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

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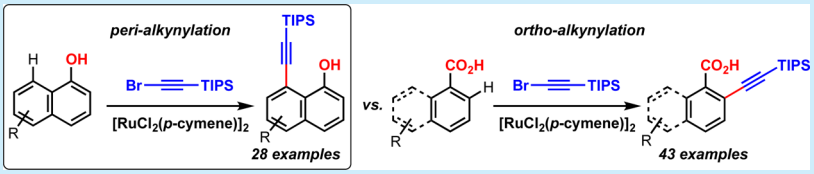
Supporting Information



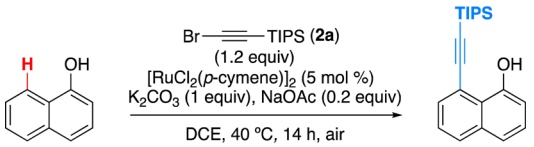
ABSTRACT: The alkynylation of naphthols takes place with total regiocontrol at the *peri* position of the hydroxyl group in the presence of $[RuCl_2(p\text{-cymene})]_2$ as the catalyst. This reaction features high functional group tolerance. The related *ortho*-alkynylation of benzoic acids proceeds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

Following the pioneering work of Miura on the Pd-catalyzed *peri* (C-8) arylation of naphthols with iodoarenes,[1] many other related transformations have been developed.[2,3] 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.[4,5] Benzo[*de*]chromenes can also be obtained from 1-naphthols using $[RuCl_2(p\text{-cymene})]_2$ as the catalyst.[6] The metal-catalyzed chelation-assisted *ortho*-alkynylation of aromatic compounds has been performed with haloalkynes[7] and with ethynylbenziodoxolone reagents (EBX).[8,9] Among the weakly coordinating directing groups,[10] carboxylic acids have been the most important.[11,12] Ru(II)-catalyzed reaction of benzoic acids with internal alkynes leads to isocoumarins.[13,14] Recently, the alkynylation of benzoic acids with (bromoethynyl)-triisopropylsilane has been reported with Ir[15] and Ru[16] 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[17] was not observed.

Under the optimal reaction conditions using $[RuCl_2(p\text{-cymene})]_2$ as the catalyst, 1-naphthol (**1a**) reacted with TIPS-protected bromoacetylene (**2a**) in 1,2-dichloroethane (DCE) to give *peri*-alkynylated derivative $\mathbf{3a_1}$ in excellent yield at 40 °C in the presence of K_2CO_3 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_2CO_3 (Table 1, entries 4 and 5). In the presence of other metal complexes, the reaction did not take place satisfactorily (Table 1,

Table 1. Ruthenium-Catalyzed *Peri* C−H Alkynylation: Deviation from Optimized Conditions[a]



1a — 3a1

entry	variation from the "standard conditions"	yield[b,c] (%)
1	none	95 (92)
2	under Ar	95
3	in MeCN	25
4	without K_2CO_3	10
5	without K_2CO_3 and NaOAc	0
6	$[Cp^*RhCl_2]_2$ instead of [Ru]	17
7	$[Cp^*IrCl_2]_2$ instead of [Ru]	32
8	$Cp^*Co(CO)I_2$ instead of [Ru]	0
9	$Pd(OAc)_2$ instead of [Ru]	0
10	with TIPS-EBX instead of **2a**	0

[a]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. [b]Yield determined by ^1H NMR using dodecane as internal standard. [c]Isolated yield in parentheses. TIPS-EBX: 1-{[tris(1-methylethyl)-silyl]ethynyl]}-1,2-benziodoxol-3(1*H*)-one.

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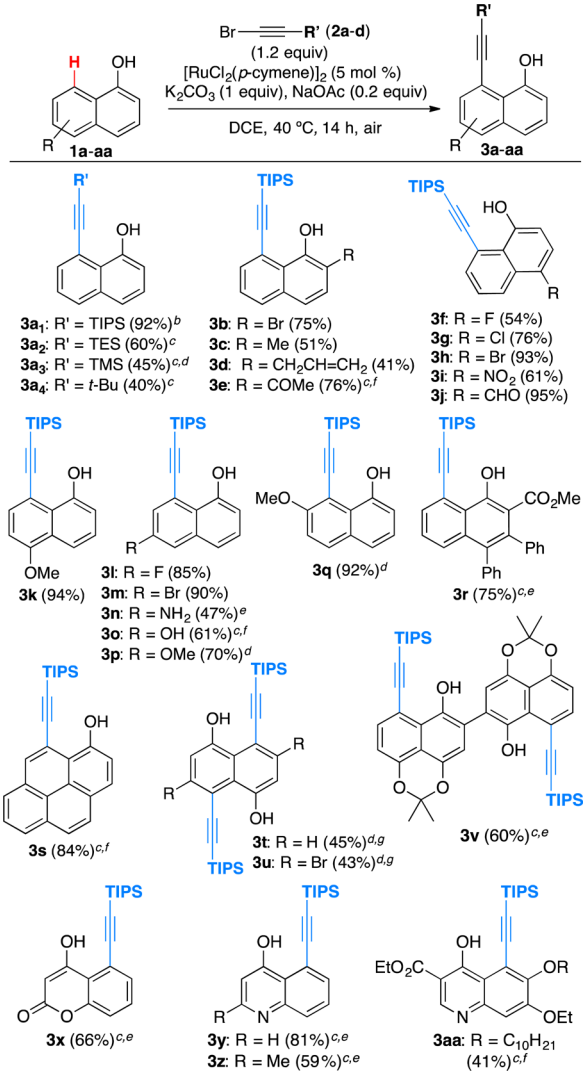
entries 6–9). No reaction was observed with TIPS-EBX instead of **2a** (Table 1, entry 10).

