Iridium Complex-Catalyzed Highly Selective Organic Synthesis

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Abstract: Two different synthetic reactions catalyzed by an iridium complex are discussed. The first is allylic alkylation and allylic amination. This reaction proceeds via a π-allyl iridium intermediate. The selectivity strongly depends on the structure of the allylic esters. Highly branched product-selective allylic substitution and highly *Z*-selective allylic substitution were achieved. The selectivities of allylic substitution described here have not been achieved in previous studies with other transition metal complexes. The second reaction is [2+2+2] cycloaddition of α,ω-diynes with monoynes. This reaction proceeds via iridacyclopentadiene and tolerates various functional groups. Functionalized monoynes can be used. These results show that an iridium complex can be a useful catalyst for carbon-carbon and carbon-heteroatom bond formation.

Key words: iridium complex, catalysis, π-allyl iridium, iridacyclopentadiene, allylic esters, alkynes

1 Introduction

Transition metal complexes are indispensable tools in modern organic synthesis. They can realize selective transformations that would be either difficult or impossible by conventional organic chemistry.[1] The first row and second row transition metal complexes of group 8–10 have been used as catalysts for organic synthesis. On the other hand, the third row transition metal complexes of group 8–10 have been less used as catalysts than the first row and second row transition metal complexes of the same group. One reason may be the stability of the carbon-metal bond. In general, the carbon-metal bond in a third row transition metal complex is more stable than that in a first or second row transition metal complex. Thus, third row transition metal complexes are likely too stable to to be used as catalysts for organic synthesis, though they have been studied as models for intermediates in catalytic reactions. For example, oxidative addition has been studied using $IrCl(CO)(PPh_3)_2$.[2]

In 1977, Crabtree reported that $[Ir(cod)PyPCy_3]PF_6$ was an efficient hydrogenation catalyst.[3] This catalyst is unusual in that it can reduce hindered alkenes. Furthermore, it shows a strong directing effect. Stork et al. reported that this catalyst can control the stereoselectivity of hydrogenation via hydroxy group coordination.[4] Pfaltz et al. reported highly enantioselective hydrogenation of unfunctionalized tri- and tetrasubstituted alkenes.[5] These impressive successes showed that an iridium complex can be a useful hydrogenation catalyst for organic synthesis. However, progress in iridium complex-catalyzed carbon-carbon or carbon-heteroatom bond formation lags far behind hydrogenation. Few examples of iridium complex-catalyzed or mediated carbon-carbon bond formation had been reported when we started our investigation in the summer of 1995.[6,7]

We had studied rhodium complex-catalyzed reactions for several years.[8] At that time, we became interested in the chemistry of iridium complexes. We believed that an iridium complex could be useful for carbon-carbon or carbon-heteroatom bond formation, and began studying iridium complex-catalyzed organic synthesis. This *Account* is a personal and non-comprehensive review of iridium complex-catalyzed organic synthesis as studied in my laboratory over the past six years.

2 Allylic Alkylation

2.1 Branched Product-Selective Allylic Alkylation

Allylic alkylation via a π-allyl metal intermediate is one of the most important carbon-carbon bond forming reactions catalyzed by a transition metal complex. This reaction is widely used to construct complex organic molecules. Generally, the substrate of allylic alkylation is an allylic ester. Allylic esters oxidatively add to a transition metal complex to give π-allyl metal intermediates. Nucleophilic attack to a π-allyl ligand gives a final product. When a π-allyl intermediate is a terminally monosubstituted, nucleophilic attack of the π-allyl intermediate gives three products [branched product and *E*- and *Z*-linear products] (Scheme 1). The control of regio- and stereoselectivity is important. Palladium complexes are general and versatile catalysts for allylic alkylation. With palladium, alkylation of **1** gives *E*-linear product.[9] Branched product-selective allylic alkylation is a challenging problem. With molybdenum,[10] tungsten,[11] ruthenium,[12] and iron,[13] alkylation of

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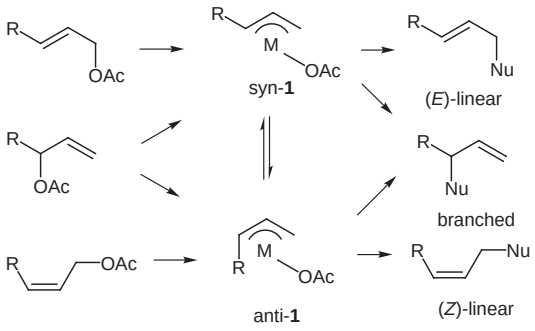
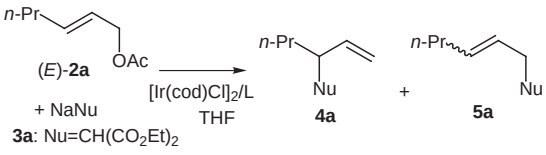
1 preferentially gives a branched product. However, the substituent in **1** is limited to an aryl group. Highly branched product-selective alkylation of not only an aryl group-substituted π-allyl intermediate but also an alkyl group-substituted π-allyl intermediate was not reported.[14,15]



Scheme 1

An iridium complex was found to be an efficient catalyst for highly branched product-selective allylic alkylation.[16] We examined the reaction of *(E)*-2-hexenyl acetate [*(E)*-**2a**] with diethyl sodiomalonate (**3a**) in the presence of a catalytic amount of $[Ir(cod)Cl]_2$ (Ir atom 4 mol%), and found that an added ligand had a substantial effect on the selectivity and yield of the products (Scheme 2), with $P(OPh)_3$ being the most efficient ligand. The reaction occurred at room temperature to give products in high yields. Branched product **4a** was obtained in 96% selectivity. The ratio of $P(OPh)_3$ to Ir was also important. One or two equivalents of $P(OPh)_3$ relative to Ir were necessary for a high yield and high selectivity. The reaction using $P(OEt)_3$ gave products in good yield, but the selectivity of this reaction for branched product was less than when using $P(OPh)_3$. The reaction using phosphine ligand gave products in low yield.

The electron-withdrawing property of $P(OPh)_3$ plays a crucial role in the high selectivity for a branched product. Based on a ^{31}P NMR study,[16b,c] a π-allyl iridium intermediate is considered to be a monophosphite species in which $P(OPh)_3$ coordinates with the metal *trans* to the substituted allylic terminus (Figure 1). The carbonium ion



$P(OPh)_3$	P/Ir=1	rt 3 h	Yield 90%	**4a** : **5a**=96 : 4
$P(OPh)_3$	P/Ir=2	rt 3 h	Yield 89%	**4a** : **5a**=96 : 4
$P(OEt)_3$	P/Ir=2	reflux 3 h	Yield 81%	**4a** : **5a**=59 : 41
PPh_3	P/Ir=2	reflux 16 h	Yield 6%	**4a** : **5a**=24 : 76
dppe	P/Ir=2	reflux 16 h	Yield 18%	**4a** : **5a**=39 : 61

Scheme 2

character of the substituted allylic terminus, enhanced by the electron-withdrawing property of $P(OPh)_3$, directs a nucleophile to this position to give a branched product.

