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Synergistic Chiral Ion Pair Catalysts for Asymmetric Catalytic Synthesis of Quaternary α,β-Diamino Acids

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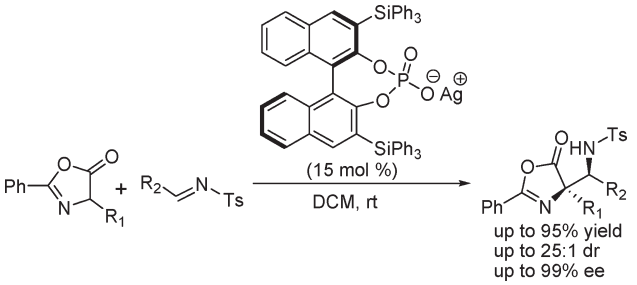
ABSTRACT



The combination of a chiral phosphate anion with a silver ion has been demonstrated as a powerful and synergistic ion pair catalyst for the aza-Mannich reaction. A series of valuable quaternary α,β-diamino acid derivatives was obtained in high yield, and with excellent diastereo- (up to 25:1 dr) and enantioselectivity (up to 99% ee). The adducts can be smoothly transformed into the corresponding protected chiral quaternary α,β-diamino acids by a one-pot hydrolysis reaction.

Optically active α,β-diamino acids are very attractive targets in organic synthesis because of their wide-ranging biological significance and high versatility as synthetic building blocks.[1] In addition, chiral quaternary α,β-diamino acids are incorporated into many biologically active peptides, such as bleomycin, peplomycin, tuberactomycin B, and the antifungal Sch37137,[2] to impart conformational stability and in some cases to impart antibiotic activity.[3] In recent years, interest in the synthesis of α,β-diamino acids in an optically pure form has increased dramatically.[4] Organic ion pair catalysis, particularly involving chiral systems, has occupied a unique place in the recent development of organic molecular catalysis,[5−7] and its useful features have attracted extensive attention from industrial and academic communities. A chiral organic ion pair catalytic approach to prepare quaternary α,β-diamino acids was first developed by Ooi group in 2008.[8] Since then, a handful of such protocols have been

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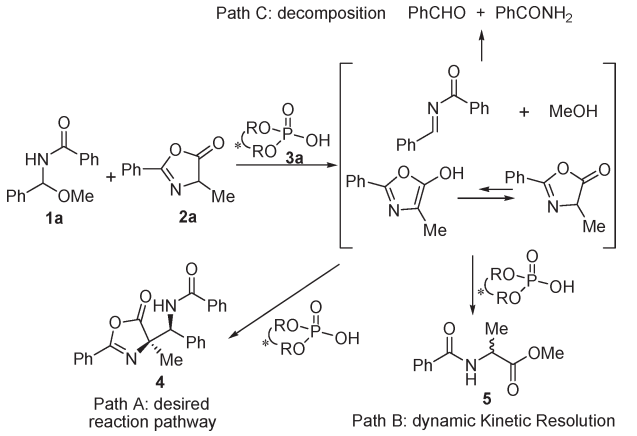
described in the literature by several groups.[8,9] Therefore, it is of widespread interest to develop new chiral organic ion pair catalytic approaches for the synthesis of chiral quaternary α,β-diamino acids.

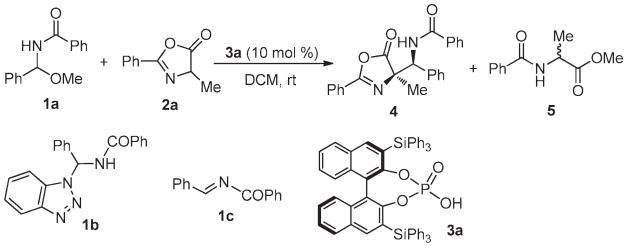
Scheme 1. Possible Pathways



The direct Mannich reaction represents one of the most straightforward approaches to access α,β-diamino acids.[1,2] Although oxazolones have been proven to be excellent masked amino acid fragments[10] and have previously been employed to synthesize chiral quaternary α-amino acids,[11] very few reports have described the efficient synthesis of chiral quaternary α,β-diamino acids by the addition of oxazolones to *N*-tosyl aldimines, except for a chiral tetraaminophosphonium carboxylate[8] and a cinchona alkaloid catalyst[12] which offered excellent diastereo- and enantioselectivitiy, respectively. As our group works on the asymmetric synthesis of amino acids,[13] we decided to apply a synergistic ion pair catalyst in the asymmetric addition of oxazolones to *N*-tosyl aldimines. As anticipated, the aza-Mannich reaction worked well to give the desired products in high yield, with excellent diastereo- and enantioselectivity.

