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Intermolecular Hydroacylation by Transition-Metal Complexes

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In this review, transition-metal-catalyzed intermolecular hydroacylation, which is a direct synthetic protocol generating ketones from aldehydes and unsaturated hydrocarbons, will be discussed. In order to avoid decarbonylation, one of the major side-reactions occurring in transition-metal-catalyzed hydroacylation, several important strategies have been developed: An aldehyde ligand bearing a coordinating heteroatom at an appropriate position, a chelation auxiliary, and a masked form of the aldehyde, such as an aldimine or allylamine. Hydroacylation or its variations can also be applied to the synthesis of cycloalkanones and an α,β-unsaturated ketone or to the carbon–carbon triple bond cleavage of an alkyne.

1. Introduction

The activation of the C–H bond is one of the current interests of organometallic chemistry.[1–9] In particular, C–H bond cleavage of a specific functional group in an organic molecule is an important tool in organic synthesis as it leads to the formation of a new carbon–carbon bond between the carbon of the original C–H bond and an incoming reagent without generating side-products. In this regard, the transformation of an aldehyde and an unsaturated hydrocarbon into a ketone, hydroacylation, is one method through which a new carbon–carbon bond can be formed

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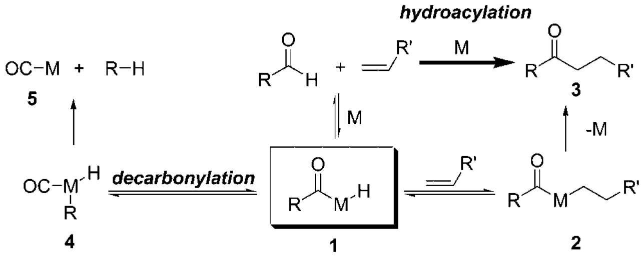
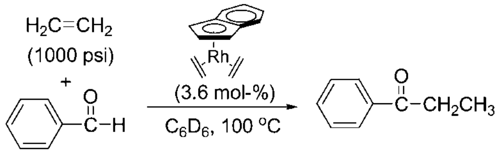
in an atom-economical way. In order to facilitate this reaction, the aldehydic C–H bond can be cleaved with transition metals to form an acyl metal hydride **1**, followed by the insertion of the hydride into an unsaturated C–C bond to generate acylmetal alkyl complex **2** (Scheme 1).[10–14] Reductive elimination of the acylmetal alkyl **2** affords ketone **3** with the regeneration of the transition metal as catalyst.



Scheme 1.

One of the important side-reactions of the hydroacylation process is decarbonylation. Since metal carbonyl complexes are so stable, the acyl metal hydride **1** is readily decarbonylated and the resulting alkylmetal hydride **4** is reductively eliminated to yield an alkane and a metal carbonyl complex **5** as the final products. Therefore, to facilitate the hydroacylation reaction, an efficient way of evading the decarbonylation process should be developed. One method involves stabilizing the acylmetal complex **1** by making it coordinatively saturated. A labile alkene, such as ethylene, at high pressure can be utilized for this purpose in the presence of indenylrhodium(I) complexes as the high-pressure ethylene causes the metal complexes to be coordinatively saturated thus retarding decarbonylation (Scheme 2).[15] However, only ethylene is suitable for this reaction.



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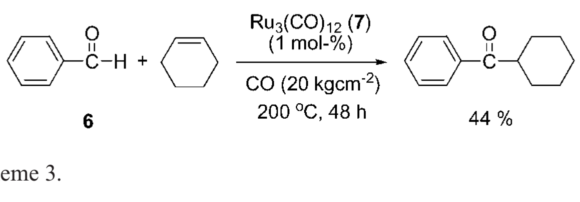
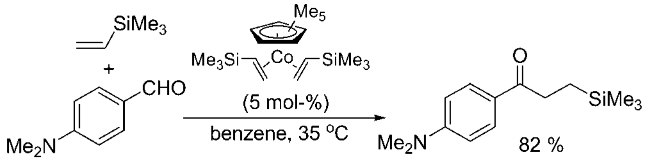
Scheme 2.

Watanabe and co-workers used high-pressure CO to stabilize the carbonylruthenium(0) complex intermediate (Scheme 3).[16,17] Excess CO likely saturates the acylruthenium(II) carbonyl hydride complex intermediate, stabilizing it. Common olefins such as cyclohexene can be used in this hydroacylation process, but the reaction requires harsh reaction conditions to obtain the products.



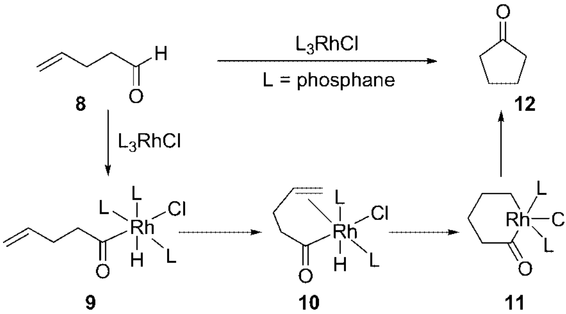
Scheme 3.

Lenges and Brookhart utilized a cobalt complex as a catalyst for the intermolecular hydroacylation of vinylsilane under very mild conditions, but the applicable substrate is limited to vinylsilane (Scheme 4).[18]



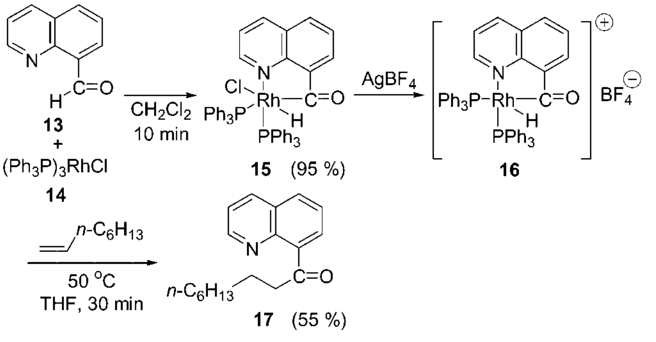
Scheme 4.

Another way of stabilizing acylmetal hydride complexes is to make a stable metallacyclic complex. As five- or six-membered metallacyclic complexes are more stable than other-sized metallacyclic complexes, generating a five- or six-membered acylmetallacyclic complex is one of the better ways to avoid decarbonylation. One good example is the intramolecular hydroacylation of 4-pentenal to furnish cyclopentanone derivatives (Scheme 5).[19–27] The transition-metal catalyst reacts with 4-pentenal (**8**) to form acylmetal hydride **9**. Subsequent hydride insertion into the coordinating alkene of stable acylmetallacyclic complex **10** forms six-membered acylmetallacyclic complex **11**. Finally reductive elimination from the metallacyclic intermediate **11** affords cyclopentanone (**12**). This intramolecular hydroacylation process can be applied to the synthesis of cyclopentanone derivatives from 4-pentenal derivatives although some substrate variations allow the synthetic scope to be extended to other cycloalkanones.[28–32] Many related articles reporting the asymmetric synthesis of cyclopentanone derivatives through the use of chiral auxiliary ligands and transition-metal catalysts have been published.[33,34]



Scheme 5.

Another example that utilizes a five-membered acylmetallacycle is the reaction of coordinating ligands such as 8-quinolinecarbaldehyde (**13**) (Scheme 6).[35] The aldehydic C–H bond and the nitrogen atom in 8-quinolinecarbaldehyde are in appropriate positions for C–H bond activation by the metal because aldehydic C–H bond cleavage by metal complexes takes place via a five-membered metallacyclic complex after coordination of the nitrogen atom to the metal complex. Aldehyde **13** bearing a coordinating nitrogen atom reacts with [$(Ph_3P)_3RhCl$] (**14**) at ambient temperature to give a five-membered ring acylrhodium(III) complex **15** which is a coordinatively saturated species. The acylrhodium(III) hydride complex **15** is so stable that it may be isolated and characterized.[35] The addition of $AgBF_4$ to **15** generates coordinatively unsaturated and catalytically active species **16**, which reacts with a 1-alkene to produce ketone **17**. A limitation of this protocol is that it is very hard to transform the coordinating quinolinyl group in **17** into other alkyl or functional groups for synthetic application as common ketones.



