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Recent advances in the ruthenium-catalyzed hydroarylation of alkynes with aromatics: synthesis of trisubstituted alkenes

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The hydroarylation of alkynes with substituted aromatics in the presence of a metal catalyst via chelation-assisted C-H bond activation is a powerful method to synthesize trisubstituted alkenes. Chelation-assisted C-H bond activation can be done by two ways: a) an oxidative addition pathway and b) a deprotonation pathway. Generally, a mixture of *cis* and *trans* stereoisomeric as well as regioisomeric trisubstituted alkenes were observed in an oxidative addition pathway. In the deprotonation pathway, the hydroarylation reaction can be done in a highly regio- and stereoselective manner and able to prepare the expected trisubstituted alkenes in a highly selective manner. Generally, ruthenium, rhodium and cobalt complexes are used as catalysts in the reaction. In this review, a ruthenium-catalyzed hydroarylation of alkynes with substituted aromatics is covered completely. The hydroarylation reaction of alkynes with amide, azole, carbamate, phosphine oxide, amine, acetyl, sulfoxide and sulpher directed aromatics is discussed.

Introduction

The alkene subunits are present in various natural products, drug molecules and materials. In addition, alkenes are versatile synthetic intermediates which are widely used for various organic transformations.[1] The transition metal-catalyzed coupling of aromatic electrophiles or organometallic reagents with carbon-carbon π-components is a powerful route to synthesize alkene derivatives in a highly regio- and stereoselective manner.[2-3]

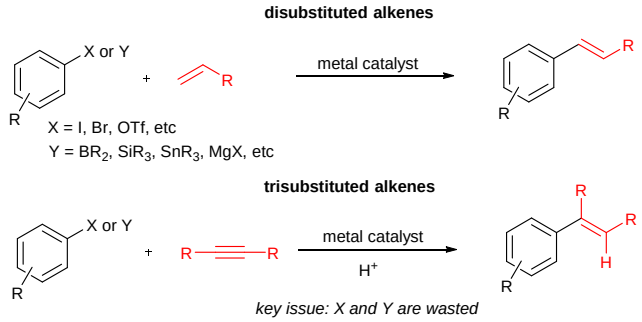

Fig. 1 Synthesis of alkenes by cross-coupling reaction.

Alkenes and alkynes are widely used as carbon-carbon π-components in the coupling reaction. Usually, alkenes reacted with aromatic electrophiles or organometallic reagents in the presence of a metal catalyst, providing disubstituted alkenes (Fig. 1)[2] and alkynes reacted with aromatic electrophiles or organometallic reagents, affording trisubstituted alkenes (Fig. 1).[3] Various metal complexes such as palladium, nickel, cobalt, rhodium, iron, etc are widely used as catalysts in this type of alkenylation reaction. Aromatic iodides, aromatic bromides and aromatic triflates are frequently used as electrophiles in the reaction. Similarly, aromatic organometallic reagents such as borane, silane, stannane and magnesium are used as a transmetallating agent. Although this type of coupling reaction is very powerful to synthesize substituted alkenes, a preactivated coupling partner such as a C-X or C-Y is usually required on the aromatic moiety. A preactivated species such as X or Y is wasted at end of the reaction. If a similar type of reaction is carried out directly by the C-H bond of aromatic moiety instead of with a C-X or C-M, it would be more useful in organic synthesis. Because, this method would be highly atom- and step economical as well as an environmentally friendly process.

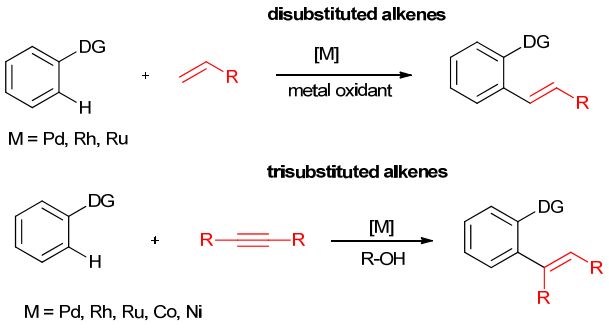

Fig. 2 Synthesis of alkenes by C-H bond activation.

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Masilmani Jeganmohan was born in Vazhapattampalayam, Tamilnadu, India in 1978. He received his master degree in organic chemistry from University of Madras in 2001. He earned his Ph.D. from the National Tsing Hua University, Taiwan under the guidance of Prof. Chien-Hong Cheng in 2005 and pursued postdoctoral work in the same laboratory (2005–2009). Then, he moved to the Ludwig-Maximilians-Universität, Munich, Germany, for a postdoctoral study with Prof. Paul Knochel supported by Alexander von Humboldt foundation (2009 to 2010). At present, he is working as an assistant professor in Indian Institute of Science Education and Research Pune (2010–till now). He was the recipient of DAE Young Scientist Research Award (2011), Science Academy Medal for a young associate, Indian Academy of Sciences (2012-2015), Science Academy Medal for Young Scientists, Indian National Science Academy (2013), Alkyl Amines – ICT Young Scientist Award by Institute of Chemical Technology Mumbai (2013) and ISCB Award of Appreciation for Chemical Science, CSIR-CDRI (2014), India. His research interest includes the development of new synthetic methods using metal complexes as catalysts, asymmetric synthesis and natural product synthesis.

Alternatively, alkene derivatives can also be prepared by a metal-catalyzed chelation-assisted alkenylation at the C-H bond of substituted aromatics with carbon-carbon π-components via C-H bond activation without having any preactivated species on the aromatic moiety (Fig. 2).[4] There are several ways to activate the C-H bond of aromatics in the presence of metal catalysts.[5] However, doing the C-H bond activation in a controlled and regioselective manner is a challenging task. This type of regioselective C-H bond activation can be done by a chelation-assisted metalation pathway (Fig. 3). Usually, heteroatom such as nitrogen or oxygen containing directing group is needed on the aromatic moiety to activate the C-H bond in a highly regioselective manner. The heteroatom of directing group coordinates with a metal centre via either σ or π bond and allows bringing the *ortho* C-H bond of aromatics to close proximity to the active metal centre. During this time, the C-H bond activation takes place very selectively at the *ortho* position and providing a five membered metalacycle intermediate. There are two pathways such as oxidative addition and deprotonation possible to activate the C-H bond of organic moiety (Fig. 3). In the oxidative addition pathway, a five membered hydrometallacycle intermediate **I** is formed and in the deprotonation pathway, a five membered metallacycle intermediate without having a hydride species **II** is formed. It is important to note that in the deprotonation pathway; usually a carbonate or acetate base is required to deprotonate the C-H bond of organic moiety. In the oxidative addition pathway, a metal species undergoes an oxidative addition with a C-H bond of aromatic moiety and providing a hydrometallacycle intermediate **I**. Generally, M(0) or M(I) active catalysts favour oxidative addition pathway and $M(II)(OR)_2$ or $M(III)(OR)_2$ catalysts favours deprotonation pathway. In this context, metal-catalyzed chelation-assisted *ortho* alkenylation of substituted aromatics with alkenes is well explored in the literature.[4] But, an *ortho* alkenylation of substituted aromatics with alkynes has gained much attention quite recently.

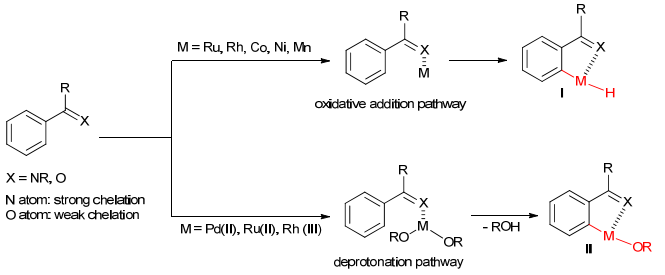


Fig. 3 Metal-catalyzed chelation-assisted C-H bond activation

In 1993, Murai's group reported a ruthenium-catalyzed chelation-assisted *ortho* alkylation of aromatic ketones with alkenes via C-H bond activation. In the reaction, aromatic ketones reacted with alkenes in the presence of $RuH_2(CO)(PPh_3)_3$, giving *ortho* alkylated aromatic ketones in a highly regioselective manner.[6a] The C-H bond activation reaction proceeds via an oxidative addition pathway. Later, the same group demonstrated an *ortho* alkenylation of aromatic ketones with alkynes, leading to trisubstituted alkenes in the presence of a ruthenium catalyst (Fig. 4).[6b] The hydroarylation reaction proceeds via a chelation-assisted oxidative addition of *ortho* C-H bond of aromatic ketone with a ruthenium catalyst providing a five-membered hydrometallacycle intermediate **III**. Later, an alkyne undergoes coordinative insertion into a metal-hydride bond of intermediate **III** followed by reductive elimination, providing a trisubstituted alkene derivative and regenerates a active Ru(0) catalyst for the next catalytic cycle. However, this type of hydroarylation reaction is not completely regio- and stereoselective. Mostly, a mixture of

regio- and stereoisomeric trisubstituted alkenes were observed. For example, aromatic ketone reacted with symmetrical alkyne, diphenylacetylene, in the presence of a ruthenium catalyst, yielding a mixture of *cis* and *trans* stereoisomeric trisubstituted alkenes. Later, Murai's group has reported the hydroarylation of alkynes with various directing groups such as ester, nitrile and aldehyde substituted aromatics in the presence of a ruthenium catalyst.[6] Later, a similar type of hydroarylation of alkynes with heteroatom substituted aromatics has been well explored by using various metal complexes such as rhodium, iridium, palladium, nickel, cobalt and manganese complexes as catalysts. Although it is one of the best methods to synthesize trisubstituted alkenes in one pot, the observation of a mixture of *cis* and *trans* stereoisomeric and regioisomeric products limits the synthetic application in organic synthesis.

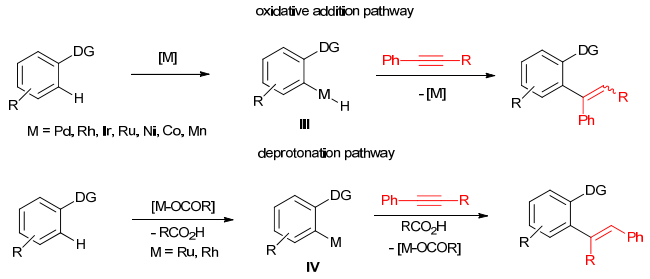


Fig. 4 Metal-catalyzed chelation-assisted hydroarylation reaction.

