DOI: 10.1002/adsc.201100482

Direct Enantioselective Three-Component Kabachnik–Fields Reaction Catalyzed by Chiral Bis(imidazoline)-Zinc(II) Catalysts

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Received: June 21, 2011; Revised: August 8, 2011; Published online: December 8, 2011

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adcs.201100482.

Abstract: A direct three-component reaction of aldehydes, amines and diaryl phosphites was catalyzed by a zinc(II) complex of 1,3-bis(imidazolin-2-ly)pyridine (pybim) giving the corresponding α-aminophosphonates in good yield with good enantioselectivity. The reaction was applied to a wide variety of aromatic aldehydes to give products with excellent yields (up to 99%) and enantiomeric excesses (up to 93% *ee*).

Keywords: asymmetric catalysis; enantioselectivity; hydrophosphonylation; imidazolines; three-component synthesis

Optically active α-aminophosphonates are important synthetic intermediates for the preparation of various natural products and biologically active compounds.[1] Accordingly, their broad utility has prompted considerable interest to develop asymmetric methods for their preparation. One of the most efficient methods for the preparation of chiral α-aminophosphonates is the stereoselective addition of phosphites to imines. Since the pioneering work on the highly enantioselective hydrophosphonylation of imines reported by Shibasaki and co-workers,[2] there are many reports about the catalytic enantioselective hydrophosphonylation of imines.[3] On the other hand, the strategy of multicomponent synthesis has attracted more attention in the scientific community as an environmentally friendly process which allows high levels of atom efficiency to be obtained because only a single reaction solvent, work-up procedure and purification step are required to obtain a product.[4] Therefore, the development of a three-component synthesis of α-aminophosphonates using a carbonyl compound, an amine, and a phosphite, often called the Kabachnik–Fields reaction, is highly desired. The pioneering work for the highly enantioselective one-pot reaction of *in situ* preformed imines and phosphites using a chiral salalen-aluminum catalyst was reported by Katsuki and co-workers to give optically active α-aminophosphonates.[5] Feng and co-workers also reported the highly enantioselective one-pot synthesis of α-aminophosphonates from *in situ* generated imines and phosphites using a chiral scandium-*N*,*N*′-dioxide complex.[6] Although remarkable progress has been made in one-pot procedures for the synthesis of optically active α-aminophosphonates, the development of a direct three-component synthesis of chiral α-aminophosphonates is desired due to the more simple operation (Figure 1). In this context, there is only one report on the direct three-component enantioselective reaction of aldehydes, amines, and phosphites. List and co-workers reported the direct three-component reaction with α-branched aliphatic aldehydes using chiral phosphoric acids as an organocatalyst to furnish β-branched α-aminophosphonates with high diastereo- and enantioselectivity by a dynamic kinetic resolution.[7] Therefore, expanding the scope of catalytic enantioselective three-component reactions with respect to both the chiral catalyst and the substrate

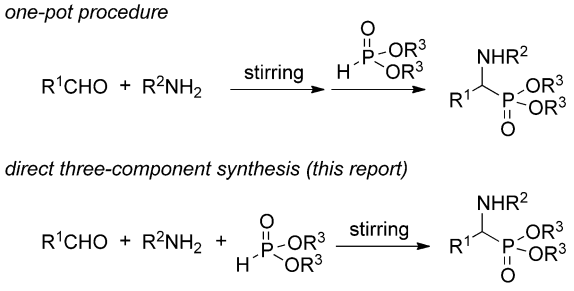


Figure 1. One-pot procedure and direct three-component synthesis of chiral α-aminophosphonates.

would be highly desirable. On the other hand, we recently developed chiral bis(imidazoline)-metal catalysts as highly tuneable chiral catalysts.[8,9] Furthermore, we reported the highly enantioselective hydrophosphonylation reaction of phosphites with aldimines or ketimines.[10] Herein, our ongoing interest was extended to a direct enantioselective three-component reaction of aldehydes, amines, and phosphites using a chiral bis(imidazoline)-metal catalyst.

