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Chiral *N*-phosphoryl imines: design, synthesis and direct asymmetric addition reactions with diketones and diesters

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ABSTRACT

Chiral *N*-phosphoryl imines derived from (*S*)-BINOL have been designed and synthesized in good to excellent chemical yields. These *N*-phosphoryl imines were found to react with diketones smoothly without the use of any bases. They can also serve as electrophiles for the reaction with diethyl malonate in the presence of potassium carbonate. Good yields (62%—quant) and excellent diastereoselectivities (up to 99:1 dr) have been achieved for 10 examples.

1. Introduction

Chiral imine chemistry has been playing an important role in asymmetric synthesis because it can result in numerous amino building blocks, such as α- and β-amino acids, amino alcohols, amino ketones, etc.[1,2] Chiral imines can be utilized as both electrophiles and dienophiles for many asymmetric reactions.[3] The search for new efficient imines for general asymmetric synthesis has become important, interesting, and challenging. In the past several years, we have designed and synthesized chiral *N*-phosphonyl imines based on the use of commercial chemicals, vicinal (1*R*,2*R*)-diaminocyclohexane, and (1*R*,2*R*)-1,2-diphenylethylene diamine as chiral auxiliaries (Fig. 1A and B).[4–9] The resulting *N*-phosphonyl imines were proven to be effective in asymmetric induction for various reactions, such as aza-Darzens reaction,[4a] aza-Henry reaction,[5a] addition of allylmagnesium bromides[5b], and 1,2-asymmetric additions of ester- and ketone-derived enolates.[6] Very recently, they have also been utilized for the asymmetric synthesis of *N*-phosphonyl β-amino Weinreb amides,[7a] β-aminomalonates,[7b] β-amino esters,[8a] α,β-diamino esters,[8b,c] and terminal-functionalized chiral propargylamines.[9]

During the study of *N*-phosphonyl imines, we also attempted to render chiral *N*-phosphoryl imine chemistry by using BINOL derivatives (Fig. 1C), but the success was limited.[4] However, these *N*-phosphoryl imines are also useful chiral auxiliaries and would potentially complement our *N*-phosphonyl imine chemistry in regard to reactivity, asymmetric control, and substrate scope. For example, when we directly subjected chiral *N*-phosphonyl imines to the reaction with cyclohexane-1,3-dione, no 1,2-addition products were observed at all. Cyclohexane-1,3-dione had to be converted into its lithium enolate form prior to the 1,2-addition reaction.[7b] In order to conduct the direct addition reaction, we re-visited chiral *N*-phosphoryl imine chemistry and found that the (*S*)-BINOL-derived chiral *N*-phosphoryl imines can be reacted with diketones smoothly without the use of any bases. In this Letter, we report our preliminary results on this study as represented by Scheme 1.

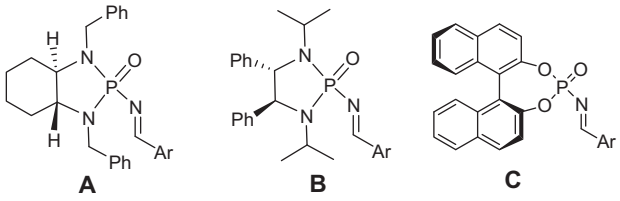

Figure 1. Structures of chiral *N*-phosphonyl and *N*-phosphoryl imines.

2. Results and discussion

The chiral phosphoramide **6** was synthesized by following the synthetic route as shown in Scheme 2. (*S*)-BINOL **3** was first treated with phosphorus oxychloride in the presence of triethylamine[10] to produce phosphoryl chloride **4** which was then converted to phosphoryl azide **5** by treating with sodium azide in acetone at room temperature.[11] The resulting phosphoryl amide **6** was obtained via catalytic hydrogenation in a quantitative yield. This chiral amide has been proven to be stable by storing it at rt for several weeks with no indication of decomposition as revealed by ^{1}H NMR analysis.