The recent observation clearly revealed that this type of regio- and stereoisomeric issues can be easily overcome by doing the hydroarylation reaction via a concerted deprotonation metalation pathway.[7] In the reaction, substituted aromatics reacted with alkynes in the presence of a ruthenium catalyst, providing trisubstituted alkene derivatives in a highly regio- and stereoselective manner. Notably, the metal oxidant is not needed for the hydroarylation reaction unlike the *ortho*-alkenylation of aromatics with alkenes in the presence of metal catalysts. The catalytic reaction proceeds via a chelation-assisted acetate accelerated deprotonation at the *ortho* C-H bond of hetero atom substituted aromatic with a metal complex (Rh or Ru), providing a metallacycle intermediate **IV**. Coordinative insertion of an alkyne into the metal–carbon bond of metallacycle followed by protonation in the presence of organic acid provides trisubstituted alkene derivative in a highly regio- and stereoselective manner (Fig. 4). The regiochemistry of product of this reaction is completely reversed when compared with the regiochemistry of product observed via an oxidative addition pathway. In the oxidative addition pathway, alkynes preferred to insert into Ru-H bond of intermediate **III** compared with Ru-C bond. In the deprotonation pathway, alkynes preferred to insert into Ru-C bond of metallacycle intermediate **IV**.

Ruthenium, rhodium and cobalt complexes are widely used as a catalyst in the reaction. In 2010, Fagnou et. al. reported a rhodium-catalyzed amide group assisted hydroarylation of alkynes with substituted indoles (Fig. 5).[8] The hydroarylation reaction proceeds via a deprotonation metalation pathway. The reaction pathway was supported by a deuterium labelling experiment. In this review, we would like to focus on a ruthenium-catalyzed direct C-H bond hydroarylation of substituted aromatics with alkynes via a chelation-assisted deprotonation metalation pathway.

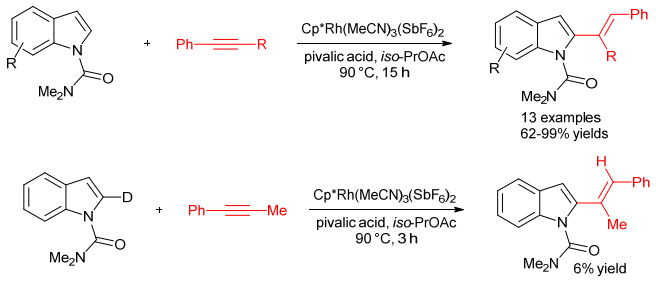
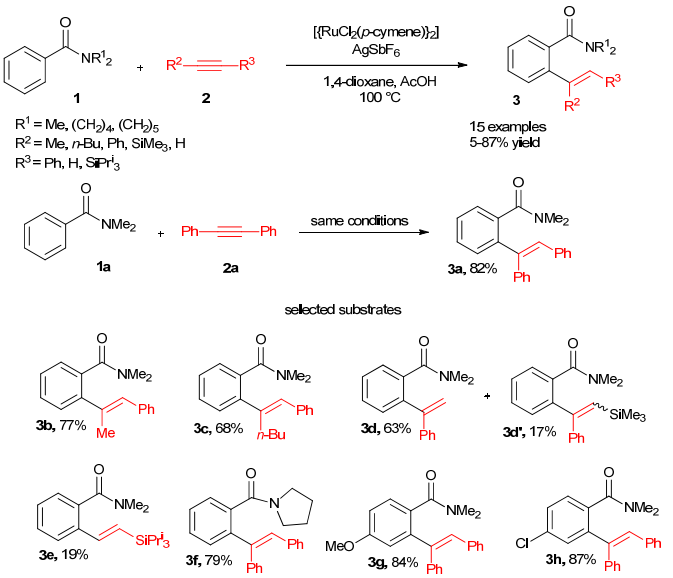


Fig. 5 Rhodium-catalyzed hydroarylation of alkynes with substituted indoles.

Ruthenium-catalyzed hydroarylation of alkynes with benzamides



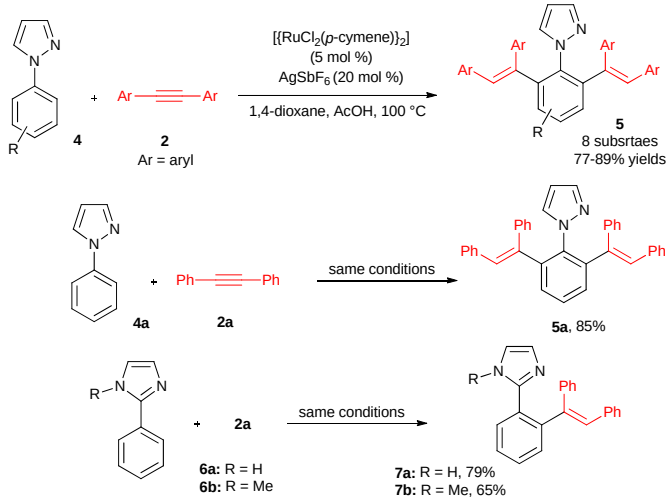
Scheme 1 Ruthenium-catalyzed hydroarylation of alkynes with *N,N*–dialkyl benzamides.

In 2012, Miura's group reported a highly regio- and stereoselective hydroarylation of alkynes with substituted benzamides, providing trisubstituted alkenes in a highly regio- and stereoselective manner.[9a-b] When *N,N*-dimethylbenzamide (**1a**) was treated with symmetrical diphenylacetylene (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %), $AgSbF_6$ (20 mol %) and acetic acid (4.0 equiv) in 1,4-dioxane at 100 °C for 5 h, a trisubstituted alkene **3a** was observed in 82% yield (Scheme 1). It is important to note that the product **3a** was observed only in 43% yield without acetic acid under similar reaction conditions. In the meantime, no hydroarylation product **3a** was observed in the presence of acetate base, KOAc, instead of acetic acid. In the reaction, acetic acid acts as a proton donor as well as base to activate the C-H bond of benzamide.

The hydroarylation reaction was compatible with various substituted alkynes. Particularly, unsymmetrical alkynes such as 1-phenyl-1-propyne (**2b**) and 1-phenyl-1-butyne (**2c**) regioselectively reacted with benzamide (**1a**), yielding

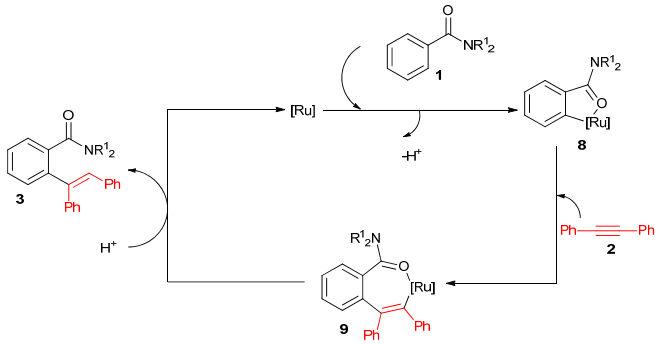
trisubstituted alkenes **3b-c** in 77% and 68% yields, respectively, in a highly regio- and stereoselective manner. In the reaction, alkyl groups such as Me and *n*-Bu substituted carbon of alkynes connected at the *ortho* carbon of **1a**. Similarly, 1-phenyl-2-(trimethylsilyl)acetylene (**2d**) provided disubstituted alkene **3d** in 63% yield along with trisubstituted alkene **3d'** in 17% yield, respectively. During the reaction, silyl group was cleaved in product **3d**. Apart from internal alkyne, the reaction was also examined with terminal alkyne, tris(isopropyl)-silylacetylene (**2e**). However, only 19% of disubstituted alkene **3e** was observed. Under similar reaction conditions, substituted benzamides and cyclic benzamides also nicely participated in the reaction with diphenylacetylene (**2a**), yielding *ortho* alkenylated products **3f-h** in good yields.

The alkenylation reaction was also compatible with substituted phenyl azoles (Scheme 2). Treatment of 1-phenylpyrazole (**4a**) with diphenylacetylene (**2a**) under similar reaction conditions gave *bis* alkenylated pyrazole derivative **5a** in 85% yield. Similarly, substituted 1-phenylpyrazole **5** reacted with various symmetrical alkynes **2**, providing the corresponding *bis* alkenylated pyrazole derivatives **5** in good yields. The alkenylation reaction was also examined with 2-phenylimidazoles. 2-Phenylimidazole (**6a**) underwent hydroarylation with **2a**, yielding the corresponding *mono* alkenylated phenylimidazole derivative **7a** in 79% yield. But, *N*-methyl-2-phenylimidazole (**6b**) provided *mono* alkenylated phenylimidazole **7b** only in 65% yield. This is most likely due to the intramolecular steric hindrance of *N*-Me group into an alkene moiety of compound **7b**.



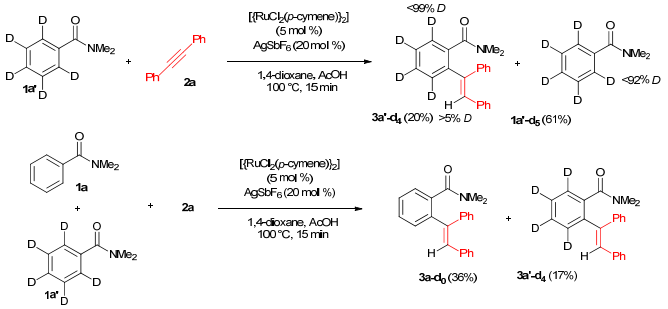
Scheme 2 Ruthenium-catalyzed hydroarylation of alkynes with substituted 1-phenylpyrazoles or 2-phenylimidazoles.

A possible reaction mechanism was proposed to account for the hydroarylation of alkynes with benzamides (Scheme 3). *ortho* Metalation of benzamide **1** with a ruthenium species, providing a five-membered metalacycle intermediate **8** with a loss of H^+ source. Coordinative insertion of an alkyne **2a** into the Ru-C bond of intermediate **8** followed by protonation with AcOH provides trisubstituted alkene **3** and regenerates an active ruthenium catalyst for the next catalytic cycle.



Scheme 3 Proposed mechanism for the hydroarylation of alkynes with *N,N*–dialkyl benzamides.

