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The first enantioselective [3+2] cycloaddition of epoxides to arylisocyanates: asymmetric synthesis of chiral oxazolidinone phosphonates

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ABSTRACT

A [3+2] cycloaddition of diethyl 1,2-oxiranephosphonate to aryl isocyanates catalyzed by lanthanide cations is described. The reaction is highly regioselective and 5-substituted 2-oxazolidinone phosphonates are obtained with a regioselectivity greater than 95:5 with respect to the 4-substituted regioisomer, and in up to 84% yield. When 20 mol % of Pybox-Yb^{3+} is used as a catalyst, enantiomerically enriched products are obtained in up to 75% ee, depending on the reaction conditions, and the nature of the isocyanate. Low temperatures benefit asymmetric induction, but have an adverse effect on the regioselectivity for *para*-substituted aryl isocyanates.

1. Introduction

The oxazolidinone unit is rarely present in natural products, but compounds with this unit have many applications.[1–3] Oxazolidinones are often used as chiral auxiliaries for a variety of asymmetric synthetic transformations[4] (the so-called Evans' auxiliaries), as protecting groups for 1,2-amino alcohols, and as building blocks in polymers. In recent years 5- and 4,5-disubstituted oxazolidinones have attracted a lot of attention because they are one of a few new classes of antibiotics that have been discovered in the past 30 years, after the quinolones.[5,6] In 2000, Linezolid of Pharmacia/Pfizer became the first to be commercialized.

This and related antibacterials are active against numerous Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE) and penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*. The treatment of mycobacterial infections, which place at risk immuno-compromised populations, is a potential area of application.[7] These antibiotics inhibit bacterial protein synthesis, do not exhibit cross-resistance, and can be administered orally as well as intravenously. The synthesis of analogues is an active area of research. Modifications of the rings, ring-substituents, as well as the C-5 side chain, have given rise to libraries of compounds[8,9] in a search for higher activity, lower toxicity, or better properties. The absolute configuration at C-5 is critical for the biological activity.[9]

We have been interested in biologically active phosphonate derivatives for a few years,[10,11] and the possibility of a phosphoryl substituent at C-5 seemed to be an attractive option. Many phosphonates have applications in medicine, such as epoxyphosphonates as antibacterials, nucleoside phosphonate analogues as antivirals, and bisphosphonates as drugs for the treatment of numerous bone diseases. Only a few examples of oxazolidinone phosphonate derivatives could be found in the literature. Wyatt et al. converted a 2-amino-1-hydroxyphosphonate into the corresponding oxazolidinone using 1,1′-carbonyldiimidazole, as a means to elucidate the stereochemistry of the parent phosphonate.[12] Jung et al. have synthesized a few biologically active oxazolidinone phosphonates via a multi-step synthesis, with the phosphoryl group separated from the ring by a three or more atom tether.[13–15] Starting from the oxazolidinone ring, it is also possible to obtain *N*-(phosphonomethyl)oxazolidinones, via reaction with phosphorus trichloride and formaldehyde.[16,17] We decided to try an approach using the 1,3-cycloaddition of epoxides to isocyanates, a reaction that to the best of our knowledge has not been applied in phosphonate chemistry.

A number of halides are known to catalyze the 1,3-cycloaddition of simple epoxides to isocyanates: tetraalkylammonium halides,[18,19] LiBr-$OPPh_3$,[20] *n*-Bu-SnI Lewis base complexes,[21] and lanthanide chlorides.[22] Also, $Pd_2(dba)_3{\cdot}CHCl_3$ and trialkyl phosphite can also be used to convert substituted vinyl oxiranes stereoselectively to *cis*-oxazolidinones.[23] Some of these methods require high temperatures and trimerization or polymerization of the isocyanate may occur as a side reaction. To the best of our knowledge, no catalytic asymmetric versions have been reported. Herein we report our results on the synthesis of enantiomerically enriched oxazolidinone phosphonates **B** (Fig. 1) with potential biological activity.

2. Results and discussion

As a test reaction, the [3+2] cycloaddition of phenyl isocyanate to diethyl 1,2-epoxyphosphonate, a simple terminal

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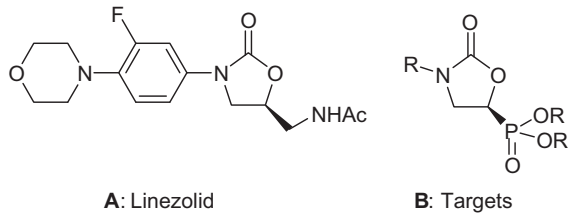


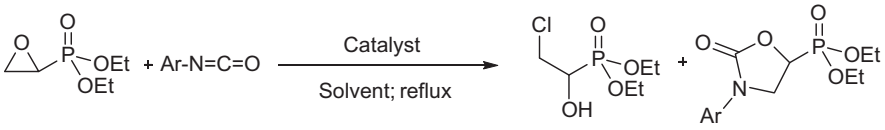
Figure 1.

