FULL PAPER DOI: 10.1002/adsc.202000335

1,2-Diamine-Derived (thio)Phosphoramide Organocatalysts in Asymmetric Michael Additions

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Manuscript received: March 10, 2020; Revised manuscript received: April 3, 2020;
Version of record online: April 23, 2020

Dedicated to the memory of Prof. Mihály Bartók

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202000335

Abstract: Phosphoramides and thiophosphoramides were prepared from optically pure C_2-symmetric 1,2-diamines and were used as chiral organocatalysts in the asymmetric Michael additions of aldehydes and ketones to *N*-substituted maleimides. The 1,2-diphenylethane-1,2-diamine derived thiophosphoramide, which could be prepared in good yield in a one-step procedure, was found to be more active and selective catalyst in the addition of aldehydes to various maleimide derivatives, when compared to sulfonamides having the same backbone. Products resulted in reactions of ketones with maleimides were also obtained in high yields and enantioselectivities.
The thiophosphoramide derivative was also efficient in the asymmetric conjugate addition of carbonyl compounds to β-nitrostyrene and in the reaction of nitromethane with α,β-unsaturated ketones.
Based on results obtained with (thio)phosphoramides in asymmetric additions to maleimides it was suggested that a weaker, more flexible hydrogen-bonding of the rigid electrophile to the catalyst is responsible for the improved performance of these bifunctional organocatalysts, as compared with sulfonamides.

Keywords: Asymmetric catalysis; Michael addition; 1,2-Diamines; Thiophosphoramide; Maleimides; Carbonyl compounds

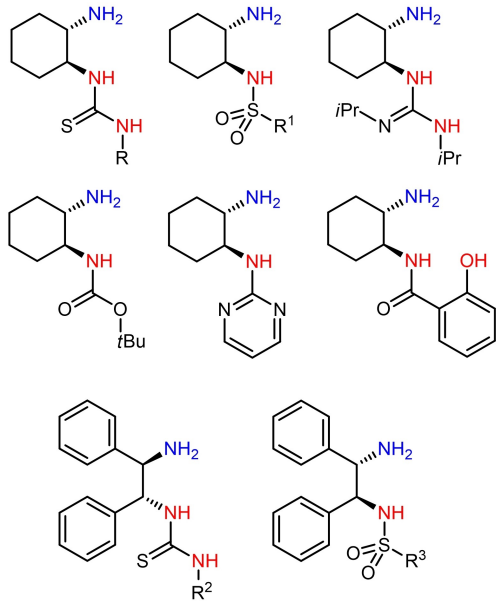
Introduction

Development of efficient chiral catalysts for the economical synthesis of optically pure compounds is a challenging task. A variety of chiral metal complexes and organocatalysts are available for the stereoselective preparation of optically enriched chemicals.[1,2] Fine-tuning the catalysts' structure has paramount importance for improving their performances.[2] Thus, besides studies aimed at finding novel catalytic materials, research focused on the effect of structural modification of the catalysts are equally important.

Asymmetric C–C bond-forming reactions have great significance in obtaining the structural complexity of the optically pure building blocks used in the pharmaceutical and fine chemical industry. Among these, conjugate additions are privileged reactions, owing to the structural diversity of the employable donors and acceptors.[3,4] Various chiral metal complexes were found efficient in these reactions.[5] Since the beginning of the present century the explosive

development of the organocatalysis led to widespread application of organic compounds as catalysts in asymmetric Michael additions,[3,6] which afforded the desired products in high yields and optical purities without metal contaminations following convenient work-up procedures.

The stereoselective Michael addition of nucleophiles to maleimides affords succinimide derivatives,[7] which are the structural units of several bioactive natural products, pharmaceuticals and drug candidates.[8] Special attention has been focused on the preparation of compounds resulting in reactions of maleimides and aldehydes or ketones, which may be further transformed easily in various high value-added products. These asymmetric Michael additions may be catalysed by bifunctional primary amine catalysts bearing a hydrogen-bond (H-bond) donor unit. Highly efficient chiral catalysts were obtained from C_2-symmetric vicinal primary diamines, such as cyclohexane-1,2-diamine or 1,2-diphenylethane-1,2-diamine, following their transformation in sulfonamide or thiourea derivatives.[9] Compounds developed so far, bearing various H-bond donor moieties (Figure 1),[10] showed that tuning the catalyst structure by proper modifications of these groups may lead to improved performances in the enantioselective conjugate additions to maleimides.



R: C_6H_5, 3,5-$(CF_3)_2C_6H_3$, $F_{17}C_8$-C_6H_4, *etc.*
R^1: CF_3, C_6H_5, CH_3-C_6H_4, 3,5-$(CF_3)_2C_6H_3$
R^2: C_6H_5, 3,5-$(CF_3)_2C_6H_3$
R^3: CH_3, C_6H_5, CH_3-C_6H_4, 3,5-$(CF_3)_2C_6H_3$

Figure 1. Structures of chiral bifunctional C_2-symmetric 1,2-diamine derivatives used in the asymmetric Michael additions of aldehydes to maleimides.[9,10]

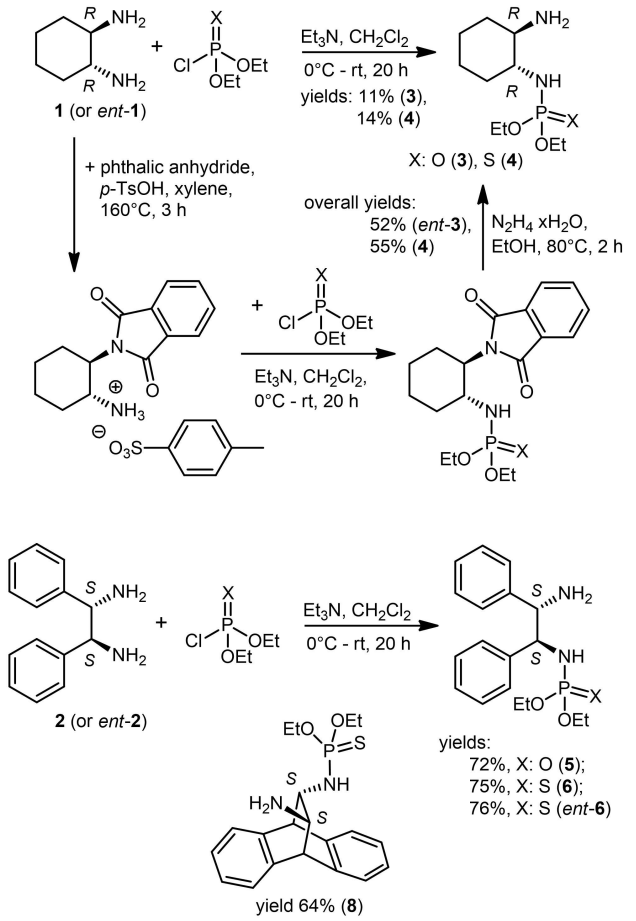
Recent studies showed that phosphinamides or (thio)phosphoramides prepared from optically pure C_2-symmetric primary diamines, besides having antiviral and antifungal effects,[11] are efficient organocatalysts in asymmetric Michael additions.[12] These derivatives afforded high yields and good enantioselectivities in the addition of ketones to β-nitrostyrene. However, the scope of these bifunctional catalysts has not yet been explored in detail. Here we disclose results of studies on extending the applicability of (thio)phosphoramides prepared from optically pure 1,2-diamines on the asymmetric addition of carbonyl compounds to maleimides. Other asymmetric conjugate additions, such as reactions of carbonyl compounds with β-nitrostyrene and that of nitromethane with α,β-unsaturated ketones were also investigated to test the versatility of these chiral organocatalysts.

