Organic LETTERS

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Ruthenium-Catalyzed Hydroarylation of Anilides with Alkynes: An Efficient Route to *Ortho*-Alkenylated Anilines

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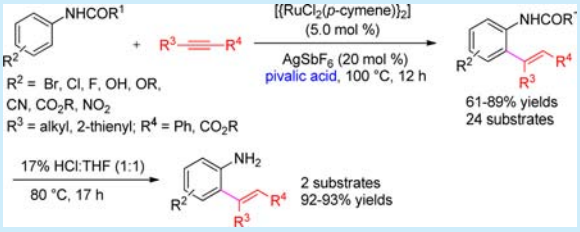
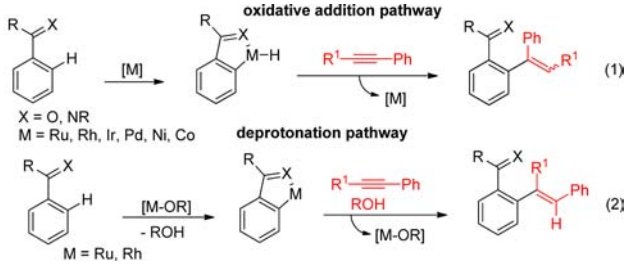
Supporting Information

ABSTRACT: Acetanilides reacted with symmetrical as well as unsymmetrical alkynes in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$, pivalic acid, and $AgSbF_6$ in *iso*-PrOH providing *ortho*-alkenylated acetanilides in a highly regio- and stereoselective manner. Later, *ortho*-alkenylated acetanilides were converted into *ortho*-alkenylated anilines in the presence of HCl.



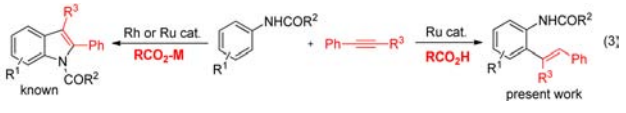
The transition-metal-catalyzed hydroarylation of aromatic electrophiles or organometallic reagents with alkynes is a convenient route for the synthesis of trisubstituted alkenes in a highly regio- and stereoselective manner.[1] Substituted alkenes are versatile synthetic precursors which are widely used for several organic transformations. The alkene unit is also present in various drug molecules and materials.[1] Although this type of reaction is very effective for synthesizing alkenes, a preactivated coupling partner such as C−X or C−M on the aromatic moiety is required. Instead of using a preactivated partner, a similar type of reaction is carried out utilizing C−H bond activation; it would be even more useful in organic synthesis.[2]

In 1995, Murai's group reported the ruthenium-catalyzed hydroarylation of aromatic ketones with alkynes through a C−H bond activation.[3a] Subsequently, this type of hydroarylation reaction has been extended with various heteroatom substituted aromatics by several groups in the presence of catalysts such as Ru, Rh, Ir, and Pd.[3,4] Meanwhile, first row transition metals such as Mn, Ni, and Co can also be used as catalysts for the hydroarylation reaction.[5] This hydroarylation reaction mechanistically proceeds via an oxidative addition pathway (eq 1). However, this reaction is not completely regio- and stereoselective with unsymmetrical alkynes and mostly provides a mixture of alkene derivatives.



This type of regio- and stereoselective problem can be solved by performing the hydroarylation reaction via a chelation-assisted concerted deprotonation−metalation pathway (eq 2).[6] In fact, both reactions proceed entirely in a different mechanistic pathway and also provide the hydroarylation product in a reverse regiochemistry (eqs 1 and 2). Chelating groups such as amide, carbamate, and phosphine oxide (P═O) substituted aromatics underwent hydroarylation with alkynes in the presence of ruthenium(II) or rhodium(III) complexes as catalysts, yielding trisubstituted alkenes in a highly regio- and stereoselective manner.[6] Recently, Miura's group reported ruthenium-catalyzed hydroarylation of biphenyl anilines with alkynes.[6f] However, in the reaction of biphenyl anilines with unsymmetrical alkynes, a mixture of regio- and stereoisomeric products were observed.

