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Rh(III) and Ru(II)-Catalyzed Site-Selective C−H Alkynylation of Quinolones

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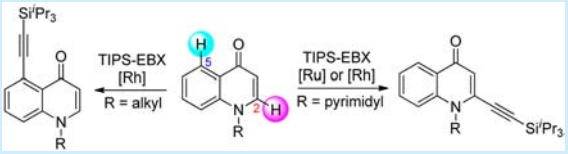
Supporting Information

ABSTRACT: C2- and C5-alkynylated quinolone scaffolds are core structures of numerous biologically active molecules. Utilizing TIPS-EBX as an alkynylating agent, we have developed an efficient and site-selective C5 alkynylation of 4-quinolones that is directed by the weakly coordinating carbonyl group. In addition, Ru(II) catalyzed C2-selective alkynylation was successfully realized via *N*-pyrimidyl group-directed cross-couplings to access valuable C2-alkynylated 4-quinolones. This strategy provides direct access to the C2 or C5 alkynylated 4-quinolones. Furthermore, the reaction was applied to isoquinolones for C3-selective alkynylation.

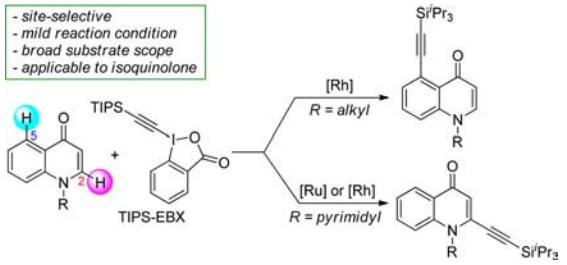


Quinolones constitute an important class of naturally occurring compounds[1] and privileged medicinal scaffolds.[2] The C2 alkynyl quinolone scaffolds are synthetically useful precursors and have been reported to be important constituents of biologically active compounds.[3] In addition, the C5 alkynyl quinolones have been reported to be key intermediates in the synthesis of aaptaminoid derivatives, which possess a wide range of pharmacological activity.[4] Consequently, the development of efficient and selective methods for the installation of alkynyl groups on the quinolones is a topic of considerable importance.

Alkynes are important structural subunits and versatile functional groups that can be transformed into a diverse range of chemical structures.[5,6] Considerable progress has been achieved in the field of direct C−H alkynylation.[7] Recently, alkynylation utilizing hypervalent iodine-alkyne reagents such as ethynylbenziodoxolones (EBX)[8] has provided powerful tools for the efficient installation of alkynyl groups on diverse privileged scaffolds.[6] Despite the successes reported thus far, the site-selective direct C−H alkynylation of 4-quinolones remains unsolved. We speculated that the coordination of the carbonyl group of 4-quinolones to the transition-metal catalyst would guide C−H alkynylation at the C5 position. In addition, the installation of a suitable director on the quinolone nitrogen atom might override the coordination of the carbonyl group and promote the direct C−H alkynylation at the 2-position of 4-quinolones. This strategy provides direct access to the C2- or C5-alkynylated 4-quinolone derivatives. Herein, we report the first example of C2 and C5 site-selective direct C−H alkynylation of 4-quinolones, which is broadly applicable to quinolone substrates and isoquinolone systems (Scheme 1).

To test the feasibility of this process in a 4-quinolone system, we initially investigated the optimization of the reaction using TIPS-EBX as an alkyne source with an *N*-benzyl-protected 4-quinolone substrate (**1a**) as a model substrate (Table 1). Our initial attempts at C−H alkynylation were not successful with Pd

Scheme 1. Site-Selective C−H Alkynylation of Quinolones



catalytic systems (entries 1−3). A ruthenium catalyst was considerably less effective in this coupling, and only a trace amount of alkynylated derivative **2a** (entry 4) was observed. More promising results were obtained using the Rh(III) complex, which exclusively afforded a C5-alkynylated product (37%), thus highlighting the favorable coordination effect of the carbonyl group to the Rh catalyst (entry 5). Encouraged by this preliminary result, an intensive screening of the reaction media with the rhodium(III) complex was conducted with the goal of optimizing the reaction for C5 alkynylation. The addition of $AgSbF_6$ led to increased yields (entries 6, 7). Among the Rh species screened, $[RhCp^*(MeCN)_3(SbF_6)_2]$ was the most effective in promoting the coupling reactions without any additives. The attempts at C−H alkynylation using other alkynylation reagents failed to provide the desired products under the catalytic systems. A systematic investigation of catalytic systems that were more reactive was conducted by testing various solvents and temperatures, which led to the establishment of optimized conditions involving the treatment of the $[RhCp^*(MeCN)_3(SbF_6)_2]$ (5 mol %) in toluene at 80 °C with an excellent yield of 81% (entry 9).

