Development of Platinum-Catalyzed Hydroarylation of Alkynes and Its Application

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Chapter 1.

Introduction

1. Direct C-H bond functionalization

Development of the cleanest and cheapest synthetic method for a useful organic compound has attracted synthetic chemists for a long time.

\[
\begin{align*}
R-\overset{\Delta}{\text{H}} & \rightarrow & R-\overset{\Delta}{\text{FG}} \quad \leftarrow \quad R-\overset{\Delta}{\text{X}} \\
\end{align*}
\]

Scheme 1

Carbon - hydrogen bonds (C-H bonds) are ubiquitous in organic compounds. If the C-H bonds can be used as functional groups that are often utilized as reaction sites in the organic synthesis, the strategy utilizing C-H bonds directly for the transformation is one of the most powerful and straightforward method for the formation of new carbon - carbon bonds (C-C bonds) or carbon-heteroatom bonds in the organic compounds (Scheme 1). The direct C-H bond functionalization method has several advantages compared to conventional synthetic methods. This method does not require prefuctionalization because it uses only C-H bonds but not reactive functional groups as a reaction site for the transformation. It does not only reduce the reaction steps but also avoids use of toxic halogenated compounds. In other words, simple and cheap organic compounds can be used as starting materials because any special functional groups are not required. Furthermore, the C-H functionalization method is favorable from the viewpoint of atom-economy because some functional groups are used as leaving groups in the reaction and are not incorporated into the products. Therefore, the direct C-H bond functionalization method would provide an ideal transformation process that is clean, simple and cheap. However, the bond dissociation energy for C-H bonds is usually very large (e.g., 105 kcal/mol for C-H bond in methane, and 110 kcal/mol in benzene). Therefore, it was believed to be difficult to cleave a C-H bond.¹
To date, many examples of direct C-H functionalization using transition metal catalysts have been reported. Among them, addition of aromatic C-H bonds to unsaturated C-C bonds (hydroarylation) is very useful reaction for the construction of C-C bond frameworks on aromatic compounds. Carbon-carbon bond formation is one of the most important reactions in organic synthesis. Moreover, it is one of the most efficient reactions from the viewpoint of atom-economy because all of the atoms in the starting material are incorporated into the products.

2. The hydroarylation of alkynes

Substituted styrenes and vinylic compounds, which are obtained from hydroarylation of alkynes, are versatile intermediates in organic synthesis and the various preparation methods have been published. Among the catalytic reactions, the representative reactions are the transition metal-catalyzed coupling reaction using organometallic compounds and the coupling reaction of organic halides or triflates with alkenes (Mizoroki-Heck reaction). However, they need use of carbon-halogen or triflate bonds for the formation of C-C bonds.

Many methods using transition metal catalysts for hydroarylation of alkynes have been reported. Yamazaki et al. reported that the addition of benzene to diphenylacetylene catalyzed by \( \text{Rh}_4(\text{CO})_{12} \) proceeded under pressure of carbon monoxide to give triphenylethylene along with 2,3-diphenylindenone (Eq. 1). The pressure of carbon monoxide is crucial for the addition reaction of benzene to diphenylacetylene. At low pressure of carbon monoxide, cyclotrimerization of diphenylacetylene is predominant to afford hexaphenylbenzene. In the case of monosubstituted benzene, the low regioselectivity on the arene is inevitable problem. It is proposed that the reaction is initiated by 1) the oxidative addition of Rh catalyst to C-H bond in benzene to give a H-Rh-Ph species, followed by 2) the insertion of diphenylacetylene to Rh-Ph bond. 3) Reductive elimination of Rh
from the resulting intermediate affords an addition product to complete the catalytic cycle. Heteroarenes such as furan, N-methylpyrrole and thiophene are also applicable to this addition reaction. In this case, the α-position of heteroaromatic ring is more reactive than the β-position. The order of the relative reactivities of these compounds is estimated as follows; furan > thiophene > N-methylpyrrole > benzene.

\[
\begin{align*}
\text{R} + \text{Ph} = \text{Ph} & \xrightarrow{\text{Rh}_4(\text{CO})_{12}} \text{R} + \text{Ph} \xrightarrow{\text{CO (25kg/cm}^2)} \text{Ph} \\
& \text{Ph} \quad \text{Ph} \\
\end{align*}
\]

The yield and regioselectivity of 1,2-diphenyl-1-arylethene

<table>
<thead>
<tr>
<th>R</th>
<th>Yield / %</th>
<th>ortho : meta : para</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>45</td>
<td>- - -</td>
</tr>
<tr>
<td>Me</td>
<td>24</td>
<td>6 65 29</td>
</tr>
<tr>
<td>OMe</td>
<td>42</td>
<td>64 26 10</td>
</tr>
<tr>
<td>F</td>
<td>49</td>
<td>49 22 8</td>
</tr>
</tbody>
</table>

Trost et al. developed the Pd-catalyzed synthesis of coumarins by the hydroarylation of ethyl propiolates with electron-rich phenols (Eq. 2). Use of formic acid is crucial for the reaction. Although the reaction with Pd(II) catalyst in acetic acid does not proceed, changing the solvent to formic acid leads to a productive reaction. It is considered that formic acid may reduce Pd(II) to Pd(0). Actually, a Pd(0) species, Pd$_2$dba$_3$, is an effective catalyst in both acetic acid and formic acid although the latter solvent gives better results. Therefore, it is suggested that a Pd(0) species is involved in the reaction rather than Pd(II).

\[
\begin{align*}
\text{MeO} & + \text{OH} + \text{R} = \text{CO}_2\text{Et} & \xrightarrow{2.5\%\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3} \\
& 10\% \text{NaOAc} & \text{HCO}_2\text{H}, 25^\circ\text{C} \\
\end{align*}
\]

We also reported that trans-hydroarylation of terminal or internal alkynes with simple arenes proceeded under very mild conditions in the presence of a catalytic amount of
Pd(OAc)$_2$ and trifluoroacetic acid (TFA) to afford thermodynamically unfavorable cis-aryl substituted alkenes in regio- and stereoselective manner (Eq. 3).$^9$ The reaction of ethyl propiolate gives a Michael-type adduct, together with a diene (Eq. 4). In particular, an electron-rich arenes like pentamethylbenzene give arylalkenes in high yields. In the reaction of methoxy-substituted arenes with ethyl propiolate, the double hydroarylation of alkynes also takes place to afford ethyl diarylpropionates. Although the hydroarylation of methoxy-substituted cinnamates was also reported in these literatures, it is revealed that the reaction proceeds with TFA even in the absence of Pd catalyst.$^{10}$

$$\text{Ar} \cdots \text{H} + \text{R}_1 \cdots \text{R}_2 \xrightarrow{\text{Pd(OAc)}_2, \text{CF}_3\text{CO}_2\text{H} (\text{TFA})} \text{Ar} \cdots \text{H} \quad (3)$$

$$\text{Ar} \cdots \text{H} + \equiv \cdots \text{CO}_2\text{Et} \xrightarrow{} \text{Ar} \cdots \text{CO}_2\text{Et} + \text{Ar} \cdots \text{CO}_2\text{Et} \quad (4)$$

In addition to Pd(OAc)$_2$, PtCl$_2$/AgOAc also catalyzes the hydroarylation of alkynes under the same reaction conditions.$^{9b}$ The Pt catalyst shows a lower catalytic activity than Pd(OAc)$_2$, but a higher selectivity. Especially, in the reaction of ethyl propiolate (Eq. 4), Pt-catalyzed reaction proceeds selectively to give an ethyl cinnamate in a high yield without the formation of dienes.

$$\text{R}_1 \equiv \cdots \text{X} \cdots \text{O} \xrightarrow{\text{Pd(OAc)}_2, \text{TFA} / \text{CH}_2\text{Cl}_2} \text{R}_1 \equiv \cdots \text{X} \cdots \text{O} \quad (5)$$

$$\text{R}_1 \equiv \cdots \text{OH} + \text{R}_2 \equiv \cdots \text{CO}_2\text{H} \xrightarrow{\text{Pd(OAc)}_2, \text{TFA}, \text{r.t.}} \text{R}_1 \equiv \cdots \text{X} \cdots \text{O} \quad (6)$$
The Pd-catalyzed reaction is applied to the synthesis of coumarins and quinolinone by intramolecular hydroarylation of aryl propiolates (Eq. 5)\(^9c\) and the synthesis of coumarins by intermolecular hydroarylation of propiolic acids with phenols (Eq. 6)\(^9f-h\). The intramolecular reaction proceeds efficiently to give cyclization products in high yields while the intermolecular reaction can directly afford coumarins. Moreover, hydroarylation of alkynes with heteroarenes such as pyrroles, indoles and furans is also achieved (Eq. 7).\(^9d,e\) In the case of heteroarenes, acetic acid or dichloromethane is used as solvent instead of TFA. A recent report on the detailed mechanistic study by Tunge and Foresee suggests that the Pd(OAc)\(_2\)-catalyzed reaction proceeds via electrophilic aromatic substitution (Scheme 2)\(^11\) although the mechanism that includes C-H bond activation of arenes by an electrophilic Pd species was proposed at the beginning of the work (Scheme 3).

Scheme 2. Electrophilic aromatic substitution mechanism of Pd-catalyzed hydroarylation.
Scheme 3. C-H bond activation mechanism of Pd-catalyzed hydroarylation.

Nolan et al. reported that the N-heterocyclic carbene palladium complexes, (IPr)Pd(OAc)$_2$ and (IPr)Pd(OCOCF$_3$)(H$_2$O) (IPr = N,N'-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, Fig. 1), also catalyzed the hydroarylation reaction under the same reaction conditions as Pd(OAc)$_2$ catalysis.$^{12}$ In this case, the reaction of ethyl propiolate proceeds selectively to give cinnamates without the formation of dienes (Eq. 4).

Inoue et al. reported that dinuclear palladium complexes, Pd$_2$R$_2$(µ-OH)(µ-dpfam) 1 (dpfam = N,N'-bis[2-(diphenylphosphino)phenyl]formamidate, R = p-Tol or Me, Fig. 2), catalyzed the cis-selective hydroarylation of unactivated alkynes in the presence of a trialkylborane as an additive (Eq. 8).$^{13}$ It is confirmed that the cis-addition to alkyne is kinetically favored. Use of dinuclear palladium complexes 1 is essential for the reaction.
The corresponding mononuclear methylpalladium complex PdMe(dpfam) or dinuclear complex [PdPh(PPh₃)(µ-OH)]₂ without binucleating ligand dpfam do not give any products. Typical palladium catalysts such as Pd(OAc)₂ and Pd₂dba₃·CHCl₃ are also ineffective for the reaction. Trialkylborane is also crucial for the reaction. Use of triethylborane or triphenylborane resulted in inferior yields while no reaction takes place in the absence of boranes. In the case of the reaction of monosubstituted arenes, hydroarylation takes place at para and meta positions in almost statistical ratio although no ortho products are formed. On the other hand, the reaction of disubstituted arenes does not occur. Electron-deficient arenes are more reactive for this reaction. The heteroarenes such as N-substituted pyrroles and thiophenes are applicable to this reaction although no products are obtained in the cases of N-unsubstituted pyrroles and furans.¹³b

\[ \text{Ar–H} + \begin{array}{c} \text{Ar} \\ \text{R'} \end{array} \begin{array}{c} \text{R'} \end{array} \xrightarrow{2\% \text{I}} \begin{array}{c} \text{Ar} \\ \text{H} \end{array} \begin{array}{c} \text{R'} \\ \text{R'} \end{array} \xrightarrow{30\% \text{BBu₃}} 100^\circ \text{C} \]

\[ \text{R'} = \text{Et, } \eta^\text{Pr, } \eta^\text{Bu, Ph} \]

![Figure 2](image-url)  

Reetz and Sommer reported that Au(I) or Au(III) catalyzed the intermolecular hydroarylation of alkynes in the presence of silver compounds such as AgBF₄, AgOTf and AgSbF₆ or BF₃·OEt₂.¹⁴ The regio- and stereochemistry of this reaction is almost same as those of the Pd(OAc)₂-catalyzed reaction. The reaction of ethyl propiolate gives Michael adducts while 1,1-diphenylalkenes are formed in the case of phenylacetylenes. Electron-rich arenes are more reactive to give higher yields. The advantage of Au-catalysts is that the
reaction proceeds in neutral conditions, whereas Pd(OAc)$_2$-catalyzed reaction needs to be conducted in TFA. It is proposed that the reaction proceeds via electrophilic aromatic substitution, similar to Pd-catalysis.

Shi and He also reported the similar hydroarylation of alkynes using AuCl$_3$/AgOTf catalyst (Eq. 9). The reaction can be applied to the solvent free reaction that involves coumarin synthesis from the intramolecular hydroarylation of aryl propiolates. The hydroarylation of alkenes, methyl acrylate and cyclohexanone, with a highly electron-rich arene also takes place with AuCl$_3$/AgOTf. AuCl$_3$/AgOTf also catalyzes the double hydroarylation of ethyl propiolate with heteroarenes such as $N$-methylindole and benzofuran to afford ethyl bis(heteroaryl)propionates as well as the hydroarylation of electron-deficient olefin with heteroarenes.

\[
\text{ArH} + \text{R}^1\text{C}=-\text{CH} \underset{\text{AuCl}_3/\text{AgOTf}}{\stackrel{\rightarrow}{\text{O}}} \text{R}^2 \text{Ar} \quad \text{(9)}
\]

Shirakawa et al. reported that metal triflate such as Sc(OTf)$_3$, In(OTf)$_3$ and Zr(OTf)$_4$ catalyzed the alkenylation of arenes with phenyl substituted alkynes to give 1,1-diarylalkenes (Eq. 10). The reaction probably proceeds by a Friedel-Crafts type mechanism through an alkenyl cation intermediate. They also reported that In(OTf)$_3$ catalyzed the double hydroarylation of alkynes with heteroarenes such as pyrroles, furans and thiophenes to afford bis(heteroaryl)alkanes (Eq. 11). 1-Octyne, 4-octyne and ethyl propiolate are applicable to the reaction of heteroarenes as well as phenyl substituted alkynes.

\[
\text{ArH} + \text{Ph} \underset{10\%\text{M(OTf)}_n/85^\circ\text{C}}{\stackrel{\rightarrow}{\text{H}}} \text{Ar} \quad \text{(10)}
\]

\[\text{M(OTf)}_n : \text{Sc(OTf)}_3, \text{In(OTf)}_3, \text{Zr(OTf)}_4\]
Lee et al. reported that the employment of hydrophobic ionic liquids, [bmim][PF₆] and [bmim][SbF₆] \((\text{bmim} = 1\text{-butyl}-3\text{-methylimidazolium, Fig. 3})\), dramatically enhanced the catalytic activities of metal triflates in the same Friedel-Crafts alkenylation of arenes. Metal triflates such as Sc(OTf)₃, In(OTf)₃ and Hf(OTf)₄ are effective catalysts similar to the Shirakawa’s report. In some cases, the reactions which are not possible in conventional organic solvents proceed in the presence of the ionic liquid. It is proposed that this significant rate acceleration may be ascribed to the stabilization of the unstable vinyl cation intermediate in a highly polar ionic liquid. The intramolecular reaction is applicable to the synthesis of coumarins and quinolinones (Eq. 12).

\[
\text{[bmim][X]} (X = \text{PF}_6, \text{SbF}_6)
\]

**Figure 3**

The transition metal catalyzed-addition reactions of \textit{ortho} C-H bonds of arenes having directing groups such as carbonyl, imino and nitrile groups to alkenes via chelation-assisted C-H bond activation have been extensively studied by Murai and others (Eq. 13). The C-C bond formation occurs exclusively at the \textit{ortho} position to the directing group. The reaction proceeds through the formation of metalacycle by chelation-assisted oxidative
addition of Ru(0) to the C-H bond. The subsequent insertion of alkenes, followed by reductive elimination completes the reaction. The C-H bond cleavage is quite facile and the reductive elimination is rate-determining step in the reaction.

\[
\text{Ph} + \text{Si(OEt)}_3 \xrightarrow{\text{RuH}_2\text{(CO)}\text{(PPh}_3\text{)}_3, \text{toluene, 2h reflux}} \text{PhSi(OEt)}_3
\]

The chelation-assisted addition reaction to alkynes has been also reported. The addition of C-H bonds in azobenzenes to diphenylacetylene is catalyzed by CoH(N_2)(PPh_3)_3, CoH_3(PPh_3)_3 or RhCl(PPh_3)_3.\textsuperscript{18} When RhCl(PPh_3)_3 is used as catalyst, the reaction gives 1-(arylamino)indole (Eq. 14).

\[
\text{Ph} + \text{Ph} \xrightarrow{\text{RhCl(PPh}_3\text{)}_3, \text{1-PrOH/AcOH (25mL/15\muL) reflux}} \text{PhN}_{\text{Ph}} \text{N}_{\text{Ph}} \text{N}_{\text{Ph}} \text{N}_{\text{Ph}} \text{H}
\]

Murai et al. reported that the reaction of α-tetralone with various internal alkynes is catalyzed by RuH_2(CO)(PPh_3)_3 to give vinylation products (Eq. 15).\textsuperscript{19a} When trimethylsilyl-substituted acetylenes are employed, the vinylation products are obtained with
high regioselectivity although the products are generally a mixture of stereoisomers. Furthermore, heteroaromatic ketones such as 2-acetylfuran and 3-acetylthiophene also undergo alkenylation with 1-phenyl-2-trimethylsilylacetylene.

\[
\text{toluene, reflux} 
\]
\[135^\circ C \text{ (bath temp.)}
\]

Similarly, the arene having both keto and imino groups also undergo the alkenylation with alkynes (Scheme 4).\textsuperscript{19b} In this case, the reaction site on the arene is controlled by choosing a catalyst. By using Ru(H\textsubscript{2})(CO)(PPh\textsubscript{3})\textsubscript{3} as the catalyst, the C-H bond at the position ortho to the carbonyl group reacts. When Ru\textsubscript{3}(CO)\textsubscript{12} is used as the catalyst, the C-H bond at the position ortho to the imino group reacts.

\textbf{Scheme 4}

Woodgate \textit{et al.} demonstrated a similar Ru(H\textsubscript{2})(CO)(PPh\textsubscript{3})\textsubscript{3}-catalyzed ortho alkenylation of diterpenoid analogue of aromatic ketones with alkynes.\textsuperscript{20} Lim \textit{et al.} reported the Wilkinson catalyst, RhCl(PPh\textsubscript{3})\textsubscript{3}, catalyzed ortho-alkenylation of 2-phenylpyridines with internal alkynes.\textsuperscript{21} Miura \textit{et al.} reported that 1-naphthols efficiently coupled with internal alkynes in the presence of an iridium catalyst to afford 8-substituted 1-naphthols selectively.\textsuperscript{22} In this case, the C-C bond formation takes place exclusively at the peri position.

Recently, Hiyama \textit{et al.} reported that the Nickel-catalyzed hydroheteroarylation of alkynes
gave heteroaryl-substituted ethenes.\textsuperscript{23} It is suggested that the reaction includes 1) oxidative addition of C-H bonds in heteroarenes by Ni(0), 2) the subsequent hydronickelation of alkynes and 3) reductive elimination.

Merlic and Pauly reported the $6\pi$-electrocyclization of heteroarylenynes catalyzed by Ru(II) complexes, RuCl$_2$(p-cymene)PPh$_3$ and RuCl$_2$(C$_6$H$_6$)PPh$_3$, to form fused heteroarenes (Eq. 16).\textsuperscript{24} It is proposed that the reaction proceeds via the pericyclic pathway as illustrated in Scheme 5. A cationic ruthenium species reacts with the alkyne moiety of diyne to form the Ru vinylidene intermediate. Cyclization via nucleophilic attack of the alkene at the electrophilic $\alpha$-carbon of the complex affords the carbene complex. $\beta$-Hydride elimination giving aryl-Ru(IV) intermediate, and subsequent reductive elimination resulted in the formation of benzene ring.
Akiyama et al. reported that N-arylated alkynyl imines underwent \([4 + 2]\) electrocycloisomerization in the presence of \(W(CO)_5(THF)\) to give quinolines (Eq. 17).\(^{25}\) A deuterium labeling study suggests that the reaction proceeds via a tungsten vinylidene complex.

\[
\begin{align*}
\text{R}=\text{N} & \quad \text{Ar} \\
\text{R} & \quad \text{N} \quad \text{Ar}
\end{align*}
\]

\[
i) \text{20\% W(CO)}_5(\text{THF}) \\
\text{THF, reflux} \\
\text{ii) NMO, CH}_2\text{Cl}_2, \text{r.t.}
\]

Murai et al. reported that the cycloisomerization of aryl-1-alkynes with catalytic amounts of metal chlorides, PtCl\(_2\) and \([\text{RuCl}_2(\text{CO})_3)_2\), gave dihyronaphthalenes or dihydrobenzocycloheptenes (Eq. 18-20).\(^{26}\) The cyclization mode is dependent on the length of tethers of aryl-1-alkynes. The reaction is limited to the substrates containing terminal alkynes. The proposed mechanism is shown in Scheme 6. A metal chloride adds to an alkyne to form a vinyl cation intermediate, which undergoes electrophilic substitution to give a cyclization intermediate. The subsequent 1,2-hydrogen shift with aromatization gives the carbenoid intermediate. β-Hydride elimination, followed by reductive elimination initially affords an \(\text{exo}\)-methylene product, which isomerizes to a more stable \(\text{endo}\)-alkene under the reaction conditions. This reaction is also limited to substrates bearing an electron-rich arene. More recently, the scope of the reaction was extended to substrates whose arenes do not have strong electron-donating groups by using GaCl\(_3\) catalyst.\(^{27}\)
Fürstner reported that biphenyl derivatives bearing an alkyne moiety at one of the ortho positions are converted to phenanthrenes (Eq. 21). The 6-endo cyclization mode is preferred in most cases. Only alkynes bearing an electron-withdrawing group cyclize by a 5-exo-dig pathway (Eq. 22). Activation of the alkyne by coordination to Pt(II) suffices to explain the observed ring closure. In addition to PtCl$_2$, other metal halides such as AuCl$_3$, GaCl$_3$ and InCl$_3$ catalyze the phenanthrene synthesis.
Sames et al. reported the PtCl₄ catalyzed intramolecular hydroarylation of arene-yne substrates including propargyl ethers, propargylamines and aryl alkynoates, affording 6-endo products (Eq. 23).²⁹ PtCl₄ is compatible with both terminal and disubstituted alkynes as well as functionality on the arene ring. The reaction is also considered to proceed via electrophilic aromatic substitution initiated by coordination of Pt to the alkyne moiety.

Nishizawa et al. reported that Hg(OTf)₂(TMU)₃ (TMU = tetramethylurea) catalyzed the cycloisomerization of ω-aryl-1-alkynes at room temperature (Eq. 24).³⁰ It is proposed that the reaction proceeds through a π-complex which leads to intramolecular electrophilic aromatic substitution.

Echavarren et al. also reported 4-aryl-1-alkynes reacted with PtCl₂ catalyst to form 1,2-dihydroquinolines (Eq. 25).³¹a Moreover, using a cationic Au(I) catalyst formed in situ from Au(PPh₃)Me and HBF₄, the reaction proceeds at room temperature efficiently.³¹b
3. Purpose of this work

Already described above, we have reported the Pd(OAc)$_2$-catalyzed hydroarylation of alkynes. The reaction proceeds under very mild conditions to afford cis-aryl substituted alkenes with high regio- and stereoselectivity in good to high yields (Eq. 1). However, in the case of ethyl propiolate, the reaction gave diethyl (1E,3Z)-4-arylbuta-1,3-diene-1,3-dicarboxylate derivatives along with the desired product, ethyl (2Z)-cinnamates, resulting in low selectivity and yield of the desired product. On the other hand, the hydroarylation of ethyl propiolate proceeded selectively to give cinnamates without the formation of the buta-1,3-diene-1,3-dicarboxylates when Pt(II) catalyst, PtCl$_2$/AgOAc, was used in stead of Pd(OAc)$_2$. However, the activity of the PtCl$_2$/AgOAc catalyst was still low and should be improved. Therefore, the following investigations were carried out to improve the activity of Pt catalyst and to find out better catalytic systems.

1. Investigation of silver compounds as additives for PtCl$_2$-catalyzed hydroarylation and its scope and limitations (Chapter 2.1).

2. Investigation of Pt catalyst precursors and its scope and limitations (Chapter 2.2).

Moreover, Pt catalysts developed in this work were applied to the following reactions:

3. Synthesis of coumarin from the hydroarylation of propiolic acids with phenols (Chapter 3).

4. Hydroarylation of alkynes with heteroarene such as pyrroles and furans (Chapter 4).
References


6. For a recent review, see: Nevado C.; Echavarren, A. M. *Synthesis* 2005, 167-182.


1. PtCl$_2$/AgOTf-catalyzed hydroarylation

More cationic Pt catalyst is required to improve the activity because the hydroarylation is considered to proceed by electrophilic aromatic substitution. Silver compounds like AgOAc are thought to react with PtCl$_2$ and exchange the ligands to afford a more cationic and active Pt species. The formation of a more active Pt catalyst than PtCl$_2$/AgOAc is expected when the silver compounds having a less basic anion such as OTf$^-$, BF$_4^-$ and PF$_6^-$ are used. Therefore, the effects of silver compounds as additives for PtCl$_2$-catalyzed hydroarylation were investigated.

