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Asymmetric Mannich Reaction of Isatin-Based Ketimines with α-Diazomethylphosphonates Catalyzed by Chiral Silver Phosphate

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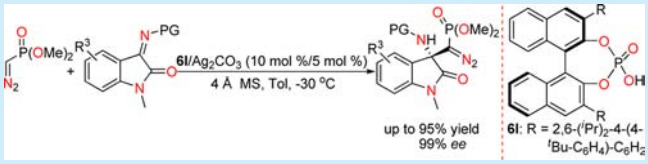
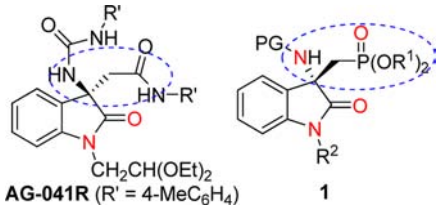
Supporting Information

ABSTRACT: An efficient asymmetric Mannich reaction of isatin-based ketimines with α-diazomethylphosphonates has been developed using a chiral binaphthanol-derived silver phosphate as the catalyst. This reaction allowed the construction of a series of chiral oxindoles bearing a quaternary stereocenter and amino group at the C3 position with up to 95% yields and 99% *ee*. Those products could be further transformed into promising densely functionalized compounds by merging of the oxindole and β-aminophosphonate.



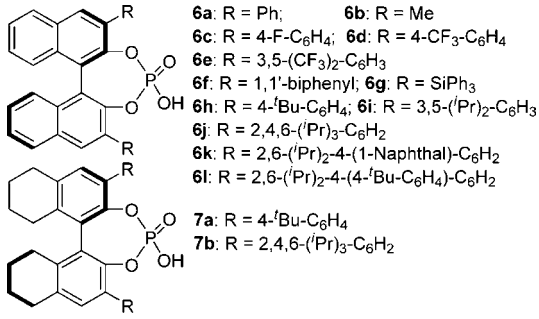
Chiral oxindole bearing a quaternary stereocenter and an amino group at the C3 position as a privileged structure motif is widely present in natural products and pharmaceutically active compounds.[1] In the past decade, much effort has been devoted to developing synthetic strategies for preparing chiral 3-aminooxindoles and their derivatives.[2−4] Among these derived bioactive compounds, AG-041R shows gastrin/cholecystokinin-B (CCK-B) receptor antagonist activity and has been selected as a drug candidate. The structure of AG-041R features the privileged structure motifs of oxindole and β-amino amide derived from β-amino acid.[4a−c] β-Amino phosphoric acid, as an isosteric analog of β-amino acid, has shown significantly improved bioactivity and stability in a pharmaceutical dynamic study.[5] We were intrigued by the prospect of combining oxindole and β-aminophosphonate in one compound that may possess interesting bioactivity. Despite the great advances that have been made in the stereoselective synthesis of 3-substituted 3-aminooxindoles, to date, there has been no direct method to access chiral β-aminophosphonates based on an oxindole framework **1**. Given our longstanding research in α-diazoalkylphosphonate chemistry, we supposed that this framework could be prepared by the asymmetric Mannich reaction of α-diazoalkylphosphonates and isatin imines followed by hydrogenation. Compared with the well-developed α-diazo carbonyl chemistry, α-diazomethylphosphonate is generally less reactive owing to the electronic effect and bulkier steric hindrance of the phosphonate group.[6] Thus, the asymmetric Mannich reactions involving α-diazomethylphosphonate as a nucleophile are mainly limited to aldimines;[7] the reactions with the less reactive ketimines are very challenging and have not yet been reported.[8] Here, we report our preliminary results on the asymmetric reaction of diazomethylphosphonate with ketimines.

The reaction of α-diazomethylphosphonate **2a** with isatin *N*-Boc ketimine **3aa** was selected as the model reaction. After a series of preliminary trials, we found that chiral phosphate salts, as one kind of chiral ion pair catalyst,[9−11] could promote this reaction in a synergistic fashion by simultaneously activating both



the electrophile and nucleophile. The results are summarized in Table 1. Chiral phosphoric acid (CPA) **6a** (Scheme 1) was first used as a pro-anion to screen metal salts in toluene at −30 °C in the presence of 4 Å molecular sieves (MS) as a water scavenger.

