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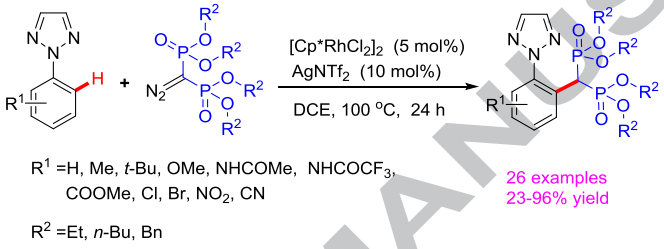

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ABSTRACT

A mild and efficient procedure was developed for the [Cp*Rh(III)]-catalyzed, 1,2,3-triazole directed C–H coupling with diazomethylene-diphosphonates. This protocol provided a step- and atom-economical protocol for C–C bond formation and led to structurally diverse 2-(1,2,3-triazol-2-yl)benzyl diphosphonates in good to excellent yields.

Introduction

Over the last 20 years, transition metal-catalyzed C-H bond activation has emerged as an attractive strategy in organic synthesis which avoids the multi-step pre-activation of starting materials and minimizes the production of unwanted by-products.[1-6] Typically, C-H bond activation requires a metal-coordinating functional group to control the regioselectivity of transition metal insertion into a C-H bond.[7] Due to an array of structural properties and the unique pharamacophore features of 1,2,3-triazoles,[8-11] our group became interested in 1,2,3-triazole directed C-H activation. For example, the ruthenium-catalyzed, 1,2,3-triazole directed intermolecular C–H amidation of arenes with sulfonylazides; the palladium-catalyzed, 1,2,3-triazole directed C–H ethoxycarbonylation of 2-aryl-1,2,3-triazoles with diethyl azodicarboxylate; the cobalt(III)-catalyzed, 1,2,3-triazole-assisted C-H amidation of arenes with dioxazolones; and the rhodium-catalyzed, 1,2,3-triazole-assisted *ortho*-cyanation of 2-aryl-1,2,3-triazoles with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (Fig. 1).[12-15]

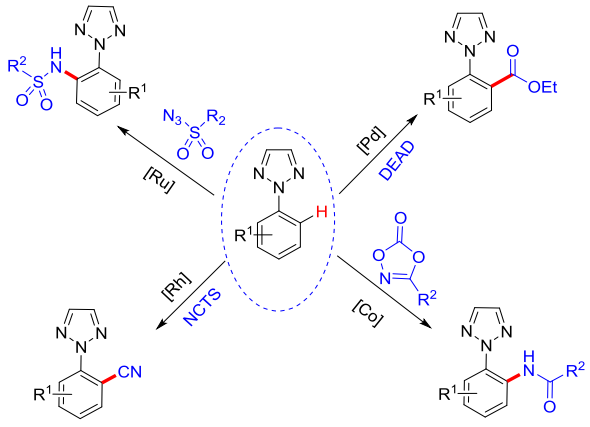

Figure 1. Our previous work on 2-aryl-1,2,3-triazoles directed C-H functionalization.[12-15]

Diazo compounds have been widely used as carbene precursors in C-H activation. For example, in 2012 Yu and co-workers reported the Rh(III)-catalyzed, *ortho*-alkylation of directing-group-containing arene C-H bonds with diazomalonates to prepare aromatic malonic acids.[16] More recently, the groups of Glorius,[17] Yao,[18] Zhu,[19] Wang,[20] Li,[21] and others[22-33] expanded and enriched this C-H functionalization method using different diazo compounds to construct heterocycles (Scheme 1a). In addition, we recently used diazomethylene-diphosphonates as carbene precursor reagents to insert into the O–H bond of carboxylic acids, which can be used to synthesize a bone-targeting prodrug,[34] and to couple with 2-phenylpyridines generating aromatic bisphosphonates, which were identified as β-

