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P-Stereogenic Chirality

Organocatalytic Enantioselective Synthesis of *P*-Stereogenic Chiral Oxazaphospholidines

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Abstract: The enantioselective synthesis of *P*-stereogenic chiral organophosphines under organocatalysis is a challenging research field, and reports that use this approach are rare. Herein, we have developed the enantioselective synthesis of *P*-stereogenic chiral oxazaphospholidines by using a bicyclic thiazole as the organocatalyst in the P–N and P–O bond-forming reaction. The *P*-chiral products were prepared in high yields with moderate enantioselectivities. The base that was used in this process had a significant influence on the enantioselectivity of the reaction and in some cases led to the opposite configuration of the *P*-chiral center.

Introduction

Chiral phosphorus compounds that have a *P*-stereogenic center are often used as ligands,[1] organocatalysts,[2] and prodrugs[3] because of their unique stereochemical and biochemical properties. *P*-Chiral phosphoramidates and oxazaphospholidines contain P–N, P–O or P=O, and P–C bonds around an organophosphorus(V) center, which results in the *P*-chirality, and these *P*-chiral phosphorus heterocycles can be used as organocatalysts and precursors in the synthesis of *P*-chiral phosphines[4] as well as in the development of pesticides and pharmaceuticals.[5]

Enantiomerically pure *P*-chiral phosphorus compounds are often prepared by the chiral resolution of a mixture or by using a stoichiometric amount of a chiral auxiliary.[6] Asymmetric catalysis remains a challenge in the area, and examples that employ this approach are rare. Early attempts of metal-catalyzed asymmetric additions of P–H bonds to alkenes and alkynes resulted in low to moderate enantioselectivity.[7] However, G. Helmchen performed the highly enantioselective synthesis of chiral triarylphosphines by using a Pd-catalyzed P–C cross-coupling reaction.[8] In addition, Glueck along with Bergman and Toste conducted extensive studies on the Pd-, Pt-, and Ru-catalyzed asymmetric arylation and alkylation of phosphine, which resulted in good enantioselectivity.[9] In 2014, Leung and Hayashi achieved the Pd-catalyzed asymmetric addition of diarylphosphines to benzoquinones with excellent enantioselectivity.[10] Besides direct *P*-functionalizations that afford chiral phosphines, the desymmetrization of achiral phosphines is another successful strategy for their preparation. In 2009, Gouverneur and Hoveyda reported the enantioselective synthesis of phosphorus compounds through a desymmetrizing Mo-catalyzed ring-closing metathesis of symmetric acyclic phosphines.[11] In 2015, Han, Duan, and Liu independently developed Pd-catalyzed desymmetrizing C–H arylations for the synthesis of *P*-stereogenic chiral phosphoramides with excellent enantioselectivity.[12]

Compared with metallocatalytic reactions for the synthesis of *P*-chiral phosphorus compounds, organocatalytic methods have been investigated much less, with two reports to date. Initial attempts in this field by Zhang employed a kinetic resolution for the preparation of *P*-chiral phosphoramidates and used a chiral imidazole as the organocatalyst. However, this approach resulted in low to moderate enantioselectivity.[13] Johnson developed a highly diastereoselective and enantioselective phosphorus version of an iodolactonization reaction, which, under chiral Brønsted acid catalysis, produced a *C*- and *P*-chiral oxazaphospholidine from an alkenyl-containing phosphoramidic acid.[14] The activation of a phosphorus substrate, the interaction of phosphorus substrate with a catalyst, and the mechanisms of stereoinduction in the formation of *P*-chiral centers are not well-known. Organocatalysis seems more challenging, but it also more promising because of its metal-free character.

An alternate strategy for the synthesis of *P*-chiral oxazaphospholidines uses ephedrine and other amino alcohols as chiral auxiliaries to induce the *P*-chirality in reactions with phosphinic dichlorides.[6h,15] This inspired us to consider whether *P*-chiral oxazaphospholidines **3** can be prepared from phosphonic dichloride **1** and simple achiral amino alcohols **2** through P–N and P–O bond formation under catalytic conditions (Scheme 1). There have been no reports of this strategy to the best of our knowledge. This method would avoid the use of stoichiometric amounts of expensive chiral auxiliaries, particularly ephedrine, and the preparation of phosphoramidic acids for cyclization.[14]

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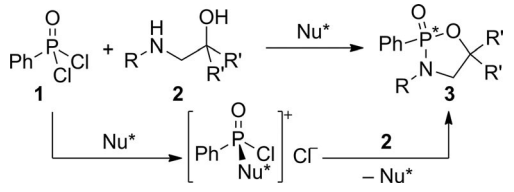
Instead, it would be a more economically viable and generally applicable process.