epoxyphosphonate analogous to the well-known antibiotic fosfonomycin, was selected. The required substrate could be obtained in high yield by a modification of the method of Sturtz and Pondaven-Raphalen,[24] with *t*-BuOK in *t*-BuOH being used to cyclize the intermediate halohydrin obtained from the reaction of diethyl allyl phosphonate with NaOCl formed from bleach-HCl. When the epoxyphosphonate and isocyanate were mixed in the absence of a catalyst, there was no reaction at room temperature, or even after refluxing for 3 h in dichloromethane. Tetrabutylammonium alkyl halides did not give the desired [3+2] cycloadducts either. However, several metal halides were found to catalyze the reaction, with different degrees of success. The results obtained are shown in Table 1. The reactions were regioselective: the 5-substituted 2-oxazolidinone was obtained in preference to the 4-substituted regioisomer, either with none or with some β-chlorohydrin, in a ratio that varied with the nature of the metal and the reaction conditions. The regiochemistry of the product is in accordance with that expected, considering the inductive effect of the phosphonate group and the steric effects on the terminal epoxide. The ^{1}H NMR spectrum of the compound has a multiplet at 5.49 ppm due to the methine proton, whose corresponding carbon atom is attached to the oxygen. A chemical shift of greater than 5 ppm is consistent with 2-oxazolidinones substituted at the 5-position by electron withdrawing groups. It is further downfield than the signal of the corresponding proton on a carbon atom attached to nitrogen, a less electronegative atom, which in similar 4-substituted oxazolidinones appears near 4.5 ppm.[25] In ^{31}P NMR spectra, a single signal was observed for the oxazolidinone phosphonate. In ^{1}H NMR spectra, two additional small multiplets centered at 4.41 and 4.72 ppm could usually be seen, suggesting that the other regioisomer may have formed albeit in low amounts: usually $\leqslant$5%. There were no other signals present that could help identify this substance, which was difficult to separate chromatographically from the oxazolidinone, another indication of structural similarity.

It is generally thought[19,22] that the mechanism of the reaction with halides involves ring opening to form a 1,2-alkoxy halide, which subsequently adds to the isocyanate, a process which would be facilitated by epoxide coordination to the metal. This mechanism is supported by computational studies.[26] The chlorohydrin found in reaction mixtures is consistent with this type of mechanism. However, it was also found that if the reactions were allowed to proceed longer than their endpoints, more chlorohydrin is formed.

As for the nature of the metal, the hard Lewis acid $TiCl_4$ gave only the halohydrin after 3 h of reflux, and there was no reaction when $SnCl_2$ was used as a catalyst. However, $BiCl_3$ gave 28% of the oxazolidinone under the same conditions. Catalyst $RuCl_3$ also worked in this transformation, but its activity was low (entry 2). The lanthanides, which are mild Lewis acid catalysts, are highly oxophilic anions and usually attain association-dissociation equilibria rapidly in ligand substitution reactions;[27] due to the liability of the Ln–O bond, product dissociation is also fast. All the lanthanide chlorides that we tested, irrespective of their position in the periodic table, were active in this [3+2] cycloaddition. The triflate (entry 11) did not yield the desired product, which supports the theory that the reaction between epoxides and isocyanates is initiated by the reaction of a chloride ion at the epoxy ring. Both the anhydrous and the hydrated metal chlorides yielded a product. The hydrated catalysts reacted faster, for example, $CeCl_3$ versus

Table 1
Screening of potential metal catalysts for the [3+2] cycloaddition of epoxyphosphonate **1** to arylisocyanates



1 **2** **3** **4**

Entry	Catalyst	Reagents			Conditions[a]		Results[b]		
		Epoxide (mmol)	Isocyanate (R, mmol)	Metal (mmol)	Solvent	Time (h)	Conv. (%)	Oxazolidinone[c] (%)	Chlorohydrin (%)
1	$TiCl_4$	1.0	Ph, 1.10	0.47	Toluene	3	100	0	100 (52)
2	$RuCl_3$	1.0	Ph, 1.10	0.50	CH_2Cl_2	20	14	14	0
3	$SnCl_2$	1.0	Ph, 0.95	0.47	$CHCl_3$	3	0	0	0
4	$BiCl_3$	1.0	Ph, 1.10	0.50	$CHCl_3$	3	70	28	42
5	$CeCl_3$	1.0	Ph, 0.95	0.50	$CHCl_3$	3	48	41	7
6	$CeCl_3{\cdot}7H_2O$	1.0	Ph, 1.00	0.54	$CHCl_3$	2.5	100	79 (62)	21
7	$SmCl_3{\cdot}6H_2O$	1.0	Ph, 1.00	0.50	$CHCl_3$	1	99.6	98.2 (59)	1.4
8	$SmCl_3{\cdot}6H_2O$	1.0	Ph, 1.00	0.50	$CHCl_3$	3	100	83 (76)	17
9	$SmCl_3{\cdot}6H_2O$	1.0	Ph, 1.20	0.25	$CHCl_3$	5	95	75	18
10	$TbCl_3$	1.0	Ph, 1.00	0.50	$CHCl_3$	1	12	12	0
11	$Yb(OTf)_3$	1.0	Ph, 0.81	0.99	$CHCl_3$	2	23	0	0
12	$YbCl_3{\cdot}6H_2O$	1.0	Ph, 0.94	0.50	$CHCl_3$	1	100	74 (66)	26
13	$YbCl_3{\cdot}6H_2O$	1.0	Ph, 1.00	0.43	CH_2Cl_2	1	83	83	0
14	$YbCl_3{\cdot}6H_2O$	1.0	Ph, 1.50	0.47	CH_2Cl_2	3	97	97 (74)	0
15	$SmCl_3{\cdot}6H_2O$	1.0	*p*MeO–C_6H_4, 1.30	0.50	CH_2Cl_2	3	100	100 (84)	0
16	$SmCl_3{\cdot}6H_2O$	1.0	*p*Ac–C_6H_4–, 1.00	0.50	CH_2Cl_2	2	88	58 (40)	30
17	$SmCl_3{\cdot}6H_2O$	1.0	Ph, 1.0	0.50	CH_2Cl_2	1	90	90	0

