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Tetraarylphosphonium Salt-Catalyzed Synthesis of Oxazolidinones from Isocyanates and Epoxides

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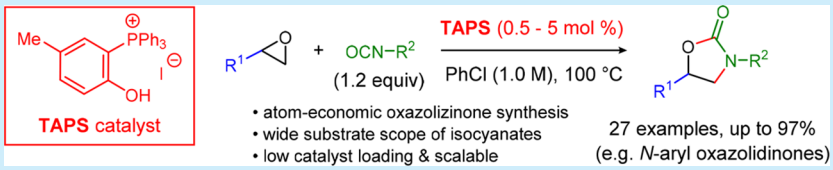
Supporting Information



ABSTRACT: Preparation of a range of oxazolidinones, including enantioenriched *N*-aryl-substituted oxazolidinones, in which tetraarylphosphonium salts (TAPS) catalyze the [3 + 2] coupling reaction of isocyanates and epoxides effectively, is described. The key finding is a Brønsted acid/halide ion bifunctional catalyst that can accelerate epoxide ring opening with high regioselectivity. Mechanistic studies disclosed that the ylide generated from TAPS, along with the formation of halohydrins, plays a crucial role in the reaction with isocyanates.

Oxazolidinones represent an important class of nitrogen and oxygen containing heterocyclic compounds, many of which exhibit great utility, not only as valuable intermediates in organic synthesis but also in their own right.[1] In particular, *N*-aryl-substituted oxazolidinones have gained increasing attention from medicinal chemists and pharmacologists due to the potent biological activity of the oxazolidinones.[2] Thus, the development of a facile, practical, and robust access to a diverse array of those derivatives, in order to expeditiously generate chemical libraries for drug discovery, has been intensively pursued.

There are a large number of strategies that have been used for the synthesis of an oxazolidinone core.[3−6] One of the most straightforward and atom-economical methods is the [3 + 2] coupling reaction of isocyanates and epoxides, which enables modular and flexible production of lead analogues by switching one or both substrates. In 1958, Speranza and Peppel demonstrated the catalytic transformation by using quaternary ammonium salts.[7] In other reports, several metal salts have been shown to catalyze the reaction, but undesirable conditions (e.g., excessive high temperature, high catalyst loadings, large excess of epoxides, or slow addition of isocyanates) were often required to afford the products.[8] Although these problems have some recent modernized solutions using metal complexes, chemical yields tend to drastically decrease when electron-deficient or aliphatic isocyanates are employed.[9]

Meanwhile, over the past two decades, organocatalysts have made remarkable progress, enabling various transformations without the use of costly and/or toxic metals. We have recently developed a tetraarylphosphonium salt (TAPS) prepared from an *ortho*-halogenated cresol and triphenylphosphine in only one step, which was proven to facilitate the reaction of carbon dioxide with terminal epoxides.[10a] In the reaction presented, an *ortho*-hydroxy group on TAPS has been found to be important for the initiation of ring opening of epoxides by the synergistic effect of a *Brønsted acid* and a nucleophilic halide ion. We hence reasoned that TAPS catalysis could be applicable to the addition of other heterocumulenes to epoxides as well as carbon dioxide. However, this remains a formidable challenge since no effective organocatalysis has been reported for the synthesis of oxazolidinones via the [3 + 2] coupling reaction to date. Herein, we describe TAPS catalysis that allows the coupling between isocyanates and epoxides (Figure 1). This approach would not only grant efficient entry to oxazolidinone synthesis but also empower bifunctional TAPS as the premier organocatalytic entities for epoxide activation and functionalization. Moreover, the present study shows that the ylide[10b]

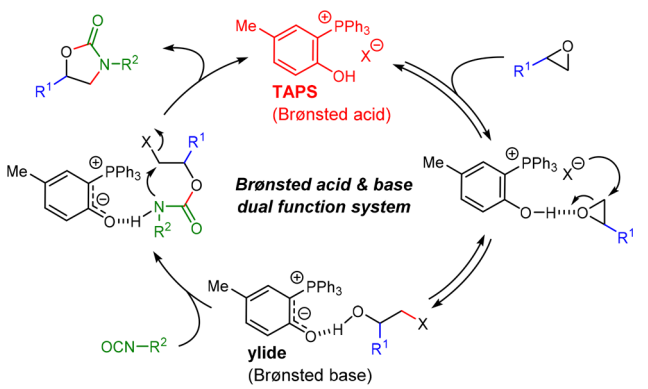


Figure 1. Strategy for [3 + 2] coupling reaction of isocyanates and epoxides by organocatalysis.

