Ruthenium-Catalyzed Direct *ortho*-Alkynylation of Arenes with Chelation Assistance

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Abstract: The ruthenium-catalyzed direct alkynylation of arenes with the chelation assistance of nitrogen-containing heterocycles including pyridine, pyrimidine, pyrazole, and imidazole are described. The alkynylation is successful even in the presence of an acidic N–H bond. Broad compatibility with functional groups is observed under catalytic conditions. The obtained alkynylated products could serve as precursors for polycyclic heteroarenes.

Key words: ruthenium, alkyne, heteroarene, C–H activation, chelation

Transition-metal-catalyzed C–H bond activation–functionalization reactions are recognized as a straightforward method for the efficient and selective synthesis of the molecules used in the pharmaceutical, agrochemical, and material industries.[1] Despite significant progress in this field, there are far fewer methods for alkynylation via C–H bond activation[2] than for arylation, alkenylation, and alkylation reactions. Since Gevorgyan's pioneering work on the palladium-catalyzed alkynylation of N-fused heteroarenes,[3b] several catalytic alkynylation of heteroarenes have been developed using palladium,[3] nickel,[4] copper,[5] and gold[6] catalysts.[7] Our group reported the palladium-catalyzed alkynylation of arenes with the aid of chelation assistance.[8] Unactivated C(sp^3)–H bonds can also be alkynylated by installing a suitable directing group.[8b] Several catalytic methods that can effect alkynylation of electronically biased arenes have been developed.[9] Recently, Waser's group reported a *para*-selective alkynylation of aniline derivatives.[10] In this paper, we report the ruthenium-catalyzed C–H bond alkynylation of arenes using an N-heteroarene directing group.

As part of our continuing research on catalytic C–H alkynylation reactions, we intended expanding the scope of the reaction with respect to directing groups. In view of a plenty of precedents using pyridine-based directing groups in *ortho* C–H bond activation[1] as well as using the π-conjugated structure of interest in materials science, we decided to identify a catalytic system applicable to 2-phenylpyridines. Our initial attempts to use palladium-catalyzed conditions, which are effective for substrates bearing an amide-based director, to 2-(2-methylphenyl)pyridine (**1**) were unsuccessful (Table 1, entry 1).[8c] Next, we turned our attention to using ruthenium-based catalysts. One of the earliest examples of directed C–H bond functionalization was achieved using a ruthenium catalyst.[11] More recently, Inoue, Oi, Ackermann, Dixneuf, and others successfully used ruthenium catalysts in C–H bond functionalization reactions, such as arylations,[12a–o] alkenylations,[12a–c,p–s] alkylations,[12t–w] and others.[1h,12x–z] However, ruthenium-catalyzed C–H bond activation has never been applied to alkynylation reactions. Extensive screening of catalyst precursors revealed that the desired alkynylation was promoted by using $[RuCl_2(p\text{-cymene})]_2$ or $RuCl_2$(cod) (Table 1, entries 2 and 3). Other ruthenium complexes, including $RuCl_2(PPh_3)_2$, Cp*$RuCl_2$, and $Ru_3(CO)_{12}$ were less effective as catalysts (Table 1, entries 4–6). The use of PivOH and Cs_2CO_3 to form CsOPiv in situ[1h] also afforded the alkynylated product **3** without reducing the yield (Table 1, entry 7). We finally found that the use of **2** (1.5 equiv) and CsOPiv (1.5 equiv) at 100 °C afforded **3** in 74% yield (Table 1, entry 9).[13]

We next investigated the effect of the directing group under the optimized conditions (Table 2). A pyrimidine ring also promoted alkynylation to give the corresponding product **4** in good yield. A five-membered pyrazole directing group, as in **5**, was also applicable to this direct alkynylation. 2-(2-Methylphenyl)-1*H*-benzimidazole underwent alkynylation to form the corresponding product **6** with the NH group remaining intact. The yield was significantly decreased when oxazoline **7** and rigid benzo[*h*]quinoline **8** were employed.

The alkynylation of 2-phenylpyridine (**9**) gave a mixture of mono- and dialkynylated product **10** and **11** under the optimized conditions (Scheme 1). It was found that the second alkynylation occurred at an early stage of the reaction. Although selective formation of **10** was not possible with this substrate, the dialkynylated product **11** was obtained exclusively by simply increasing the amount of **2**.

