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Transition-Metal-Catalyzed Hydroarylation Reactions of Alkynes Through Direct Functionalization of C–H Bonds: A Convenient Tool for Organic Synthesis

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Direct functionalization of aromatic C–H bonds with alkynes provides an efficient synthetic protocol involving fewer reaction steps without need for prefunctionalization. This microreview presents an overview of the recently developed transition-metal-catalyzed hydroarylation reactions of alkynes. Special attention is paid to hydroarylation through alkyne activation processes and through arene activation processes.

1. Introduction

Direct functionalization of C–H bonds in hydrocarbons with the aid of a catalyst is a challenging subject in organic chemistry because of low reactivity of the C–H bond and has recently been studied with great interest.[1] Direct functionalization of hydrocarbons in organic synthesis has the advantage that halogenated compounds or related substrates are not required as starting materials and so the number of reaction steps required is reduced. Such processes are therefore also attractive as environmentally benign and efficient syntheses.

Hydroarylation of alkynes can formally be regarded as a reaction in which both aryl and hydrogen moieties of an aromatic compound add across a triple bond, providing a direct and efficient approach to the synthesis of aromatic alkenes. This microreview focuses on the hydroarylation reactions of alkynes[2] developed in recent years, which are mainly divided into two pathways: through alkyne activation and through arene activation, as shown in Schemes 1 and 2.

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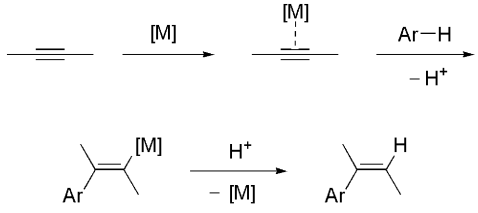
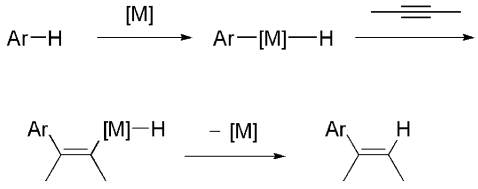


Scheme 1.



Scheme 2.

(1) Through Alkyne Triple Bond Activation

A triple bond is activated by coordination with a cationic metal and shows electrophilic character. This activated alkyne undergoes an electrophilic substitution with an electron-rich arene to form an arylvinylmetal complex. Finally, the vinyl complex is protonated to form an aryl-alkene. The

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mode of addition is therefore *trans*, whereas the regiochemistry is controlled by the electronic nature of the substituent on the triple bond.

(2) Through Arene C–H Bond Activation

A metal complex that is nucleophilic in nature undergoes C–H bond activation by oxidative addition to form an arylmetal complex, which adds to a triple bond in a *syn* manner to form an arylvinylmetal complex. Reductive elimination gives an aryl-alkene product. The presence of a directing group on the arene ring accelerates this C–H bond activation, also controlling the regiochemistry.

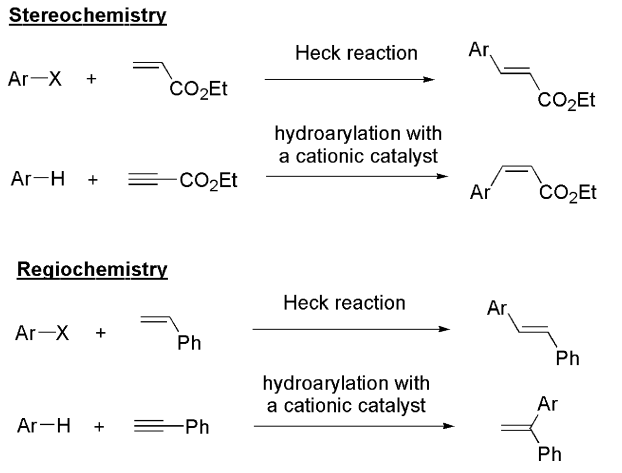
Synthetically useful characteristics of hydroarylation of alkynes are as follows.

(1) This process gives conjugated aromatic alkenes, which are important intermediates for functional materials and pharmaceuticals.

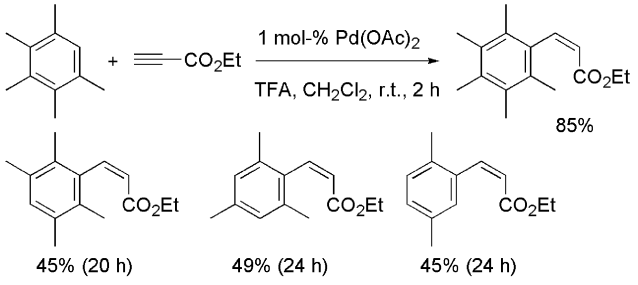
(2) This process provides direct synthesis of aryl-alkenes from simple arenes. Although aryl-alkenes have been widely synthesized by the well known Heck reaction, Stille reaction, Suzuki–Miyaura coupling reaction, and related reactions, synthesis with such reactions requires prefunctionalization of arenes to halides or triflates. The hydroarylation process is therefore an efficient alternative for aryl-alkene synthesis.

(3) This process is a catalytic, highly atom-economical, and environmentally benign reaction.

(4) This hydroarylation process affords stereo- or regio-defined isomers of aryl-alkenes different from those obtained in the Heck reaction, as illustrated in Scheme 3.



Scheme 3.



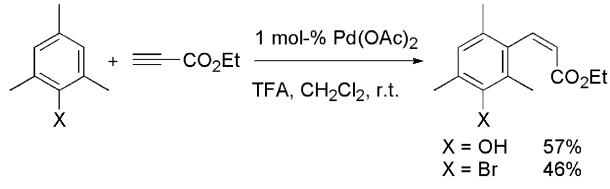
Scheme 4.

2. Hydroarylation of Alkynes through Alkyne Activation

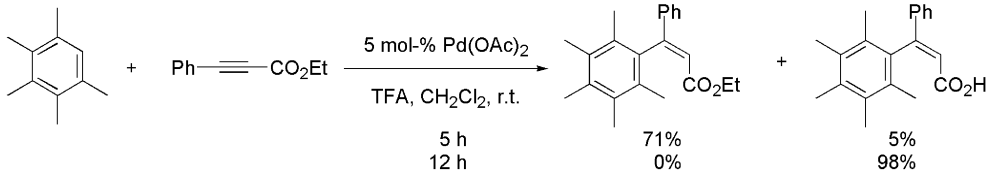
2.1 Simple Addition of Arenes to Alkynes

A simple addition of an aromatic C–H bond to a triple bond in most cases proceeds in an electrophilic manner and can be applicable to a wide range of substrates because the process does not require a directing group. A typical hydroarylation reaction is a $Pd(OAc)_2$-catalyzed reaction between an alkyne and an arene under acidic conditions.[3] The reaction was initially thought to proceed through C–H activation of the arene followed by *trans* addition of a palladium–arene bond across an alkyne, but mechanistic studies based on kinetic isotope effects have suggested that the reaction proceeds by electrophilic aromatic substitution with a metal-activated alkyne.[4]

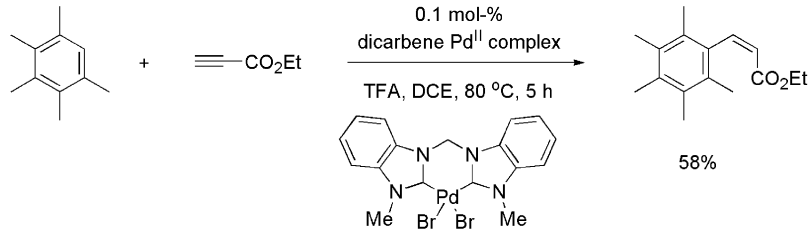
This hydroarylation reaction in most cases takes place at room temperature and affords hydroarylation products both regio- and stereoselectively.[3] The reaction between ethyl propiolate and pentamethylbenzene (Scheme 4), for example, gives ethyl *cis*-pentamethylcinnamate in a high yield. Since alkynes activated by cationic Pd catalysts show high electrophilicity in hydroarylation, electron-rich arenes such as durene, mesitylene, and xylene give good results in this reaction. Although the reaction between ethyl phenylpropiolate and pentamethylbenzene gives a high yield of the hydroarylation product after 5 h, after 12 h the same reaction affords a 98% yield of the diarylpropenoic acid



Scheme 6.



Scheme 5.



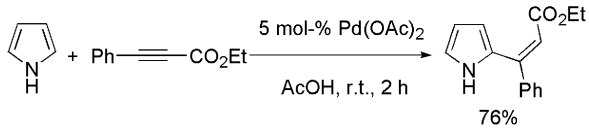
Scheme 7.