Results and discussion

1.1. Effect of silver compounds as additives

The reaction of ethyl propiolate (2a) with mesitylene (1a) was chosen for the present investigation because it gave moderate yield in the case of the Pd(OAc)$_2$ catalyst (Eq. 1). The reaction was carried out with PtCl$_2$ (0.05 mmol), silver compound (0.1 mmol), 1a (2 mmol) and 2a (2.4 mmol) in trifluoroacetic acid (TFA) (1 mL) at room temperature for 15 h.

\[
\begin{array}{c}
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et}
\end{array}
\]

\[
\text{PtCl}_2 + \text{AgOTf} \rightarrow \text{Pt}^{+} + \text{AgCl}
\]

\[
\text{Pt}^{+} + \text{Ph}_{3}
\]

\[
\text{Pt}^{+} + \text{Ph}_{3}
\]

\[
\text{Pt}^{+} + \text{Ph}_{3}
\]

\[
\text{Pt}^{+} + \text{Ph}_{3}
\]

\[
\text{Pt}^{+} + \text{Ph}_{3}
\]

1.2 eq.

\[
\begin{array}{c}
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et}
\end{array}
\]

\[
\text{1a} \quad 2 \text{mmol}
\]

\[
\text{2a} \quad 1.2 \text{eq.}
\]

\[
\text{Catalysts} \quad \text{CF}_3\text{CO}_2\text{H} \quad \text{TFA} \quad \text{r.t., 15h}
\]

\[
\begin{array}{c}
\text{1a} \\
\text{2a}
\end{array}
\]

\[
\text{C_6H_5CO}_2\text{Et} + \text{EtO}_2\text{C} \quad \text{C_6H_5CO}_2\text{Et} + \text{C_6H_5CO}_2\text{Et} \quad \text{C_6H_5CO}_2\text{Et}
\]

\[
\text{3a} \quad \text{4a} \quad \text{5a}
\]

(1)
The results are listed in Table 1. The PtCl$_2$/AgOAc-catalyzed reaction gave ethyl (2Z)-3-(2,4,6-trimethylphenyl)propenoate (3a) and ethyl (2Z)-3-{3-[(1Z)-2-ethoxycarbonyl-ethenyl]-2,4,6-trimethylphenyl}propenoate (4a) in 36 and 1% yields, respectively (Entry 2), while the reaction did not proceed in the absence of the catalyst (Entry 12). The reaction did not give diethyl (1E,3Z)-4-(2,4,6-trimethylphenyl)buta-1,3-diene-1,3-dicarboxylate (5a), similar to the previous report. However, the yield and the conversion were low and almost same as those obtained when only PtCl$_2$ was used (Entry 1). Addition of AgOCOCF$_3$ did not affect the reaction (Entry 3). Ag$_2$CO$_3$ slightly improved the yield and the conversion (Entry 4). Increasing the amount of Ag$_2$CO$_3$ did not improve the yields (Entry 5). AgBF$_4$ and AgPF$_6$ were effective (Entries 6 and 7) but AgOTf was the best additive among the Ag compounds tested (Entry 8). PtCl$_2$/AgOTf catalyst gave the highest conversion and yields among the employed Pd and Pt catalysts, revealing that PtCl$_2$/AgOTf catalyst is effective. Addition of triflic acid (TfOH) in place of AgOTf resulted in low yields (Entry 9).
reaction also proceeded by using only AgOTf in the absence of PtCl₂ but the yield was very low (Entry 10). This result suggests that the active catalyst is the Pt species generated from the reaction of AgOTf and PtCl₂. It is considered that the role of AgOTf is to transform insoluble PtCl₂ into a soluble, cationic and active Pt species.

1.2. Optimization of reaction conditions

Then, the reaction using PtCl₂/AgOTf catalyst was investigated to optimize the reaction conditions (Table 2). Prolonging the reaction time from 15 h to 45 h improved the conversion of 1a to give a higher yield of 4a (Entry 2). Higher temperature also increased the conversion of 1a but the yields of 3a and 4a decreased (Entries 3 and 4). This observation can be explained by hydrolysis of the ester products 3a and 4a to the corresponding acid forms at higher temperature in TFA. Using an excess amount of 1a is effective for the selective formation of 3a. When the reaction of 1a (4 mmol) with 2a (2 mmol) was conducted under the same conditions, 3a and 4a were formed in 86 and 12% yields, respectively (Entry 5).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time / h</th>
<th>Temp. / °C</th>
<th>Conversion of 1a /%</th>
<th>Yields / %a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3a 4a 5a</td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>r.t.</td>
<td>84</td>
<td>67 16 0</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>r.t.</td>
<td>94</td>
<td>64 28 0</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>50</td>
<td>92</td>
<td>57 24 0</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>70</td>
<td>92</td>
<td>19 10 0</td>
</tr>
<tr>
<td>5</td>
<td>15c</td>
<td>r.t.</td>
<td>50</td>
<td>44 3 0</td>
</tr>
</tbody>
</table>

a Reaction conditions : PtCl₂ (0.05 mmol), AgOTf (0.1 mmol), 1a (2 mmol), 2a (2.4 mmol), catalysts, TFA (1 mL).
b GC yields based on 1a.
c 1a (4 mmol) and 2a (2 mmol) were used.
d The yields in parentheses were based on 2a.
1.3. Effect of temperature in the hydroarylation

Again, we investigated the effect of temperature using an excess amount of 1a (Table 3). The reaction almost completed in 8 h even at room temperature (Entry 1). The reaction at 40°C improved the yields of 3a and 4a slightly but further elevation of temperature decreased their yields (Entries 2 to 5). Instead, 6a (Fig. 1), which is derived from the hydrolysis of 3a, was obtained at higher temperature. The amount of 6a was increased when the temperature was increased. The isomerization of the Z- to E-isomers also took place at higher temperature.

**Figure 2.** Time dependence of the Z/E isomerization and the hydrolysis of 3a

\begin{figure} [h]
\centering
\includegraphics[width=\textwidth]{Fig2.png}
\caption{Time dependence of the Z/E isomerization and the hydrolysis of 3a.}
\end{figure}

\begin{table}
\centering
\begin{tabular}{|c|c|}
\hline
Time / h & Yield / % \\
\hline
0 & 100 \\
2 & 80 \\
4 & 60 \\
6 & 40 \\
8 & 20 \\
10 & 0 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a} Reaction conditions: PtCl\textsubscript{2} (0.05 mmol), AgOTf (0.1 mmol), 3a (1.5 mmol), heptadecane as internal standard (10 mg), TFA (1 mL), 70°C. The yields were determined by \textsuperscript{1}H NMR.

The time dependence of 3a under the reaction conditions at 70°C clearly shows the hydrolysis and isomerization of 3a (Fig. 2). From these results, lower reaction temperature is preferred because the hydroarylation competes with the hydrolysis of the ester and the isomerization at higher temperature.
**Table 3. Effect of temperature in the PtCl₂/AgOTf-catalyzed hydroarylation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp. / °C</th>
<th>Yields / %&lt;sup&gt;b&lt;/sup&gt;</th>
<th>3a (Z/E)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>4a</th>
<th>5a</th>
<th>6a (Z/E)&lt;sup&gt;c,d&lt;/sup&gt;</th>
<th>3a(E)+6a(E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>81 (100/0)</td>
<td>9</td>
<td>0</td>
<td>-</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>83 (&gt;99/1)</td>
<td>10</td>
<td>0</td>
<td>-</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>75 (99/1)</td>
<td>10</td>
<td>0</td>
<td>7</td>
<td>(78/22)</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>60 (98/2)</td>
<td>10</td>
<td>0</td>
<td>11</td>
<td>(86/14)</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>32 (97/3)</td>
<td>6</td>
<td>0</td>
<td>39</td>
<td>(94/6)</td>
<td>3</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 1a (4 mmol), 2a (2 mmol), PtCl₂ (0.05 mmol), AgOTf (0.1 mmol), TFA (1 mL), 8h.
<sup>b</sup> GC yields based on 2a.
<sup>c</sup> Z/E ratio was determined by ¹H NMR.
<sup>d</sup> Isolated yields.

1.4. **The scope of the reaction**

Next, the reaction of 2a with various arenes was examined (Table 4). The result shows that the reaction gave the hydroarylated products in good to excellent yields. Especially, electron-rich arene, pentamethylbenzene (1b) gave the product 3b in high yield (Entry 1). The reaction of 1b resulted in low conversion after 3 h, while the reaction using the Pd(OAc)₂ catalyst completed in 2 h to give 3b and 5b (Fig. 3) in 67 and 20% yield, respectively (Entries 2 and 3). However, prolonged reaction time improved the yield of 3b. As a result, the yield was higher than that obtained by the reaction using Pd(OAc)₂ because of higher selectivity of the Pt catalyst. Slower reaction rate was also observed in the time course of the reaction of 1b (Fig. 4). The slower rate in Pt catalysis may be caused by the less activity or lower solubility of the Pt catalyst than that of the Pd catalyst. The reactions of naphthalene (1c) and p-xylene (1d) also gave adducts 3c and 3d in good yields, respectively (Entries 4 and 5). In the case of 1c, hydroarylation occurred selectively at the α-position of
Table 4. PtCl₂/AgOTf-catalyzed hydroarylation of 2a with various arenesa

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar−H</th>
<th>Temp. / °C</th>
<th>Time / h</th>
<th>Products and Yields / %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>r.t.</td>
<td>15</td>
<td>3b 91 (95)c</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>r.t.</td>
<td>3</td>
<td>Ar CO₂Et 3b (31)c</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>r.t.</td>
<td>2</td>
<td>3b (67)c,d</td>
</tr>
<tr>
<td>4</td>
<td>1c</td>
<td>r.t.</td>
<td>35</td>
<td>Ar CO₂Et 3c 65c</td>
</tr>
<tr>
<td>5</td>
<td>1d</td>
<td>r.t.</td>
<td>40</td>
<td>3d 61 (62) (Z/E = 99/1)</td>
</tr>
<tr>
<td>6</td>
<td>1d</td>
<td>50</td>
<td>15</td>
<td>Ar CO₂Et 3d (34) (Z/E = 91/9)</td>
</tr>
<tr>
<td>7</td>
<td>1e</td>
<td>r.t.</td>
<td>48</td>
<td>3e 30f</td>
</tr>
<tr>
<td>8</td>
<td>1e</td>
<td>40</td>
<td>48</td>
<td>Ar CO₂Et 3e (65)</td>
</tr>
<tr>
<td>9</td>
<td>Br</td>
<td>1e</td>
<td>50</td>
<td>3e (63)</td>
</tr>
<tr>
<td>10</td>
<td>H</td>
<td>1f</td>
<td>48</td>
<td>Ar CO₂Et 3f 76</td>
</tr>
</tbody>
</table>

a Reaction conditions: PtCl₂ (0.05 mmol), AgOTf (0.1 mmol), arene (4 mmol), 2a (2 mmol), TFA (1 mL).
b Isolated yields based on 2a. The yields in parentheses were determined by GC.
c H₂Cl₂ (0.25 mL) was used.
d Pd(OAc)₂ (0.02 mmol, 1mol%) was used instead of PtCl₂/AgOTf. 5b was obtained in 20% yield.
e CH₂Cl₂ (0.5 mL) was used. 6c was obtained in <8% yield.
f CH₂Cl₂ (0.5 mL) was used.
g CH₂Cl₂ (0.5 mL) and Cl(CH₂)₂Cl (0.5 mL) were used.
h 6e was isolated in 13% yield.
i 6e was isolated in 15% yield.

1c. Increasing temperature in the reaction of 1d resulted in low yield of 3d (Entry 6). This reaction is tolerant to unprotected OH and Br groups. The reaction of 1-bromo-2,4,6-trimethylbenzene (1e) and 2,4,6-trimethylphenol (1f) gave adducts 3e and 3f in good yields, together with bis-alkenylated products 4b and 4c (Entries 7-10). In the case of 1e, higher temperature was required to improve the yield because of low reactivity of 1e (Entry 8). In the cases of 1c and 1e, hydrolyzed products 6c and 6e (Fig. 3) were observed.
(Entries 4, 8 and 9). The yields of 3 in the PtCl₂/AgOTf-catalyzed reaction were generally higher than those in the Pd(OAc)₂-catalyzed reaction.

![Figure 3](image.png)

**Figure 3**

**Figure 4.** Time course of the PtCl₂/AgOTf-catalyzed hydroarylation of 2a with 1b

![Graph](image.png)

<sup>a</sup> Reaction condition: PtCl₂ (0.05 mmol), AgOTf (0.1 mmol), 1b (4 mmol), 2a (2 mmol), pentadecane (0.2 g, as internal standard), TFA (1 mL), CH₂Cl₂ (0.5 mL) at r.t. GC yield based on 2a.

This reaction was also applied to the reaction of internal alkyne, ethyl phenylpropionate (2b) (Eq. 2, Table 5). The reaction of 2b was slower than that of 2a and longer reaction time was required for high conversion of 2b. The reaction mainly gave products 8 which were formed by hydrolysis of esters 7 during the reaction, along with 7. In the case of 1a, higher temperature is required for good yield because the reaction was slower. The reaction gave a
small amount of decarboxylated product 9, together with 7a and 8a (Entry 2). On the other hand, the reaction of 1b proceeded smoothly at room temperature but gave 8b in high yield (Entry 3).

![Chemical Reaction](image)

**Table 5. PtCl2/AgOTf-catalyzed hydroarylation of ethyl phenylpropiolate (2b)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar=H</th>
<th>Temp.</th>
<th>Time / h</th>
<th>Products and Isolated yields / %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>r.t.</td>
<td>50</td>
<td>PhAr-HCO2Et 7a 20c 8a 22 PhAr-HCO2H 9 8</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>40°C</td>
<td>48</td>
<td>PhAr-HCO2Et 7a 14 PhAr-HCO2H 8b 80d</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>r.t.</td>
<td>50</td>
<td>PhAr-HCO2Et 7b 14d PhAr-HCO2H 8b 80d</td>
</tr>
</tbody>
</table>

**a** Reaction conditions: PtCl2 (0.05 mmol), AgOTf (0.1 mmol), arene (4 mmol), 2b (2 mmol), TFA (1 mL).

**b** The yields are based on 2b.

**c** Crude yield determined by 1H NMR. 43% of 2b was remained.

**d** CH2Cl2 (0.25 mL) was used.

Furthermore, the hydroarylation of propiolic acids was conducted because the prolonged reaction of ethyl propiolates mainly gave the hydrolyzed products 6 or 8. This catalytic system was found to be effective for the reaction of propiolic acids (Eq. 3, Table 6). The reactions of propiolic acid (2c) gave the corresponding cinnamic acids 6 in good to high yields. The reactions of 1a and 1b gave 6a and 6b in 94 and 96% yields, respectively (Entries 1 and 2). In the case of 1a, 3 equivalents of 1a were used to increase the selectivity of 6a. The reaction of 1c at 40°C gave 6c in 77% yield (Entry 3). The reaction of phenylpropioic acid (2d) gave 8b in moderate yield probably due to low solubility of 2d (Entry 4).
In summary, it was revealed that AgOTf was an effective additive for PtCl2-catalyzed hydroarylation of ethyl propiolate. It was also demonstrated that hydroarylation of ethyl propiolate catalyzed by a PtCl2/AgOTf proceeded smoothly to afford cinnamates selectively and efficiently. In the case of ethyl propiolate, the PtCl2/AgOTf-catalyzed hydroarylation gave cinnamates in higher yields compared to the Pd(OAc)2-catalyzed reaction because of higher selectivity of the Pt catalyst. Especially, this catalyst was the most effective for the reaction of propiolic acids.
2. K$_2$PtCl$_4$/AgOTf catalyzed hydroarylation

Results and discussion

2.1. Investigation of Pt salt as a catalyst precursor

In the above section, it was revealed that AgOTf was an effective additive for PtCl$_2$-catalyzed hydroarylation of alkynes. Beside PtCl$_2$, some Pt salts are commercially available and easily accessible. Therefore, several Pt salts were examined in the reaction of mesitylene with ethyl propiolate under the same conditions as Table 1 in Chapter 2.1. The results are listed on Table 7.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalysts</th>
<th>(mol%)</th>
<th>Conversion of 1a/%</th>
<th>Yields / %$^b$</th>
<th>3a</th>
<th>4a</th>
<th>5a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K$_2$PtCl$_4$ / AgOTf</td>
<td>(2.5 / 5)</td>
<td>92</td>
<td>66</td>
<td>24</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>K$_2$PtCl$_4$</td>
<td>(2.5)</td>
<td>68</td>
<td>58</td>
<td>4</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>PtCl$_2$(bpy) / AgOTf</td>
<td>(2.5 / 5)</td>
<td>93</td>
<td>59</td>
<td>21</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>PtCl$_2$(bpy)$^c$</td>
<td>(2.5)</td>
<td>17</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(Bu$_4$N)$_2$PtCl$_4$$^d$/ AgOTf</td>
<td>(2.5 / 5)</td>
<td>85</td>
<td>63</td>
<td>16</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(Bu$_4$N)$_2$PtCl$_4$$^d$</td>
<td>(2.5)</td>
<td>91</td>
<td>68</td>
<td>11</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>(Bu$_4$N)$_2$PtCl$_4$$^e$</td>
<td>(2.5)</td>
<td>92</td>
<td>73</td>
<td>12</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>PtCl$_4$ / AgOTf</td>
<td>(2.5 / 5)</td>
<td>94</td>
<td>63</td>
<td>24</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>PtCl$_4$</td>
<td>(2.5)</td>
<td>95</td>
<td>69</td>
<td>13</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>K$_2$PtCl$_6$ / AgOTf</td>
<td>(2.5 / 5)</td>
<td>37</td>
<td>33</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>K$_2$PtCl$_6$/ $^g$Bu$_4$NCl$^f$</td>
<td>(2.5 / 5)</td>
<td>37</td>
<td>22</td>
<td>trace</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>PtCl$_2$ / AgOTf</td>
<td>(2.5 / 5)</td>
<td>84</td>
<td>67</td>
<td>16</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>PtCl$_2$</td>
<td>(2.5)</td>
<td>43</td>
<td>39</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: 1a (2 mmol), 2a (2.4 mmol), catalysts, TFA (1 mL) at room temperature for 15hr.
$^b$ GC yields based on 1a.
$^c$ CH$_2$Cl$_2$ (0.4 mL) was added.
$^d$ (Bu$_4$N)$_2$PtCl$_4$ was prepared from K$_2$PtCl$_4$ and Bu$_4$NCl in water/CH$_2$Cl$_2$ (0.5 mL/0.5 mL), and was used as a CH$_2$Cl$_2$ solution.
$^e$ The resulting (Bu$_4$N)$_2$PtCl$_4$ solution (CH$_2$Cl$_2$) was concentrated before the reaction.
$^f$ K$_2$PtCl$_6$ and $^g$Bu$_4$NCl were mixed in water/CH$_2$Cl$_2$ (1 mL/1 mL). The CH$_2$Cl$_2$ layer was used as catalyst.
K$_2$PtCl$_4$/AgOTf catalyst showed high activity compared to PtCl$_2$/AgOTf catalyst (Entry 1). The activity of K$_2$PtCl$_4$ itself is also higher than PtCl$_2$ although its activity was low (Entry 2). PtCl$_2$(bpy)/AgOTf (bpy = 2,2’-bipyridyl) also showed higher activity although the activity of PtCl$_2$(bpy) is low because of low solubility (Entries 3 and 4). (Bu$_4$N)$_2$PtCl$_4$ is soluble to organic solvents and easily accessible, which can be prepared by mixing K$_2$PtCl$_4$ and Bu$_4$NCl in CH$_2$Cl$_2$ and water. A CH$_2$Cl$_2$ solution of (Bu$_4$N)$_2$PtCl$_4$ was obtained by removal of aqueous layer and was used directly as catalyst. (Bu$_4$N)$_2$PtCl$_4$/AgOTf also show high activity similar to the other Pt catalyst (Entry 5). Interestingly, (Bu$_4$N)$_2$PtCl$_4$ also showed high activity even in the absence of AgOTf (Entry 6). When the residue of a CH$_2$Cl$_2$ solution of (Bu$_4$N)$_2$PtCl$_4$ was used, the yields were slightly improved because a removal of residual water in (Bu$_4$N)$_2$PtCl$_4$ prevents the hydrolysis of products (Entry 7). Tetravalent platinum, PtCl$_4$/AgOTf catalyst showed the highest activity among the Pt salts examined (Entry 8). In this case, PtCl$_4$ itself also showed high activity (Entry 9). Sames et al. reported intramolecular hydroarylation by using PtCl$_4$ catalyst in neutral solvent such as dichloromethane, dioxane and toluene.$^1$ On the other hand, other tetravalent platinum, K$_2$PtCl$_6$/AgOTf and K$_2$PtCl$_6$/Bu$_4$NCl showed low activity (Entries 10 and 11).

2.2. Solvent effect in the PtCl$_4$/AgOTf-catalyzed hydroarylation

Then, the reaction with PtCl$_4$/AgOTf catalyst was investigated because it was expected to catalyze the hydroarylation in a neutral solvent instead of TFA (Eq. 4). The results are summarized in Table 8. The reaction took place in 1,2-dichloroethane (DCE) even at room temperature (Entries 1 and 2). Improvement of catalytic activity of PtCl$_4$ by addition of AgOTf was also observed in this reaction (Entry 3). Unfortunately, the product selectivity was low compared to that in TFA. In this case, even the formation of tri-alkenylated product 10 was observed although the yield was very low. The product selectivity was improved
when 1a was used as solvent but the selectivity was not still sufficient (Entry 4). The reaction did not take place in tert-butyl alcohol, ethanol, acetonitrile and tetrahydrofuran (THF) (Entries 5-9). The reaction in chlorobenzene gave the similar results to that of DCE (Entry 10). The low activity was observed in the reaction of AcOH (Entry 11). Addition of a small amount of TFA improved the yields but the selectivity was still low (Entry 12).

![Chemical structure]

**Table 8.** Investigation of solvent in the PtCl₄/AgOTf-catalyzed hydroarylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. / °C</th>
<th>Conversion of 1a/%</th>
<th>GC Yields / %b 3a</th>
<th>4a</th>
<th>5a</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl(CH₂)₂Cl</td>
<td>60</td>
<td>58</td>
<td>24 (25)</td>
<td>16</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>Cl(CH₂)₂Cl</td>
<td>r.t.</td>
<td>50</td>
<td>24 (14)</td>
<td>14</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>Cl(CH₂)₂Clc</td>
<td>r.t.</td>
<td>16</td>
<td>12</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1a d</td>
<td>60</td>
<td>-</td>
<td>18</td>
<td>3</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>CH₃CN</td>
<td>60</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>tBuOH</td>
<td>r.t.</td>
<td>0</td>
<td>trace</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>EtOH</td>
<td>60</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>r.t.</td>
<td>0</td>
<td>trace</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>60</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>PhCl</td>
<td>60</td>
<td>56</td>
<td>28</td>
<td>17</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>11</td>
<td>AcOH</td>
<td>r.t.</td>
<td>19</td>
<td>14</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>TFA f</td>
<td>r.t.</td>
<td>69</td>
<td>29</td>
<td>22</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>TFA</td>
<td>r.t.</td>
<td>94</td>
<td>63</td>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*a* Reaction conditions: 1a (2 mmol), 2a (2.4 mmol), PtCl₄ (0.05 mmol) AgOTf (0.1 mmol), solvent (1 mL) for 15h.

*b* Yields based on 1a. The isolated yields were in parentheses.

*c* AgOTf was not used.

*d* 1a (1mL, ca. 3 equivalents to 2a) was used.

*e* Yield based on 2a.

*f* TFA (0.1 mL) and CH₂Cl₂ (0.9 mL) were used as solvent.
2.3. K₂PtCl₄/AgOTf-catalyzed hydroarylation

2.3.1. Optimization of K₂PtCl₄/AgOTf-catalyzed hydroarylation

Then, the reaction with TFA as solvent was investigated again. As shown above, the activity of K₂PtCl₄/AgOTf is high for the hydroarylation. Moreover, K₂PtCl₄ is stable, one of the most readily available and cheapest platinum salts, and has often been used in organic synthesis. Therefore, K₂PtCl₄ was chosen as a pre-catalyst for the hydroarylation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalysts</th>
<th>(mol%)</th>
<th>Conversion of 1a /%</th>
<th>Yields / %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂PtCl₄</td>
<td>(2.5)</td>
<td>68</td>
<td>58 4 trace</td>
</tr>
<tr>
<td>2</td>
<td>K₂PtCl₄c</td>
<td>(2.5)</td>
<td>91</td>
<td>58 19 1</td>
</tr>
<tr>
<td>3</td>
<td>K₂PtCl₄ / H₂O (2.5 / 10 mmol)</td>
<td>77</td>
<td>52 7 3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>K₂PtCl₄ / CH₃CNd (2.5 / 1 mL)</td>
<td>1</td>
<td>0 0 0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>K₂PtCl₄ / AgOTf (2.5 / 5)</td>
<td>92</td>
<td>66 24 0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>K₂PtCl₄ / Ag₂CO₃ (2.5 / 5)</td>
<td>80</td>
<td>68 10 trace</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>K₂PtCl₄ / AgOAc (2.5 / 5)</td>
<td>77</td>
<td>65 11 trace</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>PtCl₂ / AgOTf (2.5 / 5)</td>
<td>84</td>
<td>67 16 0</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>PtCl₂</td>
<td>(2.5)</td>
<td>43</td>
<td>39 2 0</td>
</tr>
</tbody>
</table>

a Reaction conditions: 1a (2 mmol), 2a (2.4 mmol), catalysts, TFA (1 mL) at room temperature for 15h.
b GC yields based on 1a.
c The reaction was conducted at 70°C.
d the reaction was conducted at 50°C.

