# Iridium-Catalyzed Formation of Carbon–Carbon and Carbon–Heteroatom Bonds

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**Abstract:** The progress in catalytic organic synthesis with iridium was far behind that with rhodium or palladium in the early 1990s. However, many useful reactions have recently been reported, and iridium catalysts have now been recognized to be useful in organic synthesis. This review covers iridium-catalyzed carbon–carbon and carbon–heteroatom bond formation with particular emphasis on useful reactions for organic synthesis.



**Key words:** iridium, asymmetric catalysis, allylations, alkynes, aldol reactions

## 1 Introduction

Transition-metal complexes continue to play a major role in organic synthesis. They can realize selective transformations that would be either difficult or impossible by conventional organic chemistry. First- and second-row transition-metal complexes of groups 8–10 have been used as catalysts for organic synthesis. On the other hand, there are fewer examples of third-row transition-metal complexes of groups 8–10. One reason for this difference may be the stability of the carbon–metal bond. In general, the carbon–metal bond in a third-row transition-metal complex is believed to be more stable than that in a first- or second-row transition-metal complex. Thus, third-row transition-metal complexes are likely to be too stable for use as catalysts for organic synthesis.

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Catalytic reactions consist of several elementary steps. During catalysis, each elementary step occurs so rapidly that it cannot be observed individually. To understand the underlying mechanism and design new catalytic reactions, model complexes are needed to study elementary steps. Third-row transition-metal complexes have been studied as models for elementary steps in catalytic reactions. Oxidative addition has been studied using $IrCl(CO)(PPh_3)_2$.[1] This chemistry greatly contributed to the development of organometallic chemistry and catalytic organic synthesis, and leads to the idea that an iridium complex is a good model for understanding the mechanism of a catalytic reaction, but may be too stable for use as a catalyst for organic synthesis.[2] This is the major reason why the development of iridium-catalyzed reactions is far behind that of rhodium- or palladium-catalyzed reactions.

A breakthrough in the study of iridium-catalyzed reactions was reported by Crabtree in 1977. He reported that $[Ir(cod)PyPCy_3]PF_6$ was an efficient hydrogenation catalyst.[3,4] This catalyst was unusual in that it could reduce hindered alkenes. Furthermore, it showed a strong directing effect. Stork et al. reported that this catalyst can control the diastereoselectivity of hydrogenation via hydroxy group coordination.[5] Pfaltz et al. reported the highly enantioselective hydrogenation of unfunctionalized tri- and tetrasubstituted alkenes.[6–8] These impressive successes showed that an iridium complex could be a useful hydrogenation catalyst for organic synthesis.[9]

Although progress in iridium-catalyzed carbon–carbon or carbon–heteroatom bond formation has lagged far behind that in hydrogenation, several useful reactions for organic synthesis were reported in the early 1990s. The recent development of iridium-catalyzed reactions is significant. This review focuses on iridium-catalyzed carbon–carbon or carbon–heteroatom bond formation; hydrogenation is not reviewed. Initially, personal accounts of iridium-catalyzed carbon–carbon or carbon–heteroatom bond formation are cited.[10–12]

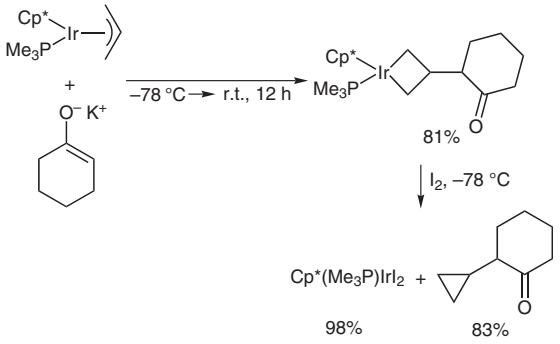
## 2 Allylic Substitution

### 2.1 Allylic Alkylation

Allylic substitution is one of the most useful transformations in organic synthesis. Transition-metal-catalyzed or -mediated allylic substitutions have been extensively

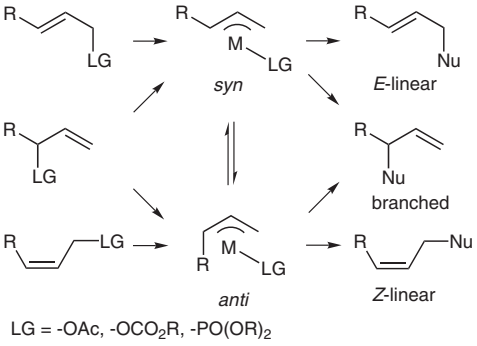
studied since they produce a variety of synthetically useful compounds. π-Allyl–metal complexes are intermediates in most of these reactions. The structures and reactivities of π-allyl–iridium complexes have been studied since the late 1960s.[13]

Stryker reported on the reactivity of π-allyl–iridium complex in 1990.[14] Potassium ketone enolate regioselectively attacked the central carbon of π-allyl–iridium complex to give α-cyclopropyl ketone in high yield (Scheme 1). This reaction is stoichiometric with iridium. The catalytic allylic substitution with nucleophiles (Tsuji–Trost reaction) is widely used in organic synthesis. Allylic esters or halides oxidatively add to a transition-metal complex to give π-allyl–metal intermediates. Nucleophilic attack to a π-allyl ligand then gives a final product, and the control of regio- and stereoselectivity is important.




**Scheme 1**

When the π-allyl intermediate is terminally monosubstituted, nucleophilic attack of the π-allyl intermediate can give three products – a branched product (abbreviated 'b') and *E*- and *Z*-linear products (abbreviated 'l') – as shown in Scheme 2. Palladium complexes are general and versatile catalysts for allylic substitution,[15] and the reaction of a π-allyl–palladium intermediate with a nucleophile gives the *E*-linear product.[16] Branched-product-selective allylic substitution was a challenging problem in the mid-1990s. We first found that $[Ir(cod)Cl]_2/P(OPh)_3$ was an efficient catalyst for branched-product-selective allylic alkylation in 1997.[17–19] Both linear allylic acetate and branched allylic acetate reacted with diethyl sodiomalonate to give branched products with high selectivities. A quaternary carbon center could be constructed by the reaction of 1,1-disubstituted-2-propenyl acetates (Scheme 3). Triphenylphosphite was essential for high branched-product selectivity. A π-allyl–iridium intermediate is considered to be a monophosphite species in which triphenylphosphite coordinates with the metal *trans* to the substituted allylic terminus (Scheme 3). The carbocationic character of the substituted allylic terminus, enhanced by the electron-withdrawing property of triphenylphosphite, directs a nucleophile to this position to give a branched product.



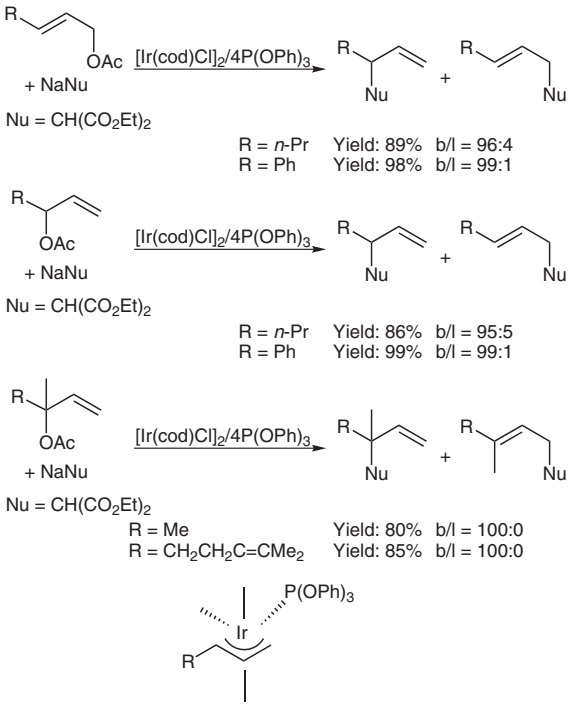

**Scheme 2**

Enantioselective allylic alkylation of achiral substrates is quite useful, since new chiral centers can be created from readily available starting materials. Since iridium-cata-

## Biographical Sketches

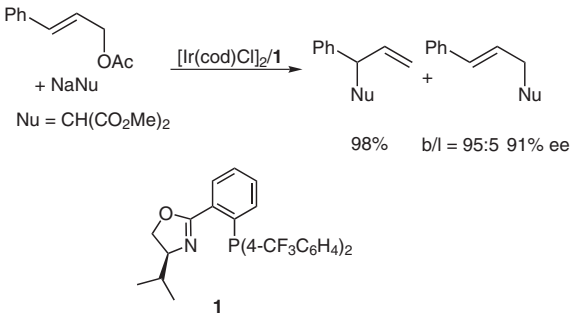
**Ryo Takeuchi** was born in Osaka, Japan, in 1958. He graduated from Kyoto University in 1981. He received his Ph.D. in 1986 from Kyoto University under the supervision of Professor Yoshihisa Watanabe. After working at Mitsui Toatsu Chemicals Company for two and a half years, he joined the faculty of Yokohama City University as a research associate in 1988 to start his independent research. He was promoted to associate professor in 1995. He received the Kuray Award in Synthetic Organic Chemistry in 1997. In 2003, he was appointed as Full Professor of organic chemistry at Aoyama Gakuin University. His research interests are the development of transition-metal-catalyzed selective reactions.

**Satoko Kezuka** was born in Hokkaido, Japan, in 1976. She studied chemistry at Keio University, where she obtained her Ph.D. in 2003 under the supervision of Professor Tohru Yamada on chiral cobalt complex catalyzed reactions in organic synthesis. In 2003, she joined the faculty of Aoyama Gakuin University as a research associate in the group of Professor Ryo Takeuchi. In 2006, she moved to Tokai University, where she has her own research group, and began independent research. Her research interests are transition-metal-catalyzed diastereo- and enantioselective reactions.