[a] The reactions were performed with a concentration of 0.22 mmol/mL with respect to the phosphonate.
[b] Percentages were determined from signal ratios in ^{31}P NMR spectra; values within brackets represent the yields of the compounds isolated after column chromatography, with respect to the initial amount of epoxyphosphonate reacted.
[c] Reaction products contained about 5% of the 4-substituted oxazolidinone.

$CeCl_3 \cdot 7H_2O$ and $TbCl_3$ (entries 5, 6 and 10). A rate enhancement in lanthanide-catalyzed reactions in the presence of water has been described previously.[28] In a hetero Dields–Alder reaction catalyzed by lanthanide bis-trifluoromethanesulfonylamide, the addition of water to the reaction mixture resulted in an increase in both chemical yield and enantioselectivity. Catalyst $SmCl_3 \cdot 6H_2O$ gave the oxazolidinone almost quantitatively after 1 h, which was isolated in 60% yield, and $YbCl_3 \cdot 6H_2O$ in 3 h, isolated in 74% yield. When the catalyst loading was lowered from 50 to 25 mol % (entry 9) the reaction took longer as expected but other unidentified products also started to form.

The synthesis of more elaborated oxazolidinones was then attempted using different arylisocyanates. The reactions of aryl isocyanate containing either an electron withdrawing or an electron donating substituent in the *para* position of the ring were slower than those of phenylisocyanate under the same conditions (cf. entries 15–17). The reactions were also regioselective, and the 4-substituted oxazolidinone was formed in less than 5% of the total amount that was converted.

Once metals suitable to catalyze the reaction were found, a few chiral ligands were tested in order to obtain enantiomerically enriched oxazolidinones. There have been a few reports on the successful use of C_2-symmetrical bis(oxazolines) as chiral ligands for lanthanide ion-catalyzed reactions.[27,29] We have been interested in this type of ligand for some time,[30] and so we decided to try some (Fig. 2) to induce chirality in the epoxyphosphonate to oxazolidinone phosphonate transformation. When a 1:1 mixture of epoxyphosphonate/phenyl isocyanate was refluxed for 3.5 h in the presence of a 1:1 complex of **A**/Yb^{3+}, 10% of the substrate converted into 6% product and 4% of an unidentified substance as determined by ^{31}P NMR spectroscopy. On the other hand, 20 mol % of Nishiyama's Pybox ligand **B** converted 79% (74% isolated) of the epoxyphosphonate into a product with 36% ee in 4.5 h. The larger bite size might be responsible for the increased efficiency of this ligand to complex the large lanthanide cation. The *iso*-propyl analogue **C** catalyzed a similar conversion (74%, 66% isolated yield) in 5 h, but this product was racemic. Some organocatalysts were also tested: 50 mol % of proline yielded no product after 3 h at rt, while with 20 mol % of quinine **E** refluxing in CH_2Cl_2 or in toluene for the same period, only starting material was recovered. Quininium chloride **F** was more promising. In CH_2Cl_2 at rt there was no reaction after 17 h, but in refluxing toluene, after 23 h, there was 44% conversion of the starting material into 29% oxazolidinone and 15% of an unidentified substance when 20 mol % of **F** was added.

Since **B**–Yb^{3+} was the most efficient catalyst for this transformation, the remaining experiments were carried out with this catalyst system. The first step was then to find an optimum solvent. The results in Table 2 show that the best turnover is obtained in dichloromethane. The reaction, as indicated in the equation in Figure 3, was then optimized with respect to the catalyst loading, temperature and other experimental conditions and the results are summarized in Table 3. The transformation was possible not only at reflux but also with temperatures as low as 13 °C. At 0 °C the reaction was slowed down to such an extent that other unidentified products started to form preferentially (entry 16). A greater ligand to metal ratio did not alter the results significantly (entries 1 and 2). Increasing the amount of catalyst from 20 to 40 or 50 mol % sped up the reaction with no benefit with regards to the asymmetric induction (entries 3, 4, 21 and 22). In MeCN the reaction was faster, but the ee was lower (cf. entries 7/8). When the temperature was lowered the enantioselectivity went up by as much as 20% (entries 1, 7, and 20) to a maximum of 63%. When the concentration of isocyanate was increased, the conversion did not vary (entries 6 and 9, or 16 and 17) indicating that the slow step of the reaction is the reaction of chloride ion with the epoxide ring. However, more oxazolidinone was formed in the same period of time. Hence, the stepwise addition of isocyanate led to a faster formation of oxazolidinone than when it was added all at once.