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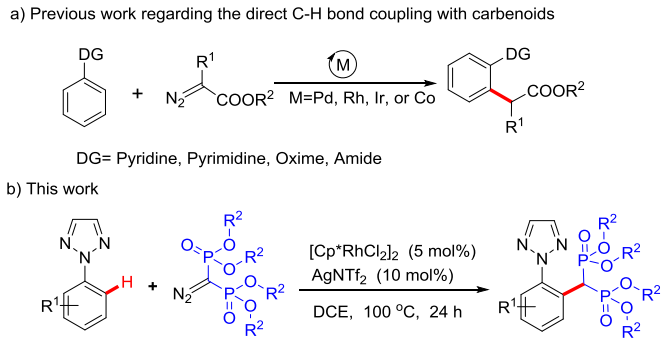
lactamase inhibitors by computational and experimental assays.[35] With the aim to enlarge the library of aromatic bisphosphonates, which may provide more possibilities to identify hit/lead compounds for clinically relevant β-lactamases as well as other protein targets, plus our interest in the C-H functionalization of 2-aryl-1,2,3-triazoles, we herein report the Rh(III)-catalyzed, 1,2,3-triazole-assisted directed C-H coupling with diazo diphosphonates (Scheme 1b).



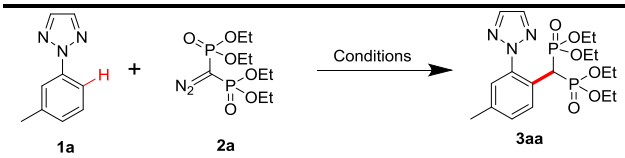
Scheme 1. C-H coupling with diazo compounds.

Results and Discussion

Initial experiments were carried out using 2-(*m*-tolyl)-2*H*-1,2,3-triazole (**1a**, 0.2 mmol) and tetraethyl diazomethylene-diphosphonate (**2a**, 0.24 mmol) in the presence of $[Cp^*RhCl_2]_2$ (5.0 mol%) and $AgSbF_6$ (10.0 mol%) at 80 °C in 1,2-dichloroethane (DCE, 2 mL) for 24 h. As expected, the desired target product **3aa** was obtained in 66% yield under these initial conditions (Table 1, entry 1). Next, the effect of the metal catalyst was investigated (Entries 2–8). Unfortunately, no coupled products were observed for the tested catalysts, except for $[Cp^*IrCl_2]_2$ which gave a moderate yield of 61% (Entry 8). Variation of the Ag salt revealed that $AgNTf_2$ was the most effective with a yield of 72% (Entries 9–12). Next, we focused our attention on the solvent. 1,2,3-Trichloropropane (TCP), CH_3CN, EtOH, THF, MeOH and hexafluoroisopropyl-alcohol (HFIP), which are typically used in direct C–H bond functionalization, were less effective in this transformation than DCE (Entries 13–18). Finally, an excellent isolated yield of 91% was obtained by increasing the temperature to 100 °C (Entries 19, 20). Interestingly, the $[Cp^*IrCl_2]_2$ catalyst also produced **3aa** with an excellent isolated yield of 90% (Entry 21). Accordingly, the optimized reaction conditions are 5 mol% $[Cp^*RhCl_2]_2$, 10 mol% $AgNTf_2$ in DCE at 100 °C for 24 h.

With the optimized reaction conditions in hand, we set out to explore the scope and limitation of the Rh(III)-catalyzed *ortho*-selective C–H carbenoid insertion of 2-aryl-1,2,3-triazoles (Scheme 2). Initially, *ortho*-substituted arenes were investigated. Amide substituted arenes underwent the coupling reaction smoothly and the corresponding products were obtained in good to excellent yields (Scheme 2, **3ba**–**da**). Notably, halogen-substituted arenes (Scheme 2, **3ea**–**ha**) gave higher yields than those with electron-withdrawing groups (EWGs) such as CN and NO_2 (Scheme 2, **3ea**–**ha**). In contrast to *ortho*-substituted substrates, *meta*-substituted arenes gave the corresponding products in moderate to excellent yields, including those with EWGs such as NO_2 and COOMe (Scheme 2, **3aa, 3ia**–**na**). These results indicate that the coupling efficiency is to some extent influenced by the electron density of the aromatic ring and by steric hindrance.