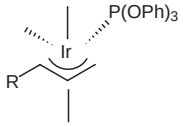
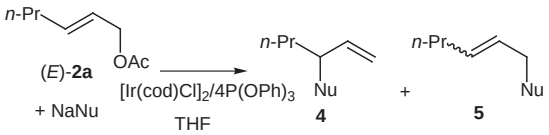


Figure 1

The reactions of *(E)*-**2a** with **3b** and **3c** were examined (Scheme 3). The reactions occurred at room temperature to give products in high yields. Both reactions were highly branched product-selective. On the other hand, the reaction with diethyl sodiomethylmalonate (**3d**), which is a more sterically demanding nucleophile than **3a**–**c**, was linear product-selective. The reaction of *(E)*-**2a** with **3d** gave the linear product **5d** in 71% selectivity.



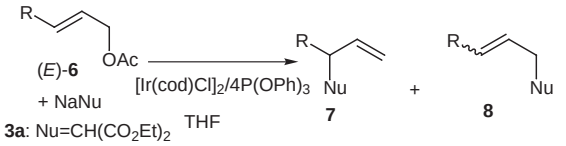
3b: Nu=$CH(CO_2Me)_2$	rt 3 h	Yield 90%	**4b** : **5b**=97 : 3
3c: Nu=$CHAcCO_2Et$	reflux 7 h	Yield 85%	**4c** : **5c**=93 : 7
3d: Nu=$CMe(CO_2Et)_2$	reflux 1 h	Yield 87%	**4d** : **5d**=29 : 71

Scheme 3

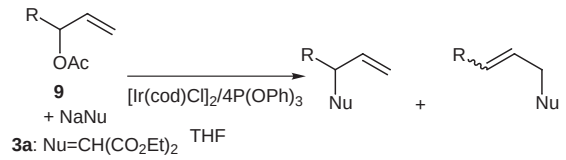
Biographical Sketch

Ryo Takeuchi was born in Osaka, Japan, in 1958. He graduated from Kyoto University in 1981. He received his PhD degree 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. He was promoted to associate professor in 1995. He received the Kuray Award in Synthetic Organic Chemistry, Japan in 1997. His research interests include the development of transition metal complex-catalyzed selective reactions.

The reactions of *(E)*-**6a**–**d** with **3a** gave branched products **7a**–**d** in 95–99% selectivity (Scheme 4). The reaction of regioisomeric acetates was also highly branched product-selective. Regioisomeric acetates **9a**,**b**,**d** reacted with **3a** to give branched products **4a**, **7b**, and **7d** in 95–99% selectivity. These results strongly suggest that a π-allyl iridium complex acts as an intermediate (Scheme 5).

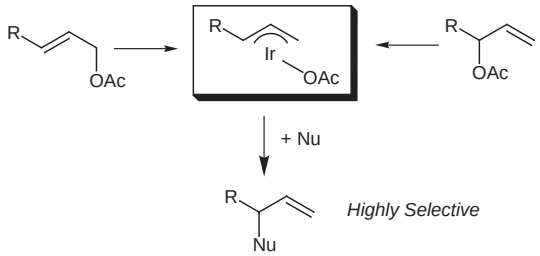


6a: R=Me	rt 2 h	Yield 77%	**7a** : **8a**=97 : 3
6b: R=Ph	rt 3 h	Yield 98%	**7b** : **8b**=99 : 1
6c: R=*n*-Hex	rt 5 h	Yield 99%	**7c** : **8c**=95 : 5
6d: R=*n*-Oct	rt 5 h	Yield 95%	**7d** : **8d**=95 : 5



9a: R=*n*-Pr	rt 3 h	Yield 86%	**4a** : **5a**=95 : 5
9b: R=Ph	rt 3 h	Yield 91%	**7b** : **8b**=99 : 1
9d: R=*n*-Oct	rt 3 h	Yield 95%	**7d** : **8d**=95 : 5

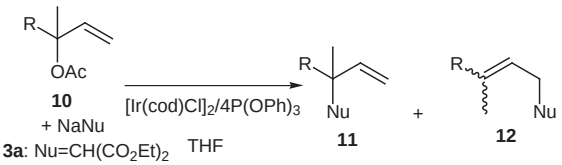
Scheme 4



Scheme 5

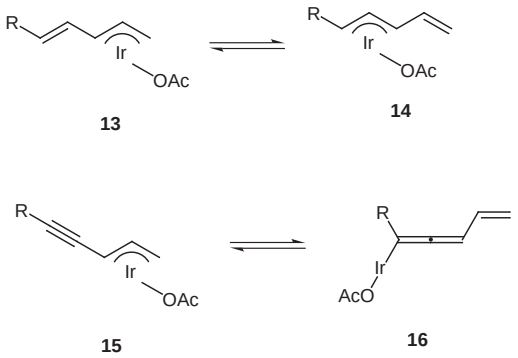
The most unique feature of iridium complex catalysis is seen in the reaction of **10** with **3a** (Scheme 6). The reactions were regiospecific at the tertiary allylic terminus to exclusively give a **11** bearing a quaternary carbon center. Iridium complex-catalyzed allylic alkylation is an efficient method for constructing a quaternary carbon center, which is a feature of a broad range of natural products. Several transition metal complex-catalyzed reactions of **10c** with **3a** have been reported. $Pd(PPh_3)_4$-catalyzed reaction[17] and $NiCl_2$(dppe)-catalyzed reaction[18] give **11c** in 38% and 10% selectivity, respectively. $Mo(CO)_6$-catalyzed reaction of **10c** with **3b** has been reported to give a product bearing a quaternary carbon center in 85% selectivity.[10b] The iridium complex led to the exclusive formation of a product bearing a quaternary carbon center.

As described above, highly branched product-selective allylic alkylation of *(E)*-2-alkenyl acetates and *(E)*-3-phenyl-2-propenyl acetate was achieved. These reactions are considered to proceed via a π-allyl iridium intermediate. Branched products result from alkylation at the substituted allylic terminus of a terminally monosubstituted π-allyl iridium intermediate. We examined the alkylation of an alkyl or aryl group-substituted π-allyl iridium intermediate. The substituent on the π-allyl ligand should strongly affect the reactivity of the π-allyl iridium intermediate. Alkenyl and alkynyl groups are particularly important as substituents on the π-allyl ligand (Scheme 7). 1-(1-Alkenyl)-π-allyl metal intermediate (**13**) isomerizes to 1-alkyl-3-vinyl-π-allyl metal intermediate (**14**) via σ-π-σ interconversion. Similarly, 1-(1-alkynyl)-π-allyl metal intermediate (**15**) isomerizes to 1-alkyl-3-vinyl-σ-allenyl metal intermediate (**16**). The selective reaction of these intermediates with a nucleophile increases the importance of this type of transformation in organic synthesis.