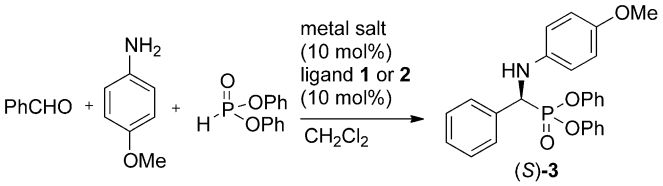
We first examined the reaction of benzaldehyde, *p*-anisidine, and diphenyl phosphite using 10 mol% of chiral Lewis acid catalysts including bis(imidazoline)s **1a**–**f**. The reaction was carried out as follows: benzaldehyde, *p*-anisidine, and diphenyl phosphite were successively added to the solution of chiral Lewis acids in CH_2Cl_2. The results are shown in Table 1.

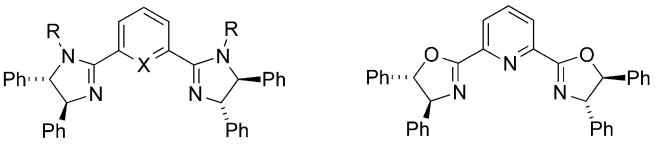
Although the reaction using various metal salts, such as $AlCl_3$, $Sc(OTf)_3$, and $Mg(OTf)_2$, afforded the almost racemic product **3** in high yield, the reaction using **1a**-$Zn(OTf)_2$ gave product **3** in 99% yield with 45% *ee* (entries 1–4). When the reaction was carried out at −50 °C, the enantioselectivity was improved slightly over that at −20 °C (entry 5). After optimization of the anion part of the zinc salts, such as NTf_2 and SbF_6, the best enantioselectivity was obtained in the reaction using $Zn(NTf_2)_2$ (entries 5–7). To improve the enantioselectivity, we next optimized the structure of bis(imidazoline). After fine-tuning various substitutions on nitrogen in imidazolines, the 2-methylpropionyl group was found to be the best substitution to obtain a high yield with high enantioselectivity (entries 8–11). On the other hand, a product was formed in low enantioselectivity by using the bidentate phenylenebis(imidazoline) (phebim) **1f** with $Zn(NTf_2)_2$ in CH_2Cl_2 (entry 12). Interestingly, the reaction using chiral Lewis acid prepared from pybox **2**, which has oxygens instead of the N-CO-*i*-Pr group in **1d**, and $Zn(NTf_2)_2$ afforded product **3** with low enantioselectivity (entry 13). It should be noted that an electron-rich phosphite such as bis(*o*-methoxyphenyl) phosphite enhanced the reactivity of the reaction and enantioselectivity of product **3** (entry 14).[11,12] Catalyst loading was successfully reduced to 5 mol% without loss of enantioselectivity (entry 15).

Under the optimized reaction conditions, a variety of aldehydes was examined by using the combination of **1d** with $Zn(NTf_2)_2$, the results of which are summarized in Table 2. The reaction of imines derived from various substituted benzaldehydes afforded products **4**–**11** with high enantioselectivity, although the reaction with *ortho*-substituted aldehydes decreased the enantioselectivity (entries 1–8). 2-Naphthaldehyde and heteroatom-containing aldehydes also resulted in high enantioselectivity (entries 9–12). The reaction with α,β-unsaturated aldehydes such as phenylpropargyl aldehyde and *trans*-cinnamaldehyde afforded products **16** and **17** in high yield with good enantioselectivity (entries 13 and 14), however the reaction with 3-methylbutanal afforded the product **18** with low enantioselectivity (entry 15). Although the reaction with cyclohexanecarbaldehyde afforded product **19** with low enantioselectivity, the slow addition of phosphite could improve the enantioselectivity of **19** (entries 16 and 17).

