Asymmetric Catalysis

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Chiral Guanidinium Salt Catalyzed Enantioselective Phospha-Mannich Reactions**

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The addition of phosphites [$(RO)_2P(O)H$] to imines (Pudovik reaction) is a widely utilized method for the formation of P–C bonds and the preparation of chiral α-amino phosphonic acids.[1,2] Successful enantioselective approaches employed catalysts such as metal complexes,[3] quinine,[4] thiourea,[5] and chiral phosphoric acid.[6] α-Amino phosphonic acids and their phosphonate esters are excellent inhibitors of proteases and antibodies.[7] The biological activities of their phosphinic acids[8] and phosphine oxides analogues have yet to be thoroughly studied and may lead to important discoveries. The lack of such studies may be a result of the absence of reports on the use of other phosphorous nucleophiles such as secondary phosphine oxides [$R_2P(O)H$] and H-phosphinates [(RO)P(O)HR] for the addition to imines. The only previous report on the preparation of P-chiral phosphinate esters involved a resolution using phosphotriesterase.[9] Zhang and Yuan reported the synthesis of optically pure α-amino-*H*-phosphinic acids employing chiral ketimines.[10]

Electrophilic activation by small-molecule hydrogen-bond donors has provided an important paradigm for the design of enantioselective catalysts.[11] Salts of organic bases[12] were shown to be successful in the activation of imines and other anionic intermediates through hydrogen bonding. The guanidinium salts[13] have also demonstrated this potential and were used elegantly by Uyeda and Jacobsen to catalyze a Claisen rearrangement.[14]

Guanidines and guanidiniums have been shown to be powerful catalysts for enantioselective reactions.[15] Our goal was to prepare simple, novel guanidine or guanidinium catalysts. Guanidinium salt **1**·2 HBF_4 was prepared from diamine **2** and pyrrolidinium salt **3** in one step [Eq. (1)]. The free base guanidine **1** was obtained after basifying the guanidinium salt **1**·2 HBF_4 with a NaOH solution.

In preliminary studies, it was found that both the guanidinium salt **1**·2 HBF_4 and guanidine **1** can catalyze the phospha-Mannich reaction between the secondary phosphine oxide **4a** and imines (Table 1, entries 1 and 5). Catalysts

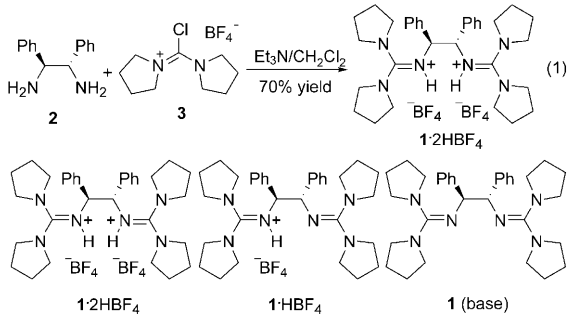
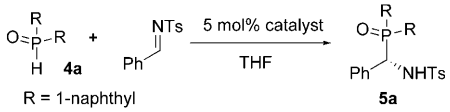


Table 1: Guanidine- and guanidinium-catalyzed phospha-Mannich reactions.



Entry	Catalyst	*T* [°C]	*t* [h]	*ee* [%][a]
1	**1** (base)	0	1.5	33
2	**1**·0.5 HBF_4	0	1.5	63
3	**1**·HBF_4	0	2.5	80
4	**1**·1.5 HBF_4	0	2.5	47
5	**1**·2 HBF_4	0	4	5
6	**1**·HPF_6	0	2.5	80
7	**1**·HBF_4	−50	14	87
8[b]	**1**·$HBAr^F_4$[c]	−50	14	92

[a] Determined by HPLC analysis on a chiral stationary phase. [b] 97% yield. [c] $HBAr^F_4 = HB(3,5\text{-}(CF_3)_2C_6H_3)_4$. Ts = 4-toluenesulfonyl.

