Organic LETTERS

Letter

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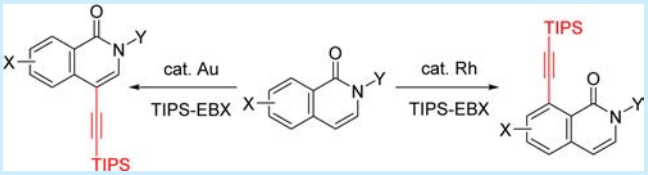
Gold vs Rhodium Catalysis: Tuning Reactivity through Catalyst Control in the C−H Alkynylation of Isoquinolones

Aslam C. Shaikh, Dinesh R. Shinde, and Nitin T. Patil*

Division of Organic Chemistry, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune 411008, India
Academy of Scientific and Innovative Research (AcSIR), New Delhi 110025, India

Supporting Information

ABSTRACT: A site-selective C-4/C-8 alkynylation of isoquinolones catalyzed by gold and rhodium complexes is reported. A broad range of synthetically useful functional groups (−F, −Cl, −Br, $-CF_3$, −OMe, alkyl, etc.) were tolerated, providing an efficient and robust protocol for the synthesis either C-4- or C-8-alkynylated isoquinolones.

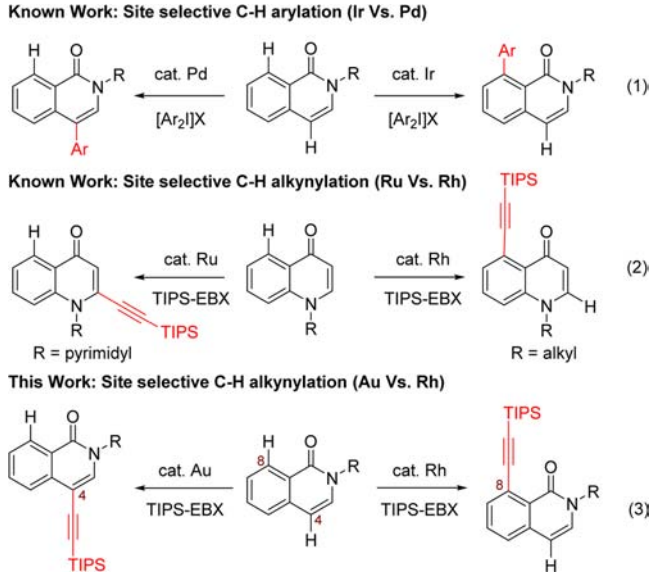


Isoquinolone is a privileged structural motif widely found in natural products and biologically valuable compounds.[1] Consequently, tremendous efforts have been devoted to the effective synthesis and functionalization of isoquinolones. Over the past few decades, transition-metal-catalyzed C−H functionalization has emerged as an attractive, economical, and environmentally benign alternative to the classical synthetic methods, allowing the expeditious formation of diverse isoquinolones.[2] In particular, the direct C−H functionalization of isoquinolones has witnessed great success for late-stage modification of the preexistent quinolone scaffolds.

Hirano and Miura, for the first time, reported a copper-mediated C6-selective heteroarylation of 2-pyridones in which the observed site selectivity was directed by a pyridyl substituent on the nitrogen atom of the isoquinolone ring.[3] Recently, Hong and co-workers reported an efficient catalytic system for the *N*-pyrimidyl group directed C-2 selective C−H alkenylation of 4-quinolones using a decarbonylative coupling strategy.[4] Very recently, pioneering work from Hong's laboratory revealed an interesting example of catalyst-controlled site selective C−H arylation of isoquinolone using aryliodonium salts as the coupling partners (Scheme 1, eq 1).[5] Recently, the site-selective direct alkynylation of quinolones was reported by them (Scheme 1, eq 2).[6] The key for the success of this reaction was the use of appropriate group placed at nitrogen atom of quinolones. We were particularly interested in the introduction of an alkyne[7] in the isoquinolones, as alkynes are a key functional group for many organic transformations. Herein, we describe a site-selective C-4/C-8 alkynylation of isoquinolones enabled by gold and rhodium complexes (Scheme 1, eq 2). Based on Hong's report (Scheme 1, eq 1)[5] and our continued interest in the exploration of molecular diversity through catalyst control,[8] we speculated that C-4 selectivity can be achieved with the use of electrophilc metal catalysts while the C-8 selectivity is expected when metal catalyst capable of coordinating the carbonyl group causing C8−H activation is employed.