We next examined the synthesis of optically active α-aminophosphoric acid **21** from *N*-PMP protected α-aminophosphonate **4** (Scheme 1). Deprotection of the PMP group from 90% *ee* of **4** using NBS afforded α-aminophosphonate **20**,[13] which can be converted to optically active α-aminophosphoric acid **21** without a

Table 1. Enantioselective three-component reaction using various chiral ligands and metal salts.[a]



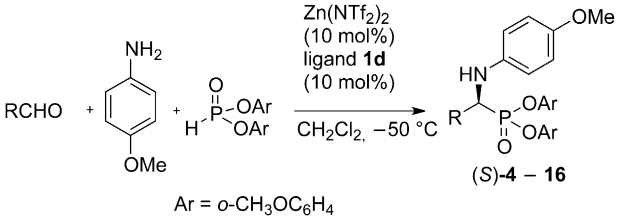


1a: R = Bz
1b: R = Ts
1c: R = CH_3CO
1d: R = *i*-PrCO
1e: R = *t*-BuCO
1f R = Bz

Entry	Metal salt	Ligand	Temp. [°C]	Time [h]	Yield [%]	*ee* [%][b]
1	$AlCl_3$	**1a**	0	48	94	0
2	$Sc(OTf)_3$	**1a**	−20	3	97	0
3	$Mg(OTf)_2$	**1a**	0	18	88	0
4	$Zn(OTf)_2$	**1a**	−20	4	99	45
5	$Zn(OTf)_2$	**1a**	−50	6	93	53
6	$Zn(NTf_2)_2$	**1a**	−50	6	99	59
7	$Zn(SbF_6)_2$	**1a**	−50	48	95	45
8	$Zn(NTf_2)_2$	**1b**	−50	30	99	6
9	$Zn(NTf_2)_2$	**1c**	−50	12	95	56
10	$Zn(NTf_2)_2$	**1d**	−50	12	99	62
11	$Zn(NTf_2)_2$	**1e**	−50	6	99	49
12	$Zn(NTf_2)_2$	**1f**	−50	48	84	3
13	$Zn(NTf_2)_2$	**2**	−50	30	99	−2
14[c]	$Zn(NTf_2)_2$	**1d**	−50	6	99	90
15[c,d]	$Zn(NTf_2)_2$	**1d**	−50	24	99	90

[a] *Reaction conditions:* PhCHO (0.10 mmol), *p*-anisidine (0.12 mmol), diphenyl phosphite (0.15 mmol), metal salt (0.01 mmol), and **1** (0.01 mmol).
[b] The *ee* was determined by HPLC analysis using chiral columns.
[c] Bis(*ortho*-methoxyphenyl) phosphite was used.
[d] **1d** (5 mol%) was used.

Table 2. Enantioselective three-component reaction of various aldehydes and phosphites using **1d**-Zn(II).[a]