(Scheme 5) originating from hydrolysis of the corresponding ethyl ester with TFA, due to a long reaction time.

This hydroarylation reaction shows chemoselectivity and is tolerant towards the presence of functional groups such as OH and Br (Scheme 6). The reaction with mesityl bromide gives no debrominated product, suggesting that no Pd^0 species is involved in this hydroarylation reaction.

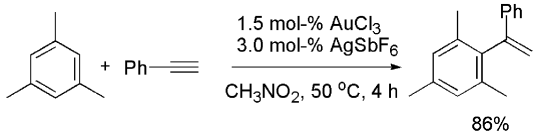
A chelating *N*-heterocyclic dicarbene palladium(II) complex also acts as a catalyst in hydroarylation of alkynes (Scheme 7).[5] Although this hydroarylation reaction affords low levels of conversion at room temperature, an increase in the reaction temperature to 80 °C gives complete conversion. The use of this dicarbene Pd^{II} complex has the advantage that the reaction proceeds with a low loading (0.1 mol-%) of the catalyst to yield hydroarylation products in good yields.

Palladium-catalyzed hydroarylation of alkynes has been applied to simple heterocycles such as pyrroles and indoles,[6] taking place in AcOH or CH_2Cl_2 under mild conditions. The reaction between ethyl phenylpropiolate and pyrrole gives the hydroarylation product in 76% yield (Scheme 8). This procedure has been extended to a direct synthesis of the β-alkenylpyrrole fragment of hemin (Scheme 9).[7]



Scheme 8.

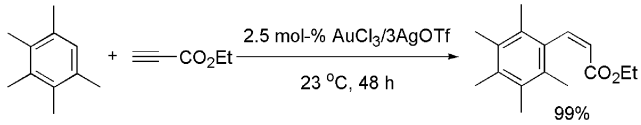
Hydroarylation of aryl-substituted alkynes with electron-rich arenes is catalyzed by $AuCl_3$ activated by silver salts such as $AgSbF_6$.[8] In the case of terminal aryl-alkynes, complete regioselectivity in favor of the 1,1-diarylethenes is observed. The reaction between phenylacetylene and mesitylene in the presence of $AuCl_3$ and $AgSbF_6$, for example, gives 1-mesityl-1-phenylethene in 86% yield (Scheme 10). On the other hand, the hydroarylation of electron-deficient alkynes such as ethyl propiolate is effectively catalyzed by Ph_3PAuCl or Et_3PAuCl activated with $AgSbF_6$ or $BF_3{\cdot}OEt_2$ (Scheme 11).



Scheme 10.

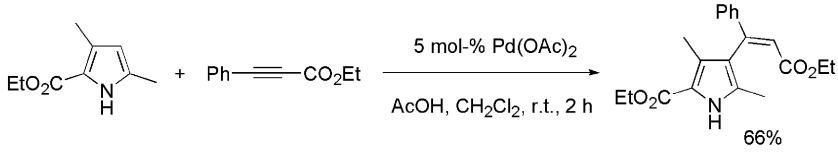
Scheme 11.

$AuCl_3$-catalyzed hydroarylation of electron-deficient alkynes can be also conducted under solvent-free conditions. In the presence of $AuCl_3$/3 AgOTf (2.5 mol-%), pentamethylbenzene reacts with ethyl propiolate at 23 °C to afford the hydroarylation product in 99% yield (Scheme 12).[9]



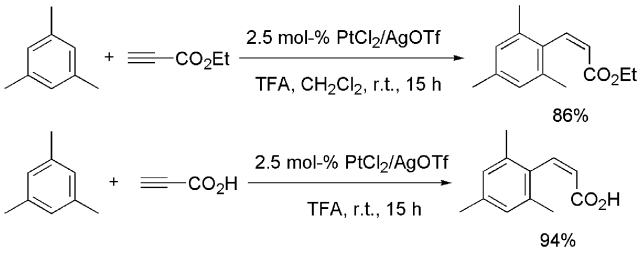
Scheme 12.

Although Pd-catalyzed hydroarylations of ethyl propiolate with simple arenes provide ethyl *cis*-cinnamates with high regio- and stereoselectivities, such hydroarylations also give diethyl (1*E*,3*Z*)-4-arylbuta-1,3-diene-1,3-dicarboxylates as byproducts.[3] Because of the formation of these arylbutadiene derivatives, the hydroarylation reactions display low chemoselectivities and decreased yields of the desired cinnamates. On the other hand, hydroarylations of ethyl propiolate proceed selectively to give the cinnamates without the formation of the arylbutadienes when a Pt^{II} catalyst – $PtCl_2$/AgOAc – is used instead of $Pd(OAc)_2$.[3] The



Scheme 9.

$PtCl_2$/AgOAc catalyst is low in activity, however, suggesting that a more cationic Pt catalyst is required to improve the activity. As shown in Scheme 13, in the presence of $PtCl_2$/AgOTf[10] as catalyst, mesitylene reacts with ethyl propiolate at room temperature to afford ethyl *cis*-trimethylcinnamate in 86% yield after 15 h. When propiolic acid is used instead of ethyl propiolate, the yield of the desired product is improved to 94%.

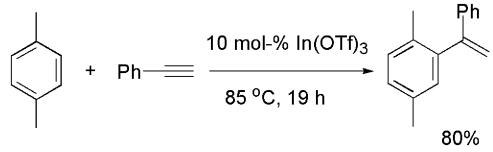


Scheme 13.

The $PtCl_2$/AgOTf catalyst is selective and effective for the hydroarylation of propiolates, leading to the predominant formation of *cis*-cinnamates. However, this catalyst exhibited low reactivity toward less reactive aromatic substrates and could not be applied to hydroarylation with benzene as a representative aromatic compound. Among platinum catalysts, K_2PtCl_4 has been found to be more effective in combination with AgOTf:[11] the hydroarylation of propiolic acid with benzene proceeds effectively in the presence of K_2PtCl_4/AgOTf as catalyst to give *cis*-cinnamic acid in 54% yield at room temperature or in 61% yield at 40 °C (Scheme 14). As would be expected, representative electron-rich aromatic substrates give high yields of cinnamic acid derivatives in hydroarylations with this catalyst, as shown in Scheme 14.

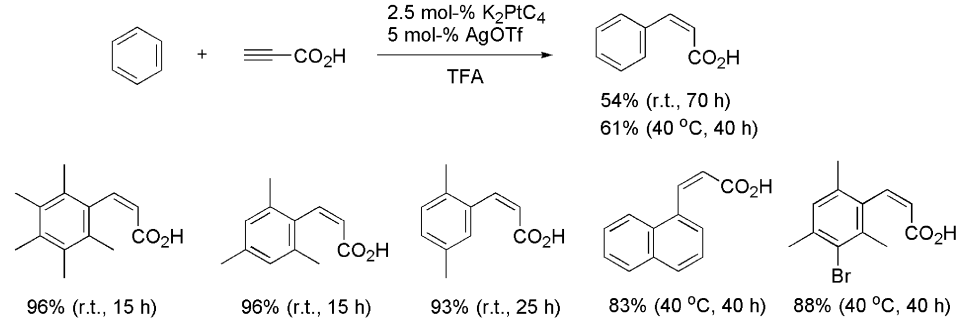
Polyolefins are ubiquitous commercial polymers, and introduction of functional groups into these polymers is an important approach in the development of new polymer materials. Hydroarylation in the presence of the K_2PtCl_4/AgOTf catalyst has been applied to polystyrenes (Scheme 15).[12] A polystyrene block copolymer reacts with propiolic acid in the presence of K_2PtCl_4 (10 mol-%) and AgOTf (40 mol-%) in TFA and $CHCl_3$ at 60 °C to give alkenylated polystyrene block copolymer with 30% introduction of acrylic acid moiety after 24 h. The same reaction between the polystyrene block copolymer and methyl propiolate also leads to 35% introduction of methyl acrylate moiety, but the reaction between polystyrene and methyl propiolate results in only 7% introduction of methyl acrylate moiety.

Metal triflates such as $In(OTf)_3$, $Sc(OTf)_3$, and $Zr(OTf)_4$ catalyze the hydroarylation of aryl-alkynes to afford 1,1-diaryl alkenes in high to excellent yields.[13] The reaction between phenylacetylene and *p*-xylene at 85 °C in the presence of $In(OTf)_3$ (10 mol-%) proceeds smoothly to give 1-phenyl-1-xylylethene in 80% yield after 19 h (Scheme 16). The same reactions in the presence of $Sc(OTf)_3$ or $Zr(OTf)_4$ afford the same product in 92 and 53% yields, respectively.

