

# Ruthenium-Catalyzed *Peri*- and *Ortho*-Alkynylation with Bromoalkynes via Insertion and Elimination

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Supporting Information



**ABSTRACT:** The alkynylation of naphthols takes place with total regiocontrol at the *peri* position of the hydroxyl group in the presence of  $[RuCl_2(p-cymene)]_2$  as the catalyst. This reaction features high functional group tolerance. The related *ortho*-alkynylation of benzoic acids proceeds under similar conditions and also shows wide functional group tolerance. Both reactions proceed through metalation, insertion of the alkyne, and bromide elimination.

**F** ollowing the pioneering work of Miura on the Pd-catalyzed peri (C-8) arylation of naphthols with iodoarenes,<sup>1</sup> many other related transformations have been developed.<sup>2,3</sup> The reaction of symmetrical disubstituted alkynes with 1-naphthols in the presence of Rh(III) catalysts leads to benzo[*de*]chromenes by C–C bond formation at the *peri* position followed by cyclization.<sup>4,5</sup> Benzo[*de*]chromenes can also be obtained from 1-naphthols using [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> as the catalyst.<sup>6</sup> The metal-catalyzed chelation-assisted *ortho*-alkynylation of aromatic compounds has been performed with haloalkynes<sup>7</sup> and with ethynylbenziodoxolone reagents (EBX).<sup>8,9</sup> Among the weakly coordinating directing groups,<sup>10</sup> carboxylic acids have been the most important.<sup>11,12</sup> Ru(II)-catalyzed reaction of benzoic acids with internal alkynes leads to isocoumarins.<sup>13,14</sup> Recently, the alkynylation of benzoic acids with (bromoethynyl)-triisopropylsilane has been reported with Ir<sup>15</sup> and Ru<sup>16</sup> catalysts.

Here, we report the first *peri*-alkynylation of readily available naphthols with bromoalkynes using  $[RuCl_2(p\text{-cymene})]_2$  as the catalyst, which proceeds without cyclization at temperatures lower than those required for most *peri*-functionalizations catalyzed by late transition metals (typically 110 °C). Furthermore, although the reaction is carried out in the presence of a mild base, the competitive formation of (*Z*)-2-bromovinyl phenyl ethers<sup>17</sup> was not observed.

Under the optimal reaction conditions using  $[RuCl_2(p-cymene)]_2$  as the catalyst, 1-naphthol (1a) reacted with TIPSprotected bromoacetylene (2a) in 1,2-dichloroethane (DCE) to give *peri*-alkynylated derivative 3a<sub>1</sub> in excellent yield at 40 °C in the presence of K<sub>2</sub>CO<sub>3</sub> and NaOAc (Table 1, entry 1). The reaction could be carried out in the presence of air (Table 1, entries 1 and 2) and required a stoichiometric amount of K<sub>2</sub>CO<sub>3</sub> 

 Table 1. Ruthenium-Catalyzed Peri C-H Alkynylation:

 Deviation from Optimized Conditions<sup>a</sup>



<sup>&</sup>quot;Reaction conditions: **1a** (0.2 mmol), **2a** (1.2 equiv),  $K_2CO_3$  (1 equiv), NaOAc (0.2 equiv),  $[RuCl_2(p\text{-cymene})]_2$  (5 mol %), air, 14 h. <sup>b</sup>Yield determined by <sup>1</sup>H NMR using dodecane as internal standard. 'Isolated yield in parentheses. TIPS-EBX: 1-{[tris(1-methylethyl)-silyl]ethynyl]}-1,2-benziodoxol-3(1*H*)-one.

(Table 1, entries 4 and 5). In the presence of other metal complexes, the reaction did not take place satisfactorily (Table 1,

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entries 6-9). No reaction was observed with TIPS-EBX instead of **2a** (Table 1, entry 10).

