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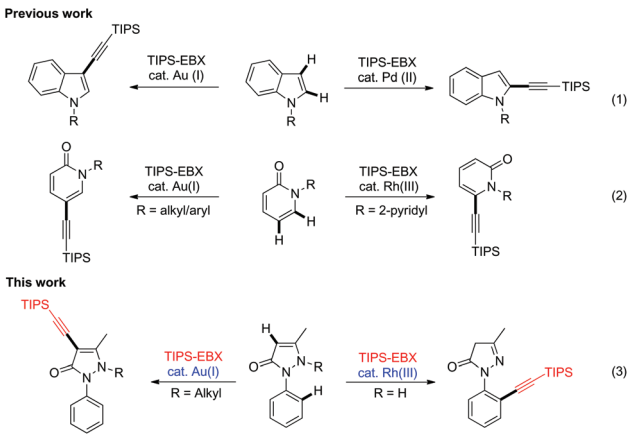
Gold(I)- and rhodium(III)-catalyzed formal regiodivergent C–H alkynylation of 1-arylpyrazolones†

Xueli Wang, [a,b] Xingwei Li, [b] Yao Zhang *[a] and Lixin Xia *[a]

Formal regiodivergent C–H alkynylation of 1-aryl-5-pyrazolones has been realized under the catalysis of Rh(III) and Au(I) complexes by using a hypervalent iodine reagent as the alkyne source. Mechanistic studies indicate that the regioselectivity is ascribed to not only the choice of the catalyst but also the nature of the substrate. The substrate scope and functional group compatibility have been fully examined.

Pyrazolones and their derivatives are important structural moieties that are widely used in the synthesis of pharmaceuticals,[1] biologically active compounds,[2] and natural products.[3] Therefore, enormous efforts have been devoted to effective synthesis of pyrazolones.[4] Over the past several decades, transition metal-catalyzed C–H activation has emerged as an atom- and step-economic, environmentally friendly, and benign alternative to the classical synthetic methods.[5] On the other hand, the alkynylation of arenes represents an important method to access arylalkynes.[6] Although it is highly desirable to realize the oxidative alkynylation of arenes using 1-alkynes owing to the high atom-economy and ready availability of such alkynes, this has only been sporadically realized due to competitive homocoupling of terminal alkynes.[7] Consequently, alkynylation using a versatile electrophilic alkynylating reagent may serve to solve this challenge. Thus, silylethynyl-1,2-benziodoxol-3(1*H*)-one (silyl-EBX) which was introduced by Zhdankin has recently risen to prominence as an efficient alkynylating reagent.[8] In particular, Waser and co-workers demonstrated the functionalization of various electron-rich heterocycles such as indoles, pyrroles, and furans using TIPS-EBX with Au(I) or Pd(II) being a catalyst under relatively mild synthetic conditions (Scheme 1, eqn (1)).[9] Quite recently, Loh, our group, Glorius, and others have significantly broadened the scope of C–H alkynylation of arenes by resorting to a C–H activation strategy using stable Rh, Co, Ru and Ir catalysts.[10] In 2014, the Yu group realized an effective alkynylation of ethers using this alkynylating reagent through radical C(sp^3)–H bond functionalization under metal-free reaction conditions.[11] In addition, in 2016 Waser also reported the thrifty oxyalkynylation of diazo compounds under mild conditions using an inexpensive copper catalyst.[12]

Despite the impressive progress, the selective alkynylation of a specific C–H bond remains a major challenge. Ideally, the selectivity is controllable by way of different catalytic conditions. In this regard, the *ortho*- and *para*-selective alkynylation of anilines using AuCl as a catalyst and TIPS-EBX as an electrophilic alkynylation equivalent has been accomplished. This selectivity was dictated by a mechanism containing a directing effect of the nitrogen functional group.[13] The C2- or C3-selective alkynylation of indoles and other heterocycles has also been achieved under different reaction conditions.[14] In 2016, our group and Patil have independently reported the site-selective alkynylation of 2-pyridones and isoquinolones under complementary Au(I) and Rh(III) catalyzed conditions using this alkynylating reagent (Scheme 1, eqn (2)).[15] With our ongoing interest in site-selective C–H bond functionalization



Scheme 1 Metal-catalyzed site-selective alkynylation.