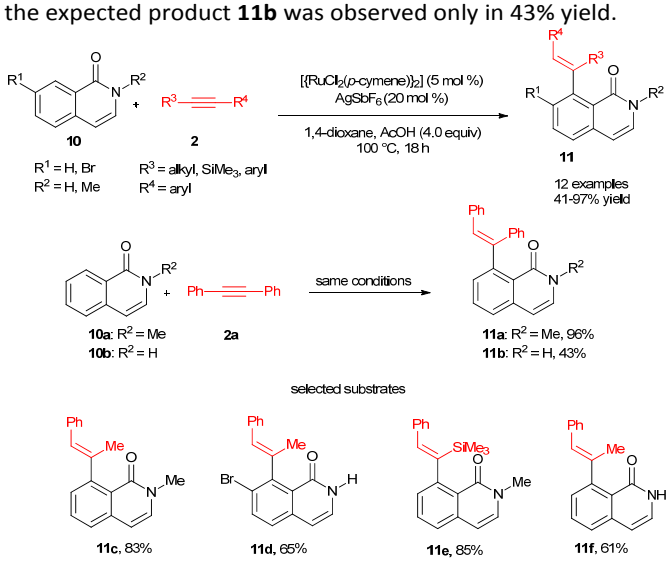
It is believed that the C-H bond activation proceeds via a deprotonation metalation pathway (Scheme 4). To confirm the deprotonation pathway, deuterated benzamide **1a'** was taken and treated with alkyne **2a** under similar reaction conditions. If the C-H bond activation proceeds via an oxidative addition pathway, *ortho* deuterium of benzamide **1a'** should be transferred into one of the alkene carbons of the expected product. Whereas, if the C-H bond activation reaction proceeds via a deprotonation pathway, deuterium incorporation should not take place and could be formed AcOD as a side product. In the product, deuterium incorporation was not observed at the alkene carbon of product **3a'-d4**. Thus, the C-H bond activation proceeds via a deprotonation metalation pathway. Later, an intermolecular competitive reaction of deuterated benzamide **1a'** with a simple benzamide **1a** was conducted. A considerable primary isotope effect of 1:2 ratios of products **3a'-d4** and **3a** were observed. This result suggested that the *ortho* C-H(D) bond cleavage is the rate-determining step as well as the cleavage proceeds via a deprotonation metalation pathway.



Scheme 4 Competitive reaction of benzamide with deuterated benzamide.

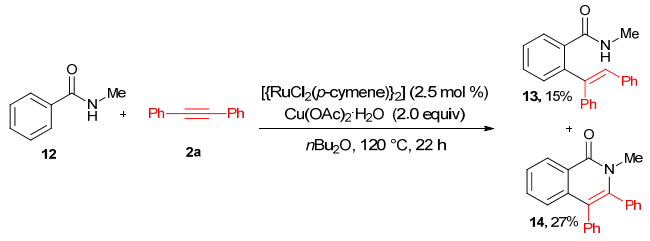
In the same year, Li's group reported a ruthenium-catalyzed hydroarylation of alkynes with isoquinolone derivatives in the presence of acetic acid (Scheme 5).[10] Treatment of *N*-methyl isoquinolone (**10a**) with diphenylacetylene (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and acetic acid (4.0 equiv) in 1,4-dioxane at 100 °C for 18 h gave the expected alkenylated isoquinolone derivative **11a** in 96% yield. The same reaction was also examined with other catalysts such as [$RhCp^*Cl_2$]$_2$ and [$IrCp^*Cl_2$]$_2$ under similar reaction conditions. In the iridium-catalyzed reaction, product **11a** was observed in 86% yield and in the rhodium-catalyzed reaction, product **11a** was observed only in 45% yield. This

result clearly reveals that a ruthenium catalyst is suitable for the reaction. The hydroarylation reaction was also examined with N-H free isoquinolone (**10b**). However, in the reaction, the expected product **11b** was observed only in 43% yield.



Scheme 5 The hydroarylation of alkynes with isoquinolone derivatives.

The hydroarylation reaction was examined with various symmetrical and unsymmetrical alkynes **2**. In all cases, the hydroarylation reaction worked very well and gave the corresponding hydroarylation products in good yields. Particularly, 1-pheny-1-propyne (**2b**) reacted with **10a** providing the expected alkenylated product **11c** in 83% yield in a highly regio- and stereoselective manner. In the reaction, Me attached carbon of alkyne **2b** connected at the C-8 position of isoquinolone derivative. Interestingly, in the reaction of 1-phenyl-1-silylacetylene with **10a**, the expected hydroarylation product **11e** was observed in 85% yield without silyl cleavage. However, in the previous Miura's reaction, the silyl group was cleaved (Scheme 1, product **3d**).

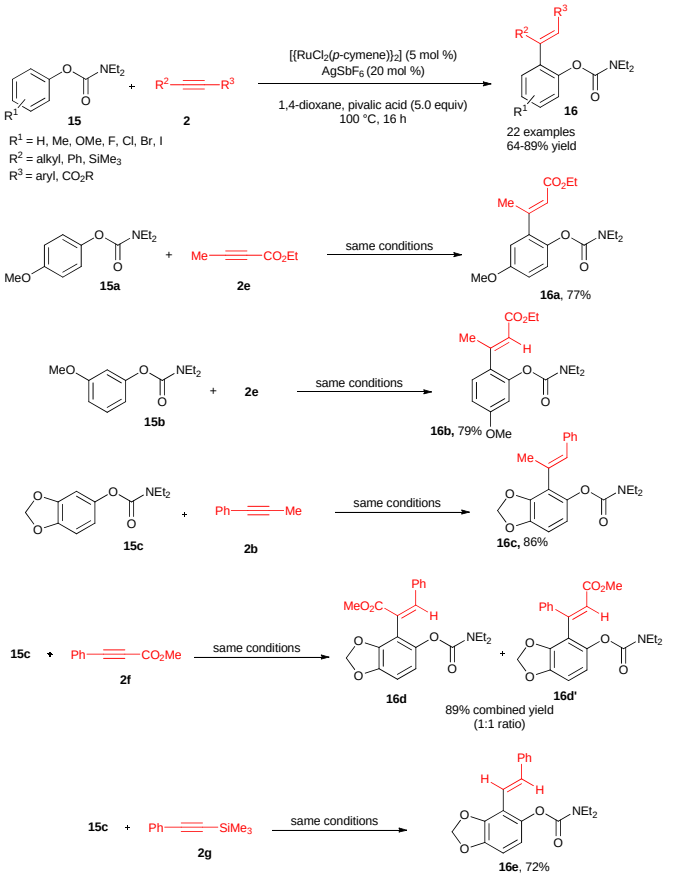


Scheme 6 The hydroarylation of diphenylacetylene with *N*-methyl benzamide.

In the reported hydroarylation of alkynes with benzamides, only *N*,*N*-disubstituted benzamides was examined. In 2011, Ackermann's group reported an oxidative cyclization of *N*-methyl benzamides with alkynes, providing substituted isoquinolone derivatives (Scheme 6).[11] In the reaction of *N*-methyl benzamide (**12**) with diphenylacetylene (**2a**) in the presence of ruthenium catalyst and $Cu(OAc)_2 \cdot H_2O$ in ether solvent, a minor amount of *ortho* alkenylated benzamide **13** was observed in 15% yield along with isoquinolone derivative **14** in 27% yield, respectively. This result clearly reveals that the *N*-methyl benzamides prefer cyclization reaction with alkynes rather than the hydroarylation reaction.

Ruthenium-catalyzed hydroarylation of alkynes with aromatic carbamates

In 2012, we have reported a highly regio- and stereoselective weakly directing carbamate group assisted hydroarylation of alkynes with aryl carbamates in the presence of a ruthenium catalyst and pivalic acid.[12a] When 4-methoxyphenyl diethylcarbamate (**15a**) was treated with ethyl but-2-ynoate (**2e**) in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$ (5.0 mol %), $AgSbF_6$ (20 mol %) and pivalic acid (5.0 equiv) in 1,4-dioxane at 100 °C for 24 h, a trisubstituted alkene derivative **16a** was observed in 77% yield (Scheme 7). The hydroarylation reaction was highly regio- and stereoselective; the *ortho* C–H bond of **15a** was selectively inserted at the methyl group substituted carbon of alkyne **2e** and only the *E*-stereoselective alkene derivative **16a** was observed.

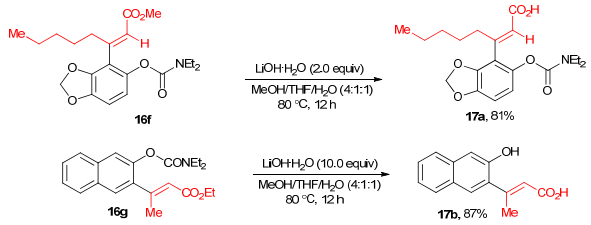


Scheme 7 The hydroarylation of alkynes with aromatic carbamates.

The scope of the hydroarylation reaction was examined with various sensitive functional groups such as I, Br, Cl, F and OMe substituted aromatic carbamates. In all reactions, the expected hydroarylation product was observed in good to moderate yields. The hydroarylation reaction was further examined with various unsymmetrical aromatic carbamates. For example, 3-methoxyphenyl diethylcarbamate (**15b**) reacted with ethyl but-2-ynoate (**2e**) at a less hindered C6-H under similar reaction conditions, yielding trisubstituted alkene derivative **16b** in 79% yield. Sesamol carbamate **15c** reacted with **2b** at the sterically

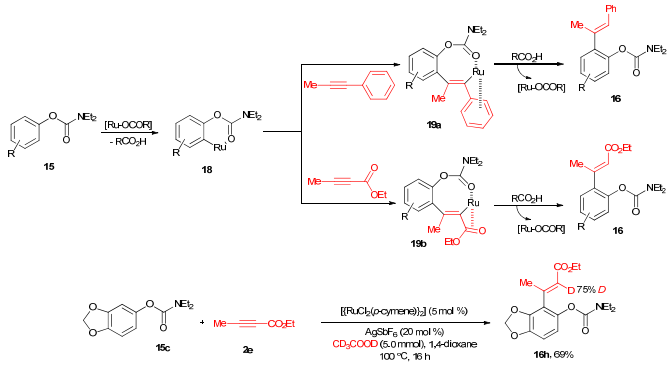
hindered C–H bond, providing **16c** in 86% yield in a highly regioselective manner.

The hydroarylation reaction was also examined with unsymmetrical alkynes such as hex-2-ynoate, methyl oct-2-ynoate, 1-phenyl-1-propyne, 1-phenyl-1-butyne and 1-phenyl-1-hexyne. In all reactions, alkyl group substituted carbon of alkyne connected at the *ortho* carbon of aromatic carbamates. But, methyl 3-phenylpropiolate (**2f**) reacted with **15c** providing a mixture of regioisomeric products **16d** and **16d'** in 89% combined yield in approximately a 1:1 ratio. Later, the ester group of trisubstituted alkene **16f** was converted into the carboxylic acid derivative **17a** in the presence of LiOH (2.0 equiv) (Scheme 8). Whereas, 10.0 equiv. of LiOH cleaved both ester and carbamate moieties of compound **16g**, giving phenol derivative **17b** in 87% yield.



Scheme 8 Synthesis of phenol derivatives.

