

Research Article

Design of Bifunctional Tetraarylphosphonium Salt Catalysts

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Abstract: The [3+2] reactions between epoxides and carbon dioxide proceeded effectively in the presence of bifunctional tetraarylphosphonium salt catalysts, affording the corresponding cyclic carbonates in high yields. The use of isocyanates instead of carbon dioxide was found to be efficient for the synthesis of oxazolidinones from epoxides. In addition, we have successfully developed a novel phosphonium ylide as a nucleophilic catalyst for selective acylation of primary alcohols.

Keywords: organocatalyst, bifunctional catalysis, phosphonium salt, [3+2] reaction, acylation

1. Introduction

Environmentally-friendly chemical syntheses are desired for creating a sustainable society. In the field of catalysis development, organocatalysts have emerged as green catalysts and great progress in their use has been made over the past two decades. Most organocatalysts have been designed to achieve stereocontrol, especially enantiocontrol, in asymmetric reactions, whereas there are relatively limited numbers of reports on catalysts that enable the control of chemoselectivity intentionally in non-asymmetric reactions. Our group focused on tetraarylphosphonium salts (TAPS), which bear four aryl groups on the phosphorus atom, and has been exploring their catalytic functions. We herein describe the design of bifunctional TAPS catalysts and TAPS-catalyzed [3+2] reactions between epoxides and heterocumulenes. The reactions using a bifunctional TAPS-derived phosphonium ylide as a novel nucleophilic catalyst are also reported.

2. Bifunctional TAPS catalysis

2-1. Catalyst design challenges

Phosphonium salts are phosphorus(V) compounds widely used in organic synthesis as precursors of Wittig reagents, phase transfer catalysts, ionic liquids, and other applications.¹ Tetraarylphosphonium salts (TAPS), which are stereoelectronically tunable, are attractive scaffolds for organocatalysts.² As shown in **Figure 1**, it is expected that TAPS bearing a hydroxyl group on an aromatic ring might serve as a bifunctional catalyst composed of a Brønsted acidic site (a phenolic hydroxy group) and a nucleophilic site (a halide ion). However, the catalytic ability of TAPS has remained unexploited.³ Therefore, we reasoned that the exploration of TAPS functions for catalysis would be fruitful from the viewpoint of developing new molecular technology.

Design of bifunctional TAPS

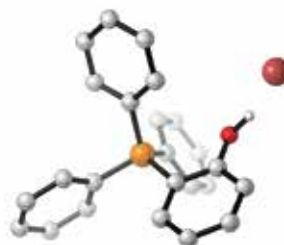
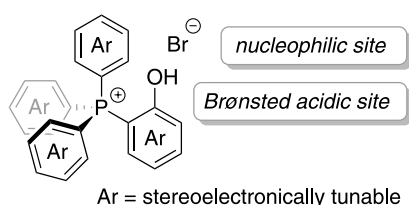
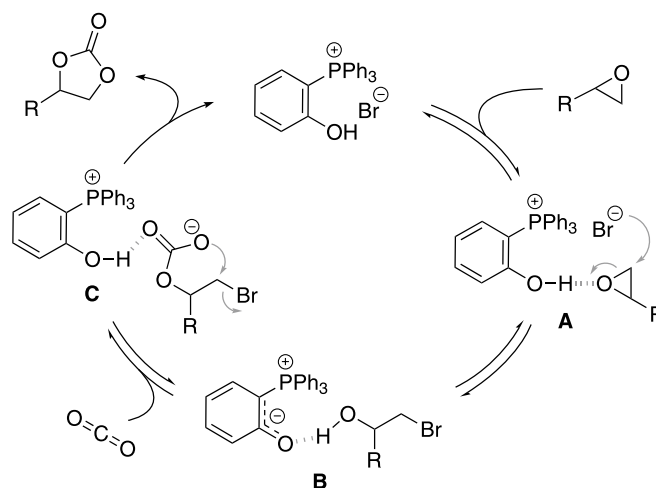


Figure 1. Design of bifunctional TAPS and an optimized structure by DFT calculations (M06-2X/6-31G(d) for C, H, O, and P, M06-2X/LanL2DZ for Br, IEFPCM=PhCl)

