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$^{n}Bu_3P$-Catalyzed Desulfonylative [3 + 2] Cycloadditions of Allylic Carbonates with Arylazosulfones to Pyrazole Derivatives

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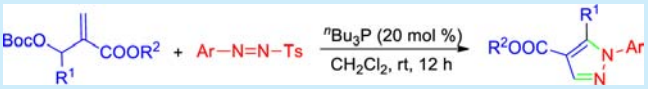
Supporting Information

ABSTRACT: Highly efficient $^{n}Bu_3P$-catalyzed desulfonylative [3 + 2] cycloadditions of allylic carbonates with arylazosulfones were developed for the synthesis of pyrazole derivatives. The reactions proceed smoothly under mild conditions to generate corresponding annulation products in good to excellent yields.

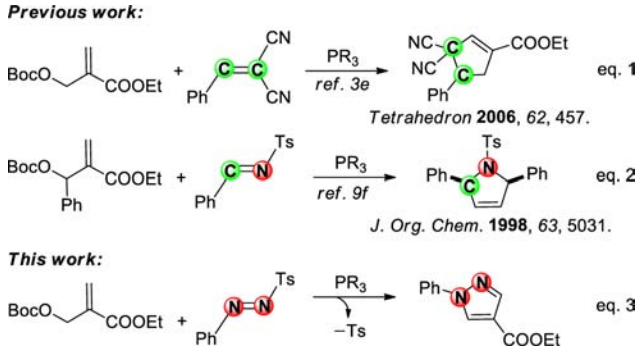


Cycloaddition is a direct method to construct cyclic molecules from simple building blocks, and the discovery of novel cycloaddition is an uninterrupted pursuit of organic chemists. Over the past decades, tertiary phosphine-mediated cycloadditions based on allylic carbonates, active alkynes or allenes with different electrophiles have been become a facile platform to cyclic compounds.[1] Among the above electrophiles,[1a] pioneer study was generally paid to the substrates involving active C=C or C=N bonds.[1a,b] For example, electron-deficient olefins have often been used as precursors for the construction of diverse cyclic compounds through a variety of cycloadditions, such as [2 + 2 + 2],[2] [3 + 2],[3] [4 + 1],[4] [4 + 2],[5] and [6 + 3][6] annulations et al.[7] In further investigation, *N*-tosylimines are also used in phosphine-catalyzed [2 + 2],[8] [3 + 2],[9] [4 + 2],[10] [4 + 1],[11] [2 + 4],[12] and sequential annulations[13] to afford *N*-containing cyclic compounds. However, there is no reported use of electron-deficient diazene as the electrophile in phosphine-promoted cyclizations.[1a]

Arylazosulfones, prepared from the coupling reaction of arenediazonium with sodium arylsulfinate, have attracted much attention due to generally using as aryl[14] or arylamine[15] source. Among various electrophiles used in the previous phosphine-catalyzed cycloadditions, especially for [3 + 2] annulations,[3,9] no report about arylazosulfones as electrophiles in tertiary phosphine-catalyzed cycloaddition to functionalized *N*-containing cyclic compound has been appeared (Scheme 1). In order to establish a new annulation, we investigate the possibility of phosphine-catalyzed cycloadditions between allylic carbonates with arylazosulfones. To our delight, desulfonylative [3 + 2] cycloadditions were observed and pyrazole derivatives were obtained with high efficiency (Scheme 1, eq 3). It is noteworthy that pyrazoles are important "druglike" heterocycles in medicinal chemistry.[16] Herein, we report the first $^{n}Bu_3P$-catalyzed desulfonylative [3 + 2] cycloadditions of allylic carbonates with arylazosulfones. The reactions undergo smoothly under mild reaction conditions to generate the corresponding pyrazole derivatives in high yields.

Our studies were initiated by addition of 20 mol % of $^{n}Bu_3P$ to ethyl 2-(((*tert*-butoxycarbonyl)oxy)methyl)acrylate (**1a**) and