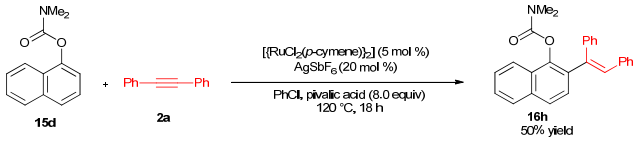
The hydroarylation reaction proceeds via a chelation-assisted deprotonation at the *ortho* C-H bond of aromatic carbamate with a ruthenium acetate species giving ruthenacycle intermediate **18** (Scheme 9). Coordinative insertion of an aromatic or ester group substituted alkyne into the metal–carbon bond of metallacycle **18** affords metalacycle intermediate **19** followed by protonation with RCOOH yielding an alkene derivative **16** in a highly regio- and stereoselective manner. Substituent on the alkyne moiety only decides the regiochemistry of the product. Coordinating groups such as Ph or ester group of alkynes **2** always prefer to stay near to the ruthenium metal in order to stabilize the ruthenacycle intermediate **19**. In the alkyne, if two coordinating groups are there, both prefer to stay near to the ruthenium metal and thus a mixture of regioisomeric products was observed.



Scheme 9 Proposed reaction mechanism of aromatic carbamates with alkynes.

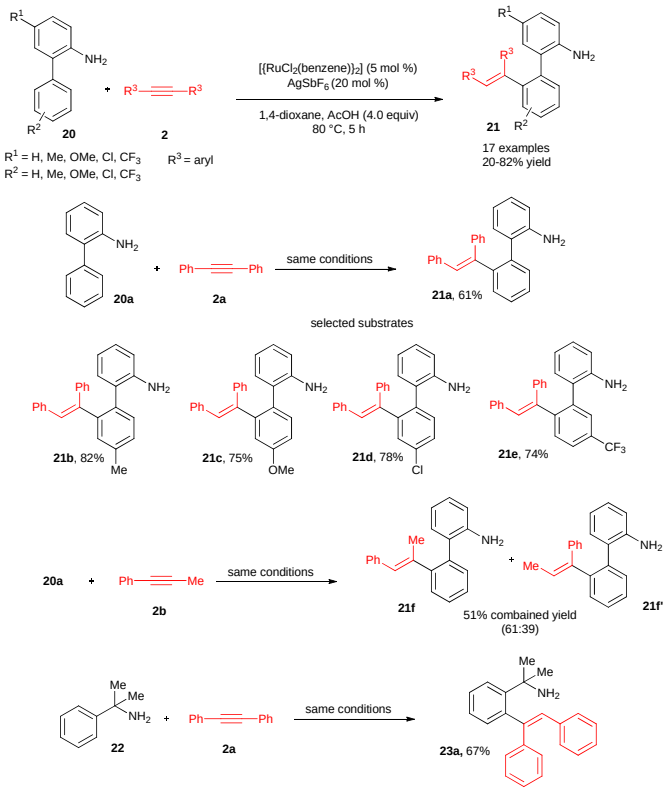
It is believed that the C-H bond activation proceeds via an acetate assisted deprotonation pathway instead of an oxidative addition pathway. The coupling reaction of sesamol carbamate **15c** with ethyl but-2-ynoate (**2e**) in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$ (5 mol %), $AgSbF_6$ (20 mol %) and CD_3COOD (5.0 equiv) in 1,4-dioxane at 100 °C for 16 h was examined (Scheme 9). In the reaction, instead of pivalic acid, CD_3COOD (5.0 equiv) was used. In the coupling product **16h**, 75% of deuterium incorporation was observed in an alkene C-H bond. This deuterium study clearly revealed that the present reaction proceeds via the deprotonation pathway.

In 2013, Wang's group reported ruthenium- and rhodium-catalyzed hydroarylation of alkynes with aromatic carbamates. In the reaction, 1-naphthyl carbamate (**15d**) reacted with diphenylacetylene (**2a**) in the presence of a ruthenium catalyst yielding the corresponding alkene derivative **16h** in 50% yield (Scheme 10).[12b]



Scheme 10 Ruthenium-catalyzed hydroarylation of alkynes with 1-naphthyl carbamate.

Ruthenium-catalyzed hydroarylation of alkynes with 2-aminobiphenyls and cumylamine



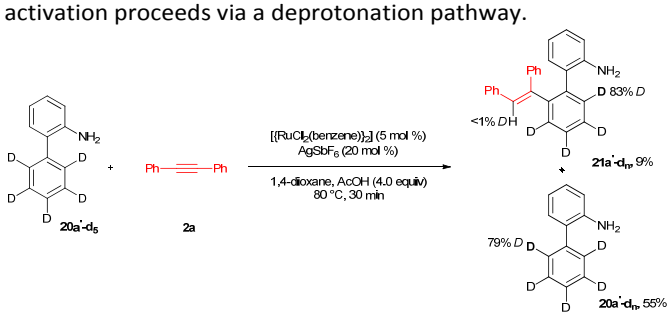
Scheme 11 The hydroarylation of alkynes with 2-aminobiphenyls and cumylamine.

In 2013, Miura's group reported a ruthenium-catalyzed hydroarylation of alkynes with 2-aminobiphenyls or cumylamine.[13] It is important to note that in the reaction a free NH_2 group acts as a directing group without any protection. Initially, the hydroarylation of diphenylacetylene (**2a**) with (1.0 equiv) 2-aminobiphenyl (**20a**) (1.0 equiv) in the

presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and CH_3COOH (4.0 equiv) in 1,4-dioxane at 100 °C for 3 h was tested (Scheme 11). However, in the reaction, hydroarylation product **21a** was observed only in 52% GC yield. When the amount of diphenylacetylene (**2a**) was increased into 2.0 equiv, the expected hydroarylation product **21a** was increased up to 70% GC yield. Further, the yield of hydroarylation product was increased up to 85% GC yield and 61% isolated yield at 80 °C in the presence of [{$RuCl_2$(benzene)}$_2$]. In the reaction, [{$RuCl_2$(benzene)}$_2$] catalyst gave better yield compared with [{$RuCl_2$(*p*-cymene)}$_2$] catalyst.

Later, the hydroarylation reaction was further examined with Me, OMe, Cl and CF_3 substituted 2-aminobiphenyls **20b-e**. In all these reactions, the expected hydroarylation products **21b-e** were observed in 74-82% yields. Particularly, in the reaction of CF_3 substituted 2-aminobiphenyl **20e**, alkenylation takes place at a less hindered C-H bond. Later, the reaction was examined with symmetrical and unsymmetrical alkynes. In the reaction of biphenyl aniline (**20a**) with 1-phenyl-1-propyne (**2b**), a mixture of stereoisomeric products **21e** and **21e'** were observed in 51% combined yield in 61:39 ratios. The hydroarylation reaction was also further examined cumylamine (**22**). When cumylamine (**22**) was treated with diphenylacetylene (**2a**) under similar reaction conditions, the hydroarylation product **23a** was observed in 67% yield.

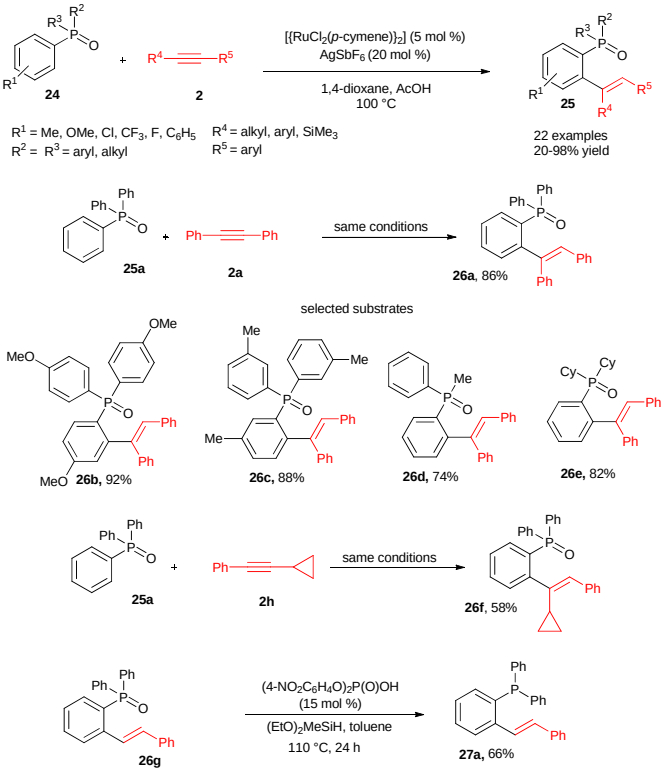
To show the C-H activation proceeds via a deprotonation metalation pathway and the corresponding metalation is a rate determining and reversible step, the reaction of deuterated 2-aminobiphenyl **20a-d$_5$** with **2a** under similar reaction conditions for 30 min was carried out (Scheme 12). In the reaction, alkenylated product **21a-d$_n$** was observed in 9% yield without any deuterium incorporation at the alkene C-H bond. This observation clearly indicates that the C-H bond activation proceeds via a deprotonation pathway.



Scheme 12 The hydroarylation of diphenylacetylene with deuterated 2-aminobiphenyl.

Ruthenium-catalyzed hydroarylation of alkynes with phenylphosphine oxides

In the same year, Miura's group demonstrated the hydroarylation of alkynes with phenylphosphine oxides in the presence of a ruthenium catalyst.[14] Treatment of triphenylphosphine oxide (**25a**) (2.0 equiv) with diphenylacetylene (**2a**) (1.0 equiv) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and 1-Ad-COOH (1.0 equiv) in 1,4-dioxane at 100 °C for 5 h gave *ortho* alkenylated triphenylphosphine oxide **26a** in 74% yield (Scheme 13). It is important to note that the phosphine oxide was surrounded by three phenyl groups and several reactive sites are around. Thus, apart from **26a**, other *ortho* alkenylated products were also observed. Interestingly, the expected product **26a** in 82% yield was observed exclusively without any other *ortho* alkenylated products in the presence of an excess amount of triphenylphosphine oxide (5.0 equiv). Pivalic acid, 2,6-dimethylbenzoic acid and AcOH were also equally effective for the reaction. Further, the hydroarylation reaction was examined with Me, OMe, F, Cl and CF_3 substituted triphenyl phosphine oxides **25**. In these substrates, the expected hydroarylation products were observed in good yields **26**. Particularly, *meta* methyl substituted triphenyl phosphine oxide **25c**, the C-H bond activation takes place at the less hindered side (product **26c**). The hydroarylation reaction was also compatible with alkyl(diphenyl) and dialkyl(phenyl)phosphine oxides **25d-e** (see, products **26d-e**). The hydroarylation reaction also worked very well with various symmetrical alkynes **2**. Unsymmetrical alkyne **2h** reacted efficiently with **25a** under similar reaction conditions providing the expected hydroarylation product **26f** in 58% yield in a highly regio- and stereoselective manner. Later, *ortho* alkenylated triphenylphosphine oxide **26g** was converted into *ortho* alkenylated triphenylphosphine **27a** in 66% yield in the presence of (4-$NO_2C_6H_4O)_2P(O)OH$ and $(EtO)_2MeSiH$.

