118)



R	Temp (°)	Yield (%)	*E*/*Z*
i-Pr	150	68	89:11
Ph	135	83	—

Scheme 111

In recent years, ruthenium, iridium, and nickel complexes have emerged as alternative catalysts to rhodium for alkyne hydroacylation. The significance of these new systems lies in the fact that the reactions proceed through mechanisms that are distinct from C─H activation, and hence chelation assistance is not required to stabilize any acylmetal hydride intermediates. However, these catalysts operate at high reaction temperatures, and the regioselectivity is often low with unsymmetrical alkynes. Studies to address catalyst reactivity and substrate scope within these systems would greatly advance the field of directing-group-free hydroacylation.

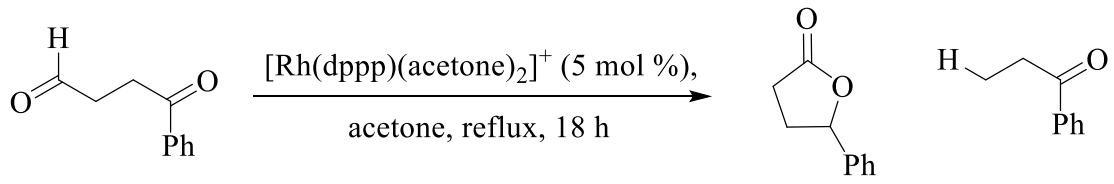
Intramolecular Carbonyl Hydroacylation

Synthesis of Small and Medium-Sized Lactones with Rh(I) Catalysts

In contrast to alkene and alkyne hydroacylations, intramolecular carbonyl hydroacylations result in the formation of new C─O bonds to generate lactones. For example, 1,4-dialdehydes readily cyclize to the corresponding γ-lactones in the presence of a cationic rhodium catalyst.{Bergens, 1990 #349} When the analogous 1,4-keto aldehyde **236** is subjected to rhodium catalysis, γ-lactone **237** is formed in

59% yield (Scheme 112). This transformation, however, is limited by the formation of ketone **238** as a result of competing decarbonylation.

(119)

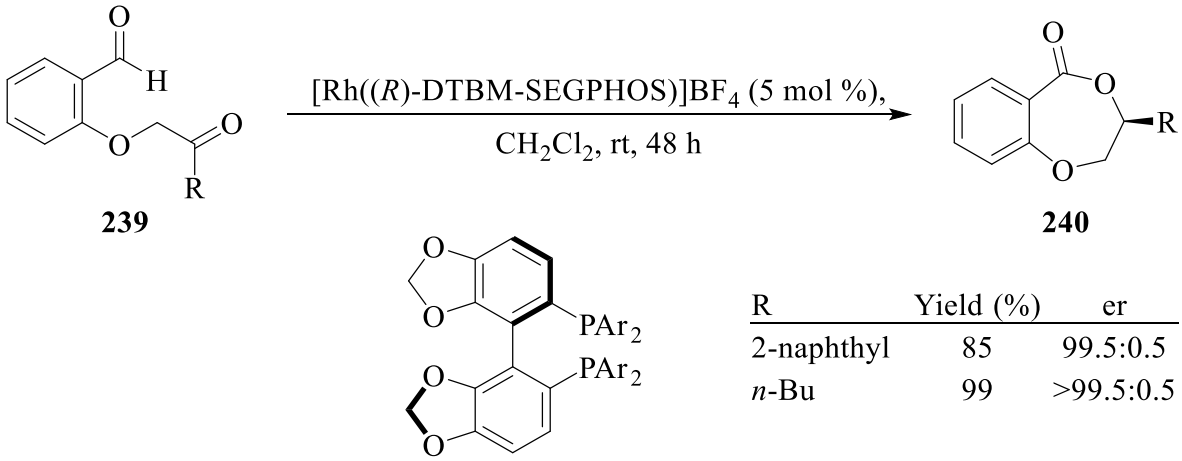


236 **237** (59) **238** (40)

Scheme 112

Efforts to expand the scope of ketone hydroacylation by the use of directing group strategies have been reported. Using 5 mol % [Rh((*R*)-DTBM-SEGPHOS)], ketoaldehydes **239** react to form seven-membered lactones in good yields and excellent enantioselectivities (Scheme 113).{Shen, 2008 #37}{Shen, 2009 #27} The presence of the oxygen heteroatom is crucial for reactivity. Aromatic ketones (*e.g.*, 2-naphthyl) as well as various aliphatic ketones (*e.g.*, *n*-butyl) work well to furnish the desired lactones. Furthermore, the choice of ligand is also critical, as (*R*)-DTBM-SEGPHOS, containing electron-donating biphenyl phosphine groups, is required to achieve high reactivity and selectivity. This oxygen-directed process represents a mild and atom-economical strategy in regio- and enantioselective carbonyl hydroacylation.

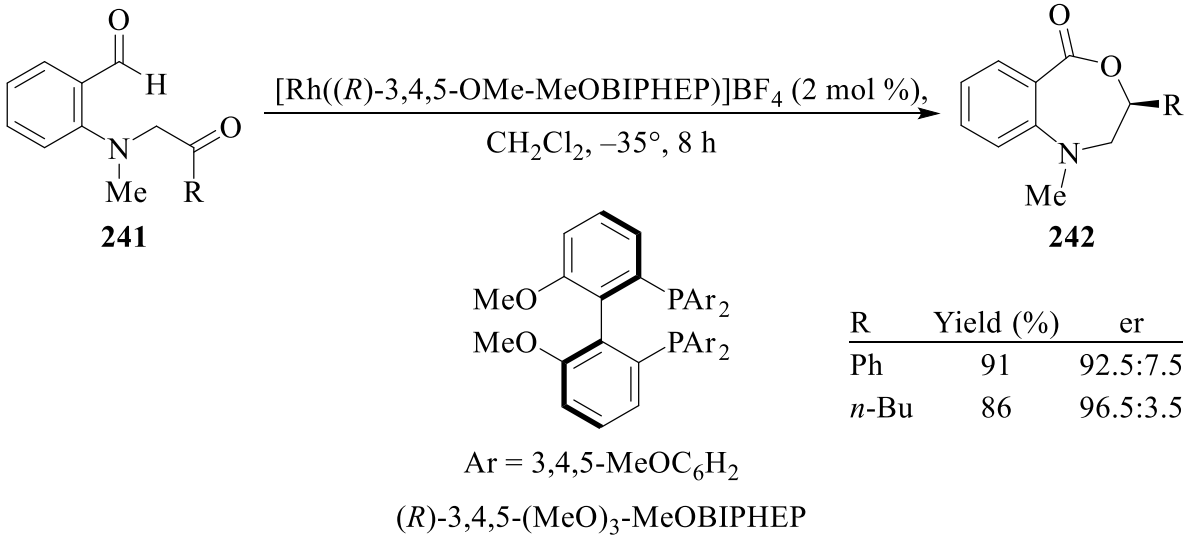
(120)



R	Yield (%)	er
2-naphthyl	85	99.5:0.5
n-Bu	99	>99.5:0.5

Scheme 113

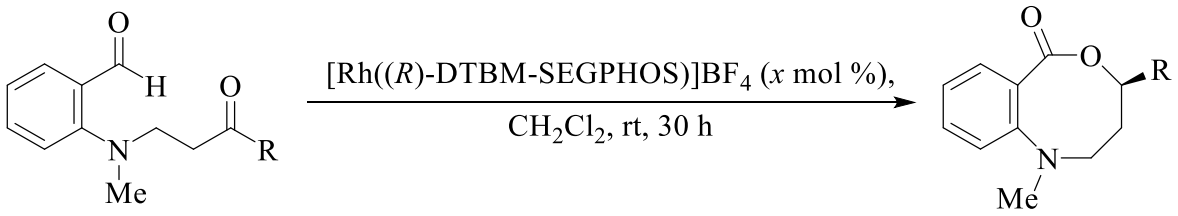
Nitrogen-directed, intramolecular ketone hydroacylation has also been reported.{Khan, 2011 #15} Using a number of alkyl- and aryl-substituted ketoaldehydes **241** and 2 mol % of [Rh((*R*)-3,4,5-$(MeO)_3$-MeOBIPHEP)]BF_4, seven-membered benzoxazepinones **242** are obtained in good yields and in moderate to high enantioselectivities (Scheme 114). This transformation works best when a Lewis basic *N*-methyl group is used. The nitrogen does not direct hydroacylation when it is substituted with strongly electron-withdrawing groups such as Ts or Ms.



R	Yield (%)	er
Ph	91	92.5:7.5
n-Bu	86	96.5:3.5

Scheme 114

Eight-membered nitrogen-containing lactones can also be prepared in this fashion. A number of keto aldehydes **243** containing alkyl- and aryl ketones cyclize when treated with 2 mol % of [Rh((*R*)-DTBM-SEGPHOS)]BF_4 to give eight-membered benzoxazecinones **244** in good yields and with high enantioselectivities (Scheme 115). High enantioselectivity is easier to achieve in the eight-membered system compared with the seven-membered system, which requires ─35˚ to achieve good selectivities. Overall, nitrogen-directed ketone hydroacylation enables access to a number of chiral nitrogen-containing heterocycles that were previously difficult to access catalytically and enantioselectively.



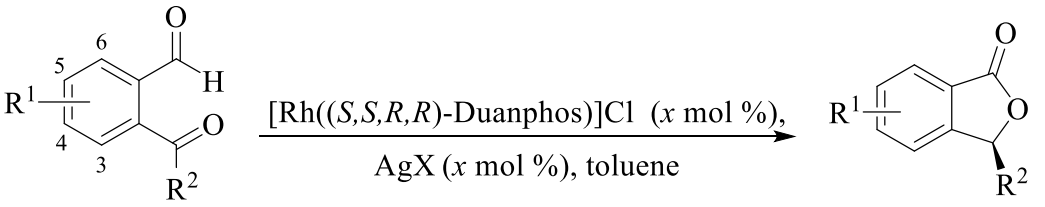
243 **244**

R	*x*	Yield (%)	er
Et	1	91	98:2
Ph	2	95	98:2

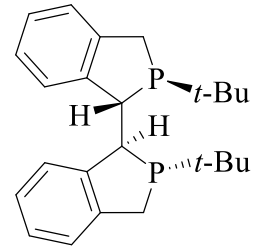
Scheme 115

Rhodium catalysis is amenable to the synthesis of butyrolactones, specifically phthalides that lack a Lewis basic heteroatom.{Phan, 2009 #23} Using [Rh((*S,S,R,R*)-Duanphos)]NO_3, ketoaldehydes{Tanaka, 2003 #360} are converted to phthalides **246** in excellent yields and enantioselectivities (Scheme 116). Both electron-donating (*e.g.*, 4-MeO) and electron-withdrawing groups (*e.g.*, 5-CO_2Me) on the aromatic ring are tolerated, however, incorporating a methyl substituent at the 3-position hinders reactivity (<5% yield). Moreover, varying the prochiral group from a methyl ketone to an ethyl or aryl ketone requires higher catalyst loadings (10 mol %). An important aspect of this method is the use of silver salts to exchange the chloride counterion for one that is less coordinating. For example, aliphatic ketones (*e.g.*, R^2 = Et) are hydroacylated efficiently with the nitrate counterion. Electron-rich aryl ketones (*e.g.*, 4-$MeOC_6H_4$) require the mesylate counterion, whereas electron-deficient aryl ketones (*e.g.*, 4-$O_2NC_6H_4$) require the triflate counterion to afford the desired products. In all cases, the reactivity and selectivity are optimized by the choice of silver salt.

(123)



245 **246**



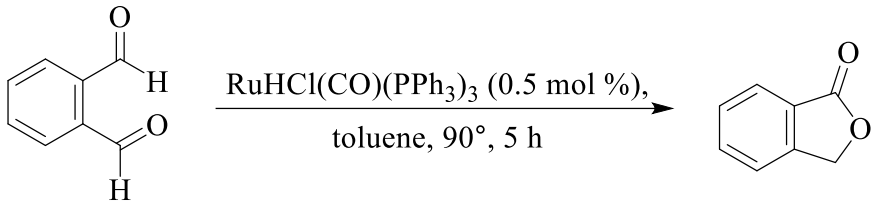
(*S,S,R,R*)-Duanphos

R^1	R^2	X	x	Temp (°)	Time (d)	Yield (%)	er
4-MeO	Me	NO_3	5	100	3	84	98:2
5-CO_2Me	Me	NO_3	5	100	1	94	97.5:2.5
3-Me	Me	NO_3	5	100	1	—	—
H	Et	NO_3	10	100	2.5	94	98:2
H	4-$MeOC_6H_4$	OMs	10	90	3	93	98:2
H	4-$O_2NC_6H_4$	OTf	10	75	3	92	98:2

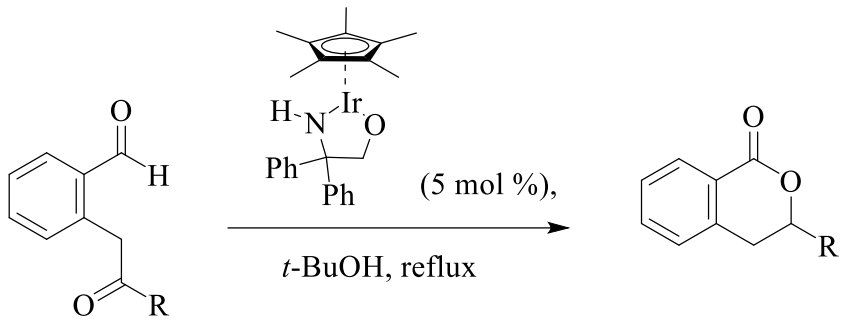
Scheme 116

Synthesis of Lactones with Metal-Hydride Catalysts

Metal hydride complexes are capable of catalyzing intramolecular carbonyl hydroacylations (Scheme 117). Complex $RuHCl(CO)(PPh_3)_3$ transforms phthalaldehyde (**247**) into phthalide (**248**) in 94% yield,{Omura, 2009 #549} whereas an iridium hydride (generated *in situ*) catalyzes intramolecular lactonization of ketoaldehyde **249** to form isochromanone **250**.{Suzuki, 2005 #550} The scope of these reactions is limited to substrates containing a rigid benzo-fused carbon backbone.



