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Rhodium-Catalyzed Azide-Alkyne Cycloaddition of Internal Ynamides: Regioselective Assembly of 5-Amino-triazoles under Mild Conditions

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ABSTRACT

A rhodium-catalyzed azide-alkyne cycloaddition of internal yanmides was described. The reaction could be carried out in a wide range of solvents, including aqueous media, under mild condition without careful exclusion of air and moisture, giving a variety of 5-amino-triazoles as single regio-isomer. The mechanism for the regioselective cycloaddition was rationalized by means of DFT calculations.

KEYWORDS

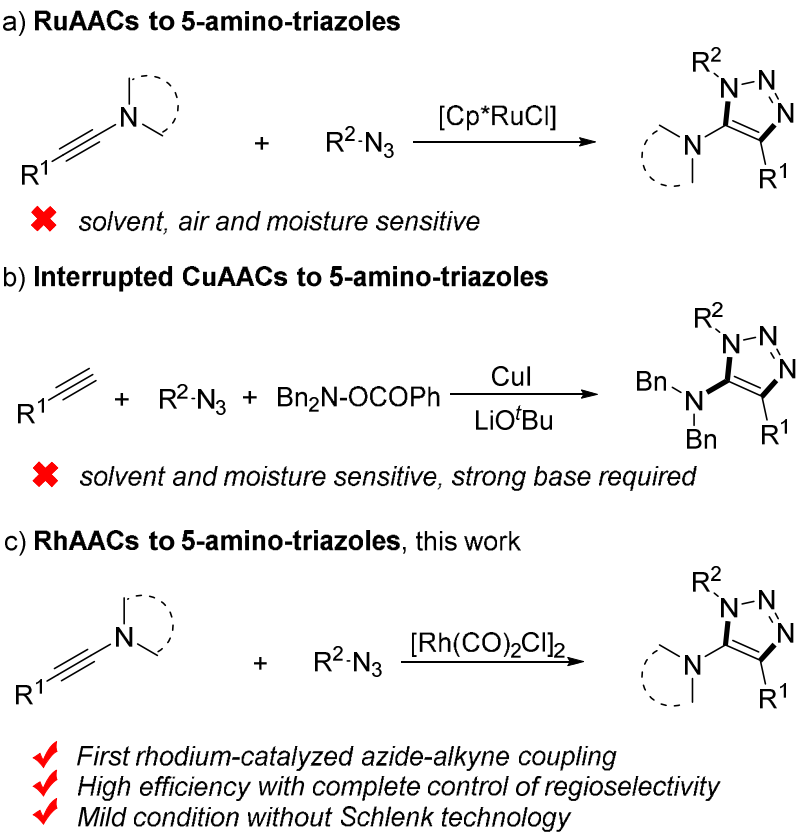
Click reaction, rhodium catalyst, azide-alkyne cycloaddition, ynamide, 5-amino-triazoles.

Introduction

1,2,3-Triazoles have emerged as versatile N-heterocyclic compounds that have been extensively used in various applications ranging from materials to biological molecules.[1] As a premier example of "Click chemistry",[2] the reaction of organic azides and alkynes,[3] namely, Huisgen 1,3-dipolar cycloaddition, represents a straightforward and atom economical approach to these heterocycles. However, because of the high activation barrier, the direct reaction of unactivated alkyne with azide often requires high temperature to proceed, giving the target triazole in low regioselectivity. In 2002, regioselective synthesis of 1,4-disubstituted triazoles through copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) at ambient temperature was realized by the groups of Sharpless, Forkin and Meldal independently.[4] Mechanistically, the formation of copper(I) acetylide intermediate is essential, thus efforts to achieve regioselective CuAAC of internal alkynes is quite challenging.[5,6]

Nevertheless, the above mentioned problems have been alleviated by recent advances through judicious choice of transition-metal catalyst. For example, ruthenium-catalyzed azide-alkyne cycloadditions exhibited remarkably wide substrate scope, even when unactivated internal alkynes were employed as reactants (Scheme 1a).[7] Compared with the CuAACs, ruthenium system is more sensitive to the reaction media, and Schlenck techniques were required during the operation.[7c,8] Although the recently reported IrAACs were generally less sensitive to air and moisture, the reactions were limited to thioalkynes and activated alkynes,[9] not applicable to ynamides.[10] 5-Amino-1,2,3-triazoles are useful structural motifs that embedded in many molecules with interesting biological activities (Scheme 2). 5-Amino-4-carbamoyl-1,2,3-triazole **1a** is a calcium influx inhibitor with antiproliferative and antimetastatic activities.[1f,1g] As a