Reaction of 1a with TMS- (2b) and TES-protected bromoacetylene (2c) gave  $3a_2$  and  $3a_3$  in lower yields (Scheme 1). Similarly, reaction of 1a with 1-bromo-3,3-dimethylbut-1-yne

# Scheme 1. Ruthenium-Catalyzed *Peri* C–H Alkynylation of Naphthols<sup>*a*</sup>



<sup>*a*</sup>Reaction conditions: **1a**–**u** (0.2 mmol),  $K_2CO_3$  (1 equiv), NaOAc (0.2 equiv),  $[RuCl_2(p\text{-cymene})]_2$  (5 mol %), **2a**–**d** (1.2 equiv), DCE (1.5 mL), 40 °C, air, 14 h. <sup>*b*</sup>7 mmol scale. <sup>*c*</sup>KOAc (2 equiv) instead of  $K_2CO_3$  and NaOAc (0.2 equiv). <sup>*d*</sup>60 °C. <sup>*e*</sup>95 °C. <sup>*f*</sup>110 °C. <sup>*g*</sup>2a (2.2 equiv) and  $K_2CO_3$  (2.0 equiv) and NaOAc (0.4 equiv).

(2d) gave  $3a_4$  in 40% yield. Reaction with 1-bromo-1-octyne, bromophenylacetylene, or TBS-protected 3-bromo-1,1-diphenylprop-2-yn-1-ol did not lead to alkynylated products. Under the conditions optimized for the formation of  $3a_1$ , or using slightly different conditions, naphthols 1b-r bearing a wide range of substituents and pyren-1-ol (1s) provided alkynylated products 3b-s in 41–93% yields. Hydrogen-bonded naphthols 1e and 1r with *o*-keto or ester groups reacted uneventfully. Similarly, free NH<sub>2</sub> (3n) and OH (3o) groups were well tolerated. The double alkynylation of 1,5-dihydroxynaphthalenes 1t,u afforded products 3t,u in 43–45% yields. On the other hand, reaction of acetal protected 1,4,5-trihydroxynapthalene 1v with 2a afforded binaphthol 3v as a result of the oxidative dimerization of the electron-rich naphthol. The structure of 3i was confirmed by X-ray diffraction.<sup>18</sup>

Alkynylation of 4-hydroxycoumarin (1x) afforded 3x in 66% yield. The reaction can also be applied for the alkynylation of nitrogen heterocycles, which are often problematic substrates in C–H functionalizations.<sup>11m,19</sup> Thus, 4-hydroxyquinolines  $1y_{,z}$  gave rise to  $3y_{,z}$ , whereas decoquinate (1aa) led to 3aa in an example of late-stage functionalization of a pharmaceutical compound.

In contrast to the known formation of benzo[*de*]chromenes by 6-*endo-dig* cyclization in metal-catalyzed reactions of 1-naphthols with internal alkynes,<sup>4,6</sup> the cyclization of  $3a_1$  with gold(I) proceeds in a 5-*exo-dig* manner to form naphtofuranylidene 5, whose structure was determined by X-ray diffraction<sup>18</sup> (Scheme 2).

# Scheme 2. Synthesis of Naphthofuranylidene 5 and Fluoranthenes 8,9



The hydroxy group can be used as a handle for the formation of C–C bonds via the corresponding triflates. Thus, we prepared benzo [k] fluoranthene (8) in three steps from aryl triflate 6 by Suzuki cross-coupling to give 7a, desilylation, and [4 + 2] intramolecular cycloaddition of  $7b^{20}$  (Scheme 2). As a second example in the context of fluoranthene synthesis, <sup>1c,21</sup> benzo-[5,6] indeno [1,2,3-cd] pyrene (9) was obtained from 3s in 10% overall yield.

Under conditions similar to those developed for the *peri*alkynylation, but using *tert*-amyl alcohol as the solvent at 90 °C, benzoic acids were alkynylated at the *ortho* position in a general manner (Scheme 3). These conditions allow the alkynylation with a broad scope. Indeed, the reaction tolerates a wide range of functional groups including halides (11a,b, 11i,j, 11m,n), hydroxyl groups (11c, 11o, 11y), nitro (11q), thioether (11r), carbonyl (11f,g, 11v), ester (11x), and nitrile (11u). Products of double alkynylation (11h-k, 11m-x, 11ac) were obtained for substrates with two free *ortho* positions, although 10l with a *tert*butyl group at *meta* gave monoalkynylated 11l as the major compound. Carboxylic acid derivatives of many heterocyclic systems, including thiophenes, benzothiophenes, benzofurans, indoles, pyrazoles, pyridines, and quinolines were also alkynylated to give the corresponding products 11ad-ar in