10a: R=Me	rt 2 h	Yield 80%	**11a** : **12a**=100 : 0
10b: R=*n*-Bu	rt 16 h	Yield 80%	**11b** : **12b**=100 : 0
10c: R=CH_2CH_2C=CMe_2	rt 16 h	Yield 85%	**11c** : **12c**=100 : 0

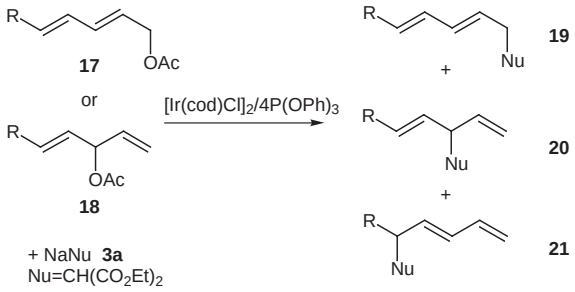
Scheme 6



Scheme 7

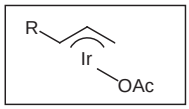
Dienyl acetates **17** and **18** smoothly underwent alkylation with **3a** to exclusively give branched products **20a**–**d** in yields of 84–94% (Scheme 8).[19] The reaction of dienyl acetates **17** and **18** was more branched product-selective than that of *(E)*-2-alkenyl acetates. Oxidative addition of **17** or **18** gives an alkenyl group-substituted π-allyl iridium intermediate **13**. Since an alkenyl group is more electron-withdrawing than an alkyl group, an alkenyl group-substituted allylic terminus is more electron-deficient than an alkyl group-substituted allylic terminus (Figure 2).[20] Therefore, alkylation occurs at the substituted allylic terminus of a π-allyl iridium intermediate **13** with perfect regioselectivity to exclusively give a branched product **20**. On the other hand, the palladium complex-catalyzed reac-

tion was linear product-selective. The major product of alkylation of **17a** with **3b** catalyzed by $Pd(PPh_3)_4$ has been reported to be linear.[21]



17a: R=Me	rt 3 h	Yield 94%	**19a** : **20a** : **21a**=0 : 100 : 0
18a: R=Me	rt 3 h	Yield 84%	**19a** : **20a** : **21a**=0 : 100 : 0
18b: R=Ph	rt 2 h	Yield 92%	**19b** : **20b** : **21b**=0 : 100 : 0
18c: R=*n*-Pr	rt 2 h	Yield 93%	**19c** : **20c** : **21c**=0 : 100 : 0
18d: R=(*E*)-*n*-BuCH=CH	rt 4 h	Yield 92%	**19d** : **20d** : **21d**=0 : 100 : 0

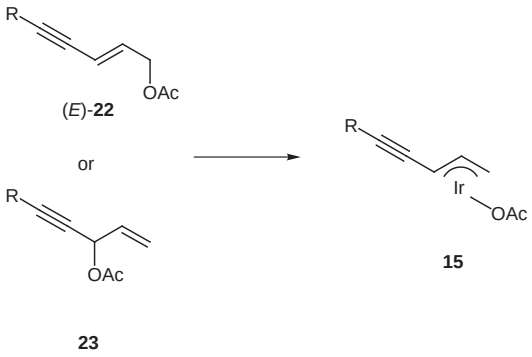
Scheme 8



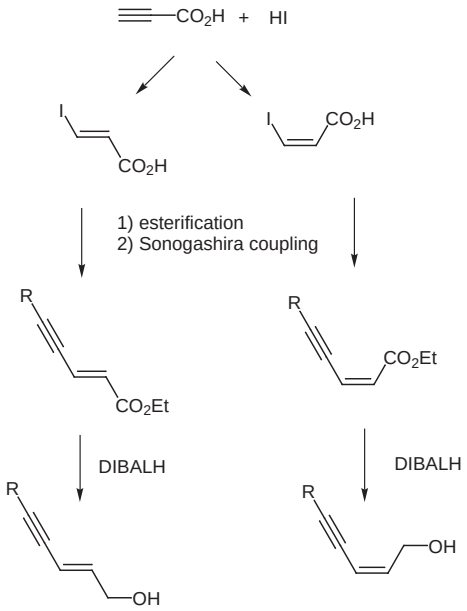
Group electronegativity	
n-Pr	2.483
MeCH=CH	2.787

Figure 2

This success prompted us to examine the allylic alkylation of enynyl acetates. Oxidative addition of *(E)*-**22** or **23** gives an alkynyl group-substituted π-allyl iridium intermediate **15** (Scheme 9). We were interested in the reactivity of this intermediate. Enynyl acetate **23** was easily prepared by reacting alkynylmagnesium bromide with acrolein, followed by acetylation. To prepare **22**, we needed a stereodefined synthesis of 2-alken-4-yn-1-ols. One efficient route to 2-alken-4-yn-1-ols is the coupling of 3-iodo-2-propen-1-ol with 1-alkynes. This protocol requires the stereodefined synthesis of *(E)*- and *(Z)*-3-iodo-2-propen-1-ol. Hydrostannation of 2-propyn-1-ol followed by iodolysis has been reported to give *(E)*-3-iodo-2-propen-1-ol.[22] However, hydrostannation of 2-propyn-1-ol with tributylstannane gave a mixture of *(E)*-3-tributylstannyl-2-propen-1-ol, *(Z)*-3-tributylstannyl-2-propen-1-ol, and 2-tributylstannyl-2-propen-1-ol. This route requires separation of these isomers prior to iodolysis. We decided to develop another route that did not use 3-iodo-2-propen-1-ol. Coupling of 3-iodo-2-propenoic acid or its derivatives with 1-alkynes followed by reduction gives 2-alken-4-yn-1-ol. 3-Iodo-2-propenoic acid is obtained by hydroiodination of 2-propynoic acid. We examined the hydroiodination of 2-propynoic acid in detail, and obtained *(Z)*-3-iodo-2-propenoic acid in high yield. Furthermore, we found that *(Z)*-3-iodo-2-propenoic acid isomerizes to *(E)*-3-iodo-2-propenoic acid in high yield. Both *(E)*- and *(Z)*-3-iodo-2-propenoic acid can be obtained from 2-propynoic acid. Sonogashira coupling of 3-iodo-2-propenoate with 1-alkynes followed by DIBALH reduction gave 2-alken-4-yn-1-ols. We have developed a stereodivergent route to *(E)*- and *(Z)*-2-alken-4-yn-1-ols from 2-propynoic acid (Scheme 10).[23]