Results and Discussion

Initially we have attempted to prepare phosphoramides and thiophosphoramides from optically pure (*R*,*R*)-1,2-cyclohexanediamine (**1**), (*S*,*S*)-1,2-diphenylethane-1,2-diamine (**2**) and *ent*-**2**, by a one-step procedure using *O*,*O*′-diethyl(thio)phosphoric chlorides (Scheme 1).[12c] In reactions of **2** (or *ent*-**2**) the corresponding products (**5**, **6** and *ent*-**6**) were obtained in good yields (72–76% after purification by flash-chromatography, Scheme 1). However, from **1** both **3** and **4** were isolated only in low yields (11% and 14%), due to extensive formation of doubly phosphorylated products. Accordingly, a three-step procedure was adopted in order to obtain these derivatives in higher yields. This protocol included the protection of one amino group as phthalimide,[13] followed by acylation with the corresponding phosphoric chloride,[12c] and deprotection using N_2H_4 hydrate.[13] Although this procedure included two flash chromatographic purifications, *ent*-**3** and **4** were isolated in over 50% overall yields. An additional thiophosphoramide with a rigid bicyclo [2.2.2]octane moiety (**8**) was prepared from (11*S*,12*S*)-11,12-diamino-9,10-dihydro-9,10-ethanoanthracene (**7**) in good yield (64%) following the one-step procedure (Scheme 1).

Asymmetric Addition of Aldehydes to *N*-Substituted Maleimide Derivatives

We started our catalytic studies by testing (thio) phosphoramides **3**, *ent*-**3**, **4**–**6**, *ent*-**6** and **8** as organocatalysts in the asymmetric conjugate addition of isobutyraldehyde (**9**) to *N*-benzylmaleimide (**10 a**) leading to the succinimide derivative **11 a** (Table 1). Their performances were compared with the corresponding chiral diamines (**1** or **2**) and sulfonamides: (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diaminocyclohexane (**12**), (1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenyl-



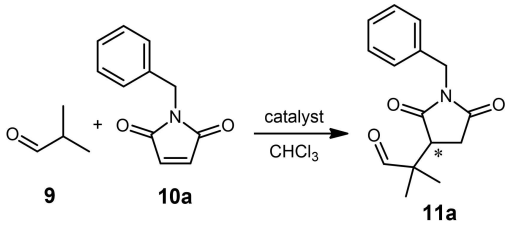
Scheme 1. Preparation of (thio)phosphoramides from optically pure C_2-symmetric 1,2-diamines.

ethane-1,2-diamine (**13**), *ent*-**13** and (1*R*,2*R*)-*N*-(methanesulfonyl)-1,2-diphenylethane-1,2-diamine (**14**). Results summarized in Table 1 showed unambiguously, that the catalyst has to contain a H-bond donor group, both chiral diamines (**1** and **2**, entries 1 and 7) were less efficient than their functionalized derivatives and provided low *ee*'s.

Phosphoramides **3** and *ent*-**3** and thiophosphoramide **4** having cyclohexane backbone were highly active catalysts in the test reaction, assuring complete conversion of **10 a** in one hour at room temperature (rt) (entries 4–6). Product **11 a** resulted in good yield and in 94% *ee*'s. The tosylamide (Ts-amide) **12** was much less efficient, providing smaller conversion and lower *ee* (entries 2, 3).

The organocatalysts with 1,2-diphenylethane scaffold were less active in this Michael addition (entries 8–22) as compared with **3**, *ent*-**3** and **4**. The Ts-amide **13** afforded low conversion at rt in 3 days (entry 8). However, high *ee* (98%) was obtained. Higher conversion, without altering the *ee* value, was reached in one day by increasing the reaction temperature to 70 °C (entry 9). Under these conditions by

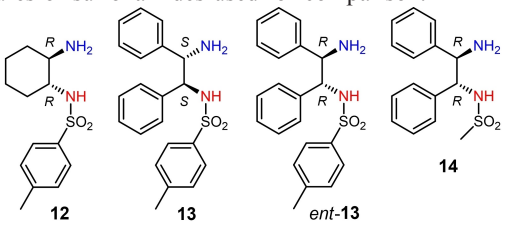
Table 1. Asymmetric Michael addition of isobutyraldehyde (**9**) to *N*-benzylmaleimide (**10 a**).[a]



Entry	Catalyst	Temp [°C]	Time [h]	Conv [%][b]	ee [%][c]
1	**1**	24	5	42	28 (*R*)
2	**12**	24	1	28	89 (*R*)
3	**12**	24	3	73	90 (*R*)
4	**3**	24	1	99 (82)	94 (*R*)
5	*ent*-**3**	24	1	99 (83)	94 (*S*)
6	**4**	24	1	99 (82)	94 (*R*)
7	**2**	70	24	89	71 (*S*)
8	**13**	24	72	43	98 (*S*)
9	**13**	70	24	94 (80)	98 (*S*)
10[d]	**13**	70	24	92 (77)	96 (*S*)
11[d,e]	**13**	70	24	80	97 (*S*)
12[d]	*ent*-**13**	70	24	93 (80)	96 (*R*)
13	**14**	70	24	98 (82)	98 (*R*)
14	**6**	24	72	97 (82)	>99 (*S*)
15[d]	**6**	50	24	90	>99 (*S*)
16[d]	**6**	70	24	99 (84)	>99 (*S*)
17[d,e]	**6**	70	24	99 (85)	>99 (*S*)
18[e,f]	**6**	70	24	92 (76)	>99 (*S*)
19[d,e,g]	**6**	70	24	96 (80)	>99 (*S*)
20[d,e,h]	**6**	70	24	97 (80)	>99 (*S*)
21[d,e]	*ent*-**6**	70	24	99 (84)	>99 (*R*)
22[d,e]	**5**	70	24	97 (83)	>99 (*S*)
23[d,e]	**8**	70	24	97 (80)	94 (*R*)