Table 1. Reaction optimization.[a]

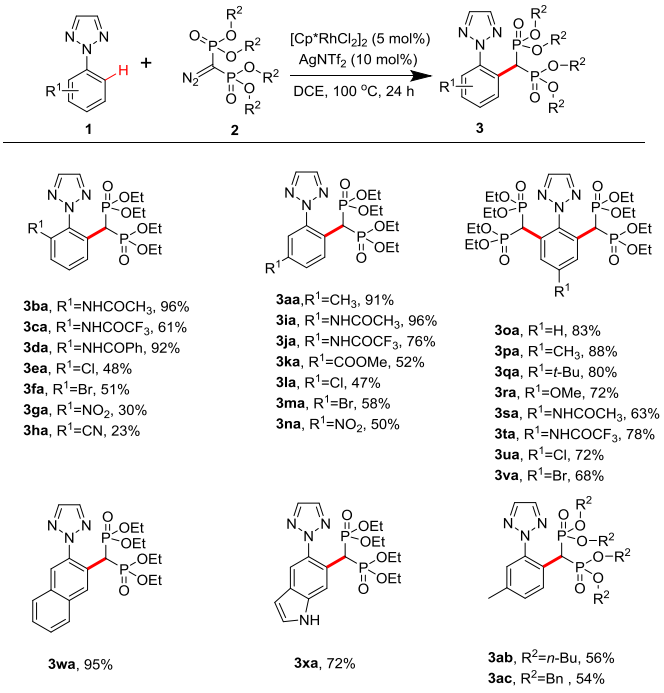


Entry	Catalyst	Ag salt	Solvent	T [°C]	Yield[b]
1	$[Cp^*RhCl_2]_2$	$AgSbF_6$	DCE	80	66%
2	$Cu(OAc)_2$	$AgSbF_6$	DCE	80	N.R.
3	$Pd(OAc)_2$	$AgSbF_6$	DCE	80	N.R.
4	$[Ru(p\text{-cymene})Cl_2]_2$	$AgSbF_6$	DCE	80	N.R.
5	$[Cp^*Co(CH_3CN)_3][SbF_6]_2$	/	DCE	80	N.R.
6	$[Cp^*Co(CO)]I_2$	$AgSbF_6$	DCE	80	N.R.
7	$[Cp^*Rh(CH_3CN)_3][SbF_6]_2$	/	DCE	80	56%
8	$[Cp^*IrCl_2]_2$	$AgSbF_6$	DCE	80	61%
9	$[Cp^*RhCl_2]_2$	$AgNTf_2$	DCE	80	72%
10	$[Cp^*RhCl_2]_2$	AgOTf	DCE	80	52%
11	$[Cp^*RhCl_2]_2$	AgOAc	DCE	80	N.R.
12	$[Cp^*RhCl_2]_2$	AgTFA	DCE	80	N.R.
13	$[Cp^*RhCl_2]_2$	$AgNTf_2$	TCP	80	51%
14	$[Cp^*RhCl_2]_2$	$AgNTf_2$	CH_3CN	80	N.R.
15	$[Cp^*RhCl_2]_2$	$AgNTf_2$	EtOH	80	23%
16	$[Cp^*RhCl_2]_2$	$AgNTf_2$	THF	80	N.R.
17	$[Cp^*RhCl_2]_2$	$AgNTf_2$	MeOH	80	42%
18	$[Cp^*RhCl_2]_2$	$AgNTf_2$	HFIP	80	55%
19	**$[Cp^*RhCl_2]_2$**	**$AgNTf_2$**	**DCE**	**100**	**91%**
20	$[Cp^*RhCl_2]_2$	$AgNTf_2$	DCE	120	88%
21	$[Cp^*IrCl_2]_2$	$AgNTf_2$	DCE	100	90%

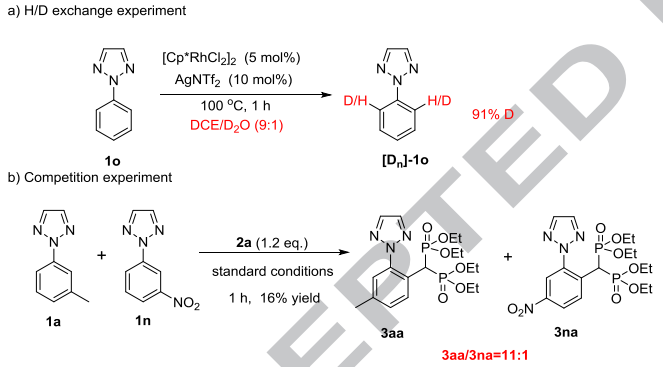
[a] Reagents and conditions: **1** (0.2 mmol), **2a** (0.24 mmol), catalyst (5 mol%), Ag salt (10 mol%), solvent (2 mL), 24 h; [b] Isolated yield