2-2. [3+2] Reactions of epoxides with carbon dioxide

The role of carbon dioxide (CO₂) as a C1 building block of valuable compounds, namely CO₂ fixation, has been recognized as crucial in organic synthesis.⁴ One of the most well-known methods is the reaction between epoxides and CO₂ to produce five-membered cyclic carbonates, and several catalytic systems including onium salt catalysis have been reported to date.⁵ Thus, we expected that bifunctional TAPS might efficiently

promote the epoxide-CO₂ reaction for the following reasons (**Scheme 1**): (i) Brønsted acid activation of the epoxide could accelerate the epoxide ring-opening step by the halide ion (**A**); (ii) the TAPS-derived phosphonium ylide could serve as a Brønsted base to facilitate CO₂ insertion into the halohydrin intermediate **B**. Notably, there are only a few reports of CO₂ fixation using bifunctional phosphonium salt catalysts.⁶

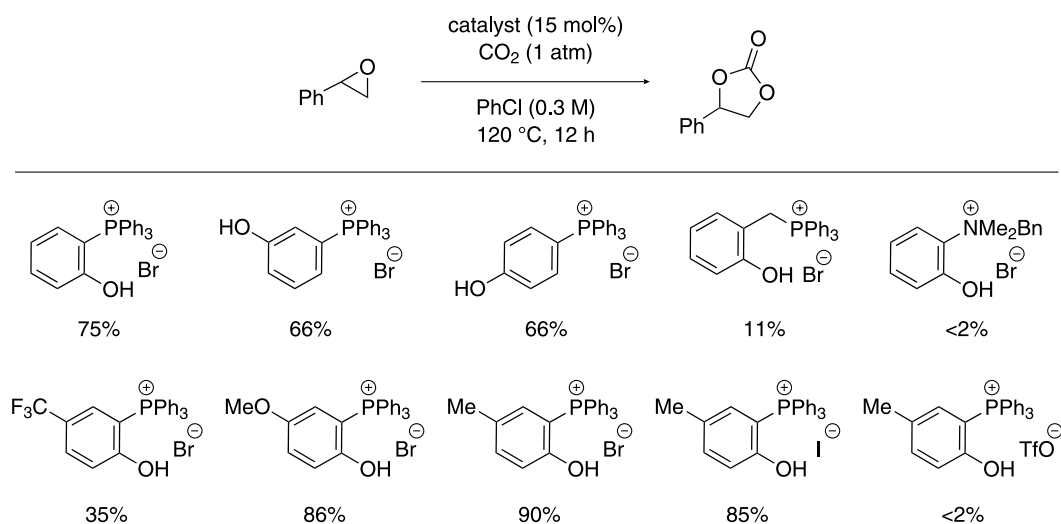


Scheme 1. Working hypothesis of the bifunctional TAPS-catalyzed CO₂ fixation

At the outset of our studies, the screening of TAPS was performed using styrene oxide with 15 mol% of catalyst and a balloon of CO₂ in 0.3 M chlorobenzene at 120 °C for 12 h (**Table 1**). We discovered that a bifunctional TAPS catalyst possessing a phenolic hydroxy group at the *ortho*-position could facilitate the present reaction, affording the corresponding carbonate in moderate yield. Interestingly, the use of different but similar types of onium salts resulted

in lower yields. The substituents on the phenol moiety were further investigated, and methyl-substituted TAPS (**MeTAPS-Br**) was found to give the highest yield under the reaction conditions.⁷ Switching the bromide ion to a less nucleophilic counterion such as triflate led to no formation of the products, while TAPS having an iodide ion (**MeTAPS-I**) showed comparable reactivity.

Table 1. Catalyst screening in CO₂ fixation

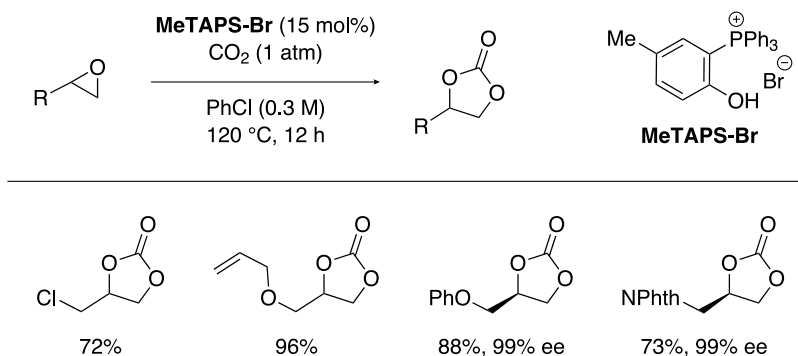


NMR yields are shown.

