Advanced Synthesis & Catalysis

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201800336

Link to VoR: http://dx.doi.org/10.1002/adsc.201800336

10.1002/adsc.201800336

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Rhodium(I)-Catalyzed Azide-Alkyne Cycloaddition (RhAAC) of Internal Alkynylphosphonates with High Regioselectivities under Mild Conditions

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Received: ((will be filled in by the editorial staff))

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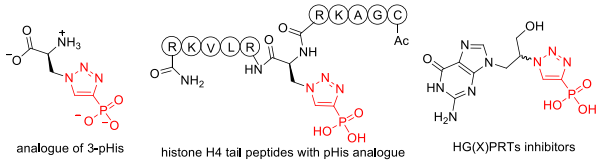
Abstract. A regioselective method to access fully substituted 1,2,3-triazolyl-4-phosphonates from the internal alkynylphosphonates by rhodium(I)-catalyzed azide-alkyne cycloaddition (RhAAC) under mild conditions is reported. This approach is water and air compatible and has a broad substrate scope, good functional group tolerance, high yields and excellent regioselectivities. Fully substituted 1,2,3-triazolyl-4-phosphonates are directly prepared from the internal alkynylphosphonates by RhAAC with high 1,4-regioselectivities. The gram-scale preparation, application to carbohydrate synthesis and the solid-phase synthesis of triazolyl-4-phosphonates are highlights of this method.

Keywords: rhodium; regioselectivity; triazolyl-4-phosphonates; internal alkynylphosphonates; mild conditions

Substituted 1,2,3-triazole is an important heterocyclic structure and has numerous applications in organic synthesis, materials science, and medicinal chemistry.[1] The phosphorus compounds can be utilized as ligands and organocatalysts or can be converted into diverse molecules by Wittig, Horner-Wadsworth-Emmons (HWE) reactions, cross-couplings and cyclization in organic synthesis.[2] Phosphorus-containing materials are highly efficient optoelectronic materials and polymeric flame retardants.[3] Phosphorus-substituted triazoles, especially phosphonates and phosphonic acids, are important and stable phosphohistidine (pHis) analogues used to study protein phosphorylation, and they have attracted increasing attention due to their potential biological activities.[4] For example, the 1,2,3-triazolyl-4-phosphonic acids (**I**, **II**) have been successfully applied to the solid-phase peptide synthesis and semi-synthesis of histone H4.[4a-4d] As the analogues of acyclic nucleoside phosphonates (ANPs), (*R*)- and (*S*)-**III** are good hypoxanthine-guanine-(xanthine) phosphoribosyltransferase (HG(X)PRT) inhibitors.[4e]

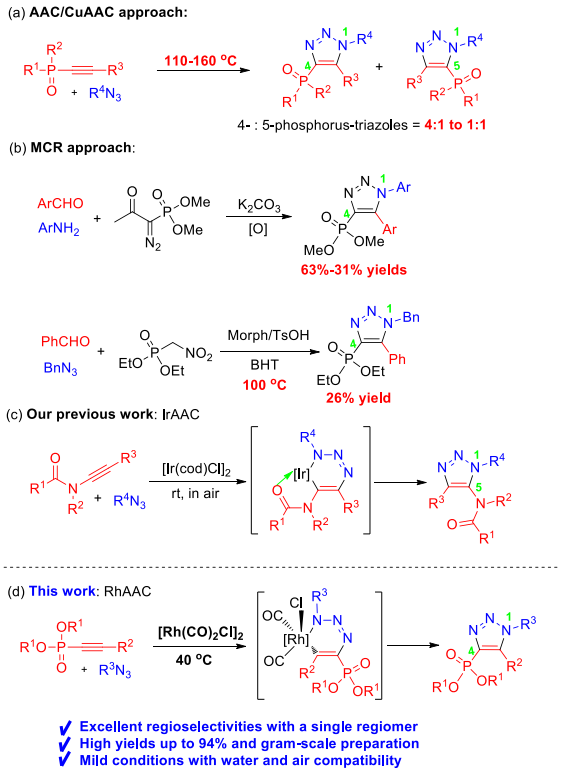


I II III

Figure 1. Selected 1,2,3-Triazolyl-4-Phosphorus Compounds.