1·*x* HBF_4 (*x* = 0.5, 1, 1.5) were prepared by mixing different ratios of the free base **1** and **1**·2 HBF_4 (ratio = 1:3, 1:1, 3:1, respectively). However, the highest *ee* value was obtained with catalyst **1**·HBF_4, which carried a single proton (Table 1, entry 3). Catalysts with different counterions, such as **1**·HPF_6 and **1**·$HBAr^F_4$,[16] were also tested for this reaction (Table 1, entries 6 and 8). The optimum conditions were found using **1**·$HBAr^F_4$ at a reaction temperature of −50 °C (Table 1, entry 8); the N-protected α-amino phosphine oxide **5a** was obtained in 92% *ee*.

Under the optimum conditions, the phospha-Mannich reaction was investigated with different imines (Table 2). Both electron-donating (Table 2, entry 1) and electron-withdrawing imines (Table 2, entry 2) provided adducts with high *ee* values. The reaction time for complete conversion of the bulky 2-naphthyl imine was 14 hours (Table 2, entry 3). A heterocyclic imine (Table 2, entry 4) resulted in a product with a high *ee* value. Imines derived from aliphatic aldehydes, such as cyclohexanecarbaldehyde, gave adduct with 70% *ee*

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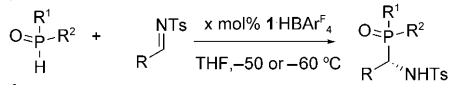
Table 2: Guanidinium-catalyzed (**1**·$HBAr^F_4$) phospha-Mannich reaction between phosphine oxides **4a**–**d** and various imines.



4a $R^1 = R^2$ = 1-naphthyl
4b $R^1 = R^2$ = Ph
4c $R^1 = R^2$ = 2-$CF_3C_6H_4$
4d R^1 = Ph, R^2 = 1-naphthyl

5b-k

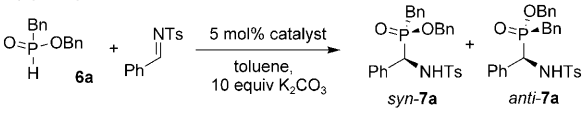
Entry	4	R	x [mol %]	5	t [h]	Yield [%][a]	ee [%][b]
1	**4a**	4-MeC_6H_4	5	**5b**[c]	14	98	92
2	**4a**	4-FC_6H_4	5	**5c**	14	97	90
3	**4a**	2-naphthyl	5	**5d**	14	98	92
4	**4a**	2-furyl	5	**5e**	14	92	87
5[d]	**4a**	Cy	10	**5f**	16	95	70
6	**4a**	*t*Bu	10	**5g**	40	89	91
7	**4a**	*trans*-PhCH=CH	5	**5h**	36	89	90
8[e]	**4b**	Ph	20	**5i**[f]	96	75	56
9	**4c**	Ph	20	**5j**[f]	14	93	82
10	**4d**	Ph	20	**5k**[g]	14	90	75;85

[a] Yield of isolated product. [b] Determined by HPLC analysis on a chiral stationary phase. [c] The absolute configuration of **5b** was assigned by using *X*-ray crystallographic analysis (see the Supporting Information for details). [d] Used *t*BuOMe as solvent. [e] Used CH_2Cl_2/Et_2O (1:1) as solvent. [f] Protecting group on the imine was 4-phenylbenzenesulfonyl. [g] Protecting group on the imine was benzensulfonyl. Cy = cyclohexyl.

(Table 2, entry 5), whereas an imine derived from pivalaldehyde afforded the adduct with 91% *ee* (Table 2, entry 6). An imine derived from *trans*-cinnamyl aldehyde provided adduct **5h** with high a *ee* value (Table 2, entry 7). Diaryl phosphine oxides **4b** and **4c** carrying phenyl and *ortho*-trifluoromethylphenyl groups respectively, provided adducts with moderate to good *ee* values (Table 2, entries 8 and 9). The racemic phosphine oxide **4d** added to phenyl imine to generate two diastereisomers with a diastereomeric ratio (d.r.) of 1:1 and high *ee* values (Table 2, entry 10).