The scope of epoxides is summarized in **Table 2**. Commercially available terminal epoxides such as epichlorohydrin and allyl glycidyl ether provided the products in good yields. Moreover, enantiopure (*S*)-phenyl

glycidyl ether and (*R*)-*N*-glycidylphthalimide underwent the CO₂ fixation in a stereoretentive manner with high enantiomeric excess.

Table 2. Scope of epoxides in CO₂ fixation

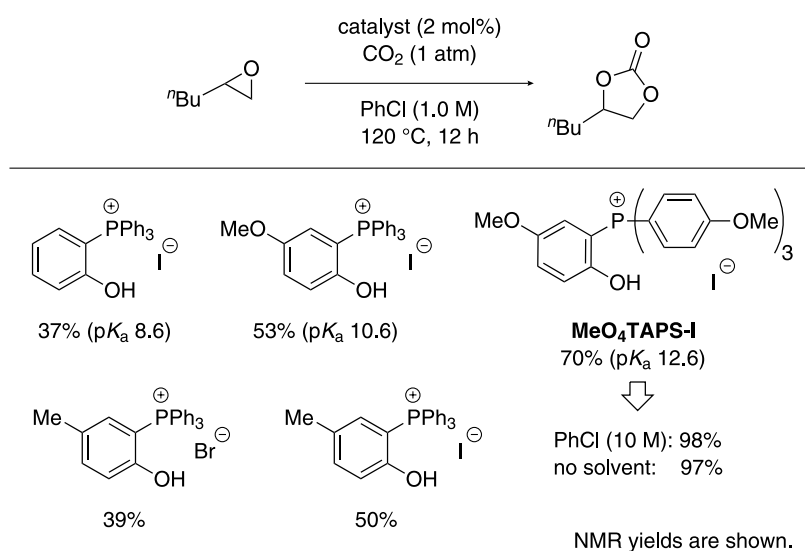


2-3. Development of 2nd generation TAPS

Although **MeTAPS-Br** can catalyze the epoxide-CO₂ reaction under atmospheric pressure of CO₂, some issues remained to be addressed, including the amount of the catalyst (15 mol%) and the reaction temperature (120 °C). Thus, we devoted our efforts to the development of highly active bifunctional TAPS in the cyclic carbonate synthesis by scrutinizing electronically-tuned TAPS. It was surprising that less-acidic TAPS bearing methoxy group(s) produced cyclic carbonates in higher yields.

Finally, we disclosed that 2 mol% of **MeO₄TAPS-I** was able to catalyze the reaction at 60 °C, leading to high yields in 10 M chlorobenzene or solvent-free conditions (**Table 3**).⁸ Furthermore, mechanistic studies by DFT calculations revealed that the enhanced catalytic activity by introduction of the methoxy groups on TAPS was attributed to the stabilization of carbonate intermediate **C** in **Scheme 1**.

