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DOI: 10.1039/C9CC01983A

Journal Name

COMMUNICATION

4-Hydroxymethyl-Substituted Oxazolidinone Synthesis by Tetraarylphosphonium Salt-Catalyzed Reactions of Glycidols with Isocyanates

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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Preparation of 4-hydroxymethyl-substituted oxazolidinones including optically active ones, in which tetraarylphosphonium salts catalyze the reaction of glycidol with isocyanates effectively, is described. The neutral catalysis facilitates glycidol addition to isocyanates followed by intramolecular cyclization. Mechanistic studies suggest that hydrogen-bonding interactions with the catalyst play an important role in the reaction progress.

Heterocyclic compounds are useful building blocks in synthetic organic chemistry and play a beneficial role in medicinal chemistry.[1] Oxazolidinones, an important class of nitrogen and oxygen containing heterocycles, are of particular interest since many of them exhibit potent biological activity.[2,3] Thus, a large number of strategies have been demonstrated for the synthesis of oxazolidinone cores to access a diverse array of derivatives.[4-9] Among these methods, the reaction of glycidol (**1**) and isocyanates **2** followed by intramolecular cyclization of the corresponding epoxy carbamates **3** under basic conditions is well-known, and has been used as a key step in natural product syntheses.[10] Accordingly, this approach using optically active glycidol enables the asymmetric synthesis of 4-hydroxymethyl-substituted oxazolidinones **4**, which can be converted into valuable chiral synthons such as β-hydroxy-α-amino acids. Despite being an attractive transformation, however, its catalytic version by basic catalysis has remained limited until today.[9,10] This is attributed to the inherent issues that must be solved, including: 1) undesirable interactions between catalysts and isocyanates that can deactivate the catalysts or decompose the isocyanates; and 2) competing ring-opening polymerization of glycidol via intermediate **A** induced by base catalysts.[11] There are also crucial issues for enantiomerically enriched glycidol including: 3) isomerization of **A** to form the enantiomer of **A** (*ent*-**A**) leading to racemization; and 4) slower protonation of **B**

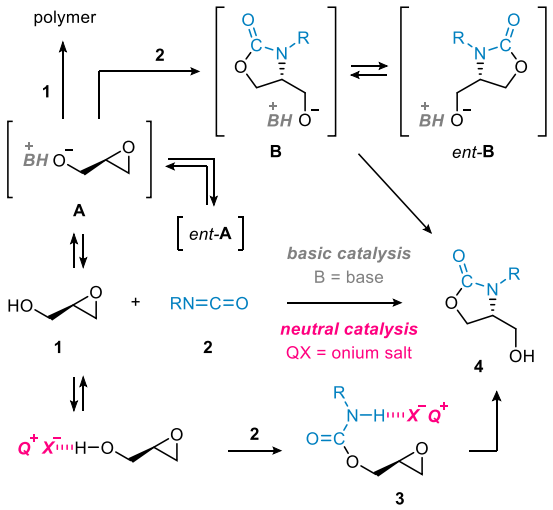

Fig 1 Working hypothesis.

than formation of *ent*-**B** causing loss of enantiomeric excess of **4**.[10c,h,12] We hence reasoned that neutral organocatalysts would inhibit the undesired polymerization and also be suitable to catalyze the sequential process under mild conditions because generation of the reactive alkoxide species would be avoided (Figure 1). In addition, the recent report by Tanaka, Sato and co-workers achieved quaternary ammonium salt-catalyzed transesterification of methyl benzoates with glycidol.[13] Herein, we found that tetraarylphosphonium salts bearing electron-rich substituents facilitate the consecutive transformation of **1** with **2** via intramolecular cyclization of intermediate **3**, which would empower neutral onium salt catalysis for glycidol addition reactions. Since their catalytic ability *as a hydrogen-bond acceptor* has rarely been explored to date, the catalysis development can be a formidable challenge.[14-16]

At the outset of our study, we attempted the reaction of racemic **1** and a slight excess of phenyl isocyanate (**2a**) in chlorobenzene at 80 °C for 24 h (Table 1). To our delight, 2 mol % of tetraphenylphosphonium chloride afforded the desired oxazolidinone **4a** in moderate yield (69% by ^{1}H NMR),

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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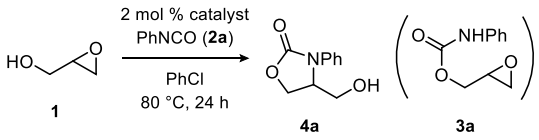
Table 1 Optimization of reaction conditions[a]