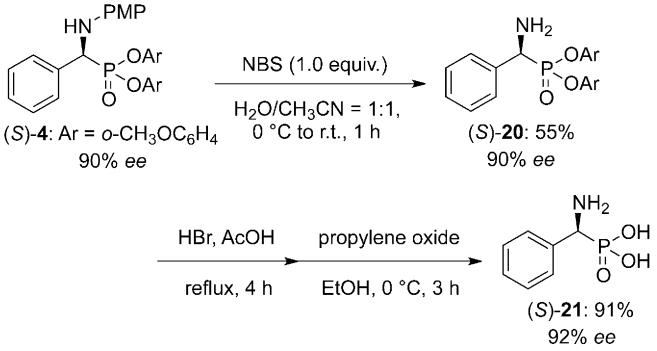


Entry	Aldehyde [R]	Product	Time [h]	Yield [%]	*ee* [%]
1	Ph	**4**	6	99	90
2	4-Me-C_6H_4	**5**	6	99	91
3	2-MeO-C_6H_4	**6**	1	99	68
4	3-MeO-C_6H_4	**7**	3	99	90
5	4-MeO-C_6H_4	**8**	4	86	90
6[b]	4-HO-C_6H_4	**9**	24	99	84
7	4-Cl-C_6H_4	**10**	4	99	76
8[b]	4-MeO_2C-C_6H_4	**11**	18	99	80
9[c]	2-naphthyl	**12**	96	99	82
10	2-thienyl	**13**	48	90	89
11	2-furyl	**14**	6	99	93
12	2-benzofuryl	**15**	1	99	82
13	*trans*-cinnamyl	**16**	1	85	68
14[d]	PhC≡C−	**17**	36	92	76
15	$(CH_3)_2CHCH_2$−	**18**	0.5	99	31
16	cyclohexyl	**19**	1	85	45
17[e]	cyclohexyl	**19**	2	98	61

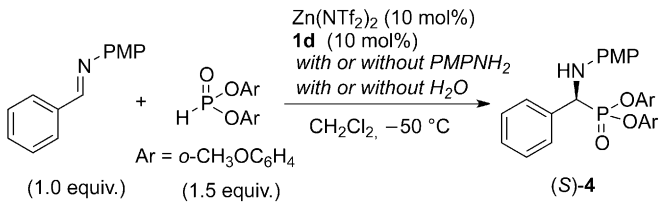
[a] *Reaction conditions:* RCHO (0.10 mmol), *p*-anisidine (0.12 mmol), bis(*ortho*-methoxyphenyl) phosphite (0.15 mmol), metal salt (0.01 mmol), and **1d** (0.01 mmol).
[b] Carried out at −40 °C.
[c] Carried out at −80 °C.
[d] Reaction mixture was warmed to −40 °C from −50 °C.
[e] Phosphite was added dropwise for 2 h.

loss of enantioselectivity. The absolute configuration of **21** was assigned to be *S* after conversion to *N*-Cbz-dimethyl phosphonate,[14] and the stereochemistry of other products was tentatively assumed by analogy.

In order to clarify the reaction mechanism, we examined the enantioselective reaction of isolated imines with bis(*o*-methoxyphenyl) phosphite using **1d**-$Zn(NTf_2)_2$, which gave product **4** in poor yield with lower enantioselectivity than that from the direct three-component reaction (Scheme 2). Although the addition of 0.2 equivalents of *p*-methoxyaniline or 1.0 equivalent of water slightly improved the yield and enantioselectivity, the addition of *p*-methoxyaniline and water afforded (*S*)-**4** with a similar enantioselectivity as that in Table 1 entry 14. This result implies that amine and water play an important role for the



Scheme 1. Synthesis of chiral α-aminophosphoric acid **21**.



$PMPNH_2$	H_2O	product
-	-	2%, 10% *ee*
0.2 equiv.	-	27%, 70% *ee*
-	1.0 equiv.	49%, 62% *ee*
0.2 equiv.	1.0 equiv.	90%, 88% *ee*

Scheme 2. Enantioselective reaction of isolated imine with phosphite.