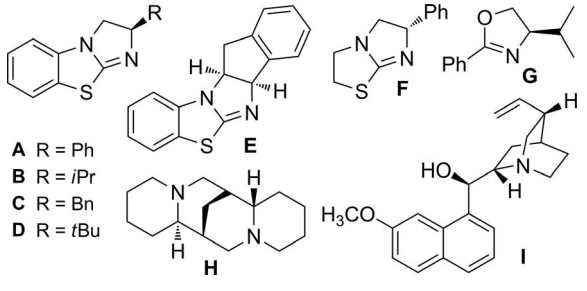


Scheme 1. Reaction design (Nu* = chiral organocatalyst).

We are interested in the use of a nucleophilic chiral organocatalyst and **1** for the reversible formation of an intermediate that is highly reactive towards achiral amino alcohols. The catalytic stereoselectivity would control the formation of the P–N and P–O bonds. In this reaction, there would be a preference by the chiral organocatalyst for the substitution of one of the chloro groups of the prochiral phosphine, which would determine the *P*-chirality of the intermediate (Scheme 1). The spatial conformation and direction then taken by the amino alcohol, upon attack of the phosphorus center, would influence the enantioselectivity of the product. By following this approach, we have conducted the enantioselective synthesis of *P*-chiral oxazaphospholidines by using chiral tertiary amines as organocatalysts and, herein, present the results.

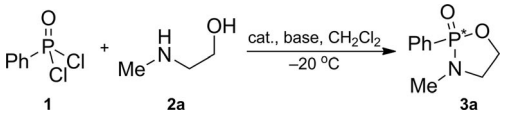
Results and Discussion

First, chiral tertiary amines **A**–**I** (Scheme 2) were screened as organocatalysts in the model reaction of **1** and *N*-methylaminoethanol (**2a**, Table 1). Amines **A**–**I** were expected to form a P–N bond with **1** through the substitution of one of its chloro groups to form a cationic intermediate, which then underwent a reaction with another substrate (Scheme 1). An initial experiment that employed 40 mol-% of **A** as the catalyst and triethylamine (TEA) as the base at –20 °C afforded an excellent yield of 94.2 % with an enantioselectivity of 36 % *ee* (Table 1, Entry 1). Catalysts **B**–**I** also gave good yields but with low or no enantioselectivity (Table 1, Entries 2–9). An increase or decrease in the catalyst loading of **A** or a change in the reaction temperature did not improve the results (Table 1, Entries 10–15). Therefore, the optimum reaction conditions for the employment of **A** as the organocatalyst at –20 °C were selected to further optimize the base.



Scheme 2. Organocatalysts that were used to optimize the reaction conditions.

Table 1. Optimization of organocatalytic conditions.[a]



Entry	Catalyst	Base	% Yield[b]	% *ee*[c]
1	**A**	TEA	94.2	36
2	**B**	TEA	75.8	12
3	**C**	TEA	72.1	11
4	**D**	TEA	53.7	0
5	**E**	TEA	78.6	0
6	**F**	TEA	65.7	–15
7	**G**	TEA	68.9	0
8	**H**	TEA	88.6	0
9	**I**	TEA	78.9	2
10	**A** (50 mol-%)	TEA	69.0	35
11	**A** (30 mol-%)	TEA	66.8	32
12	**A** (20 mol-%)	TEA	63.0	32
13	**A** (10 mol-%)	TEA	80.9	20
14[d]	**A**	TEA	91.8	33
15[e]	**A**	TEA	88.5	33
16	**A**	DIPEA	95.3	42
17	**A**	2-MeIm	89.2	–52
18	**A**	imidazole	77.5	–12
19	**A**	2-phenylimidazole	72.2	–50
20	**A**	2-ethylimidazole	72.1	–14
21	**A**	2-isopropylimidazole	55.8	–10
22	**A**	*N*-methylimidazole	80.4	–5
23	**A**	4-methylmorpholine	90.2	13
24	**A**	xylidine	50.4	12
25	**A**	DBU[f]	68.5	30
26	**A**	DABCO[f]	76.1	4
27	**A**	pyridine	86.9	–23
28	**A**	2-picoline	89.5	–5
29	**A**	2,6-lutidine	83.2	3
30	**A**	4-(dimethylamino)pyridine	60.7	2

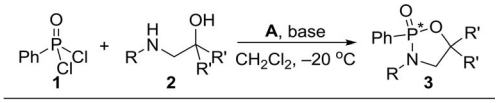
[a] Reagents and conditions: Unless otherwise noted, **2a** (0.2 mmol), **1** (0.3 mmol), base (0.6 mmol), and catalyst (40 mol-%) in CH_2Cl_2 (4 mL) were stirred at –20 °C for 12 h under N_2. [b] Isolated yields are provided. [c] Determined by HPLC analysis by using a chiral Diacel CHIRALPAK AD-H column. [d] Reaction was carried out at room temp. [e] Reaction was carried out at –40 °C. [f] DBU = 1.3-diazobicyclo[5.4.0]undec-7-ene, DABCO = 1,4-diazobicyclo[2.2,2]octane.