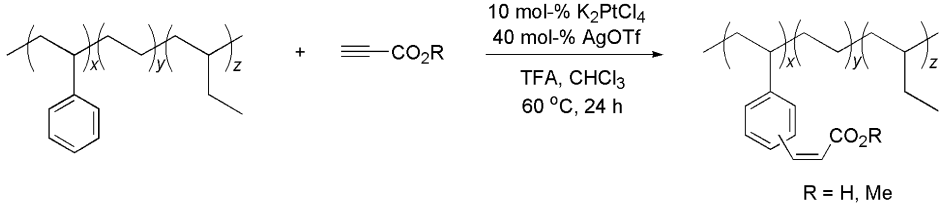


Scheme 16.

The catalytic activities of metal triflates in hydroarylations of alkynes can be enhanced by using an ionic li-

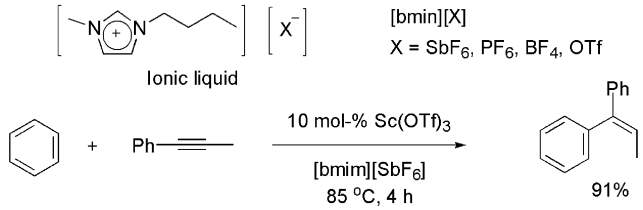


Scheme 14.



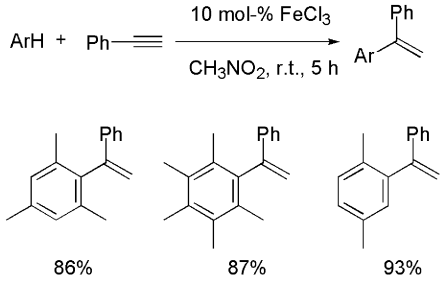
Scheme 15.

quid.[14] Hydroarylation of 1-phenylprop-1-yne with benzene in the presence of 10 mol-% $Sc(OTf)_3$ in 1-butyl-3-methylimidazolium hexafluoroantimonate ([bmim][SbF_6]) is complete within 4 h and affords 1,1-diphenylprop-1-ene in an excellent yield (Scheme 17), whereas without use of an ionic liquid the reaction gives a low yield (27%) of the product after 96 h. Of the imidazolium salts tested, [bmim][X] (X = SbF_6, PF_6, BF_4, OTf, SF_6, and PF_6 anions) provide the most active reaction media for hydroarylation.



Scheme 17.

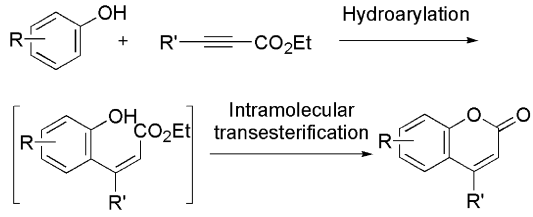
Hydroarylation of aryl-substituted alkynes with use of an iron catalyst has been achieved, as shown in Scheme 18.[15] The use of such a ubiquitous metal has recently attracted much attention, because iron is abundant, economical, and environmentally friendly. The reaction between phenylacetylene and mesitylene proceeds smoothly in the presence of $FeCl_3$ (10 mol-%) in CH_3NO_2 to produce 1-mesityl-1-phenylethene in 86% yield. Other electron-rich aromatics also give good results.



Scheme 18.

2.2 Hydroarylation of Propiolates with Phenols to Afford Coumarins

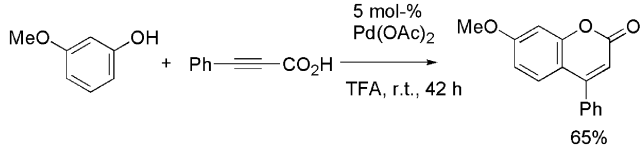
Electron-rich alkoxy-substituted phenols undergo hydroarylation with propiolates in the presence of $Pd(OAc)_2$ as catalyst in mixed solvent systems containing TFA. The subsequent intramolecular transesterification of the hydroarylation product takes place immediately to form a coumarin derivative, as shown in Scheme 19. This process provides a direct synthesis of coumarins from phenols and propiolates.[16]



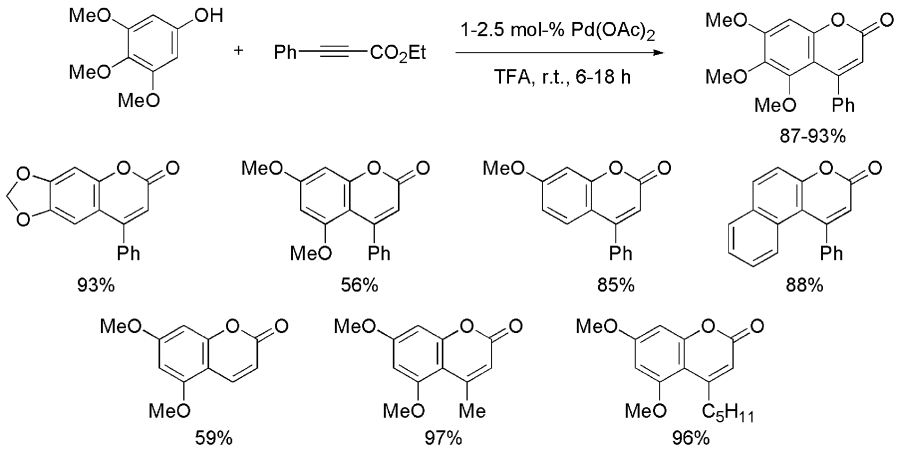
Scheme 19.

The scope of this process is illustrated in Scheme 20: the reaction between ethyl phenylpropiolate and 3,4,5-trimethoxyphenol in the presence of a catalytic amount of $Pd(OAc)_2$ in TFA proceeds smoothly at room temperature to give 5,6,7-trimethoxy-4-phenylcoumarin in a high yield. Coumarin derivatives can be also obtained in good to high yields from other electron-rich starting phenols, as shown.

A simpler direct route to coumarin derivatives is accomplished by treatment of phenols with propiolic acids (Scheme 21).[17] This process is not accompanied by the formation of alcohols as byproducts, nor does it require aryl



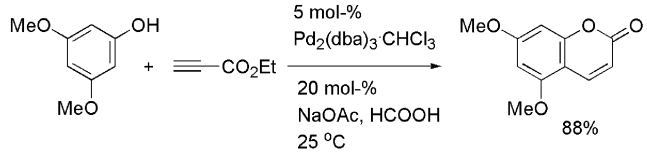
Scheme 21.



Scheme 20.

esters of propiolic acids for synthesis of coumarins by intramolecular hydroarylation as described later.

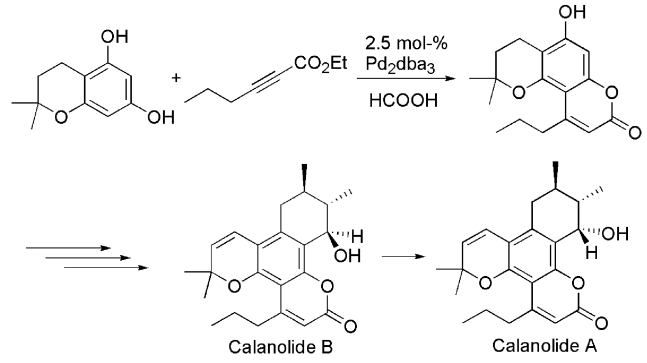
Instead of TFA, formic acid is the choice of solvent in reactions involving ethyl propiolates and phenols, although a Pd^0 species, rather than Pd^{II}, is involved as an active species in the reaction in HCOOH. Treatment of ethyl propiolate with 3,5-dimethoxyphenol in the presence of $(dba)_3Pd_2{\cdot}CHCl_3$ (5 mol-%) and NaOAc (20 mol-%) in this acid at 50 °C affords 5,7-dimethoxycoumarin in 88% yield (Scheme 22).[18] Under these conditions, several coumarin derivatives are prepared in reactions involving electron-rich phenols such as phloroglucinol, 3,4,5-trimethoxyphenol, 3,4-methylenedioxyphenol, 3-methoxyphenol, 3-methoxy-5-methylphenol, 5-methoxyresorcinol, and 2-naphthol.



Scheme 22.

Hydroarylation of propiolates with phenols has been applied to the synthesis of calanolides A and B, which are active against AZT-resistant strains of HIV-1.[19] The key step in this synthesis is the palladium-catalyzed coumarin-forming reaction (Scheme 23).

