Iridium-Catalyzed Reactions Involving Transfer Hydrogenation, Addition, N-Heterocyclization, and Alkylation Using Alcohols and Diols as Key Substrates

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Abstract: This account gives an overview of iridium-catalyzed reactions developed by our group using mainly alcohols and diols as substrates. In the presented reactions, the iridium catalyst serves as a hydrogen acceptor from the alcohols giving iridium hydride, which is a key transient species. Herein, we report hydrogenation, alkylation, esterification, N-heterocyclization, and coupling reactions using alcohols and diols as reagents.

1 Introduction

Since the discovery of Crabtree’s cationic iridium complex [Ir(cod)(py)(PCy₃)₂]^+ (cod = cycloocta-1,5-diene, py = pyridine, Cy = cyclohexyl), which was found to be a very active catalyst for the hydrogenation of tetrasubstituted amidoalkenes,¹ various organoiridium complexes have been widely employed in catalytic hydrogenations of alkenes.²⁻⁴ The effectiveness of iridium catalysts has been successfully extended to transfer hydrogenation using alcohols, and their catalytic performance has attracted much attention. The reaction involves hydrogen transfer from the alcohol to the iridium center to form an iridium hydride species as the key intermediate. Subsequently, the hydrogen atom of the resulting iridium hydride transfers to another hydrogen acceptor. Thus, the creation of various novel catalytic systems can be realized using alcohols as substrates. To date, various review papers regarding iridium- and ruthenium-catalyzed transfer hydrogenation reactions have been published.⁹⁻¹⁸ In this account, we summarize our recent research on iridium-catalyzed transformations using alcohols and diols involving transfer hydrogenation which include hydrogenation, alkylation, esterification, N-heterocyclization, and coupling reactions.

2 Hydrogenation of α,β-Unsaturated Carbonyl Compounds and Alkenes

The reduction of the carbonyl group of α,β-unsaturated carbonyl compounds to give allylic alcohols using alcohols as a hydrogen source has been well studied.¹⁹⁻²⁷ In contrast, limited examples have been reported on the chemoselective reduction of the alkenic double bond of conjugated enones through transfer hydrogenation from alcohols.²⁸⁻³¹ We found that the [Ir(cod)Cl]₂/dppp/cesium carbonate (Cs₂CO₃) [dppp = 1,3-bis(diphenylphosphino)propane] system serves as an efficient catalyst for the reduction of α,β-unsaturated carbonyl compounds using propan-2-ol as a hydrogen source.³² Thus, the treatment of 4-phenylbut-3-en-2-one (1) (0.5 mmol) with propan-2-ol (2) (5 mmol) under the influence of a catalytic amount of [Ir(cod)Cl]₂ (2 mol%), dppp (2 mol%), and Cs₂CO₃ (2 mol%) in toluene (0.5 mL) at 80 °C for 4 hours gave 4-phenylbutan-2-one (3) with 100% selectivity and 93% conversion (Scheme 1).

Scheme 1

Table 1 summarizes the results for the hydrogenation of various α,β-unsaturated carbonyl compounds using the [IrCl(cod)]₂/dppp/Cs₂CO₃ system. A variety of α,β-unsat-
urated ketones were selectively reduced at the carbon–carbon double bond giving the corresponding saturated ketones in good to excellent yields (entries 1–6). The [IrCl(cod)]2/dppp/Cs2CO3 system was also found to promote the hydrogenation of simple alkenes. For example, styrene was hydrogenated to give ethylbenzene in excellent yield (entry 7).

Spogliarich and co-workers reported a detailed study of the hydrogenation reaction of α,β-unsaturated carbonyl compounds, and the chemoselectivity of the hydrogenation was found to be dependent on the steric properties of the phosphine used, as evidenced by solution NMR spectroscopy.32,33 The authors reported that an [IrH5(PR3)2] species was formed in the presence of bulkier phosphines under a hydrogen atmosphere and this complex was found to function as the catalyst for the selective hydrogenation of the carbon–carbon double bond. On the other hand, in the presence of less-bulky phosphines, such as diethyl(phenyl)phosphine, **3-**IrH5(PR3)2 was formed and catalyzed the reduction of the carbonyl group exclusively.33 Furthermore, Tani et al. reported that simple alkynes and alkenes were reduced by a hydrido(methoxy)iridium complex prepared from [Ir(bbbp)Cl], [bbbp = 2,2'-bis(diphenylphosphino)-1,1'-biphenyl] with methanol.34 These results suggest that an iridium hydride complex is formed during the course of our reaction.

Thus, the reaction may be initiated by the coordination of an iridium hydride complex, generated in situ from the [IrCl(cod)]2/dppp complex and propan-2-ol in the presence of Cs2CO3, to the α,β-unsaturated carbonyl compound, followed by hydrogen transfer to the conjugated double bond to give the saturated carbonyl compound.

### 3 Synthesis of Vinyl and Allyl Ethers

Vinyl ethers are important raw materials in the production of glutaraldehyde,35-38 as well as vinyl polymeric materials37 containing oxygen, and are expected to degrade easily in nature. Vinyl ethers are prepared practically by the reaction of acetylene with alcohols under severe conditions at high pressures (2–5 MPa) and temperatures (180–200 °C) in the presence of potassium hydroxide (KOH) as a catalyst (Reppe process).38 We found that the [IrCl(cod)]2 catalyst promotes efficiently a new type of exchange reaction between vinyl acetate (4) and alcohols 5, including phenols, leading to the corresponding vinyl ethers 6 (Scheme 2).39 Usually, the acid-catalyzed exchange reaction between alcohols and vinyl acetate results in alkyl acetates, along with the formation of acetaldehyde, which is derived readily by isomerization from vinyl alcohol.

### Biographical Sketches

**Yasushi Obora** was born in 1969 in Shizuoka, Japan, and received his B.Sc. (1991) and Ph.D. degrees (1995) from Gifu University. After working as a post-doctoral fellow (1995–1997) at Northwestern University, USA, with Professor T. J. Marks, he moved to the National Institute of Materials and Chemical Research, AIST, Japan (1997–1999). In 1999, he joined the research group of Professor Yasushi Tsuji at the Catalysis Research Center, Hokkaido University, as Research Associate. In 2006, he was appointed to the position of Associate Professor at Kansai University. He received the Shionogi Award in Synthetic Organic Chemistry, Japan, in 2007. His current research interests include the development of new homogeneous catalysis and organometallic chemistry.