Our initial investigation focused on the reaction of *N*-methylisoquinolone (**1a**) and 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX) (**2**), which was first reported by Waser in the alkynylation of indoles with gold or palladium catalysis[9] and further applied to Rh(III)- or Ir(III)-catalyzed C−H alkynylation by Li,[10] Loh,[11] and Glorius.[12] When *N*-methylisoquinolone (**1a**) was treated with TIPS-EBX in the presence of $AuCl_3$/AuBr in DCE at 25 °C, the desired C4-alkynylation product **3a** was not obtained at all; starting material was recovered in a quantitative amount (Table 1, entries 1 and 2). Pleasingly, **3a** was obtained in 54% yield when AuCl was used as catalyst (entry 3). The reaction worked with a broad range of solvents (entries 3−6); however, more promising results were obtained in the case of dry CH_3CN. The product **3a** was isolated

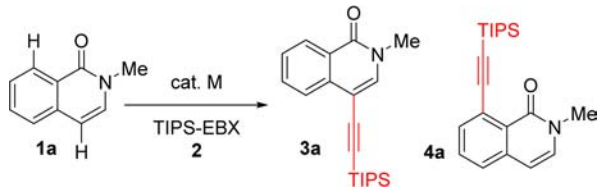
Scheme 1. Site-Selective C−H Functionalization of Isoquinolones: Known and Present Work



Received: January 19, 2016
Published: February 17, 2016

DOI: 10.1021/acs.orglett.6b00175
Org. Lett. 2016, 18, 1056−1059

Table 1. Optimization Studies[a]



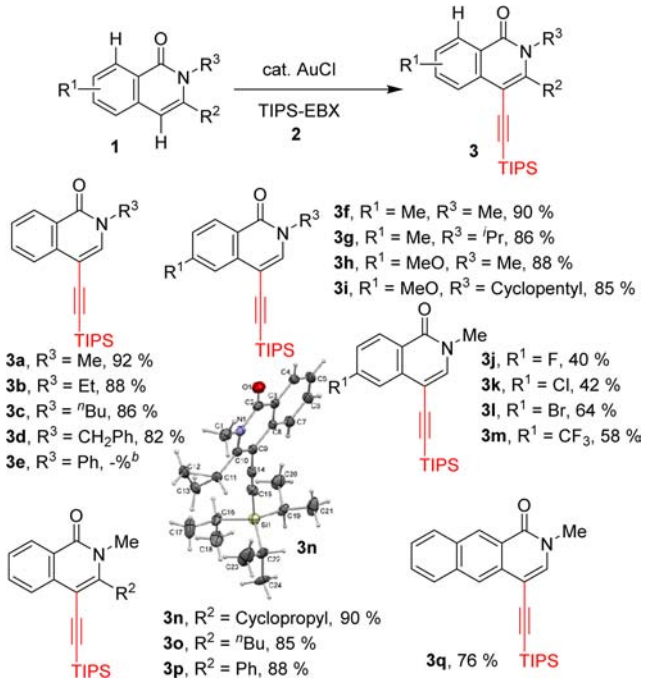
entry	cat.	additives	solvent	temp (°C)	yield[b] (%) 3a	4a
1	$AuCl_3$		DCE	25	trace	
2	AuBr		DCE	25		
3	AuCl		DCE	25	54	
4	AuCl		Et_2O	25	64	
5	AuCl		$CHCl_3$	25	74	
6	AuCl		CH_3CN	25	81	
7	AuCl		CH_3CN	50	92	
8	$[RhCp^*Cl_2]_2$		DCE	25		trace
9	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$	DCE	25		trace
10	$[RhCp^*Cl_2]_2$	$Zn(OTf)_2$	DCE	25		trace
11	$[RhCp^*Cl_2]_2$	AgOAc	DCE	25		13
12	$[RhCp^*Cl_2]_2$	$AgSbF_6$	DCE	25		44
13	$[RhCp^*Cl_2]_2$	$AgSbF_6$	DCE	50		62
14	$[RhCp^*Cl_2]_2$	$AgSbF_6$	DCE	80		88[c]