Syntheses of coumarins from phenols and propiolic acids can also be conducted with Pt catalysts such as $PtCl_2$/AgOTf and K_2PtCl_4/AgOTf.[20] The reactions between substituted propiolic acids and electron-rich phenols proceed selectively to afford coumarins in good to high yields.

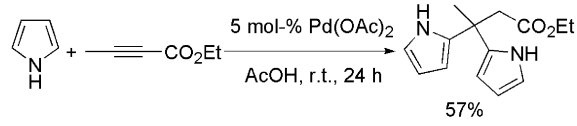


Scheme 23.

2.3 Double Hydroarylation of Alkynes

Hydroarylation of alkynes with arenes forms aromatic alkenes, which in cases of reactions with electron-rich arenes such as alkoxy-substituted benzenes and heteroaromatics can undergo subsequent hydroarylation. Double hydroarylation thus takes place in these cases. Reactions between ethyl propiolate and electron-rich arenes such as anisole, 1,4-dimethoxybenzene, or 1,3,5-trimethoxybenzene, in the presence of, for example, $Pd(OAc)_2$ (1 mol-%), give double hydroarylation products, albeit the yields are low.[3]

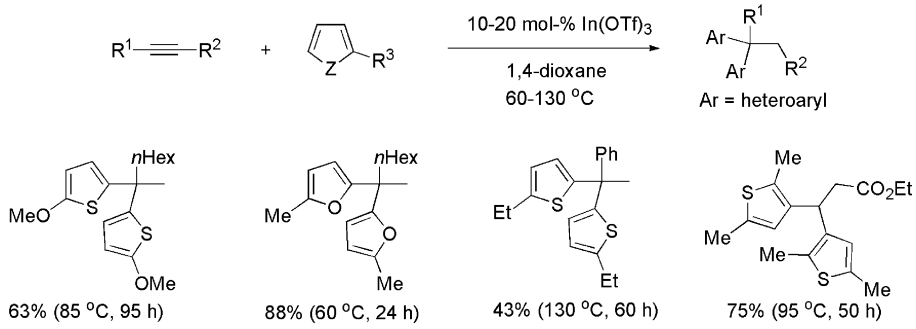
Pyrrole and indole undergo double hydroarylation in the presence of a $Pd(OAc)_2$ catalyst in AcOH at room temperature when ethyl but-2-ynoate and oct-2-ynoate are employed.[6] The reaction between ethyl but-2-ynoate and pyrrole in the presence of $Pd(OAc)_2$ (5 mol-%) in AcOH at room temperature affords ethyl 2,2-dipyrrolylbutanoate in 57% yield after 24 h (Scheme 24).



Scheme 24.

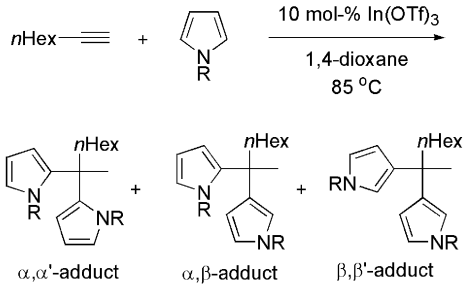
Hydroarylation with heteroaromatic compounds or electron-rich heteroaromatics occurs efficiently when indium triflate is used as a catalyst.[21] The reactions of hex-1-yne or phenylacetylene with thiophenes or 2-methylfuran proceed in the presence of $In(OTf)_3$ (10–20 mol-%) in 1,4-dioxane to afford 2,2-dithienyl- or difuryl alkanes in good yields, as shown in Scheme 25.

On the other hand, the reactions of pyrroles give mixtures of α,α′, α,β, and β,β′ adducts, suggesting that the distributions of the regioisomers vary with bulkiness of the substituent on the nitrogen atom, as shown in Scheme 26. The reaction between oct-1-yne and *N*-unsubstituted pyrrole forms the α,α′ adduct 2,2-bis(2′-pyrrolyl)octane as the major product, whereas the reactions of *N*-methyl- and *N*-butylpyrroles result in the major formation of the β,β′ ad-



Scheme 25.

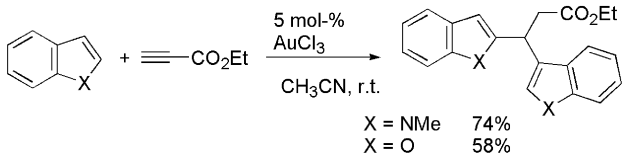
ducts. *N*-Isopropyl- and -triisopropylsilyl-substituted pyrroles give only β,β′ adducts. Isomerization from α,α′ to β,β′ adducts is suggested.



	time	yield	α,α' : α,β : β,β'
R = H	0.5 h	79%	66 : 34 : <1
R = Me	5 h	93%	1 : 15 : 85
R = *n*Bu	1.5 h	90%	0 : 6 : 94
R = *i*Pr	3 h	86%	0 : 0 : 100
R = $(i\text{Pr})_3$Si	70 h (110 °C)	61%	0 : 0 : 100

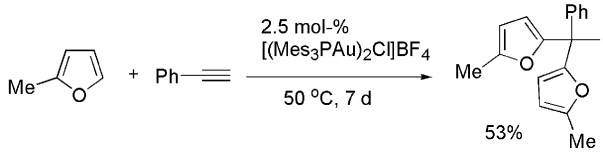
Scheme 26.

When gold(III)-catalyzed hydroarylation of alkynes is applied to heterocycles such as indole and benzofuran, two equivalents of the heterocycles add to one molecule of ethyl propiolate (Scheme 27).[22]



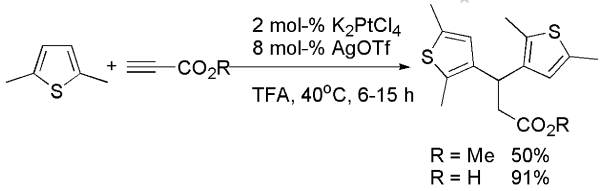
Scheme 27.

Use of a cationic binuclear catalyst – $[(Mes_3PAu)_2Cl]BF_4$ – is able to effect the hydroarylation of alkynes with 2-substituted furans.[23] This hydroarylation gives a double hydroarylation product in good yields (Scheme 28). Because the intermediate single-hydroarylation product cannot be detected or isolated, the second addition is believed to be faster than the first one.



Scheme 28.

Platinum-catalyzed hydroarylation of alkynes has been extended to thiophenes.[24] Treatment of thiophenes with ethyl propiolate or propiolic acid in TFA in the presence of K_2PtCl_4/AgOTf as catalyst affords 3,3-bis(thienyl)propionates and -propionic acids, respectively, in good to high yields (Scheme 29). As in the previous example, the first hydroarylation with thiophenes proceeds effectively and the subsequent one occurs immediately afterwards, to afford the doubly thienylated products.



Scheme 29.

3. Intramolecular Hydroarylation of Alkynes through Alkyne Activation

The hydroarylation methodology has been extended to the intramolecular version, allowing the synthesis of heterocycles and carbocycles. In particular, such intramolecular hydroarylation reactions are suitable for the synthesis of heterocycles, because of the mildness of the reaction conditions in most cases. Six-membered heterocycles and carbocycles have been synthesized by this hydroarylation method.

3.1 Coumarins

Whereas the hydroarylation of ethyl propiolates affords *cis*-cinnamates, aryl propiolates undergo intramolecular hydroarylation to give coumarin derivatives, as shown in Scheme 30.[3a,25] The reaction of 4′-*tert*-butylphenyl phenylpropiolate in the presence of $Pd(OAc)_2$ (1 mol-%) in a mixed solvent containing TFA, for example, gives 6-*tert*-butyl-4-phenylcoumarin in 90% yield within 30 min. Very recently, this reaction has been examined with an iron catalyst.[26] Intramolecular hydroarylation proceeds in the presence of $FeCl_3$ (20 mol-%) in nitromethane at 80 °C to afford the same product in 53% yield after 72 h. Various aryl alkynoates smoothly undergo intramolecular hydroarylation in the presence of $Pd(OAc)_2$ as the catalytic system in TFA.