Reaction of **1a** with TMS- (**2b**) and TES-protected bromoacetylene (**2c**) gave $\mathbf{3a}_2$ and $\mathbf{3a}_3$ 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[a]



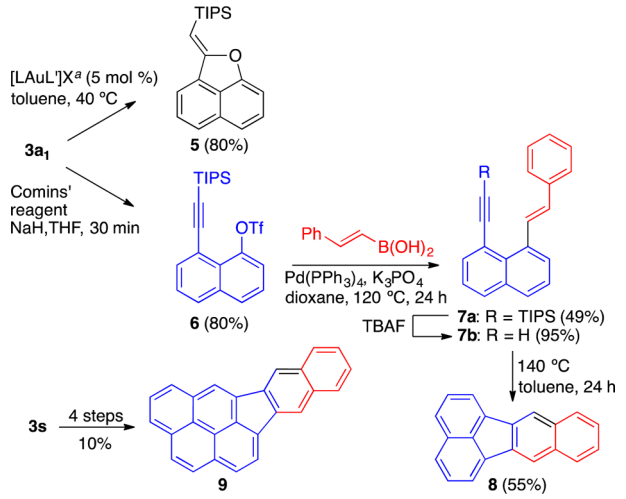
[a]Reaction conditions: **1a–u** (0.2 mmol), K_2CO_3 (1 equiv), NaOAc (0.2 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), **2a–d** (1.2 equiv), DCE (1.5 mL), 40 °C, air, 14 h. [b]7 mmol scale. [c]KOAc (2 equiv) instead of K_2CO_3 and NaOAc (0.2 equiv). [d]60 °C. [e]95 °C. [f]110 °C. [g]**2a** (2.2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

(**2d**) gave $\mathbf{3a}_4$ 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 $\mathbf{3a}_1$, 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_2 (**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.[18]

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.[11m,19] 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,[4,6] the cyclization of $\mathbf{3a}_1$ with gold(I) proceeds in a 5-*exo-dig* manner to form naphtofuranylidene **5**, whose structure was determined by X-ray diffraction[18] (Scheme 2).

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



[a][LAuL′]X = $[(2,4\text{-}t\text{Bu}_2C_6H_3O)_3PAuNCMe]SbF_6$.

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,[1c,21] 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