247 **248** (99)



249 **250**

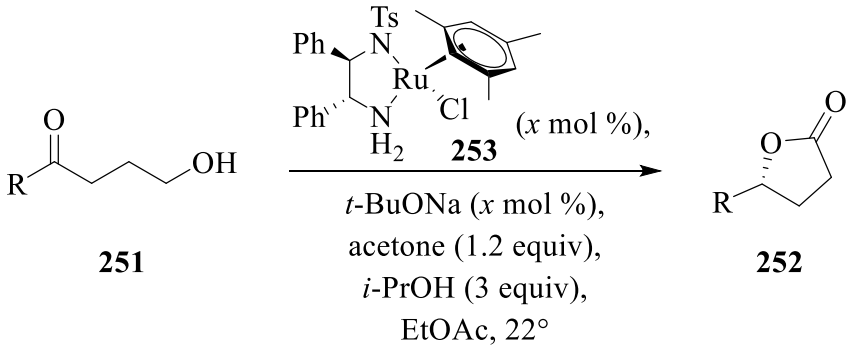
R	Yield (%)
Me	70
Ph	45

Scheme 117

Not only are substrates that lack a benzofused backbone more difficult to cyclize, they are especially air- and moisture-sensitive. The use of ruthenium complex **253** addresses some of the substrate scope limitations. Hydroxy ketones **251** containing a flexible aliphatic backbone are considerably more stable. Oxidation of the alcohol to the aldehyde *in situ*, followed by enantioselective lactonization, provides enantioenriched γ-butyrolactones **252** using 5 mol % of the catalyst (Scheme 118).{Murphy, 2013 #1} The substrate scope mirrors that of Noyori's asymmetric transfer hydrogenation of ketones.{Hashiguchi, 1995 #551}{Matsumura, 1997 #552} Aryl ketones with electron-withdrawing (*e.g.*, 3-ClC_6H_4) and electron-donating groups (*e.g.*, 3-$MeOC_6H_4$), as well as

alkynyl ketones, form strong, polar-π interactions with the ruthenium catalysts and give the desired lactones in good yields and enantioselectivities. Alkyl ketones are not good substrates for this reaction.

(125)



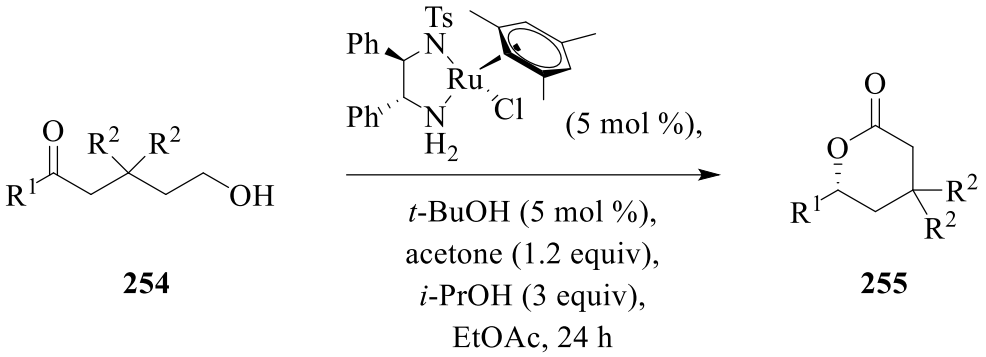
251 **252**

R	*x*	Temp (°)	Time (day)	Yield (%)	er
3-ClC_6H_4	5	22	1	83	95:5
3-$MeOC_6H_4$	5	22	1	82	95.5:4.5
2-naphthyl	5	22	3	78	95:5
Ph-C≡C	10	0	3	65	95:5:4.5

Scheme 118

The same catalyst promotes intramolecular cyclization of 5-hydroxy ketones **254** to form valerolactones **255**, structural motifs that are more difficult to access by previously reported hydroacylation methods owing to a higher ring strain (2.4 kcal/mol) (Scheme 119). Aryl-substituted ketones react similarly to their 4-hydroxy ketone analogues **251**. In contrast, 5-hydroxy furyl- and alkynyl ketones do not readily undergo lactonization, producing the desired product in <10% and 32% yields, respectively. However, introduction of a geminal dimethyl group (R^1 = 2-furyl, R^2 = Me) allows cyclization to occur efficiently to afford the desired lactone in 98% yield and 95:5 er.

(126)



254 **255**

R^1	R^2	Temp (°)	Yield (%)	er
4-MeC_6H_4	H	0	73	95.5:4.5
4-ClC_6H_4	H	22	65	98:2
2-furyl	H	22	<10	—
2-furyl	Me	22	98	95:5
PhC≡C	H	22	32	93:7

Scheme 119

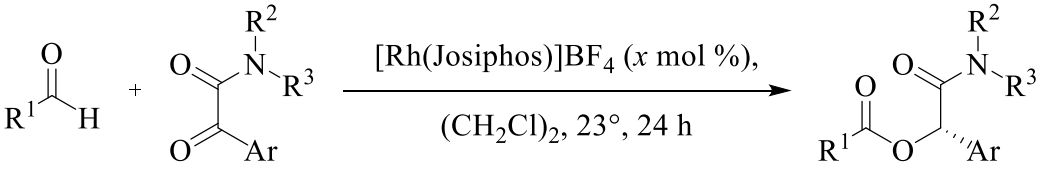
Intermolecular Ketone Hydroacylation

Rhodium Catalyzed Processes

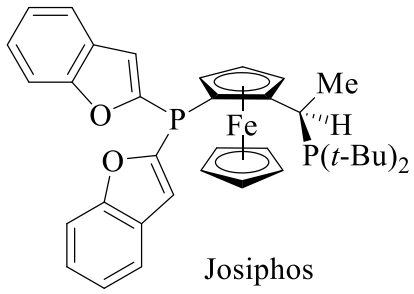
The only intermolecular ketone hydroacylation involves the cross-coupling of various non-chelating aldehydes with a number of α-keto amides **256** to afford α-acyloxyamides **257** (Scheme 120).{Kou, 2014 #553}{Kou, 2015 #759} In the presence of catalytic amounts of Rh[(Josiphos)]BF_4, aryl ketones with varying substitution patterns are combined with aliphatic, non-chelating aldehydes such as hydrocinnamaldehyde. Key to the success of this reaction is the use of a Josiphos ligand with electronically distinct phosphine donors, an electron-rich σ-donating (*t*-Bu)$_2$P and a π-accepting (2-furyl)$_2$P. Structurally similar bis(phosphine) ligands (including C_2-symmetric ligands) that do not contain electronically-distinct phosphine donors result in inferior reactivity and enantioselectivity. Reactivity increases with increasing steric bulk on the α-keto amides **227**, as seen with 2-methylphenyl and 1-naphthyl ketones, whereas higher catalyst loadings are required for α-keto amides containing

smaller aryl substituents (*e.g.*, Ph, 3,5-difluorophenyl ketone). This transformation is limited to aliphatic aldehydes, as aryl aldehydes afford <5% conversion. Compared to *N*-alkyl-*N*-arylamides, diarylamides or dialkylamides are not as effective in directing hydroacylation, providing products in lower yields and enantioselectivities.

(127)



256 **257**

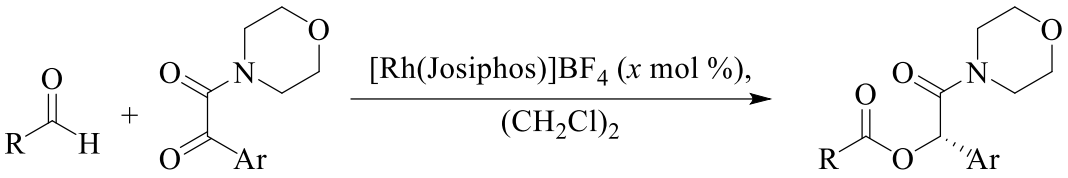


Ar	R^1	R^2	R^3	*x*	Yield (%)	er
Ph	Bn	Me	Ph	10	65	93:5:6.5
2-MeC_6H_4	Bn	Me	Ph	5	88	97.5:2.5
1-naphthyl	Bn	Me	Ph	5	86	97.5:2.5
3,5-F_2-C_6H_3	Bn	Me	Ph	10	67	94:6
Ph	Bn	Ph	Ph	10	47	89:11
Ph	Bn	Bn	Bn	10	46	90.5:9.5

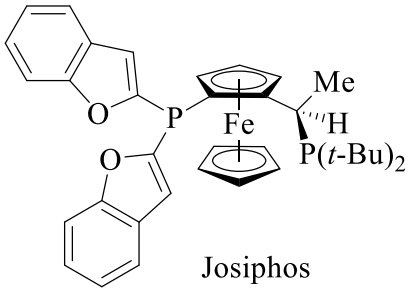
Scheme 120

α-Keto morpholine amides **258** are suitable substrates for intermolecular hydroacylation and react with both primary and α-branched aldehydes to produce ester adduct **259** (Scheme 121). Sterically encumbered α-branched aldehydes (*e.g.*, R = Cy), are more difficult to activate by rhodium, and therefore require a higher reaction temperature (50˚). The morpholine amides behave similar to Weinreb amides and provide a locus for further chemical manipulations.

(128)



258 **259**



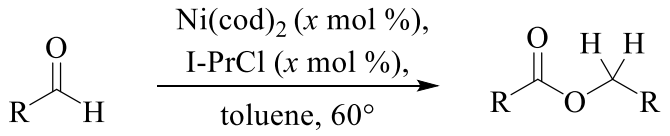
Josiphos

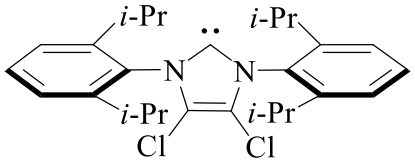
Ar	R	*x*	Temp (°)	Time (day)	Yield (%)	er
1-naphthyl	C_5H_{11}	5	23	2	71	97.5:2.5
1-naphthyl	Cy	10	50	3	59	96:4
Mes	neopentyl	10	23	2	94	97.5:2.5

Scheme 121

Nickel Catalysis

Apart from using precious metals, nickel(0) serves as an alternative metal to catalyze the formation of ester bonds by coupling of two aldehydes. Examples involving the homocoupling of aldehydes have been demonstrated using 1─3 mol % of a Ni(0) complex ligated with an *N*-heterocyclic carbene (NHC) (Scheme 122).{Ogoshi, 2010 #244} Unhindered aryl aldehydes such as 2-naphthaldehyde homocouple in a Tishchenko fashion{Koskinen, 2015 #760} to give the corresponding ester in excellent yields; however, aryl aldehydes containing sterically hindered (*e.g.*, Mes) or electron-withdrawing groups (*e.g.*, 4-CF_3) require higher catalyst loadings and reaction times. Aliphatic aldehydes, which are normally prone to aldol condensations, also work well under the reaction conditions.



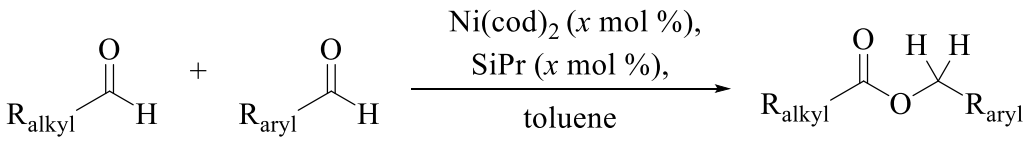


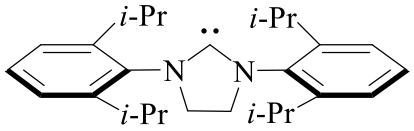
I-PrCl

R	*x*	Time (h)	Yield (%)
2-naphthyl	3	2	82
Mes	1	3	99
4-$CF_3C_6H_4$	10	4	82
$(Me)_3CCH_2(Me)CHCH_2$	1	1	96

Scheme 122

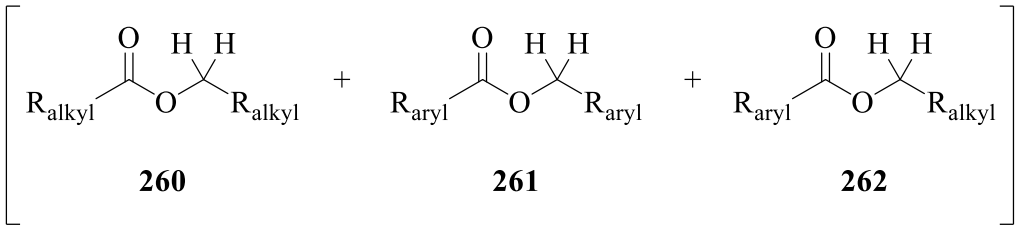
By tuning the nickel catalyst with a more electron-rich NHC-ligand, selective cross-coupling between two different aldehydes to form a single ester product is possible.{Hoshimoto, 2011 #243} Using this method, a number of aliphatic primary, secondary, and aryl aldehydes such as benzaldehyde and 1-naphthaldehyde are cross-coupled in moderate to good yields (Scheme 123). For this transformation, the aliphatic aldehyde tends to become the carboxylate whereas the aryl aldehyde makes up the alcohol portion of the ester product. Byproducts observed in the reaction mixture range from homocoupled products **260** and **261** as well as the alternative heterocoupled product **262**. Despite these limitations, the reaction proceeds with high selectivity to form a single cross-coupled ester. This method represents an effective, atom-economical way to construct cross-coupled esters using a non-precious metal. Because aldehydes are more reactive than ketones, selective ketone hydroacylation via nickel catalysis in the absence of chelation assistance will be a significant challenge. However, the mild conditions established for known carbonyl hydroacylations bode well for future applications of this chemistry.