Manual hourly additions (Methods B, or E) or additions twice daily (Method C) resulted in the formation of greater amounts of oxazolidinone over a shorter period of time (entries 6 and 20). In the first case (entry 6), with a single addition, after 17 h at rt, the conversion was 70%, but of this only 38% was oxazolidinone. On the other hand, entry 16 shows that even at 13 °C, with only 47% conversion, there is already the same amount of oxazolidinone present after 5 h, when the addition of isocyanate is carried out in a stepwise fashion. Leaving the reagents simply stirring for a longer period of time does not yield more oxazolidinone because the isocyanate polymerizes with time. These reactions were repeated a few times and gave similar results. It was also for this reason that isocyanate could not be used as the limiting reagent in these syntheses. If the additions of isocyanate are too far apart in time (entries 13 and 14), full conversion is possible, but the product racemizes slowly in time. It also appears that high concentrations of isocyanate may depress the ee (entries 6 and 9). When these two reactions were performed, the room temperature differed by 6 °C only, so the large 20% difference in ee suggests that when a large number of isocyanate molecules are present, complexation to the metal may result in the formation of a less pronounced chiral environment.

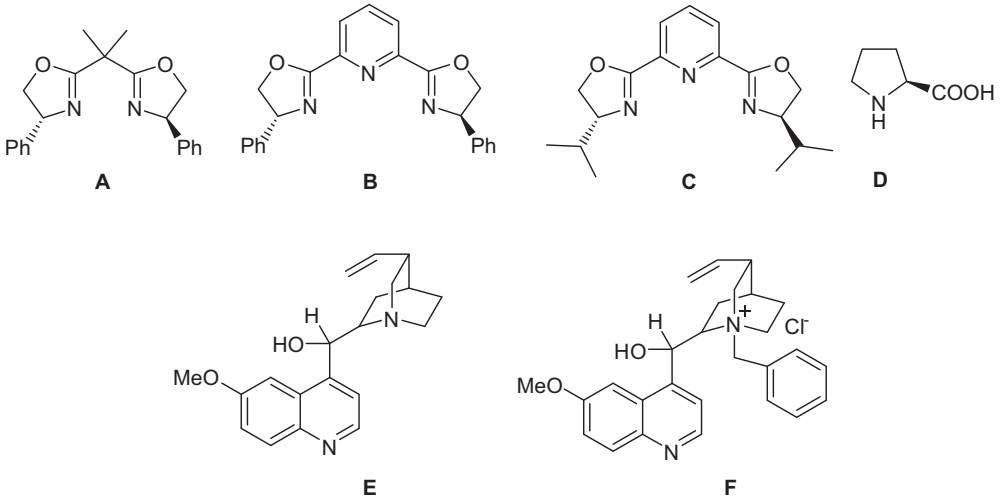


Figure 2. Chiral ligands and catalysts screened.

Table 2
Effect of the nature of the solvent on catalytic turnover[a]

Solvent	Temp (°C)	Time (h)	Conv.[b] (%)	Yield[b] (%)
CH_2Cl_2	50	5	94	84
Toluene	120	5	100	20
Tol/CH_2Cl_2[c]	50	3	94	72
DMF	50	3	52	0
THF	80	3	80	60
CH_2Cl_2[d]	50	5	100	95

[a] The reactions were performed on a scale of 0.18 mmol of epoxyphosphonate, with 1.0 equiv of phenyl isocyanate in 0.8 mL solvent and 20 mol % of $YbCl_3{\cdot}H_2O$ and of PyBox.
[b] Determined from area ratios in ^{31}P NMR spectra.
[c] A 3:2 ratio was used.
[d] Metal/ligand 40:40 mol %.

Therefore, in order to obtain a high yield of oxazolidinone with a high ee, the reaction should be performed at low temperature, that is, rt or lower, with stepwise hourly addition of isocyanate. Since manual additions over long periods of time are not practical, the process should be automated. Alternatively the reaction may be stopped after a few hours, the enantiomerically enriched product isolated, and unreacted phosphonate recovered and recycled. When higher temperatures are used, that is, refluxing at 40 °C, conversion into oxazolidinone is smooth, but the ee only goes up to 40%.

Other more substituted isocyanates were then tested in the [3+2] cycloaddition reaction. Under reflux conditions, the regioselectivity was similar to the racemic series, and the 5-substituted isomers **4a** and **4b** formed preferentially with more than 95% selectivity. For **4b** the asymmetric induction was only 27%. When the temperature was lowered, the regioselectivity of the reaction dropped considerably with the *para*-substituted aryl isocyanates. With the *p*-acyl derivative, the reactions had a regioselectivity of 3:1 in favor of the 5-substituted oxazolidinone **4c**, and the major regioisomer, which could be isolated, was found to have formed with fairly high ees, of up to 75%. However, the reactions were very slow, not only due to deactivation brought about by the electron withdrawing substituent, but probably also due to the fact that the isocyanate was rather insoluble in the solvent used. At room temperature, after 17 h, there was only 63% conversion even with an excess of isocyanate. The minor regioisomer could be identified by a signal in the ^{31}P NMR spectrum at 16.80 ppm, and by two multiplets at 4.57–4.75 ppm in the ^1H NMR spectrum. The remaining signals coincided with those of the major isomer. The *p*-methoxy substituted aryl isocyanates were more reactive but the reactions were far less regioselective, giving up to 2:1 of **4b**/**5b**. However the products were very difficult to separate on silica gel, and the ees were not determined. Regioisomer **5b** could be identified by a singlet in the ^{31}P NMR spectrum at 16.97 ppm, and by multiplets at 4.35–4.45 ppm and 4.63–4.75 ppm in the ^1H NMR spectrum.