**Yasutaka Ishii** was born in Osaka, Japan, in 1941. He received his B.A. (1964) and M.S. degrees (1967) from Kansai University. In 1967, he was appointed Assistant Professor at Kansai University. In 1971, he received his Ph.D. degree working under the supervision of Professor Masaya Ogawa. He was a postdoctoral fellow working with Professor Louis S. Hegedus at Colorado State University, USA, between 1980 and 1981. In 1990, he was appointed to full Professor at Kansai University. Since 2009, he has been Emeritus Professor at Kansai University. He received the Japan Petroleum Institute Award for Distinguished Papers in 1984, the Divisional Award (Organic Synthesis) of the Chemical Society of Japan in 1999, the Award of Synthetic Organic Chemistry, Japan, in 1999, the Award of the Japan Petroleum Institute in 2002, the Green and Sustainable Chemistry Award: Minister of Education, Sports, Culture, Science and Technology Prize in 2003, and the Chemical Society of Japan Award for Technical Development in 2004. His current research interests include the development of practical oxidation reactions using molecular oxygen and hydrogen peroxide, homogeneous catalysis, petrochemistry, and organometallic chemistry directed toward organic synthesis.
The following is a typical iridium-catalyzed reaction: vinyl acetate (2 mmol) was allowed to react with octan-1-ol (1 mmol) in the presence of \([\text{IrCl}(\text{cod})_2]\) (0.01 mmol, 1 mol%) and sodium carbonate (Na\(_2\)CO\(_3\)) (0.6 mmol) in toluene (1 mL) at 100 °C for 2 hours, giving \(\text{n-Octyl vinyl ether}\) in almost quantitative yield. It is noteworthy that the iridium-catalyzed reaction stopped at the stage of vinyl ether formation, while in the palladium-catalyzed version, the vinyl ethers formed would tend to react further with an additional alcohol to give acetals rather than vinyl ethers.\(^4\)

Under the optimized reaction conditions, a wide variety of vinyl ether derivatives could be synthesized using this iridium-catalyzed method (Figure 1). This catalytic vinylolation system was found to be applicable to the general synthesis of vinyl ethers from secondary and tertiary alcohols.

To obtain further mechanistic insight, phenol-\(d\) was allowed to react with vinyl acetate under these conditions. As a result, no deuterium incorporation was observed in the resulting phenyl vinyl ether. This suggests that the reaction pathway may proceed via intermediate 8, which results from the reaction of \([\text{IrCl}(\text{cod})_2]\), vinyl acetate (4), and alcohol 5 under the influence of Na\(_2\)CO\(_3\) (Scheme 3). Release of alkyl vinyl ether 6 from intermediate 8 gives rise to acetoxoiridium complex 9, which then reacts with alcohol 5, leading to alkoxyiridium complex 10. Subsequent coordination of vinyl acetate (4) to complex 10 followed by insertion regenerates 8.

### Table 1
Transfer Hydrogenation of Various \(\alpha,\beta\)-Unsaturated Carboxyl Compounds and Alkenes Catalyzed by \([\text{Ir(cod)Cl}]_2\)^a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Conversion (%)</th>
<th>Selectivity (%)</th>
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<td></td>
<td></td>
<td>99</td>
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<td>9</td>
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<td>64</td>
<td>84</td>
</tr>
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</table>

\(^a\) The substrate (0.5 mmol) was allowed to react with propan-2-ol (5.0 mmol) in the presence of a catalytic amount of \([\text{IrCl}(\text{cod})_2]\) (0.01 mmol, 2 mol%), dppp (0.01 mmol, 2 mol%), and Cs\(_2\)CO\(_3\) (0.01 mmol, 2 mol%) in toluene (0.5 mL) at 80 °C for 4 h.

\(^b\) Using \([\text{IrCl}(\text{cod})_2]\) (1 mol%), dppp (1 mol%), and Cs\(_2\)CO\(_3\) (1 mol%).

\(^c\) Using Cs\(_2\)CO\(_3\) (1 mol%).

\(^d\) After 15 h.

\(^e\) Using \([\text{Ir(cod)Cl}]_2\) (4 mol%), dppp (4 mol%), and Cs\(_2\)CO\(_3\) (4 mol%).
This method could be extended to the synthesis of alkyl allyl ethers from alcohols and allyl acetate. Thus, iridium cationic complex \([\text{Ir(cod)}_2]^+\text{BF}_4^–\) catalyzed the allylation of alcohols 11 with allyl acetate 12 to afford allyl ethers 13 (Scheme 4).\(^{41}\) Allyl ethers are important compounds and are frequently used as monomers for the production of polymeric materials and as starting materials for Claisen rearrangements.\(^{42,43}\) The above protocol allows the synthesis of allyl ethers from allyl acetates and simple alcohols.

\[
\begin{align*}
\text{ROH} + \text{O} & \xrightarrow{[\text{Ir(cod)}_2]^+\text{BF}_4^– (\text{cat.})} \text{toluene, 100 °C} \quad \text{RO} - \text{O} \text{13} \\
\end{align*}
\]

Scheme 4

For instance, the reaction of allyl acetate with octan-1-ol in the presence of a catalytic amount of \([\text{Ir(cod)}_2]^+\text{BF}_4^–\) afforded allyl n-octyl ether in quantitative yield. Allyl carboxylates were also prepared in good yields by the exchange reaction between carboxylic acids and allyl acetate.

On the basis of these results, a variety of alcohol derivatives were allowed to react with allyl acetate under similar conditions to give the corresponding products as shown in Figure 2.

\[
\begin{align*}
\text{MeO} & \quad 93% \\
\text{98} & \quad 82% \\
\text{O} & \quad 85% \\
\text{O} & \quad 89% \\
\end{align*}
\]

Figure 2

The reaction would proceed via the formation of a \(\pi\)-allyliridium complex, followed by nucleophilic attack of the alcohol (Scheme 5).

\[
\begin{align*}
\text{O} & \xrightarrow{\text{LnIr}} \text{RO} - \text{O} \\
\end{align*}
\]

Scheme 5

4 Synthesis of \(\gamma,\delta\)-Unsaturated Carbonyl Compounds

We previously reported the rearrangement of allyl homoallyl ethers to \(\gamma,\delta\)-unsaturated aldehydes induced by the \([\text{IrCl(cod)}]_2\) complex.\(^{44}\) Alternatively, allyl vinyl ethers can be directly prepared by the vinylation of allylic alcohols with vinyl acetate, providing the start of a very attractive route to \(\gamma,\delta\)-unsaturated carbonyl compounds because allylic alcohols are easily prepared. The one-pot synthesis of \(\gamma,\delta\)-unsaturated carbonyl compounds from allylic alcohols and vinyl or isopropenyl acetate was achieved using the \([\text{IrCl(cod)}]_2\) catalyst. The reaction proceeds via in situ-generated allyl vinyl ethers, e.g. intermediate 16 (Scheme 6), followed by Claisen rearrangement of the resulting ether.\(^{45}\)

Thus, the reaction of trans-2-methyl-3-phenylprop-2-en-1-ol (14) (0.5 mmol) with isopropenyl acetate (15) (6 mmol) in the presence of \([\text{IrCl(cod)}]_2\) (2 mol%) and Cs\(_2\)CO\(_3\) (5 mol%) at 100 °C for 3 hours, followed by the reaction at 140 °C for 15 hours, afforded 5-methyl-4-phenylhex-5-en-2-one (17) in 83% yield (Scheme 6).