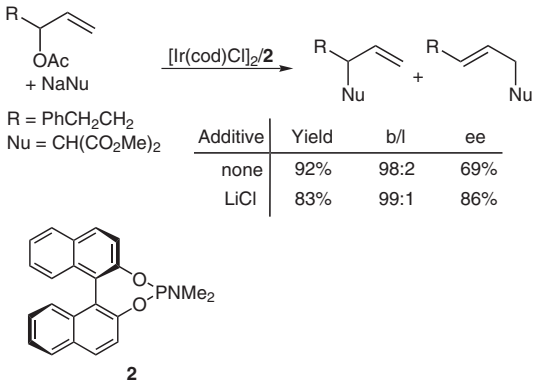

**Scheme 3**

lyzed allylic alkylation gives a broad range of branched products with high regioselectivities, this reaction is expected to be promising for asymmetric synthesis. Based on our results, Helmchen first reported the enantioselective allylic alkylation of linear allylic acetates with dimethyl sodiomalonate using $[Ir(cod)Cl]_2$/chiral phosphine-oxazoline catalyst (Scheme 4).[20] The enantiomeric excess of the branched product was 91%. They isolated and characterized a chiral π-allyl–iridium(III) complex coordinated with phosphine-oxazoline ligand.[21]



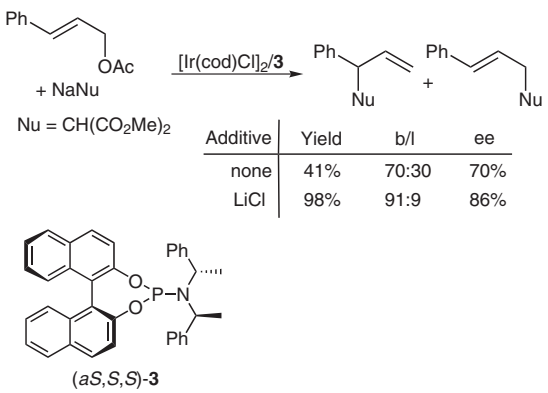

**Scheme 4**

Chiral phosphoramidite ligands have been used for enantioselective conjugate addition of enones.[22] The strong π-accepting property of monodentate phosphoramidites should be useful for iridium-catalyzed allylic alkylation, as is triphenylphosphite. Helmchen first used chiral phosphoramidites for iridium-catalyzed enantioselective allylic alkylation.[23,24] Ligand **2** was effective for the reaction of branched allylic acetates with dimethyl sodiomalonate. They found that the use of an equal amount of lithium chloride with an allylic ester as an additive increased the enantioselectivity (Scheme 5). Halide ion is thought to accelerate the isomerization of a π-allyl intermediate via a σ-allyl intermediate. On the other hand, phosphoramidites of a bulky secondary chiral amine such as ligand **3** were effective for the reaction of linear allylic acetates (Scheme 6).[25] Lithium chloride was also effective for increasing the regio- and enantioselectivity. In situ activation of the catalyst prior to the reaction improved the selectivity and the catalytic activity. $[Ir(cod)Cl]_2$/ligand **3** was activated by treatment with tetrahydrothiophen, 1,5,7-triazabicyclo[4.4.0]undec-5-ene (TBD) and copper(I) iodide prior to the reaction. 3-Phenyl-2-propenyl carbonate reacted with dimethyl sodiomalonate to give the branched product in 99% regioselectivity with 96% ee.[26] Use of a preactivated catalyst gave high enantioselectivity without the aid of lithium chloride.

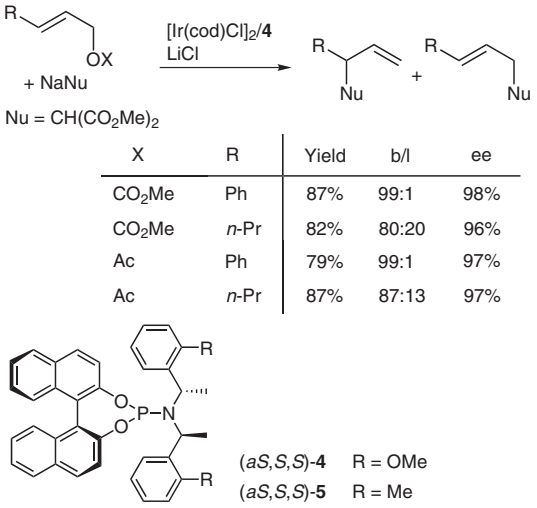



**Scheme 5**

Recently, ligand **4**, which contains two *o*-methoxy substituents on the amine part, showed high regio- and enantioselectivities in the allylic alkylation of linear allylic carbonates and acetates with dimethyl sodiomalonate without in situ activation (Scheme 7).[27] A high degree of enantioselectivity (up to 98%) was obtained from a wide range of linear allylic carbonates and acetates. The use of lithium chloride was necessary. Ligand **5**, which has a methyl group instead of a methoxy group at the same position as in ligand **4**, gave the same degree of regio- and enantioselectivity as ligand **4**.[28,29] These results show that




**Scheme 6**



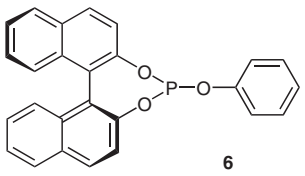

| X | R | Yield | b/l | ee |
|---|---|---|---|---|
| $CO_2Me$ | Ph | 87% | 99:1 | 98% |
| $CO_2Me$ | *n*-Pr | 82% | 80:20 | 96% |
| Ac | Ph | 79% | 99:1 | 97% |
| Ac | *n*-Pr | 87% | 87:13 | 97% |

(*aS*,*S*,*S*)-**4** R = OMe
(*aS*,*S*,*S*)-**5** R = Me

**Scheme 7**

the cone angle of the ligand plays a crucial role. The possibility that an oxygen atom in the methoxy group coordinates to the iridium center can be excluded.

Chiral aryl phosphite **6** (Figure 1) was used for the allylic alkylation of 3-phenyl-2-propenyl carbonate with enolate of dimethyl malonate.[30,31] The enantioselectivity was influenced by the counter ion of the enolate. The reaction with sodium enolate generated with the use of sodium hydride gave a branched product in 6% ee. On the other hand, the use of zinc enolate generated by *n*-butyllithium/zinc chloride increased the enantioselectivity to up to 96%.

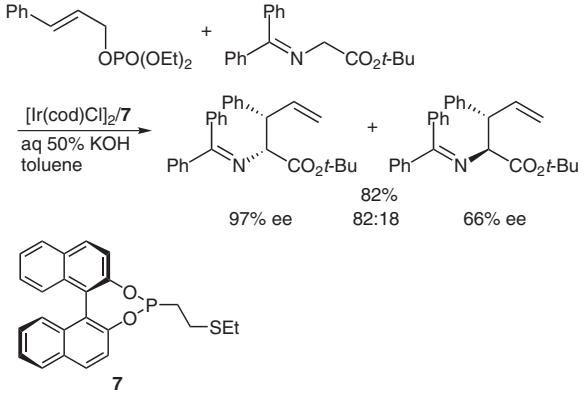


**6**

**Figure 1**

The asymmetric synthesis of amino acid derivatives by iridium-catalyzed allylic alkylation has been reported. The nucleophiles that have been described so far are dimethyl or diethyl malonates, which are symmetric C-nucleophiles. In the case of unsymmetrical C-nucleophiles such as imino glycinates, regio-, diastereo- and enantioselectivity must be controlled. Linear allylic phosphate reacted with diphenyliminoglycinate under biphasic conditions in the presence of $[Ir(cod)Cl]_2$/ligand **7** catalyst to give branched product in high regio-, diastereo- and enantioselectivity (Scheme 8).[32,33] With ligand **7**, the bidentate coordination of both the phosphorus and sulfur atoms to iridium is proposed.

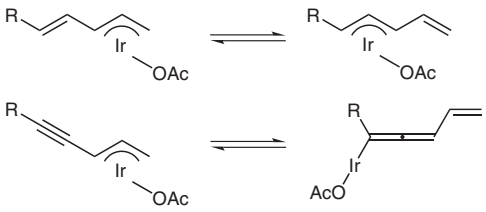
Alkenyl and alkynyl groups are particularly important as substituents on the π-allyl ligand. 1-(1-Alkenyl)-π-allyl–metal intermediate isomerizes to 1-alkyl-3-vinyl-π-allyl–metal intermediate via σ–π–σ interconversion. Similarly,




**7**

**Scheme 8**

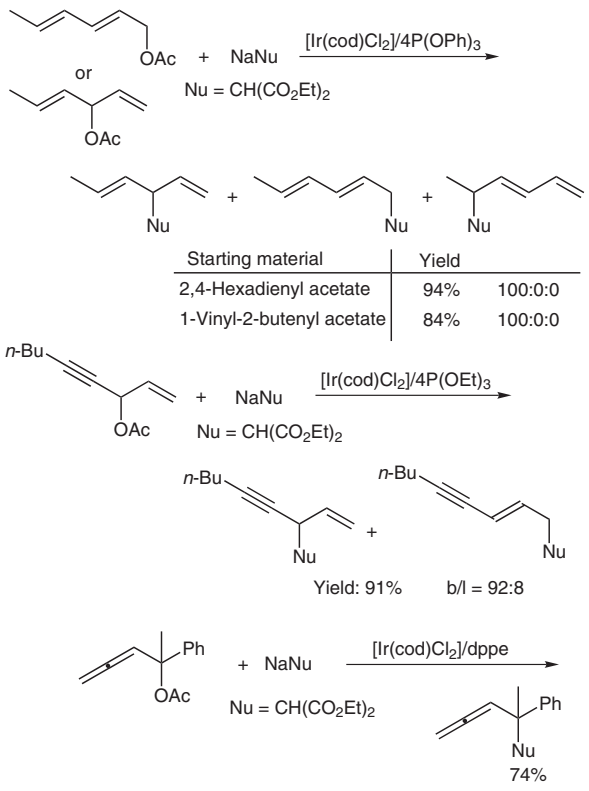
1-(1-alkynyl)-π-allyl–metal intermediate isomerizes to 1-alkyl-3-vinyl-σ-allenyl–metal intermediate (Scheme 9). The selective reaction of these intermediates with a nucleophile increases the importance of this type of transformation in organic synthesis. Dienyl acetates and bisallylic acetates smoothly underwent alkylation with diethyl sodiomalonate to exclusively give the branched product in high yields (Scheme 10).[34] The allylic alkylation of branched enynyl acetate with diethyl sodiomalonate using triethylphosphite gave a branched product in 92% selectivity.[34] The reaction of a methylene-substituted π-allyl–iridium intermediate has been reported. The allylic alkylation of 1,1-disubstituted buta-2,3-dienyl acetates gives a product bearing a quaternary carbon center α to allene in high yield (Scheme 10).[35]



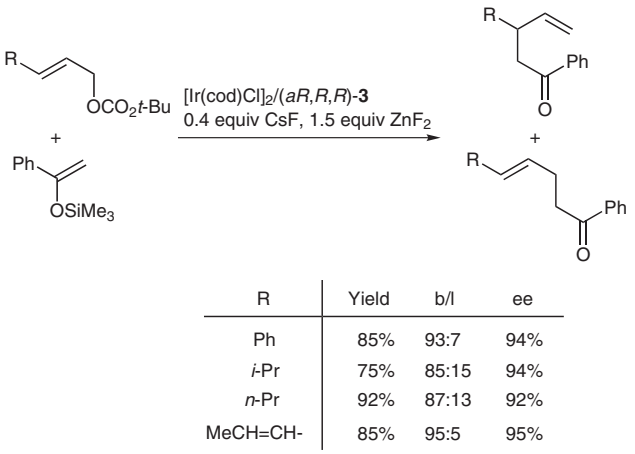
**Scheme 9**

The enantioselective allylation of ketone enolates is less developed than that of the more-stable enolates such as malonates. The regio- and enantioselective allylation of silyl enol ether with the aid of $F^-$ anion has been reported.[36] *tert*-Butyl 3-phenyl-2-propenyl carbonate reacted with the silyl enol ether of acetophenone in the presence of a catalytic amount of $[Ir(cod)Cl]_2$/(*aR*,*R*,*R*)-**3**, 0.4 equivalent of cesium fluoride and 1.5 equivalents of zinc fluoride to give branched product in high regio- and enantioselectivity (Scheme 11). Both cesium fluoride and zinc fluoride are necessary to complete the reaction.