Since water-soluble phosphonic acids usually exhibit higher biological activity than their esterified analogues, it is of interest to convert the oxazolidinone phosphonates into the corresponding phosphonic acids. This could be done with TMSBr, followed by hydrolysis of the TMS esters formed with H_2O, as shown in Figure 4.

3. Conclusions

We have shown that it is possible to synthesize 5-substituted 2-oxazolidinone phosphonates from epoxyphosphonates via a [3+2] cycloaddition to aryl isocyanates, catalyzed by lanthanide cations. The regioselectivity of the reactions is very high, giving products in 95:5 ratio with respect to the 4-substituted regioisomer. Due to the current interest in oxazolidinone antibiotics, methods leading to chiral derivatives could become very useful synthetic tools. Here, asymmetric induction was possible via Pybox-Yb^{3+} catalysis. With 20 mol % catalyst at 13 °C, ees of up to 75% were obtained. Unfortunately when *para*-substituted aryl isocyanates were used, particularly one with an electron rich methoxy substituent, the regioselectivity of the reaction dropped to nearly 2.5:1 in favour of the desired product. Isocyanate side reactions became a problem at low temperatures, preventing full conversion of the phosphonate into oxazolidinone, but this can be overcome by stepwise addition of isocyanate to the reaction mixture.

4. Experimental

4.1. General

The reactions were performed under an argon atmosphere. The reagents were obtained from commercial suppliers and used without further purification. The solvents were purified by standard methods and distilled before use. For column chromatography, Merck silica gel 60 (230–400 mesh) was used. Thin layer chromatography was performed on silica gel plates Merck 60 F_{254}. NMR spectra were obtained with a Bruker AR X400 NMR spectrometer or a Bruker Avance 400 MHz spectrometer. Chemical shifts are relative to TMS. ^{31}P NMR chemical shifts are relative to phosphoric acid, used as external standard. The multiplicity of signals in ^{13}C NMR spectra was determined with a DEPT experiment. Two-dimensional spectra (COSY 45, HMQC) were used to help with structural determinations whenever it was necessary. IR spectra were obtained with a Perkin Elmer Spectrum 1000 FT-IR spectrophotometer and a Perkin–Elmer Spectrum BX FT-IR spectrophotometer.

Elemental analysis was performed on a Thermo Finnigan Elemental Analyser 1112 series, by the Laboratory for External Services of CQFB-Lab Associado/REQUIMTE, of the Department of

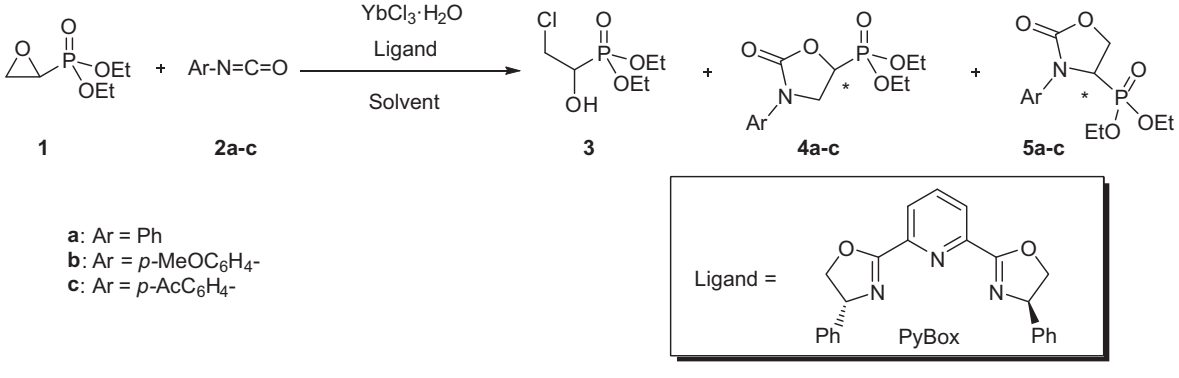


Figure 3.

Table 3
Asymmetric [3+2] cycloaddition of epoxyphosphonate **1** to arylisocyanates catalyzed by Yb^{3+}–Pybox complexes

