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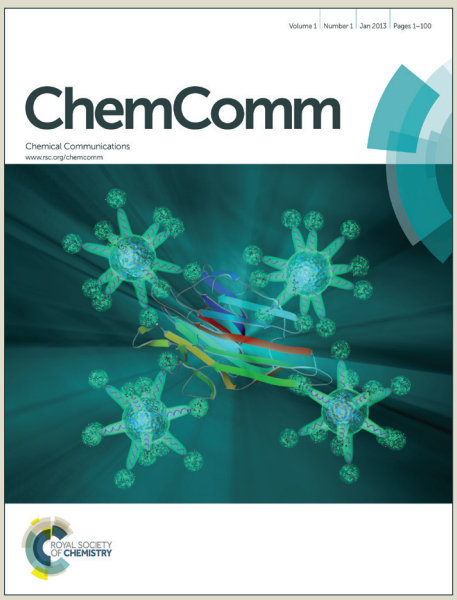

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COMMUNICATION

Ruthenium-catalyzed highly regio- and stereoselective hydroarylation of aromatic sulfoxides with alkynes via C-H bond activation

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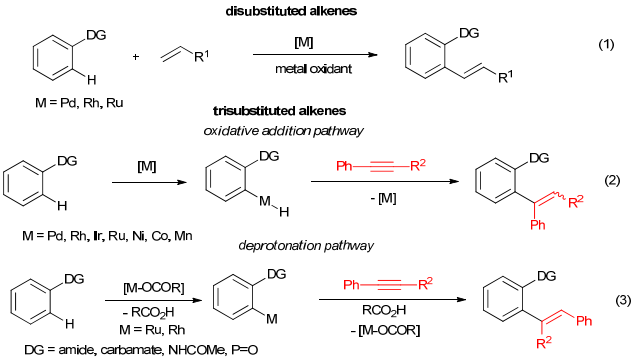
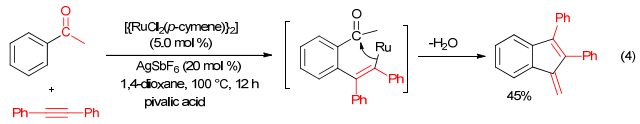
Chelation-assisted alkenylation at the *ortho* C-H bond of aromatic sulfoxides with alkynes in the presence of ruthenium catalyst, $AgSbF_6$ and pivalic acid yielding trisubstituted alkenes in good to excellent yields in a highly regio- and stereoselective manner via deprotonation metalation pathway is described. Later, *ortho*-alkenylated aromatic sulfoxides were converted into α-acyloxy-thioether and 2,3-disubstituted benzothiophene derivative.

The transition metal-catalyzed alkenylation at the *ortho* C-H bond of heteroatom substituted aromatics with carbon-carbon π-components via chelation-assisted C-H bond activation is one of efficient methods for synthesizing highly substituted alkene derivatives in one pot.[1] Alkenes and alkynes are widely used as carbon-carbon π-components in the alkenylation reaction. Usually, alkenes reacted with substituted aromatics yielding disubstituted alkenes or alkanes[2] (eq. 1) and alkynes reacted with substituted aromatics providing trisubstituted alkenes (eq. 2).[3-9] In this context, metal-catalyzed chelation-assisted *ortho* alkenylation of substituted aromatics with alkenes has been extensively studied in the literature.[2] But, *ortho* alkenylation of substituted aromatics with alkynes has not been well documented.



Generally, metal-catalyzed hydroarylation of aromatics with alkynes can be done by two ways; a) the hydroarylation of aromatics with alkynes via an oxidative addition pathway (eq. 2) and b) the hydroarylation of aromatics with alkynes via a deprotonation metalation pathway (eq. 3).[3-9] It is important to note that both reactions undergo in an entirely different pathway and providing different types of regioselective alkene derivatives. Various metals such as ruthenium,[4] rhodium,[5] iridium,[6] palladium,[7] nickel,[8] cobalt[8] and manganese[8] complexes are used as catalysts for the hydroarylation via an oxidative addition pathway. It is very effective method for preparing trisubstituted alkenes in one pot. However, unsymmetrical alkynes provided a mixture of regio- and stereoselective alkene derivatives (eq. 2). But, the regio- and stereoselective issues can be resolved by doing the hydroarylation via deprotonation metalation pathway.[9-10] Notably, metal oxidant is not needed for the hydroarylation reaction unlike the *ortho*-alkenylation of aromatics with alkenes.