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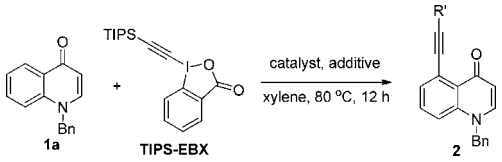
Table 1. Optimization of C5-Selective C−H Alkynylation of 4-Quinolones[a]

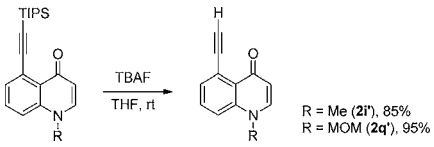


entry	catalyst (mol %)	additive (mol %)	yield (%)[b]
1[c]	$[Pd(MeCN)_4(BF_4)_2]$ (10)	–	NR
2	$[Pd(OAc)_2]$ (10)	–	NR
3	$[Pd(OAc)_2]$ (10)	$Cu(OAc)_2$ (200)	NR
4	$[Ru(p\text{-cymene})Cl_2]_2$ (4)	$Zn(OTf)_2$ (16)	trace
5	$[RhCp^*Cl_2]_2$ (4)	$Zn(OTf)_2$ (16)	37
6[d]	$[RhCp^*Cl_2]_2$ (4)	$AgSbF_6$ (16)	72
7	$[RhCp^*Cl_2]_2$ (4)	$AgSbF_6$ (16)	75
8	$[RhCp^*(MeCN)_3(SbF_6)_2]$ (10)	–	59
9	**$[RhCp^*(MeCN)_3(SbF_6)_2]$ (5)**	–	**81**
10	$[RhCp^*(MeCN)_3(SbF_6)_2]$ (2.5)	–	65

[a]Reaction conditions: quinolone (**1a**, 0.1 mmol), TIPS-EBX (1.1 equiv), catalyst, additive in xylene (1 mL) at 80 °C for 12 h under air. [b]Isolated yields. [c]CH_2Cl_2:H_2O (2:1) used as a solvent. [d]$ClCH_2CH_2Cl$ was used as a solvent.

With the optimized reaction conditions in hand, we then explored the scope and generality of this method with a variety of quinolones, as summarized in Scheme 2. In general, a wide range of quinolone derivatives are compatible with the present catalytic system, providing the corresponding C5 alkynylation products in moderate to good yields. *N*-Benzyl 4-quinolones bearing bromo (**2b**), iodo (**2c**), ester (**2d**, **2n**, **2o**), and imide groups (**2m**) at the C3 position readily reacted to afford the corresponding C5-alkynylated derivatives. Interestingly, the size and electronic properties of the substituents at the C-6 position had little influence on the reaction efficiency (**2e**−**2g**). In addition, the *N*-substituents of quinolone were flexible to include benzyl, methyl, ethyl, cyclopropyl, and MOM groups under the reaction conditions. Acridone is also a viable substrate for obtaining only a monoalkynylated product, which is likely a result of the steric repulsion of the resulting bulky TIPS group (**2p**).

The resulting alkynylation products underwent desilylation with TBAF to afford **2i**′ and **2q**′ with excellent yields (eq 1).