In contrast, monoselective alkynylation was achieved using a bulkier 3-methypyridinyl directing group (Table 3, entry 1). The steric repulsion between the methyl group in pyridine and the introduced alkynyl moiety suppresses the second alkynylation.[14] Broad compatibility with various functional groups, including ether, amine, amide, ester, ketone, and fluorine groups (Table 3, entries 2–7), was observed. The alkynylation of **18** took place at the *ortho* po-

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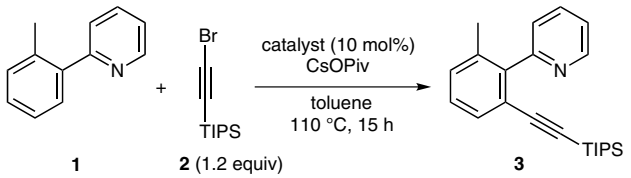
Table 1 Optimization of Catalytic Alkynylation of 2-Arylpyridine **1**[a]



1 **2** (1.2 equiv) **3**

Entry	Catalyst	Yield (%)
1	$Pd(OAc)_2$	<1
2[b]	$[RuCl_2(p\text{-cymene})]_2$	56
3	$RuCl_2(cod)$	53
4	$RuCl_2(PPh_3)_2$	24
5	Cp^*RuCl_2	17
6[c]	$Ru_3(CO)_{12}$	7
7[b,d]	$[RuCl_2(p\text{-cymene})]_2$	54
8[b,e]	$[RuCl_2(p\text{-cymene})]_2$	61
9[b,e,f]	$[RuCl_2(p\text{-cymene})]_2$	74

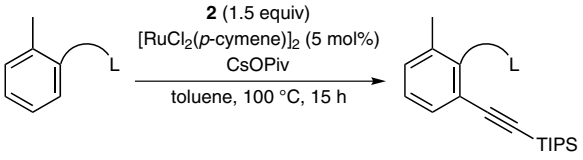
[a] Reaction conditions: 2-(2-methylphenyl)pyridine (**1,** 0.30 mmol), bromoalkyne **2** (0.36 mmol), catalyst (0.030 mmol), CsOPiv (0.30 mmol), toluene (1.0 mL), 110 °C, 15 h.
[b] Run using 5 mol% of catalyst.
[c] Run using 3 mol% of catalyst.
[d] Run using PivOH (0.30 mmol) and Cs_2CO_3 (0.15 mmol) instead of CsOPiv.
[e] Run at 100 °C.
[f] Run using **2** (0.45 mmol) and CsOPiv (0.45 mmol).

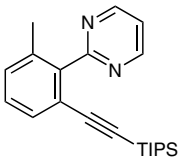
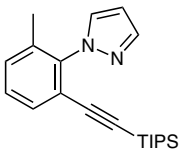
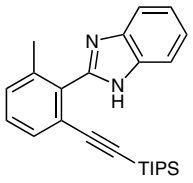
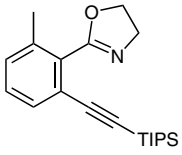
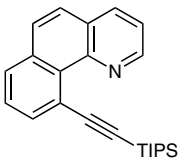
sition of the pyridine ring, not *ortho* to the acetamide group (Table 3, entry 4). This regioselectivity is in sharp contrast to the case of palladium-catalyzed direct alkynylation, in which the *ortho* C–H bond of an acetamide group was alkynylated selectively.[8a] Naphthalene (**26**) and thiophene (**28**) could serve as good substrates for this catalytic alkynylation (Table 3, entries 8 and 9).

When the alkynylation of 4,6-di(4-fluorophenyl)pyrimidine (**30**) was carried out, dialkynylated product **31**, in which two alkynes are incorporated in the same arene ring, was obtained in 50% yield, along with the trialkynylated product **32** in 11% yield (Scheme 2). The dialkynylated product **33** was not formed; this indicates that the second C–H bond cleavage was faster than the dissociation of the catalyst from the sp^2-nitrogen, as significant dialkynylation occurred in the reaction of **9** (Scheme 1).[15]

Although this method requires a bulky triisopropylsilyl-protected **2** as an alkynylating agent,[16] this silyl group is easily removed by treatment with TBAF, and the resultant terminal alkyne can be used for further elaboration. For example, the alkynylation of 2-(1-naphthyl)-1*H*-benzimidazole (**34**), followed by desilylative cyclization of **35** with TBAF gave the pentacyclic heteroarene **36** (Scheme 3).[17]