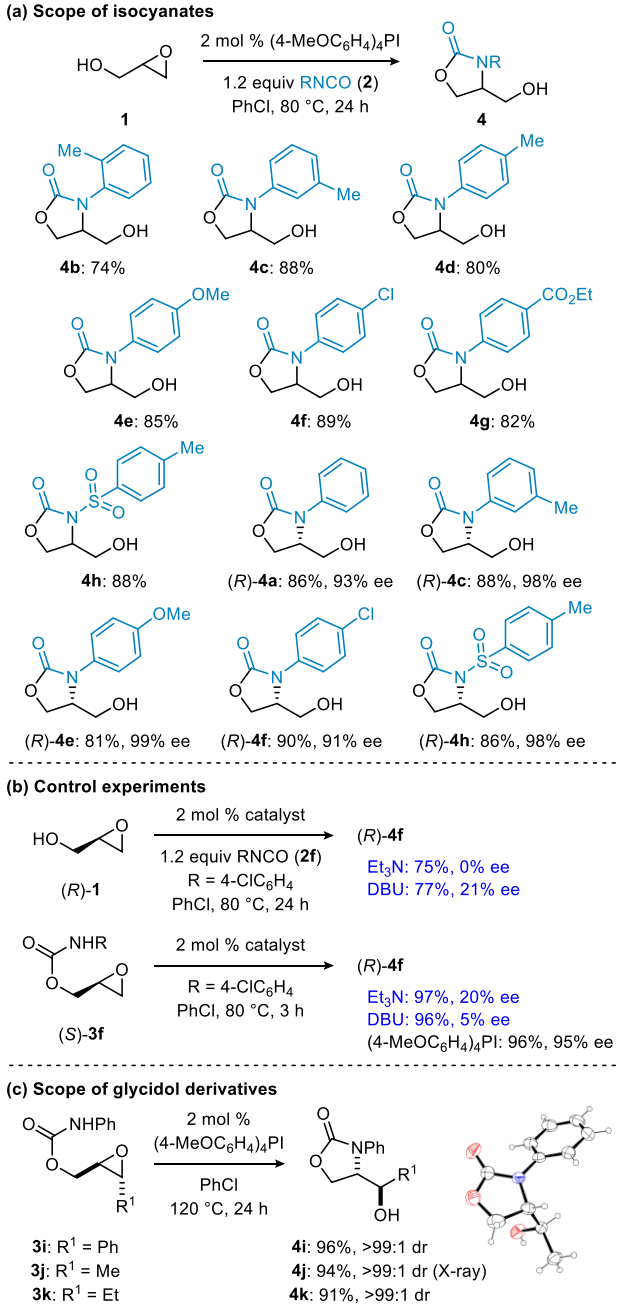


entry	Catalyst	**4a** (%)[b]	**3a** (%)[b]
1	Ph_4PCl	69	5
2	none	<2	96
3	Ph_4PBr	75	<2
4	Ph_4PI	86	<2
5	*n*-Bu_4NI	74	<2
6[c]	NaI	56	7
7[c]	KI	74	<2
8	Ph_3P	73	<2
9	Et_3N	73	<2
10	DBU	77	<2
11	$(4\text{-}FC_6H_4)_4PI$	40	48
12[c]	$(4\text{-}MeOC_6H_4)_4PI$	93 (91)[d]	<2

[a]Unless otherwise noted, all reactions were carried out with 0.60 mmol of glycidol (**1a**) and 0.72 mmol of phenyl isocyanate (**2a**) in a 1.0 M solution of PhCl (0.60 mL) at 80 °C for 24 h. [b]Determined by ^1H NMR analysis of the reaction mixture. [c]1.5 mmol scale. [d]Isolated yield.

while 96% of carbamate **3a** was observed in the absence of catalyst (Table 1, entries 1 and 2). Use of bromide as a counterion of the phosphonium ion slightly improved the yield of product **4a** (Table 1, entry 3). Switching the counterion to iodide led to a higher yield of 86% (Table 1, entry 4). Lower yields were obtained in the cases of other iodide salts such as quaternary ammonium, sodium, and potassium (Table 1, entries 5-7). Triphenylphosphine and triethylamine as weak Brønsted bases could catalyze the reaction, but resulted in modest yields (Table 1, entries 8 and 9). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was also tested, affording **4a** in 77% yield (Table 1, entry 10). Interestingly, introduction of electronic substituents (fluoro or methoxy groups) into the phenyl rings on the phosphorus center strongly affected the catalyst activity. Tetrakis(4-methoxyphenyl)phosphonium iodide afforded the highest yield (91% after isolation) among the screened catalysts (Table 1, entries 11 and 12).[17]