In the first stage of the study, we investigated the reaction of oxazolone **2a** with *N*-benzoyl-1-methoxy-1-phenylmethylamine (**1a**) in the presence of a catalytic amount of the chiral phosphoric acid **3a** in dichloromethane (Scheme 1). Unfortunately, in addition to our desired reaction pathway of trapping the oxazole enolate with the in situ generated imine (path A), possible side reaction pathways included the dynamic kinetic resolution of the oxazolone by chiral phosphoric acids (path B)[14] and the decomposition of compound **1a** (path C). In the event, the reaction gave a mixture of compounds **4** and **5**, from which the desired product **4** was isolated in 38% yield and 95% ee (Table 1, entry 1). To restrain two side reactions,

Table 1. Optimization of Chemoselectivity[a]



entry	additive	yield of **4** (%)[b]	dr of **4**[c]	ee of **4** (%)[d]	yield of **5** (%)[b]
1	—	38	3:1	95	20
2	4 Å MS (30 mg)	38	3:1	95	15
3	4 Å MS (50 mg)	45	3:1	95	12
4	Na_2SO_4 (30 mg)	35	3:1	93	19
5	$CaCl_2$ (22 mg)	trace	—	—	26
6	$CuSO_4$	trace	—	—	25
7[e]	—	28	10:1	>99	—
8[f]	—	51	5:1	80	—
9[g]	—	63 (**6a**)	8:1 (**6a**)	84 (**6a**)	—

[a] Experimental conditions: a mixture of **1** (0.3 mmol), **2** (0.2 mmol), and catalyst **3a** (0.02 mol) in DCM (1 mL) was stirred at room temperature for 12 h. [b] Isolated yield. [c] Determined by ^{1}H NMR (400 MHz). [d] The enantiomeric excess was determined by chiral HPLC analysis. [e] *N*-Benzoyl-1-benzotriazolyl-1-phenyl-methylamine (**1b**) was used. [f] *N*-Benzylidenebenzamide (**1c**) was used. [g] *N*-Benzylidene-4-methylbenzenesulfonamide (**1d**) was used.

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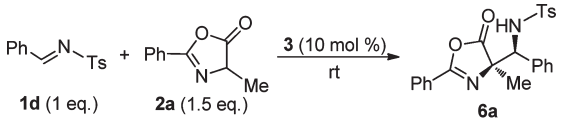
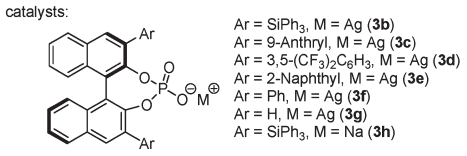
paths B and C, removal of moisture (4 Å molecular sieve and Na_2SO_4) and methanol ($CaCl_2$ and $CuSO_4$) was employed as shown in Table 1. However, various additives did not improve the chemoselectivity (entries 2−6). Moreover, *N*-benzoyl-1-methoxy-1-phenylmethylamine (**1a**) was replaced with *N*-benzoyl-1-benzotriazolyl-1-phenylmethylamine (**1b**), *N*-benzylideneben-zamide (**1c**), and *N*-benzylidenetoluene-sulfonamide (**1d**), respectively (entries 7−9). Fortunately, when substrate **1d** was used, the adduct **6a** was smoothly obtained with a moderate yield as well as diastereo- and enantioselectivity (entry 9).