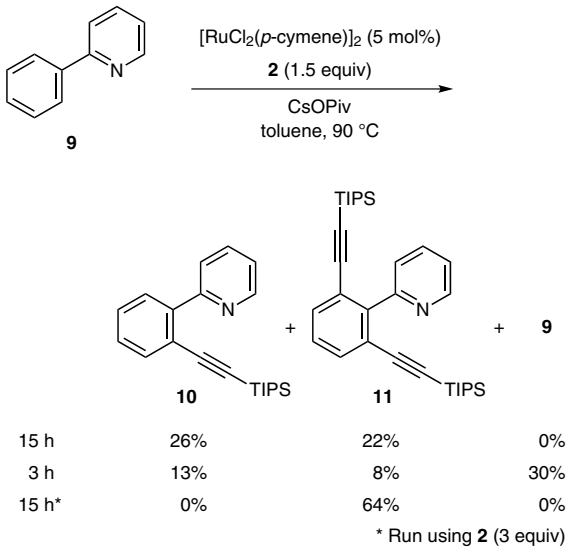
Table 2 Effect of Directing Groups[a]



Entry	Product	Yield (%)
1	 **4**	62[b]
2	 **5**	64
3	 **6**	74
4	 **7**	18[c]
5	 **8**	19[c]

[a] Reaction conditions: substrate (0.30 mmol), bromoalkyne **2** (0.45 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.015 mmol), CsOPiv (0.45 mmol), toluene (1.0 mL), 100 °C, 15 h.
[b] Run at 120 °C.
[c] Run at 130 °C.

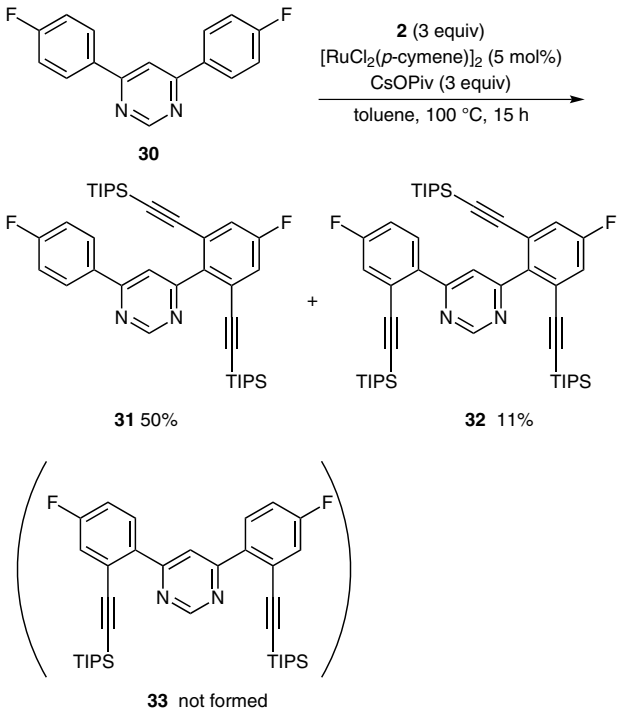
In summary, we have developed the first ruthenium-catalyzed C–H bond alkynylation of arenes with the aid of chelation assistance. In contrast to palladium-catalyzed direct alkynylation, a wide range of heteroarene-based directing groups are applicable. The method serves for the expansion of a π-conjugate system by introducing an alkyne moiety into heterobiaryl frameworks. Thus obtained alkynylated products can further be elaborated into a range of molecules, including condensed aromatic compounds.



15 h	26%	22%	0%
3 h	13%	8%	30%
15 h*	0%	64%	0%

* Run using **2** (3 equiv)

Scheme 1 Ruthenium-catalyzed direct alkynylation of 2-phenylpyridine **9** with bromoalkyne **2**