[a] Reaction conditions: 0.03 mmol (10 mol%) catalyst, 0.3 mmol **10 a**, 1.2 mmol **9**, 1 cm^3 $CHCl_3$.
[b] Conversion of **10 a** determined by gas-chromatography (GC-FID); in brackets are the isolated yields of **11 a**.
[c] Enantiomeric excess and the absolute configuration of the excess enantiomer determined by GC-FID.[9j]
[d] Using 0.6 mmol **9**.
[e] With 0.015 mmol (5 mol%) catalyst.
[f] Using 0.33 mmol **9**.
[g] Reaction in toluene.
[h] Results of reactions in toluene with addition of AcOH or BzOH (0.03 mmol) or by adding H_2O (0.06 mmol) and AcOH (0.03 mmol).

Structures of sulfonamides used for comparison:



decreasing the reactants molar ratio (**9**/**10a**) from 4/1 to 2/1 and the catalyst amount to 5 mol%, still good conversions were reached (entries 10, 11). As expected *ent*-**13** afforded identical results and the opposite product enantiomer in excess, as compared with **13** (entry 12). The methanesulfonamide **14** was slightly more efficient than **13** (entry 13), indicating that the *p*-tolyl moiety has no significant influence on the reaction. As compared to **13**, thiophosphoramide **6** was more effective, affording close to full conversion and high, over 99% *ee* value at rt in three days (entry 14). Moreover, this compound afforded high conversion even at 50 °C or complete transformation of **10a** at 70 °C following 24 h using only 2 equivalents (eq.) of **9** (entries 15, 16). The latter result was also reached with 5 mol% **6** or *ent*-**6** (entries 17, 21). Small decrease in conversion was detected only when the aldehyde amount was further decreased to 1.1 eq. (entry 18). Similar result was obtained with the phosphoramide **5** (entry 22).

Next we have changed the solvent from $CHCl_3$ to toluene with or without acid additives, such as acetic acid (AcOH), benzoic acid (BzOH), or a combination of water and AcOH (entries 19, 20). Previous reports showed that these additives may increase the conversion in the asymmetric addition of carbonyl compounds to maleimides and nitroolefins, due to acceleration of either the enamine intermediate formation or the iminium ion hydrolysis.[10,12a,14b,15] However, in this reaction the conversion slightly decreased under these conditions. Thus, we presume that acceleration of the above steps does not play role in determining the overall reaction rate in reaction of **9** with **10a** using these catalysts.

Thiophosphoramide **8**, with two phenyl rings cumulated to a bicyclo[2.2.2]octane scaffold, was slightly less active than **6** and afforded lower *ee* value (*ee* 94%, entry 23). Accordingly, besides the (thio) phosphoramide group, the hydrocarbon skeleton of the C_2-symmetric 1,2-diamine also plays role in obtaining high *ee* value. It must be stressed out that in the above reactions catalysed by **6**, *ent*-**6** or **5** very high *ee* values (over 99%) were obtained, thus optically pure **11a** could be isolated in good (82–85%) yields.

Owing to the excellent performance of **6**, shown in the addition of **9** to **10a**, as compared with the previously employed 1,2-diphenylethane-1,2-diamine derivatives,[9,10] we have examined the possibility of decreasing the organocatalyst amount. The effect of the **6** amount is presented in Figure 2. Although, 1.6 mol% of **6** was enough to obtain over 60% conversion in one day using 2 eq. of **9**, 2.5 mol% catalyst was necessary for close to complete transformation of **10a**. However, high *ee* value (99%) was obtained even with the lower amount of catalyst. The time dependence of the *ee* with 2.5 mol% **6** showed

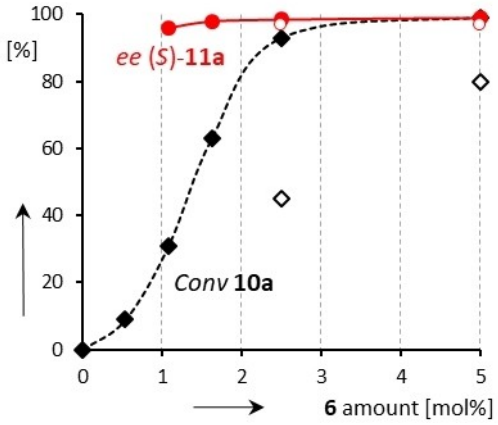


Figure 2. Effect of **6** amount on the conversion of **10a** (*Conv* **10a**) and *ee* of **11a** in the addition of **9** to **10a**. Reaction conditions: 0.3 mmol **10a**, 0.6 mmol **9**, solvent: 1 cm^3 $CHCl_3$, 70 °C, 24 h; open symbols: results obtained using **13**.

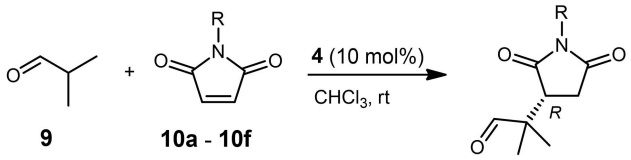
constantly high *ee* values from the beginning of the reaction (Figure SI-1, Supporting information).

The higher activities and *ee*'s obtained in the reaction of **9** with **10a** using the (thio)phosphoramides **4**, **5** and **6**, as compared with the corresponding Ts-amides motivated our study on extending the scope of these catalysts on reactions of **9** with other *N*-substituted maleimides.