Scheme 1. Typical [3 + 2] Annulations



4-(methoxyphenyl)-2-tosyldiazene (**2a**) under various reaction conditions, and the results are summarized in Table 1. The reaction of **1a** with **2a** in the presence of 20 mol % of $^{n}Bu_3P$ at room temperature for 12 h afforded **3aa** as a white solid in 42% yield. The ratio of **1a** to **2a** has an obvious effect on the product yield. The yield of product **3aa** was improved with increasing amount of **1a**, and almost quantitative yield was obtained with 3.0 equiv of **1a** used in the reaction (Table 1, entries 1−3). The amount of $^{n}Bu_3P$ also has an effect on this reaction. The desired product **3aa** was isolated in 80% yield when 10 mol % of $^{n}Bu_3P$ was used (Table 1, entries 4). Next, the influence of the solvent on the reaction was examined, CH_2Cl_2 was found to be the best one among the tested solvents. Good yields were given when the reaction was performed in CH_3CN and toluene (Table 1, entries 5 and 6). Low yield (60%) of **3aa** was obtained when DMF was used as solvent (Table 1, entry 7). Only a trace amount of **3aa** was detected when the reaction was carried out in DMSO (Table 1, entry 8). With the utilization of THF or 1,4-dioxane, the desired product was not found and most of the raw materials were recovered (Table 1, entries 9 and 10). Then, $^{n}Bu_3P$ was found to be the best catalyst in the reaction through

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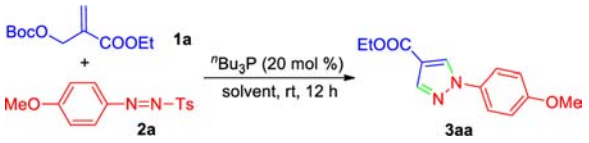
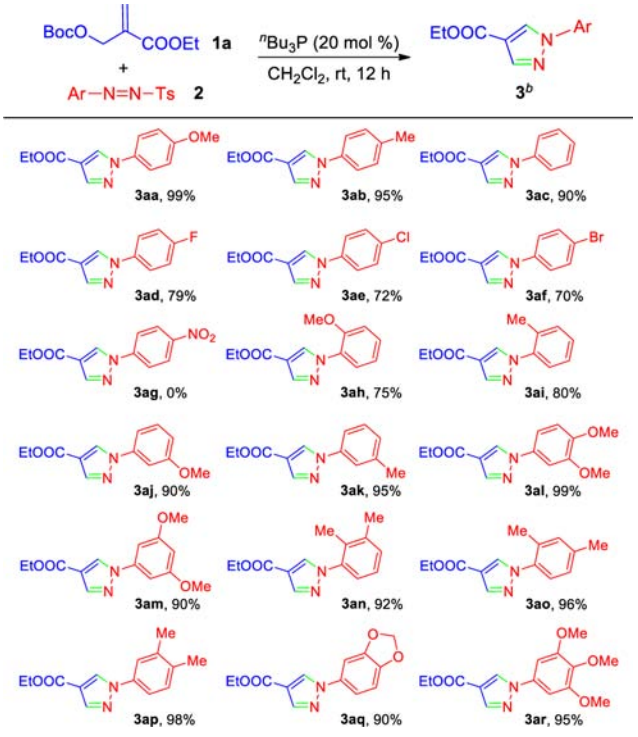
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	yield[b] (%)
1	^{n}Bu$_3$P	CH_2Cl_2	42[c]
2	^{n}Bu$_3$P	CH_2Cl_2	86[d]
3	^{n}Bu$_3$P	CH_2Cl_2	99
4	^{n}Bu$_3$P	CH_2Cl_2	80[e]
5	^{n}Bu$_3$P	CH_3CN	95
6	^{n}Bu$_3$P	toluene	93
7	^{n}Bu$_3$P	DMF	60
8	^{n}Bu$_3$P	DMSO	<10
9	^{n}Bu$_3$P	THF	ND[f]
10	^{n}Bu$_3$P	1,4-dioxane	ND
11	$PhMe_2P$	CH_2Cl_2	86
12	Cy_3P	CH_2Cl_2	75
13	Ph_2MeP	CH_2Cl_2	64
14	Ph_3P	CH_2Cl_2	NR[g]
15	DABCO	CH_2Cl_2	NR
16	DMAP	CH_2Cl_2	NR
17	DBU	CH_2Cl_2	NR
18	Et_3N	CH_2Cl_2	NR

[a]Reaction conditions: **1a** (0.60 mmol), **2a** (0.20 mmol), catalyst (0.04 mmol), solvent (2.0 mL), rt, 12 h. [b]Isolated yields. [c]1.0 equiv of **1a** was used. [d]2.0 equiv of **1a** was used. [e]10 mol % of ^{n}Bu$_3$P was used. [f]ND = no desired product was detected. [g]NR = no reaction occurred.