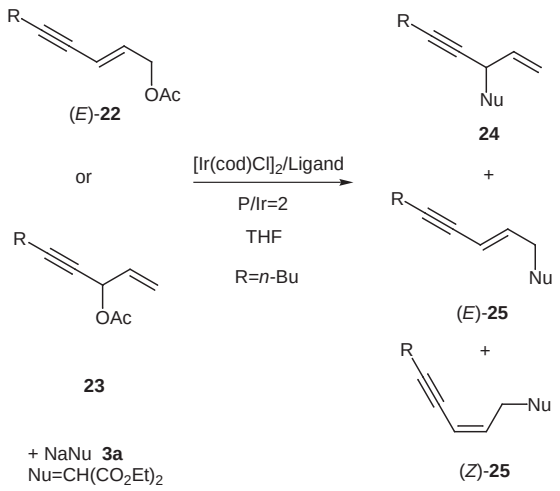
Scheme 9



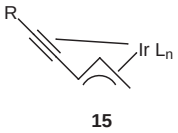
Scheme 10

The structure of the substrate and the ligand used each strongly affected the selectivity of the allylic alkylation of enynyl acetates. The reaction of *(E)*-**22** and **23** with **3a** gave three products (Scheme 11). Both reactions were less branched product-selective than those of *(E)*-**2** and *(E)*-**6**. To explain the product distributions of the reactions of *(E)*-**22** and **23**, we must consider the coordination of an alkynyl group to an Ir center. The electron-withdrawing property of $P(OPh)_3$ promoted the carbonium ion character at the substituted allylic terminus, thus directing a nucleophile to this position. With intermediate **15**, coordination of an alkynyl group would reduce the carbonium ion character at the substituted allylic terminus to

decrease the selectivity to a branched product. Therefore, nucleophilic attack occurs to some extent at the unsubstituted allylic terminus to give a linear product. To obtain a branched product in high selectivity, we surveyed phosphite ligands. $P(OEt)_3$ gave a good result. The reaction of **23** with **3a** using $P(OEt)_3$ (P/Ir = 2) was highly branched product-selective. The selectivity of **24** was 92%. It is not yet clear why $P(OEt)_3$ gives a better result than $P(OPh)_3$.



				24 : (*E*)-**25** : (*Z*)-**25**
(*E*)-**22**	$P(OPh)_3$	rt 4 h	87%	65 : 33 : 2
23	$P(OPh)_3$	rt 19 h	83%	40 : 9 : 51
(*E*)-**22**	$P(OEt)_3$	reflux 21 h	43%	21 : 77 : 2
23	$P(OEt)_3$	reflux 2 h	91%	92 : 8 : 0



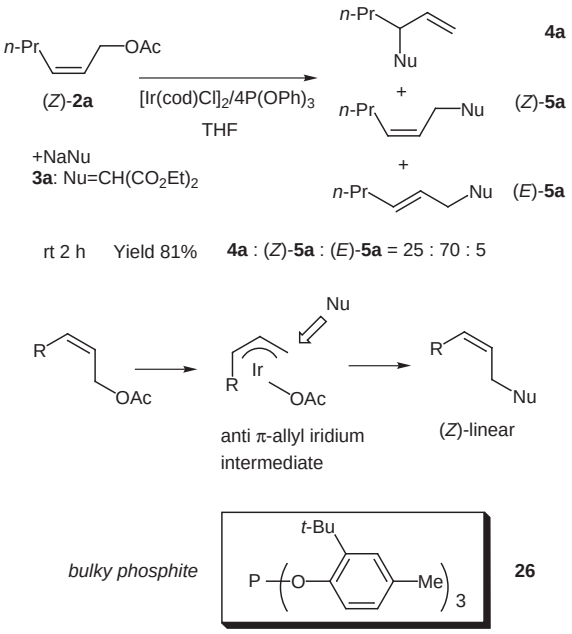
Scheme 11

Based on our studies, iridium complex-catalyzed enantioselective allylic alkylation was reported.[24]

2.2 Z-Selective Allylic Alkylation

We have described a branched product-selective allylic alkylation. In this section, we would like to describe another feature of iridium complex-catalyzed allylic alkylation.

The stereochemistry of a carbon-carbon double bond in the allyl system affected the regiochemistry of this allylic alkylation. The reaction of *(Z)*-**2a** with **3a** in the presence of a catalytic amount of $[Ir(cod)Cl]_2$ and $P(OPh)_3$ (Ir atom 4 mol%, P/Ir = 2) gave *(Z)*-**5a** in 70% selectivity. The major product was a *(Z)*-linear product (Scheme 12). Oxidative addition of *(Z)*-**2a** gives an anti π-allyl iridium intermediate. Product *(Z)*-**5a** resulted from alkylation of the anti π-allyl iridium intermediate at the unsubstituted allylic terminus. The major product was different from that in the reaction of *(E)*-**2a**. The regioselectivity of the alkylation of the *anti* π-allyl iridium intermediate was different from that of the *syn* π-allyl iridium intermediate.

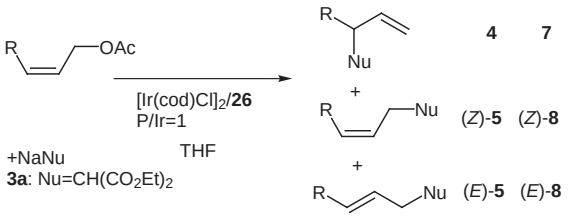


Scheme 12

Palladium complex-catalyzed allylic alkylation of *(Z)*-2-alkenyl acetate gives a *E*-linear product,[9a,b] since the anti π-allyl palladium intermediate easily isomerizes to a thermodynamically more stable *syn* π-allyl palladium intermediate prior to alkylation.[25] It has been difficult to retain the *Z*-stereochemistry in the allylic alkylation of *(Z)*-2-alkenyl acetate. Limited examples of *Z*-selective allylic substitution have been reported.[9a,11d,26]

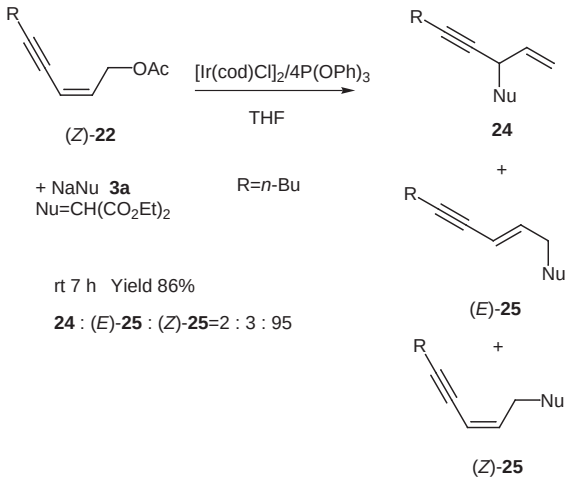
In the reaction of *(Z)*-**2a** with **3a**, the ratio *(Z)*-**5a**/*(E)*-**5a** was 93/7. We considered that while *Z*-selective allylic alkylation catalyzed by an iridium complex is possible, the regioselectivity to a linear product is not high enough (branched/linear = 25:75). To improve the selectivity for a linear product, alkylation must be directed to the unsubstituted allylic terminus. A bulky phosphite ligand is expected to increase such selectivity, since a bulky phosphite ligand increases the steric bulkiness of the metal center. We prepared tris(2-*tert*-butyl-4-methylphenyl)phosphite (**26**) by reacting PCl_3 with 2-*tert*-butyl-4-methylphenol (Scheme 14). We examined the reaction of *(Z)*-2-alkenyl acetates [*(Z)*-**2a**, **6c**, **6d**] with **3a** using **26** as a ligand (Scheme 13). As expected, *Z* linear products were obtained in 87-90% selectivities. We successfully performed *Z* selective allylic alkylation.[16b,c]

Allylic alkylation of *(Z)*-2-alken-4-ynyl acetate [*(Z)*-**22**] was also highly *Z*-selective.[19] The reaction of *(Z)*-**22** with **3a** in the presence of a catalytic amount of $[Ir(cod)Cl]_2$ and $P(OPh)_3$ (Ir atom 4 mol%, P/Ir = 2) gave a *Z*-linear



(*Z*)-**2a**: R=*n*-Pr reflux 5 h Yield 85% **4a** : (*Z*)-**5a** : (*E*)-**5a** = 3 : 90 : 7
(*Z*)-**6c**: R=*n*-Hex reflux 3 h Yield 86% **7c** : (*Z*)-**8c** : (*E*)-**8c** = 2 : 89 : 9
(*Z*)-**6d**: R=*n*-Oct reflux 3 h Yield 84% **7d** : (*Z*)-**8d** : (*E*)-**8d** = 2 : 87 : 11

Scheme 13



Scheme 14

product *(Z)*-**25** in 95% selectivity (Scheme 14). Bulky phosphite **26** was not necessary in the reaction of *(Z)*-**22** with **3a**.