Herein, we report a highly regio- and stereoselective ruthenium-catalyzed hydroarylation of acetanilides with symmetrical and unsymmetrical alkynes. The catalytic reaction provides *ortho*-alkenylated anilides in good to excellent yields. The alkyne substituents determine the regiochemistry of the product. Coordinating groups such as Ph or ester from the alkynes are *trans* to the anilides. Later, *ortho*-alkenylated anilides were converted into *ortho*-alkenylated anilines in the presence of HCl. It is important to note that *ortho*-alkenylated anilines are versatile synthetic precursors in a number of organic transformations and are also efficiently used to synthesize biologically active molecules.[7] It is known that acetanilides reacted with alkynes in the presence of rhodium or ruthenium catalysts and an acetate base to give indole derivatives (eq 3).[8]



Interestingly, if the same reaction is carried out in the presence of an organic acid instead of a base, a different type of *ortho*-alkenylated anilide is observed (eq 3). It is interesting to note

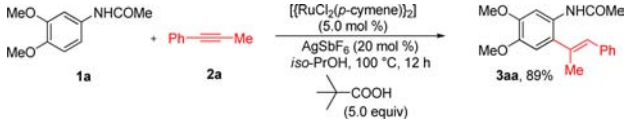
Received: December 18, 2013
Published: January 17, 2014

   dx.doi.org/10.1021/ol403666s | *Org. Lett.* 2014, 16, 912−915

that organic acids or an acetate base completely changes the reaction pattern.

Initially, the hydroarylation of 3,4-dimethoxy aniline with 1-phenyl-1-propyne (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %), $AgSbF_6$ (20 mol %), and pivalic acid (5.0 equiv) in 1,4-dioxane at 100 °C for 12 h was carried out. However, in the reaction, no expected *ortho*-alkenylated aniline was observed. Next, the hydroarylation reaction was tested with anilines having a removable directing group at the nitrogen atom such as acetanilide **1a** (NH−COMe), sulfonamide (NH−SO_2Me), and aryl urea (NHCONMe$_2$). In the reaction of acetanilide **1a** with **2a**, hydroarylation product **3aa** was observed in 41% yield (Scheme 1). In other substrates,

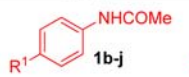
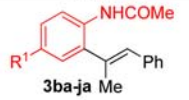
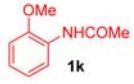
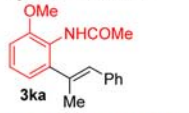
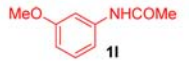
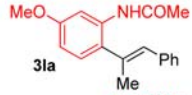
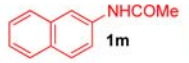
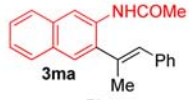
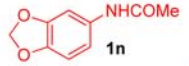
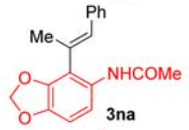
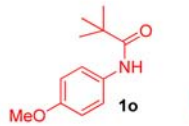
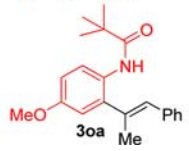
Scheme 1. Hydroarylation of 1a with 2a



no hydroarylation products were observed. The hydroarylation reaction of **1a** and **2a** is highly regio- and stereoselective, as a less hindered C−H bond of **1a** coupled with the methyl substituted carbon of alkyne **2a**. To increase the yield of hydroarylation product **3aa**, reactions of **1a** with **2a** in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %) and $AgSbF_6$ (20 mol %) with various organic acids and solvents were examined. We found that the pivalic acid (5.0 equiv) was an effective organic acid and *iso*-PrOH was an effective solvent for the reaction. In the reaction, product **3aa** was observed in 89% isolated yield (for detailed optimization studies, see the Supporting Information).