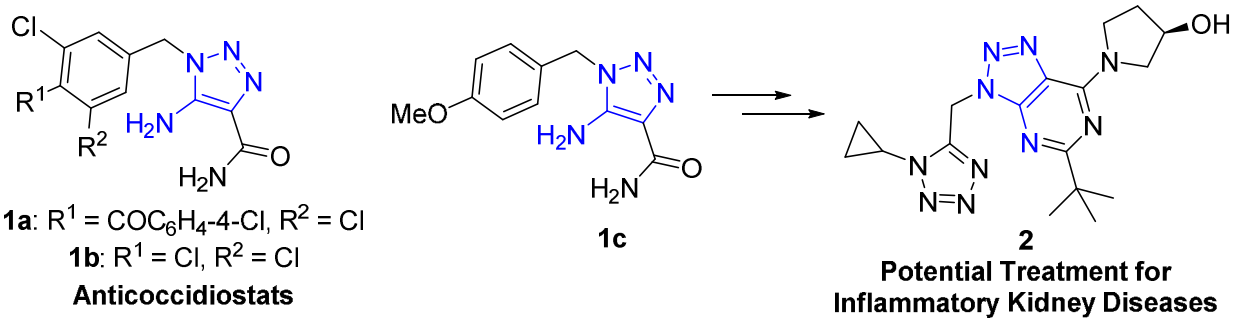
heterocyclic analogue of imidazole, compound **1b** has displayed increased potency in anticoccidial.[11] Triazolopyrimidine **2** derived from simple triazole **1c** has been found have the potential for treatment of inflammatory kidney diseases.[12] Given the well-established procedure for the synthesis of ynamides,[13] one may envision that regioselective cycloaddition of ynamides



Scheme 1. Representative approaches to substituted 5-amino-triazoles.

with azides perhaps represents an attractive approach to amino-substituted triazoles.[7c,14] Recently an interrupted Cu-catalyzed click reaction giving 5-heteroatom functionalized triazoles was realized by Xu's laboratory (Scheme 1b).[5f] In the event, electrophilic amination reagents were employed to trap the 5-cuprated triazole intermediate. Although the reactions produce 5-aminotriazoles in high yields and complete control of regioselectivity, the requirement of

relatively large amount of molecular sieves and excess of strong base may limit the potential of its future utility. Herein, we report the successful implementation of unprecedented RhAACs of ynamides, affording 5-amino-triazoles in completely regioselective control (Scheme 1c). The current transformation is compatible with a variety of solvents, and proved to be not sensitive to air and moisture. Moreover, a mechanistic rationale for the observed high regioselectivity is also strongly supported by DFT calculations.



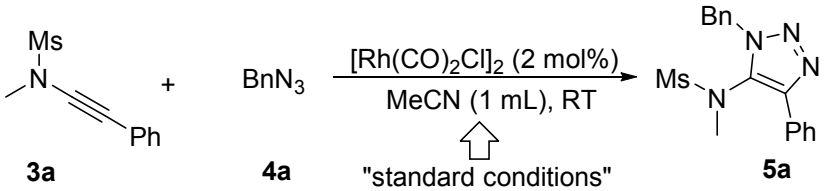
Scheme 2. Representative examples of 5-amino-triazole derivatives with interesting biological activities.

Results and discussion

As part of our interest in gold-catalyzed intermolecular nitrene transfer reactions with ynamides,[15] we sought to examine the reactivity of other transition-metal catalysts towards the reaction of ynamide **3a** and organic azide **4a**. Typical cationic gold catalysts displayed no reactivity (Table 1, entries 2 and 3).[16] Wilkinson's catalyst could not catalyze the reaction either (Table 1, entry 4). To our delight, when $[Rh(COD)Cl]_2$ was employed as the catalyst, the formal [3+2] cycloaddition adduct **5a** was obtained in 21% isolated yield (Table 1, entry 5). Much to our surprise, $[Rh(CO)_2Cl]_2$ proved to be a superb catalyst for the AAC of ynamide **3a**. The reaction was complete within 30 min, and 5-amino-triazole **5a** was isolated in nearly quantitative yield