Scheme 1. Screened Chiral Phosphoric Acids



When NaH, KO^{t}Bu, Mg(O^{t}Bu)$_2$, Ba(O^{i}Pr)$_2$, and Sr(O^{i}Pr)$_2$ were used as the source of a metal ion, no reaction was observed (Table 1, entries 1−5). When the complex of **6a** (10 mol %) with AgOAc (5 mol %) was used as the catalyst, the reaction proceeded smoothly to give the desired product **4aaa** in 37% yield with 6% *ee* and 16% of byproduct **5aaa** produced from ring enlargement of **4aaa** (Table 1, entry 6). We then turned our

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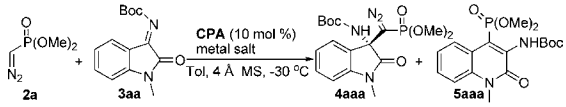
Table 1. Catalyst Screening in the Asymmetric Mannich Reaction



entry[a]	CPA	metal salt (%)	yield of **4** (%)[b]	*ee* (%)[c]	yield of **5** (%)[b]
1	**6a**	NaH (10)	NR	–	–
2	**6a**	KO^{t}Bu (10)	NR	–	–
3	**6a**	Mg(O^{t}Bu)$_2$ (5)	NR	–	–
4	**6a**	Ba(O^{i}Pr)$_2$ (5)	NR	–	–
5	**6a**	Sr(O^{i}Pr)$_2$ (5)	NR	–	–
6	**6a**	AgOAc (10)	37	6	16
7	**6a**	AgOTf (10)	37	3	8
8	**6a**	Ag_2O (5)	71	3	18
9	**6a**	Ag_2CO_3 (5)	80	7	18
10	**6b**	Ag_2CO_3 (5)	95	0	3
11	**6c**	Ag_2CO_3 (5)	46	3	8
12	**6d**	Ag_2CO_3 (5)	71	24	28
13	**6e**	Ag_2CO_3 (5)	90	17	9
14	**6f**	Ag_2CO_3 (5)	41	37	57
15	**6g**	Ag_2CO_3 (5)	39	30	0
16	**6h**	Ag_2CO_3 (5)	54	8	44
17	**6i**	Ag_2CO_3 (5)	68	18	21
18	**6j**	Ag_2CO_3 (5)	73	90	16
19	**6k**	Ag_2CO_3 (5)	61	45	37
20	**6l**	Ag_2CO_3 (5)	80	98	15
21	**7a**	Ag_2CO_3 (5)	59	11	0
22	**7b**	Ag_2CO_3 (5)	63	4	32
23[d]	**6l**	Ag_2CO_3 (5)	78	98	5
24[e]	**6l**	Ag_2CO_3 (5)	85	99	5
25[f]	**6l**	Ag_2CO_3 (5)	95	98	5
26[g]	**6l**	Ag_2CO_3 (5)	88	99	10

[a]Performed under argon with **2a** (0.1 mmol), **3aa** (0.11 mmol), 4 Å MS (50 mg), **CPA** (10 mol %), and metal salt (10 mol % or 5 mol %) in 1.0 mL of toluene at −30 °C for 60 h. [b]Isolated yield. [c]Determined by HPLC analysis. [d]In 1.0 mL of PhEt. [e]In 1.0 mL of PhMe/PhEt (1:2). [f]In 1.0 mL of PhMe/PhEt (1:1) as solvent. [g]In 1.0 mL of PhMe/PhEt (2:1).

attention to other silver salts, including AgOTf, Ag_2O, and Ag_2CO_3. The yield increased markedly when Ag_2O was used, resulting in a 71% yield with only 3% *ee*. When Ag_2CO_3 was used as the source of the metal ion, the yield further increased to 80% with 7% *ee*. These results are very interesting, as silver salts are well-known to react with a diazo-compound to give the corresponding carbene. To improve the stereocontrol efficiency, a series of chiral phosphoric acids with substituents with different stereo- and electro-properties at the 3, 3′-positions were designed and optimized (Table 1, entries 10−22). This included the introduction of a substituent at the 3, 3′-positions with little steric hindrance (**6b**) and an electron-withdrawing substituent on the aryl groups at the 3, 3′-positions (**6c**−**6e**) of the phosphoric acids. The selectivity was improved slightly with **6d** and **6e** (Table 1, entries 10−13). Moderate enantioselectivities were obtained by further increasing the steric bulk of the substituents at the 3, 3′-positions (**6f** and **6g**) (Table 1, entries 14 and 15). Interestingly, when (*R*)-TRIP **6j** was used as the chiral pro-anion, excellent enantioselectivity (90% *ee*) was achieved with a 73% yield along with a 16% rearranged byproduct (Table 1, entry 18). From these results we concluded that a proper chiral pocket formed by introduction of substituents with large steric hindrance at the 3, 3′-positions of the phosphoric acid might be crucial for the stereocontrol of the reaction. With this in mind, catalysts **6k** and **6l** with a long bulky substituent at the 3, 3′-positions were developed and applied in the model reaction. The best result was delivered with the catalyst **6l**, whereby **4aaa** was obtained in 80% yield with 98% *ee* (Table 1, entry 20).