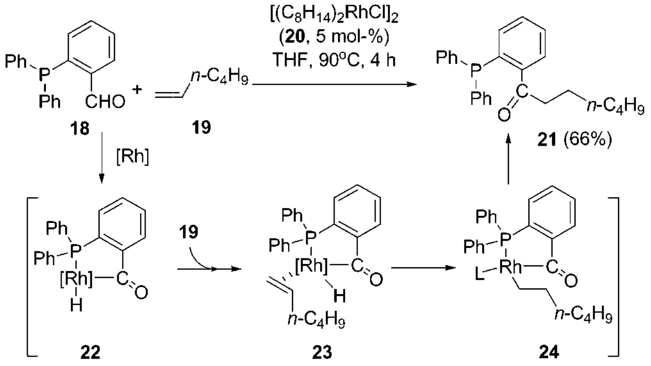
Scheme 6.

To solve this limitation, a new chelation-auxiliary ligand has recently been developed that temporarily anchors a chelating ligand to the substrate aldehyde and liberates the ligand after the reaction. A small amount of this chelation-assisted ligand can be used as a catalyst. With the assistance of this ligand, an aldehyde with no coordination site can be used in intermolecular hydroacylation reactions. In this review, we will discuss transition-metal-catalyzed intermolecular hydroacylation reactions with substrates bearing a chelating functionality and those having a chelating functionality through a chelation-assisted strategy for a common synthesis of ketones.

2. Hydroacylation of Substrates with P-, S-, or O-Coordinating Atoms

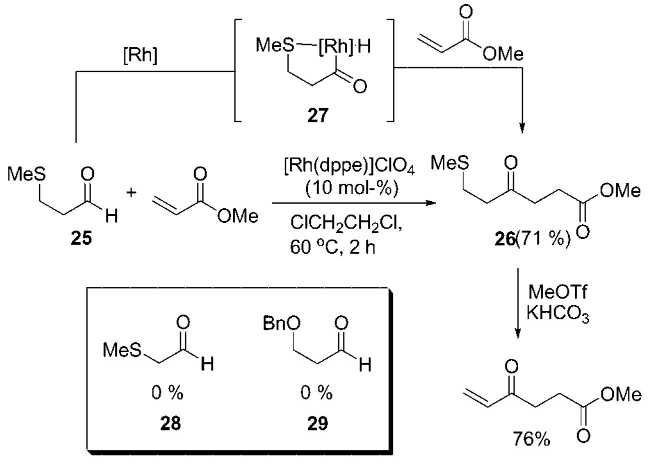
As previously mentioned in the hydroacylation of 8-quinolinecarbaldehyde and the intramolecular hydroacylation of 4-pentenal, the formation of five-membered metallacyclic complexes generated from the reaction of an aldehyde bearing coordinating ligands or substrates with metal complexes is a driving force for the hydroacylation reaction. Several atoms in the coordinating ligand can be used for this purpose: nitrogen, phosphorus, sulfur, and oxygen. There are many examples in which a nitrogen atom acts as the coordinating atom and we will discuss these examples in a later section. In this section, we will focus on the reaction of aldehydes that have phosphorus, sulfur, or oxygen heteroatoms.

Phosphorus is a good chelating heteroatom and 2-(diphenylphosphanyl)benzaldehyde (**18**) is a good candidate for a hydroacylation substrate. The reaction of **18** and 1-hexene (**19**) in the presence of $[(C_8H_{14})_2RhCl]_2$ (**20**) as catalyst gives 2-(diphenylphosphanyl)heptanophenone (**21**) (Scheme 7).[36] Initially, ligand-exchange reaction of the cyclooctene in **20** with **18** occurs and an aldehydic C–H bond is cleaved by the coordinating rhodium atom to form a stable five-membered acylmetallacyclic complex hydride **22**. Hydride insertion into the alkene moiety **19** in **23** affords the acylmetal hexyl complex **24** and subsequent reductive elimination leads to **21**. In this reaction, an additional phosphane ligand is not necessary for reductive elimination because **18** also acts as a phosphane ligand for the rhodium complexes. When the reaction was carried out with 1-alkyne instead of 1-alkene, the corresponding α,β-unsaturated ketone was obtained as expected.[37]



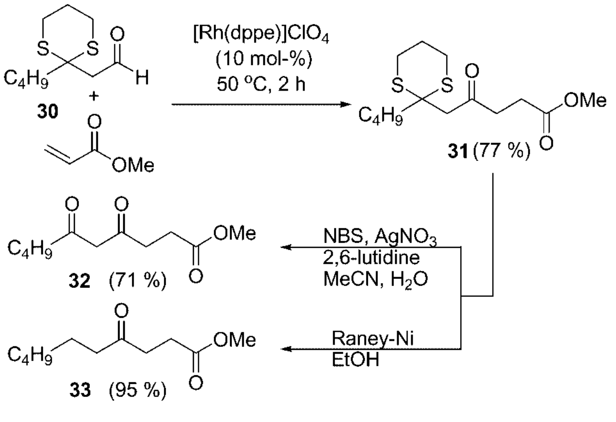
Scheme 7.

Recently, Willis et al. utilized a sulfur-coordinating atom for intermolecular hydroacylation (Scheme 8).[38] The position and type of coordinating atom is important since the reaction of an aldehyde having an α-sulfide group (**28**) or an oxygen atom in the β position (**29**) did not give any product. The use of aldehydes having a pendant sulfur atom in the β position (**25**) leads to a stable five-membered metallacyclic complex hydride intermediate **27** that affords a hydroacylated product **26**. To broaden the scope of the application of this substrate, a method was developed to eliminate the coordinating sulfide group.



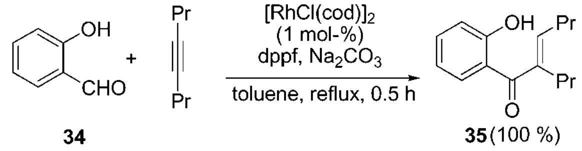
Scheme 8.

For the facile transformation or elimination of a chelating functional group, aldehyde **30** bearing a β-dithioacetal group was also developed (Scheme 9).[39] With this substrate, hydroacylated compound **31** could be readily transformed into β-diketone **32** or aliphatic ketone **33** by hydrolysis or reduction, respectively.



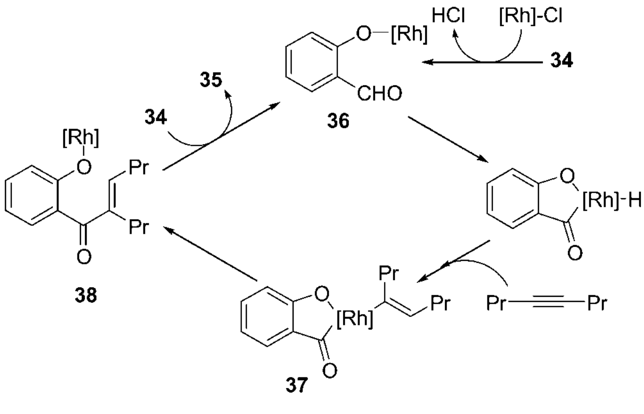
Scheme 9.

For a hydroacylation substrate with an oxygen atom as a coordination site, 2-hydroxybenzaldehyde (**34**) (salicylaldehyde) could be used (Scheme 10).[40,41] The reaction of **34** with 4-octyne in the presence of a catalytic amount of $[RhCl(cod)]_2$, Na_2CO_3, and a dppf ligand [1,1′-bis(diphenylphosphanyl)ferrocene] in refluxing toluene afforded α,β-unsaturated ketone **35** in a good yield.



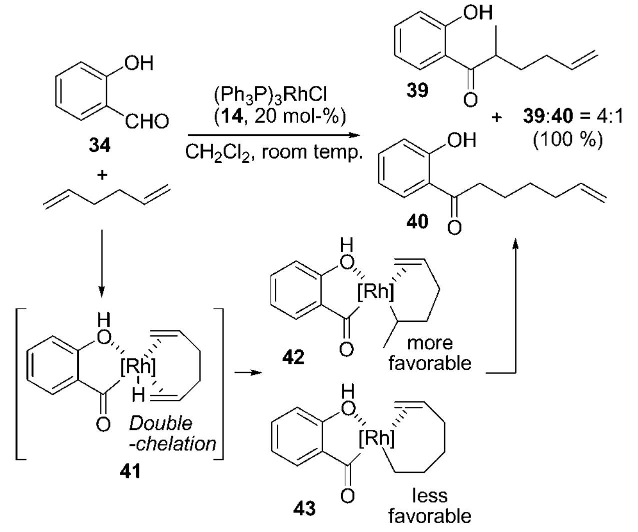
Scheme 10.

The real active catalytic species might be complex **36**, generated from **34** and the rhodium(I) chloride complex (Scheme 11). Subsequent C–H bond cleavage of the aldehyde and hydride insertion into 4-octyne leads to **37**. C–C bond coupling in **37** affords **38**, which reacts with substrate **34** to produce **35** with regeneration of the active catalyst **36**.