[a]*College of Chemistry, Liaoning University, Shenyang 110036, China*
[b]*Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China. E-mail: lixinxia@lnu.edu.cn, zhangyao@lnu.edu.cn*

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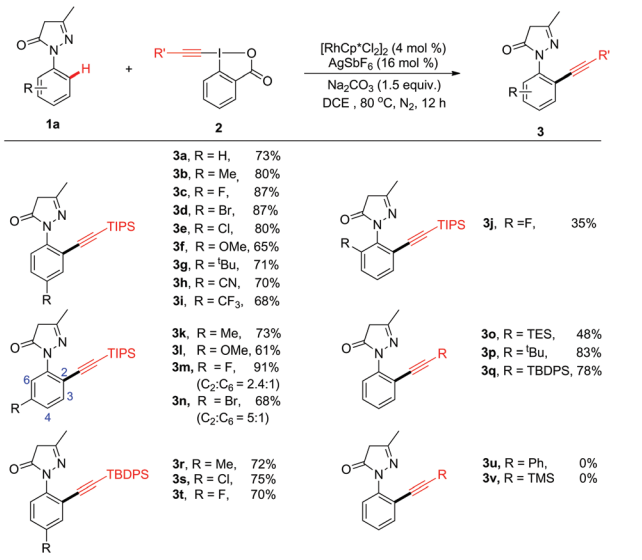
and the importance of pyrazolones in organic synthesis, we herein report on the Au(I)- and Rh(III)-catalyzed formal regiodivergent C–H alkynylation of pyrazolones (Scheme 1, eqn (3)).

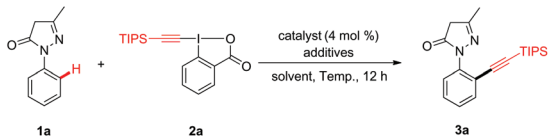
We reasoned that 1-phenyl-1*H*-pyrazol-5-one contains a phenyl group that is prone to C–H activation when assisted by the pyrazolone nitrogen coordination.[16] In addition, this heterocycle is also intrinsically reactive in a number of electrophilic functionalization reactions.[17] We initiated our studies by optimizing the reaction conditions of the coupling of 3-methyl-1-phenyl-1*H*-pyrazol-5-one (**1a**) with TIPS-EBX (**2a**), and the results are summarized in Table 1. As for the catalyst, Rh(III) catalysts were our first choice since they have proven highly efficient in catalytic C–H alkynylation.[10e,15] When $[RhCp^*Cl_2]_2$ was employed as a catalyst and $AgSbF_6$ as a halide abstractor, the desired product **3a** was obtained in 65% yield at 80 °C (entry 1). The cationic rhodium catalyst $[RhCp^*(MeCN)_3](SbF_6)_2$ and the $[IrCp^*Cl_2]_2/AgSbF_6$ catalyst led to slightly lower yields (entries 2 and 3). Effects of the reaction temperature were then examined, and couplings at both 50 °C and 100 °C gave inferior results (entries 4 and 5). We also tested the effect of acid and base additives. To our delight, the isolated yield of **3a** was improved to 73% in the presence of Na_2CO_3 (entry 6). Lewis acid additive, such as $Zn(OTf)_2$, led to lower efficiency (entry 9), which stands in contrast to our previous studies.[10e,15b]

With the optimized conditions in hand, we next examined the scope and generality of this catalytic system (Scheme 2). 3-Methyl-1-aryl-1*H*-pyrazol-5-one bearing both electron-donating and -withdrawing groups at the *para* position reacted smoothly to afford the desired products in moderate to good yields (**3b–3i**), although the introduction of an EWG tends to attenuate the yields (**3h** and **3i**). It is noteworthy that easily functionalizable halogen groups were well tolerated (**3c–3e**). The introduction of an *ortho*-fluoro group was also tolerated,



Scheme 2 Rh(III)-Catalyzed C–H activation assisted by pyrazolone. Reaction conditions: 2-Aryl-3-pyrazolone (0.20 mmol), silyl-EBX (0.24 mmol), $[RhCp^*Cl_2]_2$ (4 mol%), $AgSbF_6$(16 mol%), Na_2CO_3 (0.3 mmol), DCE (2.0 mL), 80 °C, 12 h, pressure tube, under nitrogen. Isolated yield after column chromatography.

Table 1 Optimization studies[a]