Because chiral silver binol phosphate can efficiently activate imines and imine precursors, imine precursors **1a**−**1b** and imine **1d** were used as substrates for the aza-Mannich reaction in the presence of chiral organic ion pair catalysts **3b** (10 mol %) in dichloromethane at room temperature, respectively. The results showed that the imine precursors **1a**−**1b** provided the adduct **4** with a low yield and excellent enantioselectivity (Table 2, entries 1−2),

Table 2. Representative Screening Results for the Reaction of *N*-Tosyl Imine **1d** and Oxazolone **2a**[a]





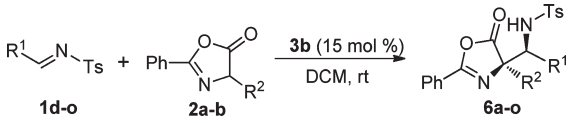
entry	catalyst	solvent	dr[b]	yield (%)[c]	ee (%)[d]
1[e]	**3b**	DCM	4:1	42	94
2[f]	**3b**	DCM	9:1	36	98
3	**3b**	DCM	15:1	94	92
4	**3c**	DCM	16:1	91	87
5	**3d**	DCM	14:1	94	81
6	**3e**	DCM	9:1	92	78
7	**3f**	DCM	7:1	94	73
8	**3g**	DCM	4:1	95	66
9	**3h**	DCM	12:1	80	89
10	**3b**	Et_2O	13:1	93	88
11	**3b**	Toluene	11:1	90	78
12	**3b**	THF	5:1	91	69
13	**3b**	DCE	6:1	88	53
14[g]	**3b**	DCM	5:1	83	31

[a] Experimental conditions: a mixture of **1d** (0.2 mmol), **2a** (0.3 mmol), and catalyst **3** (0.02 mmol) in solvent (1 mL) was stirred at room temperature for 36 h. [b] Determined by ^{1}H NMR (400 MHz). [c] Isolated yield. [d] The enantiomeric excess was determined by chiral HPLC analysis. [e] Imine precursor **1a** was used. [f] Imine precursor **1b** was used. [g] The reaction was carried out under 0 °C for 48 h.

whereas imine **1d** gave the adduct **6a** with 94% yield, 15:1 dr, and 92% ee (entry 3). Furthermore, a series of chiral silver binol phosphate catalysts **3c**−**g** were also tested in the aza-Mannich reaction between imine **1d** and oxazolone **2a**, and the results indicated that catalyst **3b** gave the best results (entries 4−8). When chiral sodium binol phosphate **3h** was used, a moderate yield and enantioselectivity were afforded due to the weak Lewis acidity of sodium compared to the silver cation (entry 9). Further screening of solvents failed to improve the yield as well as diastereo- and enantioselectivity (entries 10−13). When the reaction temperature was reduced to 0 °C, a 31% ee of product **6a** was afforded (entry 14).

To demonstrate the generality of the ion pair catalyst **3b**-promoted asymmetric aza-Mannich reaction, a variety of *N*-tosyl aldimines and oxazolones were explored (Table 3).

Table 3. Asymmetric Synthesis of Quaternary α,β-Diamino Acid Derivatives[a]



entry	R^1	R^2	time (h)	dr[b]	yield (%)[c]	ee (%)[d]
1[e]	Ph	Me	36	15:1	94 (**6a**)	92
2[e]	*p*-Me-Ph	Me	36	25:1	92 (**6b**)	94
3[e]	*p*-Cl-Ph	Me	36	11:1	95 (**6c**)	81
4	Ph	*i*-Pr	48	16:1	92 (**6d**)	95
5	*p*-Me-Ph	*i*-Pr	48	18:1	84 (**6e**)	98
6	*p*-MeO-Ph	*i*-Pr	48	17:1	83 (**6f**)	99
7	*o*-F-Ph	*i*-Pr	48	19:1	93 (**6g**)	94
8	*p*-F-Ph	*i*-Pr	48	16:1	91 (**6h**)	82
9	*o*-Cl-Ph	*i*-Pr	48	20:1	88 (**6i**)	95
10	*m*-Cl-Ph	*i*-Pr	48	19:1	85 (**6j**)	82
11	*p*-Cl-Ph	*i*-Pr	48	18:1	90 (**6k**)	91
12	*p*-Br-Ph	*i*-Pr	48	20:1	89 (**6l**)	86
13	2-$C_{10}H_7$	*i*-Pr	48	7:1	88 (**6m**)	94
14	2-C_4H_3O	*i*-Pr	48	21:1	90 (**6n**)	86
15	*n*-Pr	*i*-Pr	48	10:1	58 (**6o**)	75

[a] Experimental conditions unless otherwise stated: a mixture of **1** (0.2 mmol), **2** (0.3 mmol), and **3b** (0.03 mmol) in dichloromethane (1 mL) was stirred at room temperature. [b] Determined by ^{1}H NMR (400 MHz). [c] Isolated yield. [d] The enantiomeric excess was determined by chiral HPLC analysis. [e] 10 mol % catalyst.