The 1,2-cyclohexanediamine derivative **4** provided high conversions of **10a**–**10f** at rt, thus succinimide derivatives **11a**–**11f** were isolated in good yields (Table 2). The reaction times necessary to obtain close to complete transformations depended on the *N*-substituent. Usually up to 5 h were sufficient to obtain high conversions; longer time (22 h) was necessary to react the *N*-*t*Bu derivative **10f** (entry 7). High *ee*'s (94%–99%) were obtained in these transformations, irrespective of the *N*-substituent (Me, Et, Bn, Ph, cyclohexyl or *t*Bu). These *ee* values were higher than those reached with the Ts-amide **12** (Table SI-1, Supporting information).

Results obtained in the reaction of **9** with **10a**–**10f** using 1,2-diphenylethane-1,2-diamine derived catalysts **5** and **6** are presented in Table 3. Selection of the presented results was preceded by short optimizations with each maleimide derivative by changing the catalyst amount, reactant ratio and reaction time. High conversions and yields were obtained in reactions of most maleimides in one day or less (**10b**). Similarly with the reaction catalysed by **4**, **10f** needed longer reaction times to approach full transformation (entries 11, 12), probably due to steric hindrances of the bulky *t*Bu group. The phosphoramide derivative **5** gave smaller conversions in these reactions as compared with **6**. Most important, excellent enantioselectivities were obtained in all these reactions. The *ee*'s exceeded

Table 2. Asymmetric Michael addition of **9** to *N*-substituted maleimides **10a–10f** catalysed by **4**.[a]

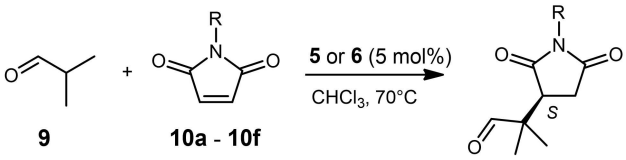


R: $C_6H_5CH_2$ (**10a**), C_6H_5 (**10b**), CH_3 (**10c**), C_2H_5 (**10d**), C_6H_{11} (**10e**), $(CH_3)_3C$ (**10f**)

Entry	Product	Time [h]	Conv [%][b]	ee [%][c]
1	**11a**	1	99 (82)	94
2	**11b**	5	99 (82)	99
3[d]	**11b**	5	93 (75)	98
4	**11c**	3	99 (83)	95
5	**11d**	5	95 (80)	96
6	**11e**	5	92 (75)	98
7	**11f**	22	86 (70)	96

[a] Reaction conditions: 0.03 mmol (10 mol%) **4**, 0.3 mmol **10a–10f**, 1.2 mmol **9**, 1 cm^3 $CHCl_3$, rt.
[b] Conversion of **10a–10f** determined by GC-FID; in brackets are the isolated yields of **11a–11f**.
[c] Enantiomeric excess (by GC-FID), the configuration of the excess enantiomer was assigned as *R* based on reactions using **12**.
[d] Using 0.015 mmol (5 mol%) **4**.

Table 3. Michael addition of **9** to maleimides **10a–10f** catalysed by **5** and **6**.[a]



R: $C_6H_5CH_2$ (**10a**), C_6H_5 (**10b**), CH_3 (**10c**), C_2H_5 (**10d**), C_6H_{11} (**10e**), $(CH_3)_3C$ (**10f**)

Entry	Product	Catalyst	Time [h]	Conv [%][b]	ee [%][c]
1[d]	**11a**	**5**	24	97 (83)	99
2[d]	**11a**	**6**	24	99 (85)	99
3	**11b**	**5**	8	88 (70)	99
4	**11b**	**6**	8	99 (84)	>99
5	**11c**	**5**	24	93 (75)	>99
6	**11c**	**6**	24	98 (82)	>99
7	**11d**	**5**	24	92 (73)	99
8	**11d**	**6**	24	96 (80)	>99
9[e]	**11e**	**5**	24	92 (75)	98
10[e]	**11e**	**6**	24	97 (82)	>99
11[e]	**11f**	**5**	96	85 (70)	99
12[e]	**11f**	**6**	96	97 (80)	>99

[a] Reaction conditions: 0.015 mmol (5 mol%) catalyst, 0.3 mmol **10a–10f**, 1.2 mmol **9**, 1 cm^3 $CHCl_3$, 70 °C.
[b] Conversion of **10a–10f** determined by GC-FID; in brackets are the isolated yields of **11a–11f**.
[c] Enantiomeric excess (by GC-FID), the configuration of the excess enantiomer was *S* based on reactions using catalyst **13**.
[d] Using 0.6 mmol **9**.
[e] With 0.03 mmol (10 mol%) catalyst.

those obtained with the sulfonamide **13** (Table SI-2, Supporting information). The thiophosphoramide **6** provided better *ee*'s than **5**, leading in many reactions to formation of less than 0.5% of the *R* enantiomer (*ee* > 99%).

Next we have explored the performances of the (thio)phosphoramides **4**, **5** and **6** in the addition of propionaldehyde (**15**) to **10a** (Table 4). The results were also compared to those obtained with the sulfonamides **12** or **13**, respectively. Significantly longer reaction times were necessary for the addition of **15** to **10a** as compared with **9**. Similarly with the addition of **9**, the cyclohexane-1,2-diamine derived **4** and **12** were more active than **5**, **6** or **13**. Almost complete conversion of **10a** was reached with **4** in 5 h (Table 4, entry 2), whereas under identical conditions, the conversion was much lower with **12** (entry 1). With both **4** and **12** the diastereomers of **16** formed in almost equal amounts, however the thiophosphoramide **4** provided slightly better *ee*.

Low conversion was obtained in one week with the 1,2-diphenylethane-1,2-diamine derived sulfonamide **13** at 70 °C (entry 3). The (thio)phosphoramides **5** and **6** led to higher conversions (entries 4–6), the latter afforded close to complete transformation of **10a** in five days. In this reaction a more pronounced difference in the performance of **5** and **6** may be observed. Both **6** and **13** gave similarly high, 99% *ee*'s, whereas the diastereomeric ratios were low (1.2–1.3). Examination of the effect of **6** amount (Figure 3) showed a