(Table 1, entry 1). Interestingly, Rh(II) catalyst was totally inactive (Table 1, entry 6). CuI, which has been identified to be excellent catalyst for the reaction of 1-iodoalkynes with azides,[5a]

Table 1. Experiments on condition studies.[a]



3a **4a** **5a**

Entry	Variation from the standard conditions	time	yield/%[b]
1	No change	30 min	94
2	$Ph_3PAuNTf_2$ was used as catalyst	24 h	-
3	JohnPhosAuNTf$_2$ was used as catalyst	24 h	-
4	$[Rh(Ph_3P)_3Cl]$ was used as catalyst	24 h	-
5	$[Rh(COD)Cl]_2$ was used as catalyst	24 h	21
6	$Rh_2(OAc)_4$ was used as catalyst	24 h	-
7	CuI was used as catalyst	24 h	-
8	$NiCl_2$ was used as catalyst	24 h	-
9	$Pd(OAc)_2$ was used as catalyst	24 h	-
10	$Co(acac)_2$ was used as catalyst	24 h	-
11	$[Ir(COD)Cl]_2$ was used as catalyst	24 h	trace
12[c]	Open flask reaction	30 min	95

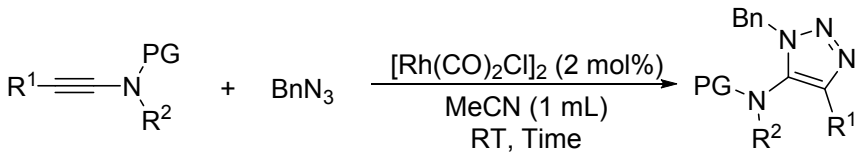
[a] **3a** (0.2 mmol), **4a** (0.3 mmol), cat. (2 mol%), MeCN (1 mL), stirring under atmosphere of Argon at room temperature. [b] Isolated yield. [c] The reaction was carried out in 0.5 mmol scale, and the ratio of **3a** : **4a** was 1:1, MeCN (not dry, 0.5 M). JohnPhos = P(^{t}Bu)$_2$(o-biphenyl), cod = cycloocta-1,5-diene, acac = acetylacetonate.

could not catalyze the reaction as expected (Table 1, entry 7). Similarly, $[Ir(COD)Cl]_2$, an effective catalyst for the reaction of azides with thioalkynes, exhibits inferior activity as well

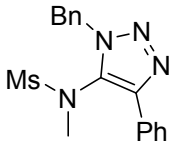
(Table 1, entry 11).[9a] In presence of other transition-metal catalysts, including $NiCl_2$, $Pd(OAc)_2$ and $Co(acac)_2$, completely recovery of the starting materials were observed (Table 1, entries 8-10). Further experiments revealed that the exclusion of air and moisture was unnecessary, as the current RhAAC of ynamide could proceed smoothly in an open flask in undried solvent while maintaining similar efficiency (Table 1, entry 12). Furthermore, the current cycloaddition could be carried out in a variety of solvents without erosion of the reaction yields.[17]

With a set of effective conditions established, a range of readily available ynamides were tested to prepare 5-amino-triazole derivatives. As summarized in Table 2, these reactions were operationally simple, not sensitive to air and moisture. We were pleased to see that most ynamides could participate in the Rh(I)-catalyzed formal [3+2] cycloadditions, giving the corresponding 5-amino-triazoles **5** in good to excellent yields under mild conditions. Another remarkable feature is that the current cycloaddition does not require the excess of either reaction partners. The ratio of ynamide **3** to azide **4** is 1:1. As depicted, ynamides bearing different protecting groups had no big influences on the reaction outcomes (cf. **5e** to **5h**). It is worth mentioning that the reaction of ynamide with nosyl- group proceeded well, giving the triazole **5e** in 84% isolated yield. The relatively longer reaction time presumably results from strong electron-withdrawing character of the nosyl- group. Compared with the model ynamide **3a**, the reactions of para- methyl, methoxy, trifluoromethyl and chloro substituted ynamides afforded the corresponding triazoles **5i**, **5j**, **5l** and **5m** in excellent yields regardless of the electronic nature. *Meta*- or *ortho*- substituents on the phenyl ring were tolerated as well (cf. **5k**, **5n** and **5o**). The ynamides containing heteroaromatic ring or additional alkenyl moiety were proved to be