SiPr

R_{alkyl}	R_{aryl}	*x*	Temp (°)	Time (h)	Yield (%)
Cy	Ph	2	40	4	84
Cy	2-naphthyl	4	50	2	83
$CH(Et)_2$	3,5-(*t*-Bu)$_2$C$_6$H$_3$	4	40	4	83



260 **261** **262**

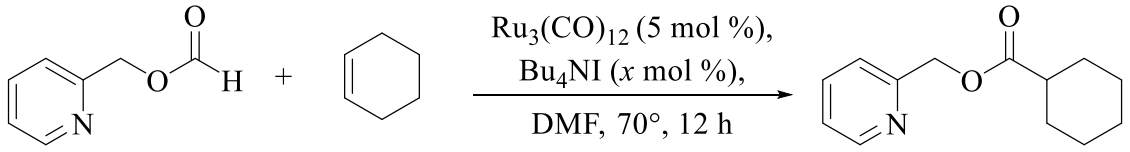
minor products

Scheme 123

Alkene Hydroesterification

Ruthenium-catalyzed alkene hydroesterification is a useful synthetic tool for one-carbon homologations. {Konishi, 2014 #735} Modern strategies use 2-pyridylmethyl formate (**263**) as the C1-source,{Ko, 2002 #492}{Na, 2003 #737}{Park, 2006 #736}{Armanino, 2013 #493} which does not require the use of CO gas as a reagent. {Kondo, 1989 #438}{Nahmed, 1990 #728}{Suzuki, 1995 #731} The use of tetrabutylammonium iodide as a co-catalyst is important for achieving high reactivity in many cases (Scheme 124), presumably because of its role in facilitating the dissociation of the $Ru_3(CO)_{12}$ precursor into a catalytically active ruthenium-halide species that does not contain bridging carbonyl units.{Park, 2006 #736} These reactions are linear-selective with terminal alkenes. Subsequent hydrolysis of the ester product reveals the homologated carboxylic acid.

(131)



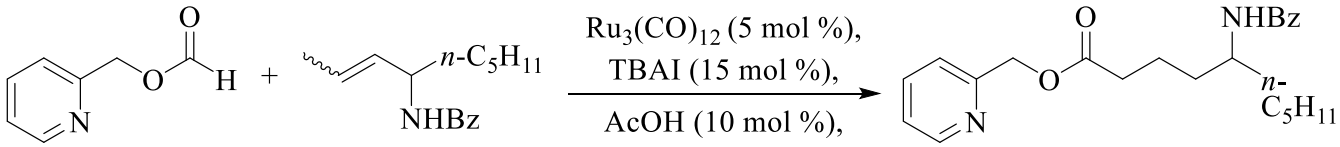
263 1.2 equiv

x	Yield (%)
0	8
15	96

Scheme 124

Internal alkenes that are not part of a cyclic system undergo an autotandem,{Fogg, 2004 #745} ruthenium-catalyzed isomerization/hydroesterification reaction (Scheme 125).{Na, 2003 #737}{Armanino, 2013 #493} The ruthenium complex first isomerizes the internal alkene to the terminal position, which more readily undergoes hydroesterification. This type of reactivity allows remotely functionalized δ-amido ester **264** to be prepared from *N*-allylic amides. In addition, enantioenriched allylic amines can be used without loss of stereochemical integrity. The acetic acid additive enhances reactivity, most likely by protonating the ruthenium cluster to form ruthenium cluster hydrides that are responsible for alkene isomerization.

(132)



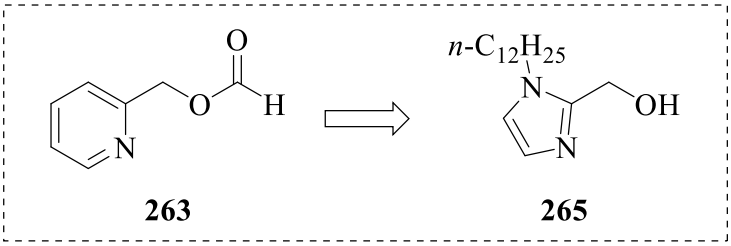
263 2 equiv **264** (82)

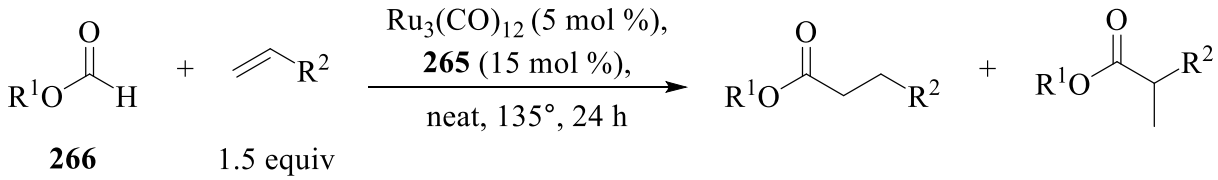
Scheme 125

It is possible to hydroesterify alkenes with more common formate esters that lack a pyridine moiety by using imidazole **265** that mimics the ligand properties of **263** (Scheme 126). {Konishi, 2012 #488} This catalyst system promotes the cross-coupling between simpler formate esters **266** and

terminal alkenes to give a mixture of linear and branched ester products. The imidazole-based ligand is unique in its ability to modulate ruthenium to catalyze hydroesterification, because phosphine-derived ruthenium complexes catalyze only the decarbonylation reaction. Although the regioselectivity is modest, this method demonstrates that a general hydroesterification process is feasible given the appropriate catalyst.

(**133**)





R^1	R^2	Yield (%)	*lin*/*br*
Bn	Ph	>99	55:45
Bn	*n*-$C_{10}H_{21}$	75	76:24
Ph	4-$MeOC_6H_4$	43	68:32

Scheme 126

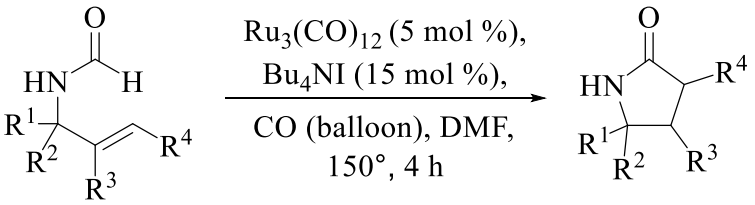
Alkene Hydrocarbamoylation

Ruthenium Catalyzed Processes

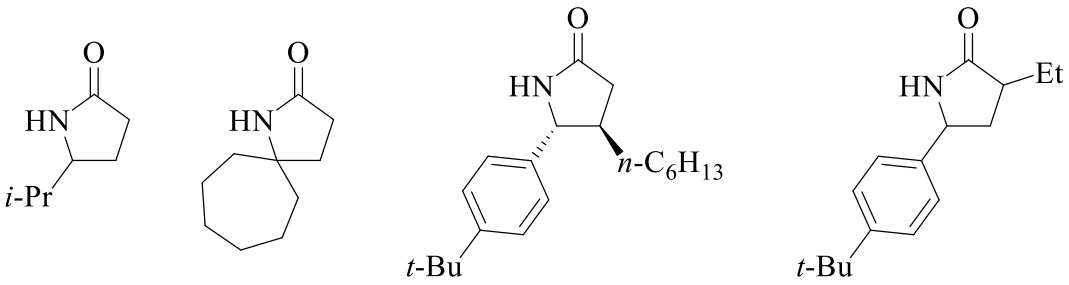
Hydrocarbamoylation represents another class of one-carbon homologations in which formamides are added across alkenes and alkynes to generate homologated amides. {Kondo, 1999 #724}{Nakao, 2009 #496} Variations of this transformation can be found in modern approaches to nitrogen-containing heterocycles. Under ruthenium catalysis and an atmosphere of carbon monoxide,

allylic formamides **267** are converted to substituted chiral pyrrolidinones **268** (Scheme 127).{Armanino, 2013 #494} Formamides containing a free N—H bond are necessary for reactivity as tertiary formamides do not cyclize under the reaction conditions (See Mechanism and Stereochemistry). Enantioenriched pyrrolidinones can be prepared from the corresponding enantioenriched allylic formamides with no erosion in enantiomeric composition (Scheme 128).

(**134**)



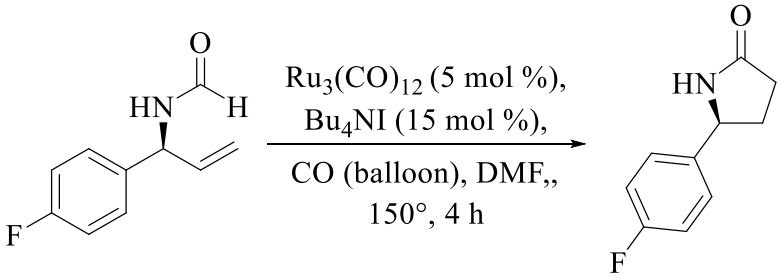
267 **268**



(87) (70) (82), dr = 8:1 (66), dr = 1:1

Scheme 127

(**135**)

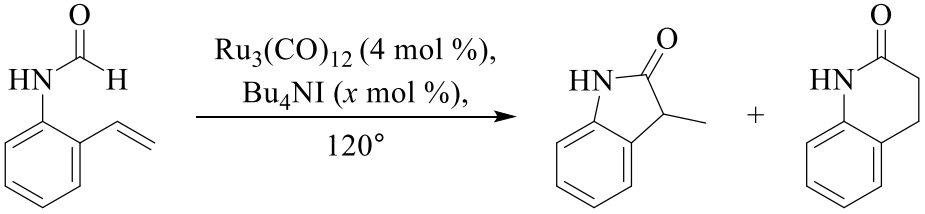


er = 94:6 (77), er = 94:6

Scheme 128

N-2-(Vinylphenyl)formamides **269** undergo regiodivergent cyclization in a similar manner to generate either 2-indolinone **270** or 3,4-dihydroquinolin-2-one (**271**), depending on the solvent and presence of halide additive (Scheme 129).{Li, 2014 #497} It is believed that different reaction mechanisms are operating with the two catalyst systems, leading to the two cyclized products. These reactions also tend to proceed under slightly lower temperatures than those involving allylic formamides (Schemes 127 and 128) and in the absence of a carbon monoxide atmosphere.

(**136**)



269 **270** **271**

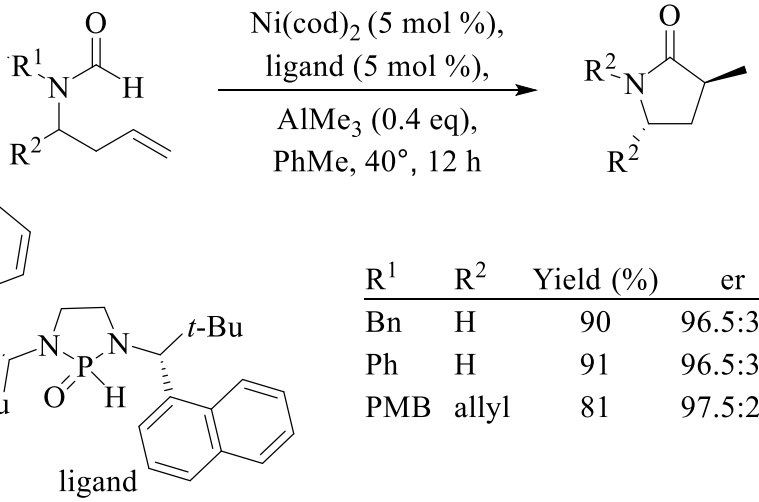
x	Solvent	Yield (%)	**270/271**
15	DMSO/PhMe (1:1)	89	11.1:1
0	DMA/PhCl (1:5)	85	1:5.1

Scheme 129

Nickel Catalyzed Processes

The nickel-catalyzed reactions accommodate tertiary formamides and are thus complementary in scope to the ruthenium-based systems.{Nakao, 2009 #496}{Miyazaki, 2012 #265}{Donets, 2013 #531} These reactions typically use a Lewis acid, such as trimethylaluminum, as a co-catalyst to help promote the C─H activation step. Of note is the ability to achieve enantiocontrol through the use of a chiral diaminophosphine oxide ligand, which interacts with both nickel and aluminum in a heterobimetallic fashion (Scheme 130).{Donets, 2013 #531}

(**137**)



R^1	R^2	Yield (%)	er	dr
Bn	H	90	96.5:3.5	—
Ph	H	91	96.5:3.5	—
PMB	allyl	81	97.5:2.5	5:1

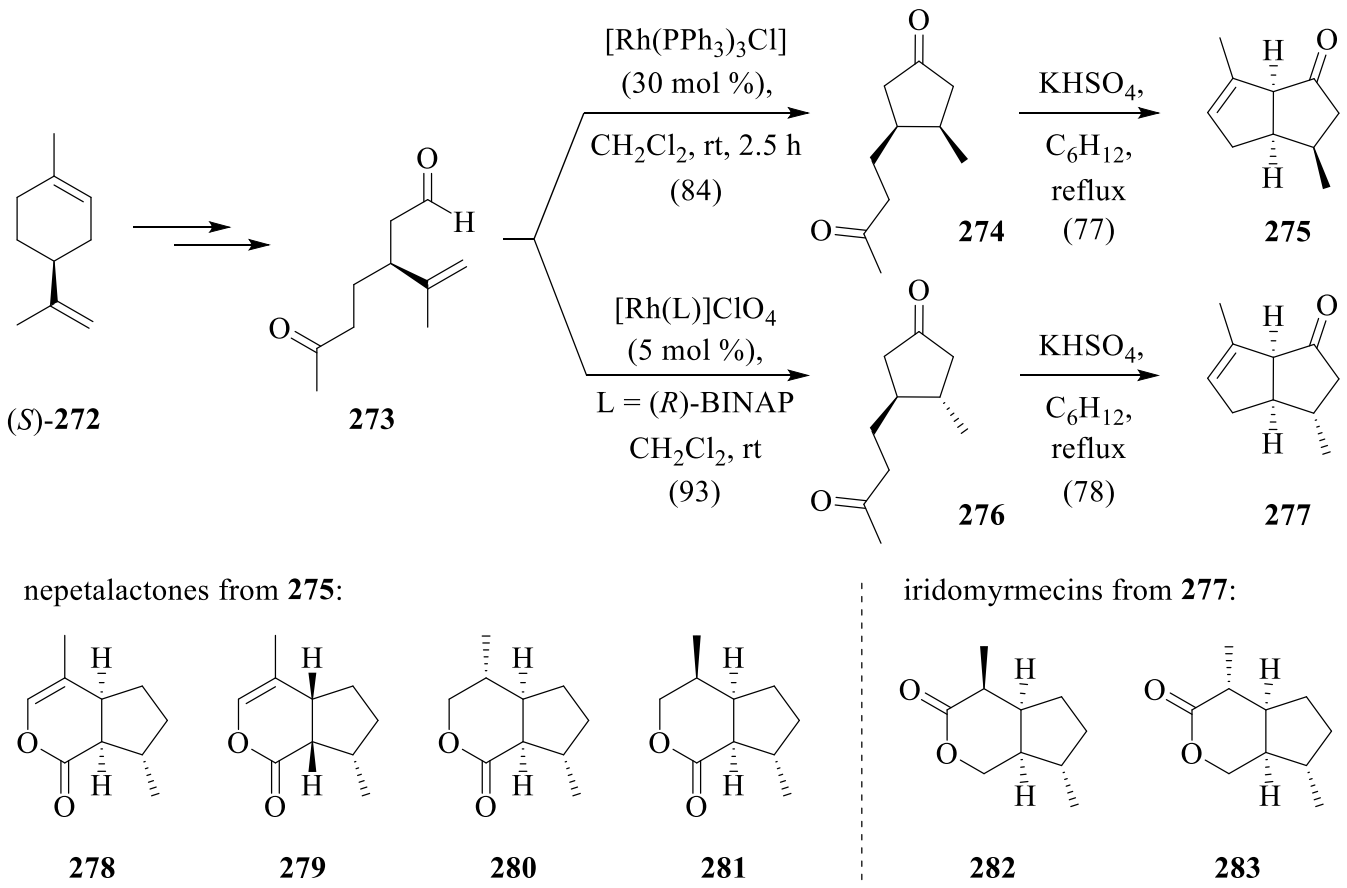
Scheme 130

APPLICATIONS TO SYNTHESIS

Total Synthesis of Natural Products

Syntheses Employing Pool of Chiral Compounds. Intramolecular alkene hydroacylation has been applied to the syntheses of biologically active prostaglandins (Scheme 9){Sakai, 1972 #216}{Suemune, 1986 #365}{Suemune, 1986 #362} and terpene natural products containing cyclopentane structures. In these examples, enantiopure products are obtained through the use of a pool of chiral compounds beginning with limonene (**272**). Three steps involving selective epoxidation, hydrolysis, and oxidative cleavage of the internal alkene of limonene provides ready access to chiral 4-alkenal **273** (Scheme 131).{Wolinsky, 1960 #703}{Takahashi, 1992 #363}. Catalyst-controlled