The scope of the catalytic reaction was tested with various substituted anilides **1b−o** (Table 1). The reaction was compatible with various functional groups such as OMe, F, Cl, Br, I, ester, CN, and OH substituted anilides. Thus, electron-donating groups such as OH, OMe, and Me substituted anilides **1b−d** reacted efficiently with **2a**, yielding hydroarylation products **3ba−da** in 78%, 85%, and 81% yields, respectively, in a highly regio- and stereoselective manner (entries 1−3). It is very interesting to note that a free hydroxyl group substituted acetanilide **1b** was also effective for the reaction. Acetanilide (**1e**) reacted nicely with **2a**, giving product **3ea** in 80% yield (entry 4). Halogen groups such as Br, Cl, and F substituted anilides **1f−h** also efficiently participated in the reaction, providing products **3fa−ha** in 79%, 76%, and 69% yields, respectively, in a highly regio- and stereoselective manner (entries 5−7). A less reactive electron-withdrawing group such as CN or ester substituted anilides **1i** and **1j** also reacted efficiently with **2a**, giving trisubstituted alkenes **3ia** and **3ja** in 68% and 71% yields, respectively (entries 8 and 9). The regiochemistry of **3ja** was assigned based on the NOESY experiment. It is also important to note that CN and ester groups are known as directing groups for the C−H bond activation reaction.[2] The present result shows that NHCOMe is a better directing group for the reaction compared with ester and CN. Sterically hindered *ortho*-methoxy acetanilide **1k** was effectively involved in the reaction, giving product **3ka** in 84% yield (entry 10). Next, the reaction was tested with unsymmetrical acetanilides **1l−n**. A sterically less hindered C−H bond of *meta*-methoxy acetanilide **1l** and 2-naphthyl acetamide **1m** underwent hydroarylation with **2a**, providing alkene derivatives

Table 1. Hydroarylation of Substituted Anilides 1b−o with 1-Phenyl-1-propyne (2a)[a]

entry	1b-o	product 3	yield (%)[b]
			
1	**1b**: R^1 = OH	**3ba**: R^1 = OH	78
2	**1c**: R^1 = OMe	**3ca**: R^1 = OMe	85[c]
3	**1d**: R^1 = Me	**3da**: R^1 = Me	81[d]
4	**1e**: R^1 = H	**3ea**: R^1 = H	80[d]
5	**1f**: R^1 = Br	**3fa**: R^1 = Br	79
6	**1g**: R^1 = Cl	**3ga**: R^1 = Cl	76
7	**1h**: R^1 = F	**3ha**: R^1 = F	69
8	**1i**: R^1 = CN	**3ia**: R^1 = CN	68
9	**1j**: R^1 = CO_2Me	**3ja**: R^1 = CO_2Me	71
10			84
11			83
12			82
13			81
14			20

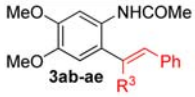
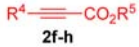
[a]All reactions were carried out using **1b−o** (100 mg), 1-phenyl-1-propyne (**2a**) (1.2 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (0.05 equiv), $AgSbF_6$ (0.20 equiv), and pivalic acid (5.0 equiv) in *iso*-PrOH (2.5 mL) at 100 °C for 12 h. [b]Isolated yield. [c]The reaction was carried out for 4 h. [d]The reaction was carried out for 3 h.

3la and **3ma** in excellent 83% and 82% yields, respectively (entries 11 and 12). The structure of **3la** was confirmed by single crystal X-ray diffraction. In contrast, in the reaction of 3,4-(methylenedioxy)anilide (**1n**) with **2a**, hydroarylation takes place at a sterically hindered C−H bond of **1n**, yielding product **3na** in 81% yield (entry 13). The hydroarylation reaction was tested with 4-methoxyphenyl pivalamide (**1o**). In the reaction, product **3oa** was observed in 20% yield (entry 14).