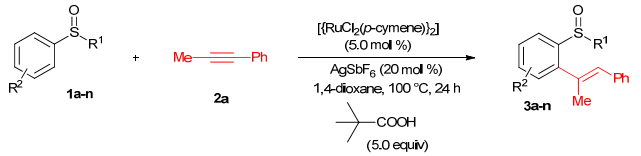
Amide, carbamate, phosphine oxide (P=O) and NHCOR substituted aromatics reacted with alkynes in the presence of ruthenium(II) or rhodium(III) catalysts, yielding trisubstituted alkenes in a highly regio- and stereoselective manner.[10] This results prompted us to explore the possibility of a weakly coordinating C=O assisted hydroarylation of acetophenone with diphenylacetylene in the presence of ruthenium catalyst. However, in the reaction, only cyclic benzofulvene derivative was observed in 45% yield and the expected hydroarylation product was not observed (eq. 4).[11] After hydroarylation, the C-Ru bond immediately inserts into the carbonyl group leading to cyclic benzofulvene which is very difficult to suppress. Next, we have paid out attention to explore the possibility of a weakly coordinating S=O assisted hydroarylation of aromatic sulfoxides with alkynes. In the meantime, very recently, Miura's group reported the hydroarylation of aromatic sulfoxides with alkynes in the presence of a highly expensive rhodium complex.[12] However, $Cu(OAc)_2$ is used as an terminal metal oxidant to regenerate the active rhodium catalyst.

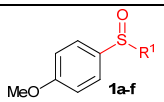
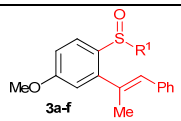
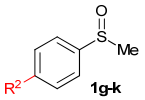
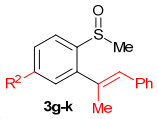
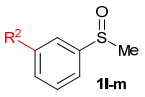
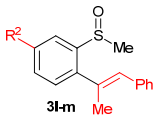
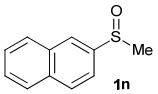
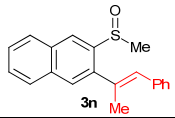
Herein, we wish to report an oxidant free a regio- and stereoselective hydroarylation of aromatic sulfoxides with alkynes in the presence of a less expensive ruthenium catalyst. In the reaction, terminal metal oxidant is not used and only Ru(II) species is involved in the whole catalytic cycle without changing the metal oxidation state. It is important to note that the phenyl sulfoxide motif is present in various natural products and drug molecules as well as it has been widely used as ligands in various enantioselective reactions.[13]

When methyl phenyl sulfoxide (**1a**) was treated with 1-phenyl-1-propyne (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and pivalic acid (5.0 equiv) in 1,4-

dioxane at 100 °C for 24 h, a hydroarylation product **3a** was observed in 75% isolated yield (Table 1, entry 1) (detailed optimization studies, see ESI). The catalytic reaction is highly regioselective and the *ortho* C-H bond of **1a** selectively inserts at the methyl group substituted carbon of alkyne **2a**. The catalytic reaction is also highly stereoselective giving only *E*-stereoisomer trisubstituted alkene derivative **3a**. Next, the methyl group of methyl phenyl sulfoxide (**1a**) was replaced into ethyl, *n*-butyl, *n*-hexyl, benzyl and *iso*-propyl phenyl sulfoxides **1b-f** to know the effect of the reactivity (entries 2-6). Among them, methyl phenyl sulfoxide (**1a**) was very effectively, providing product **3a** in 75% yield. Whereas, *n*-ethyl phenyl sulfoxide (**1b**) and *n*-butyl phenyl sulfoxide (**1c**) yielded products **3b** and **3c** in moderate 52% and 47% yields, respectively (entries 2 and 3). *n*-Hexyl phenyl sulfoxide (**1d**) and benzyl phenyl sulfoxide (**1e**) provided hydroarylation products **3d** and **3e** in less 40% and 43% yields, respectively (entries 4-5). Interestingly, *iso*-propyl phenyl sulfoxide (**1f**) afforded the hydroarylation product **3f** in good 56% yield (entry 6).

Table 1 Scope of aromatic sulfoxides **1a-n**[a]

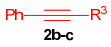
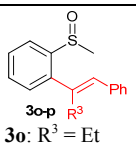
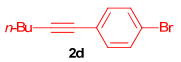
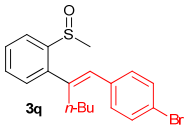
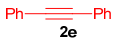
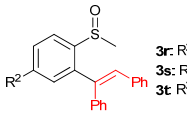
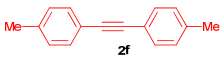
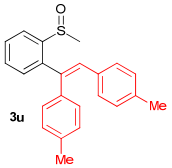


Entry	Sulfoxides **1a-n**	Product **3a-n**	Yield (%)[b]
			