Allylic alkylation of *(Z)*-2-alkenyl acetates gave a *Z*-linear product. When a nucleophile approached the substituted allylic terminus of an *anti* π-allyl iridium intermediate, the substituent and iridium moiety are close together to increase steric repulsion. Thus, the transition state of the alkylation at the substituted allylic terminus of an *anti* π-allyl iridium intermediate is less stable than that of a *syn* π-allyl iridium intermediate (Figure 3). Therefore, alkylation of an *anti* π-allyl iridium intermediate preferentially occurs at the unsubstituted allylic terminus to give a *Z*-linear product.

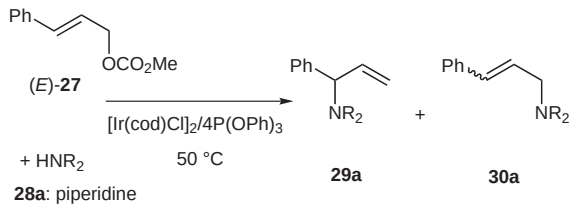
Figure 3

3 Allylic Amination

3.1 Branched Amine-Selective Allylic Amination

Transition metal complex-catalyzed allylic amination is important in carbon-nitrogen bond formation. Unfortunately, there are few efficient catalysts other than palladium complexes.[27] Recently, ruthenium,[28] rhodium,[29] iron,[30] and nickel[31] complexes have been used as catalysts for allylic amination. In the previous section, we showed that an iridium complex is an efficient catalyst for allylic alkylation. We extended this chemistry to allylic amination.[32]

We observed that the solvent strongly affects allylic amination. The reaction of *(E)*-**27** with piperidine (**28a**) in the presence of a catalytic amount of $[Ir(cod)Cl]_2$ and $P(OPh)_3$ (Ir atom 4 mol%, P/Ir = 2) was examined in various solvents (Scheme 15); EtOH and MeOH gave good results. Branched amine **29a** was obtained in high yield with high selectivity. Although THF is a common solvent for palladium complex-catalyzed allylic substitution, THF and dioxane gave products in low yields. The $E_T(30)$ value is a well-known measure of solvent polarity.[33] Solvents with $E_T(30)$ values above 40 gave products in good yield. A polar solvent clearly enhances allylic amination. It is important to note that no *(Z)*-**30a** was obtained with any of the solvents tested.

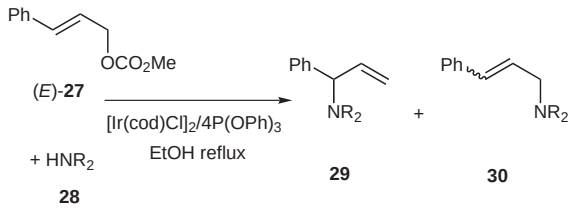


EtOH	$E_T(30)$=51.9	3 h	Yield 95%	**29a** : **30a**=95 : 5
MeOH	$E_T(30)$=55.4	3 h	Yield 84%	**29a** : **30a**=92 : 8
acetone	$E_T(30)$=42.4	reflux 17 h	Yield 71%	**29a** : **30a**=96 : 4
$MeNO_2$	$E_T(30)$=46.3	12 h	Yield 89%	**29a** : **30a**=68 : 32
MeCN	$E_T(30)$=45.6	7 h	Yield 83%	**29a** : **30a**=89 : 11
CH_2Cl_2	$E_T(30)$=40.7	reflux 22 h	Yield 90%	**29a** : **30a**=80 : 20
THF	$E_T(30)$=37.4	23 h	Yield 25%	**29a** : **30a**=89 : 11
dioxane	$E_T(30)$=36.0	22 h	Yield 39%	**29a** : **30a**=91 : 9
benzene	$E_T(30)$=34.4	reflux 16 h	Yield 58%	**29a** : **30a**=85 : 15

Scheme 15

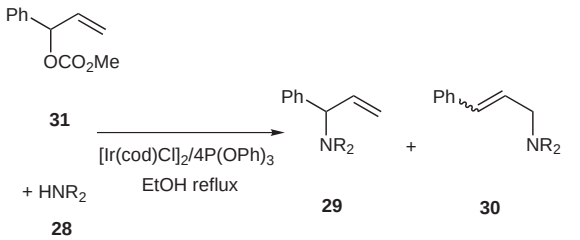
Carbonate *(E)*-**27** reacted with various amines under refluxing EtOH to give a branched amine **29** as a major product (Scheme 16). Both secondary and primary amines could be used. The yields were generally good, but the selectivities depended on the amine used. The reactions of *(E)*-**27** with pyrrolidine (**28b**), morpholine (**28c**), cyclopentylamine (**28d**), butylamine (**28e**) and benzylamine (**28h**) gave **29b**–**e**,**h** in selectivities of 92–96%. Diethylamine is more sterically demanding than piperidine.[34] The reaction with diethylamine (**28f**) was less branched amine-selective than that with piperidine (**28a**). Reactions with primary amines (**28d**,**e**,**g**,**h**) exclu-

sively gave monoallylation products. It is well known that palladium complex-catalyzed allylic amination with a primary amine gives a monoallylation product and a considerable amount of a diallylation product. For example, the reaction of *(E)*-**27** with 2 equivalents of butylamine (**28e**) has been reported to give a monoallylation product in 80% yield and a diallylation product in 11% yield.[35] Iridium complex has an advantage over palladium complex with regard to the control of monoallylation and diallylation, in that no diallylation product was obtained. Carbonate **31** also reacted with both a secondary amine and a primary amine to give a branched amine **29** with high selectivity (Scheme 17). The reaction of **31** with butylamine (**28e**) exclusively gave a monoallylation product.