Scheme 11.

When the hydroacylation process was carried out with 1,5-hexadiene, the reaction is much more facile than with a mono-ene or alkyne and the reaction even proceeds at room temperature (Scheme 12).[42,43] The reason must be that 1,5-hexadiene as well as **34** forms a metallacyclic complex **41** with the rhodium(I) catalyst. Moreover, the ratio of branched/linear alkenyl ketone (**39**/**40**) turns out to be high as the branched alkenyl complex **42** is favored over the linear alkenyl rhodium complex **43**.



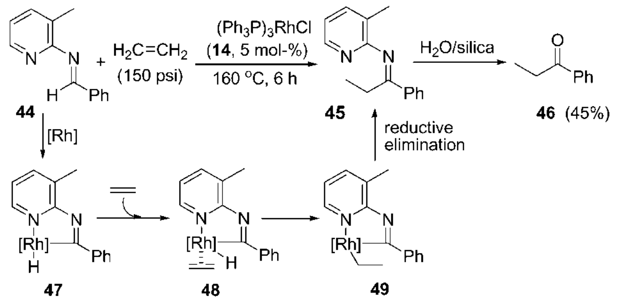
Scheme 12.

Benzaldehyde **34** was also used in the site-selective hydroacylation of norbornene (Scheme 13).[44] The hydroacylated product was determined as *exo* since the *endo* side of norbornene is sterically congested compared with the *exo* side. Therefore, the metal catalyst might coordinate to the *exo* side of the double bond in norbornene and hydrometallate to give an *exo*-hydroacylated ketone compound exclusively.

Scheme 13.

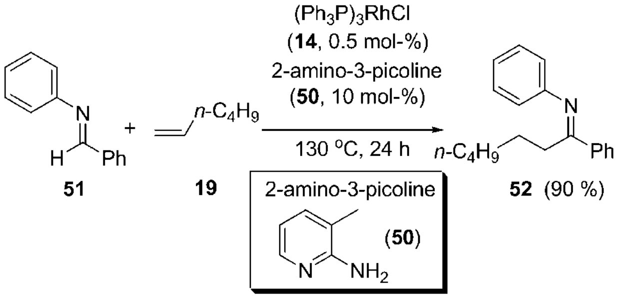
3. Hydroimination with Aldimine

One of the better ways to achieve hydroacylation involves the use of aldimine **44**, a masked form of aldehyde developed by Suggs (Scheme 14).[45] The reaction of aldimine **44** and ethylene (150 psi) was carried out at 160 °C for 6 h in the presence of $[(Ph_3P)_3RhCl]$ (**14**) to give ketimine **45** and hydrolysis of the resulting ketimine produced propiophenone (**46**). Initially, the C–H bond of aldimine **44** is cleaved by Rh^I to form a stable five-membered metallacyclic complex **47** which was spectroscopically characterized. Hydride-insertion into ethylene in **48** and reductive elimination of the resulting iminoacylrhodium(III) ethyl complex **49** leads to ketimine **45**. Ketimine **45** was then hydrolyzed by H_2O to give ketone **46** as the final product.



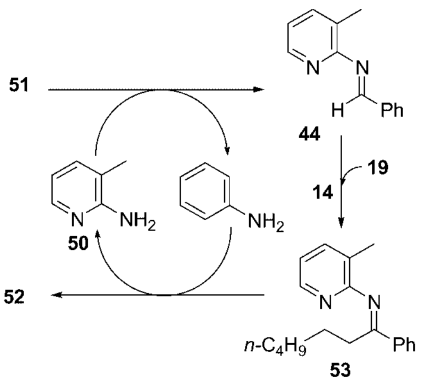
Scheme 14.

The aldimine **44** has two important qualities as a substrate in hydroacylation. The first is the 1,5-relationship between the coordinating atom and the aldimine C–H bond, which allows a metal to form a stable five-membered metallacyclic complex through C–H bond cleavage by Rh^{I}. The second is its inertness to decarbonylation resulting from the lack of an acylmetal functionality in **47** or any other intermediate. From the above result, it can be inferred that it is very important for the coordination site of aldimine to be in an appropriate position. However, we recently found that aldimines bearing no coordination site could also be applied to the synthesis of ketimine in the presence of the rhodium(I) catalyst **14** and 2-amino-3-picoline (**50**) (Scheme 15). For example, when the reaction of aldimine **51** with no coordination site and 1-hexene (**19**) was carried out at 130 °C for 24 h with a mixture of **14** and **50**, ketimine **52** was isolated in a good yield. However, without **50**, the starting aldimine **51** was completely recovered, implying that no direct hydroimination of **51** to **52** had occurred.



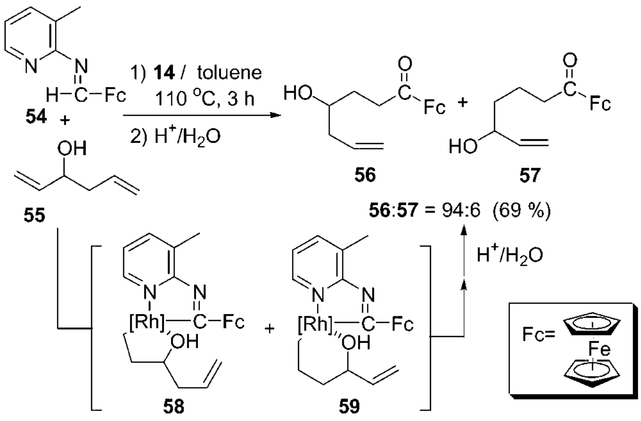
Scheme 15.

Based on this result, the following reaction mechanism can be proposed: Before hydroimination, the aldimine **51** is converted into the aldimine **44** through the transimination of **51** with **50**, liberating aniline (Scheme 16).[46] Hydroimination of **44** with **19** in the presence of the rhodium(I) catalyst produces ketimine **53** which also undergoes transimination with aniline to give ketimine **52** with regeneration of **50**. The efficiency of the catalyst was very high and only a catalytic amount of **50** was required.



Scheme 16.

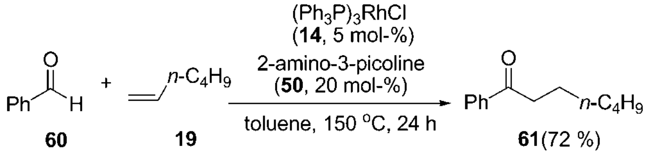
Olefins containing a functional group such as a hydroxy group are good substrates for showing the directing effect of substituents (Scheme 17).[47–49] For example, the hydroimination of 1,6-hexadien-3-ol (**55**) with ferrocenecarbaldimine **54** in the presence of the rhodium(I) complex **14** produces a mixture of 4-hydroxy-6-heptenoylferrocene (**56**) and 5-hydroxy-6-heptenoylferrocene (**57**) in a 94:6 ratio after hydrolysis. The major hydroimination takes place at the allyl alcohol group rather than at the homoallyl alcohol group in **55**. The high regioselectivity of **56** over **57** can be explained by the strong directing effect of the hydroxy group in **55** which favors the formation of a stable five-membered metallacyclic intermediate **58** over the six-membered one **59**.



Scheme 17.

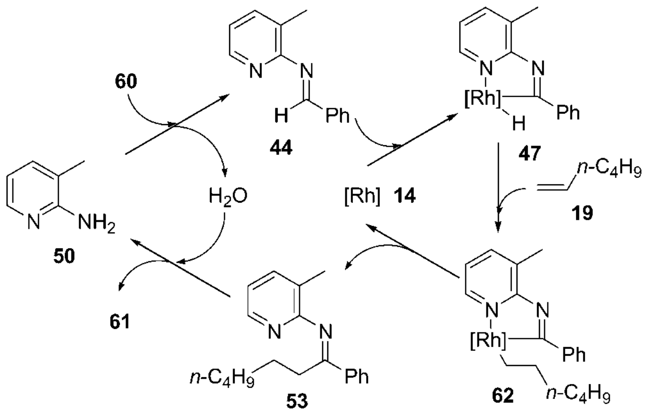
4. Direct Hydroacylation of an Alkene by a Chelation-Auxiliary

Already we have seen that the presence of a coordination site in an aldehyde substrate is very important for facile intermolecular hydroacylation. Therefore, all substrates for hydroacylation have a special structural requirement: A coordination site at a suitable position in the aldehyde substrate. For the practical use of this hydroacylation protocol, we need another strategy to remove this coordinating group after the reaction. For this purpose, a new strategy using a chelation-auxiliary, 2-amino-3-picoline (**50**), was devised: Temporarily anchoring a chelating ligand to the aldehyde substrate for hydroacylation and then liberating the chelating ligand after the reaction (Scheme 18).[50] For example, 1-hexene (**19**) reacted with benzaldehyde (**60**) at 150 °C in toluene for 24 h in the presence of a mixture of the rhodium(I) complex **14** and **50** as co-catalyst. After the reaction, heptanophenone (**61**) was obtained in a moderate yield after chromatographic isolation.