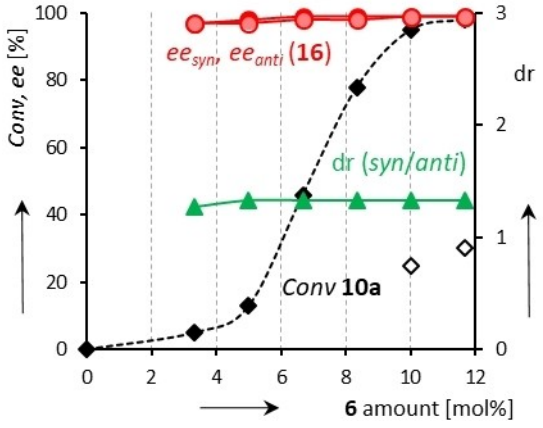
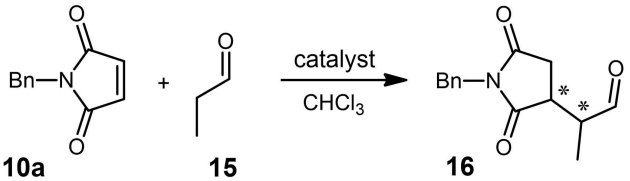


Figure 3. Effect of **6** amount on the conversion of **10a** (*Conv* **10a**), the dr and *ee* of **16** in the Michael addition of **15** to **10a**. Reaction conditions: 0.3 mmol **10a**, 1.2 mmol **15**, solvent: 1 cm^3 $CHCl_3$, 70 °C, 120 h; open symbols: conversions reached using catalyst **13**.

Table 4. Asymmetric addition of propionaldehyde (**15**) to **10a**.[a]



10a **15** **16**

Entry	Catalyst	Time [h]	Conv [%]; dr[b]	ee [%][c]
1[d]	**12**	5	61; 50/50	92; 91
2[d]	**4**	5	96 (80); 52/48	94; 95
3	**13**	168	34; 55/45	99; 99
4	**5**	120	66; 55/45	98; 98
5	**6**	72	86 (74); 56/44	99; 99
6	**6**	120	97 (83); 57/43	99; 99
7[e]	**6**	120	86; 54/46	99; 99
8[f]	**6**	72	80; 55/45	99; 99
9[g]	**6**	72	87 (74); 56/44	99; 99

[a] Reaction conditions: 0.03 mmol (10 mol%) catalyst, 0.3 mmol **10a**, 1.2 mmol **15**, 1 cm^3 $CHCl_3$, 70 °C (Bn: benzyl).
[b] Conversion determined by GC-FID, yield of the isolated product in brackets; dr: diastereomeric ratio (*syn*/*anti*).
[c] Enantiomeric excesses of the *syn* and *anti* isomers determined by GC-FID.
[d] Reaction at rt (24 °C).
[e] Reaction in toluene.
[f] In toluene using 0.03 mmol AcOH or BzOH.
[g] In toluene using 0.03 mmol AcOH and 0.06 mmol H_2O.

slow increase in the conversion at low amounts of **6** (up to 5 mol%) followed by a more accentuated elevation, whereas both the diastereomeric ratio and the *ee*'s were unaltered in the examined concentration range. The peculiarly low conversions obtained at low catalyst concentrations may be ascribed to the high **15**/**6** ratios (over 80), which may involve the formation of side-products having as effect the deactivation of the catalyst. In a reaction using catalyst **6** in toluene both the conversion and the *ee* decreased as compared with $CHCl_3$ (Table 4, entry 7), however, the addition of acid additives (AcOH or BzOH) or AcOH and water led to faster reactions, similar with that performed in $CHCl_3$ (entries 8, 9).

Accordingly, results obtained in the Michael addition of the aldehydes studied above showed the superior performances of the C_2-symmetric 1,2-diamine derived thiophosphoramides, when compared with the corresponding sulfonamides. To test the practical applicability of the former catalysts, reactions of few *N*-substituted maleimides were carried out at higher, 1 mmol scale, using catalyst **6**. Similarly high yields and high optical purities were obtained by increasing proportionally the solvent and the **9** amounts without extending the reaction time (except the reaction of **10b**), as shown in Figure 4.

Addition of Ketones to Maleimide Derivatives

Asymmetric Michael additions of ketones to maleimides were seldom reported.[16] Among the few studies published are three reports using C_2-symmetric diamine derivatives as catalysts and only one applied chiral sulfonamides, such as **13**.[16a] We continued our study on extending the scope of the thiophosphoramide catalyst **6** in these demanding asymmetric reactions (Scheme 2). Our initial attempts carried out using acetone (**17a**) as nucleophile under similar conditions as employed in reactions of aldehydes ($CHCl_3$, 70 °C, 72 h) led to almost complete recovery of **10a** (< 5% conversion). Motivated by results reached in the asymmetric addition of ketones to β-nitrostyrene and maleimides reported previously,[12a,14–16] we have carried out the reaction in toluene with the addition of AcOH and water. High conversion and *ee* value was obtained in 1 day (Table 5, entry 1). In experiments performed in toluene or using solely water both the conversions and *ee* values decreased (*Conv* 11%, *ee* 94% and *Conv* 33%, *ee* 97%, respectively). Adding AcOH or BzOH the *ee*'s were the same as with AcOH and water, while slightly smaller conversions were reached (87% and 92%, respectively; in the presence of BzOH, see entry 2).