For the synthesis of chiral *N*-phosphoryl imine, phosphoramide **6** was initially treated with benzaldehyde, $TiCl_4$, and Et_3N in CH_2Cl_2, but very little product was observed as indicated by TLC

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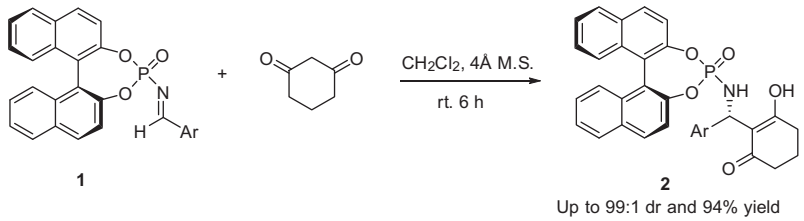
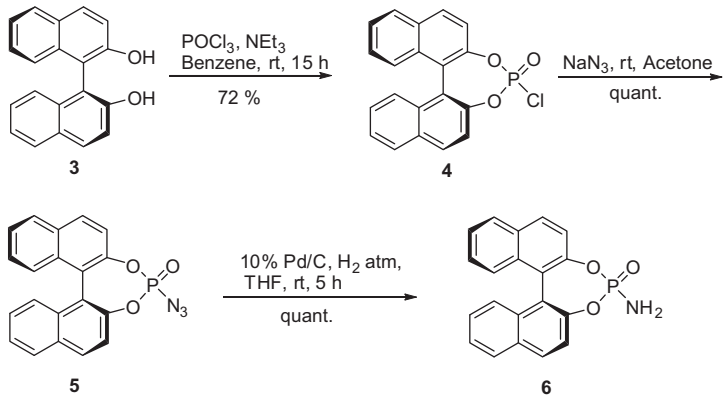


Scheme 1. 1,2-Asymmetric addition of cyclohexane-1,3-dione onto *N*-phosphoryl imines.

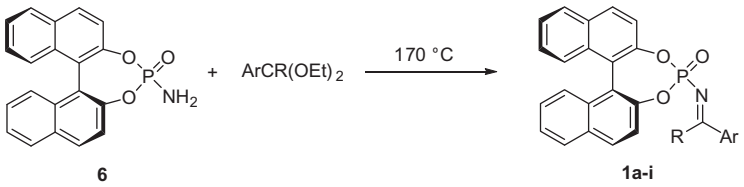


Scheme 2. Synthesis of (*S*)-BINOL-based *N*-phosphoramide.

monitoring. There are several reports on the synthesis and reactions of the corresponding thio phosphoryl analogues of imines **1**.[12] The known condensation procedure was employed for their synthesis.[11–13] As shown in Table 1, good to excellent yields (71–100%) were obtained for nine substrates that were examined. Besides aldehydes for imine formations, acetophenone was also proven to be a suitable substrate for this formation (entry 9). The resulting chiral *N*-phosphoryl imines showed good stability and solubility in most common organic solvents, such as DCM, $CHCl_3$, THF, toluene, etc. In fact, when chiral *N*-phosphoryl imine **1a** was stored in an oven at 60 °C for 2 h, there was no sign of decomposition; and only ~10% decomposition was observed when it was kept at 80 °C for 1 h as monitored by ^{1}H NMR determinations.

We then carefully studied the addition reactions of chiral *N*-phosphoryl imine **1a** with cyclohexane-1,3-dione as the model reaction. As shown in Table 2, all common solvents that were examined showed their effectiveness without the use of any bases. The imine **1a** was consumed within 6 h in both DCM and toluene in the presence of 4 Å molecular sieves. Excellent chemical yields, 90% and 92%, respectively, were obtained for these two cases (entries 1 and 2). Furthermore, the product was confirmed to be a single diastereoisomer as revealed by ^{1}H and ^{31}P NMR measurements. The more polar solvent, CH_3CN, led to a similar yield of 90%, but the diastereoselectivity was slightly decreased to 97:3 (entry 5). Other solvents, Et_2O, THF, benzene, and EtOAc, resulted in not only lower chemical yields (78–88%) but also decreased the diastereoselecivi-

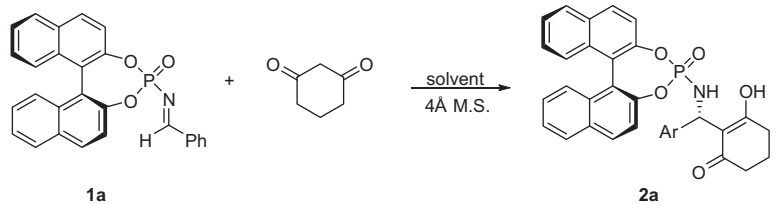
Table 1
Synthesis of chiral phosphoryl imines[a]