No	Reagents[a]				Conditions			Results[b]				
	Epoxide (mmol)	Ar	Isocyanate (mmol)	Metal/ligand (mmol)	Temp (°C)	Method[c]	Time (h)	Conv. (%)	Major product and yield[d,e] (%)		Chlorohydrin (%)	ee[f] (%)
1	1.0	Ph	**2a**, 1.0	0.2/0.2	50	A	4.5	79	**4a**	75	4	38
2	1.0	Ph	**2a**, 1.0	0.2/0.4			4.5	82	**4a**	72	10	36
3	1.0	Ph	**2a**, 1.0	0.5/0.5			5	100	**4a**	95 (42)	5	ND
4	1.0	Ph	**2a**, 1.0	0.2/0.2			5	96	**4a**	84 (75)	10	ND
5	1.0	*p*-$MeOC_6H_4$	**2b**, 1.0	0.2/0.2			16.5	100	**4b**	90	10	27
6	1.0	Ph	**2a**, 1.0	0.2/0.2	Rt	A	17	70	**4a**	38	27	60
7	1.0	Ph	**2a**, 1.0	0.2/0.2			42	83	**4a**	31	44	63
8[g]	1.0	Ph	**2a**, 1.0	0.2/0.2			42	94	**4a**	67	27	47
9	1.0	Ph	**2a**, 4.0	0.2/0.2			17	62	**4a**	62	0	40
10	1.0	*p*-$MeOC_6H_4$	**2b**, 1.0	0.2/0.2			17	82	**4b**	44:17 (17)	15	ND
11	1.0	*p*-$MeOC_6H_4$	**2b**, 4.0	0.2/0.2			17	50	**4b**	32:18 (44)	0	ND
12	1.0	*p*-AcC_6H_4	**2c**, 2.4	0.2/0.2			17	63	**4c**	7:30 (12)	0	75
13	1.0	Ph	**2a**, 4.5	0.2/0.2		C	65	87	**4a**	87	0	14
14	1.0	Ph	**2a**, 6.0	0.2/0.2			4 d	100	**4a**	90	0	0
15	1.0	Ph	**2a**, 1.5	0.2/0.2		D	6	53	**4a**	47	6	46
16	1.0	Ph	**2a**, 3.25	0.2/0.2	0	B	6	18	**4a**	7	0	ND
17	2.0	Ph	**2a**, 1.0	0.2/0.2	13	A	3.8	34	**4a**	30	4	ND
18	1.0	Ph	**2a**, 3.0	0.2/0.2			3.8	35	**4a**	32	3	ND
19	1.0	Ph	**2a**, 3.0	0.2/0.2			15.5	47	**4a**	44	3	ND
20	1.0	Ph	**2a**, 1.0	0.2/0.2		B	5	47	**4a**	40	7	57
21	1.0	Ph	**2a**, 2.25	0.44/0.44			8	71	**4a**	67 (49)	4	39
22	1.0	Ph	**2a**, 2.25	0.2/0.2			8	57	**4a**	57	0	50
23	1.0	*p*-$MeOC_6H_4$	**2b**, 2.25	0.2/0.2			8	49	**4b**	34:15	2	ND
24	1.0	*p*-AcC_6H_4	**2c**, 2.25	0.2/0.2		E	8	41	**4c**	4:13	24	73

[a] Reactions were performed in CH_2Cl_2 with a concentration of 0.22 mmol/mL with respect to the phosphonate.
[b] Percentages were determined from signal ratios in ^{31}P NMR spectra.
[c] Addition of isocyanate: Method A, single addition; B, stepwise, 50 mol % initially, then 25 mol % hourly; C, 75 mol% twice daily; D, 25 mol % hourly; E, the insoluble solid isocyanate was added in portions at hourly intervals.
[d] Values include up to 5% of the other regioisomer unless otherwise stated.
[e] Values within brackets represent the yields of the compounds isolated after column chromatography.
[f] Determined by HPLC on a chiral column.
[g] Reaction performed in MeCN.

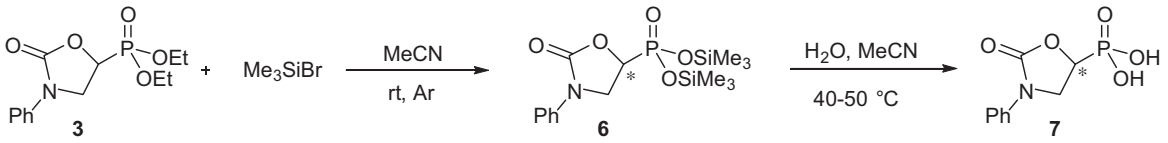


Figure 4.

Chemistry, FCT, UNL. For HPLC analysis, a Merck Hitachi instrument equipped with a Chiralpak AD-H column from Daicel, and a Merck-Hitachi-4250 UV–Vis detector were used.

4.2. General procedure for the metal-catalyzed synthesis of racemic oxazolidinones

The metal and the epoxide dissolved in solvent, in the proportions indicated in Table 1, were transferred to a reaction vessel and stirred under argon. The isocyanate was added, and the mixture was refluxed for the period of time indicated in Table 1. The resulting suspension was then cooled, diluted with solvent, and the reaction was quenched with HCl (1 M). The product was extracted three times with $CHCl_3$. The combined extracts were washed once with water, and the solution was filtered through anhydrous sodium sulfate, and the solvent was removed on a rotary evaporator to give the crude product, which was purified by chromatography on silica gel.

4.3. General procedure for the enantioselective synthesis of oxazolidinones

The metal and the ligand, in the proportions indicated in Table 3, were transferred to the reaction vessel, and solvent was added. The mixture was refluxed under argon for 1 h. The mixture was then cooled to the temperature indicated, and the epoxide dissolved in solvent was added, followed by the isocyanate. The reaction mixture was then stirred under argon, at the required temperature, for the period of time indicated in Table 3. The resulting suspension was then cooled, diluted with solvent, and the reaction was quenched with HCl (1 M). The product was extracted three times with $CHCl_3$. The combined extracts were washed once with water, the solution was filtered through anhydrous sodium sulfate, and the solvent was removed on a rotary evaporator to give the crude product, which was purified by chromatography on silica gel.