According to our previous work regarding the sulfonamidation of 2-aryl-1,2,3-triazoles with sulfonyl azides,[14] non- / *para*-substituted 2-aryl-1,2,3-triazoles were treated with 2.4 equivalents of **2a**. All substrates were dialkylated while no mono-alkylated products were observed (Scheme 2, **3oa**–**va**). Furthermore, naphthalene substituted 1,2,3-triazole (**1w**) and 1*H*-indole substituted 1,2,3-triazole (**1x**) were also tested and gave the corresponding products **3wa** and **3xa** in 95% and 72% yield, respectively. Finally, *n*-butyl and benzyl diazomethylene-diphosphonate esters were tested and products **3ab** and **3ac** were obtained in moderate yields (Scheme 2).

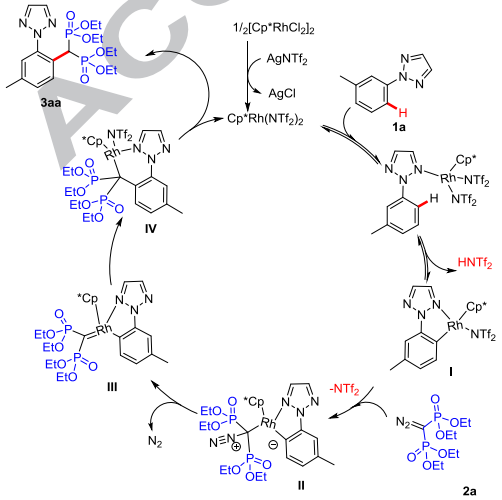
We then performed preliminary experiments to investigate the reaction mechanism. In the presence of DCE/D_2O (9:1), H/D exchange at the *ortho*-position of **1a** was observed (with 91% D incorporation), suggesting reversible C-H activation. Competition experiments with **1a** and **1n** were used to investigate the electronic preference of the reaction. The reaction resulted in a 11:1 ratio of **3aa**:**3na**, implying that electron-rich arenes react faster (Scheme 3). This result suggested the C-H bond cleavage may involve an electrophilic aromatic substitution mechanism.



Scheme 2. Rh(III)-catalyzed, directed C–H coupling of 2-aryl-1,2,3-triazoles with diazomethylene-diphosphonates. [a] Reagents and conditions: **1** (0.3 mmol), **2a** (0.36 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgNTf_2$ (10 mol%), DCE (3 mL), 100 °C, 24 h, air atmosphere; isolated yields. [b] **2a** (0.72 mmol).



Scheme 3. Mechanism studies.



Scheme 4. Possible reaction mechanism.

Based on previous work[16] and our preliminarily mechanistic experiments, a plausible mechanistic pathway is depicted in Scheme 4. Firstly, anion exchange between $[RhCp^*Cl_2]_2$ and the Ag salt generates an active catalyst, $Cp^*Rh(NTf_2)_2$, which undergoes C−H bond cleavage to form rhodacyclic intermediate **I**. Coordination of the diazo compound with **I** may form the diazonium intermediate **II** followed by extrusion of N_2 to give intermediate **III.** Next, migratory insertion of the carbene into the rhodium–carbon bond affords **IV**. Finally, protonolysis of **IV** generates the desired alkylated product and the active Rh catalyst.

Conclusion

In summary, the Rh(III)-catalyzed, 1,2,3-triazole directed C–H functionalization of arenes with diazomethylene-diphosphonates has been established. This synthetic protocol for C–C bond formation proceeded efficiently under external base-free conditions with several advantages, such as operational simplicity, high atom efficiency and a broad substrate scope. Moreover, this methodology led to structurally diverse 2-(1,2,3-triazol-2-yl)benzyl diphosphonates, which provide further possibilities to identify hit/lead compounds for clinically relevant β-lactamases as well as other protein targets.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/

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Highlights

1. 1,2,3-Triazole was used as the direct group for C-H carbenoid coupling reactions.
2. A step- and atom economical protocol constructing C-C bond was developed.
3. Bisphosphonates motifs, a unique pharmacophore, were easily assembled to arenes.