[a]Reaction conditions: (1) 0.15 mmol of **1a**, 0.18 mmol of **2**, 10 mol % of catalyst, dry solvent (2.0 mL), 24 h (entries 1−7); (2) 0.15 mmol of **1a**, 0.18 mmol of **2**, 2.5 mol % of $[RhCp^*Cl_2]_2$, 5 mol % of additives, dry DCE (2.0 mL), 16 h (entries 8−14). [b]Isolated yields. [c]10 mol % of $AgSbF_6$ was used.

in 92% yield at 50 °C when reaction was run for 24 h. Interestingly, in none of the cases was C8-alkynylation product **4a**. In the search for a catalytic system suitable for obtaining **4a**, we screened various catalysts capable of affecting chelation-assisted C−H activations. Although there exist a number of reports on the C−H functionalization using heteroatom as directing groups, very few reports exist where carbonyl (or amide carbonyl) groups have been used as directing groups.[13] Hence, rhodium catalysts in combination with metal salts have been examined at 25 °C (entries 8−10); however, the formation of **4a** was not observed. Interestingly, AgOAc, a popular additive for $[RhCp^*Cl_2]_2$ catalyzed C−H activation reactions, gave **4a**, albeit in 13% yield (entry 11). Switching the additive from AgOAc to $AgSbF_6$ increased the yield of **4a** up to 44% (entry 12). With an increase in the temperature up to 50 °C, **4a** was obtained in 62% yield (entry 13). A significant improvement in yield was noticed when the amount of $AgSbF_6$ was increased up to 10 mol % and the temperature up to 80 °C (entry 14, 88%).

With the optimized reaction conditions in hand, the scope of the reaction was examined with various isoquinolones. As shown in Table 2, C-4 selective alkynylation of isoquinolones proceeded well to give the desired products irrespective of substitution patterns on the phenyl ring. Both electron-donating and -withdrawing substituents, such as methyl (**3f** and **3g**), methoxy (**3h** and **3i**), fluoro (**3j**), chloro (**3k**), bromo (**3l**), and trifluoromethyl (**3m**), were compatible, providing alkynylisoquinolones in moderate to good yields. It should be noted that *N*-phenyl-substituted isoquinolones were unsuccessful in yielding the desired coupling products under the present reaction conditions (**3e**) probably because of the lower nucleophilicity. Interestingly, introduction of a substitution at C-2 position of isoquinolones did not hamper the outcome of the reaction, and

Table 2. Gold-Catalyzed C-4 Alkynylation[a]



[a]Reaction conditions: 0.15 mmol of **1a**, 0.18 mmol of **2**, 10 mol % of AuCl, dry CH_3CN (2.0 mL), 50 °C, 24 h. [b]No product formation, starting material recovered. [c]Isolated yields are given.

3n−p were obtained in excellent yields (85−90%). In addition, the C−H alkynylation reaction is readily found to proceed with structurally related benzoisoquinolone substrate to give the desired alkynylation product **3q** in 76% yield.

