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Rhodium(III)-Catalyzed C-H Alkynylation of Azomethine Ylides Under Mild Conditions

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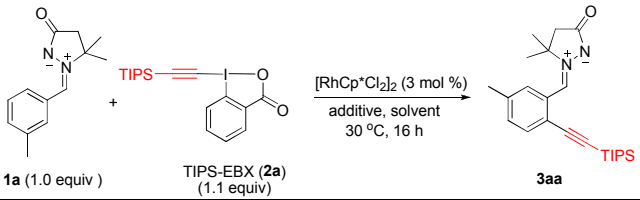
Rh(III)-catalyzed efficient C-H alkynylation of azomethine imines with alkynylated hypervalent iodine has been developed under mild conditions. A broad scope of azomethine imines and alkyne substrates has been established. The azomethine acts as a masked aldehyde and circumvents its poor directing effect.

Alkynes are one of the most versatile fundamental building blocks in synthetic chemistry owing to their diversified applications in synthetic chemistry and in material studies.[1] Therefore introduction of alkynyl functionality has attracted increasing attention. The most reliable and commonly adopted method for the introduction of alkynyl functionality is probably the Sonogashira coupling.[2] However, it is more desirable and attractive to take advantage of the abundance of C-H bonds in arenes by undertaking a transition-metal-catalyzed C-H activation strategy. While transition metal-catalyzed C-H activation has been extensively explored over the past decade,[3] C-H alkynylation remain lagged behind. Yamaguchi and co-workers reported the first example of C-H alkynylation of electron-rich arenes using chloroalkynes in 2002.[4] The C-H alkynylation of heterocycles was first reported by Gevorgyan using palladium catalysis.[5] In 2009, Chatani and co-workers described palladium-catalyzed *ortho* C-H alkynylation of acetanilide with bromoalkynes.[6] And C-H alkynylation of 2-phenylpyridines with haloalkynes have also been achieved by Chatani.[7] Although C-H alkynylation using a terminal alkyne under oxidative conditions would be highly desirable, only a narrow scope of heteroarenes have been developed via C-H/C-H oxidative coupling.[8] To expand the substrate scope, Waser and co-workers have systematically applied 1-silylethynyl-1,2-benziodoxol-3(*1H*)-ones (silyl-EBXs) as a versatile and powerful electrophilic alkyne reagent for C-H alkynylation of electron-rich aromatic substrates such as indoles, pyrroles, furans, thiophene and anilines using gold and palladium catalysts.[9] Very recently, our group[10] and other groups[11] have independently reported rhodium(III)-catalyzed C-H alkynylation using hypervalent iodonium reagents. Interestingly, we found that $[IrCp^*Cl_2]_2$ was also a suitable catalyst for this transformation.[10]

We recently reported with one example the coupling of an azomethine with TIPS-EBX under unoptimized conditions (80 °C),[10] we felt that the reaction might proceed under even mild conditions because of the high donating ability of the azomethine directing group in C-H activation reactions.[12] Importantly, the coupled product can undergo facile removal of this DG via simple hydrolysis, leading to *ortho*-alkynylated aldehydes, which have found wide application in synthetic chemistry.[13] This represents an indirect process for C-H alkynylation of aryl aldehydes, and has circumvented the issue of poor directing ability of an aldehyde functionality.[14] Therefore it is necessary to expand the scope of this reaction.

Table 1. Optimization of the reaction conditions[a]