(**138**)

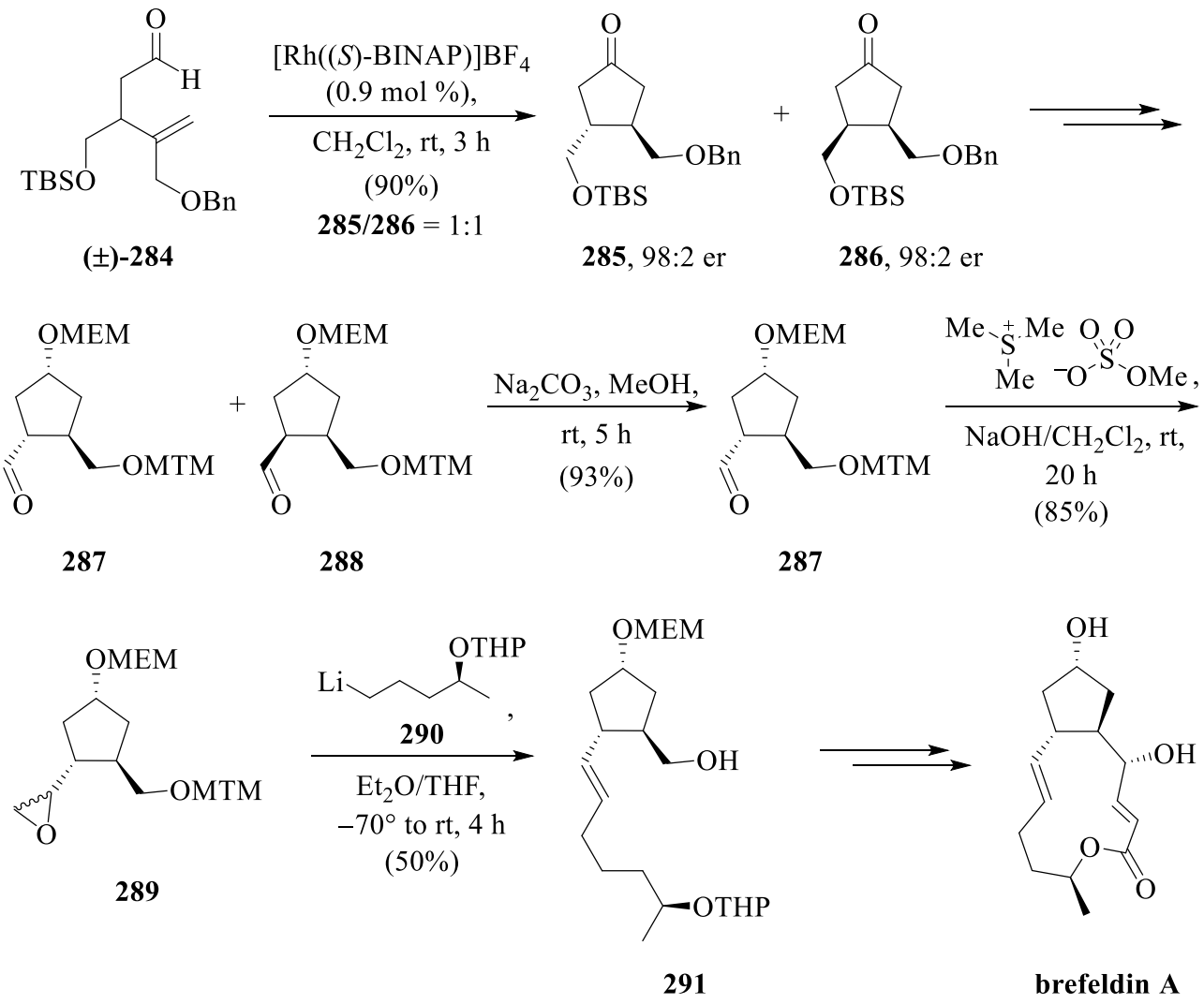


Scheme 131

Hydroacylation produces either diastereomer **274** or **276** selectively and each is subsequently transformed into bicyclic ketones **275** and **277**, respectively, with three contiguous stereogenic centers. Intermediate **275** has been advanced to nepetalactone-related natural products **278**–**281**,{Suemune, 1988 #366} and ketone **277** has been elaborated to iridomyrmecin (**282**) and isoiridomyrmecin (**283**).{Takahashi, 1992 #363} Key intermediates in the synthesis of brefeldin A{Ueno, 1985 #704} and carbacyclin{Xie, 1987 #364} are accomplished using an analogous approach starting from (+)-limonen-10-ol.

Brefeldin A.{Ducray, 1999 #371}{Gais, 1984 #372} Isolated from a variety of fungi, brefeldin A possesses antitumour, antiviral, antifungal, antimitotic, and membrane transport inhibitor activities.{Ueno, 1985 #704}{Klausner, 1992 #705} The cyclopentane unit is assembled in 90% yield as a 1:1 mixture of diastereomers **285** and **286**, both in 98:2 er, by asymmetric hydroacylation of racemic alkenal **284** (Scheme 132). A series of protecting group and redox manipulations provides diastereomeric aldehydes **287** and **288** which are converted into a single enantioenriched diastereomer **287** in 93% yield by treatment with base. Conversion of **287** into epoxide **289** is accomplished in high yield using a mixture of trimethylsulfonium methyl sulfate and sodium hydroxide. Epoxide ring-opening with alkyllithium reagent **290** intercepts intermediate **291** (with concomitant deprotection of the methylthiomethyl group) of a previous total synthesis of brefeldin A.{Gais, 1984 #372}

(139)

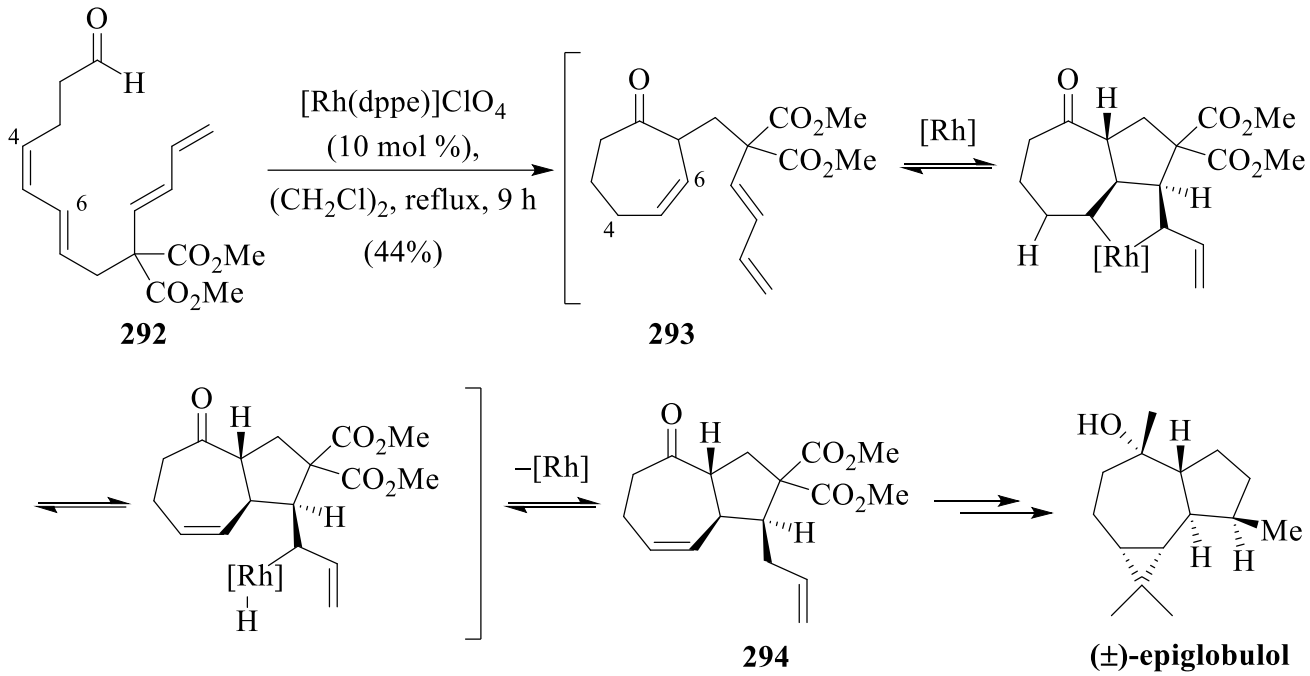


Scheme 132

(±)-Epiglobulol.{Oonishi, 2006 #378} Epiglobulol is a constituent of the oils obtained from the leaves of *Eucalyptus globulus*, which is used in traditional medicine for the treatment of upper respiratory tract infections, asthma, and some skin diseases.{Song, 2009 #706} The hydroazulene framework of epiglobulol is rapidly constructed using a cascade rhodium(I) catalyzed hydroacylation and cycloisomerization of tetraenal **292** (Scheme 133). Intramolecular hydroacylation of the 4,6-diene generates cycloheptenone **293**, which subsequently reacts with the rhodium catalyst in a cycloisomerization fashion to afford fused bicycle **294** in 44% yield. The *gem*-diester quaternary carbon

is necessary to facilitate cycloisomerization by creating a Thorpe-Ingold effect. Alkene cyclopropanation, ketone alkylation, and cleavage of the esters and ethylene unit completes the synthesis of (±)-epiglobulol.

(140)



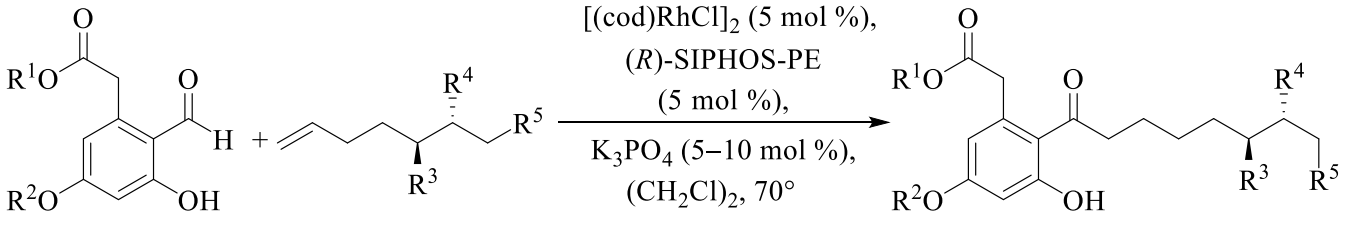
Scheme 133

Dothiorelone, Cytosporone, Phomopsin, and Related Octaketides.{von Delius, 2012 #2}

Rhodium-catalyzed, intermolecular alkene hydroacylation has been applied to the syntheses of biologically active octaketides, including the anticancer agent cytosporone B, starting from simple aryl aldehyde **295** and alkene **296** precursors (Scheme 134). Aldehydes **295** are prepared in two steps, and alkenes **296** are either commercially available or derived in one step from an epoxide. The use of the chiral ligand (*R*)-SIPHOS-PE is necessary to achieve both reactivity and selectivity. The alternative commercially available (*S*)-SIPHOS-PE is *not* the enantiomer of (*R*)-SIPHOS-PE, but rather a diastereomer. Hence, a rhodium catalyst derived from (*S*)-SIPHOS-PE provides inferior reactivity and

selectivity. This convergent strategy allows the preparation of compounds **297** in a total of four steps and facilitates the synthesis of structural analogues.