Transfer isopropenylation of alcohol 14 with substrate 15 is induced by the \([\text{IrCl(cod)}]_2\) complex to afford ether 16, followed by Claisen rearrangement to give \(\gamma,\delta\)-unsaturated carbonyl compound 17.\(^{44}\)

5 \(\alpha\)-Alkylation Using Alcohols and Diols as Alkylating Agents

5.1 \(\alpha\)-Alkylation of Methyl Ketones

The \(\alpha\)-alkylation of enolates derived from ketones with alkyl halides is an important and frequently used method for forming new carbon–carbon bonds in organic synthesis.\(^{46}\) However, the main disadvantage of this methodology is the formation of undesirable waste salts. If the \(\alpha\)-alkylation of enolates derived from ketones with alkyl halides could be replaced by the direct reaction of ketones with alcohols, this method would provide a very useful waste-free and environmentally benign route to \(\alpha\)-alkylation.

We found that the \([\text{IrCl(cod)}]_2\) complex combined with triphenylphosphine (Ph\(_3\)P) and KOH efficiently catalyzed the selective \(\alpha\)-alkylation of ketones with alcohols.\(^{47}\) Because alcohols are employed as the alkyl source, this methodology provides an efficient, clean route to \(\alpha\)-alkylated ketones from methyl ketones without the formation of any waste products other than water. For instance, the reaction of octan-2-one (18) (2 mmol) with butan-1-ol (19) (4 mmol) in the presence of \([\text{IrCl(cod)}]_2\) (0.02 mmol), Ph\(_3\)P (0.04 mmol), and KOH (0.2 mmol) at 100 °C for 4
hours without any solvent afforded dodecan-6-one (20) in 80% yield (Scheme 7). It is noteworthy that the alkylation proceeded with complete regioselectivity at the less-hindered side of octan-2-one, namely at the methyl group; the regioselectivity of the conventional alkylation of enolates with halides is very difficult to control, producing usually the α- and α'-alkylated products. The reaction is promoted by only a catalytic quantity of a base, such as KOH, in the absence of both a hydrogen acceptor and a solvent.

**Scheme 7**

It is thought that the above reaction is a novel route to various aliphatic ketones, which are obtained in mainly high yields by selecting the ketones and alcohols employed (Figure 3).

**Figure 3**

Our strategy was successfully extended to the reaction between ketones and α,ω-diols which provides a very convenient synthetic tool for preparing ω-hydroxy ketones and diketones.48 The selectivity to give ω-hydroxy ketones by monoalkylation or diketones by double alkylation was found to be controlled by varying the starting ratio of methyl ketone to α,ω-diol.

The following is a typical example of the synthesis of diketones: the reaction of acetophenone (21) (10 mmol) with hexane-1,6-diol (22) (2 mmol) in the presence of [IrCl(cod)]2 (0.1 mmol, 5 mol%), Ph3P (0.4 mmol, 20 mol%), and KOH (0.4 mmol) without any solvent at 100 °C for 15 hours gave the double-alkylation product 1,10-diphenyldecane-1,10-dione (23) in 86% isolated yield (Scheme 8), along with a small amount of the aldol condensate of 21, 1,3-diphenylbut-2-en-1-one (10%).

On the basis of the above result, several methyl ketones were reacted with various α,ω-diols under these conditions, giving the corresponding diketones in high yields (Figure 4).

**Figure 4**

As mentioned above, by varying the starting ratio of methyl ketone to α,ω-diol, ω-hydroxy ketones could also be obtained with high selectivity. Thus, the reaction of methyl ketones with excess α,ω-diols provided ω-hydroxy ketones using the same protocol as above. As a typical example, acetophenone (21) (2 mmol) was allowed to react with 4 equivalents of hexane-1,6-diol (22) (8 mmol) under the influence of [IrCl(cod)]2 (0.05 mmol), Ph3P (0.2 mmol), and KOH (0.2 mmol) in 1,4-dioxane (1.0 mL) at 100 °C for 15 hours to give selectively ω-hydroxy ketone 24 in high yield (87%) (Scheme 9). The formation of diketone 23 under these conditions was suppressed to 5% yield. In spite of the use of excess α,ω-diol 22, which serves as a hydrogen donor to 21, the formation of the hydrogenation product 1-phenylethanol was in less than 3% yield.

**Scheme 9**

Because the reaction using excess α,ω-diols results in viscous liquids that are difficult to stir magnetically, the reaction to prepare some ω-hydroxy ketones was carried out using a solvent, such as 1,4-dioxane.
Under these conditions, the reaction of methyl ketones with various aliphatic α,ω-diols afforded the corresponding ω-hydroxy ketones in good to excellent yields (Figure 5). Because this type of compound is difficult generally to prepare by a one-step reaction, this strategy gives a simple direct approach to ω-hydroxy ketones.

The above method was successfully applied to the double alkylation of acetone with α,ω-diols, resulting in a novel synthetic tool for producing α,ω-dimethyl diketones. Diketones such as hexadecane-2,15-dione (HDDO) are one of the attractive precursors of macrocyclic musks. Thus, the reaction of acetone (25) (10 mmol) with decane-1,10-diol (26) (1 mmol) in the presence of [IrCl(cod)]₂ (0.05 mmol) combined with Ph₃P (0.15 mmol) and KOH (0.4 mmol) in toluene (0.5 mL) at 100 °C for 2 hours resulted in HDDO (27) in 90% yield (Scheme 10). Under these reaction conditions, no monoalkylated product, i.e. 13-hydroxytridecan-2-one, was detected.

To obtain information on the pathway of the α-alkylation reaction, the alkylation of acetophenone (21) (1 mmol) with butan-1-ol-d₉ (C₄D₉OH) (33) (4 mmol) was examined under the conditions shown in Scheme 12. As a result, the ¹H NMR spectrum showed that a 63:37 mixture of deuterium-incorporated 1-phenylhexan-1-one-d₉ 34 and 35 was formed. The formation of these deuterated compounds is rationally explained by the following reaction pathway involving the generation of an iridium dihydride as a key intermediate (Scheme 13).