In the reactions described so far, it was an allylic ester that acted as an allylic electrophile reacting with a nucleophile. However, the iridium-catalyzed nucleophilic allylation of aldehydes and ketones to give homoallylic alcohols has also been reported.[37] The reaction of allyl alcohol with benzaldehyde in the presence of a catalytic




**Scheme 10**

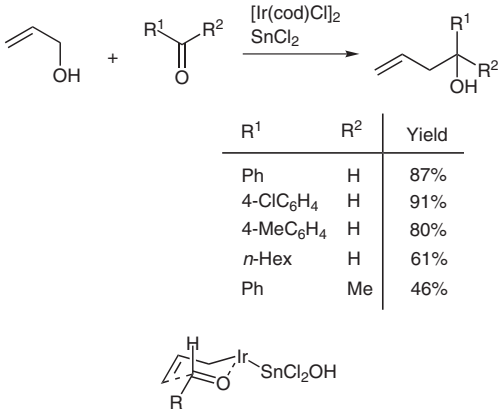



**Scheme 11**

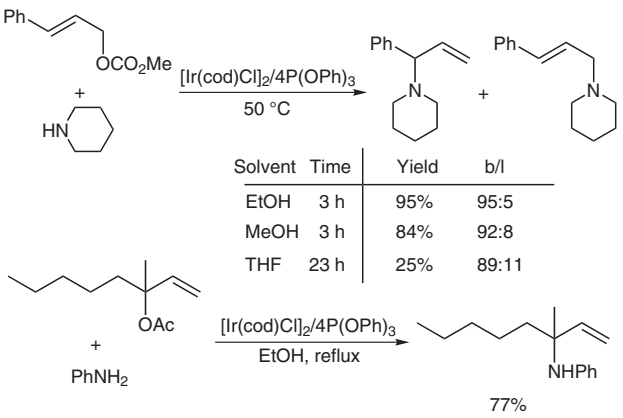
amount of $[Ir(cod)Cl]_2$ and a stoichiometric amount of $SnCl_2$ gave 1-phenylbut-3-en-1-ol in 87% yield (Scheme 12). This reaction is proposed to proceed via the reaction of a σ-allyl–iridium intermediate with the aldehyde via a six-membered-ring transition state.

## 2.2 Allylic Amination

Allylic amination is an important reaction for the synthesis of allylic amines.[38] $[Ir(cod)Cl]_2/P(OPh)_3$ was an efficient catalyst for branched-product-selective allylic amination.[39] Allylic carbonates reacted with amines to give branched products in high selectivities (Scheme 13).



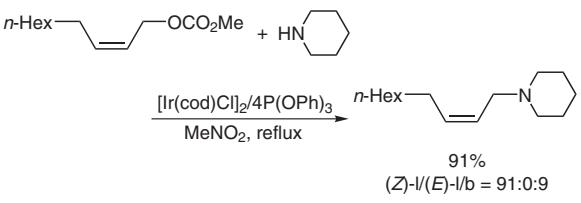

**Scheme 12**




**Scheme 13**

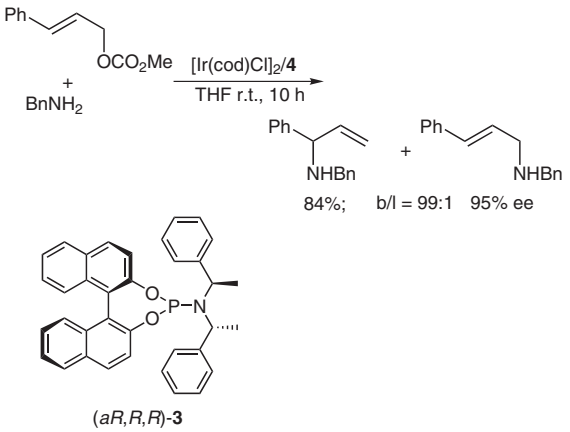
Both primary amines and secondary amines can be used for allylic amination. The solvent strongly affected the reaction: both ethanol and methanol gave branched products in high yields with high selectivities, whereas tetrahydrofuran gave a poor yield even after a long reaction time. α,α-Disubstituted allylic amines are obtained by the reaction of 1,1-disubstituted prop-2-enyl acetates.

Allylic amination of (*Z*)-2-alkenyl carbonates gives *Z*-linear allylic amines (Scheme 14).[39,40] Complete retention of *Z*-stereochemistry is achieved. On the other hand, palladium-catalyzed allylic amination of (*Z*)-2-alkenyl acetate gave *E*-linear allylic amine, since the *anti* π-allyl–palladium intermediate easily isomerized to a *syn* π-allyl–palladium intermediate prior to nucleophilic attack by an amine.[41] The retention of *Z*-stereochemistry in the palladium-catalyzed allylic substitution of (*Z*)-2-alkenyl esters has been difficult to achieve, and only limited examples have been reported.[42,43]

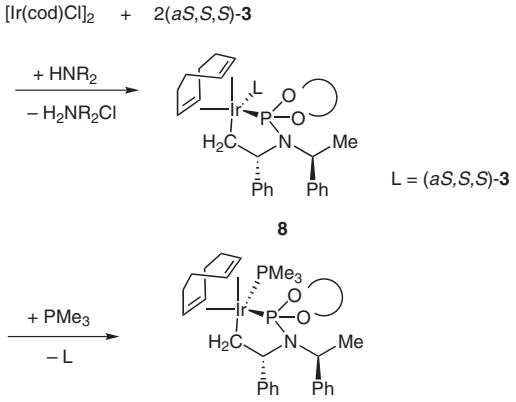



**Scheme 14**

Enantioselective allylic amination provides an efficient route to chiral allylic amines which are valuable synthetic building blocks. Chiral phosphoramidite ligand **3**, designed by Feringa for the copper-catalyzed conjugate addition of diethylzinc to enones,[44] was found to be an efficient ligand for the enantioselective allylic amination of linear allylic carbonates (Scheme 15).[45] Good yields, regioselectivities, and enantioselectivities are observed. Both primary amines and secondary amines can be used for the reaction. The choice of solvents is important for the enantioselectivity. Reactions in *N*,*N*-dimethylformamide, ethanol or methanol were fast, but the enantioselectivities were low. Reactions in tetrahydrofuran showed the most suitable balance of rate and enantioselectivity. An activated form of $[Ir(cod)Cl]_2$/ligand (*aS*,*S*,*S*)-**3** was isolated and characterized by the coordination of trimethylphosphine (Scheme 16).

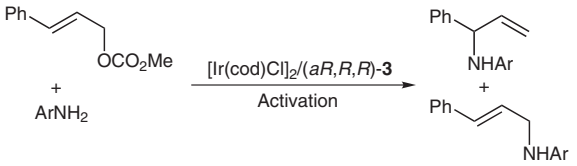



**Scheme 15**




**Scheme 16**

Cyclometalation of ligand (*aS*,*S*,*S*)-**3** generates a more reactive catalyst.[46] The reaction catalyzed by the activated catalyst is faster than that catalyzed by the original catalyst and does not show an induction period. The activated catalyst was used for the enantioselective allylation of a wide range of aromatic amines without an activating group on the nitrogen atom (Scheme 17).[47] Products were obtained with ee values of 93–96%.




| Ar | Yield | b/l | ee |
|---|---|---|---|
| 3-Ethoxylphenyl | 86% | 97:3 | 96% |
| 4-Chlorophenyl | 80% | 95:5 | 96% |
| 3-Thiomethylphenyl | 85% | 97:3 | 96% |

**Scheme 17**

Ligand **3** possesses three stereochemical elements: a resolved BINOL substituent and a diastereomerically and enantiomerically pure amino substituent containing two phenethyl groups. To improve the catalytic activity and enantioselectivity, the relation between these stereochemical elements, the rate and the enantioselectivity was studied.[48–50] Systematic changes in the different stereochemical elements showed that the distal chiral phenethyl substituent could be replaced with a cyclododecyl group (Figure 2). The reaction of 3-phenyl-2-propenyl carbonate with *p*-methoxybenzylamine using the activated catalyst from $[Ir(cod)Cl]_2$ and ligand **9** at room temperature gave the branched product in 96% ee. The result showed that the stereocenter in the β-position relative to iridium was necessary for enantioselection, and the distal chiral phenethyl group was not necessary. As described in the previous section, ligand **4** gave high enantioselectivity for allylic alkylation;[27–29] it has also been reported to be a useful ligand for allylic amination.[51]

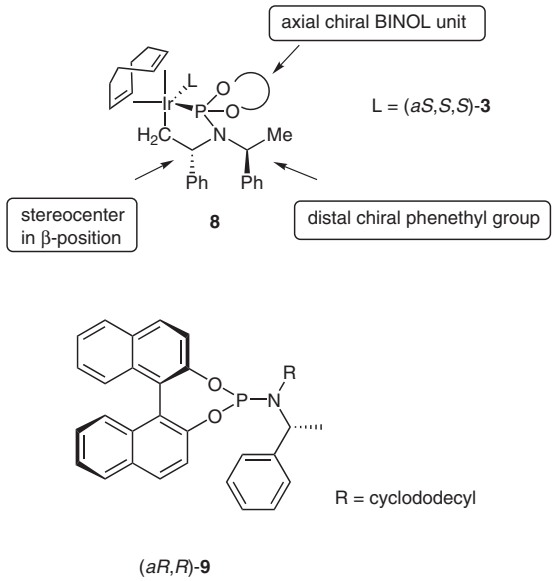
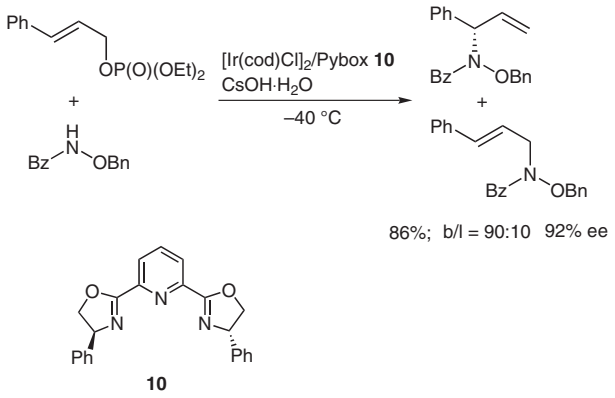



**Figure 2**

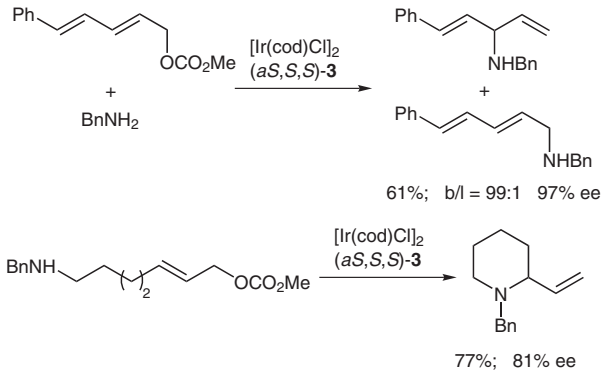
Pybox ligands are efficient nitrogen ligands in enantioselective reactions.[52] The $[Ir(cod)Cl]_2$/Pybox **10**-catalyzed reaction of an allylic phosphate with a hydroxylamine derivative gave a chiral hydroxylamine derivative. Base af-




**Scheme 18**

fected both the regio- and enantioselectivity. Weak bases such as cesium hydroxide monohydrate, cesium carbonate, or barium hydroxide monohydrate gave good results (Scheme 18).[53]