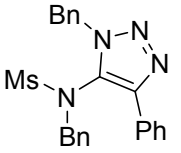
Table 2. Reaction scope of ynamides **3** with benzyl azide **4a**.[a]



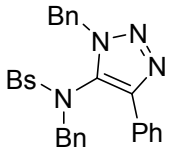
3, 0.5 mmol **4a**, 0.5 mmol **5**



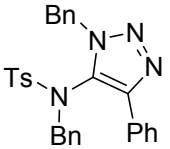
5a, 0.5 h, 94%



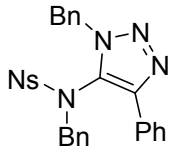
5b, 3 h, 93%



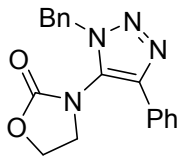
5c, 5 h, 88%



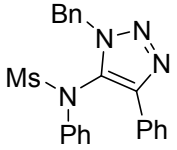
5d, 4 h, 95%



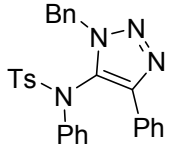
5e, 21 h, 84%



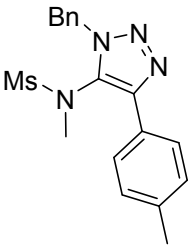
5f, 3 h, 88%



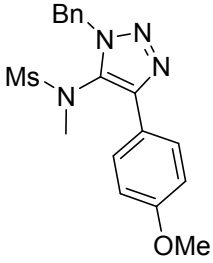
5g, 2 h, 92%



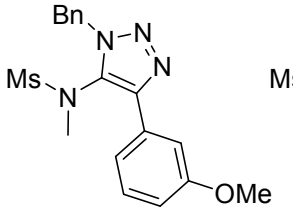
5h, 11 h, 89%



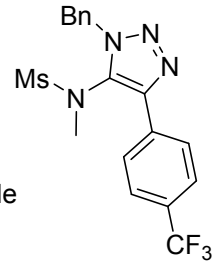
5i, 2.5 h, 96%



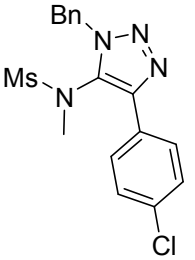
5j, 0.5 h, 90%



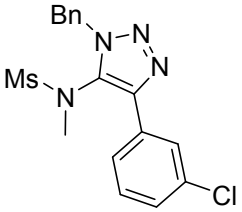
5k, 2 h, 90%



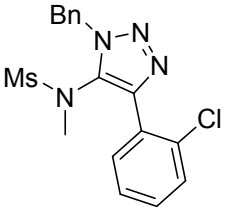
5l, 0.5 h, 94%



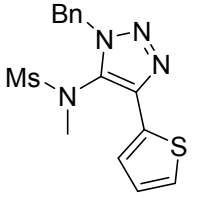
5m, 0.5 h, 95%



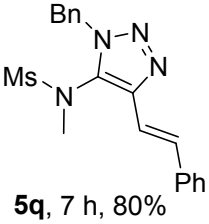
5n, 4 h, 93%



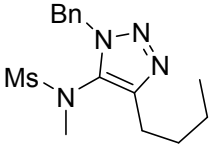
5o, 20 h, 93%



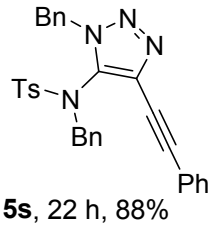
5p, 0.5 h, 86%



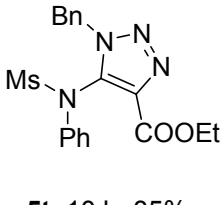
5q, 7 h, 80%



5r, 11 h, 85%



5s, 22 h, 88%



5t, 10 h, 85%

[a] Yield of isolated product. All reactions were run in open flask.