1	**1a**: R^1 = Me	**3a**: R^1 = Me	75
2	**1b**: R^1 = Et	**3b**: R^1 = Et	52
3	**1c**: R^1 = *n*-Bu	**3c**: R^1 = *n*-Bu	47
4	**1d**: R^1 = hexyl	**3d**: R^1 = hexyl	40
5	**1e**: R^1 = benzyl	**3e**: R^1 = benzyl	43
6	**1f**: R^1 = *iso*-Pr	**3f**: R^1 = *iso*-Pr	56
			
7	**1g**: R^2 = Me	**3g**: R^2 = Me	55
8	**1h**: R^2 = H	**3h**: R^2 = H	73
9	**1i**: R^2 = Br	**3i**: R^2 = Br	56
10	**1j**: R^2 = Cl	**3j**: R^2 = Cl	52
11	**1k**: R^2 = CHO	**3k**: R^2 = CHO	51
			
12	**1l**: R^2 = OMe	**3l**: R^2 = OMe	57
13	**1m**: R^2 = Me	**3m**: R^2 = Me	51
14			47

[a]All reactions were carried using **1a-n** (0.5 mmol), **2a** (0.6 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and pivalic acid (2.5 mmol) in 1,4-dioxane at 100 °C for 24 h under N_2 atmosphere. [b]Isolated yield.

Next, the hydroarylation reaction of substituted aryl sulfoxides **1g-k** with **2a** was examined (Table 1). The reaction was compatible with functional groups such as Br, Cl and CHO substituted aromatic sulfoxides. Electron-rich Me substituted sulfoxide **1g** reacted with **2a** yielding hydroarylation product **3g** in moderate 55% yield (entry 7). Whereas, unsubstituted methyl phenyl sulfoxide (**1h**) provided hydroarylation product **3h** in good 73% yield (entry 8). A less reactive halogen group such as Br and Cl substituted sulfoxides **1i** and **1j** also efficiently participated in the reaction, affording products **3i** and **3j** in 56%, and 52% yields, respectively (entries 9 and 10). Interestingly, electron-deficient CHO substituted aromatic sulfoxide **1k** provided the corresponding hydroarylation product **3k** in 51% yield without affecting a very sensitive CHO group (entry 11). Subsequently, the hydroarylation reaction was tested with unsymmetrical sulfoxides such as *meta* methoxy **1l** and methyl **1m** substituted phenyl sulfoxides with alkyne **2a** (entries 12 and 13). In the reaction, hydroarylation products **3l** and **3m** were observed in 57% and 51% yields, respectively. The hydroarylation reaction is highly regioselective and methyl attached carbon of alkyne **2a** is connected at the less hindered *ortho* C-H bond of sulfoxides **1l** and **1m**. Similarly, methyl naphthyl sulfoxide **1n** reacted with **2a**, yielding product **3n** in 47% yield, in which also, the *ortho* C-H bond activation takes place at the less hindered side (entry 14).

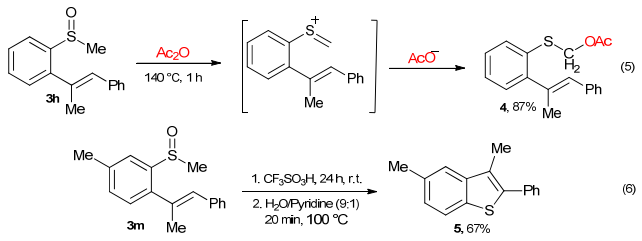
Table 2 Scope of symmetrical and unsymmetrical alkynes **2b-f**[a]

Entry	**1**	Alkynes **2b-j**	Product **3l-u**	Yield (%)[b]
				
1	**1h**	**2b**: R^3 = Et	**3o**: R^3 = Et	71
2	**1h**	**2c**: R^3 = *n*-Bu	**3p**: R^3 = *n*-Bu	67
3	**1h**			63
4	**1a**			85[c]
5	**1h**		 **3r**: R^2 = OMe **3s**: R^2 = H **3t**: R^2 = F	83[c]
6	**1o**			45
7	**1h**			66[c]

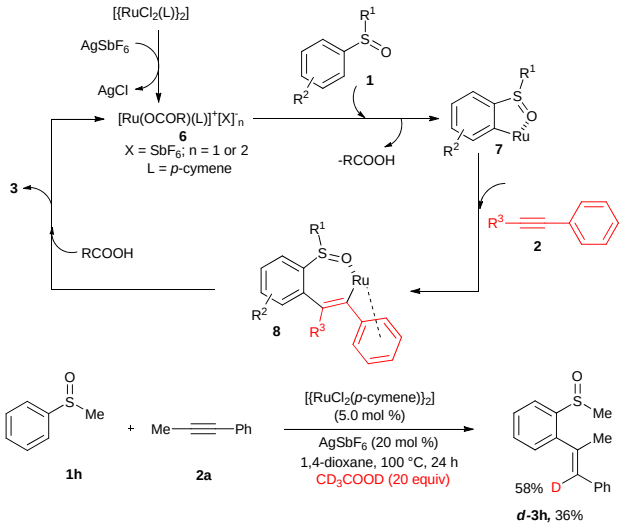
[a]All reactions were carried using **1a** or **1h** or **1o** (0.5 mmol), **2b-f** (0.6 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and pivalic acid (2.5 mmol) in 1,4-dioxane at 100 °C for 24 h under N_2 atmosphere. [b]Isolated yield. [c]The reaction was done at 100 °C for 12 h.