### Scheme 10

![Scheme 10](image)

### Scheme 11

![Scheme 11](image)

### Scheme 12

![Scheme 12](image)

### Scheme 13

![Scheme 13](image)
The iridium complex \((\text{LnIr})\) is subjected to oxidative addition by \(\text{C}_6\text{D}_6\text{OH}\ (33)\), followed by \(\beta\)-hydride elimination to give butanal-\(d_6\) (36) and \(\text{LnIr}d_6\). Under the basic conditions, the deuterium atoms at the \(\alpha\)-position of intermediate 36 may undergo rapid proton–deuterium exchange with \(\text{C}_6\text{D}_6\text{OH}\ (33)\), via enolate formation, to give eventually butanal-\(d_6\) (37). Aldol condensation with the ketone, i.e. acetoephone (21), forms 1-phenylhex-2-en-1-one-\(d_6\) (38), followed by hydrogenation with \(\text{LnIr}d_6\) to lead to deuterated products 34 and 35. Deuterium exchange at the \(\alpha\)-position of the resulting compound 35 with formed water and/or butanol seems to contribute to the preferential formation of 34 rather than 35.

5.2 \(\alpha\)-Alkylation of Arylacetonitriles

Grigg and co-workers reported the \(\alpha\)-monoalkylation of arylacetonitriles with alcohols using \([\text{Cp}^\#\text{IrCl}_2]\) (\(\text{Cp}^\#\) = pentamethylcyclopentadienyl) in the presence of \(\text{KOH}\).\(^{51}\) We successfully extended this strategy to the double alkylation of ary lacetonitriles with \(\alpha,\alpha\)-diols.\(^{58}\)

For instance, phenylacetonitrile (39) (10 mmol) was allowed to react with pentane-1,5-diol (40) (2 mmol) in the presence of \([\text{Cp}^\#\text{IrCl}_2]\) (0.05 mmol, 5 mol%) and \(\text{Cs}_2\text{CO}_3\) (0.4 mmol) at 160 °C for 15 hours to afford the double-alkylation product 2,8-diphenylnonanenitrile (41) in 93% yield (Scheme 14). The reaction is highly chemoselective and no monoalkylation product was detected at all under these conditions.

![Scheme 14](image)

By reacting various ary lacetonitriles and \(\alpha,\alpha\)-diols in the presence of \([\text{Cp}^\#\text{IrCl}_2]\) catalyst combined with \(\text{Cs}_2\text{CO}_3\), the corresponding dialyl-containing dinitriles were obtained in moderate to excellent yields (Figure 7).

5.3 \(\alpha\)-Alkylation of Active Methylene Compounds

The iridium catalytic system is applicable to the \(\alpha\)-alkylation of active methylene compounds, such as alkyl cyanoacettes.\(^{52}\) As a typical example, \(n\)-butyl cyanoacetate (42) (1 mmol) was allowed to react with butan-1-ol (19) (2 mmol) in the presence of \([\text{IrCl(cod)}]\) (0.05 mmol, 5 mol%) and \(\text{Ph}_3\text{P}\) (0.2 mmol, 20 mol%) in \(p\)-xylene (1 mL) at 130 °C for 15 hours, giving \(n\)-butyl 2-cyanohe xanoate (43) in 96% yield (Scheme 15). The reaction afforded only the saturated alkyl cyanoacetate, although in the ruthenium-catalyzed reaction of alkyl cyanoacetates with aldehydes by Murahashi and co-workers, \((E)\)-\(\alpha,\beta\)-unsaturated nitriles were formed.\(^{53,54}\) In contrast to the above-mentioned \(\alpha\)-alkylation of methyl ketones with alcohols,
methods for the synthesis of CPDL from CPDA via intramolecular cyclization have been reported.\textsuperscript{56–58} The synthesis of CPDL (48) from 2-cyano-15-hydroxy-pentadecanoate (46) was carried out as follows: Substrate 46 was refluxed with KOH (4 equiv) in ethylene glycol for 6 hours to give CPDA (47) in 72% yield according to the literature method.\textsuperscript{59} Subsequently, CPDA (47) was allowed to react with a fluoroalkyl-containing distannoxane catalyst (Otera’s catalyst)\textsuperscript{60} in a mixed solvent of FC-72 and decane, employing Otera’s method for the synthesis of lactones,\textsuperscript{58} which led to CPDL (48) in 30% yield (Scheme 17).

![Scheme 17](image)

### 5.4 α-Alkylation of Acetates

Carboxylates are one of the most widely used organic compounds which are generally prepared by the coupling of ester enolate anions with alkyl halides or tosylates\textsuperscript{61} or by the reaction of silyl ketene acetals with alkyl halides in the presence of a Lewis acid.\textsuperscript{62–64} However, these methodologies result in the formation of undesired salts and side products.

We found that the α-alkylation of acetates with alcohols can be successfully performed in the presence of a base, e.g. potassium tert-butoxide (t-BuOK), under the influence of [IrCl(cod)]\textsubscript{2}.\textsuperscript{65} This method gives a convenient direct route to carboxylates by the environmentally clean alkylation of acetates using alcohols as alkylating agents.

As a typical example, the reaction of tert-butyl acetate (49) (10 mmol) with butan-1-ol (19) (1 mmol) was carried out in the presence of [IrCl(cod)]\textsubscript{2} (0.05 mmol, 5 mol%), Ph\textsubscript{3}P (0.15 mmol, 15 mol%), and t-BuOK (2 mmol) in tert-butyl alcohol (t-BuOH) (1 mL) at 100 °C for 15 hours to produce tert-butyl hexanoate (50) in 62% yield (Scheme 18).

It is noteworthy that n-butyl acetate, which would be obtained by ester exchange between acetate 48 and alcohol

![Scheme 18](image)
was not detected in the above reaction at all under these conditions. Here, the use of acetates that are reluctant to undergo the ester exchange (e.g., tert-butyl acetate) is important to achieve the desired alkylation reaction. In addition, the alkylation was markedly influenced by the base employed, and the use of 2 equivalents of t-BuOK based on alcohol 19 gave the best result.

Under these conditions, the α-alkylation of tert-butyl acetate with various primary alcohols afforded the corresponding tert-butyl carboxylates in good to excellent yields (Figure 11).

To elucidate the role of t-BuOH as the solvent, the reaction time-course of tert-butyl acetate (49) with alcohol 19 without the use of a solvent was compared with that in t-BuOH. The reaction without the solvent reached an equilibrium of tert-butyl hexanoate (50) and n-butyl acetate (51) at an early stage (within 1 h). This observation suggests that the alkylation of tert-butyl acetate (49) with butan-1-ol (19) and the ester-exchange reaction between acetate 49 and alcohol 19, producing n-butyl acetate (51), are competitively promoted. In contrast, in the reaction using t-BuOH as a solvent, the ester exchange was rapidly induced in 0.5 hours to form n-butyl acetate (51), which then gradually decreased with the increasing formation of product 50. This observation indicates that the ester exchange proceeds faster than the alkylation, and the resulting acetate 51 undergoes exchange with t-BuOH, which exists in excess as the solvent, to regenerate substrate 49, which then reacts with alcohol 19 to form tert-butyl hexanoate (50).