We also found that the addition of H-phosphinates [(RO)P(O)HR], such as benzyl benzylphosphinate **6a**, to imines can be catalyzed by **1**·HBF_4 (Table 3); however, the reaction was slow and a low *ee* value was observed. Various additives were used and inorganic bases such as K_2CO_3 increased the reaction rate without decreasing the *ee* value (Table 3, entry 1). Guanidinium salts having different counterions were investigated (Table 3, entries 2–5), and the catalyst **1**·$HBAr^F_4$ gave the most promising result when the reaction temperature was lowered to −20°C (Table 3, entry 6). After the reaction was complete, the catalyst was recovered and NMR experiments revealed that the guanidinium catalyst **1**·HAr^F_4 was unchanged; the catalyst was not converted into guanidine **1** during the course of the reaction. When CH_2Cl_2 was used as the solvent, a better *ee* value was observed but the reaction rate was much slower (Table 3, entry 7). The racemic **6a** was used as the limiting reagent (Table 3, entries 1–7) in these experiments, resulting in a diastereomeric ratio (d.r.) of 1:1. When the amount of racemic donor **6a** was increased from 2:1 (Table 3, entry 8) to 3:1 (Table 3, entry 9), the *ee* value of the major diastereoisomer (*syn*)[17] was increased to 82%. A solvent mixture (CH_2Cl_2/toluene 1:1) was used to make a balance between the reaction rate and the *ee* value (Table 3, entry 9). The absolute and relative stereochemistries were determined using *X*-ray crystallographic analysis of *syn*-**7g**.

Table 3: Guanidinium-catalyzed phospha-Mannich reaction of benzyl benzylphosphinate **6a**.

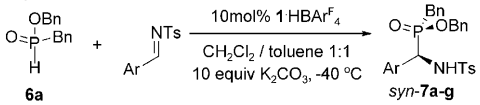


Entry[a]	Catalyst	T [°C]	t [h][b]	syn-7a ee [%][c]	anti-7a ee [%][c]
1	**1**·HBF_4	RT	<1	20	23
2	**1**·HPF_6	RT	<1	20	20
3	**1**·HCl	RT	<1	10	5
4	**1**·$HClO_4$	RT	<1	3	4
5	**1**·$HBAr^F_4$	RT	<1	30	50
6	**1**·$HBAr^F_4$	−20	48	42	70
7[d]	**1**·$HBAr^F_4$	−20	60	65	50
8[e]	**1**·$HBAr^F_4$	−20	20	72	37
9[f]	**1**·$HBAr^F_4$	−20	24	82	25

[a] H-phosphinate/imine 1:1.2. [b] Determined by TLC analysis, 100% conversion. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Used CH_2Cl_2 as solvent; d.r. 1:1. [e] H-phosphinate/imine 2:1; d.r. 3:1. [f] H-phosphinate/imine 3:1, CH_2Cl_2/toluene 1:1 as solvent; d.r. = 4:1. Bn = benzyl.

The phospha-Mannich reaction of benzyl benzylphosphinate **6a** can be additionally optimized by decreasing the reaction temperature to −40°C (Table 4, entry 1). Good yields and high enantioselectivities of the major diastereoisomer were observed. Several other aromatic *N*-benzenesulfonyl imines (Table 4, entries 2–4) and *N*-tosylated imines (Table 4, entries 5–7) were investigated and they provided the major diastereoisomers (d.r. from 4:1 to 7:1) **7a**–**7g** with high *ee* values. Different alkyl benzylphosphinates **6b**–**6e** were prepared to investigate the scope of the reaction (Table 5). Adducts **7h**,**i** were obtained with high *ee* values (Table 5, entries 1–2). H-phosphinate **6d** bearing an electron-donating

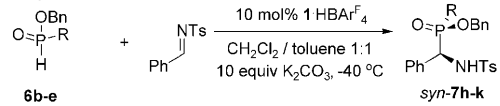
Table 4: Guanidinium-catalyzed phospha-Mannich reaction of benzyl benzylphosphinate **6a** and various imines.



Entry[a]	Ar	syn-7	t [h]	Yield [%][b]	d.r.[c]	syn-7 ee [%][d]
1	Ph	**7a**	39	83	6:1	94
2[e]	4-FC_6H_4	**7b**	35	90	6:1	90
3[e]	4-ClC_6H_4	**7c**	108	90	4:1	92
4[e]	4-MeC_6H_4	**7d**	100	85	4:1	90
5[f]	2-naphthyl	**7e**	39	93	6:1	91
6[f]	2-furyl	**7f**	40	71	7:1	94
7	*trans*-PhCH=CH	**7g**	65	92	3:1	90

[a] H-phosphinate/imine 3:1. [b] Yield of isolated product of two isomers. [c] Approximated by ^{1}H NMR analysis and confirmed by HPLC analysis on a chiral stationary phase. [d] Determined by HPLC analysis. [e] Protecting group on the imine was benzenesulfonyl. [f] Used 15 mol% catalyst.