The base that is used in this reaction has a significant influence over the enantioselectivity. Compared with TEA, *N*,*N*-diisopropylethylamine (DIPEA) improved the enantioselectivity to 42 % *ee* without compromising the yield (Table 1, Entry 16). The enantioselectivity increased along with an unexpected inverse in the chiral preference (–52 % *ee*) when 2-methylimidazole (2-MeIm) was used as the base (Table 1, Entry 17). However, when imidazole was employed, there was a sharp decrease in the enantioselectivity (Table 1, Entry 18). We then changed the substituent at the 2-position of imidazole to phenyl, ethyl, and isopropyl, but larger substituents had a negative effect (Table 1, Entries 19–21). The use of *N*-methylimidazole resulted in a marked decrease in the enantioselectivity (Table 1, Entry 22). Other bases such as aliphatic amines and aromatic amines gave poor enantioselectivity results (Table 1, Entries 23–30). Furthermore, the reaction did not proceed when inorganic bases such as K_2CO_3, Na_2CO_3, and $NaHCO_3$ were used. Alkyl or arylamines that have an sp^3-hybridized nitrogen atom or heteroarylamines

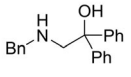
that contain an sp^2-hybridized nitrogen atom and result in a reversal in the preference for the *P*-chirality can be used for the synthesis of *P*-chiral compounds with prevailing divergent configurations. A few examples of stereoselective substitution at phosphorus and sulfur centers have also demonstrated an inverse in the chiral preference, which was induced by TEA and pyridine.[16]

Under the optimized conditions, the scope and limitations of the reaction were evaluated by using several amino alcohols (Table 2). With limited screenings to optimize the reaction for each amino alcohol, DIPEA was found to be a better base than TEA for the reactions that afforded **3a** and **3e** (Table 2, Entries 1 and 5). However, TEA was selected as the base that had the largest scope for the reaction. Considering the possibility of a base-dependent inversion of the chiral preference in the stereoselective substitution reaction at the phosphorus center,[16] we also used 2-MeIm as the base to examine whether there was a divergence in the enantioselectivity of the reaction by using different amino alcohols. The presence of different *N*-substituents in the amino alcohol substrate showed that most alkyl and aryl groups were well-tolerated under the reaction conditions to give excellent yields and moderate enantioselectivities of up to –58 % *ee*. However, *N*-tosyl-substituted **2n** and sterically hindered **2o** gave low yields (Table 2, Entries 14 and 15). The bases TEA and 2-MeIm did not provide a remarkable difference in the yields of **3**, with the exception of **3l** and **3o** (Table 2, Entries 12 and 15). In addition, TEA and 2-MeIm afforded products with opposite configurations in the synthesis of **3a**, **3e**, **3g**, and **3n** (Table 2, Entries 1, 5, 7, and 14). The results indicate that this divergence in the enantioselectivity depends on the structures of the substrates employed in the asymmetric formation of the *P*-chiral center. For the substrates with *N*-methyl, *N*-ethyl, and *N*-arylmethyl groups, that is, **2a**, **2b**, and **2e**–**2k**, the use of 2-MeIm induced a higher enantioselectivity than TEA (Table 2, Entries 1, 2, and 5–11). For **2n**, which contains an *N*-tosyl group, TEA afforded a higher enantioselectivity (Table 2, Entry 14). For the other amino alcohols, both bases induced comparable enantioselectivities. The absolute configuration of the predominant enantiomer of **3n**, which was obtained by using TEA as the base, was determined to have the (*R*) configuration by converting **3n** into a known *P*-chiral phosphorus oxide and comparing the optical rotations (see Section S6, Supporting Information).[6h,6i,15e,17]

Table 2. Scope of the **A**-catalyzed synthesis of oxazaphospholidines.[a]