K₂PtCl₄ catalyst was used in the reaction of 1a with 2a (Table 9). K₂PtCl₄ itself gave high conversion at higher temperature although the yields were not high (Entry 2). It is known that K₂PtCl₄ is easily dissolved in water. Addition of water improved the conversion of 1a but the product yields were not high probably due to hydrolysis of products (Entry 3). Addition of acetonitrile hampered the reaction (Entry 4). Addition of AgOTf was most effective among the conditions examined.
2.3.2. The scope of the reaction

Next, the reaction of various arenes with 2a was examined using K2PtCl4/AgOTf as a catalyst. The results are listed in Table 10. The reaction of 1a gave 3a and 4a in 85 and 10% yields, respectively (Entry 1). Increasing the amount of 1a improved the yield of 3a (Entry 2). The similar results were obtained when 1% K2PtCl4 and 4%AgOTf were used as catalysts (Entries 3 and 4) (The effect of the ratio of K2PtCl4/AgOTf was also examined. See Table 21 and 22 in Experimentals.). When the reaction was conducted with 3 equivalents of 2a, 4a and 10 were obtained in 56 and 25% yields, respectively (Entry 5). The reaction of electron-rich arene 1b gave cinnamate 3b in high yield (Entry 6). The high yield of 3b was observed even though a little excess of 1b was used (Entry 7). The reaction rate was similar to that of PtCl2/AgOTf catalyst and slower than Pd(OAc)2 catalyst as shown in Figure 5. In the case of 1f, the reaction gave mono-alkenylated product 3f and di-alkenylated product 4c similarly to the reaction of 1a. In this case, use of 3 equivalents of 1f improved the selectivity of 3f (Entry 8). Inversely, using an excess amount of 2a afforded 4c in good yield as a main product (Entry 9). The reaction of 1d gave adduct 3d along with formation of 6d that is derived from the hydrolysis of 3d, resulting in the low selectivity of 3d. The reaction at room temperature gave 3d and 6d in 69 and 14% yields, respectively (Entry 10). Elevation of temperature resulted in decrease in the yield of 3d (Entry 11). The similar result was obtained even when 2.5% K2PtCl4 and 10%AgOTf were used as a catalyst (Entry 12 and 13). Since the complete conversion of 2a was observed from GC analysis of the reaction mixture, it was thought that the hydroarylation was completed and the succeeding hydrolysis of 3d took place during the reaction. Therefore, it was expected that hydroarylation of propiolic acid (2c) instead of ester 2a should be the best substrate for the hydroarylation.
Table 10. K₂PtCl₄/AgOTf-catalyzed hydroarylation of 2a with various arenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar-H</th>
<th>Cat.</th>
<th>Temp.</th>
<th>Time / h</th>
<th>Products and Yields / %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a A</td>
<td>A</td>
<td>r.t.</td>
<td>15</td>
<td>3a (85) 4a (10)</td>
</tr>
<tr>
<td>2</td>
<td>1a A</td>
<td>r.t.</td>
<td>15</td>
<td>3a (89)c</td>
<td>4a (6)c</td>
</tr>
<tr>
<td>3</td>
<td>1a A</td>
<td>r.t.</td>
<td>10</td>
<td>3a 81 (83)</td>
<td>4a 9 (9)</td>
</tr>
<tr>
<td>4</td>
<td>1a B</td>
<td>B</td>
<td>r.t.</td>
<td>17</td>
<td>3a 89e 4a 6e</td>
</tr>
<tr>
<td>5</td>
<td>1a A</td>
<td>r.t.</td>
<td>40</td>
<td>4a 56g</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1b A</td>
<td>A</td>
<td>r.t.</td>
<td>10</td>
<td>3b (94)c</td>
</tr>
<tr>
<td>7</td>
<td>1b A</td>
<td>r.t.</td>
<td>20</td>
<td></td>
<td>3b 93 (89)c,d</td>
</tr>
<tr>
<td>8</td>
<td>1f A</td>
<td>r.t.</td>
<td>25</td>
<td>3f 82e</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1f A</td>
<td>r.t.</td>
<td>45</td>
<td>3f 19f</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1d A</td>
<td>A</td>
<td>r.t.</td>
<td>25</td>
<td>3d 69 (69) (Z/E = 100/2)</td>
</tr>
<tr>
<td>11</td>
<td>1d A</td>
<td>40°C</td>
<td>25</td>
<td></td>
<td>3d 45 (Z/E = 100 / 9)</td>
</tr>
<tr>
<td>12</td>
<td>1d C</td>
<td>r.t.</td>
<td>15</td>
<td>3d (68)e</td>
<td>6d 13e (Z/E = 100/2)</td>
</tr>
<tr>
<td>13</td>
<td>1d C</td>
<td>r.t.</td>
<td>25</td>
<td>3d (69)e</td>
<td>6d 13e (Z/E = 100/2)</td>
</tr>
<tr>
<td>14</td>
<td>1d B</td>
<td>r.t.</td>
<td>40</td>
<td>3d (57)  (Z/E = 100/1)</td>
<td>6d 16 (Z/E = 100/2)</td>
</tr>
</tbody>
</table>

a Reaction conditions: K₂PtCl₄, AgOTf, arene (4 mmol), 2a (2 mmol), TFA (1 mL).

b Isolated yields based on 2a. The yields in parentheses are GC yields.

c CH₂Cl₂ (0.25 mL) was added.

d 1b (2.1 mmol) was used.

e Arene 1 (6 mmol) was used.

f 1f (2 mmol) and 2a (4.8 mmol) were used. The yields were based on 1f.

g 1a (2 mmol) and 2a (6 mmol) were used. 3a (6%, GC yield) was also observed. The yields are based on 1a.
Table 11. K$_2$PtCl$_4$/AgOTf-catalyzed hydroarylation of 2c with various arenes$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar$-\text{H}$</th>
<th>Cat.$^b$</th>
<th>Temp. / °C</th>
<th>Time / h</th>
<th>Products and Yields / %$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>1a</td>
<td>r.t.</td>
<td>15</td>
<td>Ar$\equiv$CO$_2$H$^6$a 96</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1a</td>
<td>r.t.</td>
<td>12</td>
<td>Ar$\equiv$CO$_2$H$^6$a 95 (92)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1b</td>
<td>r.t.</td>
<td>15</td>
<td>Ar$\equiv$CO$_2$H$^5b$ 96$^d$</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1c</td>
<td>40</td>
<td>40</td>
<td>Ar$\equiv$CO$_2$H$^6c$ 83 (Z/E = 100/8)$^e$</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>1d</td>
<td>r.t.</td>
<td>25</td>
<td>Ar$\equiv$CO$_2$H$^6d$ 93</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>1d</td>
<td>r.t.</td>
<td>40</td>
<td>Ar$\equiv$CO$_2$H$^6d$ 96 (91)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>1e</td>
<td>40</td>
<td>40</td>
<td>Ar$\equiv$CO$_2$H$^6e$ 88$^f$</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>1g</td>
<td>r.t.</td>
<td>45</td>
<td>Ar$\equiv$CO$_2$H$^6f$ 75$^g$</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>1h</td>
<td>r.t.</td>
<td>45</td>
<td>Ar$\equiv$CO$_2$H $^9$trace$^g$</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>1h</td>
<td>40</td>
<td>96</td>
<td>Ar$\equiv$CO$_2$H $^h$trace$^h$</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: catalyst, arene (6 mmol), 2c (2 mmol) and TFA (1 mL).
$^b$ Catalyst A: K$_2$PtCl$_4$ (0.05 mmol) and AgOTf (0.1 mmol). B: K$_2$PtCl$_4$ (0.02 mmol) and AgOTf (0.08 mmol).
$^c$ Isolated yields based on 2c. The yields purified by silica-gel column chromatography are in the parentheses.
$^d$ 1b (3 mmol) was used. CH$_2$Cl$_2$ (0.25 mL) was added.
$^e$ 1c (4 mmol) was used. Cl(CH$_2$)$_2$Cl (0.75 mL) was added.
$^f$ CH$_2$Cl$_2$ (0.5 mL) was added.
$^g$ CH$_2$Cl$_2$ (1 mL) was used.
$^h$ Cl(CH$_2$)$_2$Cl (0.5 mL) was used.
Figure 5. Time course of the K$_2$PtCl$_4$/AgOTf-catalyzed hydroarylation of 2a with 1b$^a$

![Graph showing the time course of the reaction](image)

$^a$ Reaction conditions: 1b (4 mmol), 2a (2 mmol), pentadecane (0.2g, as internal standard), K$_2$PtCl$_4$ (0.05 mmol), AgOTf (0.1 mmol), TFA (1 mL) and CH$_2$Cl$_2$ (0.5 mL) at 30°C. GC yield based on 2a.

Actually, the reaction of 2c with 1d gave 6d in 93% yield (Table 11, Entry 5). The hydroarylation of 2c with various arenes generally gave the corresponding cinnamic acid 6 in high yield. The similar results were also obtained when 1% K$_2$PtCl$_4$ and 4% AgOTf were used. The reactions of 1a and 1b gave cinnamic acids 6a and 6b in high yields, respectively (Entries 1 and 3). The reaction of 1c also gave 6c in 83% yield (Entry 4). Less reactive 1e having an electron-withdrawing bromine atom also gave 6e in sufficient yield although the reaction was carried out at 40°C (Entry 7). Next, sterically hindered arenes, 1,4-di-tert-butylbenzene (1g) and 1,3,5-tri-tert-butylbenzene (1h), were examined because this reaction was applicable to sterically crowded arenes such as 1a, 1b and 1e. The reaction of 1g proceeded to afford adduct 6f in 75% yield although the yield was lower than that of the similar arene 1d (Entry 8). On the other hand, no hydroarylation products were obtained in the reaction of more sterically hindered arene 1h. The $^1$H NMR analyses of the reaction...
mixture showed that most of 2c still remained after the reaction at room temperature because the reaction was very slow (Entry 9). Elevation of temperature improved the conversion of 2c but no products were obtained (Entry 10).

**Table 12.** K$_{2}$PtCl$_{4}$/AgOTf-catalyzed hydroarylation of 2c acid with toluene.$^{a}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst$^{b}$</th>
<th>Time / h</th>
<th>Yield / %$^{c}$</th>
<th>Ratio (o-6g/p-6g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>o-6g (Z/E)</td>
<td>p-6g (Z/E)</td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>25</td>
<td>48 (100/0.4)</td>
<td>24 (100/4)</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>42</td>
<td>58 (100/1)</td>
<td>21 (100/19)</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>40</td>
<td>49 (100/1)</td>
<td>19 (100/21)</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>60</td>
<td>53 (100/1)</td>
<td>14 (100/53)</td>
</tr>
</tbody>
</table>

$^{a}$ Reaction conditions: K$_{2}$PtCl$_{4}$, AgOTf, toluene (6 mmol), 2c (2 mmol), TFA (1 mL) at 30°C.

$^{b}$ Catalyst A: K$_{2}$PtCl$_{4}$ (0.05 mmol) and AgOTf (0.1 mmol). B: K$_{2}$PtCl$_{4}$ (0.02 mmol) and AgOTf (0.08 mmol).

$^{c}$ The yields are based on 2c and determined by $^{1}$H NMR.

$^{d}$ Two regioisomers were observed in $^{1}$H NMR.

In the case of toluene, *ortho-* and *para-*isomers of hydroarylation products 6g were obtained together with the double-hydroarylation products 11a (Table 12). When 2.5% K$_{2}$PtCl$_{4}$ and 5%AgOTf were used, the *ortho-* and *para-*isomers of 6g were obtained in good yields with an almost statistical ratio (*ortho*/para* = 2.0/1) (Entry 1). After the complete consumption of 2c, a considerable amount of 11a was formed although the yields of 6g were also improved (Entry 2). At the same time, the ratio of *ortho-* and *para-*isomers was also increased to be 2.8/1. When 1% K$_{2}$PtCl$_{4}$ and 4%AgOTf were used, similar result was obtained after the consumption of 2c (Entry 3). The elongation of reaction resulted in a larger amount of 11a along with increasing the ratio of *ortho*/para* (3.9/1) (Entry 4). Such a tendency was clearly observed in the time course of the reaction (Fig. 6). At first, the
reaction gave ortho- and para-6g in the almost statistical ratio (1.8-2.0/1). After that, only the para-6g was decreased along with increasing the amount of 11a. During the decrease of the para-6g, the amount of ortho-6g was almost retained. The results mean that only para-6g participates into the second hydroarylation. It is considered that the ortho-methyl group in ortho-6g prevents the second hydroarylation probably due to steric hindrance. This is also consistent with the fact that 3a, 3b and 3d that have ortho-methyl groups did not undergo the second hydroarylation.

**Figure 6.** Time course of the hydroarylation of 2c with toluene (1%K₂PtCl₄/4%AgOTf)\(^a\)

Finally, the reaction of a parent arene, benzene, with 2c was examined by using K₂PtCl₄/AgOTf catalyst (Table 13). The reaction with 3 equivalents of benzene afforded (Z)-cinnamic acid in 26% yield (Entry 1). The yield was improved by elongation of reaction
time (Entry 2). Elevation of temperature to 40°C also improved the yield but the isomerization occurred to give (E)-cinnamic acid as a main product (Entry 3). Using 6 equivalents of benzene also improved the yield although the reaction was slower (Entries 4 and 5). Again, elevation of temperature gave the similar yield with shorter reaction time although the stereoselectivity was decreased (Entry 6). Further increasing the amount of benzene did not improve the yield (Entry 7). The reaction for 30 h improved the stereoselectivity although the yield was slightly decreased (Entry 8). The similar yields were obtained even when 1% K₂PtCl₄ and 4%AgOTf were used (Entries 9 and 10). Increasing the catalyst loading with same catalyst ratio (2.5% K₂PtCl₄/10%AgOTf) improved the yield slightly (Entries 11 and 12). Addition of trifluoroacetic anhydride only retarded the reaction (Entry 13). Although the yields were slightly improved during this examination, the highest yield in this reaction was around 60%. When the reaction was monitored by ¹H NMR, it was observed that the product selectivity was around 60% during the reaction (Table 14). The fact that the highest yield was 60% can be explained by the product selectivity.

Table 14. Time dependence of Pt-catalyzed hydroarylation 2c with benzene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time / h</th>
<th>Conversion of 2c / %b</th>
<th>Yield of 6h / %b (Z/E)</th>
<th>Selectivity / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>45</td>
<td>27 (97/3)</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>100</td>
<td>59 (88/12)</td>
<td>59</td>
</tr>
</tbody>
</table>

a Reaction conditions: K₂PtCl₄ (0.05 mmol), AgOTf (0.2 mmol), benzene (12 mmol), 2c (2 mmol), n-heptadecane (14 mg, as internal standard), TFA (1 mL), r.t. (30min) then 40°C (25h).

b The conversion of 2c, the yield of 6g and Z/E ratio were determined by ¹H NMR.
Table 13. \( \text{K}_2\text{PtCl}_4/\text{AgOTf-catalyzed hydroarylation of } 2\text{c} \) with benzene\(^a\)

\[
\text{Ph} - \text{H} + \equiv \equiv \text{CO}_2\text{H} \quad 2\text{c} \quad \text{Ph} \equiv \equiv \text{CO}_2\text{H} + \text{Ph} \equiv \equiv \text{CO}_2\text{H}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Benzene / eq.</th>
<th>Temp. / °C</th>
<th>Time / h</th>
<th>Yield of 6h / % (Z/E)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{K}_2\text{PtCl}_4/\text{AgOTf} ) (2.5/5)</td>
<td>3</td>
<td>r.t.</td>
<td>40</td>
<td>26 (100/1)</td>
</tr>
<tr>
<td>2</td>
<td>( \text{K}_2\text{PtCl}_4/\text{AgOTf} ) (2.5/5)</td>
<td>3</td>
<td>r.t.</td>
<td>72</td>
<td>50 (100/5)</td>
</tr>
<tr>
<td>3</td>
<td>( \text{K}_2\text{PtCl}_4/\text{AgOTf} ) (2.5/5)</td>
<td>3</td>
<td>40</td>
<td>40</td>
<td>53 (1/4.36)</td>
</tr>
<tr>
<td>4</td>
<td>( \text{K}_2\text{PtCl}_4/\text{AgOTf} ) (2.5/5)</td>
<td>6</td>
<td>r.t.</td>
<td>40</td>
<td>15 (100/1)</td>
</tr>
<tr>
<td>5</td>
<td>( \text{K}_2\text{PtCl}_4/\text{AgOTf} ) (2.5/5)</td>
<td>6</td>
<td>r.t.</td>
<td>70</td>
<td>54 (100/1)</td>
</tr>
<tr>
<td>6</td>
<td>( \text{K}_2\text{PtCl}_4/\text{AgOTf} ) (2.5/5)</td>
<td>6</td>
<td>40</td>
<td>40</td>
<td>61 (100/7)</td>
</tr>
<tr>
<td>7</td>
<td>( \text{K}_2\text{PtCl}_4/\text{AgOTf} ) (2.5/5)</td>
<td>12</td>
<td>40</td>
<td>45</td>
<td>55 (100/2)</td>
</tr>
<tr>
<td>8</td>
<td>( \text{K}_2\text{PtCl}_4/\text{AgOTf} ) (2.5/5)</td>
<td>6</td>
<td>40</td>
<td>30</td>
<td>58 (100/2) [55] (100/3)</td>
</tr>
<tr>
<td>9</td>
<td>( \text{K}_2\text{PtCl}_4/\text{AgOTf} ) (1/4)</td>
<td>6</td>
<td>40</td>
<td>40</td>
<td>53 (100/2)</td>
</tr>
<tr>
<td>10</td>
<td>( \text{K}_2\text{PtCl}_4/\text{AgOTf} ) (1/4)</td>
<td>6</td>
<td>r.t.</td>
<td>75</td>
<td>58 (100/2) [55] (100/2)</td>
</tr>
<tr>
<td>11</td>
<td>( \text{K}_2\text{PtCl}_4/\text{AgOTf} ) (2.5/10)</td>
<td>6</td>
<td>40</td>
<td>25</td>
<td>66 [57] (100/8)(^c)</td>
</tr>
<tr>
<td>12</td>
<td>( \text{K}_2\text{PtCl}_4/\text{AgOTf} ) (2.5/10)</td>
<td>6</td>
<td>r.t.</td>
<td>60</td>
<td>64 (100/4) [58] (100/4)</td>
</tr>
<tr>
<td>13</td>
<td>( \text{K}_2\text{PtCl}_4/\text{AgOTf} ) (2.5/10)(^d)</td>
<td>6</td>
<td>40</td>
<td>45</td>
<td>26 (45/100)</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: \( \text{K}_2\text{PtCl}_4, \text{AgOTf, benzene, 2c (2 mmol) and TFA (1 mL).} \)
\(^b\) Isolated yield based on 2c. The yields purified by silica-gel column chromatography are in [ ]. The NMR yields are in { }. Z/E ratio was determined by \(^1\)H NMR.
\(^c\) 3,3-Diphenylpropionic acid (11b) was formed in 2% yield.
\(^d\) Trifluoroacetic anhydride (1.2 mmol) was added.

Table 15. \( \text{K}_2\text{PtCl}_4/\text{AgOTf-catalyzed hydroarylation of } 2\text{d} \) with arenes\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar−H</th>
<th>Temp. / °C</th>
<th>Time / h</th>
<th>Products and Yields / %(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( 1\text{a} )</td>
<td>40</td>
<td>37</td>
<td>( \text{Ph} \equiv \equiv \text{CO}_2\text{H} \quad 8\text{a} ) 70(^c)</td>
</tr>
<tr>
<td>2</td>
<td>( 1\text{a} )</td>
<td>r.t.</td>
<td>40</td>
<td>( \text{Ar} \equiv \equiv \text{CO}_2\text{H} \quad 8\text{a} ) 86(^d)</td>
</tr>
<tr>
<td>3</td>
<td>( 1\text{b} )</td>
<td>r.t.</td>
<td>40</td>
<td>( \text{Ph} \equiv \equiv \text{CO}_2\text{H} \quad 8\text{b} ) 69</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: \( \text{K}_2\text{PtCl}_4 (0.05 mmol), \text{AgOTf (0.10 mmol), arene (4 mmol), 2d (2 mmol), TFA (1 mL).} \)
\(^b\) Isolated yields based on 2d.
\(^c\) \( \text{Cl(CH}_2)_2\text{Cl (0.5 mL) was added.} \)
\(^d\) \( 1\text{a} (6 mmol) was used. \)
The $\text{K}_2\text{PtCl}_4/\text{AgOTf}$ catalyst was again applied to the reaction of phenylpropionic acid ($2d$) as shown in Table 15. The reaction with $1a$ at 40°C gave the product $8a$ in 70% yield (Entry 1). The reaction at room temperature also proceeded to improve the yield probably due to the suppression of side reactions (Entry 2). Highly reactive arene $1b$ gave the corresponding cinnamic acid $8b$, but the yield was lower than that of $1a$ (Entry 3). The low solubility of $2d$ may cause the decrease of the yield. Unfortunately, in the case of $1d$, any hydroarylated products were not obtained. $1d$ is less reactive than $1a$ and $1b$, in addition to lower reactivity of $2c$ compared to $2b$. In this case, the formation of benzoylacetic acid which is derived from the addition of TFA to $2c$ was observed.

### 2.4. The hydroarylation of propiolic acid with benzene by other Pt catalysts

The other Pt catalysts were also examined as shown in Table 16. PtCl$_4$/AgOTf, PtCl$_2$(bpy)/AgOTf and (Bu$_4$N)$_2$PtCl$_4$/AgOTf also gave the similar results to that of K$_2$PtCl$_4$/AgOTf catalyst but (Bu$_4$N)$_2$PtCl$_4$ gave an inferior result (Entries 1-6). In the reaction with PtCl$_4$/AgOTf, a larger amount of 3,3-diphenylpropionic acid ($11b$) was observed. PtCl$_4$/AgOTf seemed to be very active because the reaction was very quick even when 1%PtCl$_4$ and 4%AgOTf were used (Entry 3). The reaction using PtCl$_2$/AgOTf was slower than that using the other Pt catalysts (Entry 7). The reaction using Pd(OAc)$_2$ gave low yield because of low selectivity although the reaction was very fast to complete the reaction in 10 h (Entries 8 and 9).
Table 16. Hydroarylation of 2c with benzene\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Benzene / eq.</th>
<th>Temp. / °C</th>
<th>Time / hr</th>
<th>Yield / % of 6h (Z/E)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PtCl(_4)/AgOTf (2.5/10)</td>
<td>6</td>
<td>40</td>
<td>25</td>
<td>56 (100/57)(^c)</td>
</tr>
<tr>
<td>2</td>
<td>PtCl(_4)/AgOTf (2.5/10)</td>
<td>6</td>
<td>40</td>
<td>10</td>
<td>61 (100/21)(^d)</td>
</tr>
<tr>
<td>3</td>
<td>PtCl(_4)/AgOTf (1/4)</td>
<td>6</td>
<td>40</td>
<td>11</td>
<td>60 (100/6)(^e)</td>
</tr>
<tr>
<td>4</td>
<td>PtCl(_2)(bpy)/AgOTf (2.5/5)</td>
<td>6</td>
<td>40</td>
<td>24</td>
<td>61 (100/10)</td>
</tr>
<tr>
<td>5</td>
<td>(NBu(_4))(_2)PtCl(_4)/AgOTf (2.5/5)</td>
<td>6</td>
<td>r.t.</td>
<td>70</td>
<td>(53) (100/7)(^f)</td>
</tr>
<tr>
<td>6</td>
<td>(NBu(_4))(_2)PtCl(_4) (2.5)</td>
<td>6</td>
<td>r.t.</td>
<td>70</td>
<td>(31) (100/18)(^f)</td>
</tr>
<tr>
<td>7</td>
<td>PtCl(_2)/AgOTf (2.5/5)</td>
<td>6</td>
<td>r.t.</td>
<td>70</td>
<td>35 (100/1)</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)(_2) (2.5)</td>
<td>6</td>
<td>r.t.</td>
<td>10</td>
<td>11 (100/0.6)(^g)</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)(_2) (2.5)</td>
<td>6</td>
<td>r.t.</td>
<td>24</td>
<td>10 (100/0.6)(^g)</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: catalyst, benzene, 2c (2 mmol) and TFA (1 mL).

\(^b\) Isolated yield based on 2c. The yield in parentheses was determined by \(^1\)H NMR. Z/E ratio was determined by \(^1\)H NMR.

\(^c\) 3,3-Diphenylpropionic acid (11b) was obtained in 7% yield.

\(^d\) 11b was obtained in 5% yield.

\(^e\) 11b was obtained in 2% yield.

\(^f\) (NBu\(_4\))\(_2\)PtCl\(_4\) was prepared from K\(_2\)PtCl\(_4\) and \(^n\)Bu\(_4\)NCl.

\(^g\) The procedure: after a mixture of Pd(OAc)\(_2\), benzene and TFA was stirred on an ice/water bath, 2c was added to the cold mixture.

2.5. Consideration of the reaction mechanism

A recent report by Tunge and Foresee suggested that the Pd(OAc)\(_2\)-catalyzed hydroarylation of alkyne proceeds via electrophilic aromatic substitution.\(^2\) Because the Pd- and Pt-catalyzed hydroarylation proceeds under the similar reaction conditions, the Pt-catalyzed hydroarylation is also considered to proceed via electrophilic aromatic substitution mechanism. The electrophilic aromatic substitution mechanism is depicted in Scheme 1. The cationic Pt species which is generated from Pt salt and Ag compound initiates the reaction by the coordination to a propiolic acid. The resulting activated propiolic acid complex attacks to an arene electrophilically to form a Wheland intermediate. Proton release followed by protonolysis of a platinum-vinyl species results in the formation of a cinnamic acid with concomitant regeneration of an active Pt species, which completes the
catalytic cycle. In the formation of a diarylpropionic acid, the resulting cinnamic acid undergoes the second hydroarylation by Pt catalyst in the similar way as describe above. In addition to the Pt-catalysis, acid catalyzed hydroarylation is also possible for the second hydroarylation because it was reported that the hydroarylation of ethyl \( p \)-methylcinnamate with 2-naphthol was catalyzed by TFA to give dihydrocoumarin.\(^3\)

**Scheme 1.** Plausible reaction mechanism of Pt-catalyzed hydroarylation.
In summary, several Pt catalyst precursors such as \( \text{K}_2\text{PtCl}_4 \), \((\text{Bu}_4\text{N})_2\text{PtCl}_4\), \(\text{PtCl}_2\text{bpy}\) and \(\text{PtCl}_4\) showed higher activity than \(\text{PtCl}_2\). \((\text{Bu}_4\text{N})_2\text{PtCl}_4\) and \(\text{PtCl}_4\) also showed high activity in the absence of \(\text{AgOTf}\). Particularly, \(\text{PtCl}_4\) catalyzed the hydroarylation even in neutral solvent. Among the Pt catalyst precursors, \(\text{K}_2\text{PtCl}_4\) is readily available and cheapest. \(\text{K}_2\text{PtCl}_4/\text{AgOTf}\) catalyst worked efficiently in the hydroarylation of propiolates to afford cinnamates in good to high yields. In particular, the reaction of propiolic acids gave cinnamic acids in high yields in most cases. Noteworthy is a high activity of \(\text{K}_2\text{PtCl}_4/\text{AgOTf}, (\text{Bu}_4\text{N})_2\text{PtCl}_4/\text{AgOTf}, \text{PtCl}_2\text{bpy}/\text{AgOTf}\) and \(\text{PtCl}_4/\text{AgOTf}\) catalysts toward less reactive benzene.
**Experimentals**

**General**

All solvents and reagents were commercially available and used as received without further purification. All reactions were conducted in a dry Pyrex tube with a rubber septum. ^1H and ^13C NMR spectra were recorded on a JEOL JNM-AL 300 FT-NMR (300 MHz) using TMS as internal standard. Melting points were measured with YANACO micro melting apparatus and are uncorrected. The GC analyses were performed on a Shimadzu GC-14B using capillary column DB-1 (15m x 0.53mm internal diameter x 1.5 µm film thickness) with a flame ionization detector. GC yield was determined by internal standard method using n-pentadecane or n-heptadecane as internal standard. Mass spectra and GC-MS were measured on a Shimadzu GC/MS 5020A. Elemental analyses were performed by the Service Center of the Elementary Analysis of Organic Compounds, Faculty of Science, Kyushu University.