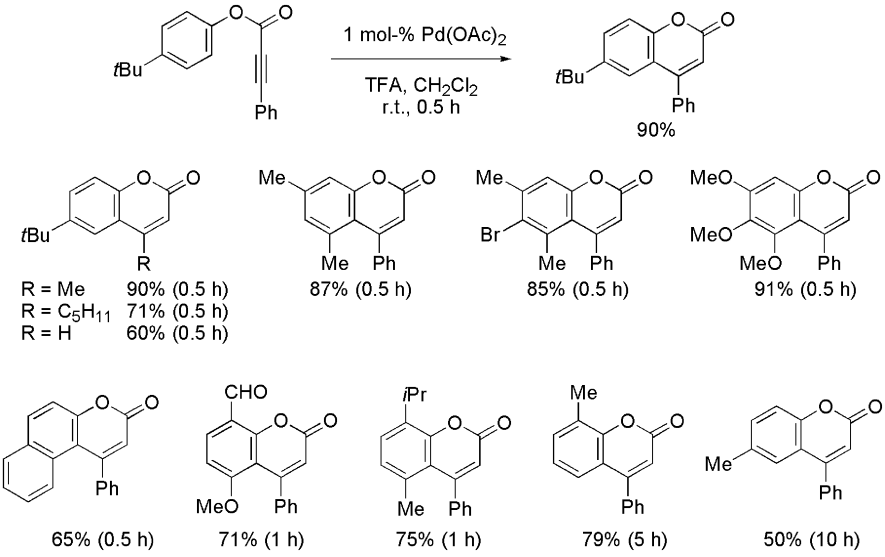
Similarly, intramolecular hydroarylation of aryl propiolates to afford coumarins can be carried out with a gold catalyst.[9] The reactions of phenyl propiolates in dichloroethane at 50 °C in the presence of $AuCl_3$/3 AgOTf (5 mol-%) give coumarins in good to high yields (Scheme 31).

$Hf(OTf)_4$-catalyzed intramolecular hydroarylation in the ionic liquid [bmim][SbF_6] has been extended to coumarin synthesis.[14] Reactions in the presence of $Hf(OTf)_4$ (10 mol-%) in mixtures of [bmim][SbF_6] and methylcyclohexane at 85 °C afford coumarins in good yields after 9 h (Scheme 32).

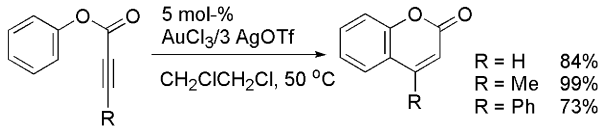
3.2 Quinolinones

Intramolecular hydroarylation has been applied to the synthesis of the nitrogen-containing 2(1*H*)-quinolinone heterocycles.[3a,25] Reactions of alkynanilides in the presence of $Pd(OAc)_2$ (2 mol-%) proceed smoothly in mixed solvents containing TFA at room temperature to give 2(1*H*)-quinolinones in good yields, as shown in Scheme 33.

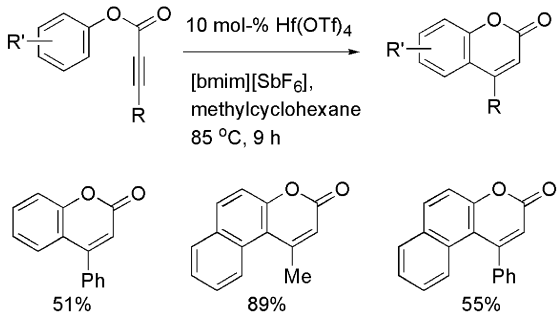
Because direct intermolecular reactions between alkynoic acids and anilides do not afford 2(1*H*)-quinolinones



Scheme 30.



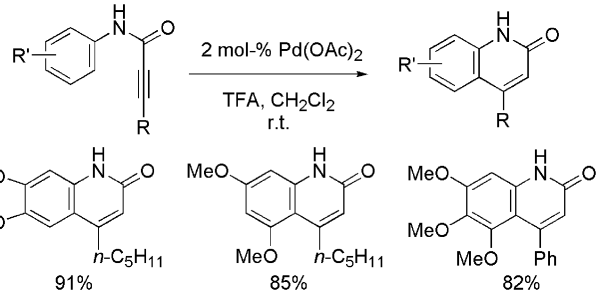
Scheme 31.



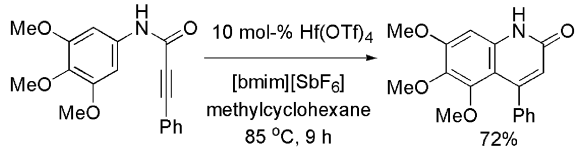
Scheme 32.

(Scheme 34), the intramolecular hydroarylation process offers a unique and efficient method for the synthesis of these heterocycles.

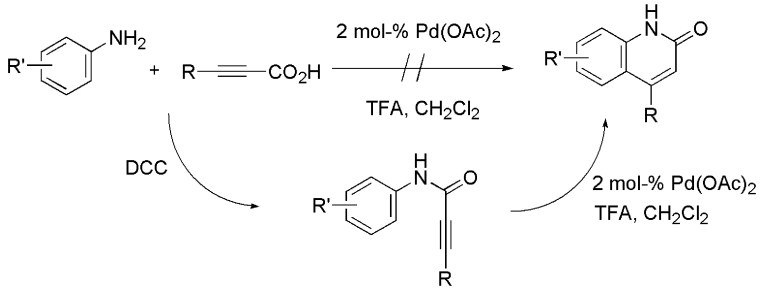
Hydroarylation in the presence of $Hf(OTf)_4$ as catalyst in an ionic liquid can be applied to quinolinone synthesis.[14] The intramolecular hydroarylation of phenylpropiolic acid 3,4,5-trimethoxyanilide in [bmim][SbF_6] and methylcyclohexane is catalyzed by $Hf(OTf)_4$ (10 mol-%) and affords the corresponding quinolinone in 72% yield (Scheme 35).



Scheme 33.



Scheme 35.



Scheme 34.

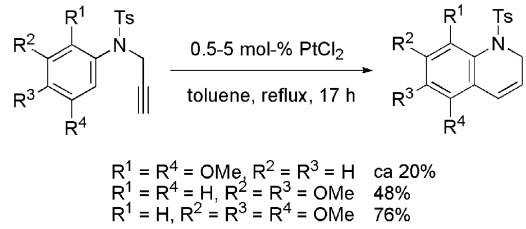
3.3 Chromenes

Intramolecular hydroarylation of aryl propargyl ethers leads to the formation of 2*H*-chromenes, as shown in Scheme 36.[26] Sesamol propargyl ether reacts in the presence of $Pt(MeCN)_2$ as catalyst to afford 6*H*-[1,3]dioxolo[4,5-*g*]chromene in 95% yield. In the presence of a cationic catalyst such as $[Au(PPh_3)Cl]/AgBF_4$, a symmetrical chromene dimer is obtained together with the 2*H*-chromene. In contrast, the catalyst $[Au(PPh_3)Cl]/HBF_4$ selectively gives the chromene.

Chromene synthesis through intramolecular hydroarylation has been applied to a total synthesis of (±)-deguelin,[27] which has been shown to be an efficacious chemopreventitive agent both in in vitro and in in vivo models. Scheme 37 shows this total synthesis, in which a key step involves platinum-catalyzed 6-*endo* hydroarylation of the alkynone derived in three steps from 3,4-dimethoxyphenol. The intramolecular hydroarylation of the alkynone in the presence of $PtCl_4$ (5 mol-%) in dioxane at 65 °C affords the desired chromene derivative, but the yield is only 40%. In contrast, the reaction in the presence of $PtCl_2$ (5 mol-%) in toluene at 55 °C gives the desired cyclization product in an excellent yield. Finally, the chromene is converted into the target molecule in 86% yield. (±)-Deguelin is thus synthesized in six linear steps in 68% yield.