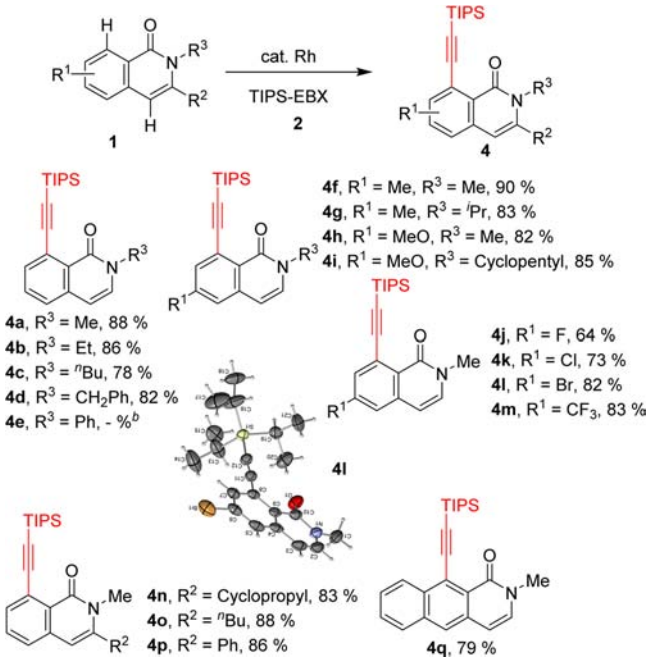
We next examined the scope of the C-8-selective alkynylation reaction. As shown in Table 3, isoquinolone bearing halogen as well as electron-donating and -withdrawing groups in the phenyl ring underwent smooth reaction with TIPS-EBX (**2**) to obtain the corresponding C-8 alkynylation products in good yields. The C-2-substituted isoquinolones were also found to be good substrates affording the corresponding products in good yields (**4n−p**, 85−90%). Similarly, when the benzoisoquinolone substrate was submitted to the optimal reaction conditions, the product **4q** was isolated in 79% yield.

Next, we endeavored to achieve C-4/C-8 dialkynylation in a stepwise as well as in a one-step fashion (Scheme 2). Thus, when **3a** was treated with standard rhodium catalysis, product **5** was obtained in 75% yield. Similarly, the treatment of **4a** with standard gold catalysis conditions afforded **5** in 48% yield. Interestingly, dialkynylation product **5** could also be obtained in a one-pot fashion under Au/Rh relay catalysis,[14] albeit in 32% yield.

On the basis of the Au-mediated alkynylation of indole, as reported by Waser[9d] and proven theoretically by Ariafard,[15] the proposed mechanism for C-4 selective C−H alkynylation is given in Scheme 3. At first, the coordination of AuCl to the triple bond of TIPS-EBX **2** would take place to form gold−alkyne complex **6**. The gold−alkyne complex **6** would readily convert into vinyl−gold complex **7** via isoquinolone metalation followed by α/β-elimination followed by 1,2-shift depending on the regioselectivity of the addition. Other mechanisms triggered by the oxidative addition of Au(I) within the C−I bond cannot be ruled out.[9g] Regarding C-8-selective C−H alkynylation, the catalytic cycle could start from $[RhCp^*Cl_2]_2$ (I). The first event would be

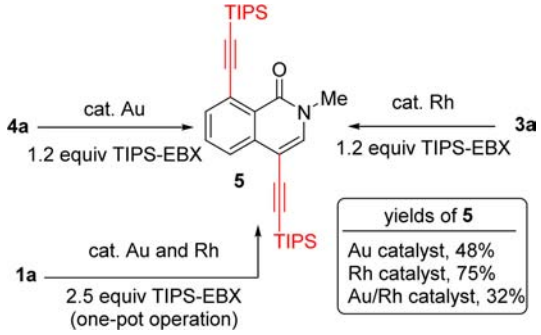
DOI: 10.1021/acs.orglett.6b00175
Org. Lett. 2016, 18, 1056−1059

Table 3. Rhodium-Catalyzed C-8 Alkynylation[a]



[a]Reaction conditions: 0.15 mmol of **1a**, 0.18 mmol of **2**, 2.5 mol % $[RhCp^*Cl_2]_2$, 10 mol % of $AgSbF_6$, dry DCE (2.0 mL), 80 °C, 16 h. [b]Reaction shows complex mixture of products. [c]Isolated yields are given.