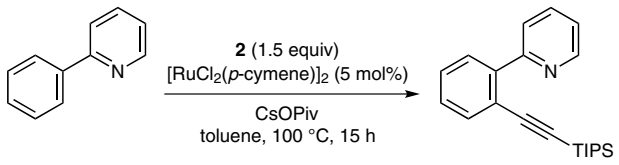


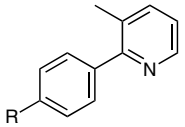
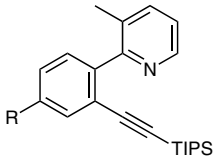
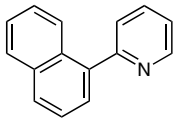
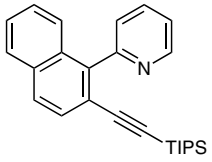
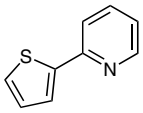
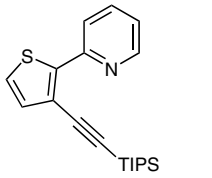
Scheme 2 Ruthenium-catalyzed direct alkynyaltion of 4,6-diarylpyrimidine **30** with bromoalkyne **2**

General Procedure

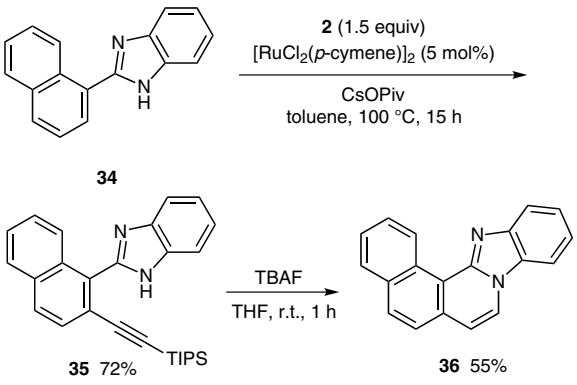
Ruthenium-Catalyzed Reaction of 1 with 2 (Table 1, Entry 9)
To an oven-dried 5 mL screw-capped vial, 2-(2-methylphenyl)pyridine (**1**, 51 mg, 0.30 mmol), (bromoethynyl)triisopropylsilane (**2**, 120 mg, 0.45 mmol), $[RuCl_2(p\text{-cymene})]_2$ (9.0 mg, 0.015 mmol), CsOPiv (110 mg, 0.45 mmol), and toluene (1.0 mL) were added under a gentle stream of nitrogen. The mixture was stirred for 15 h at 100 °C followed by cooling. The mixture was diluted with EtOAc (10 mL) and washed with NaOH aq (1 M, 2 × 10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, fil-

Table 3 Ruthenium-catalyzed direct alkynylation of 2-phenylpyridine **9** with bromoalkyne **2**[a]



Entry	Substrate	Product	Yield (%)
			
1	**12** R = H	**13**	65
2	**14** R = OMe	**15**	66
3[b]	**16** R = NMe_2	**17**	48
4	**18** R = NMeAc	**19**	74
5	**20** R = CO_2Me	**21**	68
6[b]	**22** R = COMe	**23**	57
7	**24** R = F	**25**	62
8[b]	 **26**	 **27**	48
9[c]	 **28**	 **29**	54

[a] Reaction conditions: as in Table 2 unless otherwise noted.
[b] Run at 90 °C.
[c] Run at 120 °C.



Scheme 3 Synthetic application

tered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane–EtOAc = 10:1) to afford the desired alkynylated product **3** (77 mg, 74%) as a colorless oil.

2-{2-Methyl-6-[(triisopropylsilyl)ethynyl]phenyl}pyridine (3)
^{1}H NMR (399.78 MHz, $CDCl_3$): δ = 0.90–0.94 (m, 21 H), 2.11 (s, 3 H), 7.22–7.26 (m, 3 H), 7.37–7.44 (m, 2 H), 7.72 (ddd, *J* = 7.8, 7.7, 1.9 Hz, 2 H), 8.67–8.69 (m, 1 H). ^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 111.05, 18.48, 20.10, 93.70, 105.78, 121.85, 122.80, 124.97, 127.68, 130.27, 130.34, 135.95, 136.35, 142.92, 149.21, 158.84. IR (neat): 3062 (m), 2943 (s), 2864 (s), 2148 (s), 1589 (s), 1462 (s), 1423 (s), 1383 (m), 1252 (m), 1020 (s), 993 (s), 883 (s), 789 (s), 748 (s). MS: *m/z* (%): = 349 (1) [M^+], 308 (13), 307 (48), 306 (100), 264 (15), 220 (21), 125 (29), 117 (20). HRMS: *m/z* calcd for $C_{23}H_{31}NSi$: 349.2226; found: 349.2227.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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