The enantioselective allylic amination of linear dienyl carbonate with benzylamine using (*aS*,*S*,*S*)-**3** has been reported.[54] Chiral bis-allylic amine was obtained with 97% ee (Scheme 19). Intramolecular enantioselective allylic amination gave a chiral N-heterocycle.[55]

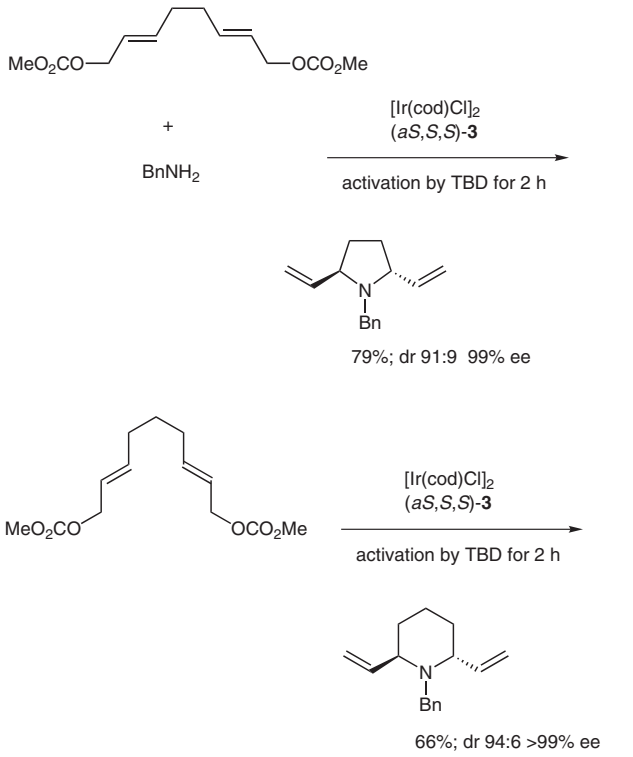



**Scheme 19**

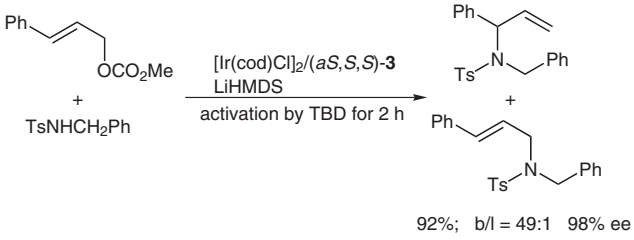
It has been reported that primary amines undergo sequential allylation with substrates having two allylic carbonate moieties to give 2,5-disubstituted pyrrolidine and 2,6-disubstituted piperidine products.[56] The enantioselective version of this cyclization gives chiral pyrrolidine and piperidine (Scheme 20).[57]

Allylic amination with a nitrogen nucleophile has generally been successful only with amines as the nucleophiles. The activated catalyst from $[Ir(cod)Cl]_2$ and ligand (*aS*,*S*,*S*)-**3** enables the use of a sulfonamide as the nitrogen nucleophile (Scheme 21).[58] The branched product was obtained in 98% ee. The product is a protected amine, which simplifies further transformations.

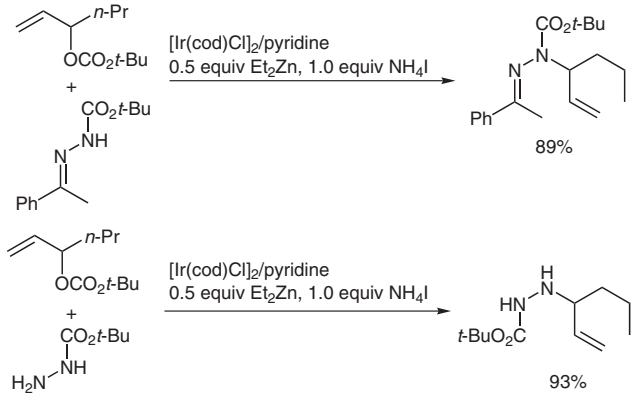
Hydrazine and hydrazone derivatives have been used as nitrogen nucleophiles. Allylic amination of branched allylic *tert*-butyl carbonates with hydrazine derivatives and hydrazone derivatives gave branched products in high yields (Scheme 22).[59] Pyridine was an effective ligand. Diethylzinc was used as a base. The use of one equivalent of ammonium iodide as an additive was necessary to give the product in high yield.




**Scheme 20**



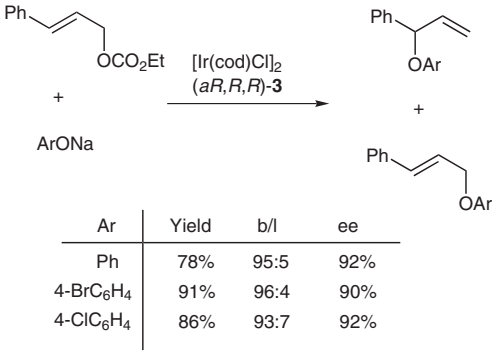

**Scheme 21**




**Scheme 22**

## 2.3 Allylic Etherification

Allylic etherification is a convenient route to allylic ethers from allylic alcohols. Palladium-catalyzed allylic etherification gives achiral linear products.[60] Iridium-catalyzed allylic etherification may make it possible to synthesize chiral allylic ethers, since iridium-catalyzed allylic substitution gives branched products in high selectivities. In 2003, Hartwig first reported the enantioselective allylic etherification of linear allylic carbonate with phenoxides using $[Ir(cod)Cl]_2$/(*aR*,*R*,*R*)-**3** (Scheme 23).[61] The reaction with sodium aryloxides containing a single substituent at the *ortho*, *meta*, or *para* position gave the corresponding branched product with high regio- and enantioselectivities. The enantiomeric excess was as high as 97%.



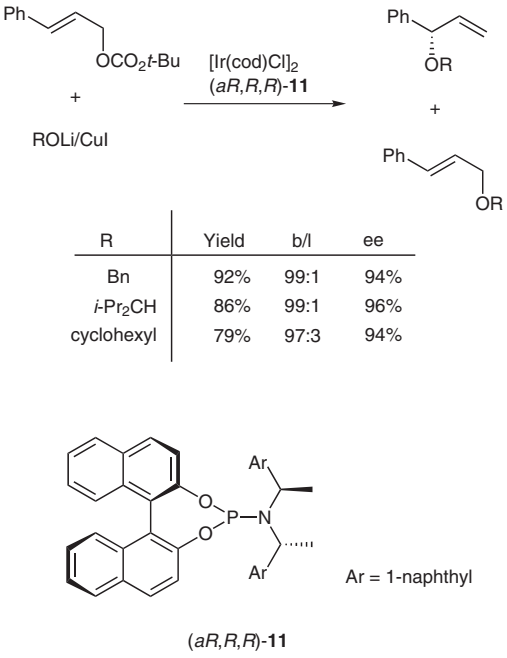

| Ar | Yield | b/l | ee |
|---|---|---|---|
| Ph | 78% | 95:5 | 92% |
| 4-$BrC_6H_4$ | 91% | 96:4 | 90% |
| 4-$ClC_6H_4$ | 86% | 93:7 | 92% |

**Scheme 23**

Enantioselective allylic etherification with an aliphatic alkoxide has also been reported (Scheme 24).[62] Transesterification with alkoxide is a more serious competitive reaction than that with aryloxide. To optimize the reaction with aliphatic alkoxide, careful selection of the carbonate, alkoxide counter ion, and ligand is essential for high yields and selectivities. Allylic carbonates with small alkyl groups underwent transesterification in competition with etherification, but *tert*-butyl carbonate prevented the transesterification and give the desired product in high yields. Copper alkoxides derived from lithium alkoxides and copper(I) iodide gave products in high yields. Ligand **11** gave better enantioselectivities than ligand **3**.

The reactions described above use a stoichiometric amount of metal alkoxides. Allylic etherification using the catalytic generation of zinc alkoxides from aliphatic alcohols and a catalytic amount of diethylzinc has been reported (Scheme 25).[63] The reaction of branched allylic carbonate using 10 mol% of diethylzinc gave branched products in high yields. L-Tryptophan was used as a ligand to activate the Zn center by N,O-chelation.

Allylic substitution with hydroxylamines has also been reported.[64,65] *N*-Benzylhydroxylamine acted as a nitrogen nucleophile to give the branched N-allylated product, whereas *N*-benzoyl-*N*-phenylhydroxylamine served as an oxygen nucleophile to give the branched O-allylated

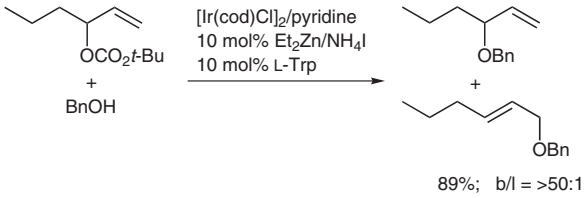



| R | Yield | b/l | ee |
|---|---|---|---|
| Bn | 92% | 99:1 | 94% |
| *i*-$Pr_2CH$ | 86% | 99:1 | 96% |
| cyclohexyl | 79% | 97:3 | 94% |




(*aR*,*R*,*R*)-**11**

**Scheme 24**




**Scheme 25**

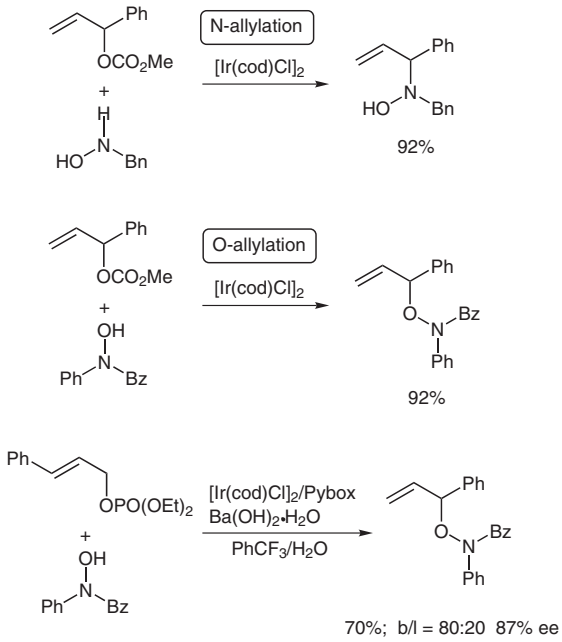
product (Scheme 26). Enantioselective allylic etherification of linear allylic phosphate with *N*-benzoylhydroxylamine using $[Ir(cod)Cl]_2$/pybox catalyst under aqueous conditions gave a branched product in 87% ee (Scheme 26).[65] Allylic substitution with oximes gives O-allylated oxime ethers, where a zinc alkoxide is generated in situ by the reaction of diethylzinc with oxime (Scheme 27).[66]

The kinetic resolution of branched *rac*-allylic carbonate using a chiral iridium diene catalyst was reported (Scheme 28).[67] Chiral diene **12** was a useful ligand for kinetic resolution. Allylic etherification with 0.5 equivalent of phenol gave a chiral allylic carbonate and chiral allylic ether. The chiral allylic carbonate was obtained in 93% ee.