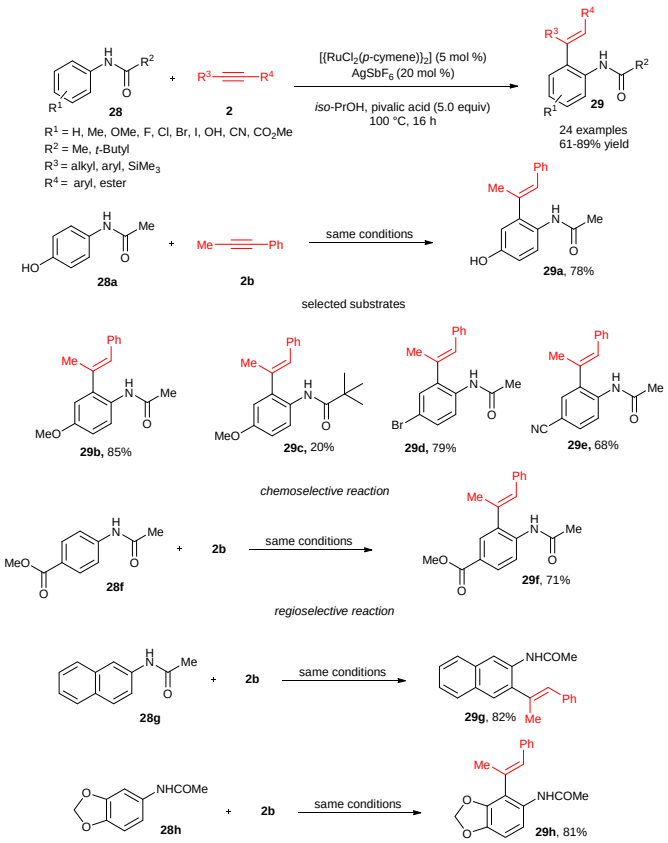


Scheme 13 The hydroarylation of alkynes with phenylphosphine oxides.

Ruthenium-catalyzed hydroarylation of alkynes with anilides

In 2014, we have reported a ruthenium-catalyzed hydroarylation of alkynes with acetanilides.[15] The catalytic reaction provides *ortho*-alkenylated anilides in good to excellent yields in a highly regio- and stereoselective manner. The reaction of 4-hydroxy anilide (**28a**) with 1-phenyl-1-propyne (**2b**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol

%), $AgSbF_6$ (20 mol %) and pivalic acid (5.0 equiv) in *iso*-PrOH at 100 °C for 12 h gave *ortho* alkenylated anilide (**29a**) in 78% yield (Scheme 14). The hydroarylation reaction is highly stereoselective, the *ortho* C-H bond of **28a** coupled with the methyl substituted carbon of alkyne **2b**. It is known that the acetanilides underwent oxidative cyclization with alkynes in the presence of rhodium or ruthenium catalysts and acetate base providing indole derivatives (Fig. 6). But, in the presence of organic acid RCOOH source instead of a base, *ortho*-alkenylated anilides were observed. It is noteworthy to note that the organic acid favours hydroarylation reaction and base favours oxidative cyclization reaction.



Scheme 14 The hydroarylation of 1-phenyl-1-propyne with anilides.

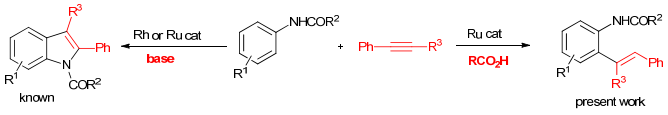
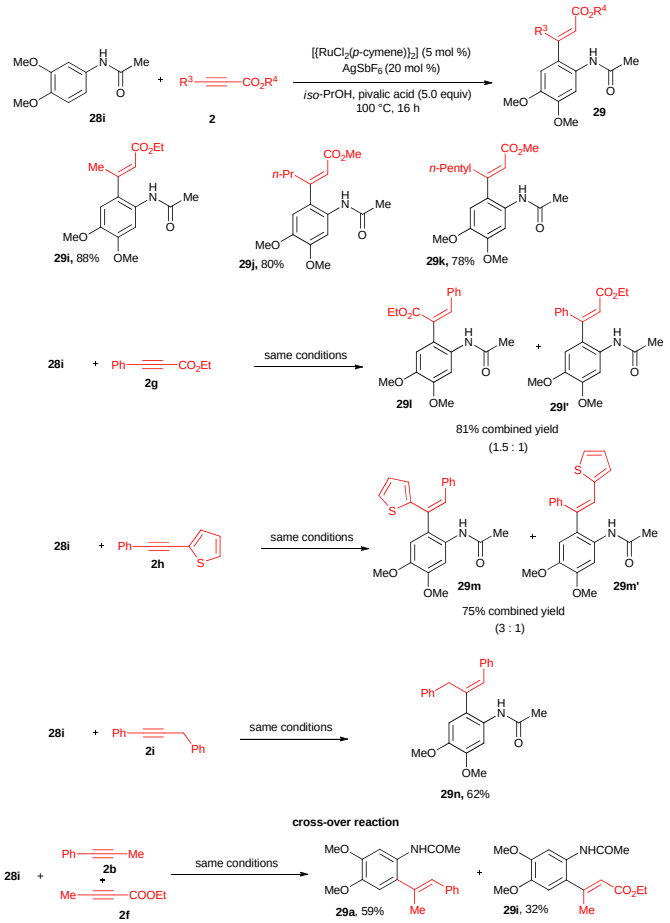


Fig. 6 Oxidative cyclization of anilides with alkynes.

The hydroarylation reaction was compatible with various functional groups such as OH, OMe, F, Cl, Br, I, CN and ester substituted anilides (Scheme 14). Treatment of ester substituted anilide **28f** with **2b** gave trisubstituted alkene **29f** in 71% yield. In the substrate **28f**, directing groups such as NHCOMe and ester were present. However, alkenylation takes place chemoselectively at the *ortho* carbon to NHCOMe of **28f**. The hydroarylation reaction was also examined with unsymmetrical acetanilides **28g-h**. 2-Naphthyl acetamide **28g** reacted with **2a**, providing trisubstituted alkene derivative **29g** in excellent 82% yield, in which C-H bond activation takes place at the C3-H of **28g**. In contrast, 3,4-(methylenedioxy)anilide (**28h**) reacted with **2a**, yielding product **29h** in 81% yield in which hydroarylation takes place at a sterically hindered C-H bond of **28h**.

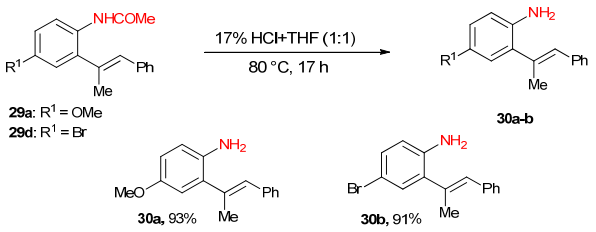


Scheme 15 The hydroarylation of unsymmetrical alkynes with anilides.

The scope of the hydroarylation reaction was further examined with various unsymmetrical alkynes such as 1-phenyl-1-butyne, 1-phenyl-1-hexyne, 1-phenyl-2-(trimethylsilyl) acetylene, ethyl 2-butynoate, methyl hex-2-ynoate and methyl oct-2-ynoate (Scheme 15). In these reactions, the expected hydroarylation product was observed in good to excellent yields. In all these alkynes, alkyl substituted carbon of alkynes was regioselectively connected at the *ortho* carbon of acetanilide. Methyl phenyl propiolate (**2g**) which having two coordinating groups such as Ph and ester on the alkyne provided a mixture of hydroarylation products **29l** and **29l'** in 81% combined yields in a 60:40 ratio. Interestingly, 2-thienyl substituted alkyne **2h** provided hydroarylation products **29m** and **29m'** in 75% combined yields in a 3:1 ratio. Surprisingly, alkyne **2i** which having Ph and CH_2Ph provided a single coupling product **29n** in 62% yield. To know the coordinating ability of Ph and ester groups, anilide **28i** was treated with **2b** (1.0 equiv) and **2f** (1.0 equiv) under similar reaction conditions. In the reaction, alkyne **2b** coupling

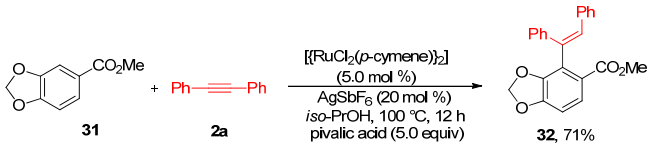
product **29a** was observed in a major 59% yield and alkyne **2f** coupling product **29i** in a less 32% yield, respectively. This result clearly reveals that the Ph coordinates with a Ru metal better than ester.

Later, *ortho*-alkenylated acetanilides **29a** and **29d** were efficiently converted into *ortho*-alkenylated anilines **30a** and **30b** in 93% and 91% yields, respectively, in the presence of a 1:1 mixture of 17% HCl and THF at 100 °C for 17 h.

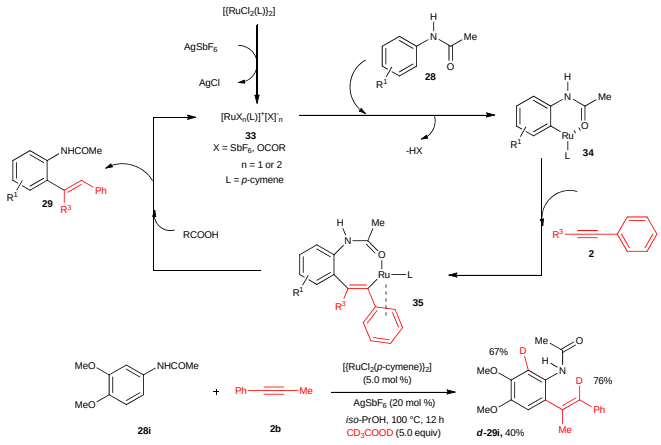


Scheme 16 Synthesis of *ortho* alkenylated aniline derivatives.

Further, the hydroarylation reaction was tested with a weak ester directing group substituted aromatic moiety. Treatment of methyl piperonate (**31**) with diphenylacetylene (**2a**) under similar reaction conditions provided the hydroarylation product **32** in 71% yield in a highly regioselective manner.



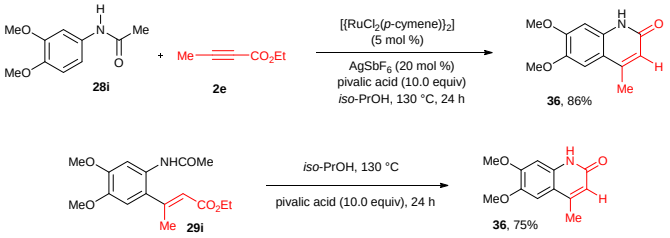
Scheme 17 The hydroarylation of diphenylacetylene with methyl piperonate.



Scheme 18 Proposed reaction mechanism of anilides with unsymmetrical alkynes.