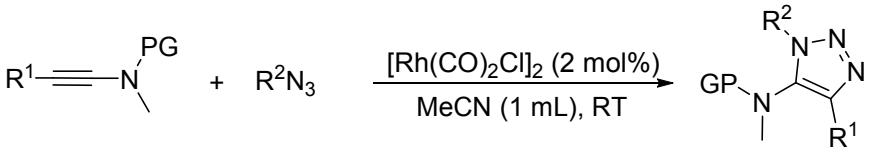
good substrates for the RhAACs, generating **5p** and **5q** in very good yields and complete regioselectivity. Replacement of the aryl substituted ynamide with ^{n}butyl has no significant influences on the yields of the corresponding triazoles (cf. **5r**). The ynamide derived from ethyl propiolate was also proved to be a suitable substrate. After stirring for 10 h under the standard condition, the desired triazole **5t** was obtained in 85% isolated yield. Of note such a structural motif containing carboxyamidotriazole core may have the potential on druglike agents synthesis.[1f] X-ray diffraction studies of product **5a** and **5f** further confirmed the structural assignments on the regioselectivity.[18]

Such an open-flask triazole synthesis can be applied to the reactions of ynamide with a variety of alkyl azides. As depicted in Table 3, functional moieties including indolyl, alkenyl, carbonyl groups were well tolerated. The reactions were complete in relatively short time (2 h to 9 h at ambient temperature), and the corresponding triazoles (cf. **5u** to **5z**) were all obtained in high yields. These functionalities offer ample opportunities for further manipulation on the corresponding triazoles. The reactions of aryl azides under standard conditions were proved to be sluggish, and only partial of the starting materials were converted to the target triazoles. Elevating the temperature to 100 ^{o}C, and increasing the catalyst loading to 5 mol%, the cycloaddition adducts could be obtained up to 83% isolated yields (cf. **5aa** to **5ad**).

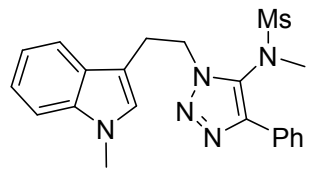
As described, the current RhAAC tolerated a variety type of solvents. Pleasingly, the reaction of ynamide **3a** with benzyl azide 4a could also be run in aqueous media on gram-scale, while without sacrifying efficiency, and triazole **5a** was isolated in 89% yield (eq 1). Besides benzyl azide 4a, other alkyl azides (**4u**, **4w**, **4x** and **4y**) could react well with ynamide **3a** in aqueous media (see SI page S18 for details). The robustness was also evidenced by adding 1 equivalent of agents containing variety of functionalities, ranging from benzoyl acid to pyridine oxide (see SI

page S19 for details). Furthermore, the catalyst generated in situ by heating less costing $RhCl_3$ rhodium salt solution in DMF for 30 min,[19] was proved to be competent for current transformation, and triazole **5a** was obtained in high yield as well (eq 2).

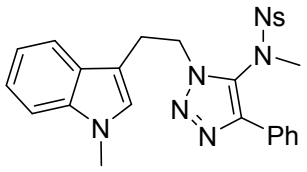
Table 3. Reaction scope of organic azides.[a]



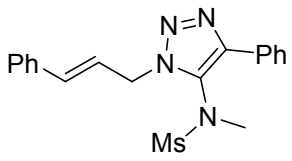
3, 0.5 mmol **4**, 0.5 mmol **5**



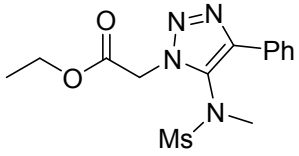
5u, 2 h, 98%



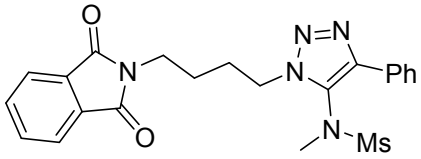
5v, 1 h, 87%



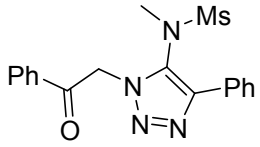
5w, 2 h, 92%



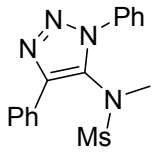
5x, 2 h, 93%



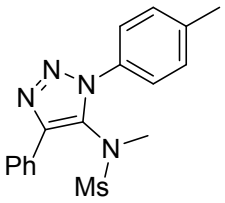
5y, 6 h, 97%



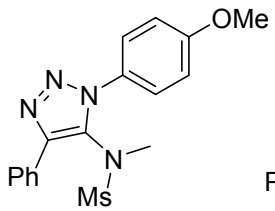
5z, 9 h, 84%



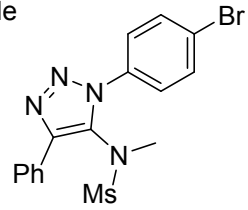
5aa, 24 h, 25%
4 h, 64%[b]