The fully substituted 1,2,3-triazole is more diverse and operable than the disubstituted one due to the additional functional group. Although the mentioned 1,2,3-triazolyl-4-phosphonates/phosphonic acids are prepared from terminal alkynylphosphonates, surprisingly, there is currently no general access to fully substituted 1,2,3-triazolyl-4-phosphonates from the internal alkynylphosphonates with high 1,4-regioselectivities under mild conditions. The Huisgen 1,3-dipolar cycloaddition[5] between azides and internal alkynylphosphonates appears to be the most straightforward and atom-efficient approach. However, low regioselectivities are achieved by azide-alkyne cycloaddition (AAC) at high temperatures without the use of catalysts (Scheme 1a).[6] Since the development of the copper-catalyzed AAC (CuAAC) reaction by the Meldal group and by the Sharpless group,[7] CuAAC has been widely used to regioselectively prepare 1,4-disubstituted and 1,4,5-trisubstituted 1,2,3-triazoles. However, the scope is very limited for the azide-internal alkynylphosphonate cycloaddition using copper as the catalyst.[6c] An indirect two-step strategy to afford 5-iodo-1,2,3-triazolyl-4-phosphonates firstly following by Suzuki or Stille coupling was also reported recently, but this approach is not atom- or step-economical.[8] In addition, multicomponent reactions (MCRs), are powerful and alternative approaches to access fully substituted 1,2,3-triazolyl-4-phosphonates, and they are developed without using internal alkynylphosphonates (Scheme 1b).[9]

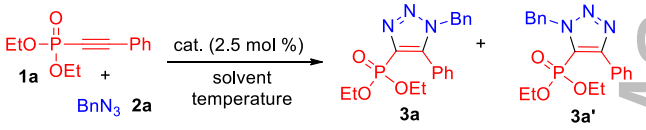
However, the substrate scope of MCRs is very limited, and the yields are generally moderate to low. Hence, it remains challenging for the internal alkynylphosphonates to directly accomplish AAC under mild conditions with high 1,4-regioselectivities. The development and application of various transition metal catalysts in AAC reactions (MAAC) may provide the opportunity to address this long-standing issue by selecting a suitable catalyst.[10] Inspired by the CuAAC and Ru-catalyzed AAC (RuAAC) reactions to afford certain fully substituted 1,2,3-triazoles in the presence of air and water,[11] we previously developed the Ir-catalyzed azide-ynamide cycloaddition (IrAAC) reaction to access fully substituted 5-amido 1,2,3-triazoles with high 1,5-regioselectivities under mild, air, aqueous and bioorthogonal conditions (Scheme 1c).[12] The high 1,5-regioselectivities for this IrAAC reaction arise from the strong coordination between ynamides and iridium. In a continuation of our studies on MAAC reactions, we report the first direct access to fully substituted 1,2,3-triazolyl-4-phosphonates with excellent 1,4-regioselectivities from the internal alkynylphosphonates by a rhodium(I)-catalyzed AAC (RhAAC) process under mild conditions (Scheme 1d).[13] Remarkably, the gram-scale preparation, the application to carbohydrate synthesis and the solid-phase synthesis of fully substituted 1,2,3-triazolyl-4-phosphonates are highlights of this mild and unique intermolecular RhAAC method.



Scheme 1. Synthesis of Fully-Substituted 1,2,3-Triazolyl-4-Phosphonates.

Internal alkynylphosphonate **1a** was chosen as the model substrate to optimize the cycloaddition conditions using dichloromethane (DCM) as the solvent without inert gas protection (Table 1). In the presence of CuI or $CuSO_4$, the CuAAC reaction failed to occur for the internal alkyne **1a** (Table 1, entries 1 and 2). Neither the neutral nor the cationic Ru(II) catalyst could mediate the reaction well. None of the desired cycloaddition product was generated in this transformation by Ir(I) or Rh(III) (Table 1, entries 5 and 6). In addition, $[Rh(cod)_2]BF_4$ and $[Rh(cod)Cl]_2$ were ineffective at catalyzing this [3+2] reaction (Table 1, entries 7 and 8). Encouragingly, we found that $[Rh(CO)_2Cl]_2$ worked efficiently at room temperature to afford the desired **3a** in moderate yield with excellent regioselectivity (Table 1, entry 9).[14] The yield could be further improved, and the absolute regioselectivity could be maintained when the reaction temperature was increased from room temperature to 40 °C (Table 1, entry 10). The reaction could also proceed smoothly in other solvents such as chloroform and MeCN (Table 1, entries 11 and 12). Notably, this reaction could be set up in aqueous media, although with a moderate yield (Table 1, entry 13). Unfortunately, the reaction failed to occur in non-polar solvents (toluene or hexane) due to the difficult polarization and combination of the alkyne with Rh(I) (Table 1, entries 14 and 15).