Entry	Ar	R	Product	Time (min)	Mp (°C)	Yield[b] (%)
1	Ph	H	**1a**	12	117–119	94
2	4-MeC_6H_4	H	**1b**	5	128–130	96
3	4-$MeOC_6H_4$	H	**1c**	10	133–135	100
4	4-ClC_6H_4	H	**1d**	10	112–114	85
5	4-FC_6H_4	H	**1e**	10	120–122	93
6	2-BrC_6H_4	H	**1f**	13	97–99	81
7	3-BrC_6H_4	H	**1g**	10	94–96	84
8	4-BrC_6H_4	H	**1h**	10	116–118	92
9	Ph	Me	**1i**	20	118–120	71

[a] Conditions: mixture of phosphoramide **6** (1.0 mmol) and $ArCR(OEt)_2$ (1.3 mmol) at 170 °C.
[b] Isolated yields after column chromatography.

Table 2
The reaction of imine **1a** with 1,3-cyclohexanedione under different conditions[a]



1a **2a**

Entry	Solvent	Time (h)	Temp (°C)	Yield[b]	dr[c]
1	CH_2Cl_2	6	25	92	>99:1
2	Toluene	6	25	90	>99:1
3	Benzene	6	25	85	95:5
4	Et_2O	6	25	87	87:13
5	CH_3CN	6	25	90	97:3
6	THF	6	25	88	94:6
7	EtOAc	6	25	78	98:2
8	CH_2Cl_2 K_2CO_3[d]	6	25	92	>99:1
9	CH_2Cl_2	12	25	92	>99:1
10	CH_2Cl_2	6	0	53	>99:1
11	CH_2Cl_2	6	−78	NR[e]	—

[a] Conditions: **1a** (0.2 mmol) and 1,3-cyclohexanedione (0.24 mmol) in the presence of 4 Å molecular sieves (100 mg).
[b] Isolated yields.
[c] Determined by ^{1}H NMR or ^{31}P NMR after column chromatography.
[d] 0.2 mmol of K_2CO_3 was added.
[e] No reaction was observed.

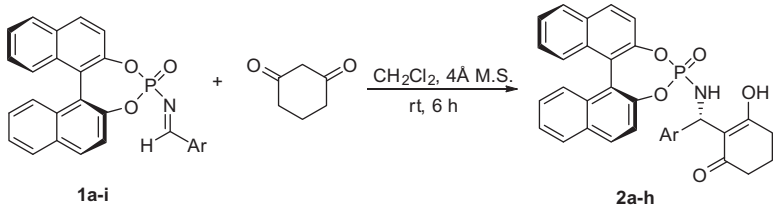
ty (98:2–87:13, entries 3, 4, 6 and 7). The addition of K_2CO_3 to the reaction mixture did not give any improvement on both the yield and diasteoselectivity (entry 8). The yield was substantially decreased to 53% when the reaction was performed at 0 °C (entry 10), and no reaction was observed at −78 °C (entry 11).

As shown in Table 3, nine substrates were examined under the optimal conditions. Good to excellent chemical yields (62–92%) and diastereoselectivities (dr = 90:10–99:1) have been achieved except for the case of acetophenone-derived imine (entry 9) which did not give any product. A slightly decreased yield was observed when a methoxy substituent is present on the aromatic ring of imine substrate, but excellent diastereoselectivity was still shown (entry 3).

We then turned our attention to linear substrates, acetylacetone and diethyl malonate. We found that these new *N*-phosphoryl imines can react with acetylacetone even at −78 °C, the reaction proceeded to completion within 5 h without the use of any bases to afford good diastereoselectivity (87:13 dr) and an excellent yield (96%) (Scheme 3). However, when diethyl malonate was used for this reaction, K_2CO_3 was found to be necessary to give good diastereoselectivity (83:17 dr) and an excellent yield (quant) (Scheme 4).