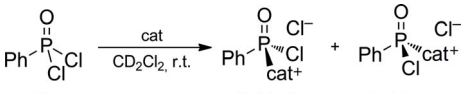
1 **2** **3**

Entry	**2**	Yield[b] (TEA / 2-MeIm)	*ee*[c] (TEA / 2-MeIm)
1[d]	**a** R = Me	94.2% / 89.2%	**42% / –52%**
2	**b** R = Et	88.8% / 90.8%	1% / –56%
3	**c** R = *i*Pr	94.2% / 92.5%	–50% / –49%
4[e]	**d** R = cyclohexyl	99.0% / 85.9%	–41% / –36%
5[d]	**e** R = Bn	99.0% / 93.7%	**11% / –54%**
6	**f** R = 2-MeBn	75.6% / 77.2%	–22% / –44%
7[f]	**g** R = 4-MeOBn	87.1% / 81.7%	**5% / –38%**
8	**h** R = 4-ClBn	95.1% / 89.9%	–18% / –56%
9	**i** R = 4-BrBn	91.9% / 75.4%	–13% / –49%
10	**j** R = 2-Br-5-MeOBn	99.0% / 98.9%	–35% / –55%
11	**k** R = 3-CNBn	87.2% / 92.1%	–44% / –58%
12	**l** R = (furan-2-yl)methyl	63.1% / 37.4%	–8% / –29%
13	**m** R = Ph	99.0% / 96.2%	45% / 36%
14	**n** R = Ts	46.0% / 44.8%	**–49%[g] / 11%**
15	**o** 	39.4% / 0%	–37% / –

[a] Reaction conditions: Unless otherwise noted, **2** (0.2 mmol), **1** (0.3 mmol), TEA or 2-MeIm (0.6 mmol), catalyst (40 mol-%) and CH_2Cl_2 (4 mL) were stirred at –20 °C for 12 h under N_2. [b] Isolated yields are provided. [c] Determined by HPLC analysis by using a chiral Diacel CHIRALCEL OD-H or CHIRALPAK AD-H column. [d] *N*,*N*-diisopropylethylamine was used as the base. [e] The reaction was carried out at 0 and –10 °C for TEA and 2-MeIm, respectively, as the base. [f] The reaction was carried out at –10 °C. [g] The (*R*) enantiomer was predominant.

Insights into the catalytic enantioselective formation of the P–N and P–O bonds were pursued through control experiments. Although 2 equiv. of **A** were used, the reaction of **1** and **2a** in the absence of a base did not proceed, which suggests that the base is vital for the activation of the amino alcohol. The reaction between **1** and **2a** in the presence of TEA but without any catalyst gave racemic **3a** in a yield of 79.0 %. Further studies of a mixture of **1** and catalysts **A**–**G** by ^{31}P NMR spectroscopic analysis revealed the formation of the presumed intermediate **Im1** in moderate yields with a diastereomeric excess (*de*) value of up to 90 % (Table 3 and Figures S1–S6, Supporting Information). **Im1** was believed to be the active species with a *P*-chiral center that undergoes a reaction with the nucleophilic substrate.[13,15e,18] However, there is a significant decrease in the enantiomeric excess values of **3a** that result from the reactions catalyzed by **A**–**G** compared with the diastereomeric excess values of **Im1** (Table 3). Products **3b**–**3o**, which are formed from reactions catalyzed by **A**, show the same trend (Table 2).

Table 3. Diasteroselective formation of complex from reaction of **1** and organocatalyst.[a]

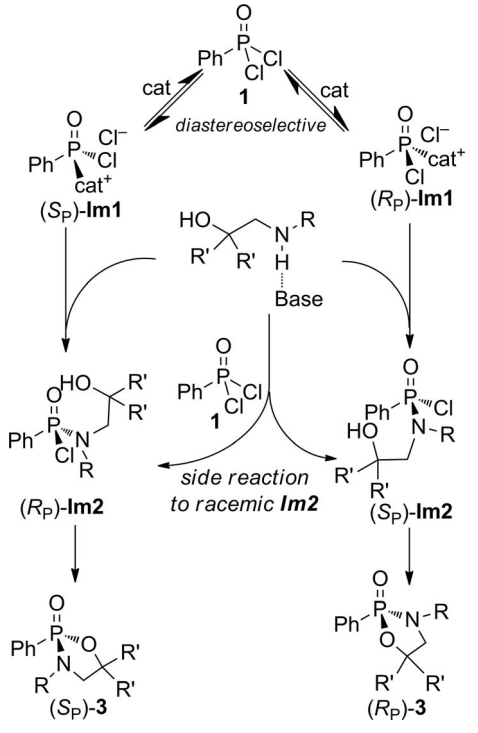


1 (S_P)-**Im1** (R_P)-**Im1**

Entry	Catalyst	Yield of **Im1**[b]	% *de* of **Im1**[c]	% *ee* of **3a**[d]
1	**A**	45 %	72	36.6
2	**B**	63 %	84	12.0
3	**C**	61 %	74	10.9
4	**D**	60 %	90	0
5	**E**	64 %	76	0
6	**G**	65 %	84	0

[a] Reagents and conditions: **1** (0.15 mmol) and a catalyst (0.04 mmol) in CD_2Cl_2 (1.0 mL) at room temp. for 1 h and then analysis by ^{31}P NMR spectroscopy. [b] Yield determined by ^{31}P NMR analysis based on the catalyst. [c] Diastereomeric excess value determined by ^{31}P NMR spectroscopic analysis. [d] See Table 1.