Indeed, the reaction of tert-butyl acetate (49) with n-butyl acetate (51) was carried out under these conditions and gave 50 in 70% yield (Scheme 19), which is a comparable result with that of the reaction of 49 with butan-1-ol (19) (74% yield, cf. Scheme 18). This finding shows that 51 undergoes the exchange reaction in t-BuOH to leave butan-1-ol (19), which subsequently serves as the alkylating agent of 49 leading to the desired product 50.

The reaction mechanism may be explained by the following pathway (Scheme 20): First, ester exchange between tert-butyl acetate (49) and alcohol 19 using t-BuOK occurs to generate n-butyl acetate (51), competing with the iridium-catalyzed dehydrogenation of 19 generating butanal and an iridium hydride complex. The resulting butanal of the latter reaction undergoes base-catalyzed aldol condensation with 49 to form an α,β-unsaturated ester, which then reacts with the iridium hydride to give product 50 and the iridium catalyst. Meanwhile, n-butyl acetate
This reaction was applied to the synthesis of a fragrant compound, ethylene brassylate (1,4-dioxacycloheptadecane-5,17-dione, Musk T) (55), which is currently manufactured on a large scale as a synthetic perfume with a musk odor.55,66–68 The reaction of tert-butyl acetate (49) (20 mmol) with nonane-1,9-diol (52) (1 mmol) under the above conditions gave di-tert-butyl tridecane-1,13-dioate (53). Subsequent hydrolysis of 53 to give dicarboxylic acid 54, followed by the reaction of 54 according to the reported method,56 led to product 55 in 17% yield (Scheme 21).

![Scheme 21](image)

### 6 β-Alkylation (Guerbet Reaction)

The Guerbet reaction is recognized as a useful synthetic tool for obtaining β-alkylated alcohols through the self-condensation/dimerization of primary alcohols, as exemplified by the conversion of butan-1-ol into 2-ethylhexan-1-ol.69 We found that the [Cp*IrCl2]2 and [IrCl(cod)]2 complexes were efficient catalysts of the Guerbet reaction of primary alcohols to afford β-alkylated alcohols.70 Several examples of iridium- and ruthenium-catalyzed Guerbet reactions of alcohols have also been reported.71,72

As an example of our method, the reaction of butan-1-ol (19) (2 mmol) in the presence of [Cp*IrCl2]2 (0.02 mmol, 1 mol%), KOH (0.8 mmol, 40 mol%), and octa-1,7-diene (0.2 mmol, 10 mol%) in p-xylene (0.5 mL) at 120 °C for 4 hours produced 2-ethylhexan-1-ol (56) in 93% yield (Scheme 22). In this reaction, the addition of a base and a small amount of a hydrogen acceptor (e.g., octa-1,7-diene) was needed. Among the iridium complexes used, [Cp*IrCl2]2 was found to give the best result, but other iridium complexes, such as [IrCl(cod)]2 and [Ir(OH)(cod)]2, also showed high catalytic activities. Needless to say, this reaction did not proceed without an iridium catalyst and a base.

A variety of primary alcohols have been shown to undergo the iridium-catalyzed Guerbet reaction under these conditions to give the corresponding condensed dimer alcohols in moderate to excellent yields (Figure 12). This method is an alternative direct route to β-alkylated primary alcohols, which are usually prepared by the aldol condensation of aldehydes, followed by hydrogenation.

![Figure 12](image)
The above iridium-catalyzed Guerbet reaction, exemplified by the conversion of ethanol (57) into butan-1-ol (19), can be rationally explained by the following sequential pathway (Scheme 24): First the iridium catalyst serves as a hydrogen acceptor from substrate 57 to give acetaldehyde and an iridium hydride species. Then, the formed aldehyde reacts via base-catalyzed aldol condensation to give crotonaldehyde and water. Finally, the unsaturated aldehyde undergoes selective hydrogenation by the iridium hydride complex to give the desired product.

Scheme 24

7 Oxidative Esterification

Esters are produced conventionally by the Fischer esterification of acids with alcohols or by the Tishchenko reaction of aldehydes. As an alternative method, the homogeneous catalytic transformation of primary alcohols into esters has been investigated using [Pd(OAc)₂], [Ru(CO)₁₂], and [RuH₂(PPh₃)₄] catalysts. Suzuki et al. and Williams and co-workers also reported the reaction of primary alcohols to give esters using (pentamethylcyclopentadienyl)iridium aminoalkoxide and [RuH₂(CO)(PPh₃)₃]/xantphos catalysts in the presence of a hydrogen acceptor, such as acetone. Here, we show our findings on the [IrCl(coe)₂] cathalysts in the presence of a hydrogen acceptor, such as butan-2-one and crotononitrile, respectively. Previously, we reported that [Cp₂ZrH₂] efficiently catalyzes the Tishchenko reaction of aldehydes to give esters through an alkoxylzirconium species, but not a hemiacetal. However, we propose that the above reaction passes through the formation of a hemiacetal as a transient intermediate because the [IrCl(coe)₂] complex did not catalyze the Tishchenko reaction of aldehydes alone in the absence of alcohols.

The above oxidative esterification should be carried out at 95 °C under open air conditions. Therefore, lower alcohols, such as ethanol, were difficult to convert into ethyl acetate using this method. Because ethyl acetate is a very important feedstock, the development of an efficient method to access ethyl acetate from ethanol is highly desired. We found that the oxidative dimerization of ethanol (57) to give ethyl acetate (62) proceeded smoothly at

Scheme 25
Synlett 2011, No. 1, 30–51 © Thieme Stuttgart · New York

**Table 2** Oxidative Dimerization of Primary Alcohols To Give Esters and Lactonization of a Diol To Give a Lactone Catalyzed by [IrCl(coe)₂]⁺

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>94</td>
</tr>
<tr>
<td>3ᵇ</td>
<td></td>
<td></td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>61</td>
</tr>
<tr>
<td>8ᶜ</td>
<td></td>
<td></td>
<td>88</td>
</tr>
</tbody>
</table>

ᵃ The alcohol (2 mmol) was allowed to react in the presence of [IrCl(coe)₂]⁺ (3 mol%) in open air at 95 °C for 15 h.
ᵇ After 20 h.
ᶜ The reaction was performed in the presence of Na₂CO₃ (5 mol%), Cy₃P (10 mol%), and toluene (1 mL).

The experimental procedure was as follows: a mixture of ethanol (57) (2 mmol) and acetone (1 mL, 13.6 mmol) was stirred in the presence of [Cp*IrCl₂]₂ (0.04 mmol, 2 mol%), 2-(methylamino)ethanol (0.12 mmol, 6 mol%), and Cs₂CO₃ (0.2 mmol, 10 mol%) at room temperature for 24 hours, giving ethyl acetate (62) in 85% yield with 96% selectivity.