A possible reaction mechanism was proposed to account for the hydroarylation of alkynes with anilides (Scheme 18). $AgSbF_6$ likely removes the Cl^- ligand from $[\{RuCl_2(p\text{-cymene})\}_2]$ complex, providing ruthenium species **33**. Coordination of the carbonyl group of anilide 3**1** to a ruthenium species **33** followed by *ortho*-metalation provides a six-membered ruthenacycle intermediate **34**. Coordinative regioselective insertion of alkyne **2** into the Ru–carbon bond of intermediate **34** provides intermediate **35**. Protonation at Ru-C bond of intermediate **35** in the presence of RCOOH affords the hydroarylation product **29** and regenerates the active ruthenium species **33** for the next catalytic cycle. To support the role of organic acid, **28i** was treated with **2b** in the presence of CD_3COOD instead of pivalic acid under similar reaction conditions. In the reaction, product ***d*-29i** was observed in 40% yield with 76% of deuterium incorporation at the alkene carbon. Meanwhile, 67% deuterium incorporation was observed at the *ortho* carbon of anilide in product ***d*-29i**. This result clearly shows that the *ortho* C-H bond cleavage of anilide **28** and intermediate **34** formation is a reversible process.

In the hydroarylation of substituted propiolates with anilides, *ortho* alkenylated anilides **29** was observed in good to excellent yields. This hydroarylation reaction was carried out at 100 °C. If the same hydroarylation reaction was carried out at 130 °C, 2-quinolinone derivative **36** was observed along with the hydroarylation product **29**. In the reaction, only 5.0 equiv of pivalic acid was used. Interestingly, only 2-quinolinone derivatives were observed in the presence of 10.0 equiv of pivalic acid. The cyclization of 3,4-dimethoxy acetanilide (**28i**) with ethyl-2-butynoate (**2e**) in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$ (5.0 mol %), $AgSbF_6$ (20 mol %) and pivalic acid (10.0 equiv) in *iso*-PrOH at 130 °C for 24 h provided 4-methyl substituted-2-quinolinone **36** in 86% isolated yield (Scheme 19).[16]



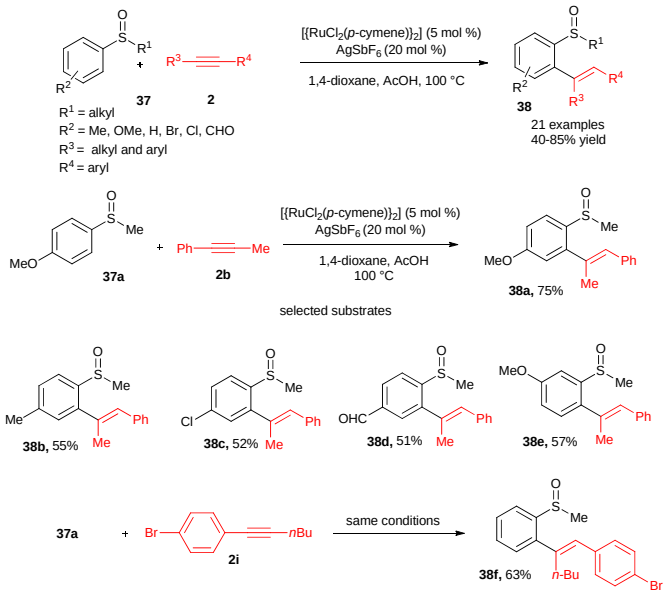
Scheme 19 Cyclization of substituted anilides with propiolates.

In the reaction, initially *ortho* alkenylated anilide **29** was formed as described in the mechanism in Scheme 18. Under the reaction conditions, *ortho* alkenylated anilide **29** was converted into 2-quinolinone derivative **36**. To confirm that the *ortho* alkenylated anilide is a key intermediate, product **29i** was prepared separately and treated with pivalic acid in *iso*-PrOH solvent at 130 °C for 24 h without a ruthenium catalyst (Scheme 19). As expected, 2-quinolinone derivative **36** was observed in 75% yield. This result clearly reveals that the carboxylic acid or solvent *iso*-PrOH accelerates *trans-cis* isomerization of the double bond of compound **28i** via Michael addition. Intramolecular nucleophilic addition of NHCOMe to the ester moiety followed by a loss of acetyl group leads to 2-quinolinone **36**. In the reaction, organic acid plays multiple roles such as acting as a proton source, the corresponding acetate anion deprotonates the C-H bond, accelerating *cis-trans* isomerization and deacylation of anilide to aniline.

Ruthenium-catalyzed hydroarylation of alkynes with aromatic sulfoxides

Recently, we have reported a regio- and stereoselective hydroarylation of alkynes with aromatic sulfoxides in the presence of a less expensive ruthenium catalyst.[17] In the

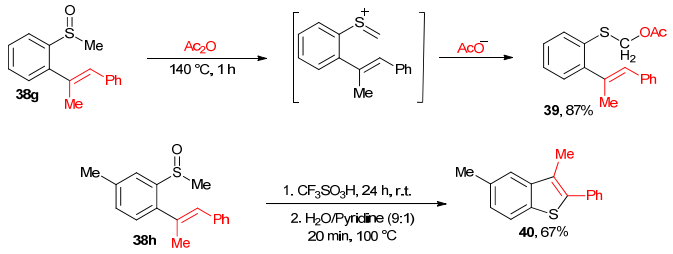
reaction, terminal metal oxidant was not used and only Ru(II) species was involved in the complete catalytic cycle without changing the metal oxidation state. It is important to note that, Miura's group reported the hydroarylation of alkynes with aromatic sulfoxides in the presence of a highly expensive rhodium complex (Scheme 20). However, $Cu(OAc)_2$ was used as an terminal metal oxidant to regenerate the active rhodium catalyst. Treatment of methyl phenyl sulfoxide (**37a**) with 1-phenyl-1-propyne (**2b**) in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$ (5 mol %), $AgSbF_6$ (20 mol %) and pivalic acid (5.0 equiv) in 1,4-dioxane at 100 °C for 24 h gave the expected hydroarylation product **38a** in 75% yield. The hydroarylation reaction was highly regioselective and the methyl group substituted carbon of alkyne **2b** was connected at the *ortho* C-H bond of **37a**. The hydroarylation reaction was also highly stereoselective giving only *E*-stereoisomeric trisubstituted alkene derivative **38a**. The hydroarylation reaction was compatible with various functional groups such as Br, Cl and CHO substituted aromatic sulfoxides. Particularly, electron-deficient CHO substituted aromatic sulfoxide **37d** reacted with **2b** providing the corresponding hydroarylation product **38d** in 51% yield. Unsymmetrical *meta* methoxy phenyl sulfoxide **37e** reacted regioselectively with alkyne **2b**, yielding product **38e** in 57% yield in which the *ortho* C-H bond activation takes place at a less hindered C-H bond of **37e**.



Scheme 20 The hydroarylation of alkynes with aromatic sulfoxides.

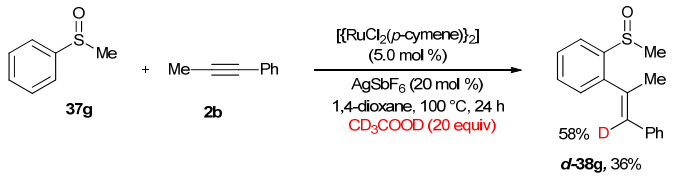
The scope of hydroarylation reaction was further examined with various unsymmetrical and symmetrical alkynes. In all reactions, the expected hydroarylation product was observed in good to moderate yields in a highly regio- and stereoselective manner. Particularly, bromo substituted alkyne **2i** reacted regioselectively with **37a**, affording the corresponding alkene derivative **38f** in 63% yield (Scheme 20). In the reaction, *n*-butyl substituted alkyne carbon connected at the *ortho* C-H bond of **37a**.

When compound **38g** was treated with acetic anhydride (10.0 equiv) at 140 °C for 1 h, α-acyloxy-thioether **39** was observed in 87% yield (Scheme 21). Subsequently, *ortho* alkenylated phenyl sulfoxide **38h** was treated with CF_3SO_3H at room temperature for 24 h followed by an addition of a 9:1 ratio of water/pyridine, affording 2,3-disubstituted benzothiophene derivative **40** in 67% yield.



Scheme 21 Transformation of *ortho* alkenylated aromatic sulfoxides.

To show the role of organic acid in the hydroarylation reaction, the reaction of **37g** with **2b** in the presence of CD_3COOD instead of pivalic acid was tested under similar reaction conditions (Scheme 22). In the reaction, deuterium incorporation was observed at the alkene carbon of hydroarylation product ***d*-38g**. This result clearly reveals that the AcOH acts as a proton donor in the reaction.



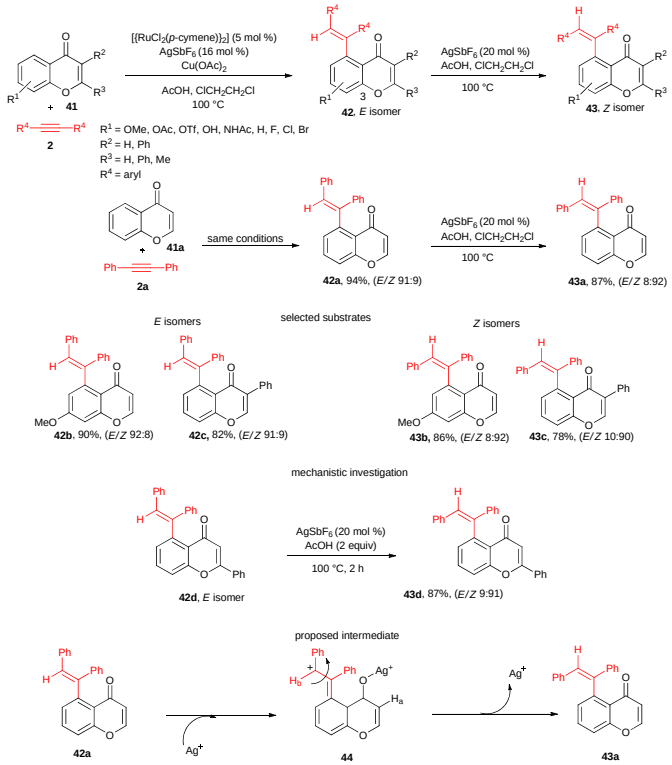
Scheme 22 The hydroarylation of alkyne with phenyl sulfoxide in CD_3COOD.