1a (1.0 equiv) TIPS-EBX (**2a**) (1.1 equiv) **3aa**

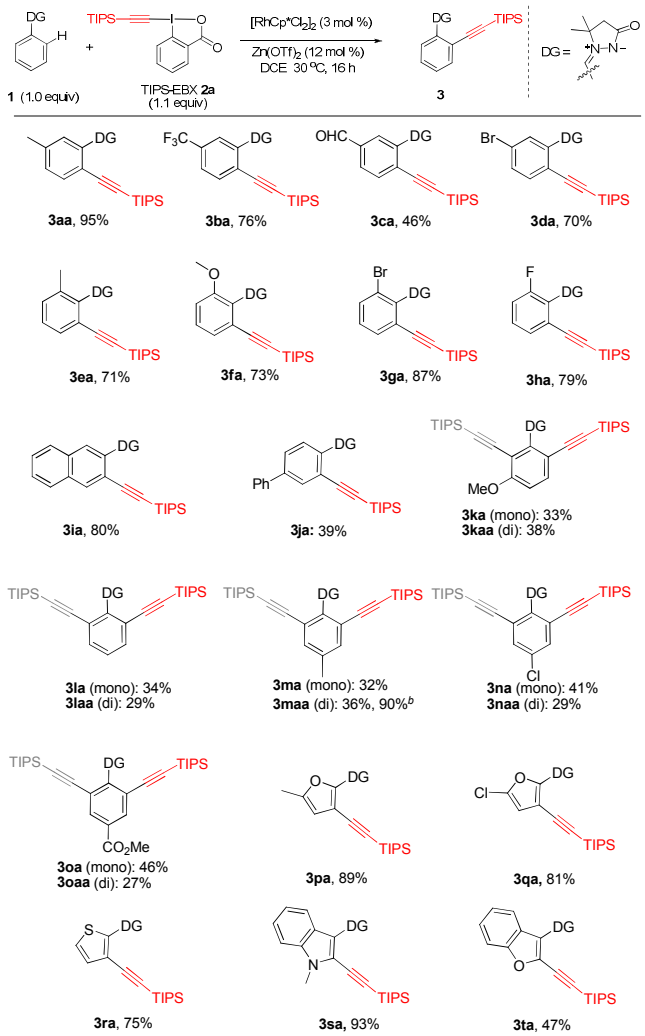
entry	additive (mol %)	solvent	yield (%)
1	none	DCE	nd
2	$AgSbF_6$ (12)	DCE	79
3	$Ca(OTf)_2$ (12)	DCE	58
4	$Cu(OTf)_2$ (12)	DCE	70
5	$Hg(OTf)_2$ (12)	DCE	72
6	$Al(OTf)_3$ (12)	DCE	24
7	$Zn(OTf)_2$ (12)	DCE	95
8	$Zn(OTf)_2$ (12)	DCM	38
9	$Zn(OTf)_2$ (12)	MeOH	31
10	$Zn(OTf)_2$ (12)	1,4-dioxane	35

[a] Reaction conditions: azomethine (0.2 mmol), TIPS-EBX (0.22 mmol), $[RhCp^*Cl_2]_2$ (0.006 mol), additive (0.024 mmol), solvent (2

mL), 30 °C, 16 h, under argon. Isolated yield after column chromatography.

We initiated our studies with the screening of the conditions in the coupling of 3-tolyl azomethine (**1a**) with TIPS-EBX (**2a**) in the presence of a rhodium catalyst. Azomethine **1a** was selected to ensure mono-alkynylation due to the steric blocking of one of the *ortho* positions (Table 1). It was found that 30 °C can warrant high coupling efficiency when a suitable Lewis acid additive was employed. Consistent with our previous findings, a synthetically useful yield of **3aa** was reached when $AgSbF_6$ was employed as an additive (entry 2), and replacement by $Zn(OTf)_2$ afforded **3aa** in excellent yield, where DCE was established as the optimal solvent. The Lewis acidity of the $Zn(OTf)_2$ additive may play a dual role by both activating the alkynylating reagent and the rhodium catalysts via reversible removal of the chloride ligand. Other triflate additive proved to be less efficient (entries 3 - 6). Thus under the mild optimal conditions, product **3aa** was isolated in 95% yield (entry 7).

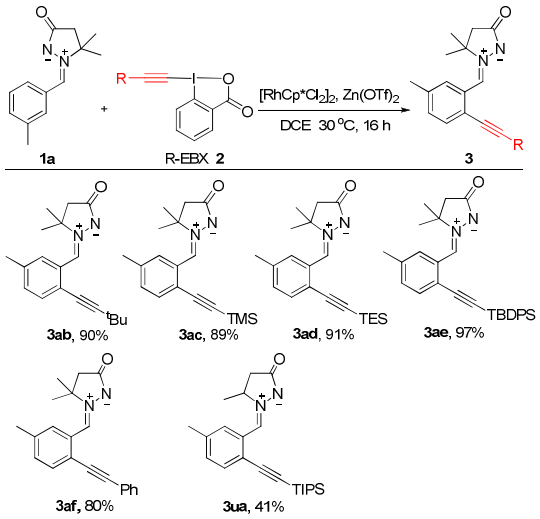
Scheme 1. Mild coupling of azoemthines with TIPS-EBX[a]



[a] Reaction conditions: azomethine **1** (0.2 mmol), TIPS-EBX **2a** (0.22 mmol), $[RhCp^*Cl_2]_2$ (0.006 mol), $Zn(OTf)_2$ (0.024 mmol), DCE (2 mL), 30 °C, 16 h, under argon. Isolated yield after column chromatography. [b] TIPS-EBX **2a** (0.42 mmol) was used, T=50 °C.