Table 1. Optimization of the Reaction Conditions.[a]



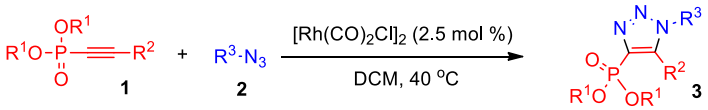
Entry	Catalyst	Solvent	Temperature	Yield (**3a**+**3a'**)[b] (%)	**3a**/**3a'**[b]
1	CuI	DCM	rt	0	-
2	$CuSO_4$	DCM	rt	0	-
3	$[Cp^*Ru(cod)Cl]_2$	DCM	rt	trace	-
4	$[Cp^*Ru(MeCN)_3]PF_6$	DCM	rt	trace	-
5	$[Ir(cod)Cl]_2$	DCM	rt	0[c]	-
6	$[Cp^*RhCl_2]_2$	DCM	rt	0	-
7	$[Rh(cod)_2]BF_4$	DCM	rt	0	-
8	$[Rh(cod)Cl]_2$	DCM	rt	0	-
9	$[Rh(CO)_2Cl]_2$	DCM	rt	72	>20:1
10	$[Rh(CO)_2Cl]_2$	DCM	40 °C	93	>20:1
11	$[Rh(CO)_2Cl]_2$	$CHCl_3$	40 °C	87	>20:1
12	$[Rh(CO)_2Cl]_2$	MeCN	40 °C	81	>20:1
13	$[Rh(CO)_2Cl]_2$	H_2O	40 °C	56	>20:1
14	$[Rh(CO)_2Cl]_2$	toluene	40 °C	trace	-
15	$[Rh(CO)_2Cl]_2$	hexane	40 °C	trace	-

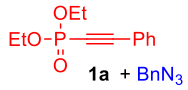
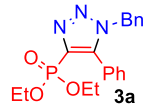
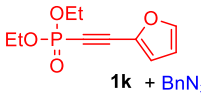
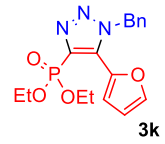
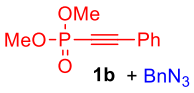
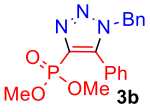
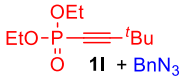
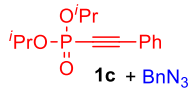
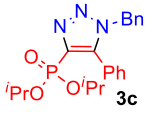
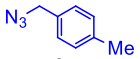
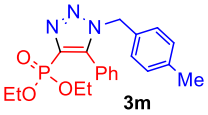
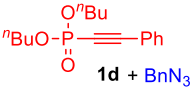
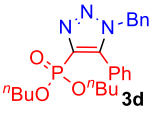
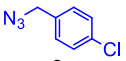
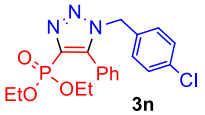
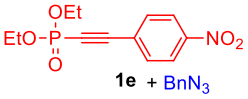
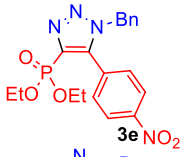
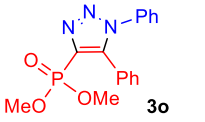
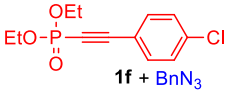
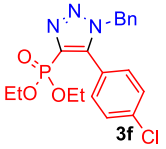
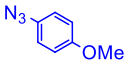
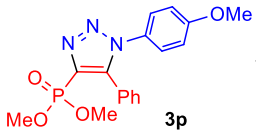
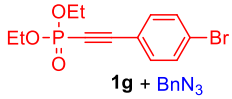
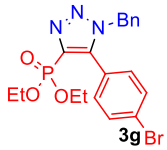
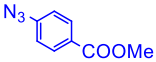
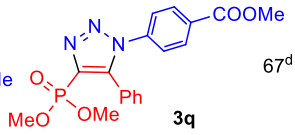
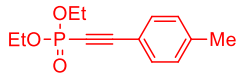
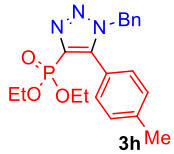
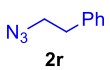
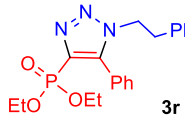
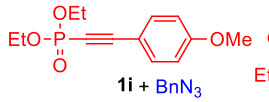
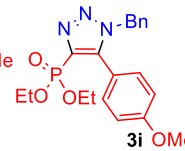
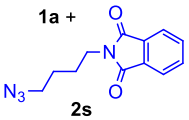
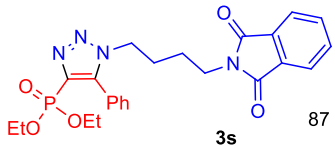
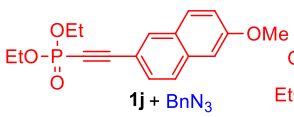
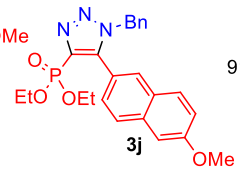
[a] Conditions: **1a** (1.0 equiv), **2a** (1.5 equiv), solvent (0.1 M), catalyst (2.5 mol%), air atmosphere, for 12 h.
[b] Determined by ^1H NMR of the crude mixture with an internal standard.
[c] The starting material **1a** was decomposed.