With the best catalyst in hand, we optimized the reaction conditions. A survey of different solvents was conducted, and we found that good yields and enantioselectivities were achieved in aromatic solvents and methyl cyclohexane (see Supporting Information (SI) and Table 1). In particular, the ratio of the byproduct **5aaa** was lower and the same enantioselectivity of **4aaa** was obtained when the reaction was performed in PhEt instead of PhMe (Table 1, entries 20 and 23). Therefore, we tried to use a mixture of PhMe and PhEt as solvent (Table 1, entries 24−26). When the reaction was conducted in 1:1 (v/v) of PhMe and PhEt, the rearrangement side reaction was inhibited to a very low degree. Other parameters, including the temperature and concentrations, were also optimized (see SI), and the best reaction conditions were established to be a 0.1 M mixture of PhMe/PhEt (1:1) at −30 °C in the presence of 10 mol % **6l**, 5% Ag_2CO_3 using 4 Å MS as a water scavenger, which led to an excellent yield (95%) with 98% *ee* (Table 1, entry 25).

The influence of the substituent at the N1 position of the isatin ketimine was also investigated (including Bn, Boc, Ac, MOM, and Me) and a methyl group proved to be the best choice (see SI).

Having established the optimal conditions of the model reaction, we proceeded to investigate the scope of the reaction with various substrates. The results are summarized in Table 2. Isatin imines derived from Boc (−CO_2Bu^t) and Eoc (−CO_2Et) protected amine are accommodated in this reaction (Table 2, entries 1, 4−16). Good to excellent yields and enantioselectivities were achieved, irrespective of whether the isatin imines contained electron-withdrawing (Table 2, entries 4−11) or electron-donating (Table 2, entries 12, 14, and 15) groups. Nevertheless, strong electron-donating substituent decreased the yields and increased the formation of the rearranged byproduct (Table 2, entry 13). The reason for this is that the rearrangement reaction proceeds by migration of the aryl with one pair of electrons. Thus, the more electron-rich of the aromatic ring, the more likely it is for the side reaction to take place. Halogens and nitro groups on the benzene rings of the isatin imines were also compatible in this reaction, which are useful handles for further functional group transformations and organic synthesis. When the alkyl group of the α-diazophosphonate changed from Me to Et and Pr^i, the yield of the desired product decreased from 95% to 64% and 43%, respectively, but with the same enantioselectivities. Conversely, the yield of the rearranged byproducts increased from 5% to 34% and 39%, respectively (Table 2, entries 1−3). This maybe ascribes to the tension, increased along with the alkyl steric hindrance, which could be released through the rearrangement. The same effect is also present in the imines owing to the steric hindrance arising from the *N*-protecting group (N-PG), in which the use of *N*-Boc isatin imines resulted in slightly higher yields of the byproducts **5** than those of *N*-Eoc imines (Table 2, entries 5−14). In some substrates, the *N*-Boc and *N*-Eoc imines showed mutually complementary effects in yields and enantioselectivities (Table 2, entries 1, 4, 5, 7, 11, 13, 15, and 16). Unfortunately, this catalytic system did not work with the *N*-Boc ketimine derived from methyl 2-oxo-2-phenylacetate.

In view of the rearrangement products observed in the reaction, we wondered whether kinetic resolution is present

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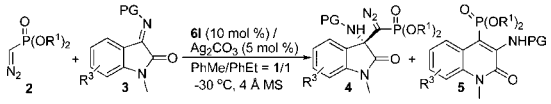
Table 2. Mannich Reaction between α-Diazophosphonates and *N*-Methyl Isatin-Derived N-PG Ketimines