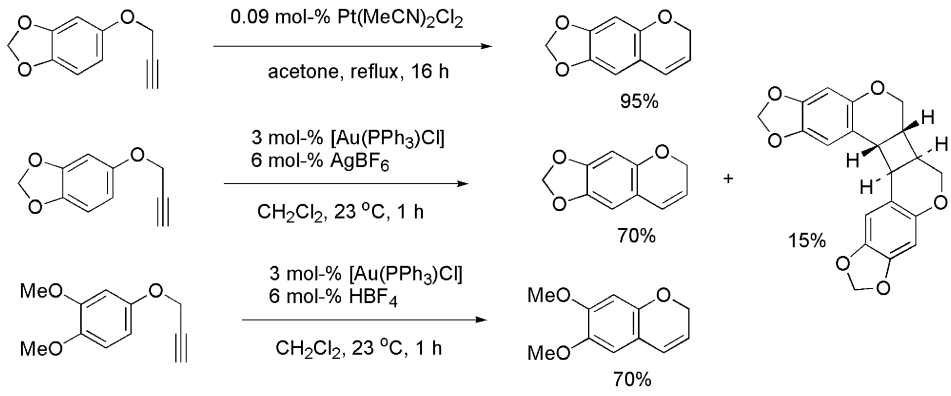
3.4 Dihydroquinolines

Intramolecular hydroarylation of *N*-propargyl-*N*-tosyl anilines proceeds in the presence of $PtCl_2$ as catalyst in toluene at reflux to form *N*-tosyl-1,2-dihydroquinolines in low to good yields (Scheme 38).[26a]

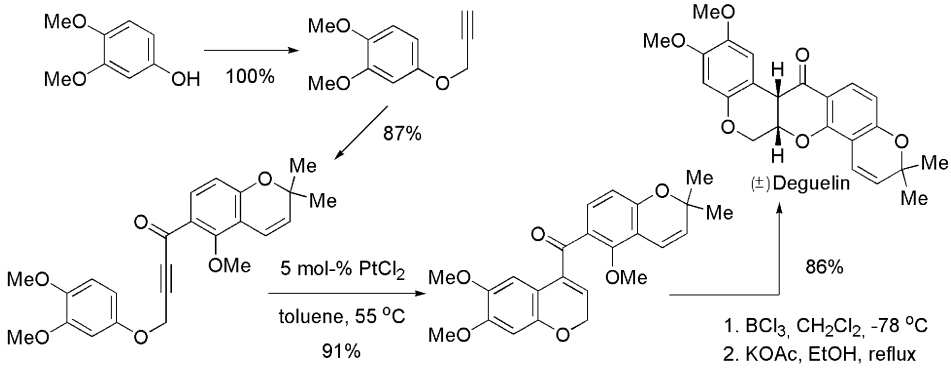


Scheme 38.

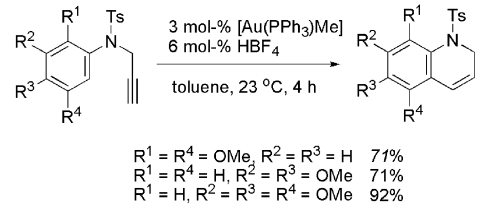
However, the use of a cationic Au^I catalyst formed in situ from $[Au(PPh_3)Me]$ and HBF_4, which presumably forms $[Au(PPh_3)]BF_4$, improves the reaction to afford the dihydroquinolines in good yield at 23–50 °C (Scheme 39).[26b] Satisfactory results are also obtained with catalysts formed from $[Au(PPh_3)Cl]$ (3 mol-%) and $AgBF_4$ or $AgSbF_6$ (3 mol-%) in CH_2Cl_2 as the solvent.



Scheme 36.



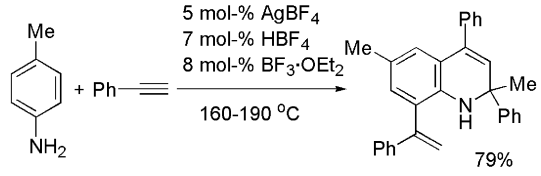
Scheme 37.



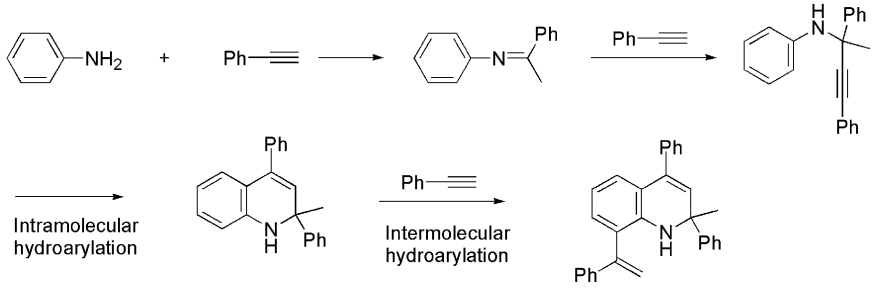
Scheme 39.

Silver-catalyzed domino reactions of simple anilines and alkynes efficiently generate 1,2-dihydroquinoline derivatives;[28] an example is shown in Scheme 40. This reaction is believed to proceed through three different sub-reactions to form the dihydroquinoline core (Scheme 41), including the formation of a ketimine, subsequent addition of phenylacetylene to form a propargylaniline, and *intra*molecular hydroarylation. The dihydroquinolinine then finally undergoes further *inter*molecular hydroarylation to give the final product. Various polysubstituted dihydroquinoline derivatives are obtained from phenylacetylenes and anilines in good yields by use of a combined $AgBF_4/HBF_4$ system.

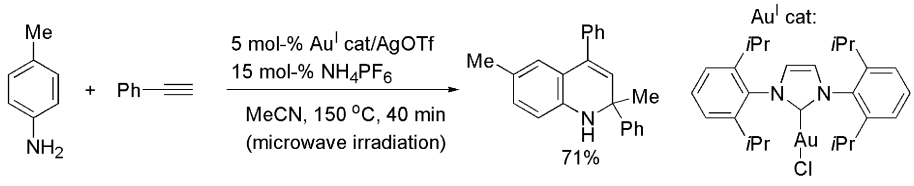
Selective formation of 1,2-dihydroquinolines is achieved through the use of a gold(I) carbene complex as catalyst under microwave conditions.[29] In the reaction between phenylacetylene and *p*-toluidine (Scheme 42) the reaction time is considerably shortened to 40 min.



Scheme 40.

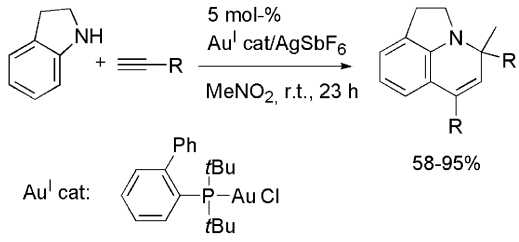


Scheme 41.



Scheme 42.

On the other hand, indoline, a secondary amine, reacts with alkynes in the presence of a Au^I phosphane complex as catalyst.[29] Treatment of indoline with phenylacetylene in the presence of the Au^I phosphane complex/AgOTf (5 mol-%) in MeCN gives a 1,2-dihydroquinoline in 91% yield under microwave irradiation conditions. This reaction can be carried out in $MeNO_2$ as solvent with Au^I catalyst/$AgSbF_6$ at room temperature without microwave irradiation, although it now requires a much longer time (23 h; Scheme 43).

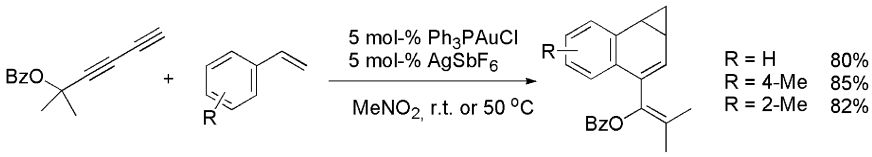


Scheme 43.

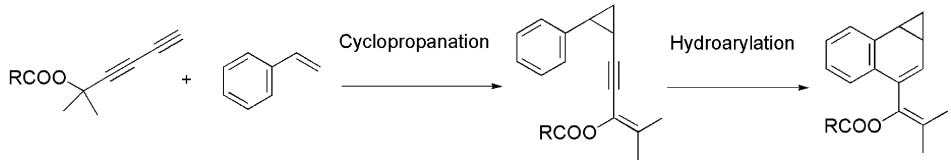
3.5 Carbocycles

Benzonorcaradine derivatives have been synthesized from styrenes and diynes containing propargyl ester moieties by [4+3] annulation (Scheme 44).[30] This synthesis involves a cationic gold(I)-catalyzed tandem-cyclopropanation/hydroarylation reaction as shown in Scheme 45.

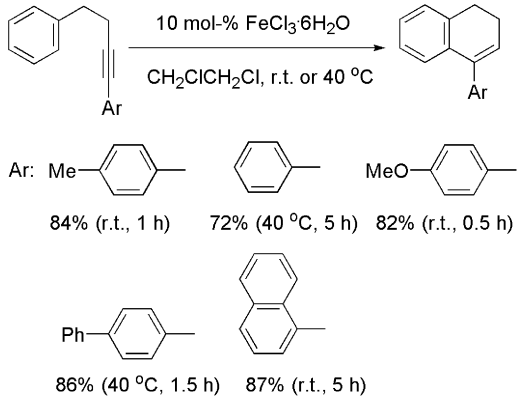
Iron(III) chloride promotes intramolecular hydroarylation of aryl-alkynes to give dihydronaphthalene derivatives.[31] The reactions of 1,4-diarylbut-1-ynes in the presence of $FeCl_3 \cdot 6H_2O$ (10 mol-%) in dichloroethane at room temperature or 40 °C afford 1-aryl-3,4-dihydronaphthalenes in good yields (Scheme 46).