With the optimized conditions in hand, we explored the scope of the internal alkynylphosphonates with azides in the RhAAC reaction. Various internal alkynylphosphonates were

10.1002/adsc.201800336

Table 2. Substrate Scope of Internal Alkynylphosphonates with Azides.[a]



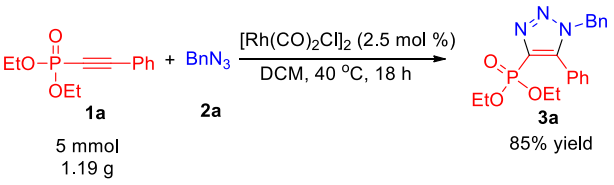
Entry	Substrate	Product (**3**)	Yield (%) [b]	Entry	Substrate	Product (**3**)	Yield (%) [b]
1	 **1a** + BnN_3	 **3a**	89	11	 **1k** + BnN_3	 **3k**	87
2	 **1b** + BnN_3	 **3b**	80	12	 **1l** + BnN_3	No reaction [c]	–
3	 **1c** + BnN_3	 **3c**	84	13	**1a** +  **2m**	 **3m**	92
4	 **1d** + BnN_3	 **3d**	71	14	**1a** +  **2n**	 **3n**	81
5	 **1e** + BnN_3	 **3e** NO_2	75[c]	15	**1b** +  **2o**	 **3o**	74
6	 **1f** + BnN_3	 **3f** Cl	81	16	**1b** +  **2p**	 **3p**	79
7	 **1g** + BnN_3	 **3g** Br	82	17	**1c** +  **2q**	 **3q**	67[d]
8	 **1h** + BnN_3	 **3h** Me	91	18	**1a** +  **2r**	 **3r**	84
9	 **1i** + BnN_3	 **3i** OMe	94	19	**1a** +  **2s**	 **3s**	87
10	 **1j** + BnN_3	 **3j** OMe	91				

[a] Standard conditions: 1 (1.0 equiv), 2 (1.5 equiv), DCM (0.1 M), catalyst (2.5 mol%), air atmosphere, for 12h.
[b] Isolated yield. Regioselectivities (3/3') were >20:1 (determined by ^{1}H NMR of the crude reaction mixture).
[c] For 24 h.
[d] 5 mol % catalyst at 60 °C for 24 h.

used as substrates at 40 °C without inert gas protection to afford fully substituted 1,2,3-triazolyl-4-phosphonates in good yields (up to 94%) and excellent regioselectivities (Table 2). Besides diethyl alkynylphosphonate, other alkynylphosphonates, such as methyl, isopropyl, and *n*-butyl alkynylphosphonates, could also participate in the RhAAC reaction smoothly (**3a-3d**). However, for *n*-butyl alkynylphosphonate, excellent regioselectivity was obtained despite the lower yield (**3d**) than the