The addition of a catalytic amount of 2-(methylamino)ethanol to [Cp*IrCl₂]₂ is indispensable to achieve the reaction. To elucidate the effect of 2-(methylamino)ethanol as an additive, the reaction of ethanol (57) catalyzed by [Cp*IrCl₂]₂ with several analogues was examined (Table 3). Like 2-(methylamino)ethanol, 2-(ethylamino)ethanol efficiently promoted the reaction (cf. entries 1 and 2). However, the yield of ethyl acetate (62) decreased with the increasing length of the alkyl group of the alkylamino moiety (entries 3 and 4), and the reaction involving the addition of 2-anilinoethanol or 2-aminoethanol was...
sluggish (entries 5 and 6, respectively). No reaction took place with ethane-1,2-diamine (entry 7).

Suzuki et al. reported that \([\text{Cp}^*\text{Ir(OCH}_2\text{CPh}_2\text{NH)}]\) is an efficient catalyst for the direct conversion of alcohols into esters.\(^8\) The above reaction employing 2-amino-2,2-diphenylethanol, prepared independently, and potassium carbonate as additives was found to give a comparable result to that using our system (Table 3, entry 8). This result suggests that a similar iridium aminoalkoxide complex would be formed, even in our catalytic system.

In addition, we tried the reaction on a multigram scale using alcohol \(57\) (2 g) and a lower amount of \([\text{Cp}^*\text{IrCl}_2]\) (0.5 mol%), 2-(methylamino)ethanol (1 mol%), and \(\text{Cs}_2\text{CO}_3\) (3 mol%) in acetone (5.5 mL) at room temperature for 48 hours; product \(62\) was obtained in high yield (1.53 g, 80% yield).

This method can be applied to the methyl esterification of ethanol using methanol. Under these conditions, ethanol \(57\) (2 mmol) was allowed to react in the presence of methanol \(63\) (10 mmol) to afford methyl acetate \(64\) in 82% yield along with the formation of ethyl acetate \(62\) in 6% yield (Scheme 28).

### Table 3 Effect of Additives on the Iridium-Catalyzed Oxidative Dimerization of Ethanol (57) To Give Ethyl Acetate (62)^a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>GC Yield (%)</th>
<th>Selectivity (%)^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeNH(CH_2)_2OH</td>
<td>85</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>EtNH(CH_2)_2OH</td>
<td>83</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>(n)-PrNH(CH_2)_2OH</td>
<td>73</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>(n)-BuNH(CH_2)_2OH</td>
<td>48</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>PhNHCH(H)_2OH</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>HNC_2H_5OH</td>
<td>16</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>HNC_2H_5NH_2</td>
<td>no reaction</td>
<td>–</td>
</tr>
<tr>
<td>8^c</td>
<td>HNCPh_2CH_2OH</td>
<td>82</td>
<td>93</td>
</tr>
</tbody>
</table>

\(^a\) Ethanol (2 mmol) was stirred in the presence of \([\text{Cp}^*\text{IrCl}_2]\) (2 mol%), the additive (6 mol%), and \(\text{Cs}_2\text{CO}_3\) (10 mol%) in acetone (1 mL) at r.t. for 24 h.

\(^b\) Selectivity based on \([\text{yield of } 62]/(\text{conversion of } 57)\) × 100.

\(^c\) Using \(\text{K}_2\text{CO}_3\) as the base.

### 8 N-Heterocyclization

#### 8.1 Synthesis of Quinolines from Amino Alcohols and Ketones

Nitrogen-containing aromatic compounds, such as quinolines, pyroles, and indoles, are very important substances in synthetic organic chemistry for the production of pharmaceuticals, herbicides, and dyes.\(^9\) For the synthesis of quinolines, the coupling of 2-aminobenzaldehyde with a ketone, namely the Friedländer reaction, is one of the most widely used methods because of its high selectivity to give the desired products.\(^9\) On the other hand, Friedländer-type reactions using 2-aminobenzyl alcohol are far more beneficial because the substrate is cheaper and more-stable than 2-aminobenzaldehyde. Therefore, several modified Friedländer reactions using 2-aminobenzyl alcohol have been reported.\(^9\)

Here, we report that our iridium-catalyzed transfer hydrogenation system can be applied to quinoline synthesis by the reaction of 2-aminobenzyl alcohol with ketones in the presence of small amounts of \([\text{IrCl(cod)}]\) and a base under solvent-free conditions (e.g., Scheme 29).\(^9\)

**Scheme 29**

Thus, treatment of 2-aminobenzyl alcohol \(65\) (2 mmol) with acetophenone \(21\) (4 mmol) in the presence of catalytic amounts of \([\text{IrCl(cod)}]\) \((0.02 \text{ mmol}, 1 \text{ mol%}), \text{Ph}_3\text{P} \text{ (0.08 mmol, 4 mol%)}, \text{and KOH (0.4 mmol, 20 mol%) at 100 °C for 3 hours without a solvent gave 2-phenylquinoline}\(66\) in 90% yield. In this reaction, 1 equivalent of ketone \(21\) was found to act as a hydrogen acceptor and was converted into 1-phenylethanol.

The iridium-catalyzed reaction of amino alcohol \(65\) with various ketones under the solvent-free conditions afforded the corresponding quinoline derivatives (Table 4).

In contrast to the reaction of 2-aminobenzyl alcohol \(65\) with ketones, the coupling reaction of benzyl alcohol \(67\) with cycloheptanone \(68\) failed to proceed selectively and led to a complex mixture (Scheme 30, cf. Table 4, entry 3). These results suggest that the quinoline may be synthesized via the formation of a ketimine, such as \(69\), obtained from 2-aminobenzyl alcohol and the ketone. Subsequent hydrogen transfer from the ketimine to an iri-
Iridium-Catalyzed Reactions Using Alcohols and Diols as Key Substrates

8.2 Synthesis of Benzimidole Derivatives from Naphthylamines and Diols

As an alternative methodology for the synthesis of quinoline and indole derivatives, the ruthenium-catalyzed N-cyclization of anilines with diols has been reported.\textsuperscript{99,100} We found that benzo[h]quinolines and benzimidole derivatives could be synthesized in high yields by the iridium-catalyzed direct cyclization of naphthylamines with 1,3- and 1,2-diols, respectively.\textsuperscript{101} As an example, using the preparation of benzo[h]quinoline, a mixture of 1-naphthylamine (75) (5 mmol) and propane-1,3-diol (76) (2 mmol) was allowed to react in the presence of IrCl\textsubscript{3}·3H\textsubscript{2}O (0.10 mmol), BINAP [BINAP = rac-2,2′-bis(diphenylphosphino)-1,1′-biphenyl] (0.15 mmol), and Na\textsubscript{2}CO\textsubscript{3} (0.16 mmol) under air at refluxing temperature (169 °C) in mesitylene for 15 hours, giving benzo[h]quinoline (77) in 96% isolated yield (Scheme 33). The reaction proceeded more rapidly under an oxygen atmosphere (1 atm) compared with that under air, whereas the reaction under nitrogen decreased the yield to 55%. These results indicate that the oxidation step is an important one in the reaction.