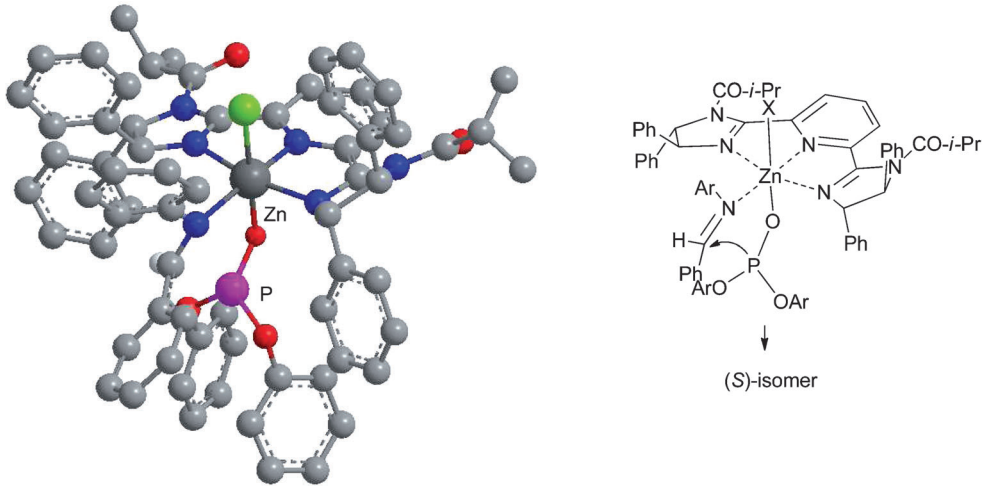


Figure 2. Assumed transition state for the hydrophosphonylation of imine with $(ArO)_2POH$ using **1d**-Zn(II).

transition state, although the presence of amine and water in the reaction mixture generally decomposes or deactivates chiral Lewis acids.

On the other hand, the enantioselective hydrophosphonylation with $TBSOP(OPh)_2$ did not afford a product, although the enantioselective hydrophosphonylation with diphenyl phosphite gave products in good yield with moderate enantioselectivity (Table 1, entry 10). This result shows that the tautomerization of phosphite $[(RO)_2POH]$ to the phosphonate $[(RO)_2P(=O)H]$ and the deprotonation of phosphonate is a key factor for the hydrophosphonylation. Although the detailed reaction mechanism remains unclear, the proposed transition state for the reaction of imines with phosphites using **1d**-Zn(II) as the catalyst is shown in Figure 2.[15]

Imines formed *in situ* coordinated to the chiral Zn(II) catalysts in the equatorial position by avoiding the steric repulsion of bis(imidazoline). Coordination of oxygen in phosphite to Zn(II) and the deprotonation of phosphite affords the phosphonate, which attacks to the imine in the coordination sphere of chiral bis(imidazoline)-Zn salt and leads to chiral addition products. The phosphonate approaches imines avoiding steric repulsion with phenyl groups in **1d**, therefore the (*S*)-isomer is preferably formed. Further studies are required to fully elucidate the mechanistic details such as the roles of water and amine in the transition state of hydrophosphonylation.

In conclusion, we have developed a direct enantioselective three-component reaction of aldehydes, amines, and phosphites catalyzed by Zn(II)-C_2-symmetrical pybim ligands to give α-aminophosphonates in good yield with high enantioselectivity. A range of aldehydes can be tolerated in the process. Due to the extremely simple operational procedure, our methodology is very accessible and it increases the utility of the work in this growing area of asymmetric three-component reactions. Further studies are in progress to study the potential of these catalytic systems to other process.

Experimental Section

General Procedure for the Enantioselective Three-Component Synthesis of α-Aminophosphonates Catalyzed by the 1d-Zn(II) Complex

A solution of ligand **1d** (0.01 mmol, 10 mol%) and Zn-$(NTf_2)_2$ (0.01 mmol, 10 mol%) in dry CH_2Cl_2 (0.55 mL) was stirred at room temperature for 1 h. An aldehyde (0.10 mmol), *p*-anisidine (0.12 mmol) and bis(*o*-methoxyphenyl) phosphite (0.15 mmol) were added, and the whole mixture was stirred at −50 °C. After completion of the reaction as monitored by TLC, the mixture was concentrated and purified over silica gel by column chromatography (benzene/EtOAc = 80:20) yielding the α-aminophosphonates.

Acknowledgements

This work was partly supported by Teijin Pharma Award in Synthetic Organic Chemistry, Japan and Commons from JST.

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[12] Alternative nitrogen sources that have been investigated include aniline, *ortho*-anisidine, *ortho*-hydroxyaniline, *para*-hydroxyaniline, benzylamine and dibenzylamine, which all gave the products in low yield or with low enantioselectivity. And we have also investigated other phosphites, including dimethyl, diisopropyl, and dibenzyl phosphite and found that bis(*ortho*-methoxyphenyl) phosphite gave the highest enantioselectivities.

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