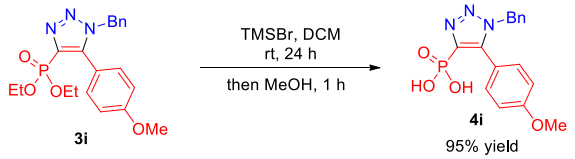
yield achieved by the other substrates. If the alkynylphosphonate contained a strong electron-withdrawing nitro group, then the yield of **3e** was reduced to 75% even with a prolonged reaction time. For a less electron-withdrawing halogen group, the yields of **3f** and **3g** increased to 81% and 82% (compared with the 75% yield of **3e**). The introduction of electron-donating groups could significantly improve the yields to 91% (**3h**, *p*-methylphenyl substituted), 94% (**3i**, *p*-methoxyphenyl substituted) and 91% (**3j**, 6-methoxynaphthyl substituted). The furyl-substituted internal alkyne could be well tolerated in this process with good yield (87%) for **3k**. Unfortunately, for alkyl-substituted internal alkynylphosphonates (**1l**), the reactions did not occur with an extended reaction time, possibly due to the combination of unfavorable electronic and steric factors. The use of alkyl or aryl azides as substrates could also give the desired products in good yields and excellent regioselectivities. Various functional groups, including halogen, ester, and carbonyl groups were well tolerated (**3n**, **3p**, **3q**, **3s**). The yield (**3m**) for the electron-rich alkyl azide was much higher (92%) than that of the electron-poor one for **3n**. When aryl azides were used as substrates, the yields dramatically decreased (**3o**-**3q**). In particular, for the methyl benzoate-substituted aryl azide, the cycloaddition reaction required a higher temperature and longer time and produced a lower yield (**3q**). Ethyl or butyl azides could offer very good yields for **3r** and **3s**. The broad substrate scope offers potential opportunities for the further manipulation of the fully substituted 1,2,3-triazolyl-4-phosphonates.

The RhAAC reaction could be performed on the gram scale. Using **1a** (5.0 mmol, 1.19 g) under the standard conditions with an extended time, **3a** was acquired in 85% yield (4.25 mmol, 1.58 g) after column purification (Scheme 2).



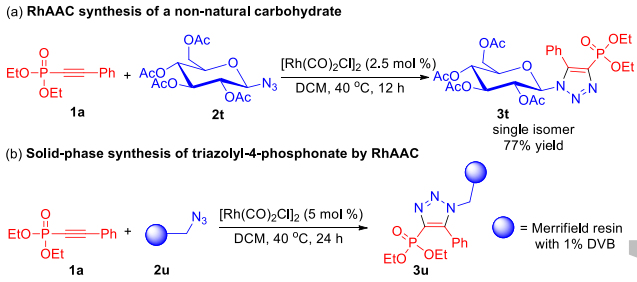
Scheme 2. Gram-scale Preparation of **3a** by RhAAC.

Phosphonic acids play the core role in protein phosphorylation. To further apply the RhAAC method in biological studies, it is necessary and important to modify our fully substituted 1,2,3-triazolyl-4-phosphonates to the related phosphonic acid. Treating with trimethylsilyl bromide (TMSBr), the phosphonic acid **4i** could be afforded in excellent yield from the corresponding triazolyl-4-phosphonate **3i** (Scheme 3).



Scheme 3. Post-modification to Afford the Related Phosphonic Acid.

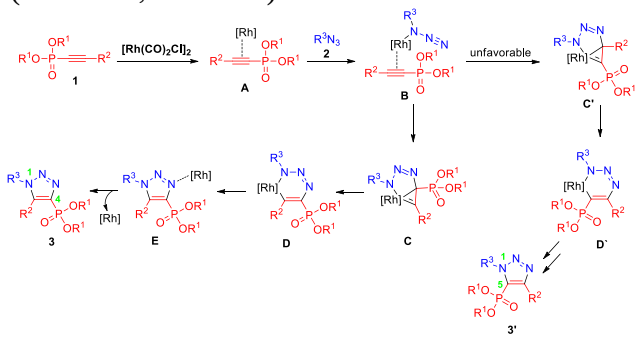
Subsequently, other applications of the RhAAC reaction were examined. The RhAAC reaction could be successfully extended to the synthesis of non-natural carbohydrates using glycosyl azide **2t** as the substrate, thus offering a unique and efficient approach to access sugar phosphates in a glycomic study (Scheme 4a). The (azidomethyl) polystyrene resin **2u** could be employed for the solid-phase synthesis of fully substituted 1,2,3-triazolyl-4-phosphonate **3u** by RhAAC, providing a powerful tool for heterogeneous catalysis and surface modification (Scheme 4b). All of the above applications demonstrate that RhAAC could be further applied in biochemistry, medicinal chemistry, material science and other areas.



Scheme 4. Applications of RhAAC.