28b: pyrrolidine	Yield 95%	**29b** : **30b**=96 : 4	(E/Z=100/0)
28c: morpholine	Yield 92%	**29c** : **30c**=92 : 8	(E/Z=100/0)
28d: cyclopentylamine	Yield 93%	**29d** : **30d**=96 : 4	(E/Z=100/0)
28e: *n*-butylamine	Yield 79%	**29e** : **30e**=95 : 5	(E/Z=100/0)
28f: diethylamine	Yield 75%	**29f** : **30f**=65 : 35	(E/Z=100/0)
28g: *tert*-butylamine	Yield 92%	**29g** : **30g**=81 : 19	(E/Z=100/0)
28h: benzylamine	Yield 89%	**29h** : **30h**=96 : 4	(E/Z=100/0)

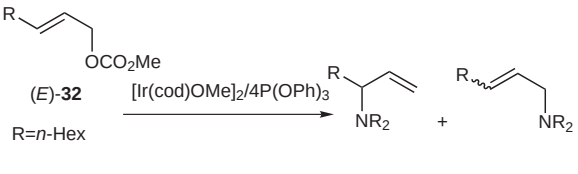
Scheme 16



28a: piperidine	Yield 85%	**29a** : **30a**=98 : 2	(*E*/*Z*=100/0)
28e: *n*-butylamine	Yield 89%	**29e** : **30e**=99 : 1	(*E*/*Z*=100/0)

Scheme 17

Allylic amination of *(E)*-2-alkenyl carbonate [*(E)*-**32**] was less branched amine-selective than that of *(E)*-3-phenyl-2-propenyl carbonate [*(E)*-**27**] (Scheme 18). We surveyed several iridium complexes and found that $[Ir(cod)OMe]_2$ was a more branched amine-selective catalyst than $[Ir(cod)Cl]_2$. The reaction of *(E)*-**32** with piperidine (**28a**) in the presence of a catalytic amount of $[Ir(cod)OMe]_2$ and $P(OPh)_3$ (Ir atom 4 mol%, P/Ir = 2) under refluxing acetone gave branched amine **33a** in 81% selectivity. Cyclopentylamine (**28d**), butylamine (**28e**) and aniline (**28i**) gave better, branched amine selectivity than piperidine (**28a**). Branched amines **33d**, **33e**, and **33i** were obtained in selectivities of 92–95%. Oxidative addition of *(E)*-2-alkenyl carbonate gives a 1-alkyl π-allyl iridium intermediate. Since an alkyl group is more electron-donating than an aryl group[20], an allylic terminus substituted with an alkyl group is less electron-deficient than that substituted with an aryl group. Thus, the amination of a 1-alkyl π-allyl iridium intermediate is less branched amine-selective than that of a 1-aryl π-allyl iridium intermediate.



28a: piperidine acetone reflux 3 h
Yield 87% **33a** : **34a**=81 : 19 (*E*/*Z*=100/0)

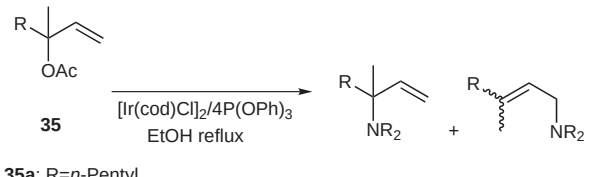
28d: cyclopentylamine MeCN reflux 24 h
Yield 76% **33d** : **34d**=92 : 8 (*E*/*Z*=100/0)

28e: *n*-butylamine MeCN reflux 24 h
Yield 70% **33e** : **34e**=95 : 5 (*E*/*Z*=100/0)

28i: aniline EtOH reflux 2 h
Yield 95% **33i** : **34i**=93 : 7 (*E*/*Z*=100/0)

Scheme 18

Allylic amination of 1,1-disubstituted-2-propenyl acetates was examined. Amination at the disubstituted allylic terminus gives α,α-disubstituted allylic amine. A general route to such amines is the addition of organometallic reagents to ketimines and their iminium salts.[36] However, when ketimines have an α-hydrogen, the addition of organometallic reagents to an imine carbon is problematic, since α-deprotonation competes with the addition reaction.[37] A more widely applicable method for the synthesis of an α,α-disubstituted allylic amine is needed. Regioselective allylic amination at the disubstituted allylic terminus should be a useful alternative route. Acetates **35** smoothly reacted with amines under refluxing EtOH to exclusively give α,α-disubstituted allylic amines **36** (Scheme 19). The use of EtOH was essential for this reaction. The same reaction under refluxing dioxane for 24 h gave no amination product, and the starting material was recovered in quantitative yield. $Pd(PPh_3)_4$-catalyzed allylic amination of 1,1-disubstituted allylic nitro compounds with piperidine (**28a**) has been reported to give both an *E*-linear allylic amine and an α,α-disubstituted allylic amine.[38] The selectivity of an α,α-disubstituted allylic amine was moderate. Only iridium complex-catalyzed allylic amination gave an α,α-disubstituted allylic amine as a single product.



35a: R=*n*-Pentyl
35b: R=Me_2C=$CHCH_2CH_2$

36 **37**

+ HNR_2

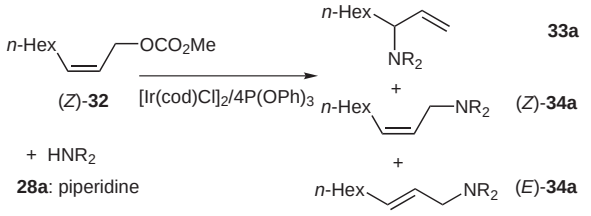
28

35a	**28a** piperidine	Yield 76%	**36aa** : **37aa**=100 : 0
35a	**28b** pyrrolidine	Yield 70%	**36ab** : **37ab**=100 : 0
35a	**28e** *n*-butylamine	Yield 59%	**36ae** : **37ae**=100 : 0
35a	**28i** aniline	Yield 77%	**36ai** : **37ai**= 100 : 0
35b	**28a** piperidine	Yield 76%	**36ba** : **37ba**=100 : 0

Scheme 19

3.2 Z-Selective Allylic Amination

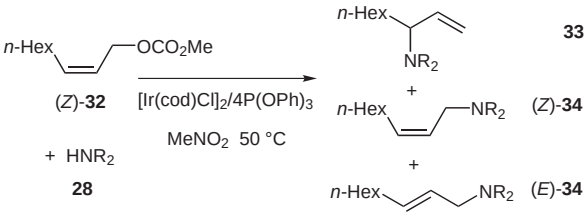
Allylic amination of *(Z)*-2-alkenyl carbonate was examined. Palladium complex-catalyzed allylic amination of *(Z)*-2-alkenyl acetate gave *E*-linear allylic amine, since the *anti* π-allyl palladium intermediate easily isomerized to a *syn* π-allyl palladium intermediate prior to nucleophilic attack by an amine. The retention of *Z* stereochemistry in the palladium complex-catalyzed allylic amination of *(Z)*-2-alkenyl esters has been difficult to achieve.[39] We developed *Z*-selective allylic alkylation of *(Z)*-2-alkenyl acetates.[16b,c] Extending this methodology, we achieved the first complete retention of *Z*-stereochemistry in allylic amination.[32] First, we examined the reaction of *(Z)*-**32** with **28a** in the presence of a catalytic amount of $[Ir(cod)Cl]_2$ and $P(OPh)_3$ (Ir atom 4 mol%, P/Ir = 2) under refluxing EtOH. The selectivity of *(Z)*-**34a** was unsatisfactory (Scheme 20). We then examined the reaction of *(E)*-**27** with **28a** in various solvents (Scheme 15), and found that the reaction in $MeNO_2$ is more linear amine-selective than that in EtOH. The reaction of *(Z)*-**32** with **28a** in $MeNO_2$ gave *(Z)*-**34a** in 94% selectivity. The solvent of choice was $MeNO_2$.