(141)



295 **296** **297**

Natural product	R (R = H when unspecified)	Yield (%)	lin/br
cytosporone B	R^1 = Et	78	93:7
dothiorelone A	R^1 = Et, R^4 = OH	79	83:17
dothiorelone B	R^1 = Et, R^3 = OH	59	>95:5
dothiorelone C	R^1 = Et, R^5 = OH	83	87:13
phomopsin C	R^1 = Et, R^2 = Me	78	>95:5
unnamed	R^1 = Et, R^2 = Me, R^4 = OH	79	90:10
cytosporone N	R^1 = Me	73	94:6
cytosporone M	R^1 = Me, R^4 = OH	73	89:11

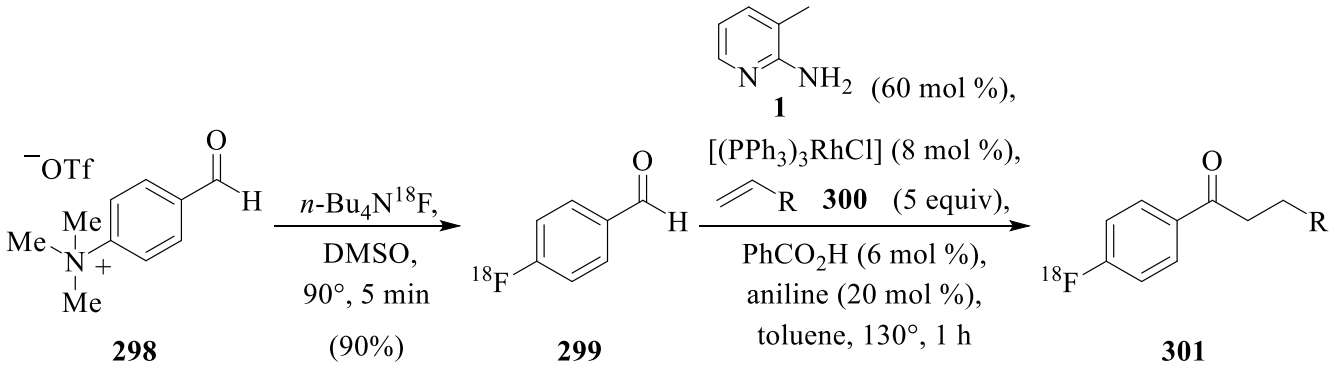
Scheme 134

Application to Radiosynthesis

^{18}F Labeling.{Khan, 002 #414} Labeling molecules with radioactive isotopes is important for developing new radiotracers for medical imaging using positron-emission tomography (PET). Incorporating fluorine-18 is popular among the various radionuclides because of its relatively convenient half-life of 110 minutes (long enough for chemists to perform several chemical operations without significant radiodecay and short enough for the radionuclide to have a relatively fleeting existence in the biological system). However, only the most robust chemical reactions such as nucleophilic aromatic substitution and S_N2 reactions are practical in the context of synthesizing

radioactive compounds because the synthetic sequence needs to be completed quickly (ideally less than 2 hours including HPLC purification) and efficiently, and not require a dry or inert atmosphere.{Welch, 2003 #709} To demonstrate the potential utility of rhodium-catalyzed hydroacylation to incorporate 4-[^{18}F]fluorophenyl groups into biomolecules, 4-[^{18}F]fluorobenzaldehyde (**299**) has been prepared by nucleophilic aromatic substitution of (4-formylphenyl)trimethylammonium triflate (**298**) with [^{18}F]fluoride at 90˚ (Scheme 135). Cooperative metal-organic catalyzed hydroacylation of alkenes **300** results in 4-[^{18}F]fluorophenyl ketones **301** in high radiochemical yields (RCY), defined as the amount of radioactivity relative to that originally present. The efficiency of this process is a consequence of the short reaction times required for the transformations to achieve full or near-full conversion.

(142)



R	RCY[a]
n-Bu	38 ± 6.7
CH_2Ph	47 ± 1.6
CH_2OPh	62 ± 4.5

[a] Average of 3 reactions

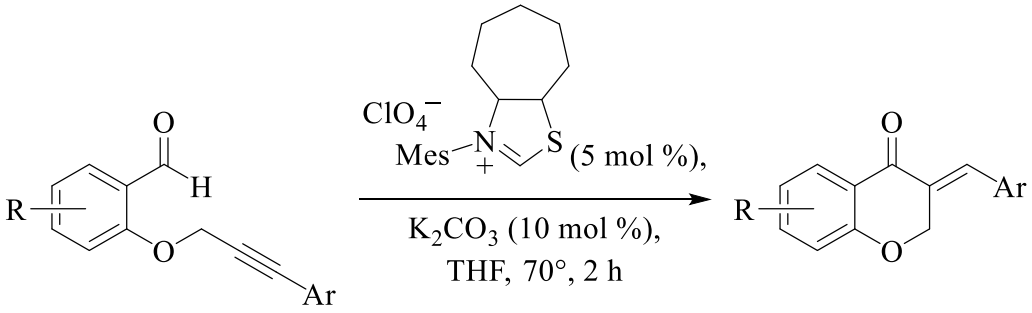
Scheme 135

COMPARISON WITH OTHER METHODS

NHC Catalysis

Hydroacylations of alkynes,{Biju, 2010 #713}{Padmanaban, 2011 #715} alkenes,{Hirano, 2009 #712}{Piel, 2011 #711}{Bugaut, 2011 #714}{Liu, 2011 #587}{Schedler, 2013 #268} and ketones {Chan, 2006 #610}{Du, 2011 #612}{Sreenivasulu, 2011 #611} have been made possible with advances in the design of *N*-heterocyclic carbene (NHC) catalysts. NHC-catalyzed, intramolecular hydroacylation of alkynes{Biju, 2010 #713} and alkenes{Hirano, 2009 #712}{Piel, 2011 #711} produces six-membered chromanone-type products (Schemes 136 and 137) and thus provides substrate scope complementary to that of transition-metal-catalysis, which gives rise to larger seven- and eight-membered ring products (Schemes 53−62). {Bendorf, 2002 #237}{Coulter, 2009 #24}{Bendorf, 2012 #353}{Arnold, 2014 #498} The difference in reactivity lies in the role of the heteroatom linking the

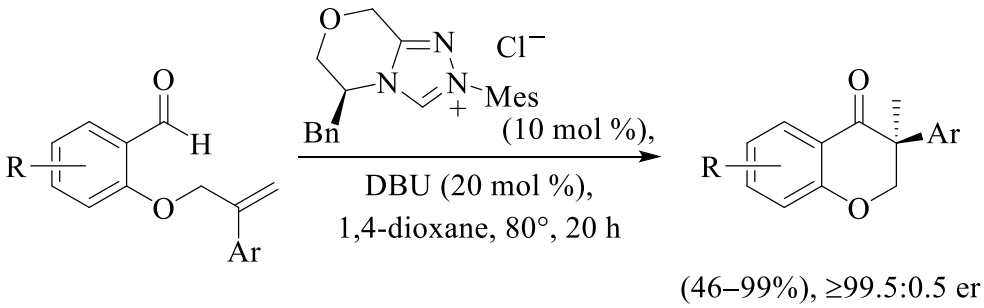
(143)



(72–95%)

Scheme 136

(144)



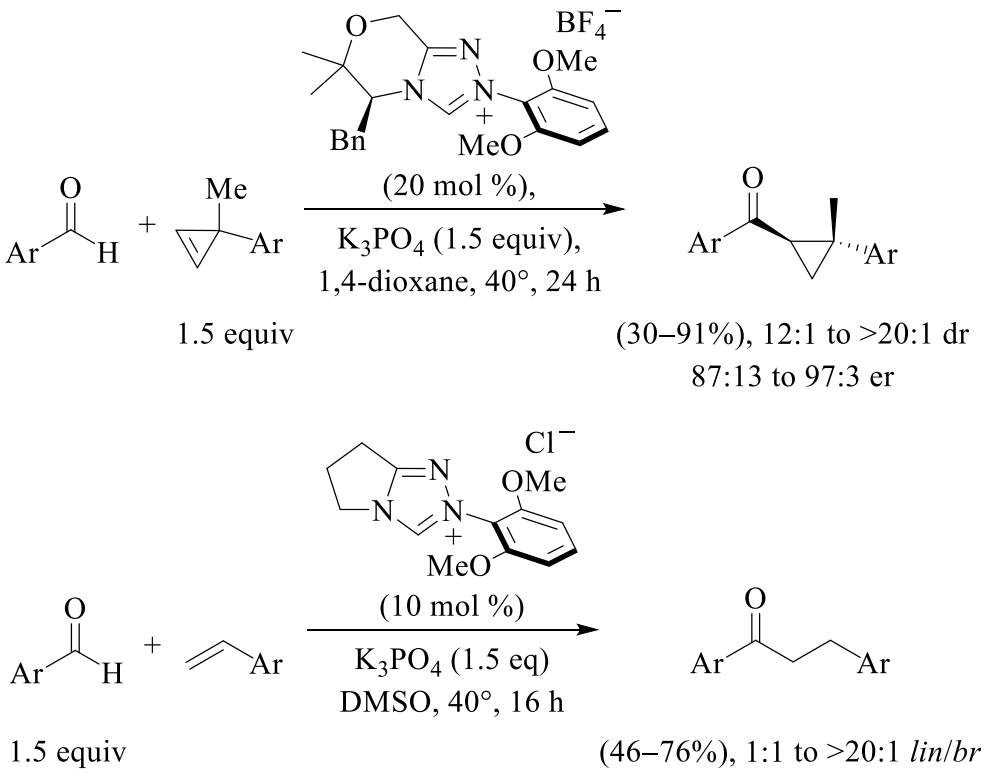
(46–99%), ≥99.5:0.5 er

Scheme 137

aldehyde to the alkyne or alkene. In contrast to rhodium catalysis, in which the heteroatom directs the regioselectivity and suppresses aldehyde decarbonylation, the oxygen heteroatom is not implicated in the mechanism of NHC-catalysis.

Because the mechanism of organocatalyzed hydroacylations does not proceed through the intermediacy of acylmetal hydrides, in principle, additional directing heteroatoms are not necessary to achieve good reactivity. As such, NHC-based catalytic methods address a major limitation in rhodium-catalyzed reactions by not requiring the use of salicylaldehyde derivatives (Schemes 63−70) or β-thioalkoxy aldehydes (Schemes 77−79). In consonance with the metal-catalyzed hydroacylations, intermolecular reactions are favored with strained or electronically activated cyclopropanes and styrenes (Scheme 138).{Bugaut, 2011 #714}{Liu, 2011 #587}{Schedler, 2013 #268} A range of aryl aldehydes

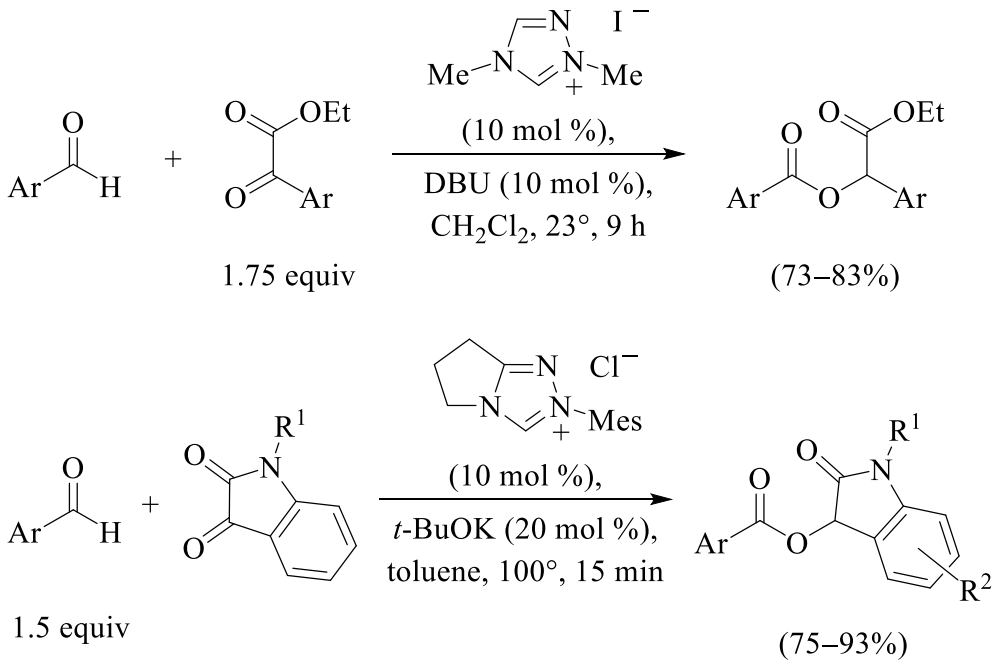
(145)



Scheme 138

combine with achiral cyclopropanes to generate enantioenriched cyclopropyl ketones. In the case of simpler alkenes, electron-deficient styrenes are more reactive and favor formation of the linear products such as when Ar = 4-NCC_6H_4 or 4-pyridyl. Electron-rich styrenes favor formation of the branched isomer, albeit in low yields (25−42%, not shown).{Schedler, 2013 #268} Nevertheless, the scope and reactivity of this system is expected to improve with advances in NHC catalysis.

In addition to forming C—C bonds, NHCs also catalyze the formation of C─O bonds between aldehydes and activated ketones, such as α-keto esters{Chan, 2006 #610}{Sreenivasulu, 2011 #611} and isatins{Du, 2011 #612} (Scheme 139). The use of activated ketones in these reactions suppresses homodimerization between two aldehydes, and allows an effective aldehyde-ketone cross-coupling. Aryl aldehydes perform best, whereas aliphatic aldehydes give lower yields, presumably because of base-catalyzed aldol condensations. These methods are thus complementary to the rhodium-catalyzed, enantioselective ketone hydroacylation approach combines aliphatic aldehydes with α- keto amides (Schemes 120 and 121).{Kou, 2014 #553}{Kou, 2015 #759}



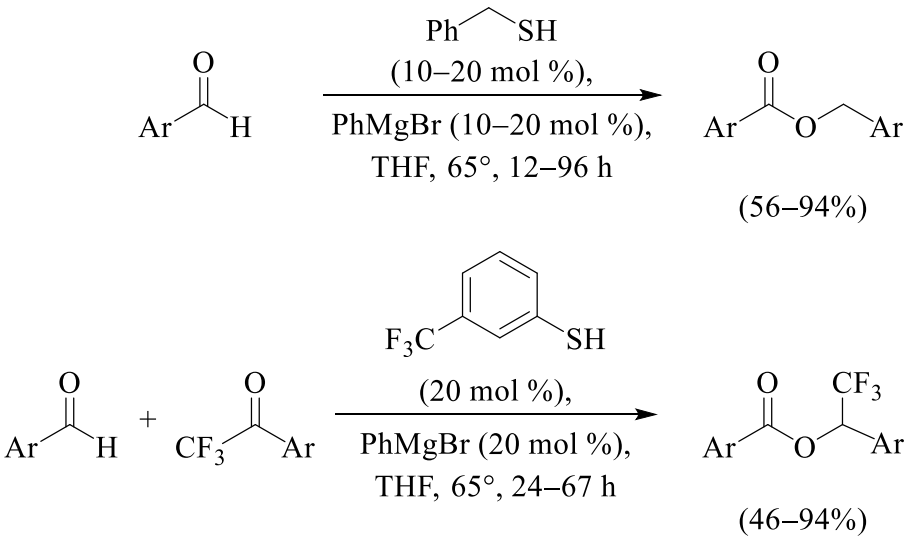
Scheme 139

Thiolate- and Selenide-Catalyzed, Intermolecular Tishchenko Reactions

Thiolate-catalyzed Tishchenko reactions take advantage of a Canizzaro-type hydride transfer to achieve disproportionation of the aldehydes to form ester products.{Cronin, 2010 #613}{O' Connor, 2011 #614}{Koskinen, 2015 #760} A nucleophilic bromomagnesium thiolate, generated *in situ* from a thiophenol derivative, promotes aldehyde homodimerization or a cross-dimerization with activated trifluoromethyl ketones (Scheme 140). In general, these reactions occur in high yields, although long reaction times are required. Microwave conditions have been developed, which shortens reaction times to 30 minutes for aldehyde homodimerization and 3 hours for cross-Tishchenko reactions with trifluoromethyl ketones.{O' Connor, 2011 #614} Selenide nucleophiles, derived from combining a diaryl diselenide and dibutylmagnesium, have been advanced as more reactive catalysts to promote homo- and cross-Tishchenko couplings at room temperature.{Curran, 2012 #615} As is the case in NHC-catalyzed reactions, the thiolate- and selenide-catalyzed methods are generally limited to aromatic

aldehydes. Synthesizing optically active esters via this approach is complicated by potential racemization owing to the presence of a strong base. For carbonyl hydroacylations that involve aliphatic aldehydes, or when stereoselectivity is desired, the milder rhodium-catalyzed methods are preferred.