4.4. Diethyl 1-chloro-2-hydroxyethylphosphonate 3

This substance, which was found to be present in many reaction mixtures as shown in the tables, had the following spectroscopic data: ^{31}P NMR ($CDCl_3$, 161.9 MHz): 20.09 ppm; ^{1}H NMR ($CDCl_3$): δ 1.31 (t, 6H, J 7.1 Hz, 2 × CH_3) 3.69 (dq, 1H, J 5.9, 9.6, 11.5 Hz, C*H*HCl), 3.83 (dq, 1H, J 2.9, 6.4, 11.6 Hz, CH*H*Cl), 4.09 (td, 1H, J 2.9, 9.4 Hz, PCH), 4.80–4.25 (m, 4H, 2 × CH_2OP), 4.34 (s, 1H, OH) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 16.35 (s, 2 × CH_3), 45.10 (d, J 11 Hz, CH_2), 63.12 (d, J 5.6 Hz, POCH*H*), 63.40 (d, J 5.4 Hz, POC*H*H), 68.75 (d, J 160.1 Hz, PCH) ppm. The spectroscopic data of this compound agrees with the published data.[31]

4.5. Diethyl *N*-phenyl-2-oxo-oxazolidin-5-ylphosphonate 4a

The oxazolidinone was prepared from diethyl 1,2-oxiranephosphonate and phenyl isocyanate with $YbCl_3{\cdot}6H_2O$ and 2,6-bis[(4*R*)-4-phenyl-2-oxazolidinyl]pyridine as described under the general procedure. The crude product was purified by column chromatography (silica gel, $CHCl_3$/acetone = 12:1 or $CHCl_3$/acetone = 12:1 followed by EtOAc/hexane = 2:1) to give the product as a white solid; mp 79–80 °C. IR (KBr): 3243, 3216, 3188, 3160, 3114, 1741, 1600, 1554, 1540, 1505, 1445, 1329, 1316, 1254, 1217, 1096, 1041, 1022, 985, 758, 692 cm^{-1}; ^{31}P NMR ($CDCl_3$, 161.9 MHz): δ 16.98 ppm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.32 (t, J 7.0 Hz, 3H, CH_3), 1.35 (t, J 7.0 Hz, 3H, CH_3), 3.84 (superimposed ddd, J_{HP} 5.9 Hz, J_{HH} 9.7, 12.2 Hz, 1H, C*H*HN), 3.95 (ddd, J_{HH} 3.1, 9.3 Hz, J_{HP} 6.4 Hz, 1H, CH*H*N), 4.12–4.33 (m, 4H, 2 × CH_2OP), 5.48 (td, J_{HH} 3.0, 11.9 Hz, J_{HP} 11.9 Hz, 1H, PCH), 7.07 (t, J 7.3 Hz, 1H, Ph-H), 7.30 (t, J 7.6 Hz, 2H, Ph-H), 7.46 (d, J 7.8 Hz, 2H, Ph-H) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 16.35 (s, 2 × CH_3), 42.21 (d, J_{CP} 9.1 Hz, CH_2N), 63.27 (s, $POCH_2$), 63.71 (s, $POCH_2$), 68.59 (d, J 165.3 Hz, PCH), 118.7 (s, CH, Ph-C), 123.7 (s, CH, 2 × Ph-C), 129.0 (s, CH, 2 × Ph-C), 137.6 (s, Cq, Ph-C), 151.9 (s, Cq, (NCOO) ppm. Anal. Calcd for $C_{13}H_{18}O_5NP{\cdot}1\frac{1}{4}H_2O$ (322.53): C, 48.41; H, 6.33; N, 4.34. Found: C, 47.47; H, 5.99; N, 3.97. HPLC: CHIRALCEL AD-H column, hexane/2-propanol = 90:10, flow rate 1.0 ml/min, t_{r1} (major) = 7.6, t_{r2} (minor) = 9.2 min.