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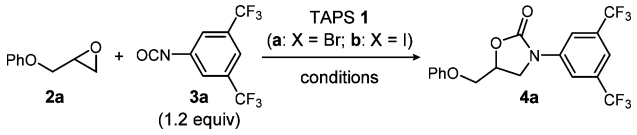
derived from TAPS exhibits a specific character as a *Brønsted base*, delivering intermediates to products wherein TAPS could be regenerated.

At the outset of our study, we selected isocyanate **3a** as the representative electron-deficient aryl isocyanate for screening of reaction conditions. The initial experiments were performed using epoxide **2a** and 1.2 equiv of **3a** in chlorobenzene at 120 °C for 6 h (Table 1). To our delight, 15 mol % of TAPS **1a**

Table 1. Optimization of Reaction Conditions[a]



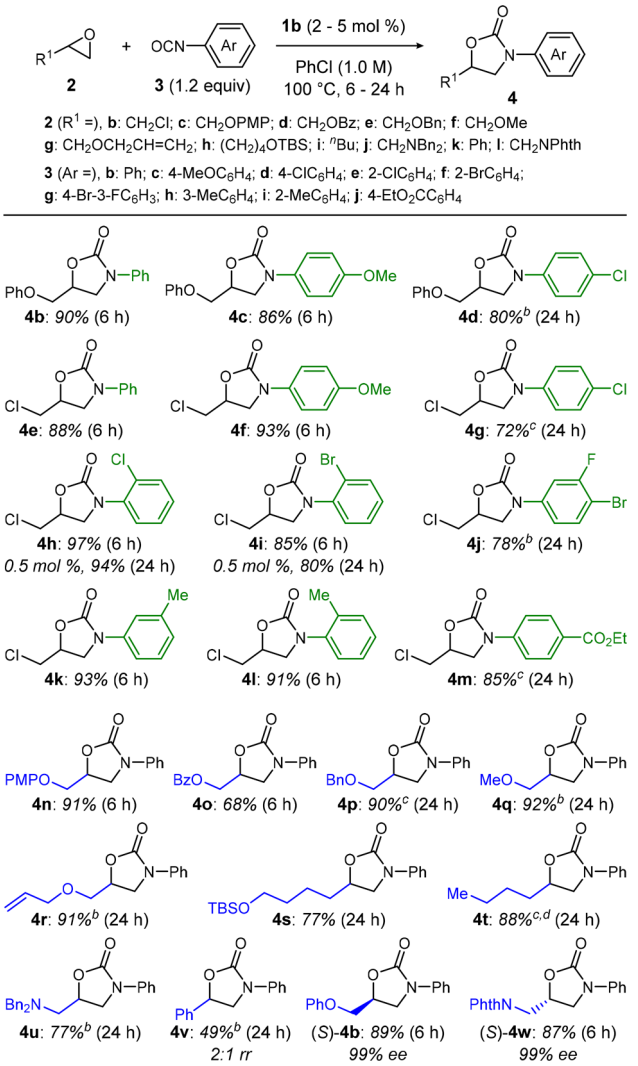
entry	1 (mol %)	conditions	4a (%)[b]
1	**1a** (15)	PhCl (0.3 M), 120 °C, 6 h	>98
2	none	PhCl (0.3 M), 120 °C, 6 h	0
3	**1a** (2)	PhCl (0.3 M), 120 °C, 6 h	45
4	**1b** (2)	PhCl (0.3 M), 120 °C, 6 h	52
5	**1b** (2)	PhCl (0.3 M), 100 °C, 6 h	35
6	**1b** (2)	1,4-dioxane (0.3 M), 100 °C, 6 h	28
7	**1b** (2)	DMA (0.3 M), 100 °C, 6 h	16
8[c]	**1b** (2)	PhCl (1.0 M), 100 °C, 6 h	81
9[c]	**1b** (2)	PhCl (1.0 M), 100 °C, 24 h	>98 (94)

[a]Unless otherwise noted, all reactions were carried out on a 0.20 mmol scale using epoxide **2a** and 1.2 equiv of isocyanate **3a**. [b]Determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard (isolated yield is shown in parentheses). [c]0.60 mmol scale.