5ab, 24 h, 17%
4 h, 69%[b]



5ac, 24 h, 22%
3 h, 83%[b]

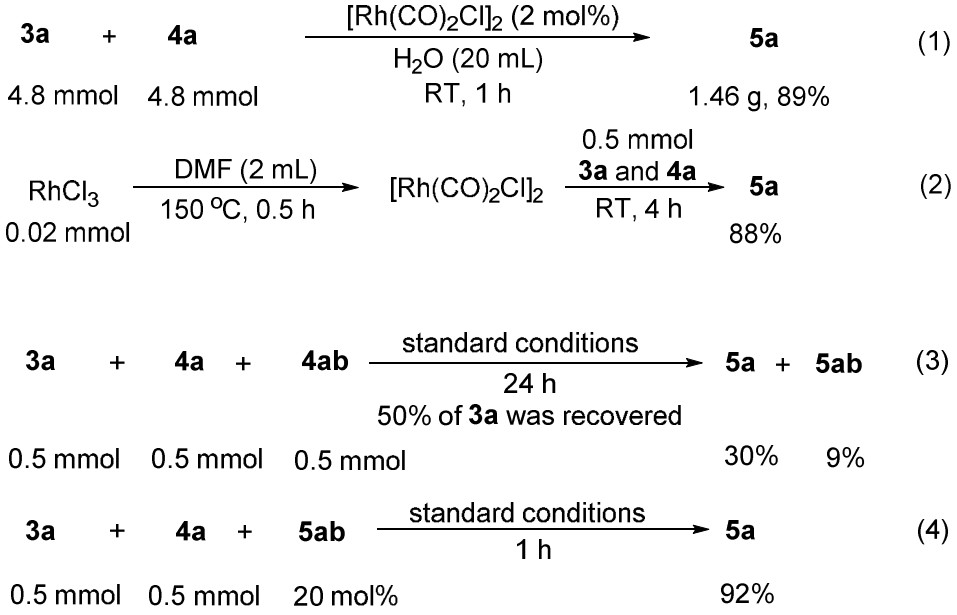


5ad, 15 h, 68%[b]

[a] Yield of isolated product. All reactions were run in open flask. [b] The reactions were carried out in 2 mL of MeCN at 100 °C, and 5 mol% $[Rh(CO)_2Cl]_2$ was employed .

To better understand the different behaviours between alkyl azides and aryl azides, a competing experiment was carried out. Benzyl azide **4a**, aryl azide **4ac** and ynamide **3a** were added to same reaction flask in a ratio of 1:1:1. Interestingly, even after stirring at room

temperature for 24 h, up to 50% of ynamide **3a** was recovered, and triazoles **5a** and **5ab** were isolated in 30% and 9% yields, respectively (eq 3). Further experiment revealed that addition of catalytic amount of 5ab had no obvious effect on the reaction of ynamide **3a** and benzyl azide 4a (eq 4). Based on these results, we reasoned that the low conversion of benzyl azide 4a in eq 3 presumably resulted from partial poisoning of rhodium catalyst by aryl azide **4ab**.[7c] This also well explained the sluggish reactions observed when aryl azides were employed for the current RhAACs.



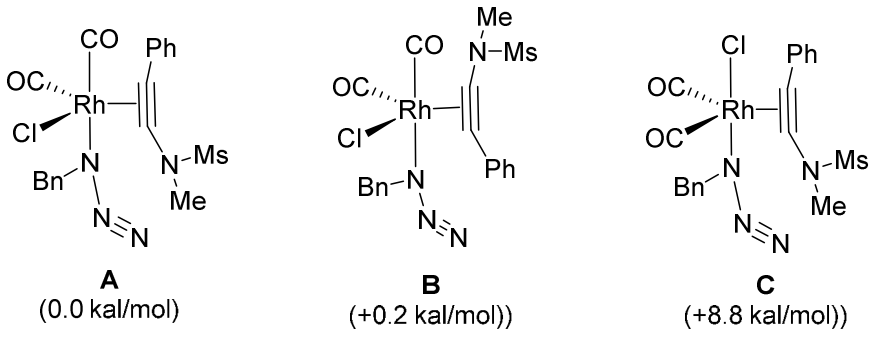


Figure 1. Three possible reactant complexes **A**, **B** and **C**.