Table 3. Correlation between the acidity and activity of TAPS

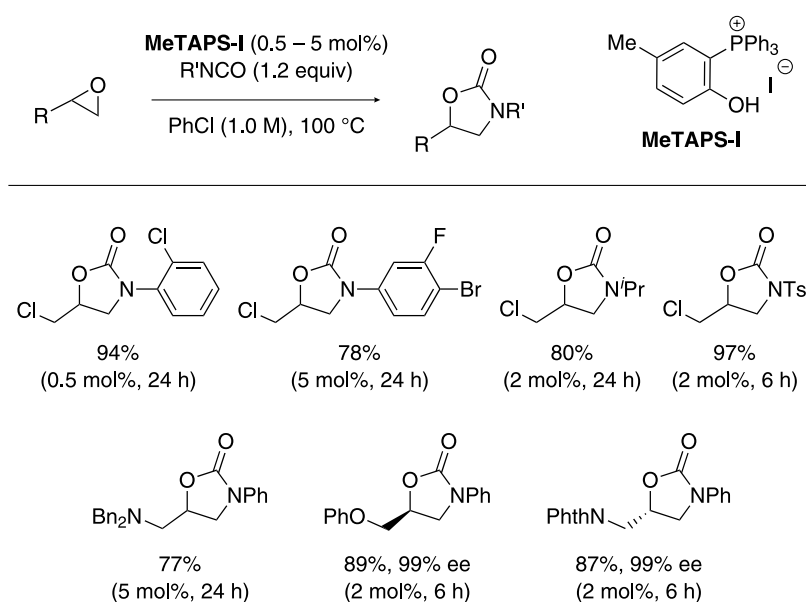


2-4. [3+2] Reactions of epoxides with isocyanates

We next focused on the synthesis of oxazolidinones which represent an important class of nitrogen and oxygen containing heterocyclic compounds. It is known that isocyanates, isoelectronic compounds of CO₂, undergo [3+2] reactions with epoxides in the presence of catalysts such as quaternary ammonium salts to form oxazolidinones.⁹ However, conventional catalysis would not be applicable to a practical synthesis because harsh reaction conditions or complicated experimental procedures are often required. These problems have some recent modernized solutions using metal (salen)

complexes,¹⁰ but the scope of isocyanates has been limited. We hence envisioned that our bifunctional TAPS catalysis might overcome the issues of the epoxide-isocyanate reaction. To our delight, the reaction using 0.5–5 mol% of **MeTAPS-I** efficiently yielded the desired oxazolidinones in 1.0 M chlorobenzene at 100 °C (**Table 4**).¹¹ It should be emphasized that our catalysis tolerated electron-deficient aryl isocyanates and aliphatic isocyanates, which led to poor yields in most previous reports.

Table 4. Bifunctional TAPS-catalyzed synthesis of oxazolidinones

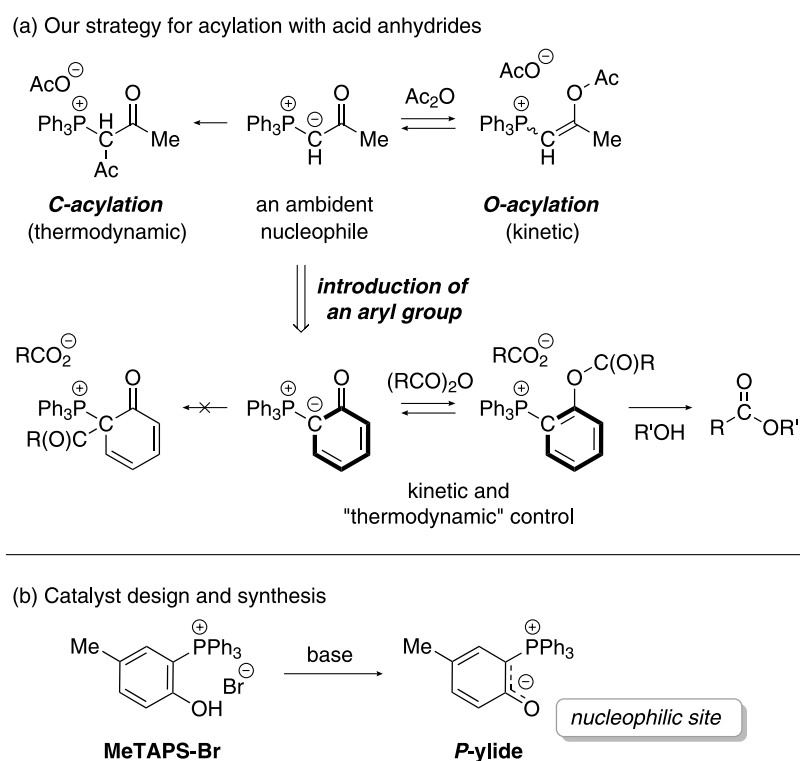


3. Phosponium ylide catalysis

3-1. Catalyst design challenges

Carbonyl-stabilized phosphonium ylides (*P*-ylides) are known as ambident nucleophiles.¹² A recent report on the mechanism of this type of *P*-ylide with acetic anhydride suggested that *O*-acylation of the ylides is kinetically favored (**Scheme 2a**).¹³ It has also been shown that the *C*-acylated, thermodynamically favored product was obtained exclusively in the same reaction, in which irreversible acyl-transfer from an *O*-acylated ylide to a *C*-acylated ylide occurred. Therefore, it could