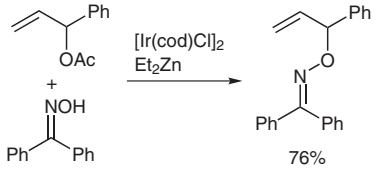
# 3 Reaction of Alkynes

## 3.1 Cyclotrimerization of Alkynes

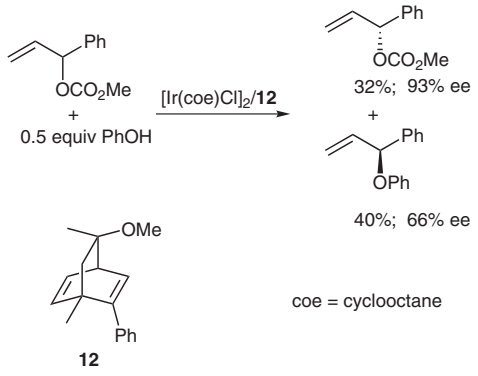
The cyclotrimerization of alkynes to give a benzene derivative has been studied extensively.[68] Metallacyclopentadienes are intermediates for the cyclotrimerization of alkynes. Collman et al. first prepared an iridacyclopentadiene by the reaction of $IrCl(N_2)(PPh_3)_2$ with dimethyl acetylenedicarboxylate.[69] They found that a tetracar-




**Scheme 26**



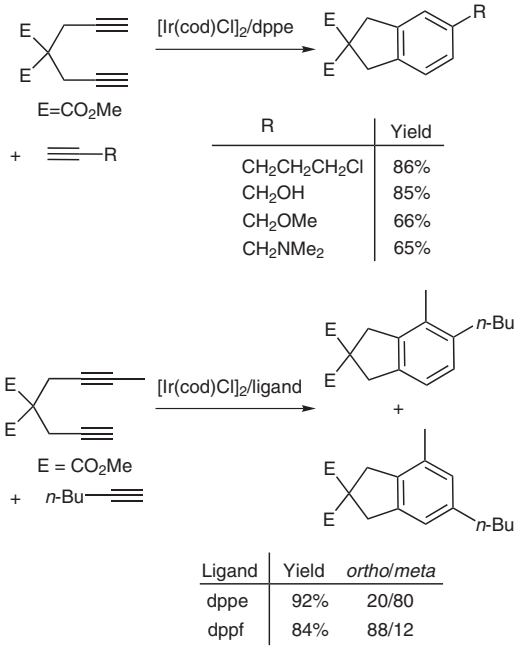

**Scheme 27**




**Scheme 28**

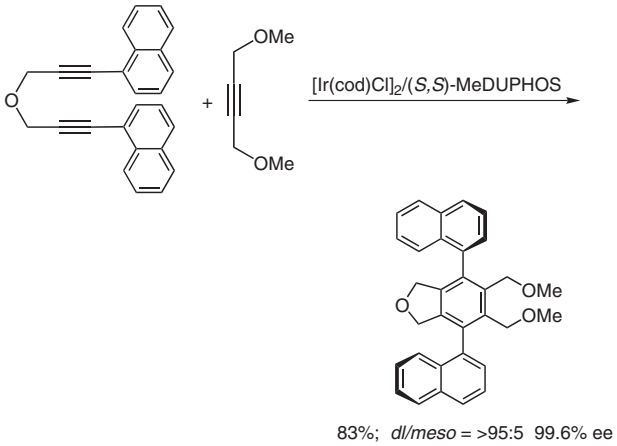
bomethoxyiridacyclopentadiene was a potential catalyst for the cyclotrimerization of dimethyl acetylenedicarboxylate. However, the method was limited to the use of dimethyl acetylenedicarboxylate as substrate. Although the structure and reactivity of iridacyclopentadienes have been studied since their discovery, catalytic organic synthesis via iridacyclopentadienes has been less developed than that via rhodacyclopentadienes or cobaltacyclopentadienes.

We first found that $[Ir(cod)Cl]_2$/DPPE was an efficient catalyst for the [2+2+2] cycloaddition of α,ω-diynes with monoynes to give indane and teraline derivatives.[70,71] The reaction tolerated various functional groups such as halide, alcohol, ether, amine, alkene and nitrile (Scheme 29). The cycloaddition of unsymmetrical α,ω-diyne with 1-alkyne gives two isomers – the control of regioselectivity is a challenging problem. Limited examples of regioselective cycloaddition of unsymmetrical α,ω-diyne with 1-alkyne have been reported.[72–74] There was no previous report on the selective synthesis of either *ortho* or *meta* products from the same substrate. A systematic survey of ligands showed that the regioselectivity of the cycloaddition was controlled by the ligand: $[Ir(cod)Cl]_2$/dppe was *meta*-selective, whereas $[Ir(cod)Cl]_2$/dppf was *ortho*-selective. In alkyne cycloaddition chemistry, Cp or Cp* metal complexes such as $CpCo(CO)_2$[75] and Cp*Ru(cod)Cl[72] have been used as catalysts. In such cases, it can be difficult to control the reaction by tuning the steric and electronic effects of the Cp ligand since the introduction of substituents to the Cp ligand requires considerable synthetic operations. In contrast, $[Ir(cod)Cl]_2$ is convenient for controlling the reaction, since various phosphine ligands are available.



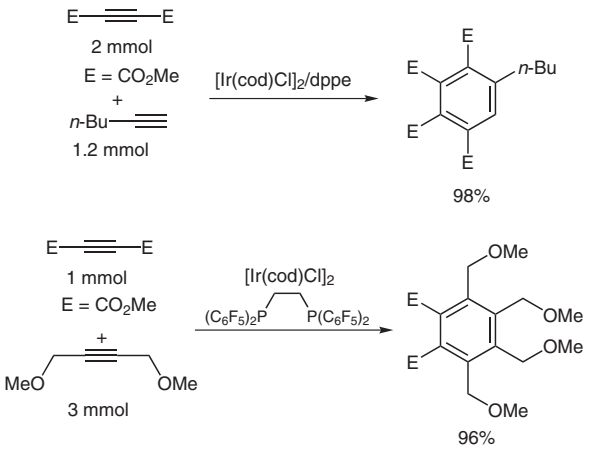

**Scheme 29**

The $[Ir(cod)Cl]_2$/dppe-catalyzed reaction of α,ω-diynes with ferrocenylalkynes gave functionalized ferrocenylarenes.[76] The use of a chiral ligand instead of dppe made asymmetric synthesis possible. Enantio- and diastereoselective [2+2+2] cycloaddition to give axially chiral teraryl compounds was reported by Shibata (Scheme 30).[77] The catalyst system of $[Ir(cod)Cl]_2$ with MeDUPHOS or EtDUPHOS gave the product in good yield with high enantio- and diastereoselectivity.




**Scheme 30**

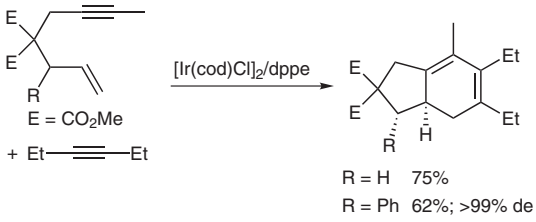
The cyclotrimerization of monoynes is an atom-economical route to polysubstituted benzenes, and the regioselective cyclotrimerization of monoynes has been reported.[78,79] The [IrH(cod)(dppe)]-catalyzed reaction of phenylacetylene gave 1,2,4-triphenylbenzene in 99% selectivity. Regioselective cyclotrimerization of two or three different monoynes is a more challenging problem. Highly selective cross-[2+2+2]-cycloaddition of two different monoynes is achieved by using a catalytic amount of $[Ir(cod)Cl]_2$ and ligand (Scheme 31).[80] The ligand had a considerable effect on the reaction. When dppe was used, two molecules of dimethyl acetylenedicarboxylate (DMAD) reacted with one molecule of a monoyne to give the 2:1 coupling product. When 1,2-bis(dipentafluorophenylphosphino)ethane was used instead of dppe, one molecule of DMAD reacted with two molecules of a monoyne to give the 1:2 coupling product.




**Scheme 31**

## 3.2 Cycloaddition of Enynes

$[Ir(cod)Cl]_2$/dppe is an efficient catalyst for the cycloaddition of 1,6-enynes with monoynes. The cycloaddition of 1,6-enyne with 3-hexyne gave a bicyclic cyclohexadiene derivative in high yield (Scheme 32).[81] These compounds are used in the Diels–Alder reaction, which provides a rich and diverse chemistry. This cycloaddition is the simplest route to a bicyclic cyclohexadiene framework, and the diastereoselective cycloaddition of enynes with monoynes was possible. The reaction of an enyne, bearing a phenyl group at an allylic position, with 3-hexyne gave a single diastereomer.




**Scheme 32**

The Diels–Alder reaction is the most important reaction for the construction of a six-membered ring. Low-valent-transition-metal complexes can realize the use of unactivated alkynes as dienophiles in the Diels–Alder reaction. The enantioselective intramolecular [4+2] cycloaddition of dienynes to give bicyclic 1,4-hexadiene was reported.[82]

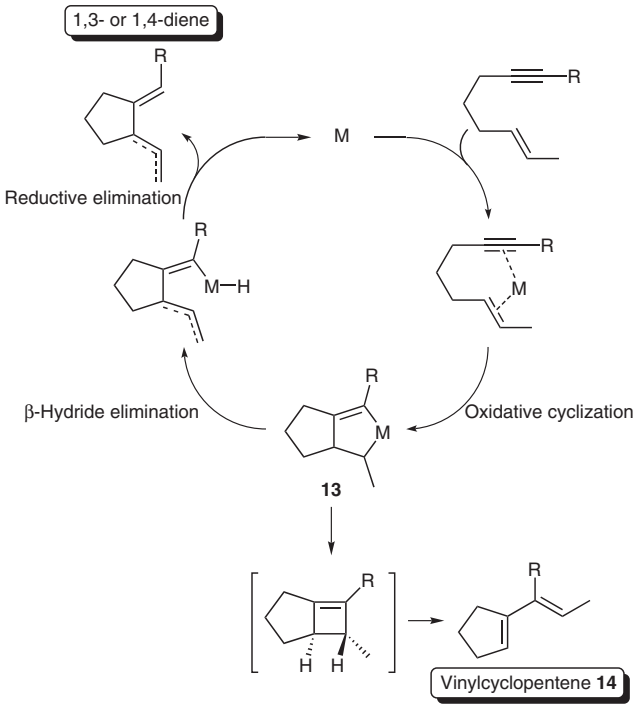
## 3.3 Cycloisomerization of Enynes

The development of new methods for the construction of a ring system from acyclic substrates is important for organic synthesis. The cycloisomerization of enynes has been extensively studied as a unique tool for the synthesis of various types of cyclic compounds.[83] The general mechanism for cycloisomerization is outlined in Scheme 33. Oxidative cyclization of enynes gives a metallacyclopentene **13**. β-Hydride elimination from **13**, followed by reductive elimination, gives 1,3- or 1,4-dienes. Reductive elimination from **13** followed by conrotatory thermal opening gives vinylcyclopentene **14**. This pathway includes cleavage of a carbon–carbon bond; thus, it may be more appropriate to refer to this pathway as a skeletal reorganization rather than a cycloisomerization.