To further probe the details on the mechanism, DFT calculations were performed at the M06/6-311+G(d,p)-SDD//B3LYP/6-31G(d)-LANL2DZ level. Solvation effects were accounted by using the SMD model with acetonitrile as the solvent. Optimization of transition states and intermediates in acetonitrile solvent do not have significant impact on the overall barriers and regioselectivity (see Figure S3 in Supporting Information). For the cycloaddition of **3a** and **4a**, the initial coordination of **3a** and **4a** to active catalyst $[Rh(CO)_2Cl]$ generates three possible complexes **A**, **B** and **C** (Figure 1). Since **C** is less stable than **A** and **B** by about 8 kcal/mol, reaction pathways from complexes **A** and **B** are calculated to be energetically more favourable than those from **C**. The detailed energy profiles for cycloaddition mechanism from **A** are shown

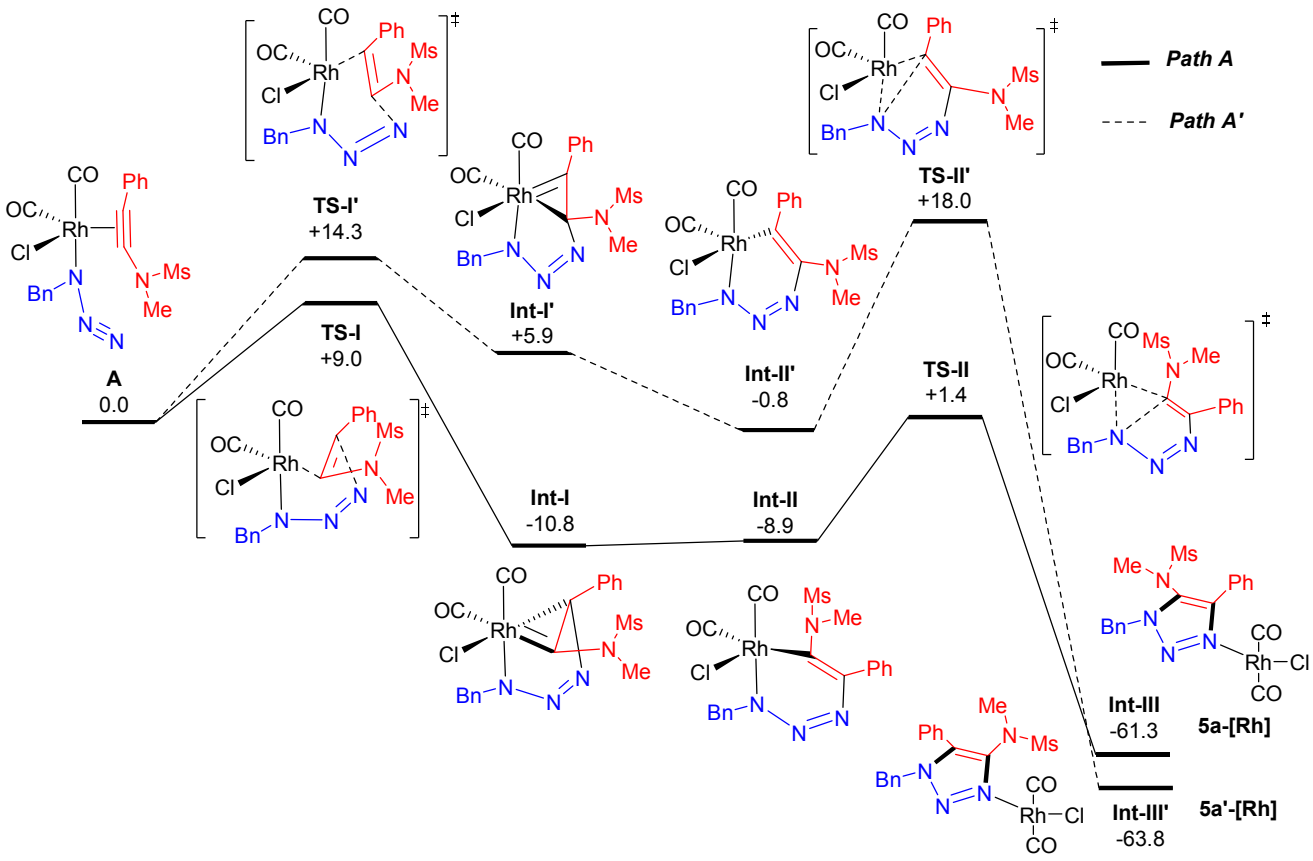


Figure 2. Energy profiles of cycloaddition from complex **A**.

in Figure 2.[20] First, oxidative coupling of azide and alkyne occurs to generate metallabicyclic Rh-carbene intermediate. Since both alkyne carbons in **A** are available for the attack from the terminal nitrogen of azide, there are two pathways to eventually deliver product **5a** and its regioisomer **5a'**. In Path A, oxidative coupling between azide and the β carbon of alkyne occurs via **TS-I** to give Rh-carbene intermediate **Int-I**. Then **Int-I** isomerizes to **Int-II**, followed by reductive elimination transition state **TS-II** to generate triazole-catalyst coordinated complex **Int-III**. In this context, the overall energy barrier of Path A is +12.2 kcal/mol (**Int-I→TS-II**). While in Path A', the oxidative coupling transition state **TS-I'** is 5.3 kcal/mol higher than **TS-I**. This is caused by the more electron-rich phenyl-substituted β carbon of alkyne, as the NBO charges of α carbon and β carbon of alkyne in **A** are 0.165 and -0.146, respectively (Table S1). In addition, except for the product-catalyst complex (i.e., **Int-III** and **Int-III'**), intermediates and transition state involved in Path A' are significantly less stable than those in Path A. Further NBO charges analysis demonstrated that electron densities of Rh center of species involved in Path A are remarkably larger than