be feasible to establish nucleophilic catalysis by *P*-ylides if the *O*-acylated intermediate is allowed to undergo acyl-transfer to external nucleophiles. For this investigation, we designed a bifunctional TAPS-derived *P*-ylide (**Scheme 2b**). The aryl group introduced into the ylide carbon moiety is expected to block undesired *C*-acylation, because *O*-acylation gives not only a kinetically stable product but also a thermodynamically stable product due to the aromatic stabilization.

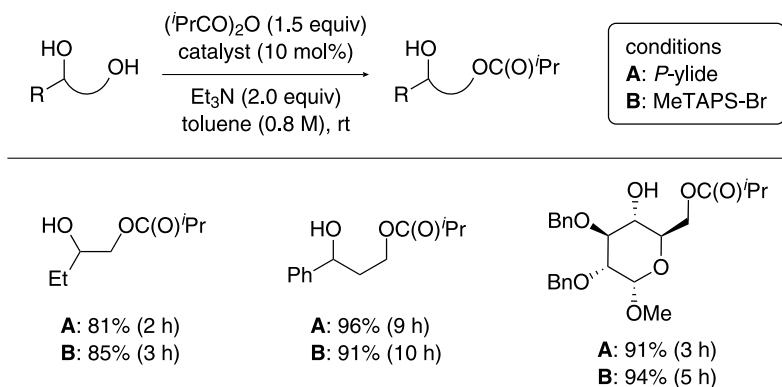


Scheme 2. Design of nucleophilic catalysis by a phosphonium ylide

3-2. Selective acylation of primary alcohols

Selective acylation of a primary alcohol in the presence of secondary alcohol(s) affords great utility in organic synthesis. Several methods such as reagent-control systems¹⁴ and metal catalysis¹⁵ have been developed to date. In contrast, few organocatalysts have been applied to selective acylation,¹⁶ and thus we sought to use the TAPS-derived *P*-ylide as a nucleophilic catalyst for this purpose. The reactions were carried

out using 1.5 equiv of isobutyric anhydride, 10 mol% of *P*-ylide (conditions A) or **MeTAPS-Br** (conditions B), and 2.0 equiv of triethylamine in toluene (0.8 M) at room temperature, leading to highly selective acylation of mixed 1,*n*-diols (**Table 5**).¹⁷ The catalysis can also achieve base-free acylation and acetylation with acetic anhydride.

Table 5. Primary alcohol selective acylation of 1,n-diols

4. Conclusion

TAPS-catalyzed [3+2] reactions between epoxides and heterocumulenes, including CO₂ and isocyanates, are described. The catalytic ability of bifunctional TAPS was proved to catalyze CO₂ fixation under atmospheric pressure of CO₂. This TAPS catalysis is also applicable to the reaction of epoxides with isocyanates, where the scope

of isocyanates has been expanded. In addition, a TAPS-derived phosphonium ylide was successfully developed, enabling selective acylation of primary alcohols. We have identified the importance of our catalyst design to exhibit unique behavior. Further synthetic applications would empower TAPS as a fascinating catalyst.

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Related Products

(2-Hydroxy-5-methylphenyl)triphenylphosphonium Bromide (= MeTAPS-Br)	1g	5g	H1748
(2-Hydroxy-5-methylphenyl)triphenylphosphonium Iodide (= MeTAPS-I)	1g	5g	H1749
Styrene Oxide	25mL	500mL	E0013
Epichlorohydrin	25g	500g	E0012
Allyl Glycidyl Ether	25mL	500mL	A0221
(S)-Glycidyl Phenyl Ether	1g	5g	G0410
(R)-N-Glycidylphthalimide	5g	25g	G0327
Isobutyric Anhydride	25mL	500mL	I0111