**General procedure for the Pd(OAc)$_2$-catalyzed hydroarylation of 2a with 1a.**

After a mixture of Pd(OAc)$_2$ (0.05 mmol), mesitylene (1a) (2 mmol) and CF$_3$CO$_2$H (TFA) (1 mL) was stirred for 5 min on an ice/water bath, ethyl propiolate (2a) was added to the cold mixture. Then, the mixture was stirred at the desired temperature for 15 h. After the reaction, n-heptadecane (0.2 g) as an internal standard was added to the reaction mixture. The mixture was poured into water (20 mL), neutralized by NaHCO$_3$ until the generation of CO$_2$ ceased. Then, the mixture was extracted with diethyl ether (20 mL x 3). The ethereal layer was analyzed by GC. The yields of the products and the conversion of 1a were determined by using the internal standard method. The results are given in Table 17.
Table 17. Pd(OAc)$_2$-catalyzed hydroarylation of 2a with 1a$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>2a / eq.</th>
<th>Time / h</th>
<th>Conversion of 1a / %</th>
<th>Yields / %$^b$</th>
<th>Selectivity / %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3a</td>
<td>4a</td>
</tr>
<tr>
<td>1</td>
<td>2.0</td>
<td>25</td>
<td>100</td>
<td>52</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>15</td>
<td>86</td>
<td>58</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>25</td>
<td>87</td>
<td>60</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>15</td>
<td>73</td>
<td>51</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
<td>25</td>
<td>76</td>
<td>55</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
<td>45</td>
<td>77</td>
<td>55</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>1.2</td>
<td>15</td>
<td>74$^c$</td>
<td>48</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>0.75</td>
<td>15</td>
<td>50</td>
<td>37</td>
<td>trace</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: 1a (2 mmol), 2a, Pd(OAc)$_2$ (0.05 mmol), TFA (1 mL) at room temperature.
$^b$ GC yields based on 1a.
$^c$ The reaction was conducted at 70°C.

General procedure for the investigation of silver additives and the optimization of the reaction conditions.

After a mixture of PtCl$_2$ (0.05 mmol), Ag compound, mesitylene (1a) (2 mmol) and CF$_3$CO$_2$H (TFA) (1 mL) was stirred for 5 min at room temperature, ethyl propiolate (2a) (2.4 mmol) was added to the mixture. The reaction mixture was stirred at room temperature (25-30°C) for 15 h. After the reaction, n-heptadecane (0.2 g) as an internal standard was added to the reaction mixture. The mixture was poured into water (20 mL), neutralized by NaHCO$_3$ until the generation of CO$_2$ ceased. Then, the mixture was extracted with diethyl ether (20 mL x 3). The ethereal layer was analyzed by GC. The yields of the products and the conversion of 1a were determined by using the internal standard method.

General procedure for effect of reaction temperature.

After a mixture of PtCl$_2$ (0.05 mmol), AgOTf (0.1 mmol), 1a (4 mmol) and TFA (1 mL) was stirred for 5 min at room temperature, 2a (2 mmol) was added to the mixture. The reaction mixture was stirred at the desired temperature for 8 h. After the reaction,
n-heptadecane (0.2 g) as an internal standard was added to the reaction mixture. The mixture was poured into water (20 mL), neutralized by NaHCO₃ and extracted with diethyl ether (20 mL x 3). The ethereal layer was analyzed by GC. The yields of the products were determined by using the internal standard method. After the ethereal layer was dried over anhydrous Na₂SO₄ and concentrated, the mixture was analyzed by ¹H NMR to determine the Z/E ratio of the products. The aqueous layer was acidified by aqueous HCl (ca. 36%) and extracted with diethyl ether (20 mL x 3). The ethereal layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford 6a. The Z/E ratio of 6a was determined by ¹H NMR.

**The procedure for time dependence of 3a under the reaction conditions.**

A mixture of PtCl₂ (0.05 mmol), AgOTf (0.1 mmol), 3a (1.5 mmol), heptadecane (12.3 mg, as an internal standard) and TFA (1 mL) was stirred for 5 min at room temperature. After a portion of the reaction mixture was analyzed by ¹H NMR, the reaction mixture was stirred at 70⁰C. After a certain period, a portion of the reaction mixture was analyzed by ¹H NMR. The yields of the products and the conversion of 3a were determined by using the internal standard method.

**General procedure for PtCl₂/AgOTf-catalyzed hydroarylation of 2a with various arenes.**

After a mixture of PtCl₂ (0.05 mmol), AgOTf (0.1 mmol), arene (4 mmol) and TFA (1 mL) was stirred for 5 minutes at room temperature, 2a (2 mmol) was added to the mixture. Then, the mixture was stirred at the desired temperature. After the reaction, the reaction mixture was poured into water (20 mL), neutralized by NaHCO₃ and extracted with diethyl ether (20 mL x 3). The ethereal layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a
mixture of ethyl acetate and hexane as eluent. To obtain the GC yield and the conversion, an internal standard, \(n\)-pentadecane or \(n\)-heptadecane, was added to the mixture after the reaction. The mixture was poured into water (20 mL), neutralized by NaHCO\(_3\) and extracted with diethyl ether (20 mL x 3). The ethereal layer was analyzed by GC.

**Typical example: the hydroarylation of 2a with 1d (Entry 5, Table 4);** After a mixture of PtCl\(_2\) (0.05 mmol), AgOTf (0.10 mmol), 1d (4 mmol) and TFA (1 mL) was stirred for 5 minutes at room temperature (25-30\(^\circ\)C), 2a (2 mmol) was added to the mixture. The mixture was continuously stirred at room temperature. After 40 h, the reaction mixture was poured into water (20 mL), neutralized by NaHCO\(_3\), and extracted with diethyl ether (20 mL x 3). The ethereal layer was dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate/hexane (1/40 to 1/20) as eluent. \((Z)\)-Ethyl 3-(2,5-dimethylphenyl)propenoate (3d) (1.26 mmol, 61.4\%) was isolated as colorless liquid and was confirmed by NMR.

**The procedure for time course of the hydroarylation of 2a with 1b (Fig. 4 and 5).**

After a mixture of PtCl\(_2\) (0.05 mmol), AgOTf (0.1 mmol), 1b (4 mmol), pentadecane (0.2 g, as an internal standard), CH\(_2\)Cl\(_2\) (0.5 mL) and TFA (1 mL) was stirred for 5 min at room temperature, 2a (2 mmol) was added to the mixture. The reaction mixture was stirred at room temperature. After a certain period, a portion of the reaction mixture (ca. 0.1 g) was poured into saturated NaHCO\(_3\) aqueous solution (1.5 mL) and extracted with CH\(_2\)Cl\(_2\) (2 mL). The organic layer was analyzed by GC. The yields of the products were determined by using the internal standard method.

**General procedure for PtCl\(_2\)/AgOTf-catalyzed hydroarylation of 2b.**

After a mixture of PtCl\(_2\) (0.05 mmol), AgOTf (0.1 mmol), arene (4 mmol) and TFA (1 mL)
was stirred for 5 min at room temperature, 2b (2 mmol) was added to the mixture. Then, the mixture was stirred at the desired temperature. After the reaction, the reaction mixture was poured into water (20 mL), neutralized by NaHCO₃ and extracted with diethyl ether (20 mL x 3). The ethereal layer was washed with aqueous 2N NaOH (20 mL) and water (20 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexane as eluent, affording 7. The combined aqueous layer was acidified by aqueous HCl (ca. 36%) and extracted with diethyl ether (20 mL x 3). The ethereal layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford cinnamic acid 8.

**General procedure for the PtCl₂/AgOTf-catalyzed hydroarylation of propiolic acids**

After a mixture of PtCl₂ (0.05 mmol), AgOTf (0.1 mmol), arene (4 mmol) and TFA (1 mL) was stirred for 5 min at room temperature, propiolic acid 2c or 2d (2 mmol) was added to the mixture. Then, the mixture was stirred at the desired temperature. After reaction, the reaction mixture was poured into water (20 mL), neutralized by NaHCO₃, and extracted with diethyl ether (20 mL). The ethereal layer was extracted with aqueous 2N NaOH (10 mL x 3). The combined aqueous layer was washed with diethyl ether (20 mL), acidified by aqueous HCl (ca. 36%), and extracted with CH₂Cl₂ (20 mL x 3). The CH₂Cl₂ layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford a cinnamic acid.

During the continuous study, it was found that a sufficient mixing of PtCl₂ and Ag compound is crucial for the efficient preparation of active catalyst. Table 18 shows the effect of the catalyst preparation method. When AgOAc was used as an additive, the yields were improved by changing method A to B which is more efficient method for active catalyst preparation than A. This is probably applicable to PtCl₂/AgOTf catalyst although it has not
been confirmed. Therefore, the mixing of PtCl₂ and Ag compound for a sufficient period is preferred for efficient catalyst preparation. Although the catalyst activity of PtCl₂/AgOAc was improved, PtCl₂/AgOTf is still more active catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalysts</th>
<th>(mol%)</th>
<th>Method b</th>
<th>Conversion of 1a (%)</th>
<th>Yields / % c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PtCl₂</td>
<td>(2.5)</td>
<td>A</td>
<td>43</td>
<td>39 2 0</td>
</tr>
<tr>
<td>2</td>
<td>PtCl₂ / AgOAc</td>
<td>(2.5 / 5)</td>
<td>A</td>
<td>41</td>
<td>36 1 0</td>
</tr>
<tr>
<td>3</td>
<td>PtCl₂ / AgOAc</td>
<td>(2.5 / 5)</td>
<td>B</td>
<td>59</td>
<td>53 4 0</td>
</tr>
<tr>
<td>4</td>
<td>PtCl₂ / AgOTf</td>
<td>(2.5 / 5)</td>
<td>A</td>
<td>84</td>
<td>67 16 0</td>
</tr>
<tr>
<td>5</td>
<td>PtCl₂ / AgOTf</td>
<td>(2.5 / 5)</td>
<td>B</td>
<td>88</td>
<td>65 18 0</td>
</tr>
</tbody>
</table>

a Reaction conditions : 1a (2 mmol), 2a (2.4 mmol), catalysts, TFA (1 mL) at room temperature for 15h.

b Method A : After a mixture of PtCl₂, Ag compound, 1a and TFA was stirred on ice/water bath for 10 min, 2a was added. Method B : After a mixture of PtCl₂, Ag compound and TFA was stirred at room temperature for 30 min, 1a and 2a were added.

c GC yields based on 1a.

**General procedure for the investigation of various Pt catalysts.**

After a mixture of Pt salt (0.05 mmol), AgOTf (0.1 mmol), 1a (2 mmol) and TFA (1 mL) was stirred for 5 min at room temperature, 2a (2.4 mmol) was added to the mixture. The reaction mixture was stirred at room temperature (25-30°C) for 15 h. After the reaction, n-heptadecane (ca. 0.2 g) as an internal standard was added to the reaction mixture. The mixture was poured into water (20 mL), neutralized by NaHCO₃ and extracted with diethyl ether (20 mL x 3). The ethereal layer was analyzed by GC. The yields of the products and the conversion of 1a were determined by using the internal standard method.

When (NBu₄)₂PtCl₄ was used as Pt salt or catalyst, the following procedure was used. K₂PtCl₄ (0.05 mmol) and Bu₄NCl (0.1 mmol) were mixed in a mix solvent of CH₂Cl₂/water
(0.5 mL/0.5 mL). After the aqueous layer become colorless and the organic layer turned to red, aqueous layer was separated. The organic layer was used as a \((\text{NBu}_4)_2\text{PtCl}_4\) solution without further purification. AgOTf (0.1 mmol) (if used) and TFA (1 mL) were added to the \((\text{NBu}_4)_2\text{PtCl}_4\) solution or \((\text{NBu}_4)_2\text{PtCl}_4\). After the mixture was stirred for 5 min., \(1\text{a}\) (2 mmol) and \(2\text{a}\) (2 mmol) was added.

In the cases of entry 7 in Table 7 and entries 5 and 6 in Table 16, the resulting \((\text{NBu}_4)_2\text{PtCl}_4\) solution was concentrated and dried under reduced pressure. The residue was used as \((\text{NBu}_4)_2\text{PtCl}_4\). Preparation of \((\text{NBu}_4)_2\text{PtCl}_4\) was conducted according to the reported method.4

In the case of \(\text{K}_2\text{PtCl}_6/\text{Bu}_4\text{NCl}\), the catalyst solution was prepared in the same way as the preparation of \((\text{NBu}_4)_2\text{PtCl}_4\).

**General procedure for the investigation of solvent in PtCl₄/AgOTf-catalyzed hydroarylation.**

**Typical example: the hydroarylation of 2a with 1a catalyzed by PtCl₄/AgOTf in 1,2-dichloroethane (DCE) (Table 8, Entry 1):** After a mixture of PtCl₄ (0.05 mmol), AgOTf (0.1 mmol), \(1\text{a}\) (2 mmol) and DCE (1 mL) was stirred for 5 min at room temperature, \(2\text{a}\) (2.4 mmol) was added to the mixture. The reaction mixture was stirred at 60°C for 15 h. After the reaction, \(n\)-heptadecane (ca. 0.2 g) as an internal standard was added to the reaction mixture. Diethyl ether (60 mL) was added to the mixture. The ethereal mixture was analyzed by GC. The yields of the products and the conversion of \(1\text{a}\) were determined by using the internal standard method. Neutralization and extraction was performed when acetic acid and TFA was used as solvent.

**General procedure for the K₂PtCl₆/AgOTf-catalyzed hydroarylation of 2a with arenes.**
After a mixture of K$_2$PtCl$_4$ (0.05 mmol) and AgOTf (0.1 mmol) in TFA (1 mL) was stirred at room temperature for 10 min, an arene and 2a were added to the mixture. Then, the mixture was stirred at the desired temperature. After the reaction, the reaction mixture was poured into water (20 mL), neutralized by NaHCO$_3$, and extracted with diethyl ether (20 mL x 3). The ethereal layer was dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexane as eluent.

**General procedure for the K$_2$PtCl$_4$/AgOTf-catalyzed hydroarylation of a propiolic acid.**

A mixture of K$_2$PtCl$_4$ (0.05 mmol) and AgOTf (0.10 mmol) in TFA (1 mL) was stirred at room temperature for 10 min. An arene and a propiolic acid were added to the mixture. Then, the mixture was stirred at the desired temperature. After a certain period, the reaction mixture was poured into water (20 mL), neutralized by NaHCO$_3$, and washed with Et$_2$O (20 mL). Then, the ethereal layer was extracted with aqueous 2N NaOH (10 mL x 3). The combined aqueous layer was washed with Et$_2$O (20 mL), acidified by aq HCl (ca. 36%) and extracted with CH$_2$Cl$_2$ (20 mL x 3). The organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure, affording cinnamic acids.

**The procedure for time course of the hydroarylation of 2c with toluene.**

After a mixture of K$_2$PtCl$_4$ (0.02 mmol) and AgOTf (0.08 mmol) in TFA (1 mL) was stirred at room temperature for 1 h, toluene (6 mmol), n-pentadecane (ca. 18 mg, as an internal standard) and 2c (2 mmol) were added. The reaction mixture was stirred at room temperature (30°C). After a certain period, a portion of the reaction mixture was analyzed by $^1$H NMR. The yields of the products and the conversion of 1c were determined by using the internal standard method. The results are given in Table 19 and Fig. 6.
Table 19. Time course of the hydroarylation of 2c with toluene

<table>
<thead>
<tr>
<th>Time / h</th>
<th>Conversion of 2c /%</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Z)-o-6g</td>
<td>(E)-o-6g</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>91</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
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</tr>
<tr>
<td>10</td>
<td>57</td>
<td>17</td>
</tr>
<tr>
<td>15</td>
<td>44</td>
<td>27</td>
</tr>
<tr>
<td>24</td>
<td>20</td>
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<td>60</td>
<td>0</td>
<td>48</td>
</tr>
<tr>
<td>85</td>
<td>0</td>
<td>48</td>
</tr>
</tbody>
</table>

Table 20. Effect of K₂PtCl₄/AgOTf preparation

<table>
<thead>
<tr>
<th>Entry</th>
<th>K₂PtCl₄ / mol%</th>
<th>AgOTf / mol%</th>
<th>Yields / %b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>3a</td>
</tr>
<tr>
<td>1</td>
<td>2.5</td>
<td>5</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>1.25</td>
<td>2.5</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>1.25</td>
<td>5</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>1.25</td>
<td>0</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>1.25</td>
<td>2.5</td>
<td>80c</td>
</tr>
</tbody>
</table>

a Reaction Conditions: 1a (4 mmol), 2a (2 mmol), K₂PtCl₄, AgOTf and TFA (1 mL), at room temperature for 15h. Procedure: K₂PtCl₄, AgOTf and 1a were stirred in TFA for 5 min, then 2a was added.

b GC yields based on 2a.

c Procedure: K₂PtCl₄ and AgOTf were stirred in TFA for 10 min, then 1a and 2a were added.

It is important to mix K₂PtCl₄ and AgOTf in TFA for active catalyst preparation. In the investigation of ratio of AgOTf to K₂PtCl₄, inconsistent results were obtained (Table 20). When the amounts of catalysts were decreased to 1.25% K₂PtCl₄ and 2.5% AgOTf, the yields were decreased (Entry 2). Increasing the amount of only AgOTf to 5% increased the yields.
(Entry 3). However, the reaction of 1.25% K$_2$PtCl$_4$ in the absence of AgOTf gave the similar yields to those of the reaction with 1.25% K$_2$PtCl$_4$ and 2.5% AgOTf (Entry 4). This result suggests that the efficiency for the formation of the active catalyst from K$_2$PtCl$_4$ and AgOTf is affected by its preparation process. Actually, when the catalyst was prepared by mixing K$_2$PtCl$_4$ and AgOTf in TFA for 10 min, the reaction with 1.25% K$_2$PtCl$_4$ and 2.5% AgOTf gave higher yields compared to the same reaction with the previous procedure (Entry 6).

### Table 21. Effect of the ratio of K$_2$PtCl$_4$/Ag compound in the hydroarylation$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalysts (mol%)</th>
<th>Method (Time)$^b$</th>
<th>Conversion of 1a (%)</th>
<th>Yields / %$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3a  4a  5a</td>
</tr>
<tr>
<td>1</td>
<td>K$_2$PtCl$_4$ / AgOAc (2.5 / 5)</td>
<td>A</td>
<td>77</td>
<td>65  11  trace</td>
</tr>
<tr>
<td>2</td>
<td>K$_2$PtCl$_4$ / AgOAc (2.5 / 5)</td>
<td>B (30 min)</td>
<td>93</td>
<td>70  21  trace</td>
</tr>
<tr>
<td>3</td>
<td>K$_2$PtCl$_4$ / AgOAc (1 / 2)</td>
<td>B (50 min)</td>
<td>54</td>
<td>48  3   0</td>
</tr>
<tr>
<td>4</td>
<td>K$_2$PtCl$_4$ / AgOAc (1 / 2)</td>
<td>B (80 min)</td>
<td>88</td>
<td>69  16  0</td>
</tr>
<tr>
<td>5</td>
<td>K$_2$PtCl$_4$ / AgOAc (1 / 4)</td>
<td>B (80 min)</td>
<td>90</td>
<td>69  17  trace</td>
</tr>
<tr>
<td>6</td>
<td>K$_2$PtCl$_4$ (1)</td>
<td>B (80 min)</td>
<td>54</td>
<td>45  2   1</td>
</tr>
<tr>
<td>7</td>
<td>K$_2$PtCl$_4$ (2.5)</td>
<td>A</td>
<td>68</td>
<td>58  4   trace</td>
</tr>
<tr>
<td>8</td>
<td>K$_2$PtCl$_4$ / AgOTf (2.5 / 5)</td>
<td>A</td>
<td>92</td>
<td>66  24  0</td>
</tr>
<tr>
<td>9</td>
<td>K$_2$PtCl$_4$ / AgOTf (1 / 2)</td>
<td>B (1 h)</td>
<td>92</td>
<td>65  22  0</td>
</tr>
<tr>
<td>10</td>
<td>K$_2$PtCl$_4$ / AgOTf (1 / 4)</td>
<td>B (1 h)</td>
<td>93</td>
<td>65  23  0</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: 1a (2 mmol), 2a (2.4 mmol), catalysts, TFA (1 mL) at room temperature for 15 h.

$^b$ Method A: After a mixture of K$_2$PtCl$_4$, Ag compound, 1a and TFA was stirred at room temperature for 10 min, 2a was added. Method B: After a mixture of K$_2$PtCl$_4$, Ag compound and TFA was stirred at room temperature for a certain period (described in Table), 1a and 2a were added.

$^c$ GC yields based on 1a.

The effect of the ratio of K$_2$PtCl$_4$ and the silver compound was also investigated because 4 equivalents of the silver compound were required for a molecule of K$_2$PtCl$_4$ theoretically if all of the chlorine atoms of K$_2$PtCl$_4$ could be substituted (Table 21). In the case of K$_2$PtCl$_4$/AgOAc, it was observed that the catalyst activity was improved when the catalyst preparation was prolonged. Changing method A to B improved the conversion and the
yields (Entries 1 and 2). When the catalyst loading was decreased, the catalyst activity was as low as that in the absence of AgOAc (Entry 3). However, the catalyst activity was improved again by the elongation of the catalyst preparation (Entry 4). When the amount of AgOAc was increased to be 4 equivalents to K₂PtCl₄, no effect was observed because the reaction was almost completed (Entries 4 and 5). Therefore, the reaction time was shortened to be 5 h (Table 22). The results revealed clearly that use of 4 equivalents of the silver compound was more effective than that of 2 equivalents. Of course, the effect was greater than the effect of Ag compound itself. Again, K₂PtCl₄/AgOTf showed higher catalytic activity than K₂PtCl₄/AgOAc.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalysts</th>
<th>(mol%)</th>
<th>Method (Time)</th>
<th>Conversion of 1a (%</th>
<th>Yields / %b</th>
<th>3a</th>
<th>4a</th>
<th>5a</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂PtCl₄/AgOAc</td>
<td>1/2</td>
<td>B (80 min)</td>
<td>38</td>
<td>35</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>K₂PtCl₄/AgOAc</td>
<td>1/4</td>
<td>B (80 min)</td>
<td>50</td>
<td>44</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>AgOAc</td>
<td>4</td>
<td>B (0 min)</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>K₂PtCl₄/AgOTf</td>
<td>1/2</td>
<td>B (1 h)</td>
<td>55</td>
<td>48</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>K₂PtCl₄/AgOTf</td>
<td>1/4</td>
<td>B (1 h)</td>
<td>68</td>
<td>58</td>
<td>7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>AgOTf</td>
<td>4</td>
<td>B (0.5 h)</td>
<td>6</td>
<td>6</td>
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<td></td>
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</table>

a Reaction conditions: 1a (2 mmol), 2a (2.4 mmol), catalysts, TFA (1 mL) at room temperature for 5 h. Method B: After a mixture of K₂PtCl₄, Ag compound and TFA was stirred at room temperature for a certain period (described in Table), 1a and 2a were added.

b GC yields based on 1a.

**Ethyl (2Z)-3-(2,4,6-trimethylphenyl)propenoate (3a)**. Colorless liquid. ¹H NMR (300MHz, CDCl₃): δ 1.10 (t, J = 7.1 Hz, 3H, CH₃), 2.16 (s, 6H, aryl-CH₃), 2.27 (s, 3H, aryl-CH₃), 4.03 (q, J = 7.1 Hz, 2H, OCH₂), 6.11 (d, J = 12.0 Hz, 1H, vinyl), 6.84 (s, 2H, aryl), 7.02 (d, J = 12.0 Hz, 1H, vinyl). ¹³C NMR (75MHz, CDCl₃): δ 13.94, 20.11, 21.01, 59.92, 122.77, 127.78, 132.77, 134.44, 136.65, 144.13, 165.47.
Ethyl (2E)-3-(2,4,6-trimethylphenyl)propenoate \(^8\) was observed with the isomers of 3a and 6a in the mixture obtained from the reaction of 3a at 70\(^\circ\)C (Figure 1). \(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta\) 1.34 (t, \(J = 7.2\) Hz, 3H, CH\(_3\)), 2.26 (s, 3H, aryl-CH\(_3\)), 2.33 (s, 6H, aryl-CH\(_3\)), 4.27 (q, \(J = 7.2\) Hz, 2H, OCH\(_2\)), 6.05 (d, \(J = 16.2\) Hz, 1H, vinyl), 6.89 (s, 2H, aryl), 7.84 (d, \(J = 16.2\) Hz, 1H, vinyl).

Ethyl (2Z)-3-(pentamethylphenyl)propenoate (3b).\(^5,6,7\) Colorless crystals. Mp 71.8-73.6\(^\circ\)C. \(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta\) 1.10 (t, \(J = 7.1\) Hz, 3H, CH\(_3\)), 2.14 (s, 6H, aryl-CH\(_3\)), 2.20 (s, 6H, aryl-CH\(_3\)), 2.22 (s, 3H, aryl-CH\(_3\)), 4.01 (q, \(J = 7.1\) Hz, 2H, OCH\(_2\)), 6.13 (d, \(J = 12.0\) Hz, 1H, vinyl), 7.12 (d, \(J = 12.0\) Hz, 1H, vinyl). \(^13\)C NMR (75MHz, CDCl\(_3\)): \(\delta\) 13.96, 16.36, 16.74, 17.59, 59.78, 122.13, 129.76, 131.89, 133.23, 133.95, 146.46, 165.42.

Ethyl (2Z)-3-(1-naphthyl)propenoate (3c).\(^5,7\) Slightly yellow liquid. \(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta\) 1.00 (t, \(J = 7.1\) Hz, 3H, CH\(_3\)), 4.00 (q, \(J = 7.1\) Hz, 2H, OCH\(_2\)), 6.24 (d, \(J = 12.0\) Hz, 1H, vinyl) 7.41-7.50 (m, 4H, naphthyl),7.55 (d, \(J = 12.0\) Hz, 1H, vinyl), 7.80-7.91 (m, 3H, naphthyl). \(^13\)C NMR (75MHz, CDCl\(_3\)): \(\delta\) 13.79, 60.11, 122.82, 124.39, 124.96, 125.81, 126.20, 126.49, 128.50, 128.67, 131.07, 133.04, 133.25, 141.79, 165.89.