$AgSbF_6$ controlled *E* to *Z* stereoselective transformation of trisubstituted alkenes

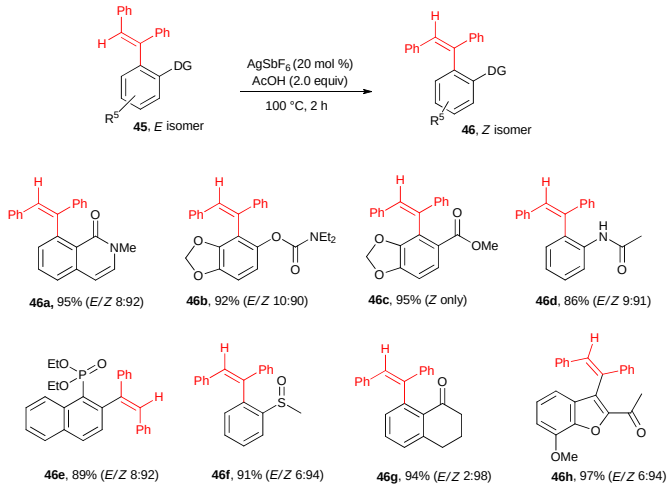
Very recently, Hong's group reported a ruthenium-catalyzed *Z* stereoselective hydroarylation of alkynes with substituted aromatics.[18] Generally, *E* stereoselective alkene derivatives can be prepared efficiently in the hydroarylation proceeds via a deprotonation pathway. In the oxidative addition pathway, a stereoisomeric mixture of *E* and *Z* alkene derivatives was prepared. In the Hong's method, *Z* stereoselective alkene derivatives were prepared efficiently in the presence of an excess amount of $AgSbF_6$. This hydroarylation reaction also proceeds via a deprotonation pathway. Initially, in the reaction, *E* stereoselective alkene derivatives were observed. But, in the presence of an excess $AgSbF_6$ catalyst, *E* stereoselective alkene derivatives were converted into *Z* stereoselective alkene derivatives.

When chromone (**41a**) was treated with diphenylacetylene (**2a**) in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$ (5 mol %), $AgSbF_6$ (16 mol %), $Cu(OAc)_2$ (10 mol %) and acetic acid (2.0 equiv) in 1,2-dichloroethane at 100 °C for 6 h, a stereoisomeric mixture of alkenylated product **42a** was observed in 94% yield in a 91:9 E/Z ratio (Scheme 23). If the same reaction was done in the presence of an excess amount of $AgSbF_6$ (20 mol %) under the same reaction conditions, the stereoisomer of alkene derivative was reversed and producing product **43a** in 87% yield in an 8:92 *E*/*Z* ratio. $AgSbF_6$ plays an important role for

the stereoselective isomerization of an alkene derivative. In the reaction, alkenylation takes place at the C-5 position of chromone (**41a**). The alkenylation reaction was examined with various substituted chromone derivatives and alkynes. In all these reactions, the expected trisubstituted alkene derivatives were observed in good to excellent yields. To prove the role of $AgSbF_6$, *E*-stereoisomeric alkene derivative **42d** was prepared separately and treated with $AgSbF_6$ in acetic acid at 100 °C for 2 h. In the reaction, the reversed stereoisomeric chromone derivative **43d** was observed in 87% yield in a 9:91 *E*:*Z* ratio. In was proposed that the isomerization process takes place through the formation of the alkyl cation **44** followed by the bond rotation to drive the transformation of *E*-alkenyl into the thermodynamically more stable *Z*-isomer in the presence of $AgSbF_6$ catalyst.



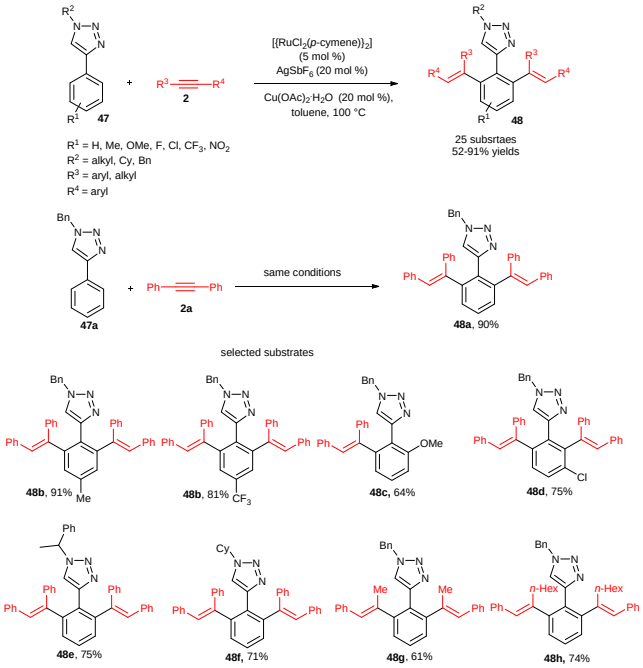
Scheme 23 The hydroarylation of alkyne with chromones.



Scheme 24 Silver-catalyzed stereoisomerization of trisubstituted alkenes.

The alkene isomerization reaction was further examined with *ortho* alkenylated anilides, aromatic carbamates, esters, sulfoxides and phosphonates in the presence of $AgSbF_6$ and acetic acid (Scheme 24). In all these reactions, a mixture of stereoselective alkene derivatives **46** were observed in a major amount of >92% of *Z* stereoisomer. The representative examples of these reactions were shown in Scheme 24.

Ruthenium-catalyzed 1,2,3-triazole directed hydroarylation of alkynes with aromatics

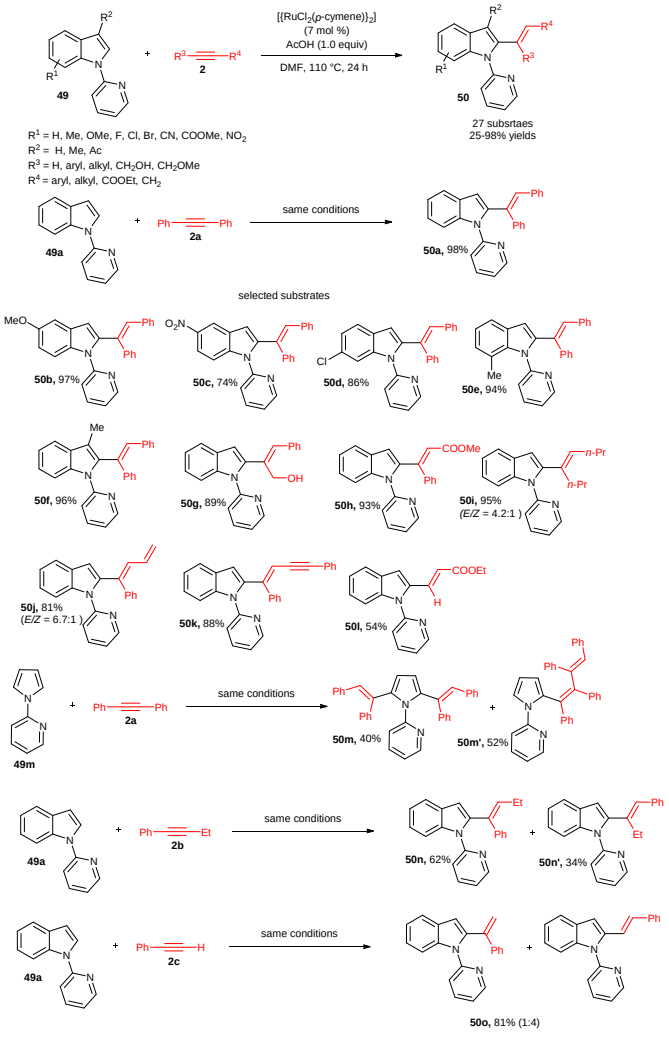


Scheme 25 The hydroarylation of alkynes with 1,2,3-triazole substituted aromatics.

Recently, Liu's group reported a ruthenium-catalyzed 1,2,3-triazole directed hydroarylation of alkynes with aromatics.[19] In the reaction, *bis* alkenylated aromatics were observed and the alkenylation takes place at the *both ortho* C–H bonds of phenyl group. Treatment of 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (**47a**) with diphenylacetylene (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (20 mol %) in toluene at 100 °C for 2.5 h gave *bis* alkenylated aromatic **48a** in 90% yield (Scheme 25). In the reaction, the active cationic ruthenium acetate species was generated by the reaction of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$ (20 mol %) and $Cu(OAc)_2$. Later, the *ortho* C-H bond of phenyl group was deprotonated by an acetate species of an active ruthenium catalyst providing a metalacycle intermediate and AcOH. The corresponding AcOH acts as a proton source and protonates at one of the alkene C-H bonds affording an alkene derivative and regenerates the active catalyst for the next catalytic cycle. Apart from $Cu(OAc)_2$, NaOAc can also be used as acetate source to activate the C-H bond for the reaction. Next, the hydroarylation reaction was examined with various substituted 1,2,3-triazole substituted aromatics. The reaction worked very

well in all cases and the expected *bis* alkenylated aromatics were observed in good to excellent yields **48b-f**. The reaction was compatible with F, Cl, CF_3, NO_2 and OMe substituents on the aromatic ring of substituted 1,2,3-triazole derivatives. The hydroarylation reaction was also examined with various symmetrical alkynes. In all cases, the expected *bis* alkenylated products were observed in good yields. Unsymmetrical alkynes such as 1-phenyl-1-propyne and 1-phenyl-1-hexyne reacted efficiently with **47a**, yielding the expected *bis* alkenylated aromatics **48g** and **48h** in a highly regio- and steteroselective manner. Methyl as well as hexyl substituted carbon of alkynes were connected at the *ortho* C-H bond of phenyl group.

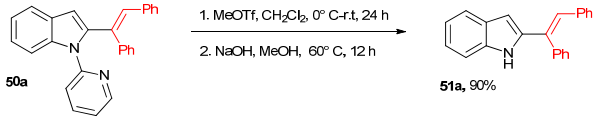
Ruthenium-catalyzed 2-pyridyl or carbamide directed alkenylation at C2-position of indole derivatives with alkynes



Scheme 26 *E*-Stereoselective C-2 alkenylation of indoles with alkynes.

In 2014, Zeng's group reported a ruthenium-catalyzed 2-pyridyl directed hydroarylation of alkynes with indoles.[20a] The reaction of N-(2-pyridyl)indole (**49a**) with diphenylacetylene (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (7 mol %), $AgSbF_6$ (20 mol %) and pivalic acid (1.0 equiv) in 1,4-dioxane solvent at 110 °C for 24 h gave C2-alkenylated N-(2-pyridyl)indole (**50a**) in 54% yield (Scheme 26). Later, the yield of the reaction was increased up to 98% by changing the solvent 1,4-dioxane into dimethylformamide. In the reaction, 2-pyridyl acts as a directing group to activate the C2-H of indole. As 2-pyridyl is a strong chelating group, the catalytic reaction can proceed efficiently with a neutral ruthenium species and the cationic ruthenium species was not needed.