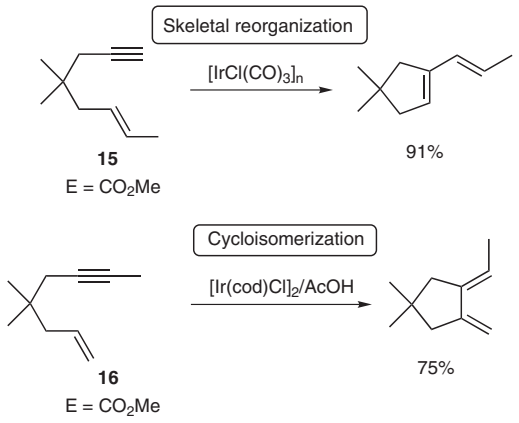
The iridium-catalyzed cycloisomerization of an enyne was first reported by Murai and Chatani (Scheme 34).[84] Enyne **15** with a terminal acetylenic moiety undergoes cycloisomerization (skeletal reorganization) in the presence of a catalytic amount of $[IrCl(CO)_3]_n$. Enyne **16**, with a substituent on an acetylenic carbon, undergoes cycloisomerization to an (*E*)-1,3-diene by an $[Ir(cod)Cl]_2$/AcOH catalyst system.

An exocyclic 1,3-diene is a good substrate for the Diels–Alder reaction, and the cycloisomerization to exocyclic 1,3-dienes can be used in catalytic domino reactions. For example, subsequent cycloisomerization/Diels–Alder reaction/dehydrogenative aromatization can give pyrrole derivatives.[85]

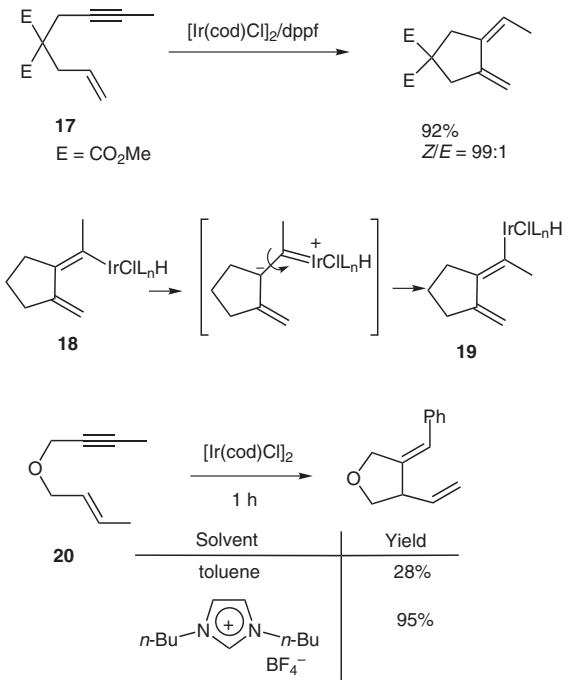
Another catalyst for the cycloisomerization to 1,3-dienes was reported (Scheme 35). $[Ir(cod)Cl]_2$/dppf catalyzed the cycloisomerization of **17** to (*Z*)-1,3-diene.[81] Intermediate **18** suffers from steric repulsion between the iridium



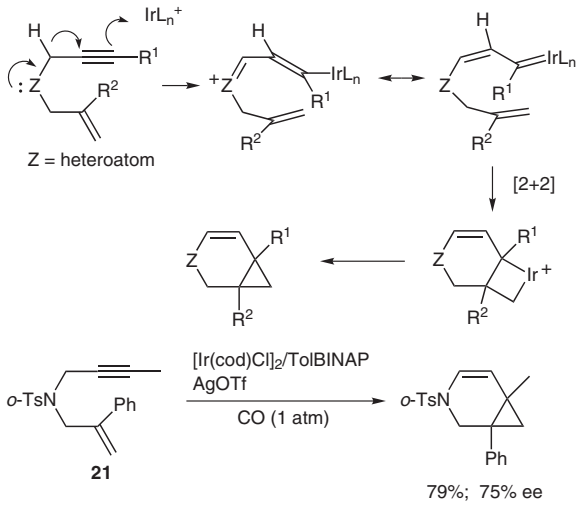

**Scheme 33**




**Scheme 34**




**Scheme 35**



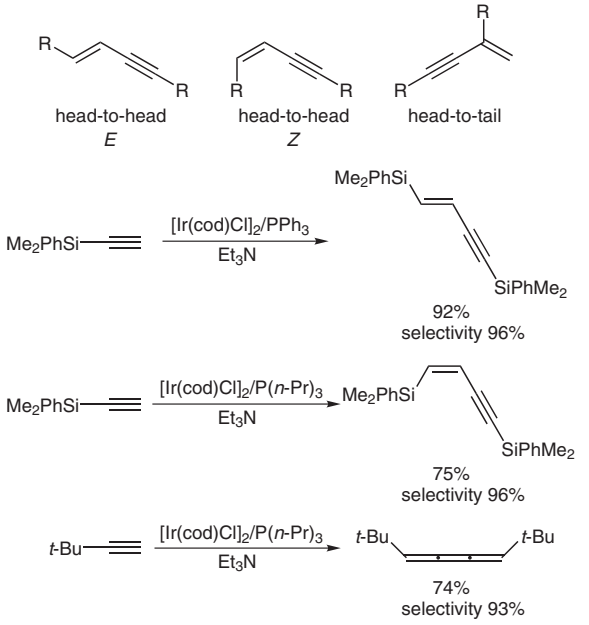

**Scheme 36**

moiety and the *cis* substituent on the alkene. Isomerization of **18** to **19** via the zwitterionic carbene intermediate releases this steric repulsion. Reductive elimination from **19** gives the (*Z*)-1,3-diene. For *Z*-selective cycloisomerization, dppf was found to be a good ligand. The large bite angle increases the steric bulkiness of the iridium moiety to promote the isomerization of **18** to **19**. The acceleration of cycloisomerizations in ionic liquids has been reported. Cycloisomerization of **20** to the 1,4-diene product proceeded more efficiently in an imidazolium salt than in toluene (Scheme 35).[86]

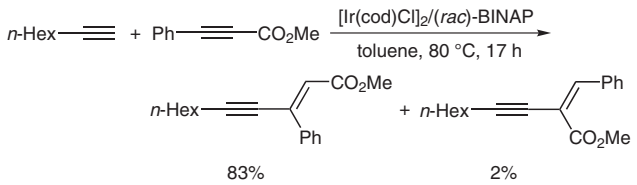
An electrophilic cationic iridium catalyst has been shown to activate the alkyne moiety of enynes to give cyclopropanes. Nitrogen-bridged 1,6-enyne **21** underwent cycloisomerization to give the chiral cyclopropane by the catalyst system $[Ir(cod)Cl]_2$/TolBINAP/AgOTf (Scheme 36).[87]

## 3.4 Dimerization

The dimerization of 1-alkynes is one of the most useful and economical reactions that give conjugated enynes, and most transition-metal catalysts give head-to-tail dimers. The dimerization of silylalkynes was studied (Scheme 37)[88] and it was found that the selectivity depends on the ligand used. $[Ir(cod)Cl]_2/PPh_3$ catalyst gave the *E*-configured head-to-head dimer, while $[Ir(cod)Cl]_2/P(n\text{-}Pr)_3$ catalyst gave the *Z*-configured head-to-head dimer. Triethylamine was necessary to give the product in high yield. Dimerization of *tert*-butylacetylene gave a butatriene. Crabtree reported *Z*-head-to-head-selective dimerization.[89] The codimerization of 1-alkynes with internal alkynes was also reported (Scheme 38).[90]



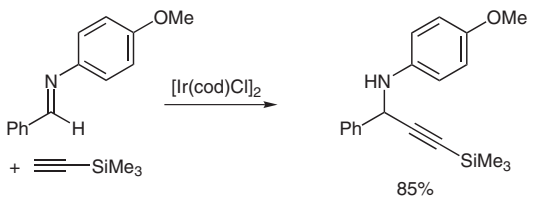

**Scheme 37**




**Scheme 38**

## 3.5 Alkynylation

The addition of alkynyl carbanion to aldimines is the most reliable method for synthesizing propargylic amines. The reaction usually requires a stoichiometric amount of metal, thus the development of a catalytic method is desired. $[Ir(cod)Cl]_2$ catalyzed the addition of silylalkynes to aldimines to give propargylic amines (Scheme 39).[91] The reaction proceeded smoothly without a base. The catalytic activity is increased by the use of a catalytic amount of $MgI_2$ as an additive.[92] Although the detailed mechanism is not clear, the activation of the bond between the sp-hybridized carbon and the acetylenic hydrogen by an iridium species is considered to be involved. The catalytic addition of a silylalkyne to an aldimine generated in situ from an aldehyde and an amine was also reported.[93]

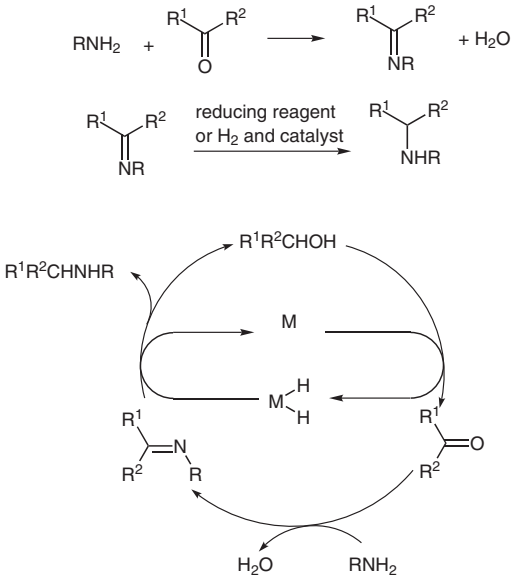



**Scheme 39**

# 4 Alkylation with Alcohols

## 4.1 N-Alkylation

N-Alkylation of primary amines to secondary or tertiary amines is an important reaction for the synthesis of amines. Reductive amination of carbonyl compounds in the presence of a reducing reagent or molecular hydrogen and a catalyst is a general reaction for N-alkylation. If alcohols can be used as a precursor of 'aldehyde or ketone and molecular hydrogen', the N-alkylation of amines with alcohols could be considered a 'green' reaction. The 'temporarily formed aldehyde or ketone (from the alcohol)' reacts with amine to give imine. Returning the 'borrowed hydrogen' to the imine gives an amine as a final product. In this process, water is the only byproduct (Scheme 40).