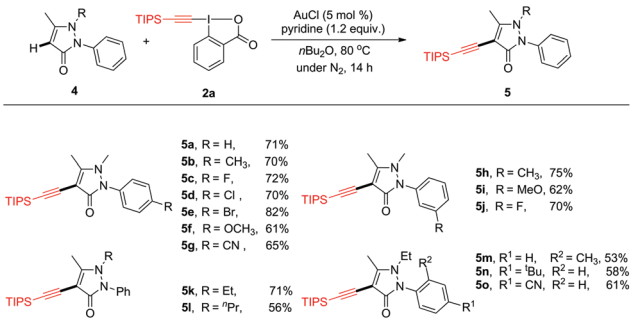


Entry	Catalyst	Additive	T (°C)	Yield[b] (%)
1	$[RhCp^*Cl_2]_2/AgSbF_6$	—	80	65
2	$[IrCp^*Cl_2]_2/AgSbF_6$	—	80	43
3[c]	$[RhCp^*(MeCN)_3](SbF_6)_2$	—	80	63
4	$[RhCp^*Cl_2]_2/AgSbF_6$	—	50	60
5	$[RhCp^*Cl_2]_2/AgSbF_6$	—	100	50
6	**$[RhCp^*Cl_2]_2/AgSbF_6$**	**Na_2CO_3**	**80**	73
7	$[RhCp^*Cl_2]_2/AgSbF_6$	Pyridine	80	<5
8	$[RhCp^*Cl_2]_2/AgSbF_6$	Li_2CO_3	80	50
9	$[RhCp^*Cl_2]_2/AgSbF_6$	$Zn(OTf)_2$	80	42

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.24 mmol), catalyst (4 mol%), $AgSbF_6$ (16 mol%) and additive (1.5 equiv.) in a solvent (2.0 mL) at 50–100 °C under N_2 for 12 h. [b] Isolated yield after column chromatography. [c] $[RhCp^*(MeCN)_3](SbF_6)_2$ (8 mol%) was used as a catalyst.

delivering **3j** in 35% yield. The *meta*-Me and -OMe groups were also compatible, and the coupling occurred at the less hindered *ortho* position (**3k** and **3l**). However, the coupling of a *meta* bromo- or fluoro-substituted arene gave a mixture of regioisomeric products in good to high combined yields and in 2–5 : 1 regioselectivity (**3m–3n**). The alkynylating reagents were successfully extended to TBDPS-EBX, TES-EBX and ^{t}Bu-EBX (**3o–3t**). As has been previously observed,[15b] TMS- and Ph-EBX either failed to participate in this reaction or reacted in poor efficiency (**3u** and **3v**), likely due to the lack of steric protection.[10e,15b]

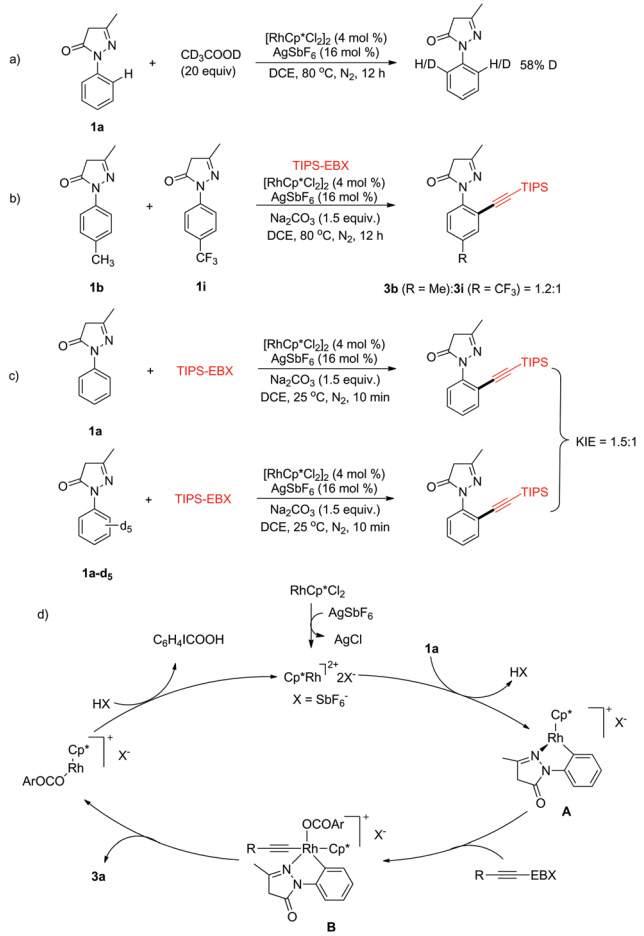
We reasoned that when the N-directing effect is overruled by the electronic effect of the heterocycle, the alkynylation may be achieved at the most electron-rich C4 position of the heterocycle *via* an electrophilic alkynylation pathway. The alkynylation of 2,3-dimethyl-1-aryl-5-pyrazolone (**4**) with TIPS-EBX (**2a**) was then explored using a gold catalyst. Indeed, after extensive screening, the coupling of 2,3-dimethyl-1-aryl-5-pyrazolone with TIPS-EBX proceeded smoothly at 80 °C, and the desired product **5a** was obtained in 71% yield when catalyzed by AuCl (Scheme 3). The C4-selectivity was fully confirmed by ^{1}H and ^{13}C NMR analyses of the product.[18] We then moved on to investigate the scope of this coupling reaction. The derivatives of 2,3-dimethyl-1-aryl-5-pyrazolone bearing various electron-donating and electron-withdrawing substituents, such as halogen (**5c–5e**, **5j**), methyl (**5b**, **5h**), and CN (**5g**) groups, at the *para* or *meta* position of the aryl ring all underwent smooth coupling without significant variation in the isolated yields (61%–82%). In contrast, the aryl ring with a *para* or *ortho* OMe (**5f**, **5i**) group gave rather low conversion, indicating that a *para* electron-donating group lowered the reactivity. Besides, *N*-ethyl