Scheme 18.

The first step must be the condensation of **60** and **50** to form aldimine **44** and H_2O (Scheme 19). C–H bond cleavage of **44** by Rh^I occurs to give iminoacylrhodium(III) hydride **47**, followed by hydride insertion into 1-alkene (**19**) to give iminoacylrhodium(III) alkyl **62**. Reductive elimination from **62** produces ketimine **53** with the regeneration of the rhodium catalyst. Hydrolysis of **53** with H_2O, previously formed from the condensation of **50** and **60**, resulted in the product ketone **61** and organic catalyst **50**. The reaction is facile because the C–H bond cleavage by Rh^I results in a stable five-membered iminoacylrhodium(III) hydride complex **47**. In this reaction, **50** is a chelation-auxiliary that is temporarily anchored to the aldehyde by condensation to form aldimine **44** and liberated from **53** by hydrolysis after hydroimination.



Scheme 19.

Besides these catalysts, the addition of two other additives, aniline and benzoic acid (**63**), dramatically accelerates the rate of hydroacylation; the reaction time is reduced from 24 to 1 h (Scheme 20).[51] Control experiments have shown that the addition of **63** accelerates the condensation of aldehyde **60** and **50**, which is thought to be the rate-determining step in the overall catalytic reaction.

The chelation-assisted hydroacylation could not be applied to a heteroaromatic aldehyde such as 2-thiophenecarbaldehyde.[52] The reason for this is not clear, but it can be speculated that the rhodium(I) catalyst **14** must coordinate to the sulfur atom in the thiophenyl group of the aldimine (**64**) generated in situ from thiophenecarbaldehyde and **50** (Figure 1). The yield of the hydroacylated product was improved by addition of another organometallic complex, [Cp$_2$TiCl$_2$]. The reason for the improved yield of the hydroacylated product must be that [Cp$_2$TiCl$_2$] binds to the sulfur atom, as in **65**, to allow the rhodium(I) catalyst to cleave the C–H bond of the aldimine.

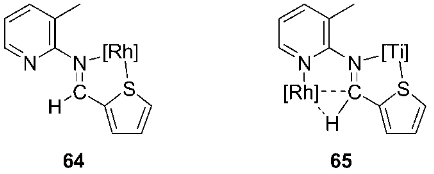
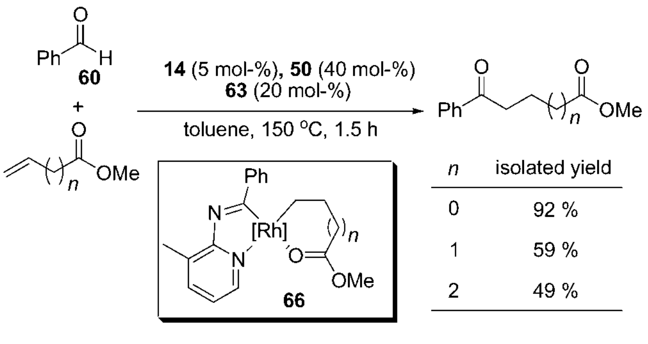


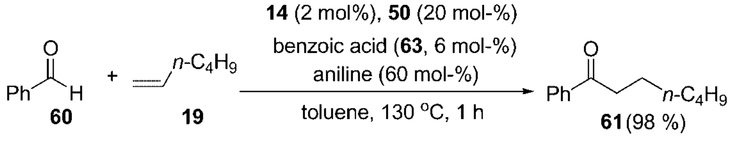
Figure 1. Presumed complexes **64** and **65** from **14** and aldimine of thiophenecarbaldehyde without and with [Cp$_2$TiCl$_2$].

By using the same chelation-assisted strategy, various oxo acid derivatives could be obtained directly from the reaction of aldehyde with ω-alkenoic acid derivatives (Scheme 21).[53] When methyl acrylate (*n* = 0), methyl 3-butenoate (*n* = 1), and methyl 4-pentenoate (*n* = 2) were used in this chelation-assisted hydroacylation reaction instead of 1-alkene under identical reaction conditions, the corresponding γ-oxo, δ-oxo, and ε-oxo esters were isolated in 92, 59, and 49% yields, respectively. The highly reactive nature of methyl acrylate compared with 3-butenoate and 4-pentenoate can be explained as follows: with methyl acrylate a stable five-membered metallacyclic complex **66** (*n* = 0) is formed through the metal–carbonyl interaction, whereas comparatively unstable six- and seven-membered metallacyclic intermediates seem to be formed with 3-butenoate and 4-pentenoate.

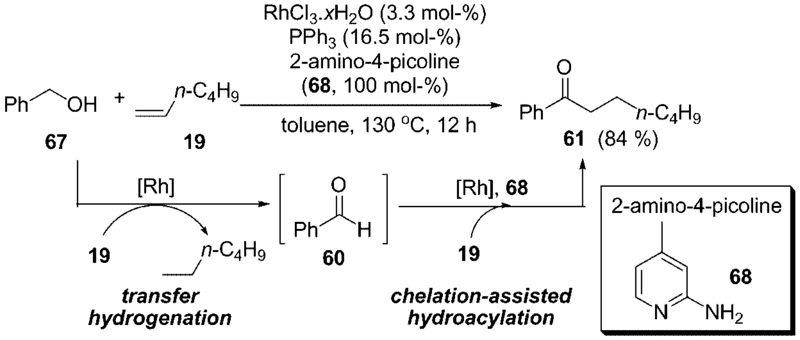


n	isolated yield
0	92 %
1	59 %
2	49 %

Scheme 21.



Scheme 20.



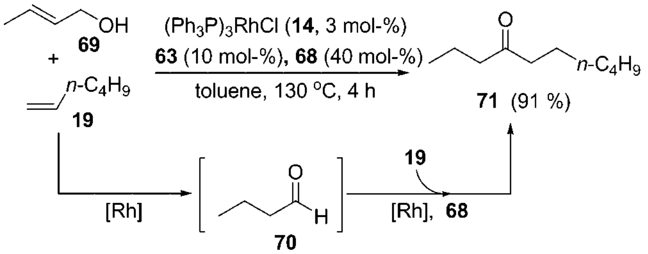
Scheme 22.

5. Hydroacylation with Alcohol

As seen previously, aldehydes are common substrates for hydroacylation. But primary alcohols can also be used as substrates for hydroacylation (Scheme 22). When benzyl alcohol (**67**) was treated with 1-hexene (**19**) at 130 °C in the presence of $RhCl_3 \cdot xH_2O$, PPh_3, and 2-amino-4-picoline (**68**), heptanophenone (**61**) was isolated in a good yield.[54]

In this reaction, $[(Ph_3P)_3RhCl]$ (**14**) is freshly generated in situ from $RhCl_3 \cdot xH_2O$ and PPh_3 in the reaction media. The reaction involves two consecutive reactions: Dehydrogenation and hydroacylation. Initially, the primary alcohol is dehydrogenated by rhodium(I)-catalyzed transfer hydrogenation to generate aldehyde **60**. As soon as the aldehyde is formed, it is trapped by **68** and becomes involved in chelation-assisted hydroacylation. The reaction requires more than 2 equivalents of **19** based on the amount of alcohol as **19** is consumed in the two different reactions: It acts as an oxidant in the transformation of alcohol **67** into aldehyde **60** and as the hydroacylation substrate. Hydroacylation of primary alcohols with olefins has also been carried out under recyclable catalysis using a polymer-supported catalyst,[55] in a biphasic system with a hydrogen-bonding solvent,[56] and with a hydrogen-bonding self-assembled catalyst.[57]