Table 5: Guanidinium-catalyzed phospha-Mannich reaction with alkyl benzylphosphinates **6b–6e**.

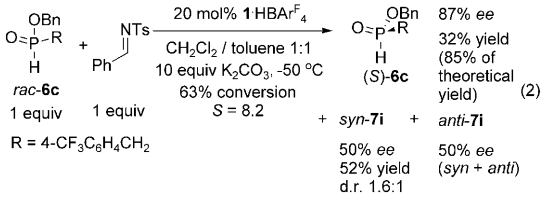


Entry	**6** (R)	*syn*-**7**	*t* [h]	Yield [%][a]	d.r.[b]	*syn*-**7** ee [%][c]
1	**6b** (2-naphthyl-CH_2)	**7h**	38	92	6.5:1	94
2	**6c** (4-$CF_3C_6H_4CH_2$)	**7i**	36	92	16:1	94
3	**6d** (4-$MeC_6H_4CH_2$)	**7j**	43	83	5:1	88
4[d]	**6e** (*trans*-PhCH=CHCH$_2$)	**7k**	168	82	7:1	82

[a] Yield of the two isolated isomers. [b] Determined by ^{1}H NMR and HPLC analyses. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 20 mol% catalyst, −60°C, the protecting group on the imine was benzenesulfonyl.

group and **6e** bearing an alkenyl chain afforded modest *ee* values (Table 5, entries 3–4). The best diastereoselectivity (16:1) was obtained when highly electron-withdrawing H-phosphinate **6c** was used (Table 5, entry 3).

Chiral phosphine oxides and phosphines are typically prepared using enantiopure starting materials, chiral auxiliaries, or by recrystallization of the racemic phosphines.[18] This methodology can provide an alternative strategy to obtaining enantiomerically pure H-phosphinates through kinetic resolution [Eq. (2)]. The phospha-Mannich reaction was re-optimized and was conducted with *rac*-**6c**. The reaction was stopped at 63% conversion and the unreacted H-phosphinate (*S*)-**6c** was found to have an *ee* of 87% and was recovered in 85% yield. When the enantiomerically enriched (*S*)-**6c** was resubjected to the reaction conditions in the absence of imine for 24 hours, no racemization was observed. Since we have determined the absolute and relative configuration of *syn*-**7** adducts, we can deduce the absolute configuration of (*S*)-**6c**.[19]



In summary, we have prepared a novel guanidinium catalyst, obtained in a single step from a commercially available diamine. With this catalyst, an asymmetric phospha-Mannich reaction was developed using secondary phosphine oxides and H-phosphinates as the P nucleophile. By using this methodology, a series of enantiomerically enriched α-amino phosphine oxides, α-amino phosphinates, and H-phosphinates containing a P-chiral center were prepared.

Experimental Section

Representative procedure for guanidinium salt **1**·HAr$^F_4$ catalyzed enantioselective reaction between H-phosphinate **6a** and phenyl *N*-tosylated imine (Table 4, entry 1): Benzyl benzylphosphinate **6a** (59.1 mg, 0.24 mmol, 3 equiv), K_2CO_3 (108.8 mg, 0.8 mmol, 10 equiv), toluene (0.2 mL), and CH_2Cl_2 (0.2 mL) were added sequentially to a 5 mL RBF containing catalyst **1**·HAr$^F_4$ (11.0 mg, 0.008 mmol, 10 mol%). The reaction mixture was then cooled to −40°C and stirred for 0.5 h before the *N*-tosylated imine (19.7 mg, 0.08 mmol, 1 equiv) was added. When the reaction was complete, the reaction mixture was purified by flash chromatography (gradient elution with *n*-hexane/ethyl acetate 10:1 to 1:1). Product **7a** (33.5 mg, 83%) was obtained with an *ee* value of 94% (*syn*-**7a**). The diastereoisomers were separated with another flash chromatography (CH_2Cl_2/ethyl acetate (10:1)).

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[19] See the Supporting Information for details of the kinetic resolution.