Ethyl (2Z)-3-(2,5-dimethylphenyl)propenoate (3d).\(^5,6\) Colorless liquid. \(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta\) 1.14 (t, \(J = 7.1\) Hz, 3H, CH\(_3\)), 2.23 (s, 3H, aryl-CH\(_3\)), 2.29 (s, 3H, aryl-CH\(_3\)), 4.09 (q, \(J = 7.1\) Hz, 2H, OCH\(_2\)), 6.00 (d, \(J = 12.0\) Hz, 1H, vinyl), 6.98-7.08 (m, 2H, aryl), 7.08 (d, \(J = 12.0\) Hz, 1H, vinyl), 7.11 (s, 1H, aryl). \(^13\)C NMR (75MHz, CDCl\(_3\)): \(\delta\) 13.94, 19.33, 20.88, 60.06, 120.99, 129.09, 129.26, 129.53, 132.61, 134.46, 134.87, 142.86, 166.09.
Ethyl (2Z)-3-(3-bromo-2,4,6-trimethylphenyl)propenoate (3e). Colorless liquid. $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 1.08 (t, $J = 7.1$ Hz, 3H, CH$_3$), 2.11 (s, 3H, aryl-CH$_3$), 2.30 (s, 3H, aryl-CH$_3$), 2.37 (s, 3H, aryl-CH$_3$), 4.02 (q, $J = 7.1$ Hz, 2H, OCH$_2$), 6.13 (d, $J = 12.0$ Hz, 1H, vinyl), 6.93 (s, 1H, aryl), 7.02 (d, $J = 12.0$ Hz, 1H, vinyl). $^{13}$C NMR (75MHz, CDCl$_3$): $\delta$ 13.89, 19.92, 21.25, 23.92, 60.09, 123.27, 125.03, 129.29, 133.19, 134.36, 134.60, 136.94, 143.59, 165.19.

Ethyl (2Z)-3-(3-hydroxy-2,4,6-trimethylphenyl)propenoate (3f). Colorless crystals. Mp 58.8-60.1$^\circ$C (Hexane). $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 1.11 (t, $J = 7.1$ Hz, 3H, CH$_3$), 2.10 (s, 6H, aryl-CH$_3$), 2.20 (s, 3H, aryl-CH$_3$), 4.03 (q, $J = 7.1$ Hz, 2H, OCH$_2$), 4.49 (s, 1H, OH), 6.13 (d, $J = 12.0$ Hz, 1H, vinyl), 6.80 (s, 1H, aryl), 7.00 (d, $J = 12.0$ Hz, 1H, vinyl). $^{13}$C NMR (75MHz, CDCl$_3$): $\delta$ 12.97, 13.96, 15.85, 19.54, 59.97, 120.18, 121.86, 122.86, 126.17, 129.15, 134.31, 143.94, 149.77, 165.39.

Ethyl (2Z)-3-{3-[(1Z)-2-ethoxycarbonylethenyl]-2,4,6-trimethylphenyl}propenoate (4a). Light yellow oil. $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 1.12 (t, $J = 7.1$ Hz, 6H, CH$_3$), 2.05 (s, 3H, aryl-CH$_3$), 2.15 (s, 6H, aryl-CH$_3$), 4.03 (q, $J = 7.1$ Hz, 4H, OCH$_2$), 6.12 (d, $J = 11.7$ Hz, 2H, vinyl), 6.88 (s, 1H, aryl), 7.04 (d, $J = 11.7$ Hz, 2H, vinyl). $^{13}$C NMR (75MHz, CDCl$_3$): $\delta$ 13.98, 17.66, 20.17, 59.90, 122.68, 128.36, 130.97, 132.98, 133.46, 144.40, 165.38.

Ethyl (2Z)-3-{3-bromo-5-{[(1Z)-2-ethoxycarbonylethenyl]-2,4,6-trimethylphenyl}-propenoate (4b). Slightly yellow oil. $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 1.11 (t, $J = 7.1$ Hz, 6H, CH$_3$), 2.02 (s, 3H, aryl-CH$_3$), 2.32 (s, 6H, aryl-CH$_3$), 4.02 (q, $J = 7.1$ Hz, 4H, OCH$_2$), 6.14 (d, $J = 11.7$ Hz, 2H, vinyl), 7.04 (d, $J = 11.7$ Hz, 2H, vinyl). $^{13}$C NMR (75MHz, CDCl$_3$): $\delta$ 13.92, 17.82, 21.76, 60.06, 123.24, 125.87, 129.91, 133.52, 134.37, 144.04, 165.11. MS (EI, m/z):
Ethyl (2Z)-3-{5-[(1Z)-2-ethoxycarbonylethenyl]-3-hydroxy-2,4,6-trimethylphenyl}-propenoate (4c). Colorless crystals. Mp 109.3-111.5ºC. $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 1.12 (t, $J = 7.1$ Hz, 6H, CH$_3$), 1.99 (s, 3H, aryl-CH$_3$), 2.10 (s, 6H, aryl-CH$_3$), 4.03 (q, $J = 7.1$ Hz, 4H, OCH$_2$), 4.53 (s, 1H, OH), 6.14 (d, $J = 12.0$ Hz, 2H, vinyl), 7.02 (d, $J = 12.0$ Hz, 2H, vinyl).

$^{13}$C NMR (75MHz, CDCl$_3$): $\delta$ 13.20, 13.98, 17.33, 59.95, 119.42, 122.87, 133.85, 144.24, 149.44, 165.33. MS (EI, m/z): 332 (M$^+$). Anal. Calcd. For C$_{19}$H$_{24}$O$_5$: C, 68.66; H, 7.28. Found: C, 68.86; H, 7.27.

Diethyl (1E,3Z)-4-(2,4,6-trimethylphenyl)buta-1,3-diene-1,3-dicarboxylate (5a). Slightly yellow oil. $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 0.90 (t, $J = 7.1$ Hz, 3H, CH$_3$), 1.31 (t, $J = 7.1$ Hz, 3H, CH$_3$), 2.15 (s, 6H, aryl-CH$_3$), 2.26 (s, 3H, aryl-CH$_3$), 3.99 (q, $J = 7.1$ Hz, 2H, OCH$_2$), 4.24 (q, $J = 7.1$ Hz, 2H, OCH$_2$), 6.23 (d, $J = 15.9$ Hz, 1H, vinyl), 6.82 (s, 2H, aryl), 7.15 (s, 1H, vinyl), 7.46 (d, $J = 15.9$ Hz, 1H, vinyl).

$^{13}$C NMR (75MHz, CDCl$_3$): $\delta$ 13.43, 14.24, 20.08, 20.93, 60.48, 60.69, 120.70, 127.79, 132.04, 134.39, 135.13, 137.28, 141.35, 143.07, 166.02, 166.79.

Diethyl (1E,3Z)-4-(pentamethylphenyl)buta-1,3-diene-1,3-dicarboxylate (5b). Slightly yellow crystals. $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 0.87 (t, $J = 7.1$ Hz, 3H, CH$_3$), 1.32 (t, $J = 7.1$ Hz, 3H, CH$_3$), 2.12 (s, 6H, aryl-CH$_3$), 2.18 (s, 6H, aryl-CH$_3$), 2.22 (s, 3H, aryl-CH$_3$), 3.97 (q, $J = 7.1$ Hz, 2H, OCH$_2$), 4.25 (q, $J = 7.1$ Hz, 2H, OCH$_2$), 6.20 (d, $J = 15.9$ Hz, 1H, vinyl), 7.26 (s, 1H, vinyl), 7.49 (d, $J = 15.9$ Hz, 1H, vinyl).
(2Z)-3-(2,4,6-Trimethylphenyl)propenoic acid (6a). Colorless crystals. Mp 143.9-145.8°C (EtOH / Hexane). $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 2.15 (s, 6H, aryl-CH$_3$), 2.27 (s, 3H, aryl-CH$_3$), 6.10 (d, $J$ = 12.0 Hz, 1H, vinyl), 6.84 (s, 2H, aryl), 7.11 (d, $J$ = 12.0 Hz, 1H, vinyl), 11.00 (s, 1H, COOH). $^{13}$C NMR (75MHz, CDCl$_3$): $\delta$ 20.00, 20.89, 122.07, 127.89, 131.99, 134.44, 136.92, 146.28, 171.10. MS (EI, m/z): 190 (M$^+$). 6a was confirmed by converting it to its ethyl ester 3a using DMAP/DCC method and comparing $^1$H and $^{13}$C NMR spectra.

(2E)-3-(2,4,6-Trimethylphenyl)propenoic acid was observed in the reaction of ethyl propiolate (2a) with mesitylene (1a) at higher temperature and obtained as a mixture of Z- and E-isomers of 6a, but was not isolated. $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 2.28 (s, 3H, aryl-CH$_3$), 2.32 (s, 6H, aryl-CH$_3$), 6.04 (d, $J$ = 16.2 Hz, 1H, vinyl), 6.89 (s, 2H, aryl), 7.91 (d, $J$ = 16.2 Hz, 1H, vinyl).

(2Z)-3-(Pentamethylphenyl)propenoic acid (6b). Colorless crystals. Mp 217.8-219.0°C (AcOEt). $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 2.13 (s, 6H, aryl-CH$_3$), 2.19 (s, 6H, aryl-CH$_3$), 2.22 (s, 3H, aryl-CH$_3$), 6.12 (d, $J$ = 12.0 Hz, 1H, vinyl), 7.20 (d, $J$ = 12.0 Hz, 1H, vinyl), 10.42 (brs, 1H, COOH). $^{13}$C NMR (75MHz, CDCl$_3$): $\delta$ 16.35, 16.76, 17.62, 121.72, 129.87, 132.22, 132.38, 134.51, 148.28, 170.38. 6b was confirmed by converting it to its ethyl ester 3b using DMAP/DCC method and comparing $^1$H and $^{13}$C NMR spectra.

(2Z)-3-(1-Naphthyl)propenoic acid (6c). Slightly yellow solid. Mp 156.8-157.8°C. $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 6.21 (d, $J$ = 12.0 Hz, 1H, vinyl) 7.39-7.53 (m, 4H, naphthyl),7.66 (d, $J$ = 12.0 Hz, 1H, vinyl), 7.81-7.87 (m, 3H, naphthyl). $^{13}$C NMR (75MHz, CDCl$_3$): $\delta$ 121.37, 124.18, 125.08, 125.97, 126.44, 126.92, 128.62, 129.15, 130.91, 132.27, 133.22, 144.66, 170.30. MS (EI, m/z): 198 (M$^+$). 6b was confirmed by converting it to its ethyl ester 3c using
DMAP/DCC method and comparing $^1$H and $^{13}$C NMR spectra

(2Z)-3-(2,5-dimethylphenyl)propenoic acid (6d). Colorless crystals. Mp 99.9-101.3°C (EtOH / Hexane). $^1$H NMR (300MHz, CD$_3$OD): $\delta$ 2.22 (s, 3H, aryl-CH$_3$), 2.27 (s, 3H, aryl-CH$_3$), 5.98 (d, $J$ = 12.3 Hz, 1H, vinyl), 7.00-7.06 (m, 2H, aryl), 7.12 (s, 1H, aryl), 7.18 (d, $J$ = 12.3 Hz, 1H, vinyl), 11.00 (brs, 1H, CO$_2$H). $^{13}$C NMR (75MHz, CD$_3$OD): $\delta$ 19.32, 20.81, 119.82, 129.35, 129.51, 129.63, 132.72, 134.20, 134.67, 145.83, 171.43. 6d was confirmed by converting it to its ethyl ester 3d using DMAP/DCC method and comparing $^1$H and $^{13}$C NMR spectra.

(2Z)-3-(3-Bromo-2,4,6-trimethylphenyl)propenoic acid (6e). Colorless powder. Mp 147.5-149.2°C (EtOAc / Hexane). $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 2.10 (s, 3H, aryl-CH$_3$), 2.28 (s, 3H, aryl-CH$_3$), 2.36 (s, 3H, aryl-CH$_3$), 6.11 (d, $J$ = 12.0 Hz, 1H, vinyl), 6.91 (s, 1H, aryl), 7.09 (d, $J$ = 12.0 Hz, 1H, vinyl), 9.86 (brs, 1H, COOH). $^{13}$C NMR (75MHz, CDCl$_3$): $\delta$ 19.89, 21.25, 23.93, 122.48, 125.14, 129.44, 133.16, 133.83, 134.30, 137.28, 145.97, 170.35. 6e was confirmed by comparing $^1$H and $^{13}$C NMR spectra of the compound that was prepared by hydrolysis of 3e by aqueous NaOH solution.

(2Z)-3-(2,5-di-tert-butylphenyl)propenoic acid (6f). Colorless crystals. Mp 152.4-153.7°C (toluene). $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 1.25 (s, 9H, 3$^t$Bu), 1.35 (s, 9H, 3$^t$Bu), 5.96 (d, $J$ = 12.0 Hz, 1H, vinyl), 7.12 (d, $J$ = 2.1 Hz, 1H, aryl), 7.25 (dd, $J$ = 2.1, 8.1 Hz, 1H, aryl), 7.33 (d, $J$ = 8.1 Hz, 1H, aryl), 7.72 (d, $J$ = 12.0 Hz, 1H, vinyl), 9.43 (brs, 1H, CO$_2$H). $^{13}$C NMR (75MHz, CDCl$_3$): $\delta$ 30.93, 31.10, 34.15, 35.36, 118.67, 125.11, 125.54, 128.41, 134.11, 144.31, 147.84, 150.24, 171.65. Anal. Calcd. For C$_{17}$H$_{24}$O$_2$: C, 78.42; H, 9.29. Found: C, 78.35; H, 9.19.

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(2Z)-3-(2-methylphenyl)propenoic acid \((o-6g)\) and (2Z)-3-(4-methylphenyl)propenoic acid \((p-6g)\) were obtained as a mixture of products. Colorless crystals. \(^1\)H NMR of the crude product (300MHz, CDCl\(_3\)): \(\delta\) 2.28 (s, 6H, \(o-6g\) aryl-CH\(_3\)), 2.35 (s, 3H, \(p-6g\) aryl-CH\(_3\)), 5.88 (d, \(J = 12.8\) Hz, 1H, \(p-6g\) vinyl), 6.02 (d, \(J = 12.3\) Hz, 2H, \(o-6g\) vinyl), 7.00 (d, \(J = 12.8\) Hz, 1H, \(p-6g\) vinyl), 7.16 (d, \(J = 12.3\) Hz, 2H, \(o-6g\) vinyl), 7.06-7.24 (m), 7.33 (d, \(J = 7.7\) Hz, 2H, \(p-6g\) aryl), 7.52 (d, \(J = 7.7\) Hz, 1H, \(p-6g\) aryl). \(o-\) and \(p-6g\) were confirmed by GC-MS. They were also confirmed by converting them to their ethyl esters using DMAP/DCC method and comparing \(^1\)H NMR spectra.\(^6\)

\((2Z)\)-cinnamic acid \((6h)\).\(^7\) Colorless crystals. Mp 64.8-66.5\(^\circ\)C (Hexane). \(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta\) 5.95 (d, \(J = 12.6\) Hz, 1H, vinyl), 7.05 (d, \(J = 12.6\) Hz, 1H, vinyl), 7.30-7.37 (m, 3H, phenyl), 7.57-7.61 (m, 2H, phenyl), 11.32 (brs, 1H, CO\(_2\)H). \(^{13}\)C NMR (75MHz, CDCl\(_3\)): \(\delta\) 118.66, 128.06, 129.36, 129.94, 134.32, 145.90, 171.67.

Ethyl (2Z)-3-(2,4,6-trimethylphenyl)-3-phenylpropenoate \((7a)\).\(^5\) Yellow oil. \(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta\) 1.10 (t, \(J = 7.1\) Hz, 3H, CH\(_3\)), 2.03 (s, 6H, aryl-CH\(_3\)), 2.32 (s, 3H, aryl-CH\(_3\)), 4.03 (q, \(J = 7.1\) Hz, 2H, OCH\(_2\) ), 6.61 (s, 1H, vinyl), 6.90 (s, 2H, aryl), 7.30-7.35 (m, 5H, phenyl). \(^{13}\)C NMR (75MHz, CDCl\(_3\)): \(\delta\) 13.98, 19.73, 21.14, 59.83, 117.54, 126.93, 127.98, 128.63, 129.45, 134.61, 135.21, 136.67, 138.35, 155.03, 165.66.

Ethyl (2Z)-3-(pentamethylphenyl)-3-phenylpropenoate \((7b)\).\(^5\) Yellow oil. \(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta\) 1.07 (t, \(J = 7.1\) Hz, 3H, CH\(_3\)), 2.01 (s, 6H, aryl-CH\(_3\)), 2.21 (s, 6H, aryl-CH\(_3\)), 2.27 (s, 3H, aryl-CH\(_3\)), 4.00 (q, \(J = 7.1\) Hz, 2H, OCH\(_2\) ), 6.62 (s, 1H, vinyl), 7.28-7.37 (m, 5H, phenyl). \(^{13}\)C NMR (75MHz, CDCl\(_3\)): \(\delta\) 13.96, 16.47, 16.82, 17.49, 59.69, 117.43, 127.14, 128.57, 129.26, 129.92, 131.93, 133.79, 135.52, 139.12, 156.87, 165.75.
(2Z)-3-(2,4,6-Trimethylphenyl)-3-phenylpropenoic acid (8a).\textsuperscript{5} Colorless crystals. Mp 195.0-196.8°C. \textsuperscript{1}H NMR (300MHz, CDCl\textsubscript{3}): \(\delta\) 2.02 (s, 6H, aryl-CH\textsubscript{3}), 2.32 (s, 3H, aryl-CH\textsubscript{3}), 6.59 (s, 1H, vinyl), 6.89 (s, 2H, aryl), 7.30-7.33 (m, 5H, phenyl). \textsuperscript{13}C NMR (75MHz, CDCl\textsubscript{3}): \(\delta\) 19.71, 21.11, 117.00, 127.11, 128.16, 128.71, 129.83, 134.50, 134.63, 137.01, 138.23, 157.22, 170.18.

(2Z)-3-(Pentamethylphenyl)-3-phenylpropenoic acid (8b).\textsuperscript{5} Colorless crystals. Mp 238.2-239.5°C (AcOEt/Hexane). \textsuperscript{1}H NMR (300MHz, CDCl\textsubscript{3}): \(\delta\) 1.98 (s, 6H, aryl-CH\textsubscript{3}), 2.18 (s, 6H, aryl-CH\textsubscript{3}), 2.24 (s, 3H, aryl-CH\textsubscript{3}), 6.61 (s, 1H, vinyl), 7.27-7.29 (m, 5H, phenyl). \textsuperscript{13}C NMR (75MHz, CDCl\textsubscript{3}): \(\delta\) 16.52, 16.90, 17.55, 117.14, 127.28, 128.73, 129.80, 130.37, 132.85, 133.87, 135.06, 138.60, 158.08, 168.33.

1-Phenyl-1-(2,4,6-trimethylphenyl)ethene (9).\textsuperscript{6,9} Colorless oil. \textsuperscript{1}H NMR (300MHz, CDCl\textsubscript{3}): \(\delta\) 2.11 (s, 6H, aryl-CH\textsubscript{3}), 2.32 (s, 3H, aryl-CH\textsubscript{3}), 5.09 (d, \(J = 1.5\) Hz, 1H, vinyl), 5.95 (d, \(J = 1.5\) Hz, 1H, vinyl), 6.91 (s, 2H, aryl), 7.23-7.28 (m, 5H, phenyl). \textsuperscript{13}C NMR (75MHz, CDCl\textsubscript{3}): \(\delta\) 20.07, 21.03, 114.52, 125.82, 127.51, 128.09, 128.39, 136.13, 136.41, 138.16, 139.56, 146.86.

Ethyl (2Z)-3-[3,5-bis-[(1Z)-2-ethoxycarbonylethenyl]-2,4,6-trimethylphenyl]propenoate (10). Slightly yellow crystals. Mp 46.8-49.0°C. \textsuperscript{1}H NMR (300MHz, CDCl\textsubscript{3}): \(\delta\) 1.12 (t, \(J = 7.1\) Hz, 9H, CH\textsubscript{3}), 2.05 (s, 9H, aryl-CH\textsubscript{3}), 4.03 (q, \(J = 7.1\) Hz, 6H, OCH\textsubscript{2}), 6.13 (d, \(J = 12.0\) Hz, 3H, vinyl), 7.04 (d, \(J = 12.0\) Hz, 3H, vinyl). \textsuperscript{13}C NMR (75MHz, CDCl\textsubscript{3}): \(\delta\) 13.99, 17.91, 59.87, 122.84, 130.15, 132.99, 144.46, 165.30. Anal. Calcd. For C\textsubscript{24}H\textsubscript{30}O\textsubscript{6}: C, 69.54; H, 7.30. Found: C, 69.51; H, 7.31.
3,3-Bis(tolyl)propionic acid (11a) was formed in the reaction of toluene and 2c. It was confirmed by GC-MS analysis of the product mixture itself and the product mixture after ethyl esterification with DMAP/DCC. $^1$H NMR and GC-MS analyses showed that two isomers of 11a were formed. They are probably 3,3-bis(p-tolyl)propionic acid and 3-p-tolyl-3-o-tolylpropionic acid because 1) only $p$-6g underwent second hydroarylation leading to 11a, 2) the reaction of toluene and 2c gave only o- and p-6g, without meta-isomer and 3) only two isomers of 11a were formed.
References


Chapter 3.

Application to coumarin synthesis

Coumarin derivatives exist widely in nature, especially in plants, and many of them show a wide range of biological activities.\textsuperscript{1,2} To date, many synthetic methods for coumarins have been developed due to the useful properties.\textsuperscript{1,3} The representative methods are the Perkin, Pechmann and Knoevenagel reactions. However, there are still limitations such as severe reaction conditions, requirement of a stoichiometric amount of condensing agents and difficulty of getting the starting materials.

Much effort has been paid to the development of coumarin synthesis through the reaction utilizing a transition metal catalyst.\textsuperscript{4-11} However, most of the syntheses require halogenated substrates such as iodophenols and iodoarenes as starting materials for the construction of the coumarin skeleton. These synthetic reactions involve bond cleavage of the C-X bonds by transition metals and produce waste halides. Considering the atom-economy of the reaction, the use of halogenated substrates is not favorable. If a direct construction of a C-C bond from the C-H bond in simple arenes is possible, this strategy will become a straightforward efficient process.

Trost \textit{et al.} have developed an atom-economic synthesis of coumarins from the reaction of propiolic acids and phenols in the presence of Pd\textsubscript{2}(dba)\textsubscript{3}·CHCl\textsubscript{3} or Pd(OAc)\textsubscript{2} catalysts in formic acid.\textsuperscript{9} Their reaction did not need halogenated phenols. Shi \textit{et al.} also reported a direct synthesis of coumarins by the reaction of aryl propiolates with AuCl\textsubscript{3}/AgOTf catalyst.\textsuperscript{10}

We have reported that the hydroarylation of alkynes proceeded by using Pd(OAc)\textsubscript{2} or PtCl\textsubscript{2}/AgOAc catalyst in trifluoroacetic acid (TFA) to give aryl-substituted alkenes.\textsuperscript{12} This direct functionalization of the C-H bonds in arenes was expanded to the synthesis of
cumarins by the intra- or intermolecular hydroarylation of propiolates with phenols. The effectiveness of the Pt catalysts which is developed in this work and described in Chapter 2 encouraged us to investigate the synthesis of coumarin.

\[
\begin{align*}
R^1\text{OH} + R^2\equiv\text{CO}_2R^3 & \xrightarrow{\text{Pt-catalysts, TFA}} R^1\text{O} \quad (1)
\end{align*}
\]

**Results and Discussion**

1. **The reaction of propiolic acids**

First, the reaction of propiolic acid (2a) \((R^2 = H, R^3 = H)\) or ethyl propiolate (2b) \((R^2 = H, R^3 = \text{Et})\) under conditions as described in Chapter 2 was examined (Eq. 1, Table 1). The reaction with 2-naphthol (1a) proceeded at room temperature to give coumarin 3a selectively in high yield (Entries 1 and 2). 3,4-Dimethylphenol (1b) gave 6,7-dimethylcoumarin (3b) and 5,6-dimethylcoumarin (3c) in 46 and 31% yields, respectively (Entry 3). In the case of 3,5-dimethylphenol (1c), (2Z)-cinnamic acid derivative 4a was obtained as the major product along with coumarin 3d (Entry 4). \(p\)-Cresol (1d) also reacted to give 6-methylcoumarin (3e) and dihydrocoumarin 5a although the reaction was slow at room temperature and required higher temperature (Entries 5 to 7). Furthermore, a small amount of dihydrocoumarin 5b was formed, which might be derived from the further reaction of 5a and 2a. The reaction using an excess amount of 2a was carried out to improve the selectivity of 3e, resulting in the decrease in the yield of 3e and the formation of 5b (Entry 8). In contrast to 1d, the reaction of 3-methylphenol (1e) proceeded smoothly at room temperature to give a mixture of 7-methylcoumarin (3f) and 5-methylcoumarin (3g) along with dihydrocoumarin 5c (Entry 9).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Phenol R₃</th>
<th>Cat. Cat.</th>
<th>Temp. / °C</th>
<th>Time / h</th>
<th>Products and Yields / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a H</td>
<td>A</td>
<td>r.t.</td>
<td>25</td>
<td>3a 86&lt;sup&gt;d,e&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>1a H</td>
<td>B</td>
<td>r.t.</td>
<td>25</td>
<td>3a 86&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>1b Et</td>
<td>A</td>
<td>r.t.</td>
<td>45</td>
<td>3b&lt;sup&gt;f&lt;/sup&gt; 46&lt;sup&gt;f&lt;/sup&gt; 3c 31&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>1c Et</td>
<td>A</td>
<td>r.t.</td>
<td>26</td>
<td>3d 37 4a 50</td>
</tr>
<tr>
<td>5</td>
<td>1d Et</td>
<td>A</td>
<td>50</td>
<td>48</td>
<td>3e 35 5a 44</td>
</tr>
<tr>
<td>6</td>
<td>1d H</td>
<td>C</td>
<td>40</td>
<td>48</td>
<td>3e 51 5a 24</td>
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<tr>
<td>7</td>
<td>1d H</td>
<td>C</td>
<td>r.t.</td>
<td>90</td>
<td>3e 51 5a 21</td>
</tr>
<tr>
<td>8</td>
<td>1d H</td>
<td>C</td>
<td>40</td>
<td>12</td>
<td>3e 27&lt;sup&gt;g&lt;/sup&gt; 5b 15&lt;sup&gt;g&lt;/sup&gt;</td>
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<tr>
<td>9</td>
<td>1e H</td>
<td>C</td>
<td>r.t.</td>
<td>25</td>
<td>3f&lt;sup&gt;g,h&lt;/sup&gt; 18&lt;sup&gt;g,h&lt;/sup&gt; 3g 17&lt;sup&gt;g,h&lt;/sup&gt;</td>
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<td>10</td>
<td>1f H</td>
<td>C</td>
<td>40</td>
<td>48</td>
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<tr>
<td>11</td>
<td>1g Br</td>
<td>H</td>
<td>C</td>
<td>40</td>
<td>90 3i&lt;sup&gt;f&lt;/sup&gt; 7 5i 34</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: Phenol 1 (4 mmol), 2a or 2b (2 mmol), catalyst, and TFA (1 mL).
<sup>b</sup> Catalyst A: PtCl₂ (0.05 mmol) and AgOTf (0.1 mmol). B: K₂PtCl₄ (0.05 mmol) and AgOTf (0.1 mmol).
<sup>c</sup> Isolated yields based on 2.
<sup>d</sup> 1a (3 mmol) was used.
<sup>e</sup> CH₂Cl₂ (0.75 mL) was added.
<sup>f</sup> The products were obtained as a mixture of the isomeric coumarins.
<sup>g</sup> The product ratios were determined by ¹H NMR.
<sup>h</sup> 1d (2 mmol) and 2a (3 mmol) were used.
<sup>i</sup> 5c was also isolated in 27% yield.