On the basis of these results, the reaction of 1-naphthylamine derivatives with propane-1,3-diol (76) was examined under the standard conditions (Table 5). Benzimidole derivatives were also synthesized from 1-naphthylamines with various 1,2-diols using the same strategy (Table 6). It is noteworthy that the reactions with naphthalene-1,5-diamine gave the monocyclization products, i.e. benzo[h]quinolin-7-amine (Table 5, entry 4) and 2,3-dimethyl-1H-benzo[g]indol-6-amine (Table 6, entry 8) were formed exclusively; the double cyclization products were not obtained.

The iridium-catalyzed quinoline synthesis from ketones and 2-aminobenzyl alcohols (Section 8.1)\textsuperscript{98} has been shown to proceed via the formation of imines, followed by hydrogenation by an iridium hydride generated during the reaction course to give cyclic amines (see Scheme 31). For the ruthenium(III) chloride catalyzed quinoline synthesis from aniline and a 1,3-diol reported by Tsuji et al.,\textsuperscript{100} the reaction path is proposed to proceed via the formation of 3-anilinopropan-1-ol (78) (Figure 13). No intramolecular cyclization of amino alcohol 78 takes place directly, but N,N′-diphenylpropane-1,3-diamine (79) may be formed from 78 and aniline. Then, the ruthenium-
catalyzed intermolecular cyclization of 79 with aniline forms quinoline.

To obtain more information regarding the reaction mechanism of our iridium-catalyzed benzo[h]quinoline synthesis, we prepared 3-(1-naphthylamino)propan-1-ol (80), and both the cyclization of 80 and the reaction of 80 with 1-naphthylamine (75) were performed under the influence of IrCl₃·3H₂O and BINAP (Schemes 34 and 35). In contrast to the above-mentioned ruthenium-catalyzed reaction of amino alcohol 78 in which the intramolecular cyclization of 78 to give quinoline does not occur, the iridium-catalyzed reaction of 80 produced benzo[h]quinoline (77) in 43% yield (Scheme 34). In addition, the reaction of amino alcohol 80 with 1-naphthylamine (75) led to product 77 in 72% yield, and substrate 75 was recovered in 19% (Scheme 35).

The product distribution of benzo[h]quinoline (77) derived from the intramolecular cyclization of amino alcohol 80 was found to be different from that derived from the reaction of 80 and 1-naphthylamine (75). These results suggest that the reaction mechanism for the formation of benzo[h]quinoline (77) in Scheme 34 is different from that of the reaction shown in Scheme 35.

Indeed, when the reaction of substrate 80 with amine 75 was performed under a lower reaction temperature (150 °C), the yield of 77 was only 3%, but N,N'-di-1-naphthylpropane-1,3-diamine (81) was obtained in 58% yield. This result suggests that diamine 81 is also a probable intermediate in our iridium-catalyzed reaction. Thus, diamine 81 was independently prepared and the reaction of substrate 81 was carried out under the same conditions to produce an approximately equimolar amount of product 77 in 76% yield and amine 75 in 83% yield (Scheme 36).

Table 5  Synthesis of Benzo[h]quinolines by the Reaction of Various Naphthylamines with Propane-1,3-diol (76) Using an IrCl₃/BINAP Catalyst

<table>
<thead>
<tr>
<th>Entry</th>
<th>Naphthylamine</th>
<th>Benzo[h]quinoline</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>MeO</td>
<td></td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>OMe</td>
<td></td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>59</td>
</tr>
</tbody>
</table>

In addition, to investigate the reactivity and selectivity of the diamine intermediates, N-1-naphthyl-N'-phenylpropane-1,3-diamine (82) was prepared and allowed to react under the above iridium-catalyzed conditions (Scheme 37). As a result, selective N-heterocyclization took place to produce benzo[h]quinoline (77) in 69% yield together with aniline (83) in 65% yield; the yield of quinoline (84) was only 7%.

Based on these results, two reaction pathways are proposed for the formation of benzo[h]quinoline (77) in the above iridium-catalyzed reaction (Schemes 38 and 39). In both mechanisms, the reaction is initiated by the iridium-
catalyzed dehydrogenation of diol 76 to give an aldehyde, which readily reacts with 1-naphthylamine (75) to give an imine intermediate followed by hydrogenation by the in-situ-generated iridium hydride leading to amino alcohol 80. Then, one possible reaction pathway is that the resulting compound 80 reacts further with 75, after the formation of aldehyde 85, to give imine 86 (Scheme 38). The formation of the desired product 77 from intermediate 86 may be explained by a similar reaction pathway to that proposed by Tsuji et al.\textsuperscript{100} However, another possible reaction pathway involves the direct intramolecular cyclization of 80 to give product 77 via the iridium-catalyzed reaction of aldehyde 85 (Scheme 39).

### 9 Coupling Reaction of Alcohols with Alkynes

#### 9.1 Synthesis of Homoallylic Alcohols

The transition-metal-catalyzed addition of alcohols to alkynes, which is generally referred to as a hydroalkoxylation reaction, is an important methodology that leads to a wide variety of oxygen-containing compounds.\textsuperscript{102} We

---

**Table 6** Synthesis of Benzoindole Derivatives by the Reaction of Various Naphthylamines with 1,2-Diols Using an IrCl$_3$/BINAP Catalyst

<table>
<thead>
<tr>
<th>Entry</th>
<th>Naphthylamine</th>
<th>Diol</th>
<th>Benzoindole Derivative</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>96</td>
</tr>
<tr>
<td>3$^{bc}$</td>
<td></td>
<td></td>
<td></td>
<td>84</td>
</tr>
<tr>
<td>4$^{bc}$</td>
<td></td>
<td></td>
<td></td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td>78</td>
</tr>
<tr>
<td>7</td>
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<td></td>
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<td>76</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td>52</td>
</tr>
</tbody>
</table>

$^{a}$ Using a procedure similar to that described for the synthesis of benzo[h]quinoline (see above).

$^{b}$ 75 (10 mmol) was used.

$^{c}$ Triphenylphosphine (0.2 mmol, 10 mol%) was used instead of BINAP.
previously reported the addition of water and alcohols to terminal alkynes using an iridium complex combined with a phosphite and a Lewis acid to give ketones and ketal.

However, Krische and co-workers reported ruthenium- and iridium-catalyzed transformations of alcohols with dienes, allyl acetates, allenes, and alkynes to afford homoallylic alcohols.15,104–109

Here, we show our findings on the iridium-catalyzed coupling of alkynes, such as 1-arylprop-1-ynes, with primary alcohols leading to secondary homoallylic alcohols as products through the formation of a π-allyl(hydrido)iridium complex as a possible key intermediate.110

For instance, butan-1-ol (19) (1 mmol) was allowed to react with 1-phenylprop-1-yne (87) (2 mmol) in the presence of [Ir(OH)(cod)]2 (0.05 mmol, 5 mol%) combined with tri-n-octylphosphine (0.30 mmol) in toluene (1 mL) at 100 °C for 15 hours, giving 3-phenylhept-1-en-4-ol (88) in 95% isolated yield (Scheme 40). The reaction is highly stereoselective and afforded the anti-isomer exclusively.