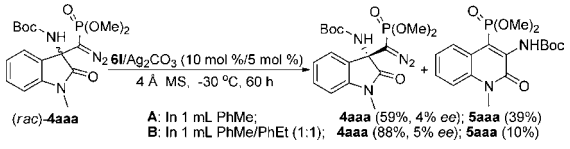


entry[a]	R^1, R^3	PG	yield of **4** (%)[b]	*ee* (%)[c]	yield of **5** (%)[b]
1	Me, H	Boc	**4aaa** (95)	98	5
		Eoc	**4aab** (73)	99	25
2	Et, H	Boc	**4baa** (64)	99	34
3	^{i}Pr, H	Boc	**4caa** (43)	96	39
4	Me, 5-F	Boc	**4aba** (93)	98	5
		Eoc	**4abb** (85)	99	3
5	Me, 7-F	Boc	**4aca** (63)	98	35
		Eoc	**4acb** (83)	99	11
6	Me, 5-Cl	Boc	**4ada** (85)	96	12
		Eoc	**4adb** (89)	99	8
7	Me, 6-Cl	Boc	**4aea** (61)	99	24
		Eoc	**4aeb** (86)	99	13
8	Me, 7-Cl	Boc	**4afa** (58)	75	31
		Eoc	**4afb** (60)	97	26
9	Me, 5-Br	Boc	**4aga** (82)	96	11
		Eoc	**4agb** (83)	91	7
10	Me, 6-Br	Boc	**4aha** (72)	95	26
		Eoc	**4ahb** (74)	98	23
11	Me, 5-I	Boc	**4aia** (65)	87	26
		Eoc	**4aib** (79)	99	15
12	Me, 5-Me	Boc	**4aja** (66)	91	30
		Eoc	**4ajb** (78)	99	19
13	Me, 5-MeO	Boc	**4aka** (55)	43	39
		Eoc	**4akb** (56)	96	23
14	Me (5-Br, 7-Me)	Boc	**4ala** (76)	69	23
		Eoc	**4alb** (80)	80	19
15	Me, 5-CF_3O	Boc	**4ama** (89)	95	9
		Eoc	**4amb** (71)	95	9
16	Me, 5-NO_2	Boc	**4ana** (84)	85	9
		Eoc	**4anb** (59)	60	8

[a]Performed under argon with **2** (0.1 mmol), **3** (0.11 mmol), 4 Å MS (50 mg), **CPA** (10 mol %) and Ag_2CO_3 (5 mol %) in 1.0 mL of PhMe/PhEt = 1/1 at −30 °C. [b]Isolated yield. [c]Determined by HPLC analysis.

during this reaction. Racemic **4aaa** was treated in the same catalytic system (Scheme 2). The reaction in toluene for 60 h

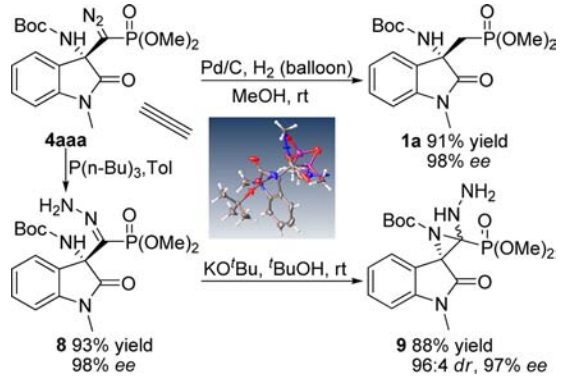
Scheme 2. Evaluation the Contribution of Kinetic Resolution to the Enantioselelctivity



(conditions **A**) led to 39% of the rearrangement product **5aaa** and recovery of **4aaa** (59%) with only 4% *ee*; whereas under the optimized reaction conditions (**B**), only 10% **5aaa** was obtained and 88% of **4aaa** was recovered with 5% *ee*. Comparing these results with those of Table 1, entry 20 and Table 1, entry 25, we can conclude that kinetic resolution along with the rearrangement of **4aaa** into **5aaa** only contributed slightly to the excellent enantioselectivities of the catalytic reactions.

To demonstrate the synthetic utility of the Mannich products in organic synthesis, product **4aaa** was subjected to hydrogenation in the catalysis of Pd/C to give the promising β-aminophosphonate **1a** (Scheme 3). Reducing the diazo group by

Scheme 3. Derivatization of the Products



$P(n\text{-}Bu)_3$ gave the chiral hydrazone **8** which underwent cyclization in the presence of KO^{t}Bu to furnish the chiral spiroaziridine oxindole derivative **9** with good yield and identical enantioselectivity. The absolute configurations of the Mannich products were determined based on the X-ray analysis of the product **4aaa** (Scheme 3).

In conclusion, the asymmetric Mannich reaction between α-diazomethylphosphonates and ketimines derived from isatin was realized with catalytic chiral silver phosphate for the first time. This methodology provides facile access to promising bioactive 3-substituted 3-amino-2-oxindoles by merging of the oxindole and β-aminophosphonate, and to densely functionalized spiroaziridine oxindole derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02095.

Experimental procedures and detailed characterization data of all new compounds (PDF)

X-ray crystal details for **4aaa** (CIF)

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Notes

The authors declare no competing financial interest.

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