Scheme 44.



Scheme 45.

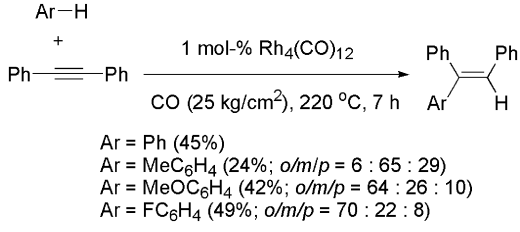


Scheme 46.

4. Hydroarylation of Alkynes through Arene Activation

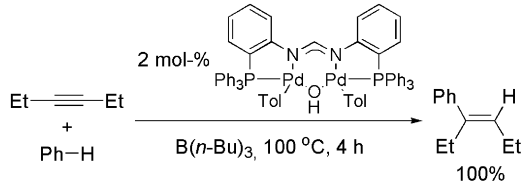
Hydroarylation of alkynes through C–H bond activation of arenes was first achieved in Rh-catalyzed reactions between arenes and internal alkynes.[32] Reactions between diphenylacetylene and arenes proceed in the presence of $Rh_4(CO)_{12}$ (1 mol-%) under CO (25 kg cm^{-2} at room temperature) at 220 °C to give aryl-alkenes in good yields after 7 h (Scheme 47).

The distributions of positional isomers from anisole and toluene show that the *ortho* position in anisole and the *meta* position in toluene are the most reactive sites. This reaction has also been applied to five-membered heterocycles such as furans, thiophenes, and *N*-methylpyrroles to give the corresponding vinyl-substituted heterocycles in good yields.[33] Similar hydroarylations of alkynes have been shown to proceed in the presence of $RhCl(CO)(PMe_3)_2$ under photochemical conditions.[34]



Scheme 47.

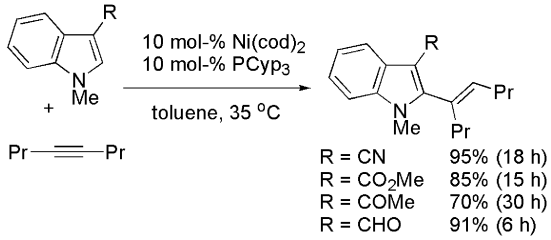
Dinuclear palladium complexes catalyze *syn*-hydroarylation of alkynes with arenes.[35] The reaction between hex-3-yne and benzene in the presence of $Pd_2Tol_2(\mu\text{-}OH)(\mu\text{-}dpfam)$ {dpfam = *N*,*N*′-bis[2-(diphenylphosphanyl)phenyl]-formamidinate} (2 mol-%) and tri(*n*Bu)borane at 100 °C quantitatively affords (*E*)-3-phenylhex-3-ene after 4 h (Scheme 48). The hydroarylation of hex-3-yne with monosubstituted benzenes such as toluene, anisole, methyl benzoate, and chlorobenzene gives (*E*)-3-arylhex-3-enes in good yields with an approximate 2:1 ratio of the *meta* and *para* isomers.



Scheme 48.

Similar hydroarylations of alkynes with pyrroles and thiophenes proceed under the same conditions.[36] The reactions with pyrroles give mixtures of 2- and 3-alkenylpyrroles, whereas the reactions with thiophenes afford 2-alkenylthiophenes.

A nickel catalyst with tricyclopentylphosphane as a ligand activates Ar–H bonds in *N*-protected 3-substituted indoles to promote hydroarylation of alkynes (Scheme 49).[37] The reaction between 3-cyano-1-methylindole and oct-4-yne in the presence of $Ni(cod)_2$ (10 mol-%) and $PCyp_3$ (10 mol-%) in toluene at 35 °C, for example, gives a hydroarylation product in 95% yield. The presence of electron-withdrawing substituents at the 3-positions in *N*-methylindoles gives good results under mild conditions. Other heterocycles such as imidazoles, benzofuran, benzothiophenes, benzoxazole, and 4,5-dimethylthiazole also participate in these hydroarylation reactions.

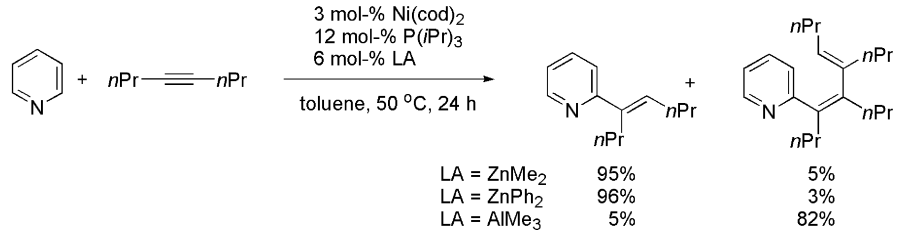


Scheme 49.

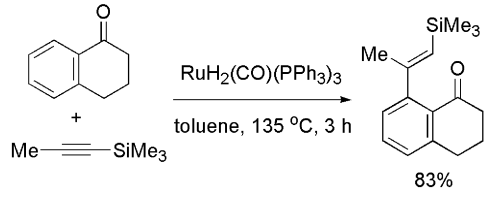
Hydroarylation of alkynes with pyridine is catalyzed by a combination of $Ni(cod)_2$ and Lewis acids such as $ZnMe_2$, $ZnPh_2$, and $AlMe_3$ (Scheme 50).[38a] The $Ni(cod)_2$-catalyzed reaction between pyridine and oct-4-yne in toluene at 50 °C in the presence of $ZnMe_2$ and $ZnPh_2$ affords a C-2 alkenylated pyridine in 95 and 96% yields, respectively, whereas the use of $AlMe_3$ as a Lewis acid catalyst dramatically changes the reaction outcome, affording the pyridine with a dienyl substituent at C-2 in 82% yield. In this reaction, a Lewis acid activates the C(2)–H bond of pyridine by coordination with the nitrogen atom to enable oxidative addition of the same bond to a nickel(0) species.

When pyridine *N*-oxides are employed in place of pyridines in $Ni(cod)_2$-catalyzed reactions with oct-4-ynes, the hydroarylation reaction proceeds without the need for Lewis acids under mild conditions to afford the corresponding 2-alkenylated pyridine *N*-oxides in good yields.[38b]

The presence of a directing group on an arene ring promotes efficient, selective activation of the *ortho* C–H bond. Hydroarylation of alkynes with aromatic ketones takes place regioselectively;[39] the reaction between α-tetralone and 1-(trimethylsilyl)propyne in the presence of $RuH_2(CO)(PPh_3)_3$ in toluene at 135 °C, for example, gives the hydroarylation product with high regioselectivity in 83% yield (Scheme 51). Heteroaromatic ketones such as furyl and thienyl ketones also undergo these hydroarylations with silylacetylenes.

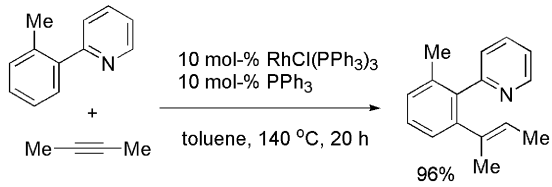


Scheme 50.



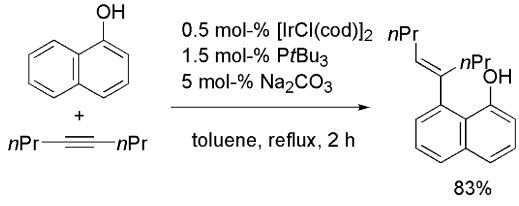
Scheme 51.

2-Phenylpyridines undergo regioselective hydroarylation with internal alkynes in the presence of $RhCl(PPh_3)_3$ as catalyst.[40] In these reactions, the pyridyl group acts as the directing group: the reaction between 2-(*o*-tolyl)pyridine and but-2-yne in the presence of $RhCl(PPh_3)_3$ (10 mol-%) and PPh_3 (10 mol-%) in toluene at 140 °C for 20 h gives the corresponding *ortho*-alkenylated product in 96% yield (Scheme 52). In the case of 2-phenylpyridine the doubly *ortho*-alkenylated product is formed as the major product.