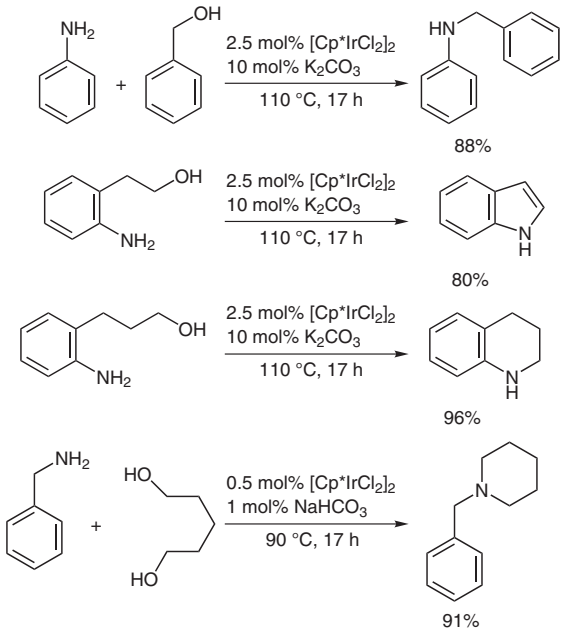



**Scheme 40**

The iridium-catalyzed transfer hydrogenation of carbonyl compounds with propan-2-ol was reported, suggesting that iridium complexes are capable of dehydrogenating propan-2-ol.[94] Indeed, $[Cp^*IrCl_2]_2/K_2CO_3$ efficiently catalyzed the N-alkylation of amines with alcohols (Scheme 41).[95] The reaction of aniline with benzyl alcohol gave *N*-benzyl aniline. Secondary alcohols as well as primary alcohols can be used for this N-alkylation. This chemistry was also extended to the synthesis of N-heterocycles: the $[Cp^*IrCl_2]_2/K_2CO_3$-catalyzed intramolecular N-alkylation of aminoalcohols gave indoles and tetrahydroquinolines,[96] and the reaction of primary amines with diols gave cyclic amines (Scheme 41).[97]

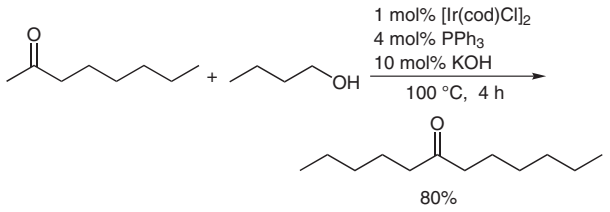
## 4.2 C-Alkylation

The α-alkylation of a ketone enolate with an alkyl halide is one of the most important carbon–carbon bond-forming reactions in organic synthesis. One of the disadvantages of this reaction is the formation of a stoichiometric amount of metal salt, but if alcohols can be used as the




**Scheme 41**

alkylating reagents, water is the only byproduct. The $[Ir(cod)Cl]_2/PPh_3/KOH$-catalyzed reaction of methyl ketones with alcohols gave dialkyl ketones in high yields (Scheme 42).[98] Various methyl ketones were alkylated with primary alcohols. Alkylation took place with complete regioselectivity at the methyl group of unsymmetric ketones. Furthermore, the reaction could be carried out without solvent.

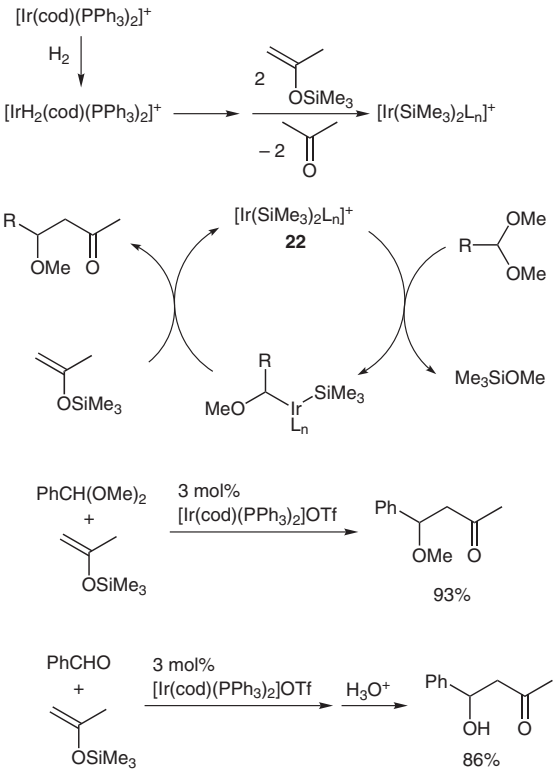



**Scheme 42**

## 5 Aldol and Related Reactions

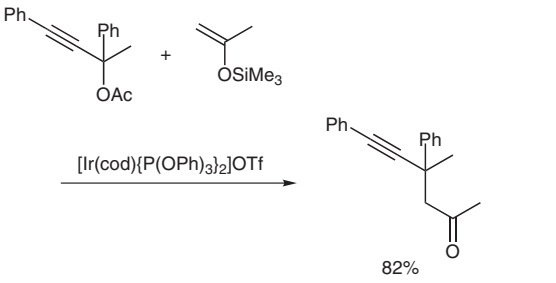
A cationic iridium complex activated by a molecule of $H_2$ was shown to be an efficient catalyst for the aldol reaction of aldehydes or acetals with silyl enol ethers (Scheme 43).[99] The catalytically active species is a $Me_3Si–Ir–SiMe_3$ species that is generated in situ. This species **22** would react nucleophilically with an acetal or an aldehyde to form an Ir–C species, which plays the role of a trigger for the aldol reaction. $[Ir(cod)_2(PPh_3)_2]OTf$ activated by a molecule of $H_2$ was also an efficient catalyst for the reaction of α,β-enones with silyl enol ethers to give 1,5-dicarbonyl compounds.[100] Silyl enol ethers act as good nucleophiles under iridium catalysis.

This chemistry was also extended to propargylic substitution. The cationic iridium-complex-catalyzed propargylic




**Scheme 43**

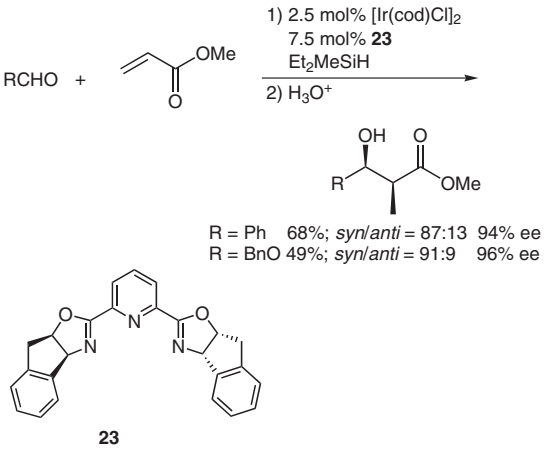
substitution of propargylic esters with silyl enol ethers, to give β-alkynyl ketones, was reported (Scheme 44).[101] Although the yields of the products were generally high, the mechanistic details were not clear.



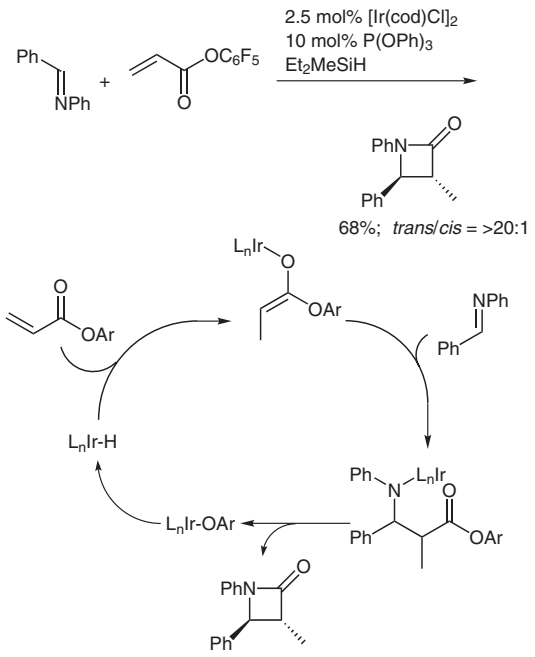

**Scheme 44**

The aldol reaction is the most important carbon–carbon bond-forming reaction in organic synthesis. Several late transition-metal complexes catalyze the aldol reaction of aldehydes with α,β-unsaturated esters in the presence of hydrosilane to give β-siloxy esters. Morken reported the iridium/pybox-catalyzed diastereo- and enantioselective reductive aldol reaction.[102] The reaction of benzaldehyde and α-benzyloxyaldehyde with methyl acrylate in the presence of diethylmethylsilane gave the *syn*-product with high diastereo- and enantioselectivity (Scheme 45). Reductive coupling of acrylates with imines gave *trans*-β-lactams with high diastereoselectivity (Scheme 46).[103] In this process, an iridium enolate generated from acrylate and hydrosilane reacts with an imine to give a β-amido es-

ter. Subsequent cyclization gives the β-lactam and the iridium hydride. It was found that electron-deficient aryl acrylates gave β-lactams in good yields.



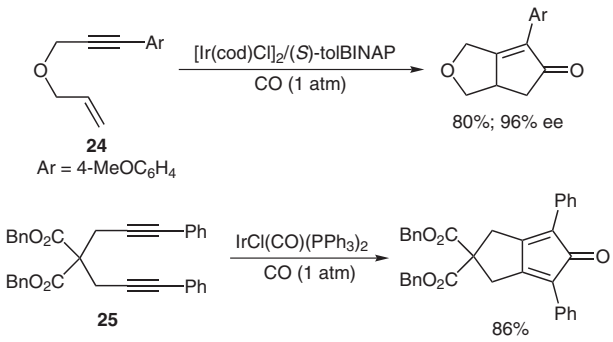

**Scheme 45**




**Scheme 46**

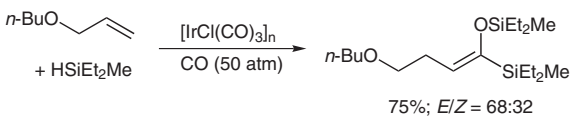
## 6 Carbonylation

The Pauson–Khand reaction is useful for producing bicyclic cyclopentenones, which are common structural components of naturally occurring and biologically active molecules. The application of the Pauson–Khand reaction in the synthesis of natural products has been extensively studied. Various transition-metal complexes are used as the catalyst or as a stoichiometric reagent for this reaction. The enantioselective Pauson–Khand reaction catalyzed by iridium diphosphine complex has been reported.[104,105] The reaction of enyne **24** under a carbon monoxide atmosphere gave the product in 96% ee (Scheme 47). The intermolecular Pauson–Khand reaction of 1-phenyl-1-propyne with norbornene gave a product in only 32% yield, but the enantiomeric excess was 93%. α,ω-Diyne **25** underwent carbonylative cyclization to give cyclopentadienone under iridium catalysis (Scheme 47).[106,107] A bulky substituent, such as an aryl group, on the alkyne is necessary in order to obtain cyclopentadienones in high yield – the methyl-disubstituted diyne did not give a cyclopentadienone. The carbonylative cyclization of allenynes to give α-methylene cyclopentenone was also reported.[108] These three reactions do not require a high pressure of carbon monoxide. Thus, iridium-catalyzed carbonylation is convenient for the laboratory-scale synthesis of cyclopentenones and cyclopentadienones.