The scope of the hydroarylation reaction was tested with various unsymmetrical and symmetrical alkynes (Table 2). Unsymmetrical alkynes such as 1-phenyl-1-butyne (**2b**), 1-phenyl-1-hexyne (**2c**) and bromo substituted alkyne **2d** reacted regioselectively with **1h**, providing the corresponding alkene derivatives **3o-q** in 71%, 67% and 63% yields, respectively (entries 1-3). In these reactions, alkyl substituted alkyne carbon

connected at the *ortho* C-H bond of **1h**. A highly reactive symmetrical diphenylacetylene (**2e**) and 1,2-di-*p*-tolylethyne (**2f**) reacted efficiently with **1a** or **1h** or *para* fluoro substituted phenyl sulfoxide **1o** giving the corresponding sterically hindered trisubstituted alkene derivatives **3r-u** in excellent yields (entries 4-7). It is important to note that the electron-deficient *para* fluoro substituted phenyl sulfoxide **1o** was not suitable substrate for hydroarylation reaction with a less reactive 1-phenyl-1-propyne (**2a**). But, it worked nicely with diphenylacetylene (**2b**).



By using aryl sulfoxides **3**, we have tried to prepare α-acyloxy-thioether via Pummerer rearrangement.[14a] Treatment of **3h** with acetic anhydride (10.0 equiv) at 140 °C for 1 h gave α-acyloxy-thioether **4** in 87% yield (eq. 5). Later, *ortho* alkenylated phenyl sulfoxide **3m** was treated with CF_3SO_3H at room temperature for 24 h followed by addition of a 9:1 ratio of water/pyridine to the reaction mixture, yielding 2,3-disubstituted benzothiophene derivative **5** in 67% yield (eq. 6).[14] It is well known that aromatic sulfoxides (Ar-S=O-R) can be easily converted into the corresponding aromatic sulfides (Ar-S-R) in good yields.[14b]



Scheme 1 Proposed mechanism

The catalytic reaction proceeds via coordination of oxygen atom of **1** into a cationic ruthenium species **6** followed by *ortho* metalation provides intermediate **7** (Scheme 1).[9, 15] Coordinative selective insertion of alkyne **2** into the C-Ru bond of intermediate **7** yields intermediate **8**. Protonation of C-Ru bond of intermediate **8** by pivalic acid affords *ortho* alkenylated product **3** and regenerates the active catalyst **6**. Intramolecular coordination of Ph group to the Ru metal could stabilize the intermediate **8**. Pivalic acid plays dual role in the reaction. It acts as an acetate source for the deprotonation of the *ortho* C-H bond of **1** and the proton source followed by the regeneration of the active catalyst. To demonstrate the role of organic acid in the hydroarylation reaction, the reaction of **1h** with **2a** in the presence of CD_3COOD instead of pivalic acid was tested. In the reaction, hydroarylation product ***d*-3h** was observed in 36% yield with 58% of deuterium incorporation at the alkene carbon.

In conclusion, we have described a ruthenium-catalyzed highly regio- and stereoselective hydroarylation of aromatic sulfoxides with alkynes providing trisubstituted alkene derivatives in good to excellent yields. By using trisubstituted alkenes, α-acyloxy-thioether and 2,3-disubstituted benzothiophene were prepared.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures and spectroscopic data. See DOI: 10.1039/b000000x/

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Graphical Abstract

Ruthenium-catalyzed highly regio- and stereoselective hydroarylation of aromatic sulfoxides with alkynes via C-H bond activation

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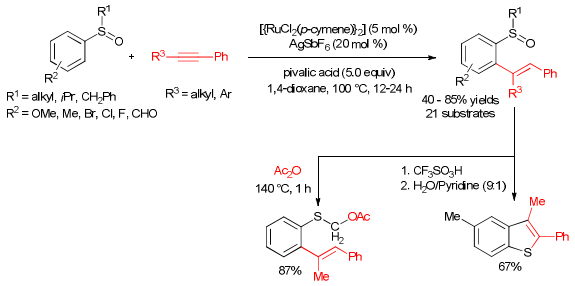

Abstract:

A ruthenium-catalyzed hydroarylation of aromatic sulfoxides with alkynes in the presence of $AgSbF_6$ and pivalic acid yielding trisubstituted alkenes is described.