The yields were low although most of 2a was consumed after the reaction. The low yields are attributed to the low selectivity toward the formation of coumarin 3, similar to the reaction of 1d. Unsubstituted, simple phenol 1f reacted to give coumarin (3h) in 33% yield (Entry 67).
Interestingly, 4-bromophenol (1g) also participated in this reaction to afford dihydrocoumarin 5d and 6-bromocoumarin (3i) in 34 and 7% yields, respectively (Entry 11).

![Figure 1](image)

**Table 2.** The reaction of propionic acid (2a) with alkoxyphenols

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phenol</th>
<th>Time / h</th>
<th>Products and Yields / %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO₂C₆H₄OH 1h 15</td>
<td>3j 38</td>
<td>3k 10</td>
</tr>
<tr>
<td>2</td>
<td>MeO₂C₆H₄OH 1h 18</td>
<td>3j 28c</td>
<td>3k 8d</td>
</tr>
<tr>
<td>3</td>
<td>MeO₂C₆H₄OH 1h 11</td>
<td>3j 28d</td>
<td>3k 9d</td>
</tr>
<tr>
<td>4</td>
<td>MeO₂C₆H₄OH 1h 11</td>
<td>3j 34da,e</td>
<td>3k 8da,e</td>
</tr>
<tr>
<td>5</td>
<td>MeO₂C₆H₄OH 1h 15</td>
<td>3j 34f</td>
<td>3k 11f</td>
</tr>
<tr>
<td>6</td>
<td>MeO₂C₆H₄OH 1i 72</td>
<td>3l 22g</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>MeO₂C₆H₄OH 1j 45</td>
<td>3m 38g</td>
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<tr>
<td>8</td>
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<td>3n 77g</td>
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<tr>
<td>9</td>
<td>MeO₂C₆H₄OH 1k 15</td>
<td>3n 81fg</td>
<td></td>
</tr>
</tbody>
</table>

a Reaction conditions: Phenol 1 (4 mmol), 2a (2 mmol), K₂PtCl₄ (0.02 mmol), AgOTf (0.08 mmol), and TFA (1 mL) at r.t.

b Isolated yields based on 2a.

c 1h (2 mmol) and 2a (3 mmol) were used.
d 1h (2 mmol) and 2a (2.4 mmol) were used.
e CH₂Cl₂ (1 mL) was added.
f AgOAc (0.08 mmol) was used instead of AgOTf.
g CH₂Cl₂ (0.5 mL) was added.

Next, alkoxyphenols having strong electron-donating groups were examined (Table 2). The reaction of 3-methoxyphenol (1h) proceeded at room temperature to give 7-methoxycoumarin (3j) and 5-methoxycoumarin (3k) in 38 and 10% yields, respectively (Entry 1). The yields were not sufficient although most of 2a used was consumed. ¹H
NMR analysis of the reaction mixture indicated the formation of dihydrocoumarins. Therefore, further investigation was carried out to improve the selectivity. However, using an excess amount of 2a or use of AgOAc did not improve the yields (Entries 2 to 5). The reaction of 4-methoxyphenol (1i) was slower than that of 1h (Entry 6). The low reactivity of 1i is in accord with the general concept that a methoxy group activates ortho and para positions but deactivates the meta position for electrophilic aromatic substitution. Sesamol (1j) also gave coumarin 3m (Entry 7). Interestingly, the reaction of 3,5-dimethoxyphenol (1k) proceeded selectively to afford coumarin 3n in high yield while 1h, 1i and 1j gave the corresponding coumarins in low yields (Entries 8 and 9).

2. The reaction of the substituted propiolic acids

Next, we examined the reaction of the substituted propiolic acids. In contrast to 2a and 2b, the reaction of substituted propiolic acids proceeded selectively to give the corresponding coumarins in good to high yields. Table 3 shows the results of the reaction of phenylpropiolic acid (2c) (R² = Ph, R³ = H). In contrast to 2a, the reaction of 1h proceeded selectively to give coumarin 3o in high yield (Entries 1-3). Furthermore, higher yield was obtained when the reaction was carried out at room temperature instead of 40°C. 1j also gave coumarin 3p in high yield (Entries 4 and 5). 3,5-Dimethoxyphenol (1k) gave coumarin 3q in good yield although the yield was a little bit lower than those of 1h and 1j (Entry 6). The lower yield of 3q is possibly attributed to the formation of 7 from the further reaction of coumarin 3q with 2c. The formation of 7 analogue has been observed in Pd-catalyzed coumarin synthesis.11b The reaction of 1a gave coumarin 3r in high yield (Entries 7 and 8). The reaction of 1b at 40°C gave coumarin 3s in moderate yield because of the lower reactivity of 1b (Entry 9). The reaction of 1c gave coumarin 3t and cinnamate 4b, being similar to the reaction of 2a (Entry 10).
Table 3. The reaction of phenylpropionic acid (2c) with phenols 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phenol</th>
<th>Cat. b</th>
<th>Temp. / °C</th>
<th>Time / h</th>
<th>Products and Yields / % c</th>
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<td>1h</td>
<td>B</td>
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<td>40</td>
<td>MeO-Ph-CH=CH-Ph=O MeO-Ph-CH=CH-Ph=O 3o 71 d</td>
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<td>1c</td>
<td>C</td>
<td>40</td>
<td>45</td>
<td>3t 50 d</td>
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* a Reaction conditions: Phenol 1 (4 mmol), 2c (2 mmol), catalyst, TFA (1 mL), and CH2Cl2 (0.5 mL).
* Catalysts B: K2PtCl4 (0.05 mmol) and AgOTf (0.10 mmol). C: K2PtCl4 (0.02 mmol) and AgOTf (0.08 mmol).
* c Isolated yields based on 2c.
* d Cl(CH2)2Cl (0.5 mL) was added instead of CH2Cl2.
* e Cl(CH2)2Cl (1 mL) was added instead of CH2Cl2.

Figure 2
Table 4. The reaction of 2-octynoic acid (2d) or its ethyl ester (2e) with phenols 1a

<table>
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<tr>
<th>Entry</th>
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<th>R^3</th>
<th>Cat.b</th>
<th>Temp. / °C</th>
<th>Time / h</th>
<th>Products and Yields / %c</th>
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<td>1</td>
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<td>H</td>
<td>A</td>
<td>40</td>
<td>45</td>
<td>3u 93</td>
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<tr>
<td>2</td>
<td>1h</td>
<td>H</td>
<td>C</td>
<td>40</td>
<td>45</td>
<td>3a 83</td>
</tr>
<tr>
<td>3</td>
<td>1h</td>
<td>H</td>
<td>C</td>
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<td>45</td>
<td>3u 83</td>
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<tr>
<td>4</td>
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<td>H</td>
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</table>

a Reaction conditions: Phenol 1 (4 mmol), 2d or 2e (2 mmol), catalyst, and TFA (1 mL) for 45 h.
b Catalysts A: PtCl_2 (0.05 mmol) and AgOTf (0.10 mmol). C: K_2PtCl_4 (0.02 mmol) and AgOTf (0.08 mmol). D: K_2PtCl_4 (0.02 mmol) and AgOAc (0.08 mmol).
c Isolated yields based on 2.
d CH_2Cl_2 (0.5 mL) was added.
e CH_2Cl_2 (0.85 mL) was added. Ethyl 3-oxooctanate (6) was isolated in 47% yield.
f CH_2Cl_2 (1 mL) was added. 6 was isolated in 55% yield.
g 1a (3 mmol) was used. Cl(CH_2)_2Cl (0.5 mL) was added.
h 2-Heptanone was formed in 39% GC yield.

Figure 3

2-Octynoic acid (2d) (R^2 = "C_9H_11, R^3 = H) also reacted with phenols to give the coumarins although the reactivity of 2d seemed to be lower than that of 2c (Table 4). The reaction of 1h gave coumarin 3u in high yield even at room temperature (Entries 1-3).
Pd(OAc)_2 catalyst also gave high yield as well as Pt catalyst (Entry 4). In the case of 1j, coumarin 3v was obtained in very low yield when the reaction was carried out at room
temperature (Entry 5). The elevation of temperature to 40°C increased the yield but it was not sufficient (Entry 6). The $^1$H NMR analysis of the reaction mixture revealed that the methylenedioxy moiety of 1j was not present probably because the acetal moiety was hydrolyzed by a strong acid derived from AgOTf. Actually, coumarin 3v was obtained in high yield when AgOAc was used as co-catalyst instead of AgOTf (Entry 7). The reaction of 1k with ethyl 2-octynoate (2e) ($R^2 = \text{C}_5\text{H}_{11}$, $R^3 = \text{Et}$) also gave coumarin 3w in high yield (Entry 8). The reaction of 1a resulted in low yield of coumarin 3x in contrast to the reaction of 1a with 2a or 2c, indicating that reactivity of 2d and 2e was lower than that of 2a, 2b and 2c (Entries 9 to 14). The reaction also gave ethyl 3-oxooctanoate (6) derived from the hydration of 2e (Entry 9). Elongation of the reaction time did not improve the yield (Entry 10). The yield of 3x was somewhat improved when 2d was used instead of 2e (Entry 11). In this case, the formation of 2-heptanone derived from hydration and decarboxylation of 2d was observed. The elevation of temperature and the use of AgOAc did not increase the yield (Entries 12 to 14). This result suggests that the coumarin formation competes with the decomposition of 2d and 2e.

3. Consideration of the reaction mechanism

The reaction is thought to proceed via the hydroarylation of propiolic acids with phenols, which affords ortho-hydroxy substituted cinnamic acids (A) followed by the intramolecular esterification of intermediate A as depicted in Scheme 1. A similar mechanism has been proposed for Pd(II)-catalyzed reaction of propiolates with phenols giving coumarins. As regards the formation of hydroxyphenyl-substituted dihydrocoumarins 5 in the reaction of 2a, it was expected that the dihydrocoumarins were formed by the further reaction of coumarins with phenols. However, the reaction of 3e with 1d under reaction conditions did not afford dihydrocoumarin 5a, resulting in the recovery of 3e and 1d (Eq. 2). This result shows that...
3e formed in the reaction is stable under the reaction conditions. It has been reported that cinnamate derivatives react with phenols in TFA via the formation of carbocation intermediates, affording dihydrocoumarins.\textsuperscript{13} A possible route is that dihydrocoumarin 5 is generated by the reaction of intermediate A with phenols prior to the cyclization of A.

\begin{center}
\textbf{Scheme 1.} Reaction mechanism for the formation of coumarins and dihydrocoumarins
\end{center}

\begin{equation}
\begin{align*}
\text{1d} & \quad 2 \text{ mmol} \\
\text{3e} & \quad 2 \text{ mmol} \\
\text{1d} + \text{3e} & \quad \text{1}\% \text{K}_2\text{PtCl}_4 \\
& \quad 4\% \text{AgOTf} \\
& \quad \text{TFA (1mL)} \\
& \quad 40^\circ\text{C}, 48\text{h} \\
\rightarrow & \quad \text{5a} \\
\end{align*}
\end{equation}
In summary, this chapter describes the synthesis of coumarins from phenols and propiolic acids by using Pt catalysts such as PtCl₂/AgOTf, K₂PtCl₄/AgOTf and K₂PtCl₄/AgOAc. The reaction of propiolic acid and its ethyl ester (2a and 2b) proceeded to give coumarin and dihydrocoumarin even in the reaction with less reactive, non-activated phenols. In the cases of substituted propiolic acids 2c, 2d and 2e, the reactions proceeded selectively to afford coumarins 3 in good to high yields.
**Experimentals**

**General**

All solvents and reagents were commercially available and used as received without further purification. All reactions were conducted in a dry Pyrex tube with a rubber septum. $^1$H and $^{13}$C NMR spectra were recorded on a JEOL JNM-AL 300 FT-NMR using tetramethylsilane (TMS) as internal standard. Melting points were measured with YANACO micro melting apparatus and are uncorrected. Mass spectra were performed on a Shimadzu GC/MS 5020A. Elemental analyses were performed by the Service Center of the Elementary Analysis of Organic Compounds, Faculty of Science, Kyushu University.

The procedure for the synthesis of coumarins by the Pt-catalyzed hydroarylation of propiolic acids with phenols. Typical example: the reaction of 3-methoxyphenol (1h) and phenylpropionic acid (2c) by using K$_2$PtCl$_2$ / AgOTf catalyst (Table 3, Entry 3)

After a mixture of K$_2$PtCl$_2$ (0.02 mmol), AgOTf (0.08 mmol) and trifluoroacetic acid (TFA) (1 mL) was stirred at room temperature for 1 h, 1h (4 mmol) and 2c (2 mmol) was added to the mixture. The mixture was continuously stirred at a room temperature (27-32°C) for 45 hours. After the reaction, the mixture was poured into water (20 mL), neutralized by NaHCO$_3$, and extracted with diethyl ether (20 mL x 4). The ethereal layer was washed with 2N NaOH aqueous solution (10 mL x 3), dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexane as eluent to give 4-phenyl-7-methoxycoumarin (3o) in 82%.

In some reactions, cinnamic acid 4 and dihydrocoumarin 5 were obtained from the water
layer. The procedure is as follows: The combined water layer was acidified by conc. HCl aqueous solution (ca. 36%) on ice/water bath and extracted with CH$_2$Cl$_2$ (20 mL x 3). The organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

3H-Naphtho[2,1-b]pyran-3-one (3a).$^{9b,11d,14}$ Pink crystals. Mp 117.0–118.2$^\circ$C (AcOEt/hexane). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 6.59 (d, $J = 9.6$ Hz, 1H, vinyl), 7.47 (d, $J = 9.0$ Hz, 1H, aryl), 7.58 (dd, $J = 6.9$, 8.1 Hz, 1H, vinyl), 7.70 (dd, $J = 6.9$, 8.4 Hz, 1H, aryl), 7.92 (d, $J = 8.1$ Hz, 1H, aryl), 8.00 (d, $J = 9.0$ Hz, 1H, aryl), 8.24 (d, $J = 8.4$ Hz, 1H, aryl), 8.50 (d, $J = 9.6$ Hz, vinyl). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 112.79, 115.44, 116.86, 121.20, 125.94, 128.16, 128.83, 128.87, 130.10, 132.95, 138.91, 153.67, 160.74.

6,7-Dimethylcoumarin (3b)$^{15,16}$ was partially isolated from the mixture of 3b and 3c. Colorless crystals. Mp 145.7–148.6$^\circ$C. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.30 (s, 3H, CH$_3$), 2.35 (s, 3H, CH$_3$), 6.33 (d, $J = 9.6$ Hz, 1H, vinyl), 7.11 (s, 1H, aryl), 7.21 (s, 1H, aryl), 7.62 (d, $J = 9.6$ Hz, 1H, vinyl). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 19.04, 20.21, 115.32, 116.54, 117.28, 127.83, 133.07, 141.81, 143.23, 152.39, 161.22.

5,6-Dimethylcoumarin (3c)$^{15}$ was obtained as a mixture of 3b and 3c. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.35 (s, 3H, CH$_3$), 2.42 (s, 3H, CH$_3$), 6.40 (d, $J = 9.9$ Hz, 1H, vinyl), 7.09 (d, $J = 8.4$ Hz, 1H, aryl), 7.31 (d, $J = 8.4$ Hz, 1H, aryl), 7.99 (d, $J = 9.9$ Hz, 1H, vinyl).

5,7-Dimethylcoumarin (3d)$^{11d,16,17}$ Colorless crystals. Mp 133.0–134.9$^\circ$C (CH$_2$Cl$_2$/hexane). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.40 (s, 3H, CH$_3$), 2.48 (s, 3H, CH$_3$), 6.35 (d, $J = 9.6$ Hz, 1H, vinyl), 6.93 (m, 1H, aryl), 6.98 (m, 1H, aryl), 7.87 (dd, $J = 9.6$, 0.9 Hz, 1H, vinyl). $^{13}$C NMR
6-Methylcoumarin (3e). Colorless crystals. Mp 73.5–74.2°C (CH₂Cl₂/hexane). ¹H NMR (300 MHz, CDCl₃): δ 2.41 (s, 3H, CH₃), 6.40 (d, J = 9.3 Hz, 1H, vinyl), 7.22 (d, J = 8.4 Hz, 1H, aryl), 7.27 (d, J = 2.1, 1H, aryl), 7.33 (dd, J = 2.1, 8.4 Hz, 1H, aryl), 7.65 (d, J = 9.3 Hz, 1H, vinyl). ¹³C NMR (75.5 MHz, CDCl₃): δ 20.58, 116.40, 118.46, 127.59, 132.69, 134.02, 143.32, 152.03, 160.90.

7-Methylcoumarin (3f). ¹H NMR (300 MHz, CDCl₃): δ 2.45 (s, 3H, CH₃), 6.35 (d, J = 9.6 Hz, 1H, vinyl), 7.10 (d, J = 7.8 Hz, 1H, aryl), 7.14 (s, 1H, aryl), 7.36 (d, J = 7.8 Hz, 1H, aryl), 7.67 (d, J = 9.6 Hz, 1H, vinyl). 7-Methylcoumarin (3f) and 5-methylcoumarin (3g) were obtained as an inseparable mixture.

5-Methylcoumarin (3g). ¹H NMR (300 MHz, CDCl₃): δ 2.53 (s, 3H, CH₃), 6.43 (d, J = 9.6 Hz, 1H, vinyl), 7.10 (d, J = 8.1 Hz, 1H, aryl), 7.18 (d, J = 8.1 Hz, 1H, aryl), 7.40 (app t, J = 8.1 Hz, 1H, aryl), 7.92 (d, J = 9.6 Hz, 1H, vinyl). 7-Methylcoumarin (3f) and 5-methylcoumarin (3g) were obtained as an inseparable mixture.

Coumarin (3h). Colorless crystals. Mp 67.3–67.9°C (hexane). ¹H NMR (300 MHz, CDCl₃): δ 6.43 (d, J = 9.6 Hz, 1H, vinyl), 7.25-7.35 (m, 2H, aryl), 7.47-7.57 (m, 2H, aryl), 7.71 (d, J = 9.6 Hz, 1H, vinyl). ¹³C NMR (75.5 MHz, CDCl₃): δ 116.67, 116.85, 118.81, 124.38, 127.83, 131.78, 143.38, 154.04, 160.71.

6-Bromocoumarin (3i). Colorless crystals. Mp 159.6–162.7°C (CH₂Cl₂/hexane). ¹H NMR (75.5 MHz, CDCl₃): δ 18.06, 21.56, 114.57, 114.91, 115.22, 126.90, 135.61, 140.30, 142.65, 154.64, 161.03.
(300 MHz, CDCl₃): δ 6.46 (d, J = 9.6 Hz, 1H, vinyl), 7.23 (d, J = 9.3 Hz, 1H, aryl), 7.60-7.65 (m, 3H, aryl). $^{13}$C NMR (75.5 MHz, CDCl₃): δ 116.92, 117.79, 118.57, 120.28, 130.12, 134.53, 142.06, 152.86, 159.89.

**7-Methoxycoumarin (3j)**. Colorless crystals. Mp 117.2−118.1°C (CH₂Cl₂/hexane). $^1$H NMR (300 MHz, CDCl₃): δ 3.87 (s, 3H, OCH₃), 6.25 (d, J = 9.6 Hz, 1H, vinyl), 6.81 (d, J = 2.7 Hz, 1H, aryl), 6.84 (dd, J = 2.7, 8.4 Hz, 1H, aryl), 7.37 (d, J = 8.4 Hz, 1H, aryl), 7.63 (d, J = 9.6 Hz, 1H, vinyl). $^{13}$C NMR (75.5 MHz, CDCl₃): δ 55.75, 100.85, 112.52, 112.56, 113.09, 128.72, 143.35, 155.91, 161.15, 162.84.

**5-Methoxycoumarin (3k)**. Colorless crystals. Mp 82.0−83.1°C (CH₂Cl₂/hexane). $^1$H NMR (300 MHz, CDCl₃): δ 3.93 (s, 3H, OCH₃), 6.33 (d, J = 9.9 Hz, 1H, vinyl), 6.71 (d, J = 8.4 Hz, 1H, aryl), 6.91 (d, J = 8.4 Hz, 1H, aryl), 7.44 (t, J = 8.4 Hz, 1H, aryl), 8.08 (d, J = 9.9 Hz, 1H, vinyl). $^{13}$C NMR (75.5 MHz, CDCl₃): δ 55.98, 105.09, 109.18, 109.60, 114.53, 132.29, 138.48, 155.11, 156.14, 160.90.

**6-Methoxycoumarin (3l)**. Yellow crystals. Mp 101.4−103.0°C (CH₂Cl₂/hexane). $^1$H NMR (300 MHz, CDCl₃): δ 3.85 (s, 3H, OCH₃), 6.42 (d, J = 9.6 Hz, 1H, vinyl), 6.92 (d, J = 2.7 Hz, 1H, aryl), 7.11 (dd, J = 2.7, 9.0 Hz, 1H, aryl), 7.26 (d, J = 9.0 Hz, 1H, aryl), 7.66 (d, J = 9.6 Hz, 1H, vinyl). $^{13}$C NMR (75.5 MHz, CDCl₃): δ 55.79, 110.00, 117.04, 117.82, 119.12, 119.40, 143.14, 148.42, 156.05, 160.91.

**6,7-Methylenedioxyxycoumarin (3m)**. Dark crystals. Mp 224.8−226.7°C (CH₂Cl₂/hexane). $^1$H NMR (300 MHz, CDCl₃): δ 6.07 (s, 2H, -OCH₂O-), 6.28 (d, J = 9.6 Hz, 1H, vinyl), 6.82 (s, 1H, aryl), 6.83 (s, 1H, aryl), 7.58 (d, J = 9.6 Hz, 1H, vinyl). $^{13}$C NMR (75.5 MHz, CDCl₃): δ
5,7-Dimethoxycoumarin (3n).\textsuperscript{11c,d} Colorless crystals. Mp 147.5–149.0°C (CH\textsubscript{2}Cl\textsubscript{2}/hexane).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta 3.85 \) (s, 3H, OCH\textsubscript{3}), \( \delta 3.89 \) (s, 3H, OCH\textsubscript{3}), 6.14 (d, \( J = 9.6 \) Hz, 1H, vinyl), 6.27 (d, \( J = 2.1 \) Hz, 1H, aryl), 6.39 (d, \( J = 2.1 \) Hz, 1H, aryl), 7.95 (d, \( J = 9.6 \) Hz, 1H, vinyl). \textsuperscript{13}C NMR (75.5 MHz, CDCl\textsubscript{3}): \( \delta 55.70, 55.86, 92.72, 94.68, 103.88, 110.79, 138.64, 156.70, 156.88, 161.40, 163.62.

7-Methoxy-4-phenylcoumarin (3o).\textsuperscript{11c,d} White powder. Mp 110.9–111.4°C (CH\textsubscript{2}Cl\textsubscript{2}/hexane).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta 3.88 \) (s, 3H, OCH\textsubscript{3}), 6.21 (s, 1H, vinyl), 6.79 (dd, \( J = 2.4, 9.0 \) Hz, 1H, aryl), 6.88 (d, \( J = 2.4 \) Hz, 1H, aryl), 7.38 (d, \( J = 9.0 \) Hz, 1H, aryl), 7.41-7.45 (m, 2H, aryl), 7.49-7.52 (m, 3H, aryl). \textsuperscript{13}C NMR (75.5 MHz, CDCl\textsubscript{3}): \( \delta 55.72, 101.02, 111.77, 112.22, 112.42, 127.91, 128.30, 128.75, 129.52, 135.49, 155.73, 155.94, 161.11, 162.72.

6,7-Methylenedioxy-4-phenylcoumarin (3p).\textsuperscript{11c,d} Slightly green crystals. Mp 141.8–143.8°C (CH\textsubscript{2}Cl\textsubscript{2}/hexane). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta 6.05 \) (s, 2H, OCH\textsubscript{2}O), 6.24 (s, 1H, vinyl), 6.83 (s, 1H, aryl), 6.89 (s, 1H, aryl), 7.39-7.42 (m, 2H, phenyl), 7.49-7.53 (m, 3H, phenyl).

\textsuperscript{13}C NMR (75.5 MHz, CDCl\textsubscript{3}): \( \delta 98.45, 102.31, 104.26, 112.09, 112.73, 128.16, 128.82, 129.53, 135.57, 144.75, 151.07, 151.24, 155.80, 161.08.