The scope and generality of this coupling were next explored. Azomethines bearing an electron-donating, -withdrawing, and halogen group at the *meta* position of the benzene ring all coupled smoothly with TIPS-EBX. In most cases mono-alkynylation was realized, and the product was isolated in 46-95% yield, where the reaction occurred selectively at the less hindered position, and an electron-withdrawing *meta* substituent tends to give lower yield. In contrast, both mono- and di-alkynylation products were isolated in similar yields for an azomethine bearing a 3-methoxy group as a result of reduced steric bulkiness of this group (**3ka** and **3kaa**). Introduction of different types of *ortho* substituents into the benzene ring is well-tolerated and the products were isolated in consistently good to high yield, indicative of tolerance of steric hindrance at the *ortho* position (**3ea**-**3ha**). The coupling of azomethines bearing a *para* substituent posed complication of mono- versus di-alkynylation. Under the optimal conditions, both mono- and di-alkynylation products were isolated in comparable yields even though the azomethine substrate was used in slight excess. The yield of a dialkynylation product was readily improved by controlling the stoichiometry of the coupling partners. Thus **3maa** was isolated in 90% when an excess (2.1 equiv) of TIPS-EBX was used at a slightly higher temperature. Significantly, the azomethine substrate is not limited to that derived from a benzaldehyde, and those bearing a heteroaryl ring such as furan, thiophene, and indole all underwent smooth coupling in moderate to high yields under the optimal conditions (**3pa**-**3ta**).

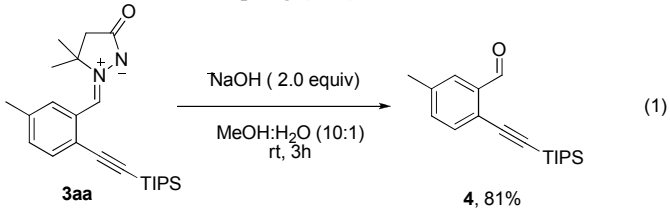
Scheme 2. Coupling using other alkynylating reagents and DGs[a]



[a] Reaction conditions: azomethine (0.2 mmol), R-EBX (0.22 mmol), $[RhCp^*Cl_2]_2$ (0.006 mol), $Zn(OTf)_2$ (0.024 mmol), DCE (2 mL), 30 °C, 16 h, under argon. Isolated yield after column chromatography.

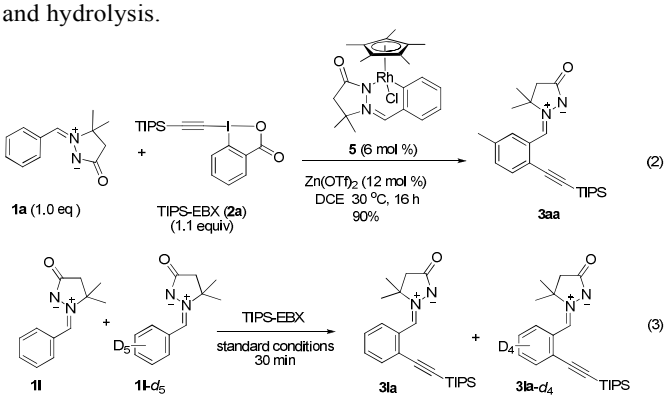
The coupling partner is not restricted to TIPS-EBX. Variation of the alkynylating reagent to those bearing different alkynyl substituents has little influence, and the product was isolated in consistently high yield. Significantly, when Ph-EBX was employed, the alkynylation product was also isolated in high yield (**3af**). This stands in contrast to previous reports where bulky alkynyl substituents are necessary for efficient coupling.[10,11] In addition to using azomethine bearing a gem-

dimethyl group, omission of one of the methyl groups led to a much less efficient coupling (**3ua**).