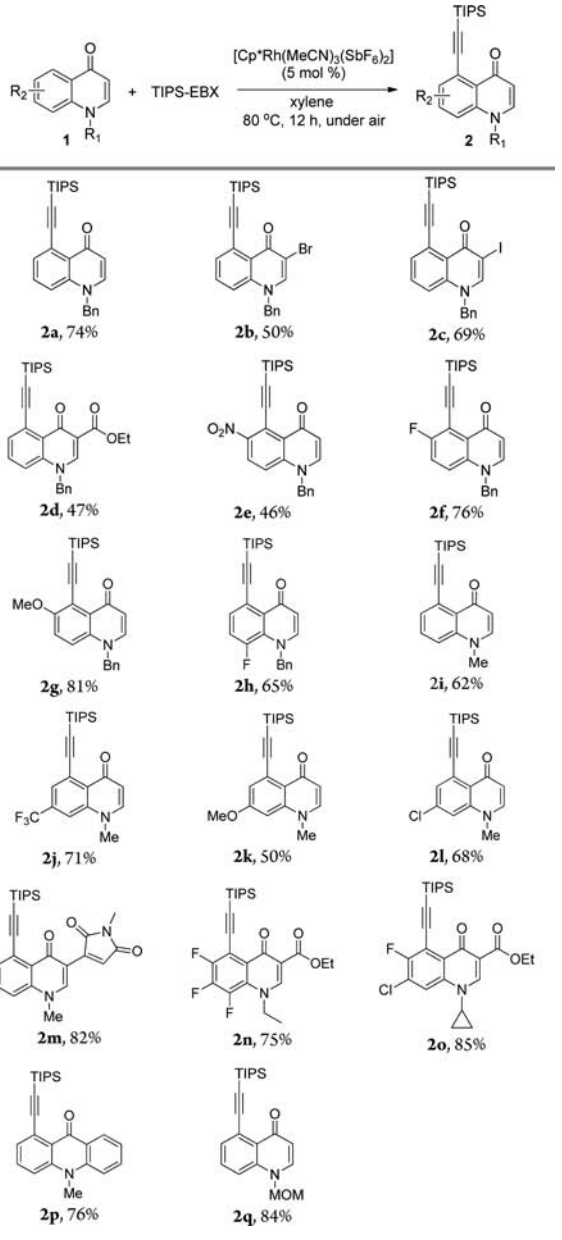


(1)

To showcase the applicability of the developed method, this protocol was employed as a straightforward synthetic route to aaptaminoid derivatives. Thus, derivative **2q** was conveniently prepared by the Rh-catalyzed C5-selective alkynylation of 4-quinolone. Next, the oxygenated aaptaminoid derivative **2qa** was obtained via 5-exo-dig cyclization, thus allowing the rapid construction of aaptaminoid derivatives[3a] from 4-quinolone in a total yield of 61% over 2 steps, as outlined in Scheme 3.[9]

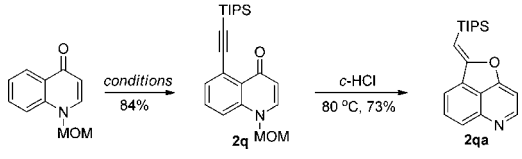
To obtain mechanistic insight into the present C5 alkynylation, deuterium-labeling experiments were performed under the standard conditions (eq 2). A significant primary kinetic isotope effect (KIE) was observed for the C5 alkynylation reactions of 4-quinolone and its deuterated derivative (k_H/k_D =

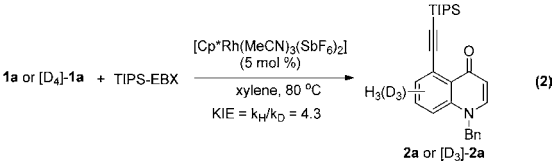
Scheme 2. Rh(III)-Catalyzed C5-Selective C−H Alkynylation of 4-Quinolones[a]



[a]Reaction conditions: quinolone (1, 0.1 mmol), TIPS-EBX (1.1 equiv), $[RhCp^*(MeCN)_3(SbF_6)_2]$ (5 mol %) in xylene at 80 °C for 12 h under air; isolated yields.

Scheme 3. Synthesis of Oxygenated Aaptaminoid Derivatives





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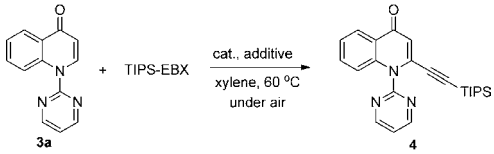
4.3). The KIE value suggested that C−H bond cleavage would be involved in the turnover-limiting step in the reactions.[10]