5,7-Dimethoxy-4-phenylcoumarin (3q).\textsuperscript{9b,11c,d} Colorless crystals. Mp 169.0–170.9°C (CH\textsubscript{2}Cl\textsubscript{2}/hexane). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta 3.42 \) (s, 3H, OCH\textsubscript{3}), 3.87 (s, 3H, OCH\textsubscript{3}), 6.00 (s, 1H, vinyl), 6.23 (d, \( J = 2.4 \) Hz, 1H, aryl), 6.53 (d, \( J = 2.4 \) Hz, 1H, aryl), 7.24-7.27 (m, 2H, aryl), 7.36-7.38 (m, 3H, aryl). \textsuperscript{13}C NMR (75.5 MHz, CDCl\textsubscript{3}): \( \delta 55.33, 55.70, 93.52, 95.68, 103.46, 112.58, 127.04, 127.28, 127.83, 139.69, 155.62, 157.09, 158.16, 160.78, 163.31.
1-Phenyl-3H-naphtho[2,1-b]pyran-3-one (3r). Light yellow crystals. Mp 159.9–161.0°C (CH₂Cl₂/hexane). ¹H NMR (300 MHz, CDCl₃): δ 6.39 (s, 1H, vinyl), 7.15 (dd, J = 6.6, 8.7 Hz, 1H, aryl), 7.26 (d, J = 8.4 Hz, 1H, aryl), 7.35-7.43 (m, 3H, aryl), 7.47-7.55 (m, 4H, aryl), 7.85 (d, J = 8.1 Hz, 1H, aryl), 8.01 (d, J = 9.0 Hz, 1H, aryl). ¹³C NMR (75.5 MHz, CDCl₃): δ 112.93, 116.71, 117.38, 125.31, 125.82, 126.65, 127.37, 128.93, 129.07, 129.15, 129.24, 131.21, 133.88, 139.47, 154.67, 156.39, 160.26.

6,7-Dimethy-4-phenylcoumarin (3s). Colorless crystals. Mp 144.3–145.8°C (CH₂Cl₂/hexane). ¹H NMR (300 MHz, CDCl₃): δ 2.23 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 6.28 (s, 1H, vinyl), 7.18 (s, 1H, aryl), 7.20 (s, 1H, aryl), 7.42-7.46 (m, 2H, phenyl), 7.51-7.54 (m, 3H, phenyl). ¹³C NMR (75.5 MHz, CDCl₃): δ 19.28, 20.11, 114.01, 116.54, 117.75, 126.85, 128.34, 128.75, 129.46, 132.86, 135.50, 141.97, 152.53, 155.56, 161.16.

5,7-Dimethy-4-phenylcoumarin (3t). White powder. Mp 93.7–95.1°C (hexane). ¹H NMR (300 MHz, CDCl₃): δ 1.79 (s, 3H, CH₃), 2.39 (s, 3H, CH₃), 6.18 (s, 1H, vinyl), 6.83 (s, 1H, aryl), 7.08 (s, 1H, aryl), 7.26-7.29 (m, 2H, aryl), 7.43-7.45 (m, 3H, aryl). ¹³C NMR (75.5 MHz, CDCl₃): δ 21.26, 23.27, 115.45, 115.77, 116.08, 127.31, 128.51, 128.67, 129.46, 137.02, 139.55, 142.32, 155.15, 156.74, 160.49.

7-Methoxy-4-n-pentylcoumarin (3u). Colorless crystals. Mp 68.0–69.5°C (CH₂Cl₂/hexane). ¹H NMR (300 MHz, CDCl₃): δ 0.92 (t, J = 7.0 Hz, 3H, CH₃), 1.38-1.40 (m, 4H, CH₂), 1.66-1.71 (m, 2H, CH₂), 2.71 (t, J = 7.7 Hz, 2H, CH₂), 3.87 (s, 3H, OCH₃), 6.12 (s, 1H, vinyl), 6.82 (d, J = 2.4 Hz, 1H, aryl), 6.85 (dd, J = 2.4, 8.7 Hz, 1H, aryl), 7.52 (d, J = 8.7 Hz, 1H, aryl). ¹³C NMR (75.5 MHz, CDCl₃): δ 13.88, 22.36, 27.91, 31.53, 31.76, 55.67, 100.98, 110.72, 112.21, 112.86, 125.25, 155.52, 156.53, 161.47, 162.43.
6,7-Methylenedioxy-4-n-pentylcoumarin (3v). Slightly yellow crystals. Mp 106.0–107.4°C (CH₂Cl₂/hexane). ¹H NMR (300 MHz, CDCl₃): δ 0.92 (t, J = 6.9 Hz, 3H, CH₃), 1.37-1.41 (m, 4H, CH₂), 1.65-1.70 (m, 2H, CH₂), 2.66 (t, J = 7.6 Hz, 2H, CH₂), 6.07 (s, 2H, OCH₂O), 6.15 (s, 1H, vinyl), 6.83 (s, 1H, aryl), 6.98 (s, 1H, aryl). ¹³C NMR (75.5 MHz, CDCl₃): δ 13.86, 22.34, 27.75, 31.47, 32.17, 98.43, 101.82, 102.24, 110.95, 113.08, 144.85, 150.74, 156.38, 161.42.

5,7-Dimethoxy-4-n-pentylcoumarin (3w). Colorless crystals. Mp 101.6–103.2°C (CH₂Cl₂/hexane). ¹H NMR (300 MHz, CDCl₃): δ 0.92 (t, J = 7.1 Hz, 3H, CH₃), 1.34-1.42 (m, 4H, CH₂), 1.53-1.62 (m, 2H, CH₂), 2.87 (t, J = 7.6 Hz, 2H, CH₂), 3.85 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃), 5.97 (s, 1H, vinyl), 6.31 (d, J = 2.4 Hz, 1H, aryl), 6.46 (d, J = 2.4 Hz, 1H, aryl). ¹³C NMR (75.5 MHz, CDCl₃): δ 13.96, 22.42, 29.29, 31.78, 36.44, 55.61, 55.70, 93.57, 95.47, 104.21, 110.55, 157.27, 158.46, 158.59, 161.18, 162.56.

1-n-Pentyl-3H-naphtho[2,1-b]pyran-3-one (3x). Colorless crystals. Mp 98.5–99.4°C (CH₂Cl₂/hexane). ¹H NMR (300 MHz, CDCl₃): δ 0.94 (t, J = 7.2 Hz, 3H, CH₃), 1.37-1.56 (m, 4H, CH₂), 1.77-1.87 (m, 2H, CH₂), 3.23 (t, J = 7.7 Hz, 2H, CH₂), 6.41 (s, 1H, vinyl), 7.47 (d, J = 9.0 Hz, 1H, aryl), 7.55 (dd, J = 6.9, 8.1 Hz, 1H, aryl), 7.65 (ddd, J = 1.5, 6.9, 8.7 Hz, 1H, aryl), 7.92 (dd, J = 1.5, 8.1 Hz, 1H, aryl), 7.97 (d, J = 9.0 Hz, 2H, aryl), 8.47 (d, J = 8.7 Hz, 1H, aryl). ¹³C NMR (75.5 MHz, CDCl₃): δ 13.90, 22.33, 28.33, 31.51, 37.47, 113.91, 115.19, 117.90, 124.89, 125.26, 127.76, 129.64, 129.66, 131.30, 133.49, 154.78, 158.17, 160.51. MS (EI, m/z): 266 (M⁺). Anal. Calcd. For C₁₈H₁₈O₂: C, 81.17; H, 6.81. Found: C, 80.97; H, 6.85.

(2Z)-3-(4-Hydroxy-2,6-dimethylphenyl)propenoic acid (4a). Slightly orange crystals. Mp 169.8–172.0°C (AcOEt/hexane). ¹H NMR (300 MHz, CD₃OD): δ 2.12 (s, 6H, CH₃), 6.08 (d,
J = 12.0 Hz, 1H, vinyl), 6.45 (s, 2H, aryl), 7.01 (d, J = 12.0 Hz, 1H, vinyl). \(^{13}\)C NMR (75.5 MHz, CD\(_3\)OD): \(\delta\) 20.53, 114.90, 123.88, 128.39, 137.40, 145.21, 157.27, 169.38. MS (EI, m/z): 192 (M\(^+\)). Anal. Calcd. For C\(_{11}\)H\(_{12}\)O\(_3\): C, 68.74; H, 6.29. Found: C, 68.58; H, 6.31.

(2Z)-3-(4-Hydroxy-2,6-dimethylphenyl)cinnamic acid (4b). Light yellow crystals. Mp 219.1–221.2\(^{\circ}\)C (AcOEt/hexane). \(^1\)H NMR (300 MHz, CD\(_3\)OD): \(\delta\) 1.97 (s, 6H, CH\(_3\)), 6.53 (s, 2H, aryl), 6.64 (s, 1H, vinyl), 7.32 (app s, 5H, phenyl). \(^{13}\)C NMR (75.5 MHz, CD\(_3\)OD): \(\delta\) 20.20, 115.08, 119.26, 128.00, 129.73, 130.56, 130.86, 137.36, 140.26, 156.35, 157.37, 169.35. MS (EI, m/z): 268 (M\(^+\)). Anal. Calcd. For C\(_{17}\)H\(_{16}\)O\(_3\): C, 76.10; H, 6.01. Found: C, 75.96; H, 6.00. The stereochemistry of 4b was determined by NOE experiment.

4-(2-hydroxy-5-methylphenyl)-6-methyl-3,4-dihydrocoumarin (5a). Colorless crystals. Mp 166.0–167.7\(^{\circ}\)C (CH\(_2\)Cl\(_2\)/hexane). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 2.15 (s, 3H, CH\(_3\)), 2.26 (s, 6H, CH\(_3\)), 2.95 (dd, J = 6.6, 16.1 Hz, 1H, COCH\(_2\)), 3.19 (dd, J = 5.7, 16.1 Hz, 1H, COCH\(_2\)), 4.59 (dd, J = 5.7, 6.6 Hz, 1H, CH), 6.05 (brs, 1H, OH), 6.54 (d, J = 2.1 Hz, 1H, aryl), 6.61 (d, J = 8.1 Hz, 1H, aryl), 6.85 (dd, J = 2.1, 8.1 Hz, 1H, aryl), 6.86 (d, J = 2.1 Hz, 1H, aryl), 7.01 (d, J = 8.1 Hz, 1H, aryl), 7.09 (dd, J = 2.1, 8.1 Hz, 1H, aryl). \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)): \(\delta\) 20.52, 20.71, 35.17, 35.26, 115.51, 116.66, 124.55, 126.48, 128.76, 129.02, 129.13, 129.97, 134.44, 149.84, 151.03, 169.83, 169.86. MS (EI, m/z): 268 (M\(^+\)). Anal. Calcd. For C\(_{17}\)H\(_{16}\)O\(_3\): C, 76.10; H, 6.01. Found: C, 75.87; H, 5.97. The structure of 5a was determined by NOE experiments.

6,6’-Dimethyl-3,4-dihydro-[4,8’]bichromenyl-2,2’-dione (5b). Colorless crystals. Mp 244.0–246.3\(^{\circ}\)C (CH\(_2\)Cl\(_2\)/hexane). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 2.27 (s, 3H, CH\(_3\)), 2.30 (s, 3H, CH\(_3\)), 3.08 (dd, J = 6.0, 15.9 Hz, 1H, COCH\(_2\)), 3.14 (dd, J = 4.5, 15.9 Hz, 1H, COCH\(_2\)),
4.98 (dd, $J = 4.5, 6.0$ Hz, 1H, CH), 6.45 (d, $J = 9.6$ Hz, 1H, vinyl), 6.77 (d, $J = 1.8$ Hz, 1H, aryl), 6.92 (d, $J = 1.8$ Hz, 1H, aryl), 7.08 (d, $J = 8.1$ Hz, 1H, aryl), 7.16 (dd, $J = 1.8, 8.1$ Hz, 1H, aryl), 7.19 (d, $J = 1.8$ Hz, 1H, aryl), 7.68 (d, $J = 9.6$ Hz, 1H, vinyl). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 20.74, 20.84, 33.69, 35.80, 116.66, 117.05, 118.93, 123.44, 127.34, 128.49, 128.84, 129.81, 131.26, 134.51, 134.72, 143.75, 149.23, 150.19, 160.36, 167.53. MS (EI, m/z): 320 (M$^+$). Anal. Calcd. For C$_{20}$H$_{16}$O$_4$: C, 74.99; H, 5.03. Found: C, 74.74; H, 5.05.

4-(4-Hydroxy-2-methylphenyl)-7-methyl-3,4-dihydrocoumarin (5c). Colorless crystals. Mp 183.2−185.2°C (AcOEt). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 2.27 (s, 3H, CH$_3$), 2.30 (s, 3H, CH$_3$), 2.88 (dd, $J = 7.2, 15.9$ Hz, 1H, COCH$_2$), 2.99 (dd, $J = 5.7, 15.9$ Hz, 1H, COCH$_2$), 4.51 (dd, $J = 5.7, 7.2$ Hz, 1H, CH), 6.48 (dd, $J = 2.1, 8.4$ Hz, 1H, aryl), 6.54 (d, $J = 8.4$ Hz, 1H, aryl), 6.63 (d, $J = 2.1$ Hz, 1H, aryl), 6.78 (d, $J = 7.8$ Hz, 1H, aryl), 6.91 (d, $J = 7.8$ Hz, 1H, aryl), 7.00 (s, 1H, OH). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): $\delta$ 19.15, 20.55, 34.78, 35.82, 113.16, 116.74, 117.39, 123.58, 125.16, 127.46, 127.86, 129.29, 137.02, 138.12, 151.58, 156.08, 167.94. MS (EI, m/z): 268 (M$^+$). Anal. Calcd. For C$_{17}$H$_{16}$O$_3$: C, 76.10; H, 6.01. Found: C, 75.98; H, 6.01. The structure of 5c was determined by NOE experiments.

4-(5-Bromo-2-hydroxyphenyl)-6-bromo-3,4-dihydrocoumarin (5d). Colorless crystals. Mp 237.4−238.4°C (AcOEt). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 3.04 (dd, $J = 5.7, 16.2$ Hz, 1H, COCH$_2$), 3.14 (dd, $J = 6.9, 16.2$ Hz, 1H, COCH$_2$), 4.62 (dd, $J = 5.7, 6.9$ Hz, 1H, CH), 6.81 (d, $J = 8.4$ Hz, 1H, aryl), 6.96 (d, $J = 2.4$ Hz, 1H, aryl), 7.12 (d, $J = 8.7$ Hz, 1H, aryl), 7.25 (d, $J = 2.1$ Hz, 1H, aryl), 7.28 (dd, $J = 2.4, 8.4$ Hz, 1H, aryl), 7.50 (dd, $J = 2.1, 8.7$ Hz, 1H, aryl). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): $\delta$ 33.45, 34.79, 110.23, 116.07, 117.65, 118.88, 127.08, 129.45, 130.51, 130.83, 131.26, 131.36, 150.82, 154.41, 167.03. MS (EI, m/z): 396, 398, 400 (M$^+$). Anal. Calcd. For C$_{15}$H$_{10}$Br$_2$O$_3$: C, 45.26; H, 2.53. Found: C, 45.36; H, 2.46.
Ethyl 3-Oxooctanoate (6). Yellow liquid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.89 (t, $J = 6.8$ Hz, 3H, CH$_3$), 1.27-1.31 (m, 4H, CH$_2$), 1.28 (t, $J = 7.2$ Hz, 3H, CH$_3$), 1.60 (p, $J = 7.4$ Hz, 2H, CH$_2$), 2.53 (t, $J = 7.4$ Hz, 2H, CH$_2$), 3.43 (s, 2H, COCH$_2$CO), 4.20 (q, $J = 7.2$ Hz, 2H, OCH$_2$).

$^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 13.83, 14.06, 22.36, 23.11, 31.13, 42.96, 49.28, 61.29, 167.25, 202.98.
References


Application to heteroarenes

Heteroarenes are important compounds because they are incorporated in a wide range of useful organic compounds such as fluorescent dyes, natural products and pharmaceuticals. Development of their functionalization methods is important for preparations of such useful compounds.

Direct C-H bond functionalization is one of the most effective methods from the viewpoint of atom-economic and environmental benign processes because it does not require the prefunctionalization like halogenation. Addition of aromatic C-H bonds to unsaturated C-C bonds is a useful method for introducing carbon framework onto arenes. To date, several methods for the addition of heteroarenes to alkynes by using transition metal catalyst have been developed.\textsuperscript{1-8} Rh\textsubscript{4}(CO)\textsubscript{12} catalyzes the addition of heteroarenes to diphenylacetylene under pressure of carbon monoxide.\textsuperscript{1} Ru(H)\textsubscript{2}(CO)(PPh\textsubscript{3})\textsubscript{3} catalyzes the addition of heteroarene having a directing group to silylalkynes via chelation-assisted metalation.\textsuperscript{2} Selective trans-addition to alkynes are catalyzed by Pd(OAc)\textsubscript{2} and gold\textsuperscript{4}. Double-hydroheteroarylation of alkyne occurs in the presence of In(OTf)\textsubscript{3} catalyst.\textsuperscript{5} Selective cis-addition to alkynes takes place in the presence of dinuclear palladium complexes.\textsuperscript{6} Double-hydroheteroarylation of ethyl propiolate with N-methylindole or benzofuran proceeds in the presence of AuCl\textsubscript{3}/AgOTf.\textsuperscript{7} Nickel complexes also catalyze the hydroheteroarylation of alkynes to give heteroaryl-substituted ethenes.\textsuperscript{8}

We have reported that hydroarylation of alkynes proceeded at room temperature by using a catalytic amount of Pd(OAc)\textsubscript{2} and trifluoroacetic acid (TFA) as solvent to give cis-aryl substituted alkenes.\textsuperscript{9} The hydroarylation was applied to the reaction with heteroarenes such
as pyrroles, indoles and furans. In these cases, the reaction did not need TFA and proceeded in acetic acid or a neutral solvent like CH₂Cl₂ to give aryl-substituted alkenes or diaryl-substituted alkanes.

Pt(II) catalysts such as K₂PtCl₄/AgOTf and PtCl₂/AgOTf were efficient in the hydroarylation of propiolic acids with arenes as described in Chapter 2. Therefore, the hydroarylation of alkynes with heteroarenes including pyrroles and furans by using K₂PtCl₄/AgOTf catalyst was examined.

Results and Discussion

1. The reaction of pyrroles

First of all, the reaction of pyrrole (1a) with ethyl phenylpropionate (2a) was examined (Eq. 1). The reaction of 1a (4 mmol) with 2a (2 mmol) in AcOH (1 mL) was carried out in the presence of K₂PtCl₄ (0.02 mmol) and AgOTf (0.08 mmol) at 30 °C for 9 h to afford ethyl (2Z)-3-(pyrrol-2-yl)cinnamate (3a) and ethyl 3-phenyl-3,3-di(pyrrol-2-yl)propionate (4a) in 4 and 46% yields, respectively. Double addition of 1a to the triple bond of 2a occurred predominantly. This result is in contrast to Pd(II)-catalyzed reaction that gives 3a exclusively. It may be attributed to the fact that K₂PtCl₄/AgOTf is more active catalyst than Pd(OAc)₂. This interesting result encouraged me to investigate the reaction conditions.

\[
\text{1a} \quad 1 \% \text{K}_2\text{PtCl}_4 \quad 4 \% \text{AgOTf} \\
\text{2a} \quad \text{AcOH (1 mL)} \quad 30 \degree \text{C, 9h} \\
\rightarrow \text{3a} \quad 4 \% \\
\text{4a} \quad 46 \%
\]
The results are listed in Table 1. When the reaction was carried out with 3 equivalents of 1a in the presence of 2% K$_2$PtCl$_4$ and 8%AgOTf, 4a was obtained in 59% yield (Entry 1). Use of AgOAc instead of AgOTf retarded the reaction, resulting in formation of 3a as a main product together with 4a (Entry 2). The yield of 4a was improved to be 68% when 6 equivalents of 1a were used (Entry 3). The increase of the amount of acetic acid retarded the reaction rate (Entry 4). A neutral solvent, 1,2-dichloroethane (DCE), can be used instead of AcOH, affording the similar yield of 4a to that in AcOH (Entry 5). The reaction did not proceed in the absence of K$_2$PtCl$_4$, revealing clearly that the active catalyst species in this reaction is Pt species (Entry 6). In order to increase the solubility of platinum catalyst, (NBu$_4$)$_2$PtCl$_4$ was examined. Interestingly, the hydroarylation using (NBu$_4$)$_2$PtCl$_4$ in AcOH proceeded even in the absence of AgOTf (Entry 7). This result proves that Pt catalyst itself plays an important role in the catalytic cycle and AgOTf is not necessarily required for the

### Table 1. Reaction of pyrrole (1a) with ethyl phenylpropiolate (2a)$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalysts (%)</th>
<th>Solvent</th>
<th>1a / mmol</th>
<th>Time / h</th>
<th>Isolatd yield / %$^b$</th>
<th>3a</th>
<th>4a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K$_2$PtCl$_4$/AgOTf (2/8)</td>
<td>AcOH</td>
<td>3</td>
<td>11</td>
<td>0</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>K$_2$PtCl$_4$/AgOAc (2/8)</td>
<td>AcOH</td>
<td>3</td>
<td>50</td>
<td>43</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>K$_2$PtCl$_4$/AgOTf (2/8)</td>
<td>AcOH</td>
<td>6</td>
<td>10</td>
<td>0</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>K$_2$PtCl$_4$/AgOTf (2/8)</td>
<td>AcOH</td>
<td>6</td>
<td>20</td>
<td>0</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>K$_2$PtCl$_4$/AgOTf (2/8)</td>
<td>Cl(CH$_2$)$_2$Cl</td>
<td>6</td>
<td>12</td>
<td>0</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>AgOTf (8)</td>
<td>AcOH</td>
<td>6</td>
<td>10</td>
<td>no reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>(Bu$_4$N)$_2$PtCl$_4$ (2)</td>
<td>AcOH</td>
<td>6</td>
<td>15</td>
<td>0</td>
<td>60</td>
<td></td>
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<tr>
<td>8</td>
<td>(Bu$_4$N)$_2$PtCl$_4$/AgOTf (2/8)</td>
<td>Cl(CH$_2$)$_2$Cl</td>
<td>6</td>
<td>15</td>
<td>0</td>
<td>66</td>
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<tr>
<td>9</td>
<td>(Bu$_4$N)$_2$PtCl$_4$ (2)</td>
<td>Cl(CH$_2$)$_2$Cl</td>
<td>6</td>
<td>59</td>
<td>no reaction</td>
<td></td>
<td></td>
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<tr>
<td>10</td>
<td>(Bu$_4$N)$_2$PtCl$_4$/AgOAc (2/8)</td>
<td>Cl(CH$_2$)$_2$Cl</td>
<td>6</td>
<td>50</td>
<td>very slow</td>
<td></td>
<td></td>
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<tr>
<td>11</td>
<td>Bu$_4$NCl (4)</td>
<td>AcOH</td>
<td>6</td>
<td>22</td>
<td>no reaction</td>
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</table>

$^a$ Reaction conditions: pyrrole (1a), ethyl phenylpropiolate (2a) (1 mmol), catalyst and solvent (1 mL) at 30°C.

$^b$ The yield based on 2a.

$^c$ AcOH (2 mL) was used.
reaction. The role of AgOTf is considered to dissolve K₂PtCl₄ and form a more active Pt species. Moreover, (NBu₄)₂PtCl₄ also catalyzed the reaction in DCE when AgOTf was added (Entry 8). However, the reaction was very slow in the absence of AgOTf that 2a was still remained after 59 h (Entry 9). These results suggest that Pt catalyst may be activated by AcOH or by AgOTf in the absence of AcOH. No reaction was occurred when AgOAc was added instead of AgOTf (Entry 10). BuN₄Cl itself did not catalyze the reaction (Entry 11).

\[
\begin{align*}
\text{NR} & \quad \text{R'} \quad \text{CO₂Et} \\
\text{1} & \quad \text{2} & \quad \text{K₂PtCl₄} & \quad \text{AgOTf} & \quad \text{AcOH} \\
& & \quad \text{3} & \quad \text{4} \\
\end{align*}
\]

(2)

**Table 2. Hydroarylation of propiolates 2 with pyroles 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Time / h</th>
<th>Products and Yield /%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Ph</td>
<td>2</td>
<td>3b 71</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
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<td>H</td>
<td>aC₅H₁₁</td>
<td>24</td>
<td>4b 50&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>EtO₂C</td>
<td>2</td>
<td>3c 43</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>EtO₂C</td>
<td>19</td>
<td>3c 37</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>H</td>
<td>2</td>
<td>3d 46&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3e 22&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: pyrrole 1 (6 mmol), propiolate 2 (1 mmol), K₂PtCl₄ (0.02 mmol), AgOTf (0.08 mmol) and AcOH (1 mL) at 30°C.

<sup>b</sup> Isolated yield based on 2.

<sup>c</sup> Cl(CH₂)₂Cl (1 mL) was used instead of AcOH.

<sup>d</sup> NMR yields. 1a (2 mmol) was used.
Next, the reaction of other pyrroles and alkynes was examined (Table 2). Interestingly, the reaction of 1-methylpyrrole (1b, R = Me) with 2a gave mono-adduct 3b exclusively in 71% yield (Entry 1). The elongation of reaction time did not give any double-adducts 4, but only 3b in the same yield (Entry 2). The result is in contrast with the reaction of 1a that gives 4a as a main product. This is probably due to the steric hindrance of methyl group in the pyrrole moiety of 3b. The reaction of 1a with ethyl 2-octynoate (2b, R′ = C5H11) gave double-adduct 4b in 50% yield (Entry 3). The reaction with diethyl acetylenedicarboxylate (2c, R′ = CO2Et) also gave mono-adduct 3c in 43% yield but the elongation of the reaction did not improve the yield (Entries 4 and 5). The reaction with ethyl propiolate (2d, R′ = H) gave the regio-isomeric products 3d and 3e in 46 and 22% yields, respectively (Entry 6). The low selectivity is attributed to the higher reactivity of 2d compared with the other substituted propiolates. From the 1H NMR spectrum, a small amount of double adducts 4 involving two isomers were formed and the elongation of reaction increased the amount of 4, resulting in the major formation of 4.