To further understand the RhAAC process, the mechanism was preliminarily investigated by ^{31}P-NMR experiments. The alkynylphosphonate **1a** and the related product **3a** were separately mixed with the $[Rh(CO)_2Cl]_2$ in a stoichiometric manner. New ^{31}P signals were observed in the NMR spectra. Then, the RhAAC process between **1a** and **2a** was monitored by ^{31}P-NMR experiments in which the same ^{31}P signal was recorded (for details, see the SI). Based on the ^{31}P-NMR experiments and previous density functional theory (DFT) calculations for MAAC reactions, a general mechanism for the RhAAC reaction is proposed in Scheme 5.[11-13] Complex **A** could be generated by the initial combination of π-acidic Rh(I) with alkynylphosphonate **1**. The azide **2** coordinates with Rh by the internal nitrogen atom in intermediate **B.** Two Rh-carbene intermediates, **C** and **C'**, could be formed through the oxidative addition between the *β*-carbon of the alkyne and the azide. The high 1,4-regioselectivity is derived from intermediate **C**. **C** may be more stable than **C'**. In addition, the phosphoryl oxygen, unlike the carbonyl oxygen, does not coordinate with Rh to favor intermediate **C'**, resulting in 1,5-regioselectivity.[12] Then, a Rh-assisted isomerization occurs from intermediate **C** to intermediate **D**. Reductive elimination of intermediate **D** affords intermediate **E**,

which results in the desired fully substituted 1,2,3-triazolyl-4-phosphonate **3** with high 1,4-regioselectivity. Intermediates **A** and **E** were confirmed by the mentioned ^{31}P-NMR experiments (for details, see the SI).



Scheme 5. Proposed Mechanism of the RhAAC Reaction.

In summary, we developed a novel rhodium(I)-catalyzed azide-alkyne cycloaddition (RhAAC) reaction of internal alkynylphosphonates for the highly regioselective synthesis of fully substituted 1,2,3-triazolyl-4-phosphonates under mild conditions. $[Rh(CO)_2Cl]_2$, as the critical catalyst for the RhAAC reaction, was insensitive to air and water. This strategy exhibits a broad substrate scope, good functional group tolerance, high yields and excellent regioselectivities. The proposed approach provides a mild and general direct access to various fully substituted 1,2,3-triazolyl-4-phosphonates from internal alkynylphosphonates. The potential advantages of this RhAAC reaction are the gram-scale preparation, the application to carbohydrate synthesis and the solid-phase synthesis of triazolyl-4-phosphonates. Further mechanistic studies and advanced theoretical calculations for the transition states and intermediates of this reaction are being performed in our laboratory.

Experimental Section

General procedure for the synthesis of 3a: To a vial containing $[Rh(CO)_2Cl]_2$ (2.0 mg, 0.025 equiv, 0.005 mmol) in DCM (2 mL) under air was added diethyl (phenylethynyl)phosphonate (47.6 mg, 1 equiv, 0.2 mmol) and (azidomethyl)benzene (40.2 mg, 1.5 equiv, 0.3 mmol). It was necessary to add the azides last. The vial was closed and the mixture was stirred at 40 °C for 12 h. The mixture was purified with flash column chromatography (50% EtOAc in petroleum ether) to give the pure product (66 mg, 89%) as a yellow oil.

Acknowledgments

This work was supported by grants from the Doctoral Program Foundation of Liaoning Province (Nos. 20170520378, 20170520274), the Fundamental Research Funds for the Central Universities (Nos. DUT16RC(3)114, DUT18LK25) and the National Natural Science Foundation of China (Nos. 21702025, 51703018). We thank Prof. Baomin Wang (Dalian University of Technology) for his enthusiastic assistance.

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10.1002/adsc.201800336

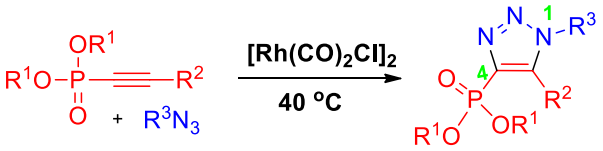
COMMUNICATION

Rhodium(I)-Catalyzed Azide-Alkyne Cycloaddition (RhAAC) of Internal Alkynylphosphonates with High Regioselectivities under Mild Condition

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Wangze Song,* Nan Zheng, Ming Li, Karim Ullah, and Yubin Zheng

RhAAC of Internal Alkynylphosphonates



- Excellent regioselectivities with a single regiomer
- High yields up to 94% and gram-scale preparation
- Mild conditions with water and air compatibility