(counterion X^- = Br^-) afforded oxazolidinone **4a** in quantitative yield, while no reaction was observed in the absence of a catalyst (Table 1, entries 1 and 2). An attempt to lower the catalyst loading of **1a** (2 mol %) resulted in low yield, but TAPS **1b**, bearing an iodide ion (X^- = I^-), afforded an over 50% yield of **4a** (Table 1, entries 3 and 4). To establish a procedure under mild reaction conditions, the temperature, solvent, and concentration were further screened (Table 1, entries 5–8). As a result, good conversion was achieved with a higher concentration of substrates in chlorobenzene, and finally **4a** was obtained in 94% isolated yield by prolonging the period of a reaction (Table 1, entry 9).

The scope of substrates is summarized in Scheme 1. First, a series of aryl isocyanates **3** was examined to probe the generality of the TAPS-catalyzed coupling reaction. For reactions involving **2a**, phenyl and *p*-methoxyphenyl isocyanates (**3b** and **3c**) showed higher reactivity than **3a** (6 h for **4b** and **4c** vs 24 h for **4a**). On the other hand, 5 mol % of **1b** was required when *p*-chlorophenyl isocyanate (**3d**) was employed (**4d**: 80%). For reactions involving epichlorohydrin (**2b**), a similar tendency was observed: higher yields were obtained with use of **3b** and **3c** while **3d** gave a lower yield (**4e**: 88% and **4f**: 93% vs **4g**: 72%). In contrast, *ortho*-halogenated aryl isocyanate **3e** was accommodated efficiently, affording the corresponding oxazolidinones **4h** in 97% yield. Only 0.5 mol % of **1b** was able to catalyze the coupling with **3e** and **3f** (**4h**: 94% and **4i**: 80%), while aryl isocyanate with dihalogen substituents **3g** was challenging presumably due to the decomposition of **3g** (**4j**: 78%). Steric effects of **3** were also investigated (**3h** vs **3i**), but there was no significant difference between the *meta*- and *ortho*-position (**4k**: 93% vs **4l**: 91%). In addition, isocyanate **3j** having an ester group furnished **4m** in good yield. Next, a

Scheme 1. Substrate Scope[a]



[a]Unless otherwise noted, all reactions were carried out on a 0.60 mmol scale using 2 mol % of **1b**, epoxide **2** and 1.2 equiv of isocyanate **3** in PhCl (1.0 M) at 100 °C. [b]5 mol %. [c]3 mol %. [d]120 °C.

variety of terminal epoxides **2** were screened to couple with **3b**. Glycidol derivatives **2c–g** afforded **4n–r** in high yields except for **4o**. Epoxides **2d–g** bearing amino and alkyl groups were also applicable to give **4s–u** in good to high yields. Styrene oxide (**2k**) underwent the [3 + 2] reaction; however, a regioisomer of **4v** was apparently observed. Moreover, enantiopure epoxides (*S*)-**2a** and (*S*)-**2l** were submitted to the optimized reaction conditions to provide the optically active oxazolidinones, and (*S*)-**4b** and (*S*)-**4w** were obtained with high enantiomeric excesses without stereochemical erosion.[11] Cyclohexene oxide was challenging; thus, only 5% of the corresponding product was observed by ^{1}H NMR analysis. To expand the applicability of our methodology, other isocyanates **5** were tested (Scheme 2a). Delightfully, TAPS catalysis tolerated isocyanates **5a–d**, whereas aliphatic isocyanates led to poor yields in most previous reports.[9a,c] Furthermore, the reaction **2b** with **3h** was performed on gram scale in the presence of 1 mol % of TAPS **1b**, affording **4k** in excellent yield (Scheme 2b). Toloxatone (**4x**)[12] was synthesized in three steps from commercially available **2d** and **3h**. For the enantioenriched product (*S*)-**4w**, *para*-selective iodination