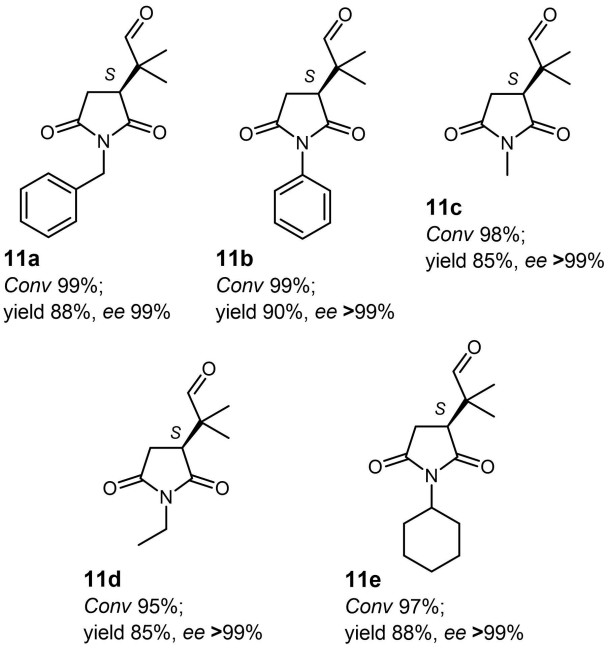
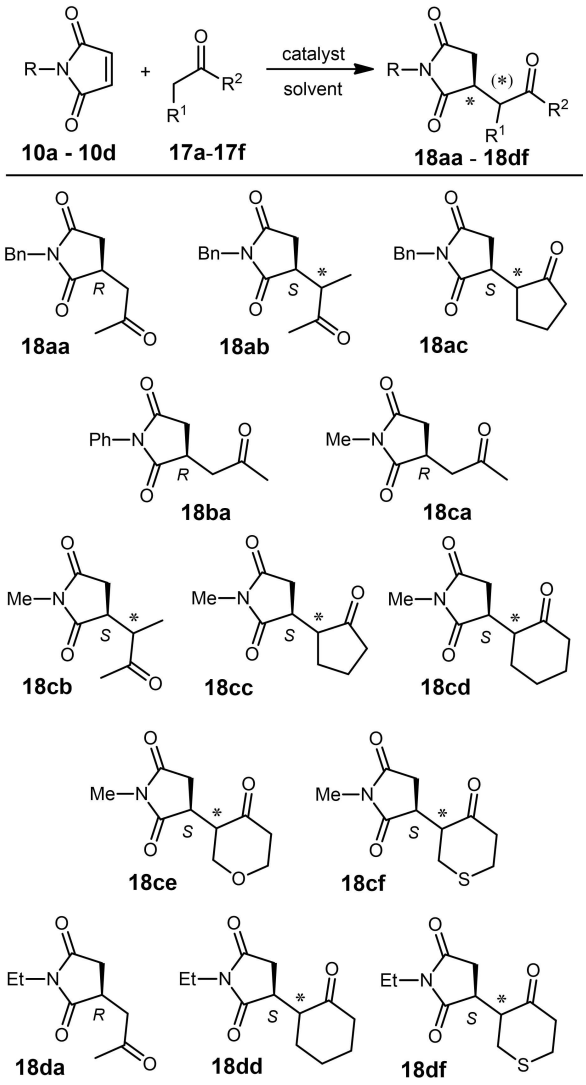


Figure 4. Products obtained in the Michael addition of **9** to *N*-substituted maleimides at 1 mmol scale; reaction conditions: 0.05 mmol (5 mol%) **6**, 1.0 mmol maleimide derivative, 4.0 mmol **9**, 3 cm^3 $CHCl_3$, 70 °C, 24 h.



Scheme 2. Products obtained in the Michael addition of ketones to *N*-substituted maleimides using **6**.

Based on these observations the reactions of maleimides **10a–10d** and ketones **17a–17f** using catalyst **6** (Scheme 2) were performed in two solvents ($CHCl_3$ and toluene with addition of AcOH and water). The best results were selected in Table 5. For comparison, reactions catalysed with **13** (some with **2**) were also carried out (Table SI-3, Supporting information). High conversions and *ee* values were reached in these additions either with catalyst **6** or **13**. In reactions of acetone (products **18aa**, **18ba**, **18ca**, **18da**) the *ee*'s obtained with **6** were slightly higher than those reached using **13**, the *N*-substituent had little influence on both the conversions and the *ee*'s (entries 1, 7, 8, 17). The *R* configuration of the chiral centre was assigned based on reported results obtained using catalysts *ent*-**13**.[16a] Furthermore, high yield of **18aa** was reached in a reaction carried out with 1 mmol **10a** in two days (entry 3).

Table 5. Michael addition of ketones to *N*-substituted maleimides catalysed by **6**.[a]

	Product	Solvent; time[b]	*Conv* [%]; dr (*syn*/*anti*)[c]	*ee* [%][d]
1	**18aa**	A; 24	94 (82)	99 (*R*)
2[e]	**18aa**	A; 24	92 (80)	99 (*R*)
3[f]	**18aa**	A; 48	99 (90)	99 (*R*)
4	**18ab**	A; 12	98[i] (90); 54/46	99; >99
5	**18ab**	B; 72	92[i] (80); 54/46	99; >99
6[g]	**18ac**	A; 72	80 (70); 85/15	98; nd
7	**18ba**	A; 24	96 (85)	98 (*R*)
8	**18ca**	A; 24	90 (80)	98 (*R*)
9[h]	**18cb**	A; 24	99[i] (90); 50/50	>99; 99
10[h]	**18cb**	B; 24	85[i] (70); 50/50	>99; 99
11	**18cc**	A; 72	92 (81); 75/25	97; 92
12	**18cd**	A; 72	99 (90); 62/38	96; 95
13	**18cd**	B; 72	99 (90); 85/15	98; nd
14	**18ce**	A; 120	75 (60); 58/42	94; 94
15	**18ce**	B; 120	97 (88); 65/35	91; 90
16	**18cf**	A; 48	96 (88); 62/38	98; 98
17	**18da**	A; 48	99 (90)	98 (*R*)
18	**18dd**	A; 24	98 (88); 68/32	97; 95
19	**18dd**	B; 48	99 (90); 86/14	98; nd
20	**18df**	A; 72	98 (90); 60/40	99; 98

[a] Reaction conditions: 0.03 mmol (10 mol%) **6**, 0.3 mmol **10a–10d**, 1.5 mmol **17a** or 1.2 mmol **17b–17d** or 0.6 mmol **17e**, **17f**, 1 cm^3 solvent, 70 °C, nd: not determined.

[b] Solvent used and reaction time [h]; A: toluene + 0.03 mmol AcOH + 0.06 mmol H_2O; B: $CHCl_3$.

[c] Conversion determined by GC-FID, isolated yields in brackets; dr: diastereomeric ratio (*syn*/*anti*).[16]

[d] Enantiomeric excesses of both enantiomer pairs (if two chiral centres are formed) by GC-FID; the configuration was identified based on a previous report.[16a]

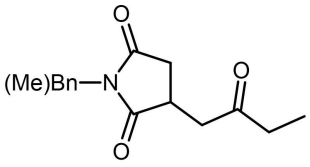
[e] Reaction in toluene with 0.03 mmol BzOH.

[f] Using 1 mmol **10a** and 5 mmol **17a** in 3 cm^3 solvent.

[g] Reaction at rt.

[h] Using 0.015 mmol (5 mol%) **6**.

[i] *Cca.* 2% of regioisomers with the following structures are formed:



The effect of the catalyst amount in reactions of **17a** with **10a** or **10d** showed that 5 mol% **6** was sufficient to reach high conversion in the former reaction in one day, whereas in the latter 15 mol% was necessary under identical conditions (Figure SI-2, Supporting information). However, in the reaction of **10d** close to complete transformation could be obtained with low amount of **6** (5 mol%) by extending the reaction to 48 h (94% conversion). In both reactions high *ee*'s were obtained even with the lowest catalyst amounts.