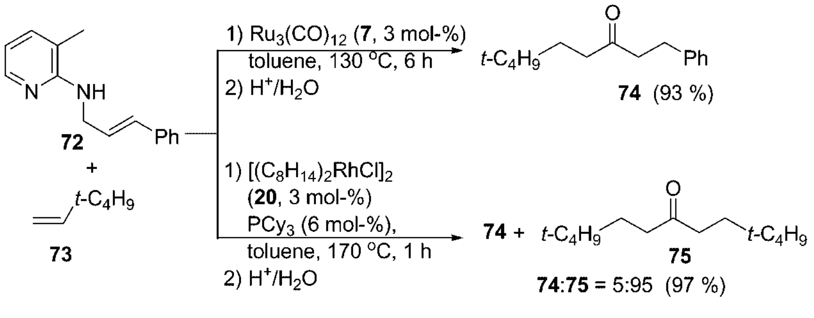
Allyl alcohol is another good candidate for hydroacylation as indicated by reports on transition-metal-catalyzed isomerization of allyl alcohol to aldehyde.[58–60] In this reaction, allyl alcohol **69** isomerizes to aldehyde **70** in the presence of the rhodium(I) catalyst **14** and subsequent chelation-assisted hydroacylation of 1-alkene **19** was achieved with the rhodium(I) complex **14** and 2-amino-4-picoline (**68**) to produce **71** (Scheme 23).[61]



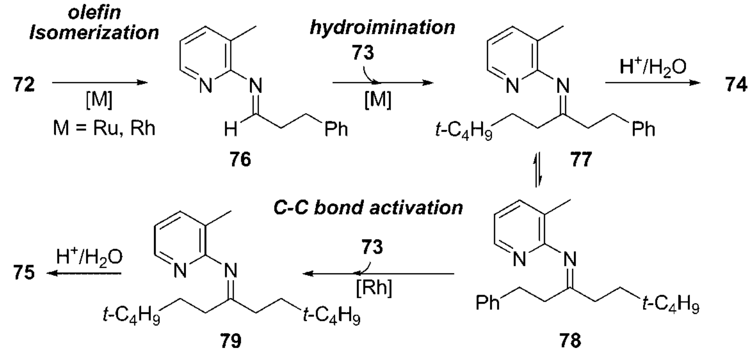
Scheme 23.

6. Hydroacylation with Allylamine Derivatives

In a chelation-assisted hydroacylation reaction, the aldimine is an important substrate or intermediate. Since aldimines can be generated in situ through double bond migration in allylamines in the presence of transition-metal complexes, allylamine is also a good substrate for hydroacylation (Scheme 24).[62] For example, allylamine **72** reacted with *tert*-butylethylene (**73**) in the presence of a $[Ru_3(CO)_{12}]$ catalyst to give ketone **74** in a high yield after hydrolysis (Scheme 24). However, when the reaction was performed in the presence of the rhodium(I) catalyst and the PCy_3 (tricyclohexylphosphane) ligand, symmetric dialkyl ketone **75** was obtained in high yield along with a small amount of **74** in a 95:5 ratio (Scheme 24).



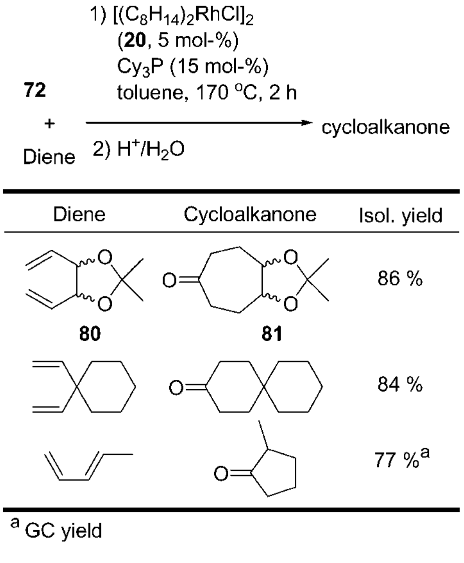
Scheme 24.



Scheme 25.

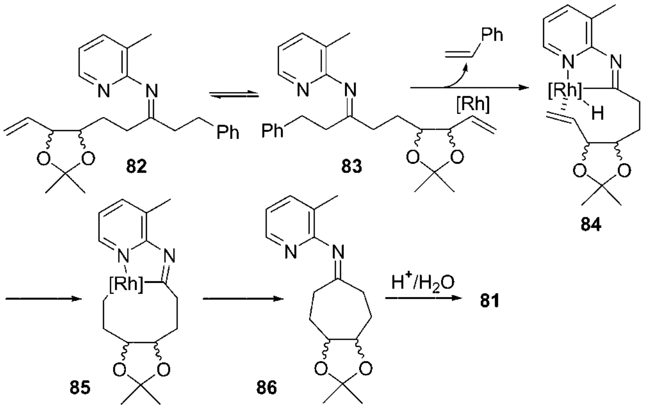
Allylamine **72** undergoes olefinic isomerization with Ru^0 and Rh^I catalysts to form aldimine **76**. Subsequent hydroimination of **73** with **76** produces ketimine **77**. With the rhodium(I) catalyst, initially formed ketimine **77** undergoes C–C bond activation to produce a symmetric dialkyl ketimine **79**. C–C bond activation of aliphatic alkyl ketones or ketimines by rhodium(I) complex **14** has been reported previously.[63] From these results, it can be inferred that Ru^0 in **7** cleaves only the C–H bond, whereas the rhodium(I) complex cleaves both C–H and C–C bonds in aliphatic aldimine **76** (Scheme 25). Therefore, allylamine **72** can be used as a masked form of formaldehyde (the chelation-assisted double hydroacylation of formaldehyde did not give a corresponding dialkyl ketone compound).

Additionally, the use of a diene instead of a 1-alkene produces cycloalkanone.[64] For example, when the reaction of allylamine **72** and 1,5-hexadiene **80** was carried out in the presence of the rhodium(I) catalyst, cycloheptanone **81** was isolated in a high yield after hydrolysis (Scheme 26).



Scheme 26.

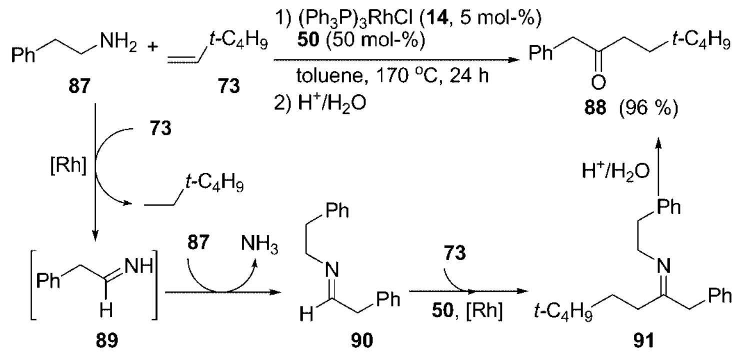
Hydroimination of **80** with **72** gives ketimine **82** and subsequent *syn–anti* isomerization of this imine allows the rhodium(I) catalyst to cleave the C–C bond of **83** giving intermediate **84**. Intramolecular hydrometallation of **84** and reductive elimination of the resulting metallacyclic complex **85** produces ketimine **86**, a cycloheptanone derivative (Scheme 27). The reaction of 1,4-pentadiene and 1,3-butadiene derivatives with **72** in the presence of the rhodium(I) catalyst produced the corresponding cyclohexanone and cyclopentanone derivatives in high yields.



Scheme 27.

It is quite interesting that each olefin in 1,3-pentadiene worked as an isolated olefin in this reaction to give cyclopentanone even though hydroacylation of conjugate dienes usually produces β,γ-unsaturated ketones via the π-allyl complexes generated from the reaction of the conjugate diene and acylmetal hydride.[65,66] Cyclooctanone could not be obtained from 1,6-heptadiene. As a result, this reaction can only be applied to the synthesis of five- to seven-membered cycloalkanone derivatives.

Primary amines are also good substrates for chelation-assisted hydroacylation because aldimines can readily be generated by transition-metal-catalyzed dehydrogenation of primary amines (Scheme 28).[67] For example, phenethylamine (**87**) reacted with 1-alkene **73** in the presence of [(Ph$_3$P)$_3$RhCl] (**14**) and 2-amino-3-picoline (**50**) to give hydroacylated ketone **88** after hydrolysis of the resulting ketimine **91**. Initially, amine **87** is dehydrogenated with 1-alkene through rhodium(I)-catalyzed transfer hydrogenation to give imine **89**, which is transformed into a more stable imine **90** by transimination with unreacted amine **87** with extrusion of NH$_3$. Hydroimination of imine **90** with 1-

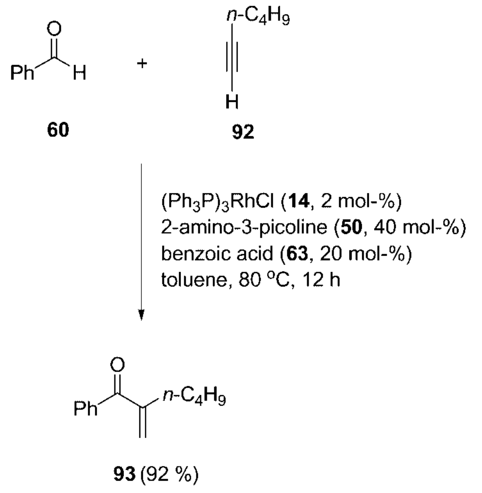


Scheme 28.

alkene **73** in the presence of the rhodium(I) catalyst **14** affords ketimine **91**. Hydrolysis of the resulting ketimine **91** produces ketone **88**. In this reaction, only half the amine **87** is consumed in the formation of ketone **88** as the ketimine **91** consists of two starting amine moieties.