A mechanism for the catalytic enantioselective synthesis of *P*-stereogenic chiral oxazaphospholidines is proposed that is in agreement with the above results (Scheme 3). First, intermediate **Im1** forms from the reaction of **1** and a catalyst, whereupon a rapid equilibrium between **1**, the catalyst, (S_P)-**Im1**, and (R_P)-**Im1** is established. The base-activated amino alcohol then attacks **1** and both enantiomers of **Im1** to form the P–N bonds and produce phosphoramide intermediates (R_P)-**Im2** and (S_P)-**Im2**. The enantioselectivity of this step is determined by the preference of the activated amino alcohol to undergo a reaction with the major diastereomer of **Im1** over the minor enantiomer and **1**. This side reaction between **1** and the activated amino alcohol, which gives racemic **Im2**, hinders the possibility of achieving a highly enantioselective reaction, but it difficult to avoid under the current conditions. Finally, (R_P)- and (S_P)-**Im2** are converted into the corresponding *P*-stereogenic chiral oxazaphospholidines (S_P)- and (R_P)-**3**, respectively, through an intramolecular cyclization and P–O bond formation. Both the formation of P–N and P–O bonds are assumed to be S_N2-type reactions at the phosphorus center.[18]



Scheme 3. Proposed reaction mechanism.

Conclusions

In summary, a catalytic approach to the enantioselective synthesis of *P*-stereogenic chiral oxazaphospholidines was developed by using a bicyclic thiazole as an organocatalyst to assist the P–N and P–O bond-forming reaction. The reaction between phenylphosphonic dichloride (**1**) and the organocatalyst afforded active intermediate **Im1** with good diastereoselectivity. However, the enantioselectivity of the reaction that gave the *P*-stereogenic chiral oxazaphospholidines was moderate with high yields. The possibility of a side reaction between base-activated amino alcohol and **1** is the most likely explanation for this moderate selectivity. The employed base had a significant influence on the enantioselectivity and in some cases led to the opposite configuration at the *P*-chiral center of the product. This study demonstrates the synthesis of *P*-chiral phosphorus compounds by employing an organocatalytic approach and has potential applications toward the development of *P*-chiral catalysts, ligands, and bioactive compounds.

Experimental Section

General Methods: The *N*-substituted aminoethanols **2a**–**2e**, **2m**, and **2n** were obtained from commercial sources, and the other *N*-substituted aminoethanols **2** were prepared according to a literature procedure.[19] Catalysts **A**, **F**, **H**, and **I** were purchased from commercial sources, and **B**–**E** and **G** were prepared according to a literature procedure.[20] The NMR spectroscopic data were recorded with a Bruker Avance III spectrometer. $CDCl_3$ or CD_2Cl_2 was used as the NMR solvent. Either the solvent or TMS was used as the internal standard for the ^1H and ^{13}C NMR spectroscopic data, and phosphoric acid was used as the external standard for ^{31}P NMR spectroscopy. High resolution mass spectrometry was performed with a Bruker Autoflex III MALDI-TOF mass spectrometer. HPLC analysis was performed on a Shimidzu LC-10AD with a Class-VP system and by using Diacel ChiralPak® AD-H or ChiralCel® OD-H columns.

General Procedure for the Catalytic Synthesis of *P*-Stereogenic Oxazaphospholidines 3: The catalyst (0.08 mmol, 0.4 equiv.) and *N*-substituted aminoethanol **2** (0.2 mmol, 1.0 equiv.) were dissolved in DCM (4.0 mL), and the resulting mixture was stirred at the corresponding temperature for 5 min. The base (0.6 mmol, 3.0 equiv.) and $PhP(O)Cl_2$ (0.3 mmol, 1.5 equiv.) were successively added. The mixture was stirred for 12 h and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether) to afford compound **3** (for analysis and characterization of the products, see Supporting Information).

Acknowledgments

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Keywords: Synthetic methods · Organocatalysis · Asymmetric synthesis · Enantioselectivity · Phosphorus heterocycles

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