those in Path A' (Table 4). Considering the decreased NBO charge of N atom and the increased NBO charge of Rh during the conversion of **A** to **Int-II**/**TS-II**, we proposed that the thermodynamic stability of species in Path A arises from the electron-donating property of α carbon-connected N substituent. Note that although the minor product **Int-III'** is more stable than the major product **Int-III**, it has no impact on the regioselectivity since the reductive elimination step is irreversible. Therefore, our calculated results indicate that Path A is the dominant mechanism with the generation of triazole **5a**, and this is in accordance with the experimental observations.

Table 4. NBO charges analysis of selected intermediates and transition states

Species	NBO Charge on Rh atom	NBO Charge on N atom
A	-0.426	-0.725
Int-II	-0.510	-0.617
Int-II'	-0.386	-0.742
TS-II	-0.414	-0.661
TS-II'	-0.391	-0.757

Conclusions

In summary, we have described the first rhodium(I)-catalyzed azide-alkyne cycloaddition of internal ynamides, furnishing the corresponding 5-amino-triazoles in good to excellent yields (up to 98%) with exclusive control on the regioselectivity. The current transformation is operationally simple, can be proceeded under mild condition in an open flask. Careful exclusion of air and moisture is not required. It is also amenable to gramscale synthesis in aqueous media. Control experiments revealed that partial poisoning of the rhodium catalyst might take place when aryl azides were employed. Moreover, DFT calculations provided details on the energy profiles for each plausible reaction pathways, and well explained the observed regioselectivity in this work.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interests.

Supporting Information.

Supporting Information. Experimental details, characterization data, geometries of optimized structure/transition states, and ^{1}H and ^{13}C NMR spectra of isolated compounds (PDF), crystal data of compounds **5a** and **5f** (CIF)[18]

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(18) CCDC 1564513 (**5a**) and 1564519 (**5f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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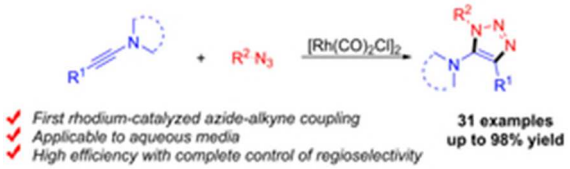

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