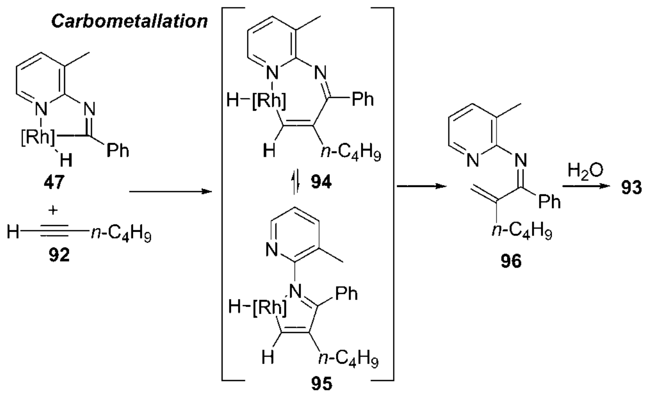
7. Alkyne Hydroacylation and its Application to the C–C Triple Bond Cleavage of an Alkyne

Whilst the chelation-assisted hydroacylation of a 1-alkene with an aldehyde gives an aliphatic ketone, that of a 1-alkyne leads to the formation of an α,β-unsaturated ketone.[68] Note that the regioselectivity of each product is different: Hydroacylation of a 1-alkyne produces a branched α,β-enone whereas that of a 1-alkene affords a linear alkyl ketone. For example, chelation-assisted hydroacylation of 1-hexyne (**92**) with benzaldehyde (**60**) produces exclusively branched α,β-enone **93** in high yield (Scheme 29).



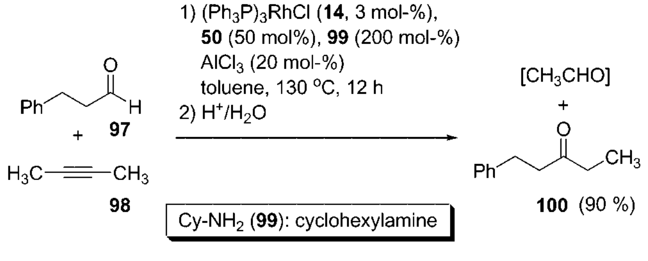
Scheme 29.

The reason for this is not clear, but we speculate that the hydroacylation of **92** might proceed by carbometallation of **92** to form the carbometallated complex **94** or **95**, whereas the hydroacylation of a 1-alkene takes place by hydrometallation to give a linear alkyl ketimine, as shown in Scheme 19 (Scheme 30).



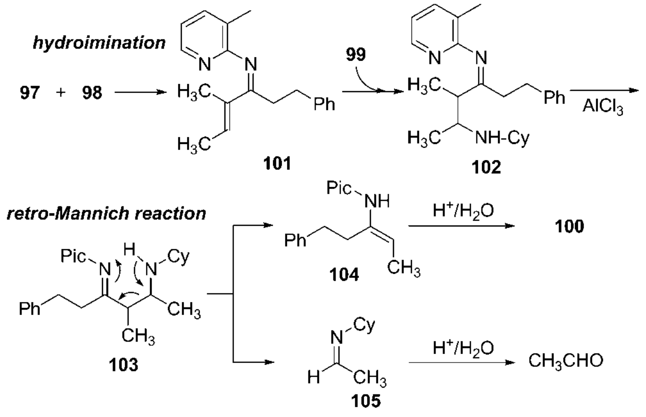
Scheme 30.

Alkyne hydroacylation was also applied to the C–C triple bond cleavage of an alkyne.[69] When the reaction of hydrocinnamaldehyde (**97**) and 2-butyne (**98**) was carried out at 130 °C for 12 h in the presence of [$(Ph_3P)_3RhCl$] (**14**), 2-amino-3-picoline (**50**), cyclohexylamine (**99**), and $AlCl_3$, a high yield of ketone **100** was isolated along with acetaldehyde after hydrolysis of the resulting imines (Scheme 31).



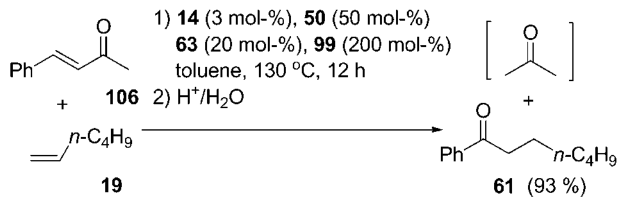
Scheme 31.

The reaction mechanism can be explained as follows (Scheme 32). Initially, chelation-assisted hydroimination of **98** with **97** gives α,β-unsaturated ketimine **101** and the 1,4-addition of **99** to **101** leads to the formation of β-amino ketimine **102**. The acid-catalyzed retro-Mannich reaction of **103** affords enamine **104** and imine **105**, which are hydrolyzed to give ketone **100** and acetaldehyde.



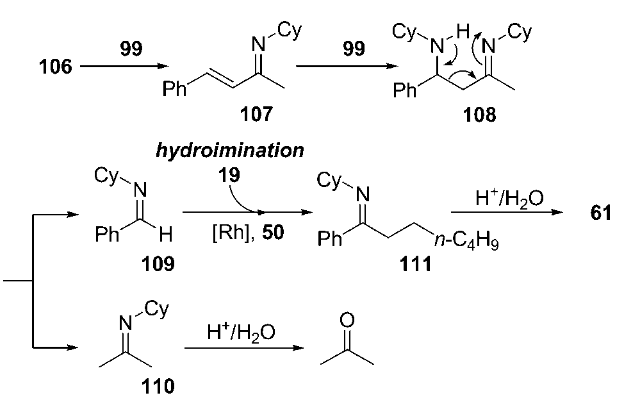
Scheme 32.

This type of retro-Mannich reaction can be proved by cleavage of the C–C double bond of an α,β-unsaturated ketone.[70] When the reaction of an α,β-unsaturated ketone **106** and 1-hexene (**19**) was performed with similar catalyst components, heptanophenone (**61**) was isolated in a high yield after hydrolysis of the resulting ketimine (Scheme 33).



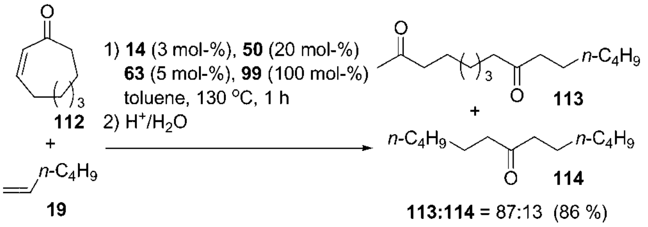
Scheme 33.

The reaction mechanism (Scheme 34) is very similar to that of the previous C–C triple bond cleavage of alkyne described above. β-Aminoketimine **108** is first formed through both condensation and 1,4-addition reactions of cyclohexylamine (**99**) and an α,β-unsaturated ketone **107**. Subsequent retro-Mannich reaction of **108** generates aldimine **109** and ketimine **110**. The aldimine **109** is trapped in the chelation-assisted hydroimination of **19** to give ketimine **111**.



Scheme 34.

In the same manner, ring-opening of cyclononenone (**112**) to give **113** was also achieved through the retro-Mannich reaction and trapping of the resulting aldimine by chelation-assisted hydroimination (Scheme 35).[71] A small amount of **114** was also obtained as a final side-product as the aliphatic C–C bond of the ketimine of **113** could be further cleaved by chelation-assisted rhodium(I)-catalyzed C–C bond activation.



Scheme 35.