To determine the absolute configuration, product **8** was subject to deprotection using HCl/MeOH at rt followed by the treatment with $(Boc)_2O$ in the presence of $NaHCO_3$ to afford (*R*)-diethyl 2-[(*N*-*t*-Boc-amino)(phenyl)methyl]malonate **9** (Scheme 5). The *R* absolute configuration was confirmed by comparing its optical

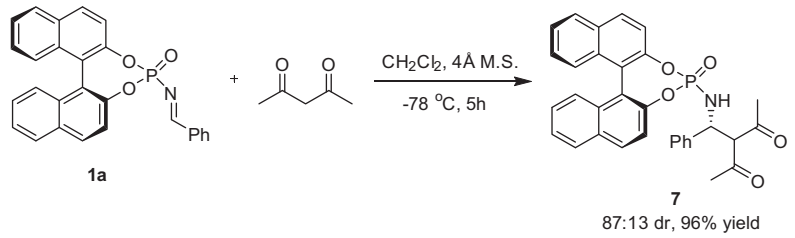
Table 3
Reaction of 1,3-cyclohexanedione with *N*-phosphoryl imines[a]



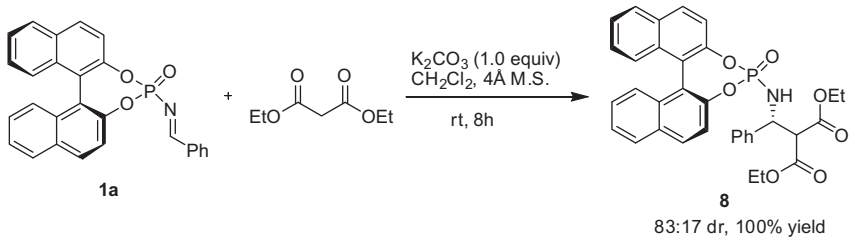
1a-i **2a-h**

Entry	Ar	R	Product	Mp (°C)	Yield[b] (%)	dr[c]
1	Ph	H	**2a**	154–156	92	>99:1
2	4-MeC_6H_4	H	**2b**	136–138	78	94:6
3	4-MeOC_6H_4	H	**2c**	121–123	62	>99:1
4	4-ClC_6H_4	H	**2d**	150–152	87	95:5
5	4-FC_6H_4	H	**2e**	130–132	94	98:2
6	2-BrC_6H_4	H	**2f**	141–143	64	90:10
7	3-BrC_6H_4	H	**2g**	150–152	80	92:8
8	4-BrC_6H_4	H	**2h**	138–140	91	96:4
9	Ph	Me	—	—	NR[d]	—

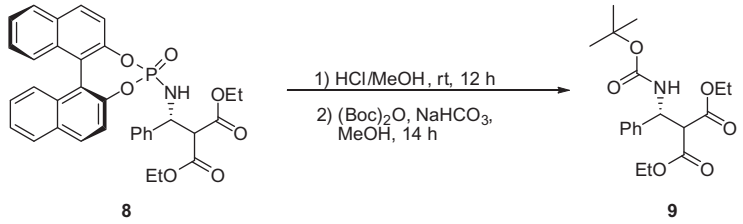
[a] Conditions: **1a** (0.2 mmol) and 1,3-cyclohexanedione (0.24 mmol) in CH_2Cl_2 in the presence of 4 Å molecular sieves (100 mg) at rt for 6 h.
[b] Isolated yields.
[c] Determined by ^{1}H NMR or ^{31}P NMR after column chromatography.
[d] No reaction was observed.



Scheme 3. Addition of acetylacetone onto chiral *N*-phosphoryl imine.



Scheme 4. K_2CO_3-assisted addition of diethyl malonate onto chiral *N*-phosphoryl imine.



Scheme 5. Conversion of product **8** to an authentic sample.

rotation with that of an authentic sample as reported in the literature which showed the opposite sign.[14]

Since the polarity of BINOL is very weak, it can be recovered near quantitatively simply by washing the crude cleavage mixture with 15:85 ratio EtOAc/hexane through a silica gel column.

Finally, it is anticipated that the resulting bis-carbonyl products can be further subjected to various reactions, such as $NaBH_4$-based reduction and RMgX- or RLi-based carbonyl additions to give other useful synthetic building blocks, which will be conducted in our laboratories in due course.

3. Conclusions

In summary, (*S*)-BINOL-based chiral *N*-phosphoryl imines have been designed and synthesized. These *N*-phosphoryl imines have been proven to be efficient for the direct 1,2-addition reaction with both cyclic and linear diketones without the use of any bases. They can also serve as electrophiles for the reaction with diethyl malonate in the presence of potassium carbonate. The absolute configuration has been unambiguously determined by converting the product into an authentic sample.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.072.

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