With the optimized reaction conditions in hand, we investigated the scope of isocyanates (Scheme 1a). Although a somewhat lower yield was obtained in the case of *ortho*-tolyl isocyanate (**2b**), no significant steric effects were observed (**4b**: 74%; **4c**: 88%; **4d**: 80%). Aryl isocyanates **2e**-**2g**, bearing electron-rich or electron-deficient aryl groups, provided oxazolidinones **4e**-**4g** in good to high yields (82-89%).[18] Tosyl isocyanate (**2h**) was tolerated to give **4h** in 88% yield. Moreover, enantiopure glycidol ((*R*)-**1**, 99% ee) was employed for the synthesis of optically active oxazolidinones **4**, resulting in enantio-enriched **4a** (93% ee), **4c** (98% ee), **4e** (99% ee), **4f** (91% ee) and **4h** (98% ee) in high yields, albeit a slight erosion of the enantiomeric excess was observed in some cases.[19] On the basis



Scheme 1 Substrate scope of tetraarylphosphonium salt-catalyzed reactions of glycidol with isocyanates.

of these results, it was suggested that carbamates **3** undergo S_N2-type cyclization at the chiral carbon center (C2). This mechanism was supported by the outcome of the cyclization of enantiopure **1** (Scheme 1a, third row). To compare neutral phosphonium catalysis with typical Brønsted base catalysis, control experiments were performed (Scheme 1b). It was found that triethylamine and DBU caused a notable decrease of enantiopurity under the same conditions (0% ee and 21% ee, respectively).[20] To ascertain whether racemization (**B** vs. *ent*-**B** in Figure 1) was involved in the intramolecular cyclization step, we conducted the reaction using (*S*)-**3f** (99% ee). Indeed, a low

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ee of (*R*)-**4f** was obtained in the presence of triethylamine or DBU despite the clean conversion. In addition, no racemization of (*R*)-**4f** was confirmed by heating the mixture of (*R*)-**4f** and 2 mol % of catalysts (the phosphonium salt, triethylamine, or DBU) in chlorobenzene at 80 °C. Therefore, the protonation of **B** may be sluggish in the base catalysis, because the salt catalysis enabled asymmetric transfer from **3** to **4**. Further reaction scope studies were focused on glycidol derivatives having a substituent at the 3-position (Scheme 1c). An initial attempt using 3-phenylglycidol under the standard conditions resulted in 11% yield of oxazolidinone **4i**, where carbamate **3i** was formed in 67% yield. The same reaction was also run at 120 °C, but gave only a 43% yield of **4i** (**3i**: 35%). Thus, isolated **3i** was submitted to the conditions at 120 °C, affording *anti*-**4i** as a single diastereomer in excellent yield. 3-Methyl-substituted-carbamate **3j** and 3-ethyl-substituted-carbamate **3k** were applicable to furnish *anti*-**4j** and **4k** as well,[21] and their relative configuration was confirmed by X-ray crystallographic analysis of **4j** (ORTEP drawing with 30% probability ellipsoids is shown on the right in Scheme 1c).[22]

In order to elucidate the role of the phosphonium salt, we first examined substituent effects on the nitrogen atom of carbamate **3** by tracking the reaction progress (Figure 2a). By comparison between an electron-donating group (**3e**: R = 4-$MeOC_6H_4$, blue line) and an electron-withdrawing group (**3f**: R = 4-ClC_6H_4, red line), it was revealed that the order of reactivity was **3e** < **3f** based on the yield of the product. Accordingly, we assumed that hydrogen-bonding activation by the iodide ion could be crucial in the carbamate cyclization step since the more acidic **3** showed faster conversion.[23] Next, we evaluated the initial carbamate formation step. Although glycidol (**1**) reacted with phenyl isocyanate (**2a**) without a catalyst to give intermediate **3a** quantitatively (see Table 1, entry 2), the reaction monitoring clearly showed that the phosphonium salt exhibited a substantial effect (Figure 2b). Most of **1** was consumed within 5 minutes under the influence of the catalyst, in which both **3a** and **4a** were observed. Since significant amounts of **3a** were formed at an early stage of the reaction, the latter cyclization step was implicated as the rate-determining step. Lastly, we revealed the superior function of the neutral catalysis by the following experiments. The chlorobenzene solution of **1** with 2 mol % of catalysts was heated at 80 °C for 3 h to observe the rate of undesired decomposition.[24] Notably, 94% of **1** remained unreacted in the case of the optimal catalyst. In contrast, the use of triethylamine or DBU led to a complex mixture, where less than 10% of **1** was recovered. We hence concluded that the key to the successful transformation of **1** to **4** was the rapid addition of **1** to **2**, which prevented decomposition of **1**, generating **3** as the resting state in the overall process.