The scope of the catalytic reaction was further examined with substituted alkynes **2b−k** (Table 2). Thus, diphenylacetylene (**2b**), 1-phenyl-1-butyne (**2c**), 1-phenyl-1-hexyne (**2d**), and 1-phenyl-2-(trimethylsilyl) acetylene (**2e**) reacted very selectively at the sterically less hindered C−H bond of **1a**, providing alkene derivatives **3ab−ae** in 87%, 83%, 81%, and 61% yields, respectively (entries 1−4). In alkynes **2c−d**, the aromatic C−H bond of **1a** was selectively inserted at the alkyl substituted carbon of alkynes. In the product **3ae**, sensitive $SiMe_3$ was cleaved under the reaction conditions. Interestingly, ethyl 2-butynoate (**2f**), methyl hex-2-ynoate (**2g**), and methyl oct-2-ynoate (**2h**) also nicely participated in the reaction, yielding products **3af−ah** in 88%, 80%, and 78% yields, respectively (entries 5−7). In these reactions also, the alkyl substituted

dx.doi.org/10.1021/ol403666s | *Org. Lett.* 2014, 16, 912−915

Table 2. Hydroarylation of 3,4-Dimethoxy Acetanilide (1a) with Substituted Alkynes 2b–h[a]

entry	alkynes **2b-h**	product **3**	yield (%)[b]
	2b-e	 **3ab-ae**	
1	**2b**: R^3 = Ph	**3ab**: R^3 = Ph	87
2	**2c**: R^3 = Et	**3ac**: R^3 = Et	83
3	**2d**: R^3 = *n*-Bu	**3ad**: R^3 = *n*-Bu	81
4	**2e**: R^3 = $SiMe_3$	**3ae**: R^3 = H	61
	 **2f-h**	 **3af-3ah**	
5	**2f**: R^4 = Me, R^5 = Et	**3af**: R^4 = Me, R^5 = Et	88
6	**2g**: R^4 = *n*-Pr, R^5 =Me	**3ag**: R^4 = *n*-Pr, R^5 = Me	80
7	**2h**: R^4 = *n*-Pentyl, R^5 = Me	**3ah**: R^4 = *n*-Pentyl, R^5 = Me	78

[a]All reactions were carried out using **1a** (100 mg), **2b–h** (1.2 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (0.05 equiv), $AgSbF_6$ (0.20 equiv), and pivalic acid (5.0 equiv) in *iso*-PrOH (2.5 mL) at 100 °C for 12 h. [b]Isolated yield.

carbon of alkynes **2f–h** was regioselectively connected at the *ortho* carbon of **1a**. The regiochemistry of **3af** was assigned based on the NOESY experiment.

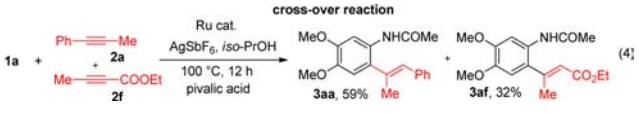
But, an alkyne, ethyl phenyl propiolate (**2i**), having two coordinating groups such as Ph and ester, gave a mixture of hydroarylation products **3ai** and **3ai′** in 81% combined yields in a 60:40 ratio (Table 3, entry 1). Interestingly, 2-thienyl

Table 3. Hydroarylation of 1a with Alkynes 2i–k[a]

entry	alkyne	yield[b]	ratio
1	**2i**	81%	**3ai**:**3ai′** = 1.5:1
2	**2j**	75%	**3aj**:**3aj′** = 3:1
3	**2k**	62%	**3ak** only

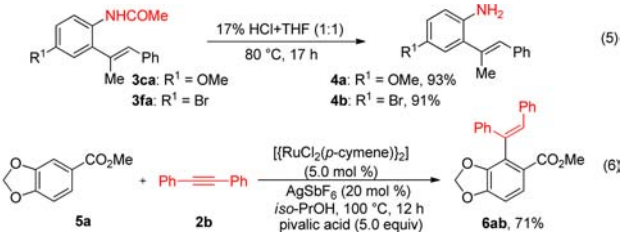
[a]All reactions were carried out using **1a** (100 mg), alkyne **2i–k** (1.2 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (0.05 equiv), $AgSbF_6$ (0.20 equiv), and pivalic acid (5.0 equiv) in *iso*-PrOH (2.5 mL) at 100 °C for 12 h. [b]Isolated yield (combined yield).

