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# Ruthenium-catalyzed highly regio- and stereoselective hydroarylation of aryl carbamates with alkynes *via* C–H bond activation†

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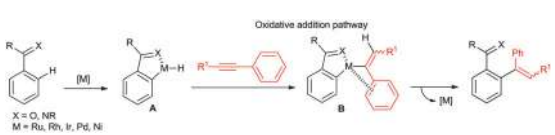
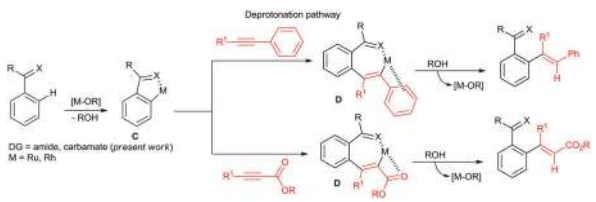
**Chelation-assisted alkenylation of *ortho* C–H bond of aryl carbamates with alkynes in the presence of a ruthenium catalyst, $AgSbF_6$ and pivalic acid gives highly substituted alkene derivatives in good to excellent yields in a highly regio- and stereoselective manner.**

Transition metal-catalyzed chelation-assisted C–H bond hydroarylation of heteroatom group substituted aromatics with alkynes is a convenient method to synthesize highly substituted alkene derivatives in a highly atom-economical and environmentally friendly manner.[1,2] Alkene structural units are present in various organic materials, natural products and drug molecules.[1,2] In 1995, Murai's group reported alkenylation at the C–H bond of carbonyl group substituted aromatics with alkynes in the presence of a ruthenium catalyst.[3a,b] Since then, various metal complexes, including rhodium, palladium, iridium and nickel complexes have been successfully used as catalysts for hydroarylation of various heteroatom group substituted aromatics with alkynes.[4–6] It is believed that this coupling reaction proceeds mechanistically *via* chelation-assisted oxidative addition of the *ortho* C–H bond of a heteroatom-substituted aromatic to the metal complex, yielding a five-membered hydrometallacycle intermediate **A** (eqn (1a)). Then, an aromatic group substituted alkyne undergoes coordinative insertion into metal hydride intermediate species **A**, followed by reductive elimination, providing the corresponding alkene derivative. Usually, Ph groups from both the alkyne and the heteroatom substituted aromatic attach to the same carbon of the alkene, providing a mixtures of *cis* and *trans* stereoisomeric addition products. This reaction is also not completely regioselective and mostly gives mixture of regioisomers.




(1a)

These kinds of regio- and stereoisomeric issue can be easily overcome by doing a similar type of hydroarylation reaction *via* a concerted deprotonation–metalation pathway instead of an oxidative addition pathway.[7–9] In 2010, Fagnou's group reported a strongly directing amide group-assisted rhodium-catalyzed hydroarylation of substituted indoles with alkynes.[9a] Very recently, Miura's group reported a strongly directing amide group-assisted ruthenium-catalyzed hydroarylation of benzamides with alkynes.[9b] The catalytic reaction proceeds *via* chelation-assisted acetate accelerated deprotonation at the *ortho* C–H bond of the heteroatom group substituted aromatic compound by the metal complex (Rh or Ru), providing metallacycle intermediate **C** (eqn (1b)). Coordinative insertion of the aromatic group substituted alkyne into the metal–carbon bond of metallacycle **C** provides metallacycle intermediate **D**. Subsequent protonation by an organic acid gives the corresponding alkene derivative in a highly regio- and stereoselective manner (eqn (1b)). The regiochemistry of the product of this reaction is completely reversed when compared with the regiochemistry of product obtained *via* the oxidative addition pathway (eqn (1a)). A possible explanation for the reversed regiochemistry of the product is that it is probably due to intramolecular coordination of the phenyl group of the alkyne to the metal species which stabilizes the corresponding intermediate (eqn (1b)).




(1b)

Until now, for this type of hydroarylation reaction, only strongly directing amide group directed hydroarylation reactions have been studied. Herein, we wish to report an unprecedented weakly directing carbamate group assisted hydroarylation of aryl carbamates with alkynes in the presence

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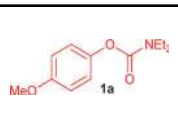
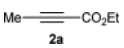
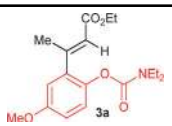
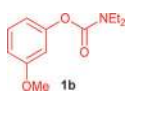
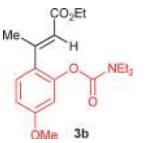
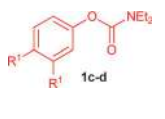
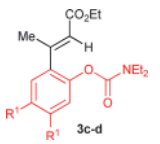
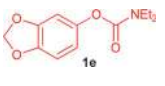
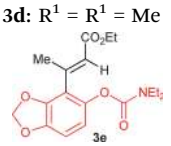
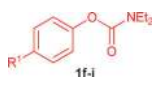
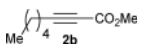
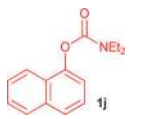
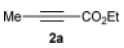
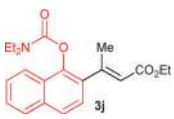
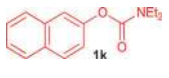
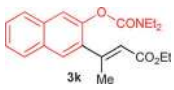
of [{$RuCl_2$(*p*-cymene)}$_2$], $AgSbF_6$ and pivalic acid, which affords highly substituted alkene derivatives in good to excellent yields in a highly regio- and stereoselective manner. The alkyne substituents determine the regiochemistry of the coupling product. In the alkene products, Ph or ester groups from the alkyne are *trans* to the aromatic carbamate.