Both catalysts, **13** and **6**, provided similarly high (over 99%) *ee* in less than one day when ketone **17b** was employed (entries 4, 9). Reactions of this ketone was also significantly faster in toluene than in $CHCl_3$ (entries 5, 10), providing identical *ee* values in both solvents. Reactions of cycloaliphatic ketones **17c**–**17f** needed longer time to obtain almost complete transformations of the maleimides, attributable to the steric hindrances of the cycloaliphatic rings (entries 6, 11–16, 18–20). Similar conversions and yields were obtained in these reactions using **6** and **13** as catalysts, accompanied by high *ee*'s (97–99%), except **17e**. Moreover, the diastereomeric ratio increased from 1–1.2 (obtained with **17b**) up to 5.6 (85/15) in reactions of cyclopentanone (**17c**) and cyclohexanone (**17d**).

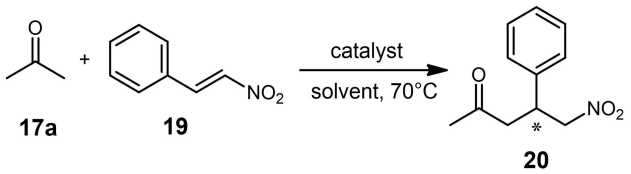
Summing up, based on the above results one may conclude that the thiophosphoramide derivative prepared from (*S*,*S*)-1,2-diphenylethane-1,2-diamine is an efficient catalyst in the enantioselective conjugate addition of carbonyl compounds to *N*-substituted maleimides.

Addition of Carbonyl Compounds to β-Nitrostyrene

The asymmetric organocatalyzed conjugate addition of carbonyl compounds to nitroolefins is a convenient preparation procedure of optically pure γ-nitroaldehydes and ketones, which may be transformed in valuable nitrogen containing pharmaceutical intermediates.[14] Recently it was reported the application of some (thio)phosphoramides in the asymmetric addition of ketones (mostly **17a**) to nitroolefins.[12,14] However, the diamine derivatives used in the present work with the exception of **4**[12b] were not yet tested, although other derivatives, among which sulfonamides, proved to be efficient.[17] Thus, our investigation was extended on using the above employed (thio)phosphoramides in the addition of **17a** and **9** to β-nitrostyrene (**19**).

Reactions were performed in two solvents, *i.e.* toluene (in the presence of AcOH and water) and $CHCl_3$. Selected results obtained in the addition of **17a** to **19** are presented in Table 6. Contrary to the addition of aldehydes to maleimides, in this reaction the catalysts having 1,2-cyclohexane backbone (**12**, *ent*-**3**, **4**) were less active, than the 1,2-diphenylethane derivatives (**13**, **5**, **6**). With the formers the *ee* values were also lower. Nevertheless, the (thio)phosphoramides *ent*-**3** and **4** (entries 2, 3) provided better *ee*'s than **12** (entry 1). In contrast, 10 mol% of the 1,2-diphenylethane-1,2-diamine derivatives afforded high conversions in one day (entries 5–7). Good *ee* values (94–95%) were obtained with **13** and **6**, the latter also provided the highest yield. Decrease of the **6** amount to 5 mol% led to the same *ee* value (95%) and slightly lower conversion (entry 8), whereas decrease of the reaction temperature to 50 °C afforded close to complete transformation of **19** in two days and small increase in the *ee* (96%, entry 9). In reactions carried out in toluene without additives (entry 10) or in $CHCl_3$ (entry 11) the conversion of **19** decreased.

Table 6. Asymmetric Michael addition of acetone (**17a**) to β-nitrostyrene (**19**).[a]



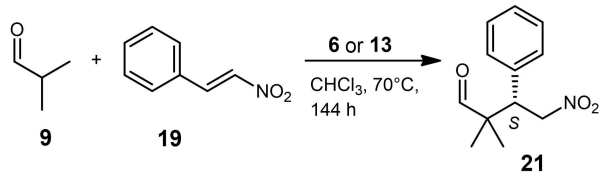
Entry	Catalyst	Solvent[b]; time [h]	Conv [%][c]	ee [%][d]
1	**12**	A; 24	58	68 (*S*)
2	*ent*-**3**	A; 24	44	73 (*R*)
3	**4**	A; 24	60 (45)	77 (*S*)
4	**4**	B; 24	32	76 (*S*)
5	**13**	A; 24	93 (82)	94 (*R*)
6	**5**	A; 24	99 (90)	90 (*R*)
7	**6**	A; 24	99 (90)	95 (*R*)
8[e]	**6**	A; 24	87 (80)	95 (*R*)
9[f]	**6**	A; 48	98 (90)	96 (*R*)
10[g]	**6**	A; 24	67	95 (*R*)
11	**6**	B; 48	68	93 (*R*)

[a] Reaction conditions: 0.04 mmol (10 mol%) catalyst, 0.4 mmol **19**, 2 mmol **17a**, 1 cm^3 solvent, 70 °C.
[b] Solvent; A: toluene + 0.04 mmol AcOH + 0.08 mmol H_2O, B: $CHCl_3$.
[c] Conversion of **19** determined by GC-FID, yields of the isolated products in brackets.
[d] Enantiomeric excess and the absolute configuration of the excess enantiomer determined by GC-FID.[12a,17d]
[e] Using 0.02 mmol (5 mol%) catalyst.
[f] Reaction at 50 °C.
[g] Without using AcOH and water additives.

Although, amino acids, oligopeptides and various optically pure pyrrolidine derivatives were found efficient in the asymmetric addition of aldehydes to **19**,[14,18] studies on using C_2-symmetric diamine derivatives as catalysts have been seldom reported.[19] Investigation of the conjugate addition of **9** to **19** confirmed the better activity of the thiophosphoramide **6** as compared with **13** (Scheme 3), although both provided low conversions even with 20 mol% catalyst in 6 days. Similarly high *ee*'s were reached with both **6** and **13**, respectively. Contrary to the previous reaction of **19**, these experiments proceeded better in $CHCl_3$, as compared with toluene even when additives were used in the latter solvent (not shown).