Scheme 2. Dialkynylation of Isoquinolones

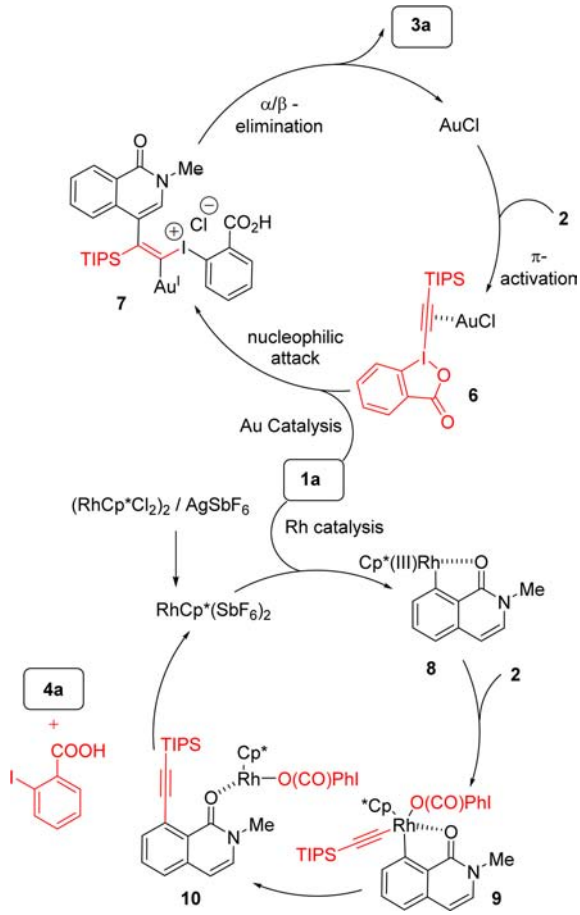


the coordination of catalyst to **1a** followed by C−H activation. This process could be the rate-determining step and may follow a concerted metalation/deprotonation pathway leading to intermediate **8** as reported by Glorius and co-workers.[12] Next, the acetylene may coordinate to Rh(III) to yield intermediate **9**. From this point, insertion of acetylene in the Rh−C bond can occur to give intermediate **10**, which would finally lead to the formation of **4a** with the regeneration of Rh catalyst.[11a]

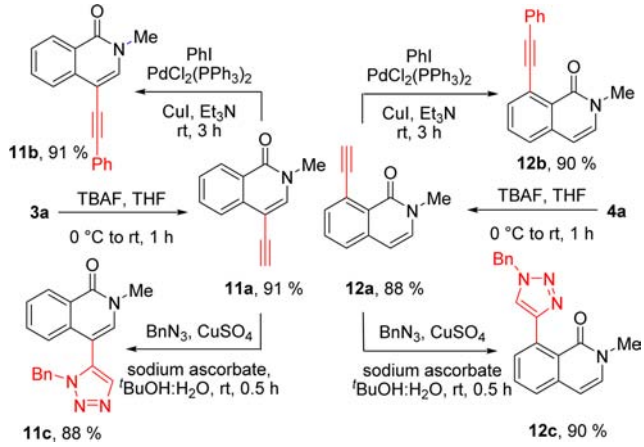
To demonstrate the synthetic utility of alkynylated products, a few interesting organic transformations of **3a** and **4a** were carried out (Scheme 4). The deprotection of the TIPS group in **3a** and **4a** was achieved with TBAF to obtain terminal alkynes **11a** and **12a** in 91 and 88% yield, respectively. The terminal alkynes **11a**/**12a** were then subjected to Sonogashira reactions and copper-catalyzed azide−alkyne cycloadditions to afford **11b**/**12b** and **11c**/**12c**.

In summary, we developed site-selective (C-4 vs C-8) C−H alkynylation of isoquinolones catalyzed by gold and rhodium catalysts. The silyl-protecting groups could be easily removed to give terminal alkynes, a functional handle for many organic transformations.

Scheme 3. Plausible Mechanism



Scheme 4. Utility of Products



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00175.

Experimental procedures, analytical data, and ^1H and ^{13}C NMR spectra of all newly synthesized products (PDF)
X-ray data for **3n** (CIF)
X-ray data for **4l** (CIF)

DOI: 10.1021/acs.orglett.6b00175
Org. Lett. 2016, 18, 1056−1059

AUTHOR INFORMATION

Corresponding Author

*E-mail: n.patil@ncl.res.in.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Generous financial support by the Department of Science and Technology (DST), New Delhi (Grant No. SB/S1/OC-17/2013) and the Council of Scientific and Industrial Research (CSIR), New Delhi (Grant Nos. CSC0108 and CSC0130) is gratefully acknowledged. A.C.S. thanks CSIR for the award of an SPM Fellowship.

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DOI: 10.1021/acs.orglett.6b00175
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