Next, we hypothesized that the installation of a suitable director on the quinolone nitrogen atom might override the coordination of the carbonyl group and promote the direct alkynylation at the 2-position of 4-quinolones. To test these hypotheses, we began our studies by investigating C2-selective alkynylation with *N*-pyrimidyl 4-quinolone (**3a**), as summarized in Table 2. Gratifyingly, the *N*-pyrimidyl moiety[11] was a viable

Table 2. Optimization of C2-Selective C−H Alkynylation of 4-Quinolones[a]



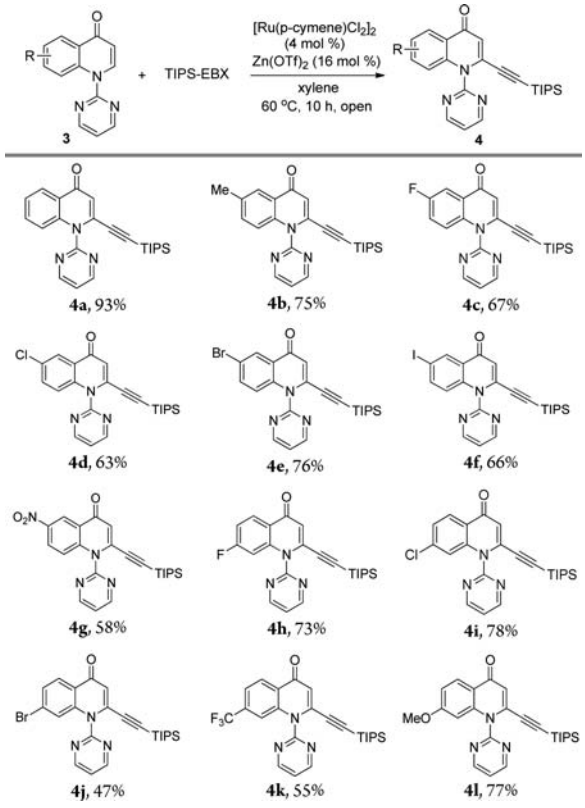
entry	catalyst (mol %)	additive (mol %)	temp (°C)	yield (%)[b]
1	$[RhCp^*Cl_2]_2$ (4)	$AgSbF_6$ (16)	60	47
2	$[RhCp^*Cl_2]_2$ (4)	$Zn(OTf)_2$ (20)	60	74
3	$[RhCp^*Cl_2]_2$ (4)	$Zn(OTf)_2$ (20)	80	85
4[c]	$[RhCp^*Cl_2]_2$ (4)	$Zn(OTf)_2$ (20)	80	84
5	$[RhCp^*(MeCN)_3(SbF_6)_2]$ (5)	–	80	71
6	$[Ru(p\text{-cymene})Cl_2]_2$ (4)	$AgSbF_6$ (16)	60	37
7	$[Ru(p\text{-cymene})Cl_2]_2$ (4)	Ag_2CO_3 (16)	60	trace
8	$[Ru(p\text{-cymene})Cl_2]_2$ (4)	$AgNTf_2$ (16)	60	61
9	$[Ru(p\text{-cymene})Cl_2]_2$ (4)	AgOTf (16)	60	89
10[d]	$[Ru(p\text{-cymene})Cl_2]_2$ (4)	$Zn(OTf)_2$ (16)	60	93
11	$[Ru(p\text{-cymene})Cl_2]_2$ (4)	$Zn(OTf)_2$ (16)	80	75

[a]Reaction conditions: quinolone (**3a**, 0.1 mmol), TIPS-EBX (1.1 equiv), catalyst (4 mol %), additive, xylene (1.5 mL), 60 °C, 10−15 h under air. [b]Isolated yield. [c]Under N_2. [d]Open to air conditions.

directing group for successfully inducing C−C bond formation exclusively at the C2 position, indicating the pivotal role of the directing effect of the 2-pyrimidyl group to the Rh(III) center (entries 1−5). Although $[RhCp^*Cl_2]_2$ was optimal for the C2-selective alkynylation (85%, entry 3), further exploration using ruthenium catalysts was performed due to the high cost of $[RhCp^*Cl_2]_2$. Notably, comparable reactivity was observed when the ruthenium catalyst was employed in place of the rhodium catalyst. Encouraged by this result, an intensive screening of the Ru(II) catalytic systems was conducted with the goal of optimizing the reaction for C2 alkynylation. To the best of our knowledge, this is the first example of Ru(II)-catalyzed alkynylation with hypervalent alkynyl iodine reagents. Screening of the additives showed Lewis acid additives such as $Zn(OTf)_2$ to be the optimal choice, and the use of basic additives, such as Ag_2CO_3 or $AgNTf_2$, was ineffective (entries 6−9). Several solvents were also evaluated, and the use of xylene as the solvent was necessary to achieve a higher conversion. The reaction was finally achieved with an excellent yield of 93% by applying an open flask system (entry 10). Remarkably, no C-5 alkynylation reaction was detected with the *N*-pyrimidyl substrate, thus showing the extremely high regioselectivity.