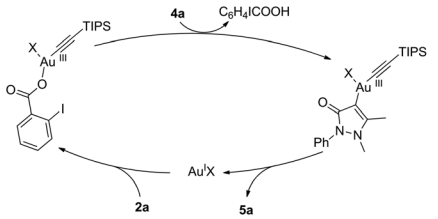
Scheme 3 Au-Catalyzed C4-alkynylation of *N*-alkyl pyrazolone. Reaction conditions: 2-Aryl-3-pyrazolone (0.20 mmol), TIPS-EBX (0.24 mmol), AuCl (5 mol%), pyridine (0.24 mmol), $^{n}Bu_2O$ (2.0 mL), 80 °C, 14 h, under nitrogen. Isolated yield after column chromatography.

and -propyl groups were also compatible (**5k–5o**), although slightly lower yields were isolated due to steric hindrance.

A series of experiments were conducted to investigate the reaction mechanism (Scheme 4). H/D exchange experiment was performed between **1a** and CD_3COOD under the Rh(III)-catalyzed conditions. Deuteration was detected at both *ortho*



Scheme 4 Mechanistic consideration of Rh(III)-catalyzed alkynylation.



Scheme 5 Mechanistic consideration under Au-catalyzed conditions.

positions of the benzene ring, indicating the reversibility of the C–H cleavage in the absence of any coupling partner (Scheme 4a). In addition, a competition reaction using TIPS-EBX and two electronically differentiated compounds **1b** and **1i** afforded the corresponding products **3b** and **3i** in a ratio of 1.2 : 1, suggesting that an electron-rich arene exhibited slightly higher reactivity (Scheme 4b). The measurement of kinetic isotope effect (KIE) was performed to further understand the C–H activation process. A relatively small value KIE = 1.5 : 1 was obtained from two parallel reactions (Scheme 4c), which suggested that the C–H bond cleavage was not involved in the turnover-limiting step. On the basis of previous literature and our experimental studies,[10e] we proposed a plausible mechanism involving the formation of rhodacycles (Scheme 4d). Initially, the formation of $[Cp^*RhCl_2]$ *via* ligand substitution and chelation-assisted C–H activation of **1a** leads to a rhodacycle intermediate **A**, followed by oxidative addition of the C–I bond of silyl-EBX to generate a Rh(v) alkynyl benzoate intermediate **B**. Subsequent C–C reductive elimination gives the alkynylated product **3a** along with a Rh(III) benzoate intermediate **C**. Finally, the protonolysis of **C** regenerates the Rh(III) catalyst and releases the 2-iodobenzoate coproduct.[10e]

On the other hand, the H/D exchange (D 50%) of **4a** was observed at the C(4) position of the pyrazolone moiety when the reaction was carried out under the Au(I)-catalyzed conditions as shown in Scheme 3 by using CD_3COOD as a deuterium source (Fig. S1 in the ESI†). This surely suggests the relevancy of electrophilicity at this position. Therefore, a plausible mechanism, which involves an Au(I)/Au(III) cycle, has been proposed as a working hypothesis (Scheme 5). The oxidative addition of Au(I) with R-EBX leads to the formation of the Au(III) alkynyl intermediate, which then undergoes an electrophilic arylation. Next, the reductive elimination affords the final product and regenerates the Au(I) catalyst to complete the catalytic cycle.[15b]

Conclusions

In summary, we have developed a formal regiodivergent C–H alkynylation of different 2-aryl-3-pyrazolones catalyzed by rhodium and gold catalysts. The regioselectivity depends on the nature of the substrate, as well as the choice of the transition metal catalyst. Under the catalysis of Rh(III), the alkynylation occurred at the aryl ring with the assistance of an

N-chelation group. The Au-catalyzed C4-selective alkynylation of pyrazolones proceeded *via* an electrophilic pathway. Future studies are directed to the regiodivergent functionalization of other heteroarenes *via* metal-catalyzed C–H activation.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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