substituted alkyne **2j** provided hydroarylation products **3aj** and **3aj′** in 75% combined yields in a 3:1 ratio (entry 2). In the major product **3aj**, the 2-thienyl attached carbon of alkyne **2j** was connected with a less hindered carbon of **1a**. Surprisingly, in the reaction of alkyne **2k** having Ph and CH_2Ph with **1a**, a single coupling product **3ak** in 62% yield was obtained (entry 3). In the reaction, **1a** was connected selectively at the CH_2Ph attached carbon of alkyne **2k**. To know the coordinating effect of Ph and ester groups, the following crossover reaction was examined (eq 4). Treatment of **1a** with **2a** (1.0 equiv) and **2f**



(1.0 equiv) under similar reaction conditions gave alkyne **2a** coupling product **3aa** in a major 59% yield and alkyne **2f** coupling product **3af** in a lesser yield of 32%, respectively. This result clearly reveals that Ph coordinates better with Ru metal than ester.

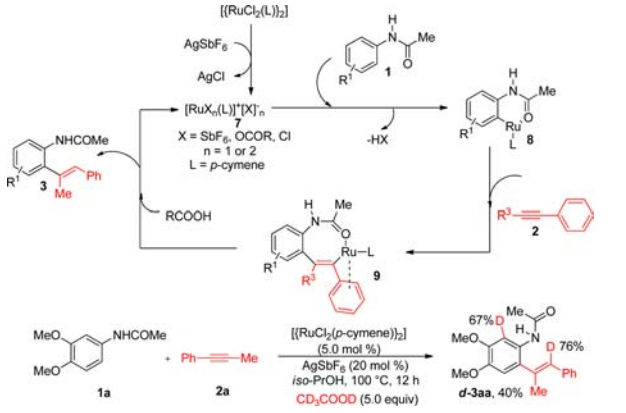
Later, *ortho*-alkenylated acetanilides **3ca** and **3fa** were converted into *ortho*-alkenylated anilines **4a** and **4b** in 93% and 91% yields, respectively, in the presence of a 1:1 mixture of 17% HCl and THF at 100 °C for 17 h (eq 5). The catalytic



reaction was successfully extended with a weak ester directing group substituted aromatic moiety. Methyl piperonate (**5a**) reacted with diphenylacetylene (**2b**) under similar reaction conditions, yielding hydroarylation product **6ab** in 71% yield in a highly regioselective manner (eq 6).

A possible reaction mechanism for the hydroarylation reaction is proposed in Scheme 2. $AgSbF_6$ likely removes the

Scheme 2. Proposed Mechanism



Cl^- ligand from the [{$RuCl_2$(*p*-cymene)}$_2$] complex, giving a cationic ruthenium species **7**. Coordination of the carbonyl group of **1** to a cationic species **7** followed by *ortho*-metalation provides a six-membered ruthenacycle intermediate **8**. Coordinative regioselective insertion of alkyne **2** into the Ru–carbon bond of intermediate **8** gives intermediate **9**. Protonation at the Ru–C bond of intermediate **9** in the presence of RCOOH affords hydroarylation product **3** and regenerates the active ruthenium species **7** for the next catalytic cycle. In the reaction, organic acid acts as a proton source. To support the role of an organic acid, the following deuterium labeling experiment was carried out. Treatment of **1a** with **2a** under similar reaction conditions in the presence of CD_3COOD instead of pivalic acid gave product ***d*-3aa** in 40% yield with 76% of deuterium incorporation at the alkene carbon. In the meantime, 67% deuterium incorporation was observed at the *ortho* carbon of anilide in product ***d*-3aa**. It clearly indicates that the *ortho* C–H bond cleavage of anilide **1** along with intermediate **8** formation is a reversible process.

In conclusion, we have described a highly regio- and stereoselective ruthenium-catalyzed hydroarylation of acetanilides with alkynes. The catalytic reaction was compatible with

dx.doi.org/10.1021/ol403666s | *Org. Lett.* 2014, 16, 912–915

various sensitive functional group substituted acetanilides and alkynes. Further extension of hydroarylation of substituted aromatics with alkynes and a detailed mechanistic investigation are in progress.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the DST (SR/S1/OC-26/2011), India for the support of this research. R.K. thanks the CSIR for a fellowship.

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