4.6. Diethyl *N*-(4-methoxyphenyl)-2-oxo-oxazolidin-5-ylphosphonate 4b

The oxazolidinone was prepared from diethyl 1,2-oxiranephosphonate and 4-methoxyphenyl isocyanate with $YbCl_3{\cdot}6H_2O$ and 2,6-bis[(4*R*)-4-phenyl-2-oxazolidinyl]pyridine as described under the general procedure. The crude product was purified by column chromatography (silica gel, EtOAc/hexane = 2:1) to give the product, as a white solid, which in the case of the chiral reactions was an inseparable mixture of regioisomers; mp 118–119 °C. IR (KBr): 3247, 3197, 3130, 3067, 2986, 2956, 2846, 1739, 1603, 1548, 1515, 1470, 1442, 1418, 1396, 1370, 1314, 1297, 1231, 1215, 1181, 832, 745, 721 cm^{-1}; ^{31}P NMR ($CDCl_3$, 161.9 MHz): δ 17.12 ppm; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.25–1.50 (m, 6H, 2 × CH_3), 3.75 (s, 3H, OCH_3), 3.75–3.90 (m, superimposed, 1H, CH_2N), 3.90–4.06 (m, 1H, CH_2N), 4.12–4.35 (m, 4H, 2 × $POCH_2$), 5.43 (td, 1H, J 2.7, 12.0 Hz, PCH), 6.82 (d, 2H, J 8.8 Hz, 2 × Ar-H), 7.30 (d, J 7.24 Hz, 2 × ArH) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 16.36 (s, 2 × CH_3), 42.31 (d, J_{CP} 10.3 Hz, CH_2N), 55.45 (s, OCH_3), 63.20 (d, J_{CP} 5.9 Hz, $POCH_2$), 63.54 (d, J_{CP} 6.2 Hz, $POCH_2$), 68.62 (d, J_{CP} 164.7 Hz, PCH), 114.2 (s, CH, 2 × Ar-C), 120.6 (s, CH, 2 × Ar-C), 130.5 (s, C_q, Ar-C), 152.2 (s, C_q, Ar-C), 156.1 (NCOO) ppm. Anal. Calcd for $C_{14}H_{20}O_6NP{\cdot}H_2O$ (347.304): C, 48.42; H, 6.39; N, 4.03. Found: C, 46.52; H, 6.02; N, 3.73. HPLC: CHIRALCEL AD-H column, hexane/2-propanol = 90:10, flow rate 1.0 ml/min, t_{r1} (major) = 14.8, t_{r2} (minor) = 19.1 min.

4.7. Diethyl N-(4-acetylphenyl)-2-oxo-oxazolidin-5-ylphosphonate 4c

The oxazolidinone was prepared from diethyl 1,2-oxiranephosphonate and phenyl isocyanate with $YbCl_3{\cdot}6H_2O$ and 2,6-bis[(4*R*)-4-phenyl-2-oxazolidinyl]pyridine as described under the general procedure. The crude product was purified by column chromatography (silica gel, DCM/hexane/MeOH = 5:5:1) to give **4c** as a white solid; mp 113.5–114 °C. IR (KBr): 3241, 3178, 3104, 3056, 2987, 1752, 1682, 1597, 1537, 1513, 1458, 1410, 1359, 1315, 1273, 1249, 1230, 1211, 1182, 1093, 1049, 1026, 994, 956, 855, 828, 800, 757, 722 cm^{-1}; ^{31}P NMR ($CDCl_3$, 161.9 MHz): δ 16.63 ppm; ^{1}H NMR ($CDCl_3$): δ 1.31 (t, 3H, J 6.9 Hz, CH_3), 1.34 (t, 3H, J 7.0 Hz, CH_3), 2.54 (s, 3H, Ac-CH_3), 3.79–3.84 (m, 1H, CH_2N),

3.90–3.96 (m, 1H, CH_2N), 4.19 (quint, 4H, 2 × OCH_2), 5.45 (td, *J* 2.9, 11.4 Hz, 1H, PCHO), 7.54 (d, *J* 8.6 Hz, 2 × CH, Ph-H), 7.90 (d, *J* 8.6 Hz, 2 × CH, Ph-H) ppm; ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 16.40 (s, 2 × CH_3), 26.39 (s, $COCH_3$), 42.16 (s, (d, J_{CP} 9.1 Hz, CH_2N), 63.34 (s, $POCH_2$), 63.77 (s, $POCH_2$), 69.00 (d, *J* 166.0 Hz, PCH), 117.9 (s, 2 × CH, Ph-C), 129.8 (s, 2 × CH, Ph-C), 132.5 (s, Cq, Ph-C), 142.1 (s, Cq, Ph-C), 151.7 (s, Cq, NCOO), 196.9 (s, CO) ppm. Anal. Calcd for $C_{15}H_{20}O_6NP{\cdot}H_2O$ (359.315): C, 50.14; H, 6.17; N, 3.90. Found: C, 47.20; H, 6.11; N, 3.57. HPLC: CHIRALCEL AD-H column, hexane/2-propanol = 90:10, flow rate 1.0 ml/min, t_{r1} (major) = 31.8, t_{r2} (minor) = 37.8 min.

4.8. *N*-Phenyl-2-oxo-oxazolidin-5-ylphosphonic acid 7

Diethyl *N*-phenyl-2-oxo-oxazolidin-5-ylphosphonate (0.042 g, 0.140 mmol) was dissolved in acetonitrile (0.71 mL) and bromotrimethylsilane was added (0.18 mL, 1.40 mmol). The solution was stirred at room temperature for 24 h. Water (0.040 mL, 2.22 mmol) was added and the solution was stirred for 1 h at 40–50 °C. The solvent and volatiles were then removed under reduced pressure and the product was dried to give an oil: 0.038 g, 41%. ^{31}P NMR ($CDCl_3$, 161.9 MHz): δ 12.11 ppm; ^{1}H NMR (D_2O): δ 3.70–3.85 (m, 1H, C*H*HN), 3.85–4.06 (m, 1H, CH*H*N), 5.13 (br t, *J* 9.7 Hz,b 1H, CHO), 7.04–7.14 (m, 1H, Ph-H), 7.24–7.39 (m, 4H, Ph-H) ppm; ^{13}C NMR (D_2O, 100.6 MHz): δ 44.05 (s, CH_2), 71.64 (d, J_{CP} 158.0 Hz, PCO), 120.5 (s, Ph-C), 124.8 (s, Ph-C), 129.6 (s, Ph-C), 137.7 (s, Ph-C), 155.5 (s, NCOO) ppm.

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