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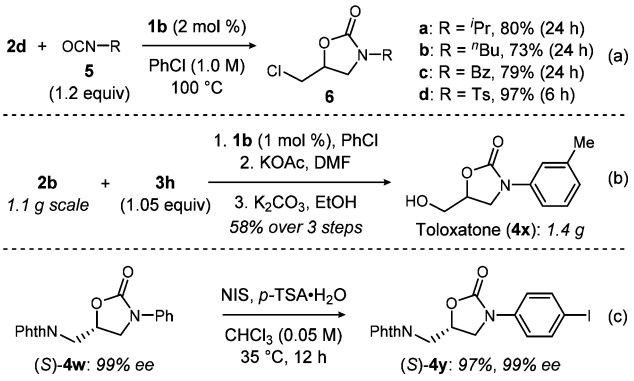
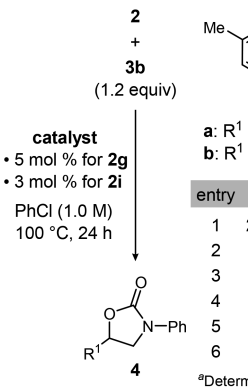
Scheme 2. Synthetic Application

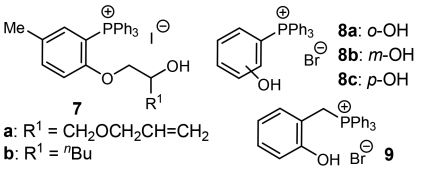


of the *N*-aryl ring produced (*S*)-**4y** without loss of enantioselectivity (Scheme 2c).[13]

In order to evaluate the TAPS catalysis established, we conducted control experiments by using several catalysts **7**–**9** (Table 2). In the case of previously reported TAPS-catalyzed

Table 2. Evaluation of TAPS Catalysis for [3 + 2] Coupling Reaction of Isocyanates and Epoxides





entry	2	cat.	4r (%)[a]	entry	2	cat.	4t (%)[a]
1	2g	1b	96 (<1)	7	2i	1b	74 (<1)
2		7a	31 (61)	8		7b	24 (73)
3		8a	72 (34)	9		8a	45 (22)
4		8b	56 (41)	10		8b	40 (50)
5		8c	32 (65)	11		8c	8 (88)
6		9	25 (73)	12		9	<1 (99)

[a]Determined by ^{1}H NMR (SM recovery is shown in parentheses).

CO_2 fixation, it has been revealed that the epoxide-adduct **7a** was formed *in situ* that could activate epoxides to afford cyclic carbonates.[10a] Interestingly, only a 31% yield of **4r** (R^1 = allyl) was obtained in the reaction of **2g** with **3b** using **7a**, which strongly suggested that the adduct **7a** was not an active species in the present reaction (Table 2, entry 2). Furthermore, compared with TAPS **8a** (*ortho*-OH), the use of **8b** (*meta*-OH), **8c** (*para*-OH), and **9** led to decreased yields of **4r** (Table 2, entries 3–6). The effect of catalysts was also investigated for epoxide **2i** (R^1 = ^{n}Bu), and as expected, **1b** marked the highest yield with similar tendency (Table 2, entries 7–12).[14] This result motivated us to scrutinize the mechanism of the [3 + 2] coupling reaction. First, we conducted ^{1}H NMR experiments in $CDCl_3$ at 25 °C to monitor the behavior of the catalysts (Figure 2a; see Supporting Information (SI)). When TAPS **1b** was mixed with a stoichiometric amount of epoxide **2i**, the Ar–H protons on the cresol moiety significantly shifted upfield. It should be emphasized that iodohydrin **11** was observed within 10 min upon the addition of **2i**. At the period of 60 min, the aromatic protons gave sharp signals, indicating the generation of the corresponding ylide **10**. We postulated that the difference of catalytic ability might be attributed to the epoxide ring-opening step, and attempted the same experiments for catalysts **8a**–**c** and **9** as well. Indeed, TAPS **1b** showed much