Treatment of 4-methoxyphenyl diethylcarbamate (**1a**) with ethyl but-2-ynoate (**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 gave hydroarylation product **3a** in 77% isolated yield (Table 1, entry 1) (for detailed optimization studies see ESI†). The catalytic reaction is highly regioselective and the *ortho* C–H bond of **1a** very selectively inserts at the methyl-substituted carbon of alkyne **2a**. The catalytic reaction is also highly stereoselective, giving only the *E*-stereoisomer of **3a**.

**Table 1** The reaction of aryl carbamates **1a–k** with alkynes **2a–b**[a]

| Entry | Carbamates **1a–k** | Alkynes **2a–b** | Product **3** | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  |  |  | 77 |
| 2 |  | 2a |  | 79 |
| |  | 2a |  | |
| 3 | **1c**: $R^1 = R^1$ = OMe | 2a | **3c**: $R^1 = R^1$ = OMe | 83 |
| 4 | **1d**: $R^1 = R^1$ = Me | 2a | **3d**: $R^1 = R^1$ = Me | 80 |
| 5 |  | 2a |  | 82[c] |
| |  |  |  | |
| 6 | **1f**: $R^1$ = I | **2b** | **3f**: $R^1$ = I | 80 |
| 7 | **1g**: $R^1$ = Br | **2b** | **3g**: $R^1$ = Br | 75 |
| 8 | **1h**: $R^1$ = Cl | **2b** | **3h**: $R^1$ = Cl | 73 |
| 9 | **1i**: $R^1$ = F | **2b** | **3i**: $R^1$ = F | 64 |
| 10 |  |  |  | 65 |
| 11 |  | 2a |  | 69 |

[a] All reactions were carried out under the following reaction conditions: **1a–k** (1.0 mmol), **2a–b** (1.5 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol%), $AgSbF_6$ (20 mol%) and pivalic acid (5.0 mmol) in 1,4-dioxane at 100 °C for 24 h under a $N_2$ atmosphere. [b] Isolated yield. [c] The reaction was carried out at 100 °C for 16 h.

To explore the scope of the present hydroarylation reaction, the reactions of various substituted aryl carbamates **1b–k** with **2a–b** were examined (Table 1). 3-Methoxyphenyl carbamate **1b** underwent hydroarylation with ethyl but-2-ynoate (**2a**) under the optimized reaction conditions, providing coupling product **3b** in 79% yield in a highly regio- and stereoselective manner (entry 2). In substrate **1b**, there are two C–H bonds which could undergo hydroarylation with **2a**. The coupling reaction was very selective for the less hindered C–H bond of **1b**. Similarly, 3,4-dimethoxyphenyl carbamate **1c** and 3,4-dimethylphenyl carbamate **1d** afforded alkene derivatives **3c** and **3d** in 83% and 80% yields, respectively, in a highly regio- and stereoselective manner (entries 3 and 4). As for **1b**, in this reaction, alkenylation takes place selectively at the less hindered C–H bond of **1c** and **1d**. In contrast, sesamol carbamate **1e** reacted with **2a** at the more sterically hindered C–H bond, yielding **3e** as the product of the *E*-stereoselective coupling in 82% yield in a highly regioselective manner (entry 5). Next, the hydroarylation reaction was tested with halogen group substituted carbamates **1f–i**. Thus, 4-iodo **1f**, 4-bromo **1g**, 4-chloro **1h** and 4-fluoro **1i** phenyl carbamates efficiently reacted with methyl oct-2-ynoate (**2b**) giving *E*-stereoselective alkene derivatives **3f–i** in 80%, 75%, 73% and 64% yields, respectively (entries 6–9). Similarly, 1-naphthalenyl diethylcarbamate (**1j**) reacted with ethyl but-2-ynoate (**2a**) affording coupling product **3j** in 65% yield in a highly stereoselective manner (entry 10). Interestingly, 2-naphthalenyl diethylcarbamate (**1k**) reacted with ethyl but-2-ynoate (**2a**) at the less sterically hindered *ortho* C–H bond of the naphthyl moiety, providing coupling product **3k** in 69% yield, in a highly regio- and stereoselective manner (entry 11).