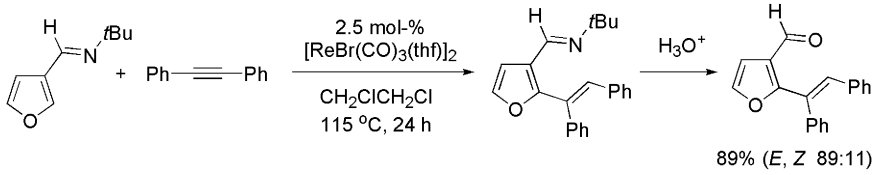
Scheme 52.

Similarly, 1-naphthols undergo hydroarylation with internal alkynes in the presence of $[IrCl(cod)]_2$ as catalyst to afford 8-alkenyl-1-naphthols (Scheme 53).[41] In these reactions, the hydroxy groups act as directing groups to cause alkenylation at the *peri* position. The reaction between 1-naphthol and oct-4-yne in the presence of $[IrCl(cod)]_2$ (0.5 mol-%), $PtBu_3$ (1.5 mol-%), and Na_2CO_3 (5 mol-%) in toluene at reflux, for example, gives the corresponding 8-alkenyl-1-naphthol in 83% yield after 2 h. A sterically hindered phosphane ligand is suitable for this reaction.



Scheme 53.

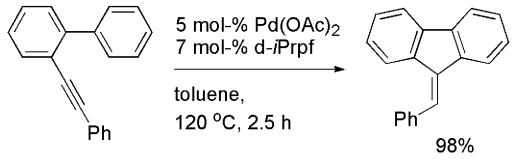
Imine moieties act as directing groups in the presence of a rhenium catalyst to promote activation of *ortho* C–H bonds in aldimines. Although the reactions between 1-phenylprop-1-yne and aromatic aldimines in the presence of $[ReBr(CO)_3(thf)]_2$ as catalyst result in the formation of indene derivatives,[42] hydroarylation is observed in the reactions of heteroaromatic compounds – such as furans, indoles, and thiophenes – bearing imino groups.[43] The reaction between diphenylacetylene and a furan derivative bear-



Scheme 54.

ing an imino group at its 3-position in the presence of $[ReBr(CO)_3(thf)]_2$ (2.5 mol-%), for example, gives an 2-alkenylated furan-3-carbaldehyde in 89% yield, with a 89:11 ratio of stereoisomers (*E* and *Z*; Scheme 54). During column chromatography the imino group is hydrolyzed to the aldehyde carbonyl group.

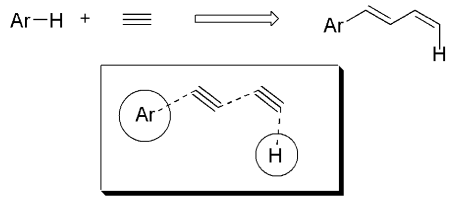
In an *o*-alkynyl biaryl system, a triple bond promotes *ortho* C–H activation by coordination and participates in hydroarylation. The reaction of 2-(phenylethynyl)biphenyl in the presence of $Pd(OAc)_2$ (5 mol-%) and 1,1′-(diisopropylphosphanyl)ferrocene (d-*i*Prpf, 7 mol-%) in toluene at 120 °C gives 9-benzylidene-9*H*-fluorene in 98% yield (Scheme 55).[44] This intramolecular hydroarylation proceeds through 5-*exo*-*dig*-type carbocyclization, unlike in the case of electrophilic activation of the triple bond followed by 6-*endo*-*dig* carbocyclization.



Scheme 55.

5. Hydroarylation Involving Two Alkyne Components

Although arylbutadienes are useful and versatile compounds, they have not been prepared by a hydroarylation technique. $Pd(OAc)_2$-catalyzed hydroarylation of alkynes with simple arenes in the presence of TFA proceeds in regio- and stereoselective manner to give *cis*-aryl-substituted alkenes.[3] In the case of ethyl propiolate, an arylbutadiene is formed as a minor product. However, little attention has been paid to the formation of arylbutadienes from simple arenes and alkynes by means of the hydroarylation method.



Scheme 56.

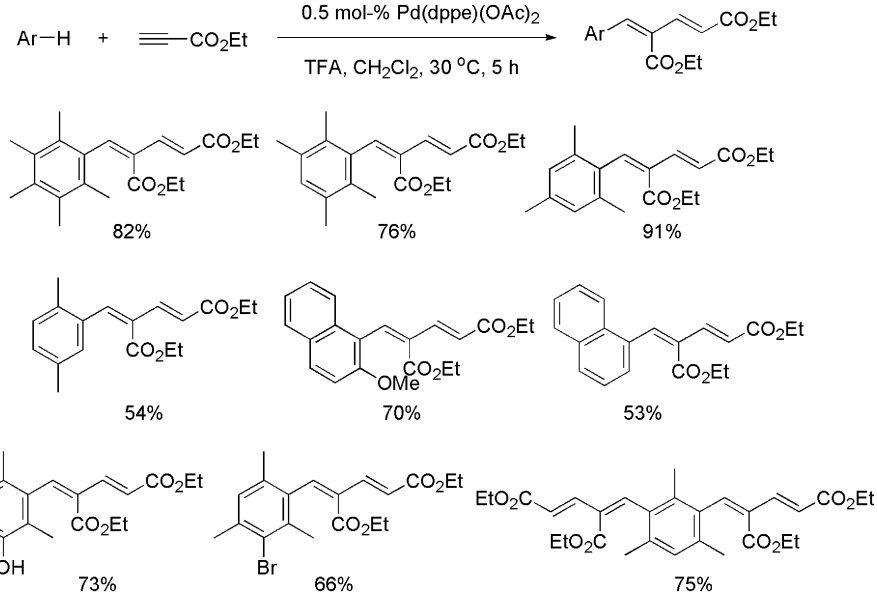
In the process leading to arylbutadienes, two alkyne molecules are formally incorporated into an aromatic C–H bond, as shown in Scheme 56.

The selective formation of arylbutadienes has been achieved when a palladium complex with a bidentate phosphane ligand – $Pd(dppe)(OAc)_2$ [dppe = 1,2-bis(diphenylphosphanyl)ethane] – is used as a catalyst.[45] Reactions between arenes (2 mmol) and ethyl propiolate (2 mmol) in the presence of this complex (0.005 mmol) in TFA and CH_2Cl_2 at 30 °C for 5 h give the corresponding arylbutadienes in good to high yields both regio- and stereoselectively (Scheme 57). Among other bidentate phosphane ligands, 1,2-bis(diphenylphosphanyl)methane is found to be effective when the reaction is carried out in neat TFA.

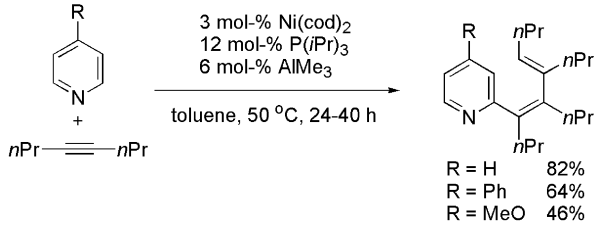
The presence of a Lewis acid such as $ZnMe_2$ in Ni(cod)$_2$-catalyzed reactions between pyridines and oct-4-yne causes C-2 alkenylation of pyridines, whereas the use of $AlMe_3$ results in C-2 dienylation of pyridines.[38] Reactions between pyridines and oct-4-yne in the presence of Ni(cod)$_2$ (3 mol-%), P(*i*Pr)$_3$ (12 mol-%), and $AlMe_3$ (6 mol-%) in toluene at 50 °C for 24–40 h give the corresponding 2-dienylpyridines in 46–82% yields (Scheme 58). The strong Lewis acidity of $AlMe_3$ under milder conditions thus favors the dienylation process of pyridines over the alkenylation process.

6. Conclusions

We have developed hydroarylation reactions of alkynes catalyzed by transition metals, especially Pd and Pt. These reactions have been demonstrated to be useful for the synthesis of thermodynamically unstable *cis*-cinnamic acids, aromatic and heteroaromatic alkenes, coumarins, isoquinolinones, and arylbutadiene derivatives. In different reactions, other transition metals have been reported to be effective for hydroarylation of alkynes. Au, In, Sc, Zr, Hf, and Fe act as effective catalysts. These catalysts activate alkynes to promote reactions with arenes by electrophilic aromatic substitution. On the other hand, hydroarylation also proceeds through activation of arenes by oxidative addition of aromatic C–H bonds to transition metals, such as Rh, Pd, Ni, Ru, and Re, although most reactions require higher temperatures. Because hydroarylation with alkynes is an efficient and atom-economic process, this should provide wide applications for synthesis of valuable compounds such as functional materials and pharmaceuticals.



Scheme 57.



Scheme 58.

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