We next examined the scope of the C2-selective alkynylation reaction, as summarized in Scheme 4. Halogens such as fluoride,

Scheme 4. Ru(II)-Catalyzed C2 Selective C−H Alkynylation of 4-Quinolones[a]



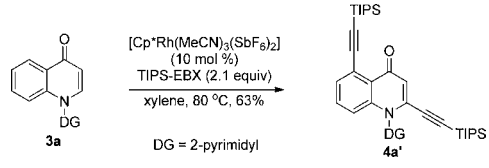
[a]Reaction conditions: quinolone (3, 0.1 mmol), TIPS-EBX (1.1 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %) in xylene at 60 °C for 10 h under open to air conditions; isolated yields.

chloride, bromide, and iodide were all tolerated under the ruthenium catalytic system (**4c−4f**, **4h−4j**), thus providing the opportunity for further transformations. Both electron-donating (Me− and OMe−) and electron-withdrawing groups (F−, Cl−, Br−, CF_3−, and NO_2) on the 4-quinolone scaffold were viable under the reaction conditions to afford the corresponding C2-alkynylated products.

Because C2 alkynylation also performed well with a rhodium catalyst, we explored the potential of the one-pot catalytic reactions as a more efficient synthetic route to obtain C2 and C5 functionalized quinolones. Indeed, we were delighted to observe that the one-pot C2/C5-alkynylation process was facile in the presence of a rhodium catalyst and TIPS-EBX, affording the dialkynyl quinolone **4a′** in 63% yield (Scheme 5).

To expand the reaction utility further, we next explored the potential applicability of the present procedure to isoquinolone

Scheme 5. One-Pot Catalytic C2/C5 C−H Alkynylation of 4-Quinolones



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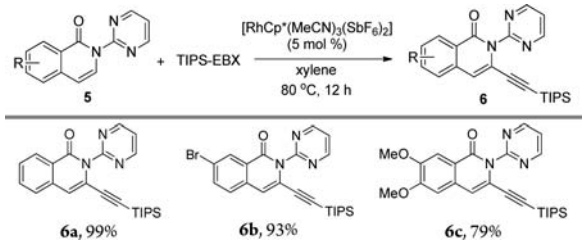
core **5**, as functionalization of isoquinolones is important because of the resulting biological activity.[12] We were delighted to observe that the alkynylation of isoquinolones **5** occurred exclusively at the C3 position in excellent yield under the rhodium catalytic system (Scheme 6). As expected, substrates bearing bromo (**6b**) or dimethoxy groups (**6c**) were alkynylated at the C3 position, thereby affording the corresponding alkynylated products.

Scheme 6. Rh(III)-Catalyzed C3-Selective C−H Alkynylation of Isoquinolones[a]



[a]Reaction conditions: quinolone (**5**, 0.1 mmol), TIPS-EBX (1.1 equiv), $[RhCp^*(MeCN)_3(SbF_6)_2]$ (5 mol %) in xylene at 80 °C for 12 h; isolated yields.

In summary, we have developed an efficient and site-selective C5 alkynylation of 4-quinolones that is directed by the carbonyl group. This method provided a straightforward synthetic route to aaptaminoid derivatives, thus allowing the rapid construction of aaptaminoid derivatives. In addition, the Ru(II) catalyzed C2-selective alkynylation reaction was successfully realized via the *N*-pyrimidyl group-directed cross-couplings to access valuable C2-alkynylated 4-quinolones. The present reactions exhibited a broad range of substrate scope and were successfully applied to the C3-selective alkynylation of an isoquinolone scaffold.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of new compounds (^1H and ^{13}C NMR spectra). 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.

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