$MeNO_2$	50 °C	16 h	Yield 87%	**33a** : (*Z*)-**34a** : (*E*)-**34a** = 6 : 94 : 0
EtOH	reflux	2 h	Yield 93%	**33a** : (*Z*)-**34a** : (*E*)-**34a** = 12 : 88 : 0
acetone	reflux	47 h	Yield 82%	**33a** : (*Z*)-**34a** : (*E*)-**34a** = 9 : 91 : 0
THF	reflux	24 h	Yield 14%	**33a** : (*Z*)-**34a** : (*E*)-**34a** = 8 : 92 : 0
CH_2Cl_2	reflux	24 h	Yield 65%	**33a** : (*Z*)-**34a** : (*E*)-**34a** = 7 : 93 : 0

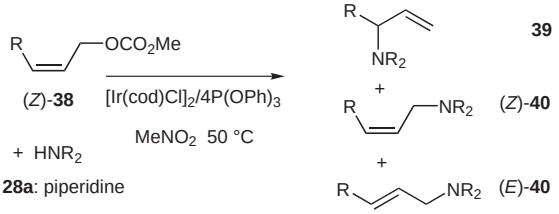
Scheme 20

The reaction of *(Z)*-**32** with various amines in $MeNO_2$ gave *Z*-linear allylic amines in selectivities of 97–79% (Scheme 21). No *E*-isomer was obtained in any of the cases. In contrast to the results obtained with secondary amines, the yield was decreased in the reaction of *(Z)*-**32** with butylamine (**28e**). Carbonates *(Z)*-**38a–c** were successfully reacted with piperidine (**28a**) to give *(Z)*-**40a–c** in selectivities of 92–99% (Scheme 22). No *E*-isomer was obtained. We achieved the complete retention of *Z*-stereochemistry in allylic amination.



28b: pyrrolidine	Yield 80%	**33b** : (*Z*)-**34b** : (*E*)-**34b** = 6 : 94 : 0
28c: morpholine	Yield 80%	**33c** : (*Z*)-**34c** : (*E*)-**34c** = 12 : 88 : 0
28e: *n*-butylamine	Yield 56%	**33e** : (*Z*)-**34e** : (*E*)-**34e** = 21 : 79 : 0
28f: diethylamine	Yield 69%	**33f** : (*Z*)-**34f** : (*E*)-**34f** = 3 : 97 : 0

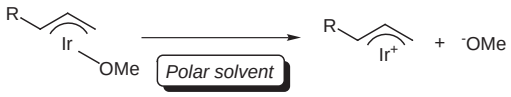
Scheme 21



(*Z*)-**38a**: R=*n*-Oct	Yield 86%	**39a** : (*Z*)-**40a** : (*E*)-**40a** = 6 : 94 : 0
(*Z*)-**38b**: R=$Ph(CH_2)_3$	Yield 89%	**39b** : (*Z*)-**40b** : (*E*)-**40b** = 8 : 92 : 0
(*Z*)-**38c**: *n*-$BuOCH_2$	Yield 95%	**39c** : (*Z*)-**40c** : (*E*)-**40c** = 1 : 99 : 0

Scheme 22

In this allylic amination, the use of a polar solvent such as EtOH or $MeNO_2$ is essential to obtain a product in high yield. This effect of a polar solvent may be explained as follows. A neutral π-allyl Ir intermediate formed by oxidative addition of an allylic carbonate can dissociate methoxide with the aid of a polar solvent to give a cationic π-allyl Ir intermediate (Scheme 23). Since a cationic π-allyl intermediate is more reactive to a nucleophile than a neutral π-allyl intermediate, the reaction in a polar solvent increases the yield of an amination product. If this hypothesis is correct, methoxide will be formed by dissociation from a neutral π-allyl Ir intermediate. Thus, allylic alkylation with diethyl malonate in EtOH may give an alkylation product without using a base. To test this hypothesis, we examined the reaction of *(E)*-**27** with diethyl malonate in the presence of a catalytic amount of $[Ir(cod)Cl]_2$ and $P(OPh)_3$ (Ir atom 4 mol%, P/Ir = 2) under refluxing EtOH for 24 hours. No alkylation product was obtained. The starting material was recovered in quantitative yield. This



Scheme 23

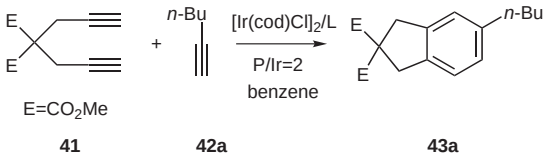
result strongly suggests that a π-allyl Ir intermediate is neutral and does not dissociate methoxide.

When the substrate and nucleophile in an S_N2 reaction are both neutral, the charge density in the transition state is greater than that of the initial reactants. A polar solvent can stabilize the transition state to enhance an S_N2 reaction.[40] It is well known that oxidative addition to a low-valent transition metal complex proceeds via an S_N2-type mechanism. Oxidative addition to an Ir (+1) complex in a polar solvent, were reported to be enhanced by stabilization of the transition state.[41] Due to this solvent effect, oxidative addition in this reaction might be enhanced. Furthermore, a polar solvent plays an important role in the nucleophilic attack by an amine to a π-allyl Ir intermediate. As described above, a π-allyl Ir intermediate generated in this reaction is a neutral species. The transition state of the nucleophilic attack is more polar than the initial reactants. As a consequence, nucleophilic attack by an amine to a π-allyl Ir intermediate is also enhanced by a polar solvent. Thus, this allylic amination in a polar solvent is enhanced to give an amination product in high yield.

4 [2+2+2]Cycloaddition of α,ω-Diynes with Monoynes

The transition metal complex-catalyzed synthetic transformation of alkynes has been studied extensively. From the standpoint of atom economy, dimerization, and cyclotrimerization are particularly important. Vollhardt enhanced the synthetic value of the cyclotrimerization of alkynes by using α,ω-diyne as one component and a monoyne as the other component.[42] Several transition metal complexes such as those of Co,[42] Ni,[43] Rh,[44] Pd[45] and Ru[46] have been reported to be catalysts for this reaction. However, new catalysts are still needed to expand the reaction scope and selectivity. Collman et al. first prepared an iridiacyclopentadiene complex by reacting $IrCl(N_2)(PPh_3)_2$ with dimethyl acetylenedicarboxylate and found that an iridacyclopentadiene complex was a potential catalyst for the cyclotrimerization of alkynes.[47] However, this chemistry has not yet been developed. We first found that $[Ir(cod)Cl]_2$ combined with dppe was an efficient catalyst for the [2+2+2] cycloaddition of α,ω-diynes with monoynes to give polysubstituted benzene derivatives.[48]

Diyne **41** reacted with 1-hexyne (**42a**) to give an indane derivative **43a** in the presence of a catalytic amount of $[Ir(cod)Cl]_2$ (Ir atom 4 mol%). The catalytic activity depended on the ligand used (Scheme 24). Dppe was found to be the most efficient ligand. When dppe was used as a ligand, diyne **41** reacted with **42a** at room temperature to give **43a** in 84% yield. Although $P(OPh)_3$ was an efficient ligand for $[Ir(cod)Cl]_2$-catalyzed allylic substitution,[16,19,32] $P(OPh)_3$ was a less efficient ligand than dppe for [2+2+2] cycloaddition.