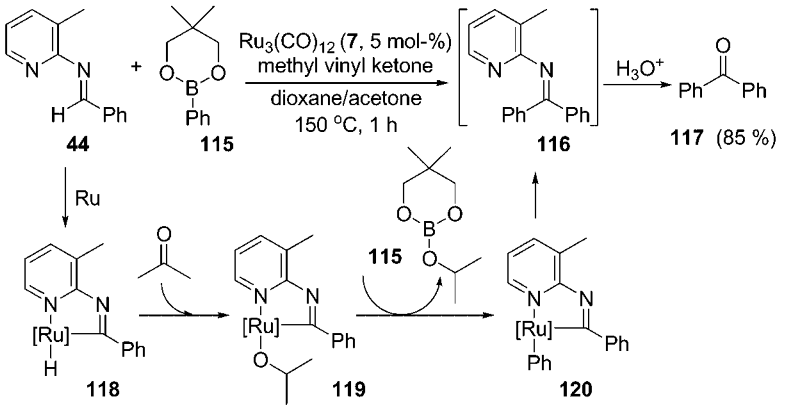
8. Miscellaneous Acylation Reactions

Until now we have seen many synthetic methods involving a ketone bearing an alkyl group because the final step of hydroacylation and hydroimination includes the reductive elimination of the resulting alkyl or alkenyl metal complexes generated from the hydrometallation (or carbometallation) of an alkene or alkyne in the metal hydride intermediate. However, a method for the synthesis of a diaryl ketone from an aldehyde (or corresponding imine) has hardly been developed. In order to overcome this limitation, an organometallic reagent, such as an aryl boronate, was used instead of an alkene or alkyne (Scheme 36).[72] For example, when the reaction of aldimine **44** with phenyl boronate **115** was carried out in acetone/dioxane in the presence of [$Ru_3(CO)_{12}$] (**7**), benzophenone (**117**) was isolated after hydrolysis of the resulting ketimine **116**. In this reaction, a ketone such as acetone is required for the reaction to proceed.

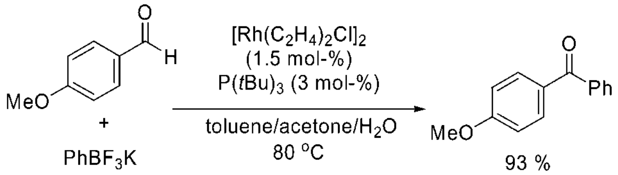
As previously noted, Ru^0 cleaves the C–H bond of aldimine **44** to generate iminoacylruthenium(II) hydride **118** and the subsequent hydrometallation of acetone leads to an isopropoxyruthenium(II) complex **119**. Transmetallation of **119** with phenyl boronate **115** affords iminoacylruthenium(II) phenyl complex **120**, which is reductively eliminated to give ketimine **116** of benzophenone.

The direct synthesis of aromatic ketones from aldehydes and organometallic compounds was developed by Ganet and co-workers (Scheme 37).[73] It is pointless using an aldimine as aldehydes react directly with arylborates in the presence of a rhodium(I) catalyst to produce the corresponding ketone. For example, *p*-anisaldehyde reacted with potassium trifluorophenylborate in the presence of the chlorobis(ethylene)rhodium dimer and tri-*tert*-butylphosphane at 80 °C in toluene/acetone to give 4-methoxybenzophenone in a high yield.

Instead of an aldehyde, a 1-alkyne could be used as the substrate (Scheme 38).[74] When the reaction of 1-octyne



Scheme 36.

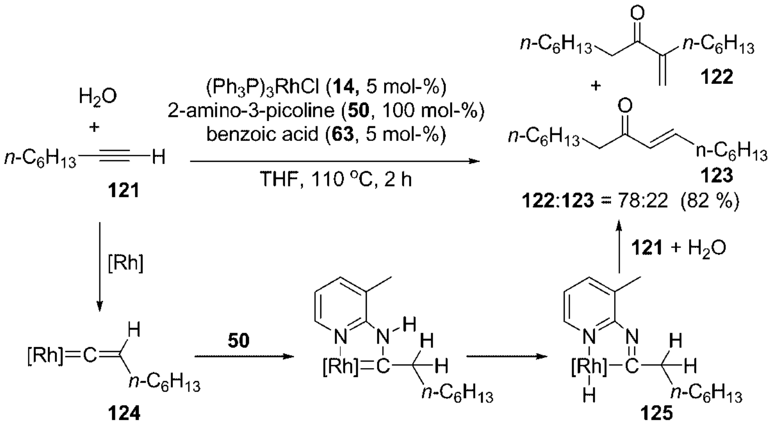


Scheme 37.

(**121**) with H_2O was performed without aldehyde in the presence of the same chelation-assisted catalysts, branched and linear α,β-unsaturated enones **122** and **123** were obtained in a 78:22 ratio. In this reaction, 1-alkyne **121** has two roles: As a precursor of the aldehyde and as a substrate for hydroacylation. Rh^I reacts with 1-alkyne **121** to form the alkylidene complex **124**, followed by the N–H addition of **50** to **124** and olefin isomerization to give the complex **125**, the identical intermediate for the chelation-assisted hydroacylation of the aldehyde. Carbometallation of 1-alkyne in the Rh–C bond in complex **125** leads to the formation of branched α,β-unsaturated enone **122** along with a small amount of linear **123** after hydrolysis.

9. Conclusion

We have seen many different types of transition-metal-catalyzed intermolecular hydroacylation reactions, a direct synthetic protocol for the formation of ketones from aldehydes and alkenes or alkynes. Several ways of evading the decarbonylation process that frequently arises in hydroacylation reactions have been developed: Use of high-pressure alkene or CO to stabilize the acylmetal hydride intermediate, the formation of five-membered acyl metallacyclic complexes using a ligand bearing a coordinating heteroatom at an appropriate position. Among them, the use of the chelation-auxiliary 2-amino-3-picoline (**50**) is one of the best ways to overcome the decarbonylation problem and to achieve facile C–H bond activation by the transition-metal catalyst. By using this strategy the chelating ligand can be temporarily anchored to the substrate aldehyde in situ and this auxiliary ligand can be liberated from the ketimine of the product ketone after the reaction. The overall hydroacylation reaction proceeds efficiently and conveniently. The chelation-assisted hydroacylation process can be applied to the synthesis of cycloalkanones and an α,β-unsaturated ketone or to the carbon–carbon triple bond cleavage of an alkyne.



Scheme 38.