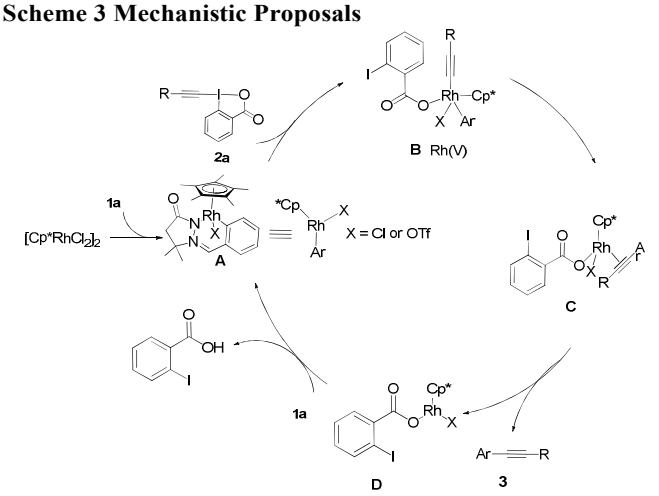
(1)

The directing group in the coupled product can be readily cleaved as demonstrated in the simple hydrolysis of **3aa** under basic conditions (eq 1), under which the silyl group remains intact. This result indicates that the current method offers an efficient process for the C-H alkynylation of benzaldehyde via a sequence of DG installation (condensation), C-H alkynylation, and hydrolysis.



Several experiments have been performed to probe the mechanism. To explore the relevancy of C-H activation, a cyclometalated Rh(III) complex (**5**) was prepared[12b] and was designated as a catalyst in the presence of $Zn(OTf)_2$. Under these conditions, the coupling of **1a** and **2a** afforded the product in 90% yield (eq 2), a yield comparable to that of the catalytic system using $[RhCp^*Cl_2]_2$. In addition, a small amount of **3laa** was also detected as a result of the functionalization of the chelating ligand in complex **5**. Since C-H activation is very likely involved, KIE was next studied. An intermolecular competitive coupling between azomethines derived from benzaldehyde and benzaldehyde-d_5 at a low conversion afforded a mixture of isotopologues. ^{1}H NMR analyses revealed a KIE value of 3.8, and this suggests that C-H activation is probably involved in the rate-limiting step.

Scheme 3 Mechanistic Proposals



Given the relevance of the azomethine and the 2-phenylpyridine substrates and our previous mechanistic studies on the alkynylation of the 2-phenylpyridine system, a plausible mechanism has been proposed to account for this transformation (Scheme 3). Cyclometalation of an azomethine affords a rhodacyclic intermediate, and subsequent oxidative addition of the hypervalent iodine reagents leads to the formation of a Rh(V) alkynyl intermediate. C(sp^2)-C(sp) reductive elimination furnishes the coupled product together with the formation of a Rh(III) benzoate intermediate, protonolysis of which regenerates the active Rh(III) catalyst and closes the catalytic cycle.

Conclusions

In summary, we have examined the rhodium-catalyzed C-H alkynylation of azomethines under rhodium catalysis. A broad scope of azomethine substrates has been established, and the coupling occurred under mild conditions with high efficiency for azomethines bearing various aryl and heteroaryl rings under assistance of an *ortho* directing group. In most cases, mono-alkynylation was observed when a *meta* blocking group was introduced into the arene ring. In contrast, both mono- and di-alkynylartion products were generated when both *ortho* positions are sterically accessible. Preliminary mechanistic studies have been performed and this coupling reaction can provide a method for the *ortho* C-H alkynylation of aryl aldehydes, and may find applications in the synthesis of related structures.

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Notes and references

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† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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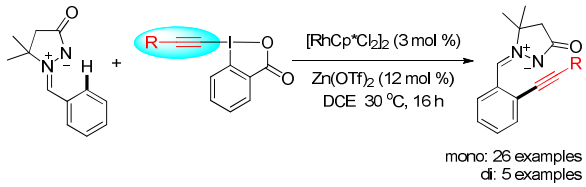

Rh(III) complexes cam catalyzed the *ortho* C-H alkynylation of azomethine imine, which acts as a masked aldehyde group.