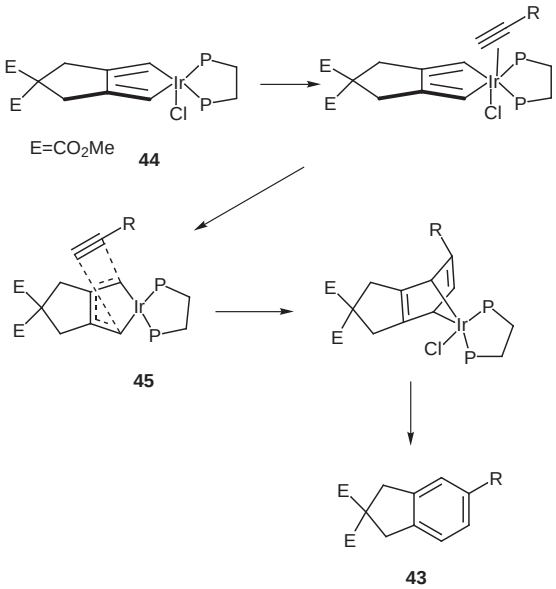
41 **42a** **43a**

PPh_3	50 °C 24 h	Yield 45%
$Ph_2PCH_2PPh_2$	50 °C 24 h	Yield 45%
$Ph_2P(CH_2)_2PPh_2$	rt 20 min	Yield 84%
$Ph_2P(CH_2)_3PPh_2$	50 °C 24 h	Yield 68%
$P(OPh)_3$	reflux 24 h	Yield 12%

Scheme 24

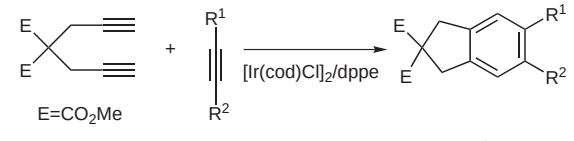
The reaction mechanism may involve the formation of an iridacyclopentadiene complex as an intermediate (Scheme 25). The reaction of $[Ir(cod)Cl]_2$ with dppe gives a mononuclear species Ir(cod)Cl(dppe). Oxidative cyclization of diynes with Ir(cod)Cl(dppe) would give an iridiacyclopentadiene **44**. The reaction of **44** with a monoyne by insertion or a Diels–Alder type process[49] followed by reductive elimination gives a final product **43**. Bidentate coordination of dppe produces a vacant coordination site above the plane of an iridiacyclopentadiene **44**. Coordination of a monoyne to this position would facilitate a Diels–Alder type process via transition state **45**. Among bidentate ligands, dppe might give the most stable chelation. This may explain the efficiency of dppe.

It is important to note that this cycloaddition can tolerate various functional groups. Diyne **41** reacted with various

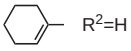


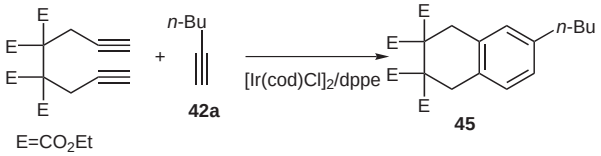
Scheme 25

functionalized monoynes to give indane derivatives in good to excellent yields (Scheme 26). The optimal reaction conditions depended on the monoyne component used. Diyne **41** reacted with 1-hexyne (**42a**), 1-decyne (**42b**), 5-phenyl-1-pentyne (**42c**) and 5-chloro-1-pentyne (**42d**) at room temperature. The reaction with phenylacetylene (**42e**), propargylic alcohol (**42f**), propargylic ether (**42g**) and conjugated enyne (**42h**) required more drastic conditions. Interestingly, the reaction with *N*,*N*-dimethylpropargylic amine (**42i**) gave **43i** in 65% yield. The reaction of α,ω-diyne with **42i** has been reported to require a stoichiometric amount of a Ni(0) complex.[50] 1,7-Diyne (**44**) and dipropargyl ether (**46**) could be used for this [2+2+2] cycloaddition (Scheme 26).



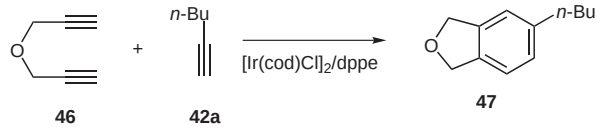
41 **42** **43**

42b: R^1=*n*-Oct R^2=H	rt 20 min	Yield 82%
42c: R^1=Ph$(CH_2)_3$ R^2=H	rt 1 h	Yield 81%
42d: R^1=Cl$(CH_2)_3$ R^2=H	rt 30 min	Yield 86%
42e: R^1=Ph R^2=H	dioxane reflux 2 h	Yield 83%
42f: R^1=CH_2OH R^2=H	dioxane reflux 8 h	Yield 85%
42g: R^1=CH_2OMe R^2=H	benzene reflux 10 h	Yield 66%
42h: R^1=  R^2=H	benzene reflux 6 h	Yield 65%
42i: R^1=CH_2NMe_2 R^2=H	dioxane reflux 2 h	Yield 65%



44 **42a** **45**

benzene reflux 2 h Yield 53%



46 **42a** **47**

benzene 50 °C 1 h Yield 63%

Scheme 26

5 Conclusion

We found that an iridium complex is an efficient catalyst for carbon-carbon and carbon-heteroatom bond formation. In the chemical industry, the importance of iridium continues to increase. Iridium-catalyzed methanol carbonylation is now a commercial process.[51] This new process offers significant improvements over the rhodium-catalyzed process, and is a good example of practical iridium chemistry.

It is well known that the choice of a ligand is important for transition metal complex-catalyzed reactions. This is also true for iridium complex-catalyzed reactions. In addition, an important consideration when using an iridium complex for organic synthesis is the choice of a solvent. Most iridium catalyst precursors are iridium (+1) complexes. The catalytic cycle is iridium (+1) ⇆ iridium (+3). The substrate oxidatively adds to an iridium complex to give an iridium (+3) complex. The bond-forming reaction occurs with the iridium (+3) complex. The product is then reductively eliminated from iridium (+3) complex to regenerate iridium (+1) complex. An iridium (+3) complex has six coordination sites. Ligand as well as solvent can coordinate to the iridium center. Weakly coordinated solvent can sometimes considerably affect the catalytic activity. To optimize the reaction conditions, we should try various solvents.

As described above, the chemistry of π-allyl iridium intermediate and iridiacyclopentadiene can be quite useful in organic synthesis. It is important to note that the selectivities of allylic substitution described here have not been achieved in previous studies with other transition metal complexes. An iridium complex is potentially useful as a catalyst for carbon-carbon and carbon-heteroatom bond formation. In fact, many useful reactions catalyzed by an iridium complex have been reported since our report in 1997.[52]

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