(141)



Scheme 140

EXPERIMENTAL CONDITIONS

Catalyst Preparation

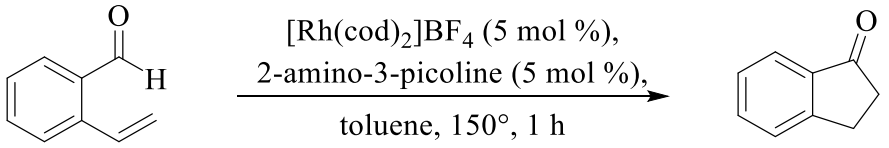
A typical hydroacylation reaction should be performed using anhydrous and rigorously degassed solvents and reagents in a nitrogen or argon environment. Generally, these reactions require preforming the metal-catalyst complex followed by addition of the desired substrate. Commercially available rhodium(I) metal precursors are typically stabilized with bidentate olefin ligands {*e.g.*, $[Rh(cod)_2]BF_4$, $[Rh(nbd)_2]BF_4$, etc.}. These non-spectator ligands compete with phosphines and substrates for binding rhodium, and thus hinder reactivity. To prepare the olefin-free catalyst, a mixture of the rhodium precursor and desired ligand is dissolved in an appropriate solvent such as CH_2Cl_2, $(CH_2Cl)_2$, or acetone

and subjected to hydrogenation for 15−30 minutes (see Experimental Procedures for details).{Shen, 2008 #37}{Shen, 2009 #27}{Coulter, 2009 #24}{Khan, 2011 #15}{Kou, 2014 #553}{Kou, 2015 #759} The resulting catalysts have two vacnt coordination sites, and are extremely oxygen-sensitive. Once prepared, they should be used immediately and not stored. This procedure allows the preparation of a variety of rhodium catalysts modified with different bidentate phosphine ligands.

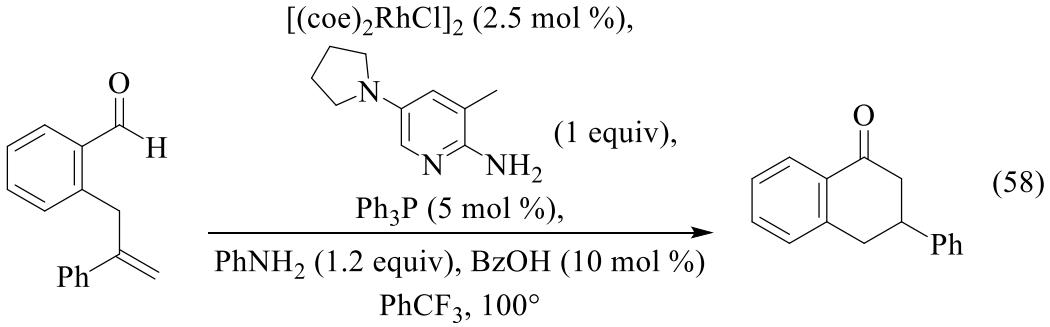
Rhodium precursors chelated by two bidentate olefin ligands, such as $[Rh(cod)_2]BF_4$ and $[Rh(nbd)_2]BF_4$ tend to be less reactive than those chelated by only one bidentate olefin ligand, such as $[(cod)Rh(dppb)]BF_4$. In a recent intramolecular alkene hydroacylation, commercially available $[(cod)Rh(dppb)]BF_4$ was found to perform just as well as $[Rh(dppb)]BF_4$ generated by hydrogenating a mixture of $[Rh(nbd)_2]BF_4$ and dppb.{Arnold, 2014 #498} In one intramolecular ketone hydroacylation report, catalysts derived from a combination of $[(cod)RhCl]_2$, diphosphine ligand, and a silver salt such as $AgBF_4$ or $AgNO_3$ to sequester the chloride anion, are also active without hydrogenation of cod.{Phan, 2009 #23}

An alternative approach to generate an active catalyst involves stabilizing the cationic rhodium(I)-diphosphine complex with the weakly coordinating ligand fluorobenzene.{Douglas, 2008 #716}{Douglas, 2008 #717}{Dallanegra, 2011 #718}{Chaplin, 2012 #253} A representative procedure is to hydrogenate a mixture of $[Rh(cod)_2][BAr^F{}_4]$ and the desired diphosphine ligand in fluorobenzene solvent. The fluorobenzene-ligated rhodium complex can then be precipitated with pentane. Rhodium(I) complexes prepared in this fashion are air-stable and may be stored on the benchtop. Because fluorobenzene is weakly coordinating, it can be readily displaced by alkene or alkyne substrates. These precatalysts can be used directly in hydroacylation.

EXPERIMENTAL PROCEDURES



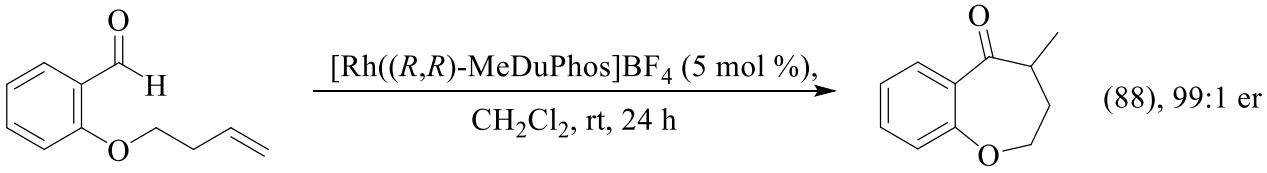
Preparation of 2,3-dihydro-1*H*-inden-1-one [Intramolecular Alkene Hydroacylation of 2-Vinylbenzaldehyde to form Five-Membered Cyclic Ketone].{Vautravers, 2011 #262} To an 8-mL Schlenk tube equipped with a stir bar was added 2-vinylbenzaldehyde (29.1 mg, 0.22 mmol), $[Rh(cod)_2BF_4]$ (4.5 mg, 0.011 mmol), 2-amino-3-picoline (3.4 mg, 0.011 mmol), and toluene (0.20 mL) under an atmosphere of argon. The reaction mixture was stirred for 1 h at 150° and was then concentrated in vacuo. The product was purified by silica gel flash chromatography (CH_2Cl_2) to afford the title product (28.2 mg, 97%) as a white powder: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.7 Hz, 1H), 7.57 (td, *J* = 7.5, 1.3 Hz, 1H), 7.47 (br d, *J* = 7.7 Hz, 1H), 7.36 (br t, *J* =7.5 Hz, 1H), 3.14 (m, 2H), 2.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.1, 155.2, 137.2, 134.7, 127.4, 126.8, 123.8, 36.3, 25.9; HRMS (EI). calcd for C_9H_8O: 132.0575, found: 132.0577.



(58)

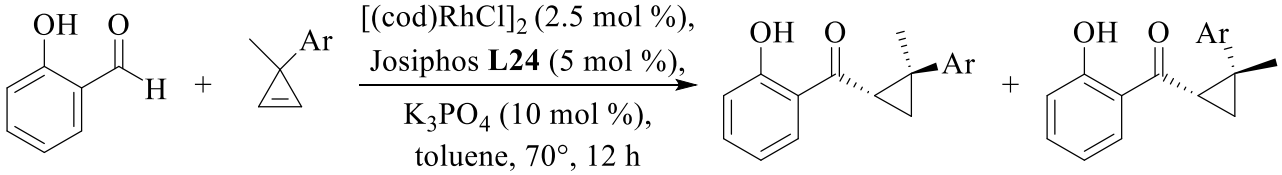
Preparation of 3-Phenyl-3,4-dihydronaphthalen-1(*2H*)-one [Intramolecular Alkene Hydroacylation to Form Six-Membered Cyclic Ketone] {Beletskiy, 2012 #482} {Fillion, 2005 #708} To a dram vial equipped with a stir bar was added 2-(2-phenylallyl)benzaldehyde (66.8 mg, 0.30 mmol), 3-methyl-5-(pyrrolidin-1-yl)pyridin-2-amine (53.1 mg, 0.30 mmol), aniline (0.36 mmol), benzoic acid

(3.6 mg, 0.03 mmol), and Ph_3P (3.9 mg, 0.015 mmol) in a nitrogen-filled glove box. Benzotrifluoride (0.60 mL) and $[(coe)_2RhCl]_2$ (5.4 mg, 0.0075 mmol) were subsequently added. The reaction mixture was stirred for 15 h at 100°, and then cooled to rt and added CH_2Cl_2 (1 mL) and 1 M HCl (0.6 mL). The mixture was stirred for an additional 10 min, and the organic layer was concentrated with silica gel in vacuo. The product was purified by silica gel flash chromatography (2:1 CH_2Cl_2/hexanes) to afford the title product (38.9 mg, 58%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.39-7.24 (m, 7H), 3.51-3.40 (m, 1H), 3.21-3.17 (m, 2H), 2.97 (dd, *J* = 16.7, 3.5 Hz, 1H), 2.83 (dd, *J* = 16.6, 12.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 143.4, 133.8, 132.1, 128.8, 127.2, 127.0, 126.9, 126.7, 45.9, 41.1, 37.7; HRMS (EI). calcd for $C_{16}H_{14}O$: 222.1045, found: 222.1044.



4-Methyl-3,4-dihydrobenzo[*b*]oxepin-5(*2H*)-one [Intramolecular Alkene Hydroacylation to Form a Medium-Sized Cyclic Ketone] {Coulter, 2009 #24} To a 1-dram vial was added (*R*,*R*)-MeDuPhos (3.1 mg, 0.01 mmol), $[Rh(nbd)_2]BF_4$ (3.7 mg, 0.01 mmol) and degassed CH_2Cl_2 (1 mL) inside a nitrogen-filled glove box. This solution was transferred to a Schlenk tube equipped with a stir bar, and the tube was sealed. The Schlenk tube was removed from the glove box, the mixture was stirred for 5 min, and subjected to one freeze-pump-thaw cycle. The catalyst mixture was hydrogenated for 30 min at rt with stirring and then degassed by three freeze-pump-thaw cycles. The sealed Schlenk tube was brought back into the glove box. A solution of 2-(but-3-en-1-yloxy)benzaldehyde (35.2 mg, 0.2 mmol) in degassed CH_2Cl_2 (1 mL) was then added to the Schlenk tube and the mixture was stirred at rt for 24 h. The mixture was concentrated in vacuo and the residue was purified by preparative thin-layer

chromatography (9:1 hexanes/EtOAc) to afford the title product (30.8 mg, 88%) as a colorless oil: IR (neat): 2932, 1683, 1601, 1478, 1449, 1274, 1203, 1051, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.39 (ddd, *J* = 8.0, 7.3, 1.8 Hz, 1H), 7.03-7.09 (m, 2H), 4.53 (ddd, *J* = 12.4, 7.0, 2.3 Hz, 1H), 3.90 (td, *J* = 12.3, 5.0 Hz, 1H), 3.19 (ddq, *J* = 10.6, 7.6, 6.7 Hz, 1H), 2.53 (ddt, *J* = 13.5, 12.2, 7.2 Hz, 1H), 1.73 (dddd, *J* = 13.2, 10.7, 5.0, 2.4 Hz, 1H), 1.23 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 162.4, 133.1, 129.6, 128.6, 122.2, 120.1, 72.5, 44.1, 36.5, 15.3. HRMS (EI). calcd for $C_{11}H_{12}O_2$: 176.0837, found 176.0841; GC-FID analysis: 99:1 er (Cyclodex-β, H_2 mobile phase, 3.2 mL/min flow rate, oven temperature: 150–160° at 0.7°/min, t_{R1} = 9.77 min, t_{R2} = 9.92 min); $[\alpha]^{25}_D$ –126 (*c* = 0.77, $CHCl_3$). The absolute configuration of the product was not determined.