The substrate scope of the hydroarylation reaction was extended successfully to include various substituted alkynes **2b–k** (Table 2 and eqn (2)). Thus, 1-phenyl-1-propyne (**2c**), 1-phenyl-1-butyne (**2d**) and 1-phenyl-1-hexyne (**2e**) reacted very selectively at the sterically hindered C–H bond of sesamol carbamate **1e**, providing the corresponding alkene derivatives **3l–n** in 86%, 84% and 81% yields, respectively, in a highly stereoselective manner (Table 2, entries 1–3). The catalytic reaction is highly regioselective and the C–H bond of **1e** added at the Me, *n*-Pr or *n*-pentyl group-substituted carbon of alkynes **2c–e**. Similarly, methoxy ether **2f** and methyl ester **2g** substituted alkynes also successfully participated in the reaction, affording coupling products **3o** and **3p** in 83% and 75% yields, respectively (entries 4 and 5). Methyl hex-2-ynoate (**2h**) and methyl oct-2-ynoate (**2b**) provided the corresponding *E*-stereoselective alkene derivatives **3q** and **3r** in 79% and 76% yields, respectively (entries 6 and 7). Similarly, trimethyl(phenylethynyl)silane (**2i**) also efficiently participated in the reaction with **1e** affording alkene derivative **3s** in 72% yield (entry 8). However, in product **3s**, the TMS moiety of the alkyne was cleaved under the reaction conditions. 4-Iodophenyl carbamate **1f** efficiently reacted with 1-phenyl-1-propyne (**2c**) under similar reaction conditions providing the corresponding alkene derivative **3t** in 75% yield (entry 9). Diphenylacetylene (**2j**) also reacted

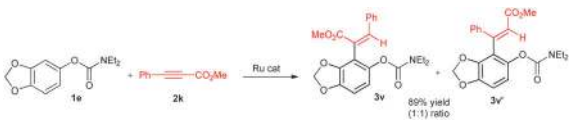
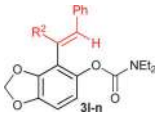
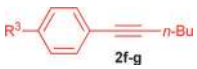
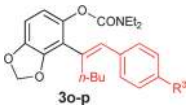
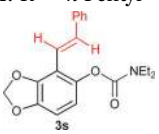
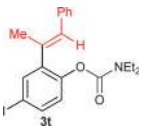

(2)

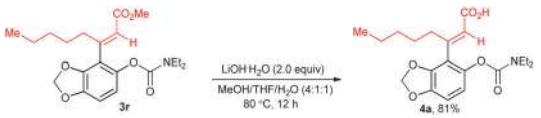
**Table 2** The reaction of carbamates **1e** or **1f** with alkynes **2b–j**[a]

| Entry | 1 | Alkynes 2b–j | Product 3l–u | Yield[b] (%) |
|---|---|---|---|---|
| | |  2c-e |  3l-n | |
| 1 | **1e** | **2c:** $R^2$ = Me | **3l:** $R^2$ = Me | 86 |
| 2 | **1e** | **2d:** $R^2$ = Et | **3m:** $R^2$ = Et | 84 |
| 3 | **1e** | **2e:** $R^2$ = *n*-Bu | **3n:** $R^2$ = *n*-Bu | 81 |
| | |  2f-g |  3o-p | |
| 4 | **1e** | **2f:** $R^3$ = OMe | **3o:** $R^3$ = OMe | 83 |
| 5 | **1e** | **2g:** $R^3$ = $CO_2Me$ | **3p:** $R^3$ = $CO_2Me$ | 75 |
| | |  2h and 2b |  3q-r | |
| 6 | **1e** | **2h:** $R^4$ = *n*-Pr | **3q:** $R^4$ = *n*-Pr | 79 |
| 7 | **1e** | **2b:** $R^4$ = *n*-Pentyl | **3r:** $R^4$ = *n*-Pentyl | 76 |
| 8 | **1e** |  2i |  3s | 72 |
| 9 | **1f** |  2c |  3t | 75[c] |
| 10 | **1e** |  2j |  3u | 89 |

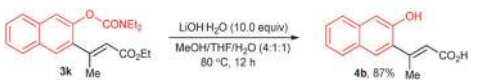
[a] All reactions were carried out under the following reaction conditions: **1e** or **1f** (1.0 mmol), **2b–j** (1.5 mmol), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol%), $AgSbF_6$ (20 mol%) and pivalic acid (5.0 mmol) in 1,4-dioxane at 100 °C for 16 h under a $N_2$ atmosphere. [b] Isolated yield. [c] The reaction was done at 100 °C for 24 h.

efficiently with **1e** yielding alkenylated product **3u** in excellent 89% yield (entry 10). Subsequently, the reaction of **1e** with methyl 3-phenylpropiolate (**2k**) was also tested under similar reaction conditions (eqn (2)). In this reaction, a mixture of regioisomeric products **3v** and **3v′** were observed in 89% yield in approximately a 1 : 1 ratio.

It was found that ester **3r** was converted into carboxylic acid derivative **4a** in the presence of LiOH (2.0 equiv.) (eqn (3a)), whereas 10.0 equiv. of LiOH cleaved both ester and carbamate moieties of compound **3k**, giving phenol derivative **4b** in 87% yield (eqn (3b)). The structures of compounds **4a** and **4b** were confirmed by single crystal X-ray diffraction (see ESI†). For detailed mechanistic studies of this, see the ESI.†



(3a)



(3b)

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