<sup>*a*</sup>Reaction conditions: **10a**–**at** (0.2 mmol),  $K_2CO_3$  (0.5 equiv), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (5 mol %), **2a** (1.2 equiv), *tert*-amyl alcohol (1.5 mL), 90 °C, air, 14 h. <sup>*b*</sup>10 mmol scale. <sup>*c*</sup>70 °C. <sup>*d*</sup>**2a** (2.2 equiv) and  $K_2CO_3$  (1.0 equiv) <sup>*c*</sup>MeI (5 equiv),  $K_2CO_3$  (2 equiv), and MeCN added after 14 h. <sup>*f*</sup>120 °C and KHCO<sub>3</sub> (0.5 equiv) instead of  $K_2CO_3$ . <sup>*g*</sup> $K_2CO_3$  (1 equiv). <sup>*h*</sup> $K_2CO_3$  (1.5 equiv).

moderate to good yields. As an exception, the alkynylation of 2-hydroxynicotinic acid (**10an**) had to be performed at higher temperature (120  $^{\circ}$ C). Under the developed conditions, the late stage functionalization of analgesic niflumic acid (**10ar**) led

selectively to 11ar. The structures of 11h, 11af, 11aj, and 11aq were confirmed by X-ray diffraction.  $^{18}$ 

The C–H ruthenation has been proposed to be the ratedetermining step,<sup>13</sup> which is supported by DFT calculations in the reaction of  $[Ru(p-cymene)(OAc)_2]$  with diphenylacetylene.<sup>22</sup> According to our DFT data, this is also the case for the *peri*-alkynylation reaction (Scheme 4).<sup>18,23</sup> Thus, I leads to

Scheme 4. Simplified Mechanism of the Ru-Catalyzed Peri-Alkynylation Based on DFT Calculations<sup>a</sup>



<sup>*a*</sup>Values in parentheses are free energies in kcal·mol<sup>-1</sup> (T = 298.15 K)

ruthenacycle II by acetate-assisted C-H activation via TS<sub>I-II</sub>  $(\Delta G^{\ddagger} = 19.9 \text{ kcal} \cdot \text{mol}^{-1})$ , which is followed by dissociative ligand substitution through a coordinatively unsaturated complex (not shown) to form III. Alternative ortho-ruthenation was also considered and ruled out on the basis of higher activation energy  $(\Delta G^{\ddagger} = 26.0 \text{ kcal} \cdot \text{mol}^{-1})$ . Subsequent alkynylation proceeds via insertion to produce IV ( $\Delta G^{\ddagger} = 13.5 \text{ kcal} \cdot \text{mol}^{-1}$ ), which then undergoes KOAc-assisted bromide elimination from V with a minimal barrier of 0.5 kcal·mol<sup>-1</sup> to furnish VI and VII. Exchange with the potassium salt of the starting naphthol liberates the product of *peri*-alkynylation and closes the catalytic cycle. The C-C bond formation via oxidative addition of the C-Br bond to the Ru(II) center was found to be much less likely ( $\Delta G^{\ddagger} = 31.7$  $kcal mol^{-1}$ ). Calculations for the benzoic acid show similar activation barriers 20.0 and 13.7 kcal/mol for C-H activation and alkyne insertion, respectively.<sup>23</sup>

In summary, we have found that the *peri*-alkynylation of naphthols takes place in a general manner with total regiocontrol and high functional group tolerance in the presence of commercially available  $[RuCl_2(p\text{-cymene})]_2$  as the catalyst. In most cases, the *peri*-alkynylation can be performed at 40–95 °C. Under similar conditions, benzoic acids are *ortho*-alkynylated. Both reactions can be applied to heterocyclic substrates, including those containing basic nitrogen. Application of these results for the synthesis of large polyarenes is underway.

ASSOCIATED CONTENT

#### **S** Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02655.

Experimental procedures, characterization data, and theoretical results (PDF)

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#### Notes

The authors declare no competing financial interest.

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