In summary, we have demonstrated a phosphonium salt-catalyzed reaction sequence of glycidols **1** and isocyanates **2** for the synthesis of oxazolidinones **4**. It was found that electron-rich aryl groups enhanced the reactivity of the tetraarylphosphonium salts. 4-Hydroxymethyl-substituted oxazolidinones including enantio-enriched ones were obtained in high yields. The results of mechanistic studies suggested that

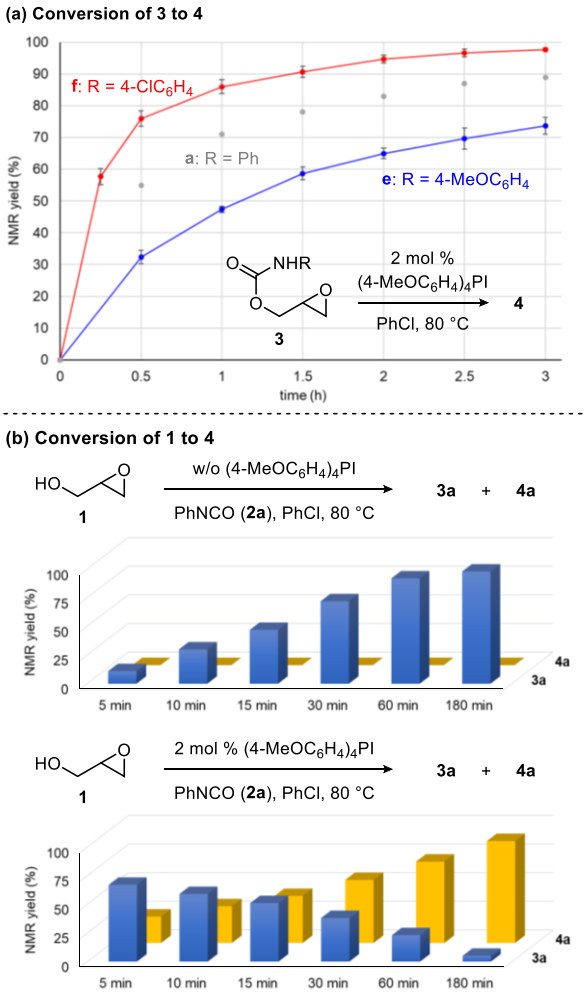

Fig 2 (a) ^{1}H NMR yields of reaction progress in tetraarylphosphonium salt-catalyzed intramolecular cyclization of **3** (**3a**: gray; **3e**: blue; **3f**: red). (b) Yields of **3a** and **4a** within the time period indicated in the bottom of the graph (top: without catalyst; bottom: with catalyst).

catalyst coordination through hydrogen-bonding can accelerate not only the intramolecular cyclization of carbamate intermediate **3** but also the formation of **3**. Efforts are currently underway to extend this phosphonium salt catalysis.

This work was partially supported by the Japan Society for the Promotion of Science (JSPS) through a Grant-in-Aid for Young Scientists (B) (Grant No. JP17K14483). We are extremely thankful to Kimiya Sukegawa (Shinshu University) for his kind support in X-ray crystallographic analysis.

Conflicts of interest

There are no conflicts to declare.

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18 The reaction of *n*-butyl isocyanate only afforded the corresponding carbamate intermediate.

19 The absolute configuration of **4f** was determinized to be (*R*) by X-ray crystallographic analysis.

20 The reaction of **2f** using 5 mol % of *n*-Bu_4NI and KI afforded **4f** in 71% (86% ee) and 72% (85% ee), respectively.

21 The reaction of *cis*-epoxide selectively afforded *syn*-oxazolidinone in good yield. See ESI for details.

22 CCDC 1898009 (**4f**) and CCDC 1898013 (**4j**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

23 ^{1}H NMR experiments using the phosphonium salt in were conducted on a $CDCl_3$ solution of carbamate **3a**. The N−H proton of **3a** shifted upfield along with addition of the salts, indicating hydrogen-bond interaction between the N−H group and the salt. The analysis was also performed for a mixture of the salt and glycidol (**1**). See ESI for details.

24 It has been reported that **1** undergoes oligomerization at a higher temperature in the presence of $(n\text{-Oct})_3MeNCl$, see ref 13.