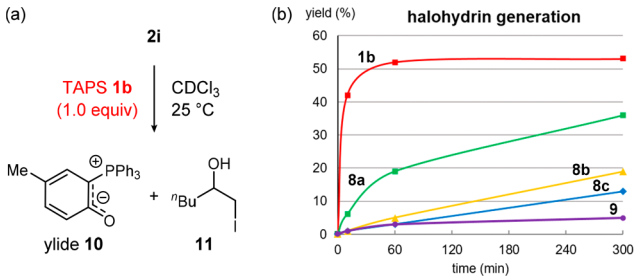
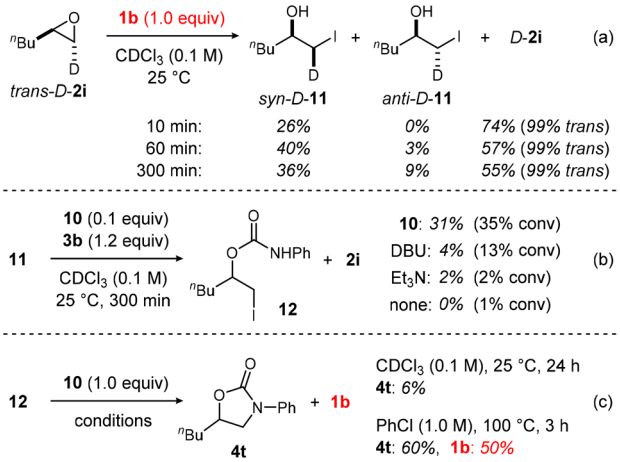


Figure 2. (a) ^{1}H NMR experiments. (b) Effect of catalysts on the ring opening of epoxides.

faster conversion of **2i** into **11**, which mostly correlated to the chemical yields of **4i** (Figure 2b). On the basis of the results above, the iodohydrin formation seemed to attain equilibrium after 1 h. As shown in Scheme 3a, a moderate amount of *syn*-*D*-

Scheme 3. Mechanistic Studies



11 was epimerized to *anti*-*D*-**11** during the course of the reaction, while *trans*-*D*-**2i** maintained the stereochemistry at the *β*-carbon. This observation evidently disclosed halide ion substitution on alkyl halides started occurring. Next, iodohydrin **11** was reacted with isocyanate **3b** to gain insight into the second step (Scheme 3b). It should be noted that ylide **10** advantageously produced carbamate **12** in comparison with other Brønsted bases.[15] We confirmed that treatment of this carbamate **12** with 1 equiv of ylide **10** leads to formation of the oxazolidinone **4t** and regeneration of TAPS **1b** (Scheme 3c). Importantly, although the cyclization proceeded insufficiently at 25 °C, elevated temperature facilely enabled the process to yield both **4t** and **1b**. Supported by these experiments, we propose the mechanism of TAPS-catalyzed formal [3 + 2] cycloaddition in Figure 1. The catalysis involves a three-step sequence: (i) halohydrin formation; (ii) carbamate formation; (iii) oxazolidinone formation. It is strongly suggested that the ring-closing step determines the rate of the whole transformation, where a less acidic N–H proton needs to be released. The pivotal factor of a successful coupling between **2** and **3** would be a rapid halohydrin addition to **3**, which prevents decomposition of **3**, generating carbamate intermediate **12** as a resting state of the overall process.

In summary, we have demonstrated a TAPS-catalyzed [3 + 2] coupling reaction of isocyanates and epoxides for the synthesis of oxazolidinones. This method was found to be robust for a series of isocyanates and applicable to various

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terminal epoxides. In addition, the origin of the behavior of TAPS has been identified by mechanistic studies. Efforts are currently underway to extend TAPS catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02722.

Experimental procedures; spectroscopic data for all new compounds (PDF)

Crystallographic data for (*S*)-**4y** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) The result of the reaction using enantiopure styrene oxide (*S*)-**2k** is shown in SI.

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(14) For a comparison of catalytic ability, other onium and metal salts were examined. See SI for details.

(15) Epoxide **2i** was observed to be less than 5% in the case of the ylide catalysis, while DBU afforded about 10% of **2i**.

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