Under optimized conditions, the reactions of various primary alcohols with 1-arylprop-1-ynes were carried out to afford the corresponding homoallylic alcohols in good to excellent yields (Figure 14). The methyl substituent on the alkyne plays a crucial role in achieving this reaction.
Thus, no coupling product was obtained from the reaction of oct-4-yne or 1-phenylbut-1-yne.

To obtain further information on the reaction pathway, we carried out the reaction of secondary alcohols, such as butan-2-ol (89), with 87 under these reaction conditions. As a result, allylbenzene (90) was formed in quantitative yield with concomitant formation of butan-2-one (91) (Scheme 41). This result indicates that the alcohol behaves as a hydrogen source, and transfer hydrogenation to the iridium complex occurs to form an iridium hydride species, followed by the formation of a $\pi$-allyliridium complex as a key intermediate.

Scheme 41

For further evidence of the formation of a $\pi$-allyliridium species in this reaction, Esteruelas et al. reported the stoichiometric transformation of alk-2-ynes (including a prop-1-yne derivative) using an osmium dihydride complex, leading to $\pi$-allyl(hydrido)osmium complexes. Thus, our above study demonstrates the catalytic transformation of 1-arylprop-1-ynes with primary alcohols through the possible formation of a $\pi$-allyl(hydrido)iridium complex as an intermediate.

On the basis of these experimental results, the reaction mechanism of Scheme 42 can be postulated. The iridium catalyst initially serves as the hydrogen acceptor from alcohol 92 giving aldehyde 93 and an iridium hydride. Then, alkyne 94 inserts into the iridium–hydrogen bond of the iridium hydride to form alkenyl(hydrido)iridium species 95. Intermediate 95 is subjected to hydrogenation by the iridium hydride, followed by abstraction of hydrogen from the methyl group of the alkyne, resulting in the formation of $\pi$-allyl(hydrido)iridium species 96. Finally, complex 96 reacts with aldehyde 93 to give homoallylic alcohol 98 as the product via the formation of six-membered transition state 97.

Scheme 42

9.2 Synthesis of $\alpha,\beta$-Unsaturated Ketones (Hydroacylation)

The above-mentioned iridium-catalyzed coupling reaction of 1-arylprop-1-ynes with primary alcohols is also applicable to the synthesis of $\alpha,\beta$-unsaturated ketones, realizing overall the intermolecular hydroacylation of alkynes with aldehydes. To date, the hydroacylation of alkynes has been mainly achieved with intramolecular reactions and intermolecular alkyne hydroacylation has been mostly limited to reactions with substrates bearing directing groups. The intermolecular hydroacylation of alkynes with simple aldehydes without directing groups has been far less explored. Ruthenium-catalyzed hydroacylation reactions of alkynes with alcohols or aldehydes were more-recently reported by Krische and co-workers.

Using our method, the reaction of benzyl alcohol (99) (0.5 mmol) and but-2-yne (100) (1 mmol) in the presence of [IrCl(cod)]$_2$ (0.025 mmol, 5 mol%) combined with tri-n-octylphosphine (0.1 mmol, 20 mol%) in toluene (1 mL) at 120 °C for 15 hours gave 2-methyl-1-phenylbut-2-en-1-one (101) in 92% isolated yield (Scheme 43).

Scheme 43
Under the optimized conditions, the reaction of various primary alcohols with alk-2-ynes was examined and afforded the corresponding hydroacylation products in good to excellent yields (Figure 15).

![Figure 15](image_url)

In this reaction, the iridium catalyst serves as a hydrogen acceptor from alcohols to give aldehydes, which are proposed to react with the alk-2-yne to afford α,β-unsaturated ketones. Therefore, the reaction of aromatic aldehydes with alk-2-ynes under these reaction conditions was examined. For instance, the reaction of benzaldehyde (0.5 mmol) (102) with but-2-yne (2 mmol) (100) in the presence of [IrCl(cod)]₂ (0.025 mmol, 5 mol%) and tri-n-octylphosphine (0.1 mmol, 20 mol%) in toluene (1 mL) at 120 °C for 15 hours gave α,β-unsaturated ketone 101 in 84% isolated yield (Scheme 44).

![Scheme 44](image_url)

Similarly, various aromatic aldehydes reacted with but-2-yne to produce the corresponding α,β-unsaturated ketones in good yields (Figure 16). To obtain further experimental evidence regarding the reaction mechanism, the reaction of homoallylic alcohol 103 with alk-2-yne 100 was carried out and gave 2-methyl-1-phenylbut-2-en-1-one (101) in 74% yield (Scheme 46).

![Scheme 46](image_url)

Furthermore, when 4-methylpent-2-yne (105) bearing a bulky isopropyl group was used, the desired hydroacylation product 106 was not formed at all and β,γ-unsaturated ketone 107 was obtained exclusively in 81% yield (Scheme 47).

![Scheme 47](image_url)

The above-mentioned results strongly suggest that the resulting hydroacylation products are obtained through the formation of homoallylic alcohols and β,γ-unsaturated ketones as intermediates. Thus, we suppose that this reaction proceeds by dehydrogenation of homoallylic alcohol 108, derived from the reaction involving the π-allyl(hydri-
do)iridium intermediate mentioned in Section 9.1, leading to $\beta,\gamma$-unsaturated ketone 109, which undergoes isomerization to produce 110 as the final product (Scheme 48).

![Scheme 48](image)

### 10 Concluding Remarks

In this account, we have reported various organic transformations using alcohols and diols which include hydrogenation, alkylation, N-heterocyclization, and coupling reactions with alkenes. In the presented reactions, the formation of an iridium hydride generated through transfer hydrogenation from alcohols is a key intermediate. These reactions provide efficient and greener processes compared with the conventional methods. Therefore, we believe that the further application and broadening of the scope of this protocol will contribute to catalytic organic chemistry and industrial process chemistry.

### Acknowledgment

We acknowledge that these studies were carried out in collaboration with the co-workers at Kansai University listed in the references. These studies were supported in part by a Grant-in-Aid for Scientific Research from MEXT (Ministry of Education, Culture, Sports, Science and Technology), the Research for the Future Program of the Japan Society for the Promotion of Science, and the High-Tech Research Center Project for Private Universities and the Strategic Project to Support the Formation of Research Bases at Private Universities (matching fund subsidy from MEXT).

### References

30. See also ref. 24 and references cited therein.