Table 3. Hydroarylation of phenylacetylene (2d) with pyrroles 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>1 / mmol</th>
<th>Time / h</th>
<th>Products and Yield / %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>10</td>
<td>20</td>
<td>4c : R = H, 65</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>10</td>
<td>20</td>
<td>4d : R = Me, 65</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>6</td>
<td>20</td>
<td>4d : R = Me, 45</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>6</td>
<td>21</td>
<td>4d : R = Me, 0c</td>
</tr>
</tbody>
</table>

a Reaction conditions: pyrrole 1, phenylacetylene (2d) (1 mmol), K2PtCl4 (0.02 mmol), AgOTf (0.08 mmol) and AcOH (1 mL) at 30°C.
b Isolated yield based on 2d.
c without K2PtCl4/AgOTf.
Phenylacetylene (2e) also participated in the reaction as well as propiolates (Table 3). The reaction of 1a and 1b gave the corresponding double-adduct 4c and 4e in good yields although a larger amount of pyrroles was required. On the other hand, use of 6 equivalents of 1b resulted in as inferior yield. The reaction of 1a with ethyl cinnamate was also examined because a second hydroarylation of the alkene formed took place in the most of the reaction of pyrroles. However, the reaction did not proceed (Eq. 3).

\[
\begin{array}{ccc}
\text{N} & \text{H} & \text{Ph} \\
\text{CO}_2\text{Et} \\
3 \text{ mmol} & 1 \text{ mmol} \\
\end{array}
\xrightarrow{2\%\text{K}_2\text{PtCl}_4, 8\%\text{AgOTf}}
\begin{array}{c}
\text{N} \\
\text{Ph} \\
\text{CO}_2\text{Et} \\
\end{array}
\xrightarrow{\text{AcOH (1 mL)}
30^\circ\text{C}, 25\text{h}}
\begin{array}{c}
\text{N} \\
\text{Ph} \\
\text{CO}_2\text{Et} \\
\end{array}
\]

2. The reaction of furan

**Table 4. Reaction of 2-methylfuran (5a) with ethyl phenylpropiolate (2a)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalysts (%)</th>
<th>Solvent</th>
<th>5a / mmol</th>
<th>Time / h</th>
<th>Isolated yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂PtCl₄/AgOTf (2/8)</td>
<td>AcOH</td>
<td>6</td>
<td>4</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>K₂PtCl₄/AgOTf (2/8)</td>
<td>AcOH</td>
<td>6</td>
<td>12</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>K₂PtCl₄/AgOTf (2/8)</td>
<td>AcOH</td>
<td>3</td>
<td>18</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>(Bu₄N)₂PtCl₄ (2)</td>
<td>AcOH</td>
<td>6</td>
<td>60</td>
<td>very slow</td>
</tr>
<tr>
<td>5</td>
<td>K₂PtCl₄/AgOTf (2/8)</td>
<td>Cl(CH₂)₂Cl</td>
<td>3</td>
<td>72</td>
<td>44&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>AgOTf (8)</td>
<td>AcOH</td>
<td>6</td>
<td>45</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 2-methylfuran (5a), ethyl phenylpropiolate (2a) (1 mmol), catalyst and solvent (1 mL) at 30°C.
<sup>b</sup> The yield based on 2a.
<sup>c</sup> Ethyl benzoylacetate was also obtained in 20% as a mixture of products.

This reaction was applied to furans like 2-methylfuran (5a) and 2,5-diemethylfuran (5b) (Table 4). The reaction of 5a with 2a under the same reaction conditions proceeded to give a
double-adduct, ethyl 3,3-bis(4-methylfur-2-yl)-3-phenylpropionate (6a) in 78% yield (Entry 1). The yield was improved to 90% by elongation of reaction (Entry 2). Decrease in the amount of 5a resulted in lower yield (Entry 3). (Bu₄N)₂PtCl₄ did not catalyze the reaction of furan effectively, resulting in almost no reaction (Entry 4). In contrast to the reaction of 1a, the reaction in DCE resulted in the low yield of 6a because of the formation of ethyl benzoyleacetate that is derived from the hydration of 2a (Entry 5). Again, the fact that AgOTf does not catalyze the reaction suggests that an active species in the reaction is a Pt species (Entry 6).

<table>
<thead>
<tr>
<th>Entry</th>
<th>5b / mmol</th>
<th>2</th>
<th>R'</th>
<th>Time / h</th>
<th>Product and Yield / %</th>
<th>a</th>
<th>b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>2a</td>
<td>Ph</td>
<td>48</td>
<td>7a 80 (Z/E = 1.3/1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>2a</td>
<td>Ph</td>
<td>50</td>
<td>7a 81 (Z/E = 1.3/1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>2d</td>
<td>H</td>
<td>40c</td>
<td>7b 62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>2d</td>
<td>H</td>
<td>41c</td>
<td>7b 36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>2d</td>
<td>H</td>
<td>40d</td>
<td>6b 51 7b 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>2d</td>
<td>H</td>
<td>65d</td>
<td>6b 53 7b 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>2d</td>
<td>H</td>
<td>40d</td>
<td>6b 49 7b 5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Reaction conditions: 2,5-dimethylfuran (5b), ethyl propiolate 2 (1 mmol), K₂PtCl₄ (0.02 mmol), AgOTf (0.08 mmol) and AcOH (1 mL) at 30°C.
b Isolated yield based on ethyl propiolate 2.
c 2d (2 mmol) was used.
d The reaction was carried out at 50°C.

Table 5. Reaction of 2,5-dimethylfuran (5b) with ethyl propiolates 2

The reactions of 2,5-dimethylfuran (5b) with alkynes were also examined (Table 5). The reaction of 2a with 5b gave mono-addition products 7a in 80% yield (Entry 1). In this case, the product was obtained as a mixture of the stereoisomers (E/Z = 1.3/1). Any double
adducts were not observed probably due to the steric reason. The use of more amount of 5b did not improve the yield (Entry 2). In the case of 2d, the reaction of 5b in the presence of 1%K₂PtCl₄ and 4%AgOTf gave a mono-adduct 7b selectively (Entry 3). Decreasing the amount of 5b gave lower yield (Entry 4). The second addition reaction of 2,5-dimethylfuran to the mono-adduct 7b is slower and requires higher reaction temperature. Actually, the second addition of 5b occurred to afford double-adduct 6b as a main product when the reaction was carried out at 50°C. The reaction of 2b with 5a resulted in the formation of ethyl 2-oxooctanoate by hydrolysis of 2b. The reaction of 2c did not afford hydroarylation products although Diels-Alder adducts 8 were isolated (Eq. 4). These results are explained by a low reactivity of furans for hydroarylation relative to pyrroles.

3. Consideration of the reaction mechanism

The hydroarylation is considered to proceed via electrophilic aromatic substitution mechanism. The mechanism is illustrated in Scheme 1. An alkyne is activated by the coordination of Pt catalyst which is formed by K₂PtCl₄ and AgOTf, followed by attack to an arene electrophilically to form a Wheland intermediate. Proton release followed by protonation of the resulting intermediate affords an arylalkene. Further hydroarylation of the resulting arylalkene leading to a diarylakane is also considered to proceed in the same way. In some cases, the reactions give mono-adducts exclusively. This is explained by the electronic and steric reasons. In the case of the reaction of 2a with 1b or 5b which gives
momo-adducts, steric hindrance at the β-position of the resulting cinnamate probably inhibits the further addition because methyl group is present at the 2-position of the heteroaryl group. In the case of 2c, the second hydroarylation is considered to be prevented because 3c is an electron-deficient alkene. Heteroarylalkenes obtained from this hydroarylation are usually electron-rich alkenes and reactive enough to undergo the second hydroarylation.

In summary, this chapter describes the K₂PtCl₄/AgOTf catalyzes hydroarylation of alkyne with pyrroles and furans. The reaction proceeds smoothly under mild conditions to give a double-hydroarylation product in most cases. In some cases, the second addition reaction is inhibited and results in the selective formation of a mono-adduct.
Experimentals

General

All solvents and reagents were commercially available and used as received without further purification. All reactions were conducted in a dry Pyrex tube with a rubber septum. In the case of furans, the reaction was conducted in the tube with screw cap. $^1$H and $^{13}$C NMR spectra were recorded on a JEOL JNM-AL 300 FT-NMR using tetramethylsilane (TMS) as internal standard. Melting points were measured with YANACO micro melting apparatus and are uncorrected. Mass spectra were performed on a Shimadzu GC/MS 5020A. Elemental analyses were performed by the Service Center of the Elementary Analysis of Organic Compounds, Faculty of Science, Kyushu University.

General procedure for the K$_2$PtCl$_4$/AgOTf catalyzed hydroarylation of alkynes with pyrroles or furans; Typical example: The K$_2$PtCl$_4$/AgOTf-catalyzed reaction of pyrrole with ethyl phenylpropiolate (Table 1, run 3)

After a mixture of K$_2$PtCl$_4$ (0.02 mmol) and AgOTf (0.08 mmol) in acetic acid (1 mL) was stirred for 1 h, pyrrole (6 mmol) and ethyl phenylporpiolate (1 mmol) were added to the mixture. The reaction was monitored by TLC. After the reaction, the reaction mixture was poured into water (20 mL), neutralized by NaHCO$_3$ and extracted with CH$_2$Cl$_2$ (10 mL x 4). The organic layer was dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography eluting a mixture of AcOEt/hexane, to give 4a in 68% yield.

Ethyl (2Z) 3-(1H-pyrrol-2-yl)cinnamate (3a).$^{3a}$ Light yellow liquid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.32 (t, $J = 7.1$ Hz, 3H, CH$_3$), 4.23 (q, $J = 7.1$ Hz, 2H, OCH$_2$), 5.58 (s, 1H, vinyl),
6.09 (m, 1H, pyrrolyl), 6.21 (m, 1H, pyrrolyl), 7.07 (m, 1H, pyrrolyl), 7.35-7.42 (m, 5H, Ph), 12.96 (brs, 1H, NH). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 14.26, 60.60, 109.71, 109.74, 118.97, 122.82, 127.78, 128.16, 128.86, 130.31, 142.50, 149.18, 168.89.

**Ethyl (2Z) 3-(1-methyl-1H-pyrrol-2-yl)cinnamate (3b).** Light yellow liquid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.19 (t, $J = 7.1$ Hz, 3H, CH$_3$), 3.32 (s, 3H, Me), 4.11 (q, $J = 7.1$ Hz, 2H, OCH$_2$), 6.12 (dd, $J = 1.8$, 3.7 Hz, 1H, pyrrolyl), 6.19 (dd, $J = 2.6$, 3.7 Hz, 1H, pyrrolyl), 6.37 (s, 1H, vinyl), 6.73 (dd, $J = 1.8$, 2.6 Hz, 1H, pyrrolyl), 7.31-7.35 (m, 5H, Ph). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 14.14, 34.34, 60.04, 107.74, 111.60, 118.83, 123.69, 127.98, 128.42, 129.51, 129.85, 140.36, 147.03, 165.95.

**Diethyl (2Z) 2-(1H-pyrrol-2-yl)fumarate (3c).** Yellow liquid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.33 (t, $J = 7.1$ Hz, 3H, CH$_3$), 1.38 (t, $J = 7.1$ Hz, 3H, CH$_3$), 4.24 (q, $J = 7.1$ Hz, 2H, OCH$_2$), 4.36 (q, $J = 7.1$ Hz, 2H, OCH$_2$), 5.94 (s, 1H, vinyl), 6.29 (m, 1H, pyrrolyl), 6.73 (m, 1H, pyrrolyl), 7.04 (m, 1H, pyrrolyl), 12.60 (brs, 1H, NH). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 14.09, 14.11, 61.13, 61.99, 110.08, 110.47, 117.84, 123.59, 125.94, 139.04, 167.80, 168.58. Anal. Calcd. for C$_{12}$H$_{15}$NO$_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.79; H, 6.38; N, 5.86.

**Ethyl (2Z)-3-(1H-pyrrol-2-yl)acrylate (3d).** Light yellow liquid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.32 (t, $J = 7.1$ Hz, 3H, CH$_3$), 4.21 (q, $J = 7.1$ Hz, 2H, OCH$_2$), 5.52 (d, $J = 12.6$ Hz, 1H, vinyl), 6.26 (m, 1H, pyrrolyl), 6.50 (m, 1H, pyrrolyl), 6.76 (d, $J = 12.6$ Hz, 1H, vinyl), 6.99 (m, 1H, pyrrolyl), 12.24 (brs, 1H, NH). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 14.24, 60.39, 107.67, 110.09, 118.54, 122.87, 129.09, 134.66, 169.18.

**Ethyl (2Z)-3-(1H-pyrrol-3-yl)acrylate (3e).** Yellow liquid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$
1.31 (t, J = 7.1 Hz, 3H, CH₃), 4.20 (q, J = 7.1 Hz, 2H, OCH₂), 5.62 (d, J = 12.6 Hz, 1H, vinyl), 6.70 (m, 1H, pyrrolyl), 6.74 (m, 1H, pyrrolyl), 6.82 (d, J = 12.6 Hz, 1H, vinyl), 7.75 (m, 1H, pyrrolyl), 8.57 (brs, 1H, NH). ¹³C NMR (75.5 MHz, CDCl₃): δ 14.33, 59.64, 111.80, 112.27, 118.15, 119.65, 123.99, 138.33, 167.07. Anal. Calcd. for C₉H₁₁NO₂: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.20; H, 6.75; N, 8.36.

Ethyl 3-phenyl-3,3-di(1H-pyrrol-2-yl)propionate (4a). Colorless crystals. Mp 123.0-125.3°C (CH₂Cl₂/Hexane). ¹H NMR (300 MHz, CDCl₃): δ 1.17 (t, J = 7.1 Hz, 3H, CH₃), 3.59 (s, 2H, CH₂CO), 4.06 (q, J = 7.1 Hz, 2H, OCH₂), 5.69 (m, 2H, pyrrolyl), 6.11 (dd, J = 2.6, 5.9 Hz, 2H, pyrrolyl), 6.70 (dd, J = 2.6, 4.2 Hz, 2H, pyrrolyl), 6.98-7.01 (m, 2H, Ph), 7.21-7.29 (m, 3H, Ph), 9.05 (brs, 2H, NH). ¹³C NMR (75.5 MHz, CDCl₃): δ 13.95, 46.14, 46.89, 61.10, 107.50, 107.59, 117.27, 126.86, 127.32, 128.07, 135.57, 145.97, 173.31. Anal. Calcd. for C₁₉H₂₀N₂O₂: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.16; H, 6.55; N, 9.15.

Ethyl 3,3-bis(1H-pyrrol-2-yl)octanonate (4b). Yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 0.84 (t, J = 6.6 Hz, 3H, CH₃), 1.16 (t, J = 7.1 Hz, 3H, CH₃), 1.25 (m, 6H, CH₂), 2.05 (m, 2H, CH₂), 3.01 (s, 2H, CH₂CO), 4.03 (q, J = 7.1 Hz, 2H, OCH₂), 6.00 (m, 2H, pyrrolyl), 6.12 (m, 2H, pyrrolyl), 6.64 (m, 2H, pyrrolyl), 8.55 (brs, 2H, NH). ¹³C NMR (75.5 MHz, CDCl₃): δ 13.98, 14.01, 22.47, 24.07, 32.12, 40.86, 41.77, 43.54, 60.63, 105.29, 107.64, 116.92, 135.45, 172.73. Anal. Calcd. for C₁₈H₂₆N₂O₂: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.39; H, 8.64; N, 9.23.

1,1-Bis(1H-pyrrol-2-yl)-1-phenylethane (4c). Light orange crystals. Mp 113.9-116.6°C (CH₂Cl₂/Hexane). ¹H NMR (300 MHz, CDCl₃): δ 2.05 (s, 3H, CH₃), 5.97 (m, 2H, pyrrolyl), 6.17 (dd, J = 2.7, 6.0 Hz, 1H, pyrrolyl), 6.65 (dd, J = 2.7, 4.2 Hz, 1H, pyrrolyl), 7.09-7.13 (m,
2H, Ph), 7.19-7.30 (m, 3H, Ph), 7.76 (brs, 2H, NH). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 28.84, 44.76, 106.30, 108.26, 116.87, 126.66, 127.41, 128.16, 137.46, 147.28.

**1,1-Bis(1-methyl-1H-pyrrol-2-yl)-1-phenylethane (4d).** Yellow viscous oil. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.08 (s, 3H, CH$_3$), 3.09 (s, 6H, CH$_3$), 5.86 (dd, $J$ = 2.1, 3.6 Hz, 1H, pyrrolyl), 6.02 (dd, $J$ = 3.0, 3.6 Hz, 1H, pyrrolyl), 6.55 (dd, $J$ = 2.1, 3.0 Hz, 1H, pyrrolyl), 7.11-7.14 (m, 2H, Ph), 7.21-7.31 (m, 3H, Ph). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 29.76, 35.24, 45.00, 105.90, 109.23, 123.57, 126.34, 127.81, 127.88, 136.96, 146.99. The regiochemistry of the compound was determined by NOE experiments. Anal. Calcd. for C$_{18}$H$_{20}$N$_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.94; H, 7.55; N, 10.32.

**Ethyl 3,3-Bis(5-methylfur-2-yl)-3-phenylpropionate (6a).** Light yellow liquid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.09 (t, $J$ = 7.1 Hz, 3H, CH$_3$), 2.25 (s, 6H, CH$_3$), 3.40 (s, 2H, CH$_2$CO), 4.00 (q, $J$ = 7.1 Hz, 2H, OCH$_2$), 5.90 (dd, $J$ = 0.9, 3.0 Hz, 2H, furyl), 5.93 (d, $J$ = 3.0 Hz, 2H, furyl), 7.11-7.15 (m, 2H, Ph), 7.21-7.29 (m, 3H, Ph). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 13.61, 13.92, 43.10, 48.92, 60.15, 106.01, 108.98, 126.82, 127.56, 127.91, 143.46, 151.18, 154.25, 170.25. Anal. Calcd. for C$_{21}$H$_{22}$O$_4$: C, 74.54; H, 6.55. Found: C, 74.45; H, 6.61.

**Ethyl 3,3-bis(2,5-dimethylfur-3-yl)propionate (6b).** Yellow liquid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.16 (t, $J$ = 7.1 Hz, 3H, CH$_3$), 2.18 (s, 6H, CH$_3$), 2.19 (s, 6H, CH$_3$), 2.70 (d, $J$ = 7.8 Hz, 2H, CH$_2$CO), 4.05 (q, $J$ = 7.1 Hz, 2H, OCH$_2$), 4.07 (t, $J$ = 7.8 Hz, 1H, CH), 5.84 (s, 2H, furyl). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 11.47, 13.47, 14.05, 28.88, 41.12, 60.23, 105.34, 121.52, 144.72, 149.44, 171.80. IR (neat, cm$^{-1}$) 2982, 2922, 1736 (C=O), 1639, 1582, 1442, 1372, 1259, 1222, 1172, 1037, 798.
Ethyl 3-(2,5-dimethylfur-3-yl)cinnamate (7a) was obtained as a mixture of Z- and E-stereoisomers. Z-isomer was partially isolated from the mixture of the stereoisomers. The stereochemistry of 7a was determined by NOE experiments.

**Ethyl (2Z)-3-(2,5-dimethylfur-3-yl)cinnamate (7a-Z).** Slightly yellow liquid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.25 (t, $J = 7.1$ Hz, 3H, CH$_3$), 1.99 (s, 3H, CH$_3$), 2.26 (s, 3H, CH$_3$), 4.16 (q, $J = 7.1$ Hz, 2H, OCH$_2$), 5.83 (s, 1H, furyl), 6.21 (s, 1H, vinyl), 7.33-7.37 (m, 5H, Ph). 13C NMR (75.5 MHz, CDCl$_3$): $\delta$ 12.80, 13.41, 14.24, 59.97, 108.55, 117.54, 118.22, 128.16, 128.31, 129.24, 140.92, 149.19, 149.29, 149.54, 165.89. Anal. Calcd. for C$_{17}$H$_{18}$O$_3$: C, 75.53; H, 6.71. Found: C, 75.20; H, 6.73.

**Ethyl (2E)-3-(2,5-dimethylfur-3-yl)cinnamate (7a-E).** Colorless liquid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.09 (t, $J = 7.1$ Hz, 3H, CH$_3$), 1.76 (s, 3H, CH$_3$), 2.21 (s, 3H, CH$_3$), 4.01 (q, $J = 7.1$ Hz, 2H, OCH$_2$), 5.92 (s, 1H, furyl), 6.05 (s, 1H, vinyl), 7.19-7.22 (m, 2H, Ph), 7.34-7.36 (m, 2H, Ph).

**Ethyl (2Z)-3-(2,5-dimethylfur-3-yl)acrylate (7b).** Light yellow liquid. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.31 (t, $J = 7.1$ Hz, 3H, CH$_3$), 2.24 (s, 3H, CH$_3$), 2.31 (s, 3H, CH$_3$), 4.20 (q, $J = 7.1$ Hz, 2H, OCH$_2$), 5.65 (d, $J = 12.6$ Hz, 1H, vinyl), 6.63 (d, $J = 12.6$ Hz, 1H, vinyl), 6.82 (s, 1H, furyl). 13C NMR (75.5 MHz, CDCl$_3$): $\delta$ 11.79, 13.16, 14.23, 59.82, 107.30, 114.15, 117.63, 133.79, 149.84, 154.36, 166.46. IR (neat, cm$^{-1}$) 2983, 1719, 1627, 1444, 1399, 1030.

**Diethyl 1,4-dimethyl-7-oxabicyclo[2,2,1]hepta-2,5-diene-2,3-dicarboxylate (8a).** $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.31 (t, $J = 7.1$ Hz, 6H, CH$_3$), 1.80 (s, 6H, CH$_3$), 4.25 (q, $J = 7.1$ Hz, 4H, OCH$_2$), 6.95 (s, 2H, vinyl). 13C NMR (75.5 MHz, CDCl$_3$): $\delta$ 14.08, 15.36, 61.14,
Diethyl 7-oxabicyclo[2,2,1]hepta-2,5-diene-2,3-dicarboxylate (8b). \(^{12}\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 1.32 (t, \(J = 7.1\) Hz, 6H, CH\(_3\)), 4.27 (q, \(J = 7.1\) Hz, 4H, OCH\(_2\)), 5.68 (m, 2H, H1 and H4), 7.22 (m, 2H, vinyl). \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)): \(\delta\) 14.06, 61.38, 85.06, 143.21, 152.66, 163.03.
References


   

   


   


Chapter 5

Conclusion

Platinum-catalyzed hydroarylation of alkynes has been developed and applied to the synthesis of arylated alkenes and coumarins.

Silver compounds were investigated as additives for PtCl₂-catalyzed hydroarylation to improve the catalytic activity of the Pt catalyst. As a result, it was revealed that AgOTf was most effective additives among the silver compound examined although AgBF₄ and AgPF₆ were also effective. The reaction using PtCl₂/AgOTf also proceeded selectively to afford cinnamate 3a. Optimization of the reaction conditions showed that an excess amount of an arene was preferred to obtain a mono-alkenylated adduct 3a selectively. Higher reaction temperature is not desirable for this reaction because hydrolysis and isomerization of the resulting adduct occurred at higher temperature. PtCl₂/AgOTf-catalyzed hydroarylation of ethyl propiolate with various arenes such as pentamethylbenzene, p-xylene and naphthalene gave the corresponding cinnamates in good to high yields. In the case of ethyl propiolate, the PtCl₂/AgOTf-catalyzed hydroarylation gave cinnamates in higher yields compared with the Pd(OAc)₂-catalyzed reaction because of higher selectivity of the Pt catalyst. However, the PtCl₂/AgOTf-catalyzed reaction was slower than the Pd(OAc)₂-catalyzed reaction. Moreover, the reaction was also applicable to internal alkyne, ethyl phenylpropiolate. The hydroarylation of propiolic acids was effective for this catalyst system because the hydrolysis of the product was observed when the reaction was prolonged.

Several Pt salts were investigated as Pt catalyst precursors, revealing K₂PtCl₄, PtCl₂(bpy), (Bu₄N)₂PtCl₄ and PtCl₄ were active catalyst precursors. (Bu₄N)₂PtCl₄ and PtCl₄ catalyzed the hydroarylation in the absence of AgOTf. In particular, PtCl₄ catalyzed the reaction even in the absence of TFA although the product selectivity was low. K₂PtCl₄ is one of the most
readily available and cheapest platinum salts. K$_2$PtCl$_4$/AgOTf-catalyzed hydroarylation of ethyl propiolate gave cinnamate in good to high yields. Again, the hydroarylation of propiolic acids generally gave cinnamic acid in high yields. Sterically hindered, 1,4-di-tert-butylbenzene also participated into the reaction although 1,3,5-tri-tert-butylbenzene did not react. Moreover, hydroarylation of propiolic acid with benzene also proceeded in the presence of K$_2$PtCl$_4$/AgOTf to give cinnamic acid in around 60% yield. Other Pt catalysts such as PtCl$_2$(bpy)/AgOTf, (Bu$_4$N)$_2$PtCl$_4$/AgOTf and PtCl$_4$/AgOTf were also effective although PtCl$_2$/AgOTf showed poor activity. On the other hand, Pd(OAc)$_2$ showed low selectivity although the reaction was very fast.

K$_2$PtCl$_4$/AgOTf-catalyzed hydroarylation was successfully applied to the coumarin synthesis from propiolic acid and phenols. Propiolic acid showed high reactivity to react with less reactive phenols but the selectivity for coumarin was low. In this case, the formation of dihydrocoumain was observed. On the other hand, the substituted propiolic acid, phenylpropiolic acid and 2-octynoic acid, gave coumarins in good to high yields. The reactivity of substituted propiolic acids was lower than propiolic acid. Therefore, substituted propiolic acids reacted with electron-rich phenols.

K$_2$PtCl$_4$/AgOTf-catalyzed hydroarylation was also applicable to heteroarenes like pyrroles and furans. The reaction proceeded smoothly under mild conditions to give double-hydroarylation products in most cases. In some cases, the second addition reaction was inhibited and resulted in the selective formation of a mono-adduct. In the case of pyrroles, the fact that AgOTf does not catalyze the reaction and that (Bu$_4$N)$_2$PtCl$_4$ itself works as catalyst suggests that Pt species is an active catalyst. Similarly, it is suggested that Pt species is an active catalyst in the case of furan.
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