When the aza-Mannich reaction of aldimines **1e**−**f** and oxazolone **2a** were examined under the optimized conditions, products **6b** and **6c** were obtained with 94% and 81% ee, respectively (entries 2 and 3). When the reaction of aldimines **1d** and oxazolone **2b** was carried out under these conditions, the product **6d** was obtained in 70% yield due to greater steric hindrance of the isopropyl group in oxazolone **2b** compared with the methyl group in **2a**. Thus, the aza-Mannich reactions of oxazolone **2b** with aldimines **1d**−**o** were conducted in the presence of 15 mol % catalyst **3b** for 48 h. As expected, our aza-Mannich reaction could be extended to a range of *N*-tosyl aldimines, bearing aromatic and heteroaryl groups (entries 1−14). High yields

(14) Lu, G.; Birman, V. B. *Org. Lett.* **2011**, *13*, 356.

and enantioselectivities were obtained. It should be noted that *N*-tosyl aldimines with electron-donating aryl showed excellent enantioselectivities (entries 5 and 6); aldimines bearing electron-withdrawing groups at the *para*-position of R^1 aryl group gave slightly low enantioselectivities (entries 8, 11, and 12). With respect to *ortho*-position substituents and the 2-naphthyl group, high enantioselectivities were also obtained, probably due to steric effects (entries 7, 9, and 13). Gratifyingly, alkyl-substituted *N*-tosyl aldimine (**1o**) smoothly reacted with oxazolone **2b** and product **6o** was obtained with 58% yield and 75% ee (entry 15).

The structures of the products **6a**−**o** were characterized by spectroscopic data and X-ray crystal structure analysis (Figure 1).[15] The absolute configuration of the product was determined to be (*R*,*S*)-**6e** and (*R*,*S*)-**6k** by comparing the optical rotation value with the literature.[12] The absolute configuration of the other products was assigned by analogy.

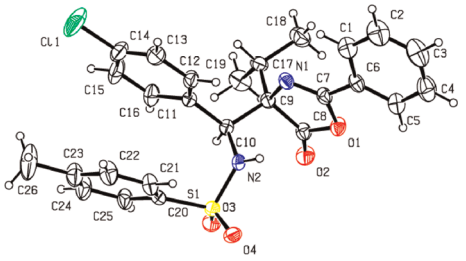


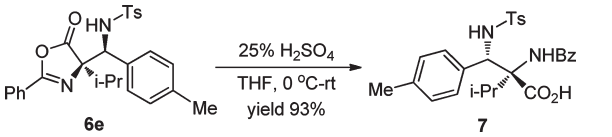
Figure 1. X-ray crystal structure of compound **6k**.

In an illustration of the synergistic catalytic cycle,[16] this protocol probably involved the basic binol phosphate anion abstracting the active proton of oxazolone to give the corresponding chiral phosphonium enolate. Simultaneously, the Ts-imine was activated by the coordination of the counter silver ion with Ts-imine. At last, chiral phosphonium enolate attacked the active imine to form product **6**.

(15) CCDC 868973 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/daa_request/cif.

(16) Please see the Supporting Information for a figure of proposed cooperative catalytic model.

Scheme 2. Hydrolyzed to the Corresponding Protected Quaternary α,β-Diamino Acids



The synthetic versatility of the aza-Mannich adducts in this reaction was illustrated by a further transformation. Optically active quaternary α,β-diamino acid **7** was obtained by using the protocol developed by Ooi et al. (Scheme 2).[8] The adduct **6e** could react efficiently to afford the corresponding Ts- and Bz- diprotected quarternary α,β-diamino acid **7** with 93% yield.

In conclusion, we have developed a synergistic ion pair catalyst that consists of a silver ion and a chiral phosphate anion which can catalyze the aza-Mannich addition of oxazolones to *N*-tosyl aldimines. Quaternary α,β-diamino acid derivatives were obtained in high yield, with excellent diastereo- and enantioselectivity. In addition, the methodology for the synthesis of α,β-diamino acid derivatives is a supplement to our previous work.

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Supporting Information Available. Experimental procedure, characterization data for the products, crystallographic data of compound **6k** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.