Scheme 2. ^{n}Bu$_3$P-Catalyzed [3 + 2] Cycloadditions of Arylazosulfones (2) with Allylic Carbonate (1a)[a]



[a]Reaction conditions: **1a** (0.60 mmol), **2** (0.20 mmol), ^{n}Bu$_3$P (0.04 mmol), CH_2Cl_2 (2.0 mL), rt, 12 h. [b]Isolated yields.

use of different tertiary phosphines including $PhMe_2P$, Cy_3P, and Ph_2MeP (Table 1, entries 11−13). Further investigation indicated that Ph_3P could not trigger the cycloaddition due to its weaker nucleophilicity (Table 1, entry 14). On the other hand, tertiary amines, such as DABCO, DMAP, DBU, and Et_3N were examined, but no reaction occurred (Table 1, entries 15−18).

With the optimized conditions in hand (20 mol % ^{n}Bu$_3$P as catalyst, CH_2Cl_2 as solvent, at room temperature for 12 h), the substrate scope for the annulations of arylazosulfones (**2**) with ethyl 2-(((*tert*-butoxycarbonyl)oxy)methyl)acrylate (**1a**) was studied. For a wide range of arylazosulfones with either electron-rich or electron-poor aryl groups, the corresponding [3 + 2] annulations with **1a** proceeded smoothly, giving 1,4-disubstituted pyrazoles (**3**) with high efficiency, as shown in Scheme 2. However, the efficiency of the reaction was relatively sensitive to the substituents on the aromatic rings in different arylazosulfones. Arylazosulfones with an electron-donating group on the aromatic ring gave a better yield than that of an electron-withdrawing group on the aromatic ring. For example, the substrates with an electron-donating group, such as CH_3O or CH_3, on the phenyl ring reacted with **1a** to afford the corresponding products in almost quantitative yields. Arylazosulfones with an electron-withdrawing group (F, Cl or Br) on the phenyl ring reacted with **1a** to generate the desired products in 70−79% yields. Notably, the reaction was complicated when 4-(nitrophenyl)-2-tosyldiazene was used as diazene substrate, and no corresponding product was formed. When CH_3O and CH_3 group were located at the *ortho*-position of the benzene rings, the corresponding product **3ah** and **3ai** were obtained in low yields owing to the steric hindrance. Treatment of 3-(methoxyphenyl)- and 3-(methylphenyl)-2-tosyldiazene with **1a** afforded the desired products (**3aj** and **3ak**) in 90 and 95% yields, respectively. Arylazosulfones with two electron-rich groups, such as 3,4-dimethoxy, 3,5-dimethoxy, 2,3-dimethyl, 2,4-dimethyl, and 3,4-dimethyl, could give the corresponding products (**3al**−**ap**) in excellent yields. Furthermore, the reactions of benzo[d][1,3]dioxol-5-yl-2-tosyldiazene and 3,4,5-(trimethoxyphenyl)-2-tosyldiazene with **1a** proceeded very well and generated the desired products **3aq** and **3ar** in 90 and 95% yields, respectively. X-ray crystallographic analysis for representative **3af** provided unequivocal evidence for the reaction.[17]

To further evaluate the scope of this reaction, different allylic carbonates with arylazosulfones were examined under the standard conditions. As can be seen from Scheme 3, as expected, allylic carbonates with different ester groups could react with 4-(methoxyphenyl)-2-tosyldiazene (**2a**) smoothly to generate the desired products (**3ba**−**fa**) in excellent yields. The size of the ester group in **1** had no effect on the efficient of the reaction. Further, *β*-methyl-substituted allylic carbonates also gave the desired products (**3ga**, **3gc**, **3gl**, and **3gp**) in 96, 91, 90, and 94% yields, respectively. A moderate yield of **3ha** was obtained when *β*-aryl-substituted allylic carbonates reacted with **2a**.

On the other hand, arylazosulfones with different sulfonyl groups, such as phenylsulfonyl and methylsulfonyl, were examined for the reaction with **1a**, as shown in Scheme 4. The results indicated that the reactions underwent smoothly to generate the desired product **3aa** in excellent yields.