Acknowledgments

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[1] F. Kakiuchi, S. Murai in *Activation of Unreactive Bonds and Organic Synthesis* (Ed.: S. Murai), Springer, Berlin, Heidelberg, New York, **1999**, pp. 47–79.
[2] C.-H. Jun, J.-B. Hong, D.-Y. Lee, *Synlett* **1999**, *1*, 1–12.
[3] J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507–514.
[4] V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731–1770.
[5] C.-H. Jun, C. W. Moon, H. Lee, D.-Y. Lee, *J. Mol. Catal. A* **2002**, *189*, 145–156.
[6] C.-H. Jun, C. W. Moon, D.-Y. Lee, *Chem. Eur. J.* **2002**, *8*, 2422–2428.
[7] *Handbook of C-H Transformations* (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**, vol. 1 and 2.
[8] Y. J. Park, C.-H. Jun, *Bull. Korean Chem. Soc.* **2005**, *26*, 871–877.
[9] K. Godula, D. Sames, *Science* **2006**, *312*, 67–72.
[10] G. W. Parshall, S. D. Ittel, *Homogeneous Catalysis*, 2nd ed., Wiley Interscience, New York, **1992**, pp. 111–113.
[11] H. M. Colquhoun, D. J. Thomson, M. J. Twigg, *Carbonylation: Direct Synthesis of Carbonyl Compounds*, Plenum Press, New York, **1991**.
[12] J. Tsuji, K. J. Ohno, *J. Am. Chem. Soc.* **1968**, *90*, 94–98.
[13] D. H. Doughty, L. H. Pignolet, *J. Am. Chem. Soc.* **1978**, *100*, 7083–7085.
[14] T. Kondo, S. Tanayanon, Y. Tsuji, Y. Watanabe, *Tetrahedron Lett.* **1989**, *30*, 4137–4140.
[15] T. B. Marder, D. C. Roe, D. Milstein, *Organometallics* **1988**, *7*, 1451–1453.
[16] T. Kondo, Y. Tsuji, Y. Watanabe, *Tetrahedron Lett.* **1987**, *28*, 6229–6230.
[17] T. Kondo, M. Akazome, Y. Tsuji, Y. Watanabe, *J. Org. Chem.* **1990**, *55*, 1286–1291.
[18] C. P. Lenges, M. Brookhart, *J. Am. Chem. Soc.* **1997**, *119*, 3165–3166.
[19] C. F. Lochow, R. G. Miller, *J. Am. Chem. Soc.* **1976**, *98*, 1281–1283.
[20] R. E. Campbell Jr, C. F. Lochow, K. P. Vora, R. G. Miller, *J. Am. Chem. Soc.* **1980**, *102*, 5824–5830.
[21] R. E. Campbell Jr, R. G. Miller, *J. Organomet. Chem.* **1980**, *186*, C27–C31.
[22] K. P. Vora, C. F. Lochow, R. G. Miller, *J. Organomet. Chem.* **1980**, *192*, 257–264.
[23] R. C. Larock, K. Oertle, G. F. Potter, *J. Am. Chem. Soc.* **1980**, *102*, 190–197.
[24] D. Milstein, *J. Chem. Soc., Chem. Commun.* **1982**, 1357–1358.
[25] D. P. Fairlie, B. Bosnich, *Organometallics* **1988**, *7*, 936–945.
[26] K. Sakai, J. Ide, O. Oda, N. Nakamura, *Tetrahedron Lett.* **1972**, *13*, 1287–1290.
[27] K. Sakai, O. Oda, *Tetrahedron Lett.* **1972**, 4375–4376.
[28] T. Sattelkau, P. Eilbracht, *Tetrahedron Lett.* **1998**, *39*, 1905–1908.
[29] T. Sattelkau, P. Eilbracht, *Tetrahedron Lett.* **1998**, *39*, 9647–9648.
[30] M. Tanaka, M. Takahashi, E. Sakamoto, M. Imai, A. Matsui, M. Fujio, K. Funakoshi, K. Sakai, H. Suemune, *Tetrahedron* **2001**, *57*, 1197–1204.
[31] G. Kim, E.-J. Lee, *Tetrahedron: Asymmetry* **2001**, *12*, 2073–2076.
[32] Y. Oonishi, A. Taniuchi, M. Mori, Y. Sato, *Tetrahedron Lett.* **2006**, *47*, 5617–5621.
[33] B. Bosnich, *Acc. Chem. Res.* **1998**, *31*, 667–674.
[34] G. C. Fu in *Modern Rhodium-Catalyzed Reactions* (Ed.: P. A. Evans), Wiley-VCH, New York, **2005**, pp. 79–91.
[35] J. W. Suggs, *J. Am. Chem. Soc.* **1978**, *100*, 640–641.
[36] H. Lee, C.-H. Jun, *Bull. Korean Chem. Soc.* **1995**, *16*, 66–68.
[37] H. Lee, C.-H. Jun, *Bull. Korean Chem. Soc.* **1995**, *16*, 1135–1138.
[38] M. C. Willis, S. J. McNally, P. J. Beswick, *Angew. Chem.* **2004**, *116*, 344–347; *Angew. Chem. Int. Ed.* **2004**, *43*, 340–343.
[39] M. C. Willis, H. E. Randell-Sly, R. L. Woodward, G. S. Currie, *Org. Lett.* **2005**, *7*, 2249–2251.
[40] K. Kokubo, K. Matsumasa, M. Miura, M. Nomura, *J. Org. Chem.* **1997**, *62*, 4564–4565.
[41] K. Kokubo, K. Matsumasa, Y. Nishinaka, M. Miura, M. Nomura, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 303–311.
[42] M. Tanaka, M. Imai, Y. Yamamoto, K. Tanaka, M. Shimowatari, S. Nagumo, N. Kawahara, H. Suemune, *Org. Lett.* **2003**, *5*, 1365–1367.
[43] M. Imai, M. Tanaka, K. Tanaka, Y. Yamamoto, N. Imai-Ogata, M. Shimowatari, S. Nagumo, N. Kawahara, H. Suemune, *J. Org. Chem.* **2004**, *69*, 1144–1150.
[44] K. Tanaka, M. Tanaka, H. Suemune, *Tetrahedron Lett.* **2005**, *46*, 6053–6056.
[45] J. W. Suggs, *J. Am. Chem. Soc.* **1979**, *101*, 489.
[46] C.-H. Jun, J.-B. Hong, *Org. Lett.* **1999**, *1*, 887–889.
[47] C.-H. Jun, J.-B. Kang, J.-Y. Kim, *Tetrahedron Lett.* **1993**, *34*, 6431–6434.
[48] C.-H. Jun, J.-S. Han, J.-B. Kang, S.-I. Kim, *J. Organomet. Chem.* **1994**, *474*, 183–189.
[49] J.-B. Hong, C.-H. Jun, *Bull. Korean Chem. Soc.* **1995**, *16*, 363–369.
[50] C.-H. Jun, H. Lee, J.-B. Hong, *J. Org. Chem.* **1997**, *62*, 1200–1201.
[51] C.-H. Jun, D.-Y. Lee, H. Lee, J.-B. Hong, *Angew. Chem.* **2000**, *112*, 3214–3216; *Angew. Chem. Int. Ed.* **2000**, *39*, 3070–3072.
[52] C.-H. Jun, D.-Y. Lee, J.-B. Hong, *Tetrahedron Lett.* **1997**, *38*, 6673–6676.
[53] E.-A. Jo, C.-H. Jun, *Eur. J. Org. Chem.* **2006**, *11*, 2504–2507.
[54] C.-H. Jun, C.-W. Huh, S.-J. Na, *Angew. Chem.* **1998**, *110*, 150–152; *Angew. Chem. Int. Ed.* **1998**, *37*, 145–147.
[55] C.-H. Jun, H.-S. Hong, C.-W. Huh, *Tetrahedron Lett.* **1999**, *40*, 8897–8900.
[56] D.-H. Chang, D.-Y. Lee, B.-S. Hong, J.-H. Choi, C.-H. Jun, *J. Am. Chem. Soc.* **2004**, *126*, 424–425.
[57] D.-W. Kim, S.-G. Lim, C.-H. Jun, *Org. Lett.* **2006**, *8*, 2937–2940.
[58] B. M. Trost, R. J. Kulawiec, *Tetrahedron Lett.* **1991**, *32*, 3039–3042.
[59] D. V. McGrath, R. H. Grubbs, *Organometallics* **1994**, *13*, 224–235.
[60] C. Slugovc, E. Rüba, R. Schmid, K. Kirchner, *Organometallics* **1999**, *18*, 4230–4233.
[61] D.-Y. Lee, C. W. Moon, C.-H. Jun, *J. Org. Chem.* **2002**, *67*, 3945–3948.
[62] C.-H. Jun, H. Lee, J.-B. Park, D.-Y. Lee, *Org. Lett.* **1999**, *1*, 2161–2164.
[63] C.-H. Jun, H. Lee, *J. Am. Chem. Soc.* **1999**, *121*, 880–881.
[64] D.-Y. Lee, I.-J. Kim, C.-H. Jun, *Angew. Chem.* **2002**, *114*, 3157–3159; *Angew. Chem. Int. Ed.* **2002**, *41*, 3031–3033.
[65] T. Kondo, N. Hiraishi, Y. Morisaki, K. Wada, Y. Watanabe, T. Mitsudo, *Organometallics* **1998**, *17*, 2131–2134.
[66] C.-H. Jun, B. T. Koo, J.-B. Kang, K.-H. Kim, *Bull. Korean Chem. Soc.* **1994**, *15*, 1064–1069.
[67] C.-H. Jun, K.-Y. Chung, J.-B. Hong, *Org. Lett.* **2001**, *3*, 785–787.
[68] C.-H. Jun, H. Lee, J.-B. Hong, B.-I. Kwon, *Angew. Chem.* **2002**, *114*, 2250–2251; *Angew. Chem. Int. Ed.* **2002**, *41*, 2146–2147.
[69] D.-Y. Lee, B.-S. Hong, E.-G. Cho, H. Lee, C.-H. Jun, *J. Am. Chem. Soc.* **2003**, *125*, 6372–6373.

[70] S.-G. Lim, C.-H. Jun, *Bull. Korean Chem. Soc.* **2004**, *25*, 1623–1624.
[71] C.-H. Jun, C. W. Moon, S.-G. Lim, H. Lee, *Org. Lett.* **2002**, *4*, 1595–1597.
[72] Y. J. Park, E.-A. Jo, C.-H. Jun, *Chem. Commun.* **2005**, 1185–1187.
[73] M. Pucheault, S. Darses, J.-P. Genet, *J. Am. Chem. Soc.* **2004**, *126*, 15356–15357.
[74] Y. J. Park, B.-I. Kwon, J.-A. Ahn, H. Lee, C.-H. Jun, *J. Am. Chem. Soc.* **2004**, *126*, 13892–13893.

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