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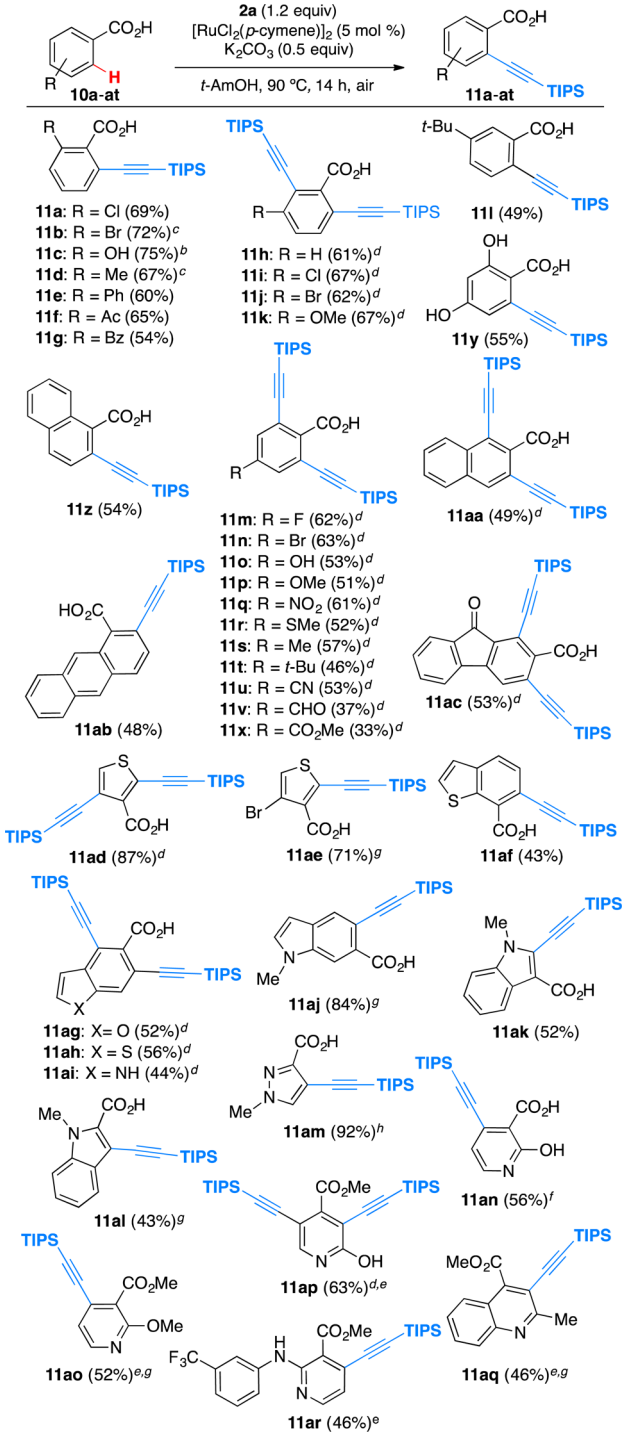
Scheme 3. Ruthenium-Catalyzed *Ortho* C−H Alkynylation of Benzoic Acids[a]

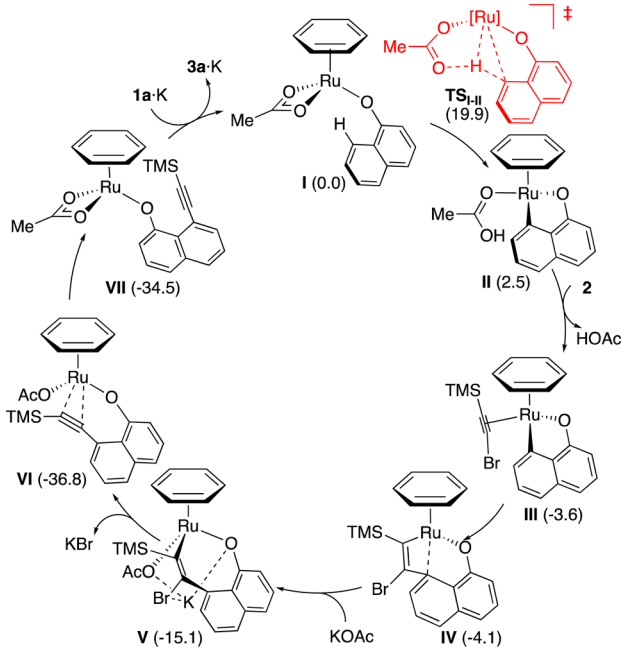


[a]Reaction conditions: **10a−at** (0.2 mmol), K_2CO_3 (0.5 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), **2a** (1.2 equiv), *tert*-amyl alcohol (1.5 mL), 90 °C, air, 14 h. [b]10 mmol scale. [c]70 °C. [d]**2a** (2.2 equiv) and K_2CO_3 (1.0 equiv) [e]MeI (5 equiv), K_2CO_3 (2 equiv), and MeCN added after 14 h. [f]120 °C and $KHCO_3$ (0.5 equiv) instead of K_2CO_3. [g]K_2CO_3 (1 equiv). [h]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 °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 rate-determining step,[13] which is supported by DFT calculations in the reaction of $[Ru(p\text{-cymene})(OAc)_2]$ with diphenylacetylene.[22] According to our DFT data, this is also the case for the *peri*-alkynylation reaction (Scheme 4).[18,23] Thus, **I** leads to

Scheme 4. Simplified Mechanism of the Ru-Catalyzed *Peri*-Alkynylation Based on DFT Calculations[a]



[a]Values in parentheses are free energies in kcal·mol^{-1} (T = 298.15 K)

ruthenacycle **II** by acetate-assisted C−H activation via $\mathbf{TS}_{\mathbf{I-II}}$ ($\Delta G^{\ddagger}$ = 19.9 kcal·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 kcal·mol^{-1}). Subsequent alkynylation proceeds via insertion to produce **IV** ($\Delta G^{\ddagger}$ = 13.5 kcal·mol^{-1}), which then undergoes KOAc-assisted bromide elimination from **V** with a minimal barrier of 0.5 kcal·mol^{-1} 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.[23]

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.

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■ ASSOCIATED CONTENT

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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