On the basis of the above experimental results and previous reports, a plausible reaction mechanism was proposed in Scheme 5. The reaction might be triggered by addition of ^{n}Bu$_3$P to allylic carbonate **1**, and then an allylic phosphorus

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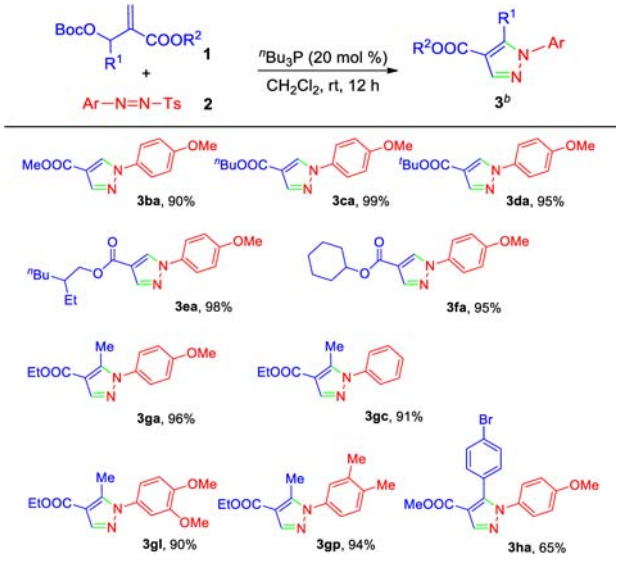
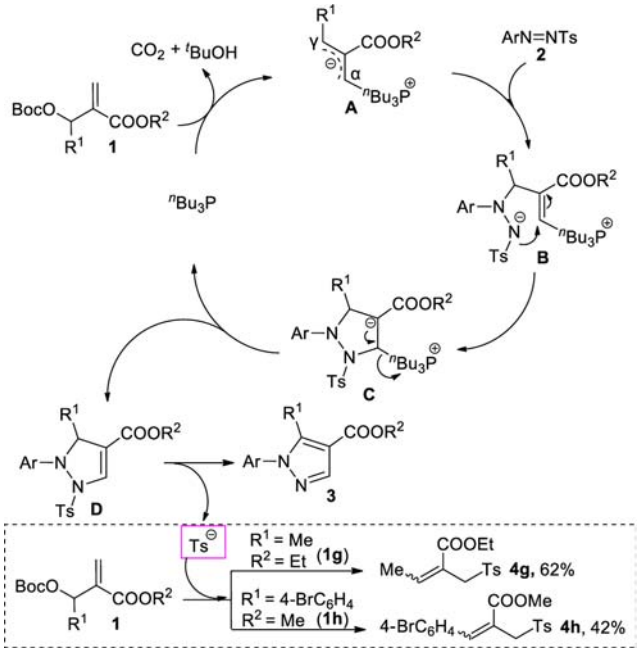
Scheme 3. Scope of Allylic Carbonates (1)[a]



[a]Reaction conditions: **1** (0.60 mmol), **2** (0.20 mmol), $^{n}Bu_3P$ (0.04 mmol), CH_2Cl_2 (2.0 mL), rt, 12 h. [b]Isolated yields.

Scheme 4. Sulfonyl Group Effect on the Desulfonylative [3 + 2] Cycloadditions

Scheme 5. Possible Mechanism



ylide intermediate **A** was formed via an elimination−deprotonation process and concomitantly removed carbon dioxide and *t*-BuOH.

Subsequent γ-addition[3e] of the ylide **A** to arylazosulfone **2** generated intermediate **B**, which underwent an intramolecular nucleophilic attack of nitrogen anion to the olefinic double bond (Michael type) to give intermediate **C**, followed by elimination of $^{n}Bu_3P$ to afford dihydropyrazole **D**. Further desulfonylation led to pyrazole product **3**.[12] It is worth noting that **D** was not isolated, owing to its unstable property. The generation of side product **4g** and **4h** provided evidence in support of this proposed mechanism.

In conclusion, highly efficient $^{n}Bu_3P$-catalyzed desulfonylative [3 + 2] cycloadditions of allylic carbonates with arylazosulfones were developed for the synthesis of pyrazole derivatives. These cyclization reactions proceed smoothly under mild conditions to produce a broad range of pyrazole derivatives in good to excellent yields. This protocol has advantages of using available starting materials and simple manipulation. In addition, a plausible reaction mechanism has been proposed. Efforts in our laboratory seek electron-deficient diazenes as electrophiles in the presence of nucleophilic phosphine catalysis for other annulations.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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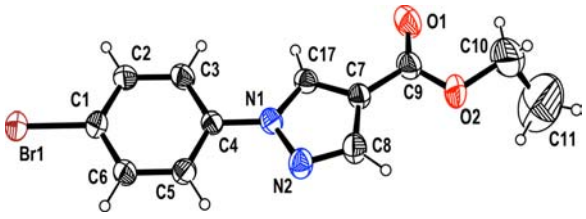
(17) X-ray single crystal structure of **3af** (CCDC: 1036532).



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