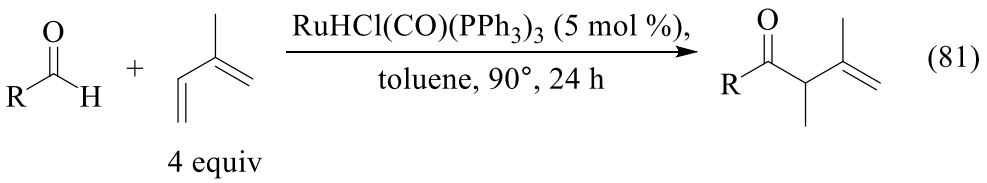


trans *cis*

trans/*cis*	*trans*	er (*trans*)	*cis*	er (*cis*)
13:1	(86)	99:1	(8)	94:6

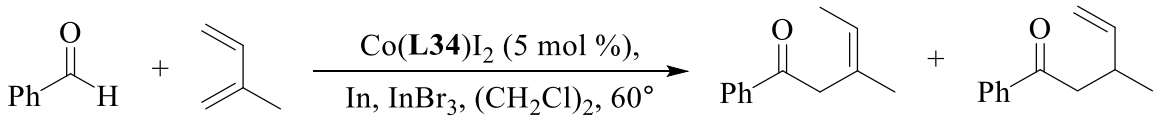
Preparation of (2-hydroxyphenyl)((1*S*,2*S*)-2-methyl-2-phenylcyclopropyl)methanone [Intermolecular Alkene Hydroacylation using Rh Catalysis] {Phan, 2010 #17} To a 1-dram vial equipped with a stir bar was added salicylaldehyde (24.4 mg, 0.2 mmol) and K_3PO_4 (4.2 mg, 0.02 mmol). In a separate 1-dram vial was added **L24** (5.0 mg, 0.01 mmol). Both vials were brought into a nitrogen-filled glove box. The ligand was dissolved in toluene (0.2 mL) and then added to the 1-dram vial containing $[Rh(cod)Cl]_2$ (2.5 mg, 0.01 mmol) The precatalyst mixture was then transferred to the vial containing salicylaldehyde and K_3PO_4. (1-Methylcycloprop-2-en-1-yl)benzene (39 mg, 0.3 mmol) in toluene (0.3 mL) was then added to the reaction vial. The reaction mixture was stirred for 12 h at 70°,

cooled to rt, and filtered through a silica gel plug using Et_2O (10 mL) as the eluent. The organic solvent was removed in vacuo. The dr was determined by ^1H NMR analysis of the crude reaction mixture. The product was purified by preparative thin layer chromatography (19:1 hexanes/EtOAc) to afford the title products as the *trans* isomer (43.6 mg, 86%) as a colorless oil and the *cis* isomer (4.3 mg, 8%) as a white solid: (1*S*,2*S*)-*trans*, IR (neat): 2928, 1630, 1604, 1486, 1446, 1398, 1352 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.53 (s, 1H), 7.85 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.47 (ddd, *J* = 1.6, 7.2, 8.6 Hz, 1H), 7.38 (d, *J* = 1.1 Hz, 1H), 7.38-7.35 (m, 3H), 7.30-7.25 (m, 1H), 7.01 (dd, *J* = 1.1, 8.4 Hz, 1H), 6.90 (ddd, *J* = 1.2, 7.2, 8.2 Hz, 1H), 2.91 (dd, *J* = 6.1, 7.9 Hz, 1H), 1.90 (dd, *J* = 4.7, 6.1 Hz, 1H), 1.65 (dd, *J* = 4.7, 7.9 Hz, 1H), 1.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 162.2, 145.2, 136.0, 130.2, 128.8, 126.7, 126.6, 121.1, 119.0, 118.5, 34.5, 33.3, 20.5, 19.0. HRMS (ESI+). calcd for $C_{17}H_{17}O_2$: 253.1223, found: 253.1212. HPLC analysis: 99:1 er (CHIRALCEL OD-H, i-PrOH/ hexanes = 1:99, 1.0 mL/min, 254 nm, t_{R1} = 6.0 min, t_{R2} = 7.1 min); $[\alpha]^{28}_D$ +320 (*c* = 1.8 in $CHCl_3$). (1*S*,2*R*)-*cis*, mp 91−93 °; IR (neat): 2959, 1627, 1606, 1580, 1484, 1443, 1398, 1355, 1279, 1236, 1201, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.05 (s, 1H), 8.05 (dd, *J* = 1.6, 8.1 Hz, 1H), 7.46 (ddd, *J* = 1.6, 7.3, 8.6 Hz, 1H), 7.22-7.14 (m, 5H), 6.98 (ddd, *J* = 1.1, 7.3, 8.2 Hz, 1H), 6.92 (dd, *J* = 1.0, 8.4 Hz, 1H), 2.95 (dd, *J* = 5.6, 7.4 Hz, 1H), 2.23 (t, *J* = 4.8 Hz, 1H), 1.66 (s, 3H), 1.36 (dd, *J* = 4.4, 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 162.0, 140.5, 135.8, 129.8, 128.8, 128.3, 126.9, 121.1, 118.9, 118.4, 37.5, 32.7, 28.8, 20.6. HRMS (EI). calcd for $C_{17}H_{16}O_2$: 252.1150, found: 252.1155. HPLC analysis: 94:5 er (CHIRALPAK IA, IPA/hexanes = 1:99, 1.0 mL/min, 254 nm, t_{R1} = 4.5 min, t_{R2} = 4.8 min); $[\alpha]^{26}_D$ –48 (*c* = 0.33 in $CHCl_3$).



(81)

Preparation of 2,3-dimethyl-1-phenyl-3-buten-1-one [Intermolecular Alkene Hydroacylation Using Ru-H Catalysis] {Omura, 2008 #441} To a screw-capped test tube was added isoprene (0.407 mL, 4.07 mmol), distilled benzaldehyde (107.9 mg, 1.02 mmol), $RuHCl(CO)(PPh_3)_3$ (47.9 mg, 0.05 mmol), and toluene (6 mL). The test tube was purged with argon, sealed, and the mixture was stirred at 90 ° for 24 h. Since isoprene is a volatile liquid (bp = 34˚), the test tube should be sealed quickly. The solvent was then removed in vacuo and the residue was purified by silica gel flash chromatography (50:1 hexanes/EtOAc) to afford the title compound (144.2 mg, 81%) as a yellow oil: IR (neat) 1685, 1643 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.96-8.00 (m, 2H), 7.52-7.56 (m, 1H), 7.42-7.46 (m, 2H), 4.90 (m, 1H), 4.89 (s, 1H), 4.13 (q, *J* = 6.90 Hz, 1H), 1.75 (s, 3H), 1.34 (d, *J* = 6.90 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.9, 145.2, 136.7, 132.8, 128.4, 128.4, 113.6, 49.1, 20.5, 16.0; HRMS (EI). calcd for $C_{12}H_{14}O$: 174.1045, found: 174.1019.

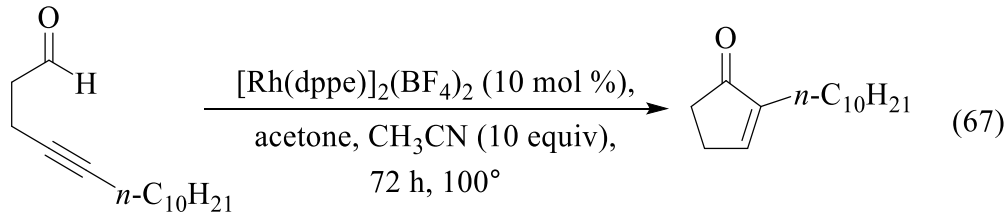


A B

A/B	A	*Z/E* (A)
>20:1	(87)	19:1

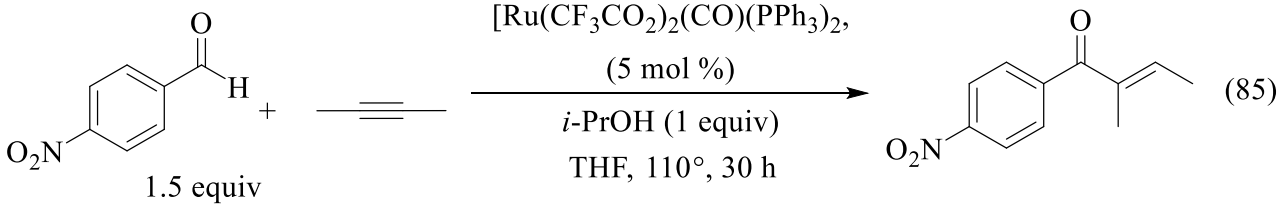
(*Z*)-3-Methyl-1-phenyl-3-penten-1-one [Intermolecular Alkene Hydroacylation using Co Catalysis] {Chen, 2014 #508} To a dram vial equipped with a stir bar was added In powder (2.3 mg, 0.02 mmol), $InBr_3$ (3.5 mg, 0.01 mmol), Co(**L34**)I_2 (9.7 mg, 0.01 mmol), and $(CH_2Cl)_2$ (0.5 mL) in a nitrogen-filled glove box. The mixture was stirred for 15 min and then benzaldehyde (21.2 mg, 0.20 mmol) and isoprene (0.060 mL, 0.60 mmol) were added to the resulting catalyst mixture. Since isoprene is a volatile liquid (bp = 34˚), the test tube should be sealed quickly. After heating the reaction mixture at 60° for 20–24 h, and then it was cooled to rt. The product selectivity was determined by ^1H NMR or GC-FID of the

crude reaction mixture. The product was directly purified by silica gel column chromatography (10:1 hexanes/EtOAc) to afford the title compound (30.3 mg, 87%) as a colorless oil: ^{1}H NMR(500 MHz, $CDCl_3$): δ 7.99–7.97 (m, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 5.53–5.49 (m, 1H), 3.72 (s, 2H), 1.74–1.73 (m, 3H), 1.64 (dd, *J* = 6.8, 0.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.4, 137.3, 133.2, 129.9, 128.8, 128.4, 123.0, 42.0, 24.3, 14.0. HRMS (ESI). calcd for $C_{12}H_{14}ONa$: 197.0942, found: 197.0938.



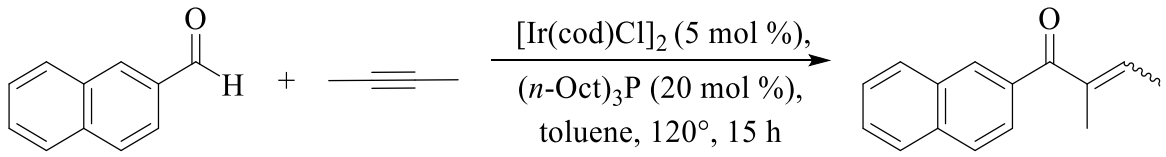
(67)

Preparation of 2-*n*-decylcyclopent-2-en-1-one [Intramolecular Alkyne Hydroacylation using Rh Catalysis] {Tanaka, 2001 #448} To a 5-mL vial equipped with a stir bar was added $[Rh(dppe)]_2(BF_4)_2$ (13 mg, 0.023 mmol), pentadec-4-ynal (50 mg, 0.23 mmol), MeCN (117μL, 2.3 mmol), and acetone (2.5 mL) in a nitrogen-filled glove box. The reaction mixture was stirred at 100° for 72 h. The reaction was quenched with MeCN (1 mL), and the resulting solution was concentrated in vacuo. The product was purified by silica gel flash chromatography (3:1 pentane/Et_2O) to give the title compound (34.3 mg, 67%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.27 (m, 1H), 2.57–2.51 (m, 2H), 2.40–2.37 (m, 2H), 2.17–2.11 (m, 2H), 1.51–1.38 (m, 2H), 1.32–1.19 (m, 14H), 0.86 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 157.5, 146.8, 34.8, 32.1, 29.83, 29.80, 29.65, 29.63, 29.5, 28.0, 26.7, 25.0, 22.9, 14.3.



(85)

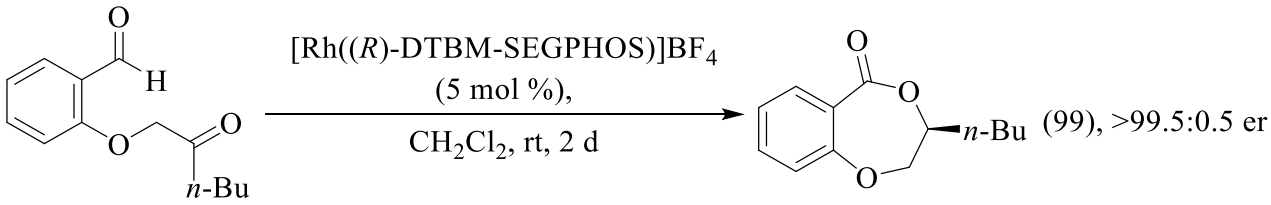
Preparation of (*E*)-2-methyl-1-(4-nitrophenyl)but-2-en-1-one [Intermolecular Alkyne Hydroacylation using Ru-H Catalysis] {Williams, 2009 #359} To an 8 mL borosilicate pressure tube equipped with a stir bar was added $Ru(CF_3CO_2)_2(CO)(PPh_3)_2$ (13.2 mg, 0.015 mmol) and 4-nitrobenzaldehyde (45.3 mg, 0.300 mmol). The tube was then sealed with a rubber septum, purged with argon, and THF (1.5 mL, 0.2 M with respect to aldehyde), and *i*-PrOH (36 mL, 0.300 mmol) were added. After the reaction tube was cooled to -78°, 2-butyne (35 mL, 0.450 mmol) was added, and the rubber septum was quickly replaced with a screw cap. The reaction tube was allowed to reach rt, then heated to 110° and to the contents were stirred for 30 h. The reaction mixture was concentrated in vacuo, and the product was purified by silica gel flash chromatography (9:1 hexanes/EtOAc) to afford the title compound (52.5 mg, 85%) as a light-brown oil: IR (neat): 3022, 1709, 1650, 1524, 1347, 1278, 1104, 748, 715, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.7 Hz, 2H), 7.72 (d, *J* = 8.7 Hz, 2H), 6.41 (q, *J* = 6.8 Hz, 1H), 1.99 (s, 3H), 1.93 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 149.0, 144.6, 144.2, 137.7, 129.7, 123.2, 15.0, 11.7; HRMS (CI). calcd for $C_{11}H_{12}NO_3$: 208.0809, found: 208.0811.