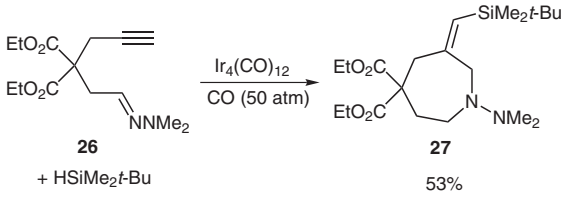

**Scheme 47**

Silylcarbonylations catalyzed by dicobalt octacarbonyl have been explored by Murai.[109] Carbon monoxide and trialkylsilane were introduced to alkenes, aldehydes, and cyclic ethers. Chatani and Murai found a novel silylcarbonylation. $[IrCl(CO)_3]_n$ and $Ir_4(CO)_{12}$ catalyzed the reaction of alkenes with a trialkylsilane and carbon monoxide to give silyl enol ethers of acylsilanes (Scheme 48).[110] Carbon monoxide was regioselectively introduced at the terminal carbon atom as a siloxy(silyl)methylene unit. Recently, it was reported that $[Ir(cod)(OSiMe_3)]_2$ was an efficient catalyst for the same reaction of vinyltrimethylsilane.[111] Alkynes also reacted with carbon monoxide and a trialkylsilane. The reaction of alkyne hydrazone **26** with a trialkylsilane under carbon monoxide (50 atm) gave nitrogen heterocycle **27**.[112] This reaction involved cyclization with the incorporation of one molecule of carbon monoxide, and reduction of the incorporated CO carbon to a methylene group (Scheme 49).



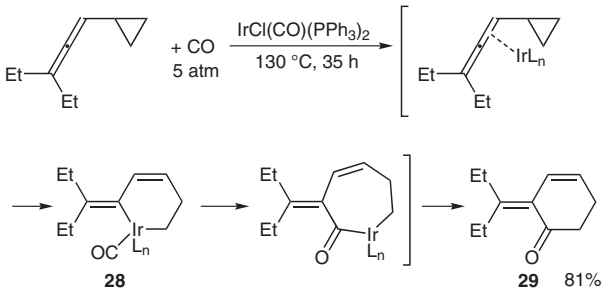

**Scheme 48**

The cleavage of a carbon–carbon single bond by a transition-metal catalyst is a challenging area in organic synthesis. As shown in Scheme 50, an allenylcyclopropane underwent carbonylative [5+1] cycloaddition with the




**Scheme 49**

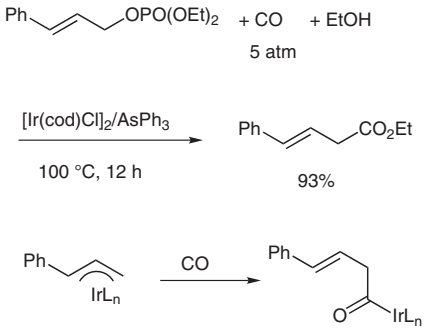
cleavage of a carbon–carbon single bond to give cyclohexenone **29** in the presence of a catalytic amount of $IrCl(CO)(PPh_3)_3$.[113] Initial coordination of the allenyl group brings the metal into the proximity of the cyclopropane ring, which is then opened by the metal to form the six-membered iridacycle **28**. Insertion of carbon monoxide followed by reductive elimination gives **29**. Interestingly, the same reaction catalyzed by rhodium complexes did not give cyclohexenone **29**.




**Scheme 50**

As described in Section 2, the reaction of a π-allyl intermediate with a nucleophile is a versatile reaction in organic synthesis. Another important version of this reaction is the insertion reaction with an unsaturated molecule such as carbon monoxide. $[Ir(cod)Cl]_2/AsPh_3$ showed high catalytic activity for the carbonylation of allylic phosphates in the presence of alcohols to give the corresponding β,γ-unsaturated esters (Scheme 51).[114] The key step of the reaction is the insertion of carbon monoxide into the π-allyl–iridium bond to give 3-butenoyl iridium species.

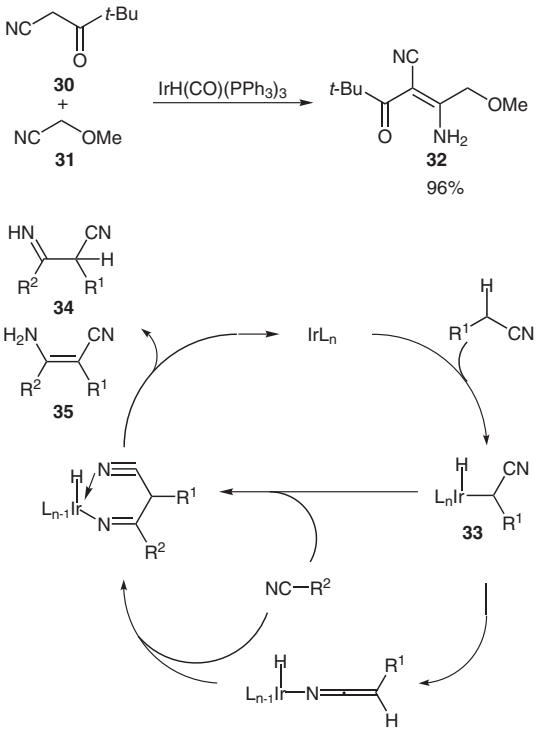
The carbonylation of methanol to acetic acid is one of the most successful examples of the industrial application of homogeneous catalysis. In 1996, BP Chemicals announced a new methanol carbonylation process, called Cativa™, based on a promoted iridium/iodide catalyst.[115,116] The Cativa process offers a significant improvement over conventional rhodium-based technology – improved catalyst stability – that allows for low water concentrations, high reaction rates, reduced formation of by-products and improved yield on carbon monoxide. A detailed mechanistic study on this new process has been reported.[117]




**Scheme 51**

## 7 Miscellaneous Reactions

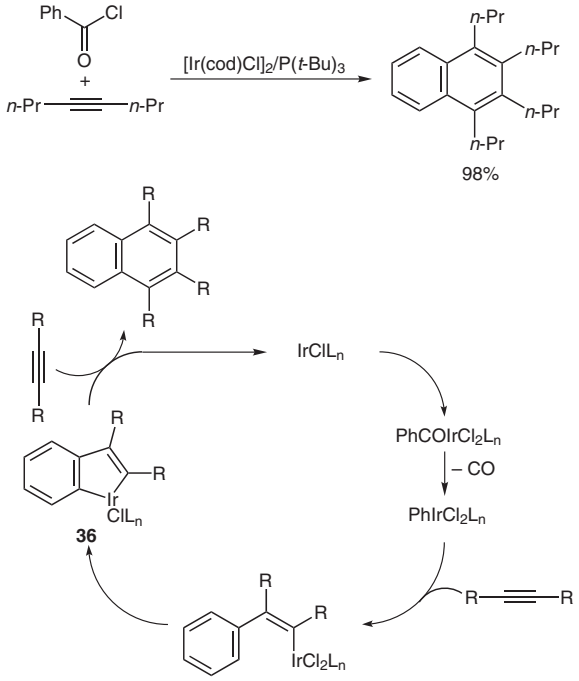
The addition of carbon nucleophiles to carbon–nitrogen triple bonds is one of the most useful synthetic reactions for nitriles. Generally, a stoichiometric amount of strong base is used for the reaction. $IrH(CO)(PPh_3)_3$ has been shown to be an efficient catalyst for the reaction under neutral conditions. Activated nitrile **30** added to the second nitrile **31** to give cyanoenamine **32** (Scheme 52).[118,119] The reaction involves the oxidative addition to the α-C–H bond of the nitrile to give **33**. Insertion of the second nitrile to the Ir–C bond in **33** followed by reductive elimination gives imine **34**, which isomerizes to the more stable enamine **35** under these reaction conditions.




**Scheme 52**

Alcohols reacted with vinyl acetate in the presence of $[Ir(cod)Cl]_2$ catalyst and sodium carbonate to give the corresponding vinyl ethers in high yield;[120] the method was appropriate for various alcohols, including phenols. Notably, the reaction of adamantanol gave 1-adamantyl vinyl ether in 91% yield.

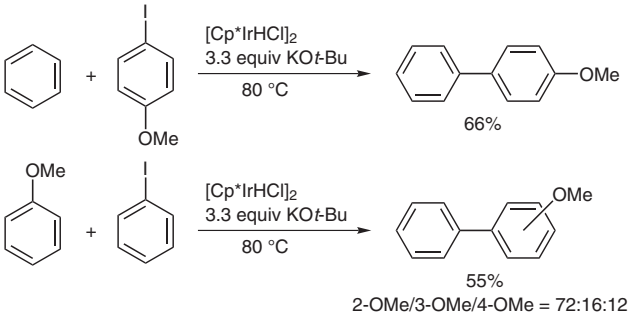
Much attention has been paid to the transition-metal-catalyzed synthesis of polycyclic aromatic compounds. Iridium catalysis provides a new method for aromatic homologation. Aroyl chlorides reacted with two molecules of an internal alkyne to give substituted naphthalenes with catalysis by $[Ir(cod)Cl]_2/P(t\text{-}Bu)_3$ (Scheme 53).[121] The reaction of 2-naphthoyl chloride gave a mixture of an anthracene and a phenanthrene. In this process, oxidative addition of aroyl chlorides to an iridium complex gives an aroyliridium species, which undergoes decarbonylation to give an aryliridium species. Insertion of alkyne to the Ar–Ir bond followed by *ortho*-iridation gives iridacycle **36**. Insertion of the second alkyne, followed by reductive elimination, gives the desired product.




**Scheme 53**

The iridium-catalyzed Mizoroki–Heck-type reaction of organosilanes has been reported.[122] The reaction of main-group organometallic reagents containing elements such as boron, tin and silicon with α,β-unsaturated carbonyl compounds has been extensively studied. The selectivity of the product depends on the nature of the transition metals. The reaction of trimethoxyphenylsilane with butyl acrylate in the presence of tetrabutylammonium fluoride and $[Ir(cod)Cl]_2$ catalyst gave butyl 3-phenyl-2-propenoate in 71% yield. No conjugate addition product was obtained. Mechanistically, transmetallation from organosilanes to iridium gives aryl iridium species. Insertion of acrylate into the Ar–Ir bond, followed by β-hydride elimination, gives the final product.

Benzene was arylated by a reaction with aryl iodide in the presence of potassium *tert*-butoxide and $[Cp^*IrHCl]_2$ catalyst (Scheme 54).[123] The reaction of anisole with iodobenzene gave a 72:16:12 mixture of 2-, 3-, and 4-methoxybiphenyls in 55% yield. The regioselectivity is different from that with electrophilic aromatic substitution. An aryl radical is proposed to be an intermediate.




**Scheme 54**

## 8 Conclusion

Iridium catalysts have turned out to be versatile for organic synthesis, and recent publications show that this area is still growing and promising. The success of the Cativa process, in particular, shows the importance of iridium catalysis in the chemical industry. In most of the cases reviewed here, the catalytic cycle is Ir(+1) ↔ Ir(+3). The substrate oxidatively adds to Ir(+1) to give Ir(+3). The bond-forming reaction occurs with Ir(+3). The product is then reductively eliminated from Ir(+3) to regenerate Ir(+1).

To develop new catalytic reactions, another catalytic cycle needs to be explored. Considering that Ir(+5) has seven coordination sites, the catalytic cycle Ir(+3) ↔ Ir(+5) is more challenging. A bond-forming reaction that cannot occur on Ir(+3) may be possible on Ir(+5), since it has more available coordination sites than Ir(+3). Several Ir(+3) complexes are readily available as a catalyst precursor. This concept could lead to the development of new catalytic reactions. Finally, we hope that this review encourages young chemists to use iridium catalysts in their research.

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