The hydroarylation reaction was examined with various sensitive functional groups such as OMe, F, Cl, Br, NO_2, CN and CO_2Me substituent on the aromatic ring of indole derivatives. In all these substrates, the hydroarylation reaction worked very nicely and yielding the expected alkene derivatives in good to excellent yields **50b-f**. Next, the hydroarylation reaction was examined with various unsymmetrical alkynes. Particularly, 3-phenylprop-2-yn-1-ol reacted nicely with **52a** giving the corresponding alkene derivative **50g** in 89% yield, in which, CH_2OH group substituted carbon of alkyne was connected at the C2-position of indole. Meanwhile, the hydroarylation reaction was examined with diyne and enyne (products **50j** and **50k**). Interestingly, the hydroarylation reaction was compatible with terminal alkynes. However, in the reaction, a mixture of 1,1-disubstituted alkene and 1,2-disubstituted alkene derivatives were observed. The hydroarylation reaction was also nicely worked with N-(2-pyridyl)pyrrole (**49m**). However, in the reaction, a mixture of diene derivatives **50m** and **50m'** were observed. Later, 2-pyridyl group of alkene derivative **50a** was cleaved in the presence of MeOTf and a free N-H indole derivative **51a** was observed in 90% yield (Scheme 27).

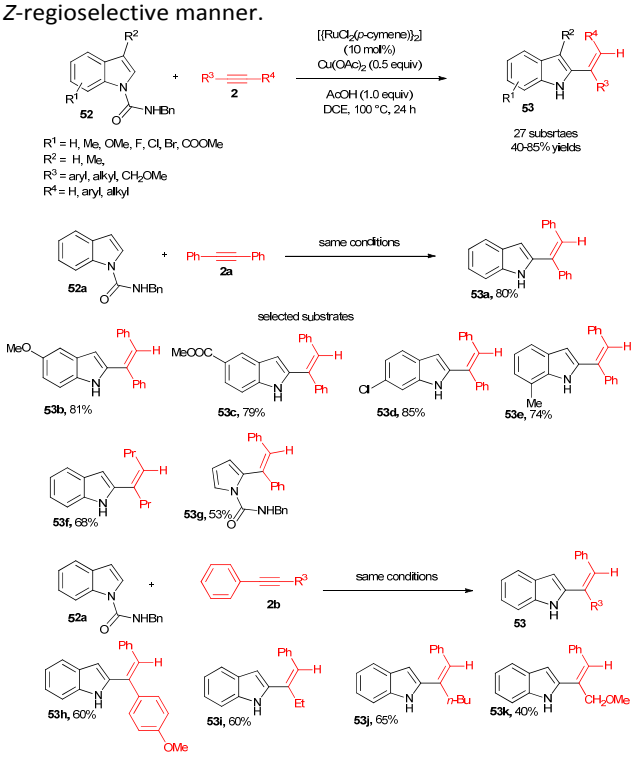


Scheme 27 Synthesis of *E*-stereoselective C2-alkenylated indole derivative.

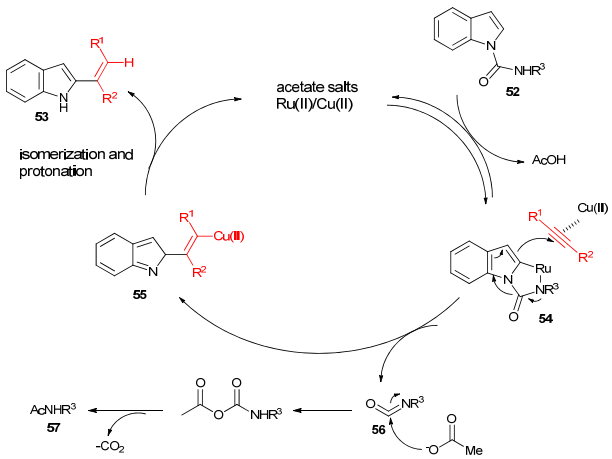
Very recently, the same group reported a ruthenium-catalyzed carbamide directed *Z*-stereoselective hydroarylation of alkynes with indole derivatives.[20b] In the previous report, by employing 2-pyridyl group, alkenylation was done at the C2-position of indole in a highly E-steroselective manner. In the present work, by employing carbamide group, alkenylation was done at the C2-position of indole in a highly Z-steroselective manner. It is important to note that during the reaction, carbamide group was cleaved and only providing Z-stereoselective alkene derivatives. When *N*-benzyl-1*H*-indole-1-carboxamide (**52a**) was treated with diphenylacetylene (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (10 mol %), $Cu(OAc)_2$ (0.5 equiv) and acetic acid (1.0 equiv) in 1,2-dichloroethane at 100 °C for 24 h, a Z-stereoselective C2-alkenylated indole derivative **53a** was observed in 80% yield (Scheme 28). The optimization studies clearly revealed that the AcOH is crucial to increase the yield of the product **53a**.

The scope of hydroarylation reaction was examined with OMe, F, Br, Cl and CO_2Me substituted indole derivatives and N-carbamide substituted pyrrole. In all these reactions, Z-stereoselective alkene derivatives were observed in good to excellent yields **53b-g**. The hydroarylation reaction was also

examined with various unsymmetrical alkynes. Interestingly, 1-phenyl-1-propyne, 1-phenyl-1-butyne and 4-methoxylphenyl phenyl alkynes reacted regioselectively with **52a** providing C2-alkenylated indole derivatives **53h-k** in good yields in a highly *Z*-regioselective manner.



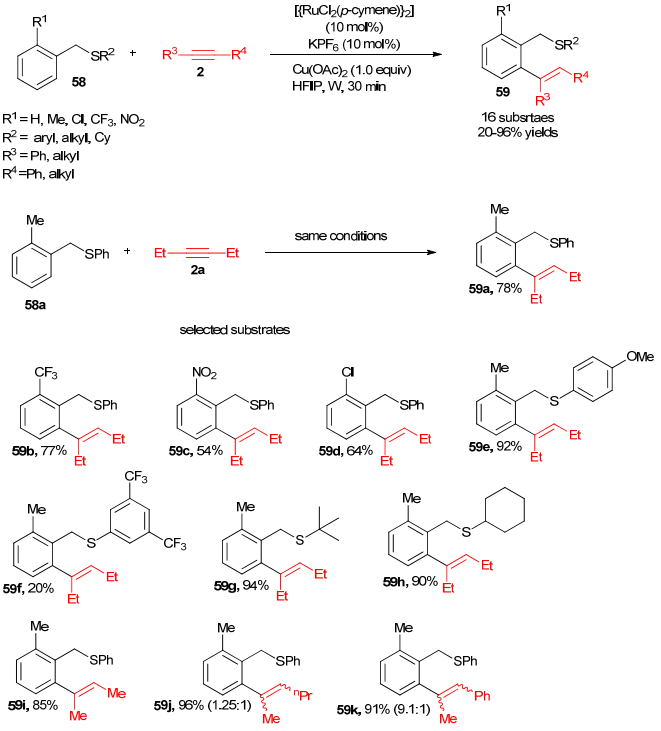
Scheme 28 *Z*-Stereoselective C-2 alkenylation of indoles with alkynes.



Scheme 29 Proposed mechanism for the hydroarylation of alkynes with indoles.

A possible reaction mechanism was proposed to account for the present Z-stereoselective alkenylation reaction (Scheme 29). The *ortho* C-H bond of indole group was deprotonated by an acetate species of ruthenium catalyst providing a metalacycle intermediate **54**. Later, the nucleophilic attack of amide nitrogen **54** into an alkyne **2** with the assistance of $Cu(OAc)_2$ forms an alkenylated intermediate **55** and isocyanate **56** as a byproduct. Later, acetate anion undergoes nucleophilic attack with isocyanate **56** forming amide **57** with the release of CO_2. In the same time, an alkenylated metal intermediate **55** could be further isomerized followed by protonation produces the final free (N–H) (Z)-alkenyl indoles **53** and regenerates the active catalyst.

Ruthenium-catalyzed sulfur assisted hydroarylation of alkynes with benzylthioethers



Scheme 30 The hydroarylation of alkyne with benzylthioethers.

Very recently, Villuendas and Urriolabeitia reported a ruthenium-catalyzed hydroarylation of alkynes with benzylthioethers leading to *ortho* alkenylated benzylthioethers in good to moderate yields.[21] Treatment of thioether **58a** with hex-3-yne (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (10 mol %), KPF_6 (10 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv) in electron deficient HFIP solvent at 100 °C for 0.5 h under the microwave irradiation (150 W) gave a mixture of *mono* as well as *bis* alkenylated benzylthioether **59a** in 78% yield. To avoid the bis alkenylation, one of the *ortho* carbons of benzylthioether was blocked by Me, CF_3, Cl and NO_2 groups and treated with **2a** under similar reaction conditions. In the reaction, only *mono* alkenylated benzylthioethers **59b-e** were observed in good to moderate yield. The hydroarylation reaction was examined with various S substituted benzylthioethers. In these reactions also, the expected alkenylated product was observed in good yields **59f-h**. Later, the hydroarylation reaction was examined with unsymmetrical alkynes. However, in the reaction, a mixture of regio- as well as stereoisomeric products was observed **59i-k**.

Conclusions

In the present review, a ruthenium-catalyzed hydroarylation of alkynes with substituted aromatics providing trisubstituted

alkene derivatives in a highly regio- and stereoselective manner was discussed elaborately. The hydroarylation reaction was explored with amide, azole, carbamate, phosphine oxide, amine, acetyl and sulfoxide directed aromatics with alkynes. The hydroarylation reaction was examined with various symmetrical and unsymmetrical alkynes. In all these reactions, the expected alkene derivatives were observed in a highly regio- and stereoselective manner. In the alkyne, if coordinating group such as aryl or ester is present in one of the carbons and non-coordination alkyl group in the another carbon, the C-H bond of aromatic moiety prefers to connect at the alkyl substituted carbon of alkyne and the coordinating group of alkyne and aromatic moiety are *trans* to each other. In the unsymmetrical alkyne, if both carbons having coordinating groups such as Ph and ester, a mixture of regioisomeric products were observed. A possible reaction mechanism of these reactions was proposed and the proposed mechanism was strongly supported by experimental evidence. Particularly, deuterium labelling and kinetic studies clearly revealed that the C-H bond activation step is a rate determining step and the C-H bond activation proceeds via a deprotonation pathway.

There are still several challenges in a ruthenium-catalyzed hydroarylation reaction. Mostly, a higher reaction temperature is needed for the C-H bond functionalization. We believe that it can be done at room temperature by designing the new ruthenium catalysts or to find out the proper reaction conditions with the existing catalysts. The hydroarylation reaction can be explored with a weak chelating group substituted aromatics. Apart from sp^2 C-H bond functionalization, sp^3 C-H bond functionalization should also be explored. In addition, in the hydroarylation reaction, only alkyne carbon-carbon π-component is used. It can also be extended with other carbon-carbon π-components such as alkenes and allenes. We believe that these issues could be easily overcome in the future investigations.

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