4 equiv

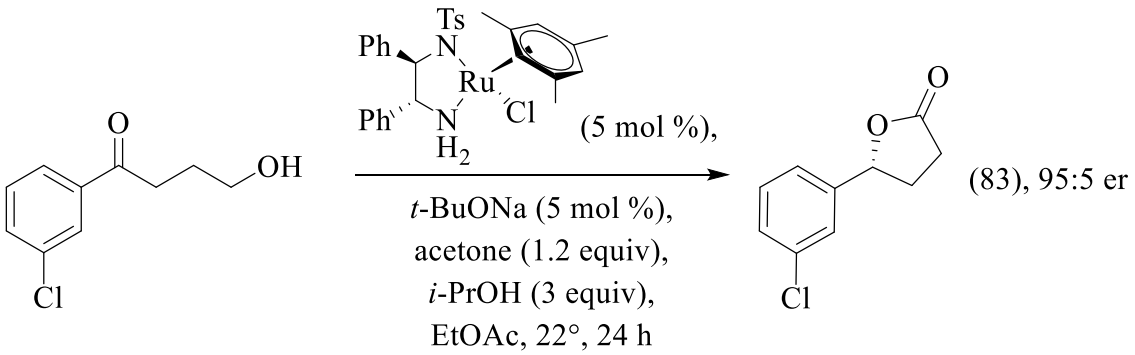
(81), *E*/*Z* = 43:57

Preparation of 2-methyl-1-(naphthalen-2-yl)but-2-en-1-one [Intermolecular Alkyne Hydroacylation using Ir Catalysis] {Hatanaka, 2010 #266} To an 8 mL pressure tube equipped with a stir bar under argon was added $[Ir(cod)Cl]_2$ (16 mg, 0.025 mmol), P(*n*-Oct)$_3$ (37 mg, 0.1 mmol), 2-naphthaldehyde (78 mg, 0.5 mmol), and 2-butyne (108 mg, 2 mmol) in toluene (1 mL). The mixture was stirred at 120° for 15 h. The product was purified by silica gel column chromatography (20:1 hexanes/EtOAc) and distilled using a Kugelrohr apparatus to give the title compound (85.2 mg, 81%): IR (neat): 3055, 2974, 2917, 1640, 1466, 1356, 1281, 1160, 1120, 821, 757, 717 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) for the *E* isomer: δ 8.42–7.48 (m, 7 H), 6.46 (q, *J* = 7 Hz, 1 H), 2.05–2.01 (m, 3H), 1.90 (d, *J* = 7 Hz, 3H); ^{1}H NMR (400 MHz, $CDCl_3$) for the *Z* isomer: δ 8.42–7.48 (m, 7H), 5.86 (q, *J* =7 Hz, 1 H), 2.05–2.01 (m, 3 H), 1.55 ppm (d, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) for the *E*,*Z* mixture: δ 200.7, 198.9 (2*C*=O, *E* and *Z* isomers), 141.3 (C=*C*H, *E*-isomer), 137.8, 136.5, 136.0, 135.7, 134.7, 133.8, 132.7, 132.2 (8C, *E*- and *Z*-isomers), 131.6, 130.1, 129.6, 129.0, 128.6, 128.5, 127.9, 127.8, 127.7, 127.6, 126.7, 126.5, 125.7, 124.3 (14CH, *E*- and *Z*-isomers) 126.8 (C=*C*H, *Z*-isomer), 21.28, 21.29 (2CH_3, *E*- and *Z*-isomers), 15.5 (CH_3, *Z* isomer), 14.8 (CH_3, *E*-isomer); HRMS (EI). calcd for $C_{15}H_{14}O$: 210.1045, found: 210.1046.



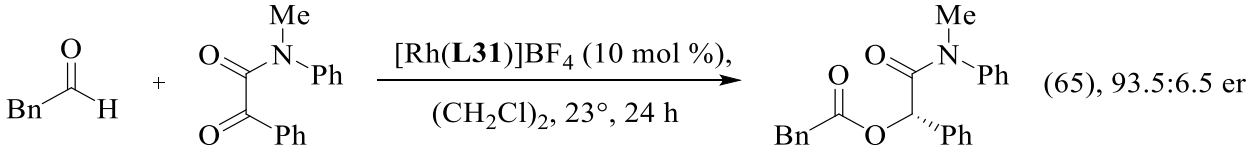
Preparation of (*S*)-3-butyl-2,3-dihydro-5*H*-benzo[*e*][1,4]dioxepin-5-one [Intramolecular Carbonyl Hydroacylation using Rh Catalysis] {Shen, 2008 #37} To a 25 mL Schlenk tube equipped with a stir bar was added a solution of $Rh(nbd)_2BF_4$ (3.7 mg, 0.01 mmol) and (*R*)-DTBM-SEGPHOS (13 mg, 0.011 mmol) in dry and degassed CH_2Cl_2 (1 mL) inside a nitrogen-filled glove box. The Schlenk tube

was removed from the glove box, and the resulting solution was stirred for 5 min. H_2 gas was then bubbled through the solution for 30 min at rt. During this time the solution changed from orange to deep-red in color. The resulting solution was degassed by three freeze-pump-thaw cycles and argon gas was added. A solution of 2-((2-oxohexyl)oxy)benzaldehyde (44 mg, 0.2 mmol) in dry and degassed CH_2Cl_2 (1 mL) was then added to the catalyst solution via syringe. The reaction mixture was stirred at ambient temperature for 2 d, concentrated in vacuo, and directly purified by silica gel flash chromatography (9:1 hexanes/EtOAc) to afford the title compound (43.6 mg, 99%) as an oil: IR (film): 2956, 1726, 1605, 1480, 1295, 1116, 755, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 2.0, 9.6 Hz, 1H, Ar), 7.46-7.51 (m, 1H, Ar), 7.12 (t, *J* = 7.2 Hz, 1H, Ar), 7.00 (d, *J* = 8.0 Hz, 1H, Ar), 4.49-4.53 (m, 1H, COO-CH), 4.29-4.38 (m, 2H, O-CH_2), 1.25-1.82 (m, 6H, $(CH_2)_3$), 0.91 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 155.2, 134.7, 133.4, 122.8, 120.8, 120.2, 76.2, 74.7, 30.4, 27.3, 22.4, 13.8; HRMS (EI) calcd for $C_{13}H_{16}O_3$: 220.1099, found: 220.1093; HPLC analysis: >99.5:0.5 er (DAICEL CHIRALCEL OJ, eluent, hexane/*i*-PrOH = 93/7, flow rate 1.0 mL/min, detection 225 nm, t_{R1}: 12.5 min and t_{R2}:15.5 min); $[\alpha]^{25}_D$ +66.3º (*c* = 1.64, $CHCl_3$).



Preparation of (+)-(*R*)-γ-(3-Chlorophenyl)-γ-butyrolactone [Intramolecular Carbonyl Hydroacylation using Ru-H Catalysis] {Murphy, 2013 #1} To a dram vial equipped with a stir bar was added the Ru catalyst (9.6 mg, 0.015 mmol) and *t*-BuONa (1.4 mg, 0.015 mmol) in a nitrogen-filled

glove box. EtOAc (0.6 mL), acetone (26 µL), *i*-PrOH (69 µL), and 1-(3-chlorophenyl)-4-hydroxybutan-1-one (59.6 mg, 0.3 mmol) were subsequently added. The vial was sealed with a Teflon-lined polypropylene screw cap and removed from the glove box. The mixture was stirred at rt for 24 h and the product was purified by preparative silica gel thin layer chromatography (3:2 hexanes/EtOAc) to give the title compound (49.0 mg, 83%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 3H), 7.25–7.19 (m, 1H), 5.51–5.45 (m, 1H), 2.73–2.61 (m, 3H), 2.24–2.09 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 141.5, 134.8, 130.1, 128.6, 125.4, 123.3, 80.2, 30.9, 28.7; HRMS (ESI). calcd for $C_{10}H_9ClO_2NH_4$: 214.0635, found: 214.0638; HPLC analysis: 95:5 er (CHIRALPAK ADH, 5:95 MeOH/CO_2, 1.8 mL/min, 44°, 210 nm, t_{R1} = 3.8 min, t_{R2} = 4.2 min); $[\alpha]^{25}_D$ + 14.3 (*c* = 1.0, CH_2Cl_2).



Preparation of (*S*)-2-(methyl(phenyl)amino)-2-oxo-1-phenylethyl 3-phenylpropanoate [Intermolecular Ketone Hydroacylation using Rh Catalysis] {Kou, 2014 #553} In a nitrogen-filled glovebox, Josiphos **L31** (3.1 mg, 0.005 mmol) was dissolved in CH_2Cl_2 (0.3 mL) and was added to a vial containing $[Rh(cod)_2]BF_4$ (2.0 mg, 0.005 mmol). The resulting solution was transferred to a 25 mL Schlenk tube. Additional CH_2Cl_2 (0.3 mL) was used to rinse the vial containing the ligand, and this liquid was also added to the Schlenk tube. The Schlenk tube was then connected to a Schlenk line (vacuum gas manifold), and the pre-catalyst solution was degassed by two freeze-pump-thaw cycles. The Schlenk tube was backfilled with H_2 gas, and the solution was stirred at rt under a gentle flow of H_2 for 45−60 min. The CH_2Cl_2 solvent was subsequently removed under reduced pressure to give the rhodium catalyst as a dark-red oil/film. To the catalyst residue was added a solution of *N*-methyl-2-oxo-*N*,2-diphenylacetamide (23.9 mg, 0.10 mmol) in $(CH_2Cl)_2$ (0.4 mL), followed by 2-phenylacetaldehyde

(13.2 mg, 0.11 mmol). The reaction mixture was stirred at rt for 24 h and the crude product was purified by preparative silica gel thin layer chromatography (4:1 hexanes/EtOAc) to give the title compound (24.2 mg, 65% yield) as a colorless oil: IR (ATR): 2923, 1733, 1671, 1595, 1495, 1454, 1385, 1245, 1151, 989, 911, 755, 730, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (br s, 3H), 7.29–7.33 (m, 1H), 7.22–7.28 (m, 4H), 7.15–7.21 (m, 3H), 7.10 (br. s, 2H), 7.05 (d, *J* = 7.3 Hz, 2H), 5.85 (s, 1H), 3.26 (s, 3H), 2.92–3.05 (m, 2H), 2.80 (ddd, *J* = 16.0, 9.2, 6.7 Hz, 1H), 2.69 (ddd, *J* = 16.4, 9.8, 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 168.3, 142.5, 140.6, 134.1, 129.9, 129.3, 128.8, 128.7, 128.6, 128.5, 128.3, 126.4, 74.0, 38.1, 35.7, 30.9. HRMS (ESI). calcd for $C_{24}H_{23}NO_3Na$: 374.1756; found: 374.1762; SFC analysis: 93.5:6.5 *er*, 150 mm CHIRALPAK AD-H, 5:95 MeOH/CO_2, 2.0 mL/min, 220 nm, 44°, nozzle pressure = 200 bar CO_2, t_{R1} (minor) = 4.21 min, t_{R2} (major) = 5.09 min; $[\alpha]^{27}_D$ +88 (*c* = 1.3, $CHCl_3$).

TABULAR SURVEY

The hydroacylation of alkenes, alkynes and carbonyls are surveyed. These are grouped into intramolecular and intermolecular reactions, and further subdivided into reactions with alkenes, alkynes, aldehydes, and ketones. The tables contain all examples of the title reaction that were found in the open literature through December 2014 and select literature from 2015. Examples within Table 1 (Intramolecular Hydroacylation of Alkenals) are arranged by increasing carbon count of the main carbon skeleton. To optimize the proximity of like examples, carbons owing to substituents appended to the main skeleton are not included in the carbon count. Examples within Table 2 (Intermolecular Hydroacylation of Alkenes) are primarily arranged in order of increasing carbon count of the alkene. When the alkene coupling partner is the same, the entries are arranged (secondarily) based on increasing

carbon count of the aldehyde coupling partner. Tables 2A and 2B include examples of intermolecular hydroacylation of activated alkenes. The term “activated” is used in a broad sense to encompass substrates that are ‘activated’ by electronics (conjugation), strain, and by virtue of a directing group. Tables 3A, 3C, and 3D (Intramolecular Hydroesterification and Hydrocarbamoylation) are arranged based on the increasing carbon count. Examples within Tables 3B and 3E (Intermolecular Hydroesterification) are primarily arranged in order of increasing carbon count of the alkene. When the alkene coupling partner is the same, the entries are arranged (secondarily) based on the increasing carbon count of the formate ester or formamide. Examples within Table 4A (Intramolecular Hydroacylation of Alkynes) are arranged by increasing carbon count. Examples within Table 4B (Intermolecular Hydroacylation of Alkynes) are primarily arranged in order of the increasing carbon count of the alkyne. When the alkyne coupling partner is the same, the entries are arranged (secondarily) based on increasing carbon count of the aldehyde coupling partner. Examples within Table 5A (Intramolecular Hydroacylation of Ketones) are arranged by the increasing carbon count of the substrate. Examples within Tables 5B and 5C (Intermolecular Hydroacylation of Aldehydes and Ketones) are primarily arranged in order of increasing carbon count of the aldehyde coupling partner. When the aldehyde coupling partner is the same, the entries are arranged (secondarily) based on the increasing carbon count of the second aldehyde or ketone coupling partner. With the exception of Table 1, all carbons, including those attached to nitrogen, oxygen, and sulfur heteroatoms are included in the count. When the numbers of carbon atoms are equal, the entries are arranged based on the increasing number of heteroatoms in order of nitrogen, oxygen, sulfur, and phosphorus. All reported yields are provided in parentheses. A dash indicates that no data is provided in the primary reference. Pressure and enantioselectivity units vary in the literature and are converted to atmospheres (atm) and enantiomeric ratio (er), respectively, in the tabulation survey.

The following abbreviations, not included in The Journal of Organic Chemistry Standard Abbreviations and Acronyms, are used in the tables:

BDPP	2,4-bis(diphenylphosphino)pentane
BINAP	2,2-bis(diphenylphosphino)-1,1’-binaphthyl
[BMI][NTf_2]	1-*n*-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide
coe	cyclooctene
cot	cyclooctatetraene
Cp*	pentamethylcyclopentadienyl
dcpe	1,2-bis(dicyclohexylphosphino)ethane
DIOP	1,4-bis(diphenylphosphino)-1,4-dideoxy-2,3-*O*-isopropylidene-L-threitol
DIPMC	*trans*-1,2-bis[(diphenylphosphino)methyl]cyclohexane
DPEphos	bis[2-(diphenylphosphino)phenyl]ether
dpm	dipivaloylmethanato
dppb	1,4-bis(diphenylphosphino)butane
dppben	1,2-bis(diphenylphosphino)benzene
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1’-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
GLC	gas-liquid chromatography
MOP	2-(diphenylphosphino)-2’-methoxy-1,1’-binaphthyl
nbd	norbornadiene
4-PBA	4-diphenylphosphinobenzoic acid
Phth	phthalyl

[PNN]Cl	bis(triphenylphosphine)iminium chloride
p-TSA	*para*-toluenesulfonic acid
SPO	secondary phosphine oxide
TBDPS	*tert*-butyl diphenylsilyl

REFERENCES