Addition of Nitromethane to α,β-Unsaturated Ketones

The Michael additions examined above proceed through activation of the Michael donors by formation



Catalyst	*Conv* [%]	*ee* [%]
13	33	96 (*S*)
6	63 (50)	95 (*S*)

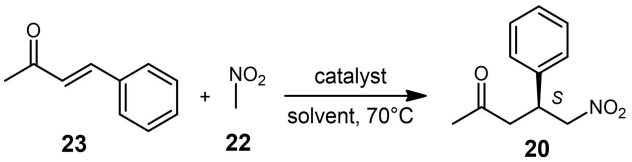
Scheme 3. Asymmetric addition of **9** to **19**. Reaction conditions: 0.08 mmol (20 mol%) **6** or **13**, 0.4 mmol **19**, 2 mmol **9**, 1 cm^3 $CHCl_3$ (isolated yield of **21** in brackets).

of the corresponding enamines. In continuation we have attempted the use of the thiophosphoramide **6** in conjugate additions occurring through formation of iminium ion upon condensation of the catalyst with an appropriate Michael acceptor. As test reactions additions of nitromethane (**22**) to *trans*-4-phenylbut-3-en-2-one (**23**) and 2-cyclohexen-1-one (**24**) were selected. The most efficient stereoselective catalysts employed in these reactions were 2-pyrrolidine, cyclohexane-1,2-diamine and cinchona alkaloid derivatives, respectively. Reactions catalysed by the former two occur through iminium ion transition states.[3,20] Until now 1,2-diphenylethane-1,2-diamine derived catalysts have not yet been tested in these transformations.

In the addition of **22** to **23** the thiophosphoramide **6** was found to be efficient (Table 7), affording over 90% conversions in four or three days using 10 or 15 mol% **6**, respectively (entries 5, 6), whereas **13** was less active (entries 2, 3). The *ee* values obtained with these catalysts were high (up to 95%); **6** afforded the same value as **13** when 15 mol% was used. Lower conversions were obtained in $CHCl_3$ than in toluene with the use of additives. It is worth noting that in this reaction the opposite enantiomer of 3-phenyl-4-nitropentane-2-one (*S*-**20**) in the same optical purity was prepared, as compared with the addition **17a** to **19** by applying the same organocatalyst (**6**).

The addition of **22** to the cycloaliphatic 2-cyclohexen-1-one (**24**) proceeded faster than the previous reaction with both **13** and **6** reaching over 90% conversions of **24** in one day in toluene in the presence of AcOH and water (Table 8). Both catalysts afforded identically high *ee* values (97%).

Table 7. Asymmetric Michael addition of nitromethane (**22**) to *trans*-4-phenylbut-3-en-2-one (**23**).[a]



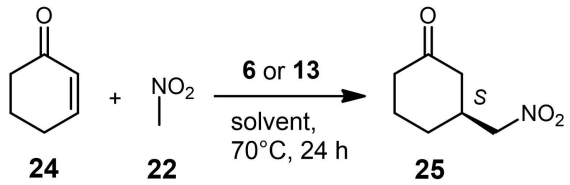
Entry	Catalyst; amount[b]	Solvent	time [h]	Conv [%][c]	ee [%][d]
1	**13**; 10	$CHCl_3$	96	43	95
2	**13**; 10	A	96	66	95
3	**13**; 15	A	72	77 (50)	95
4	**6**; 10	$CHCl_3$	96	50	93
5	**6**; 10	A	96	91 (77)	94
6	**6**; 15	A	72	94 (80)	95

[a] Reaction conditions: 0.3 mmol **23**, 3 mmol **22**, 0.5 cm^3 solvent, 70 °C, A: toluene + 0.03 mmol AcOH + 0.06 mmol H_2O.
[b] Amount of catalyst used [mol%].
[c] Conversion determined by GC-FID, yield of the isolated product in brackets.
[d] Enantiomeric excess determined by GC-FID, the configuration of the excess enantiomer was *S*.[12a,17d]

Interpretation of the Results

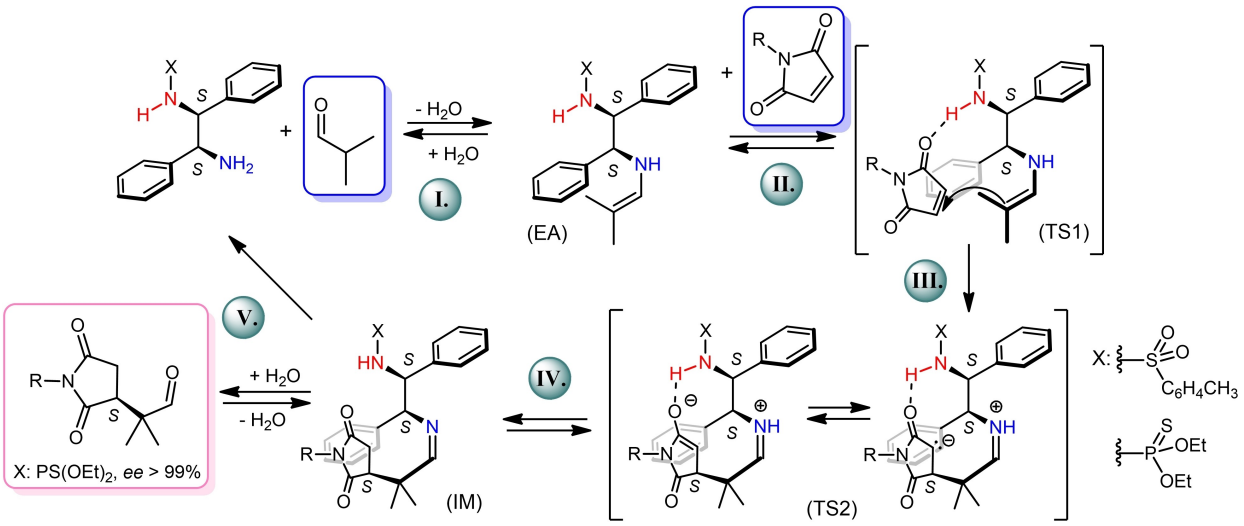
Additions of carbonyl compounds to activated olefins catalysed by primary amines proceed through enamine intermediates (EA), as illustrated in Scheme 4. H-bond donor groups activate the Michael acceptor (such as the *N*-substituted maleimides) by increasing its electrophilicity and also orientates the reacting species, directing the formation of the C–C bond (TS1). The present results indicated higher activity of (thio) phosphoramides, as compared with the corresponding sulfonamides in additions of carbonyl compounds to maleimides, also accompanied by increase in the *ee* values. The phosphoramide group's acidity is lower than that of the sulfonamide, similarly with the corresponding acids.[21] Moreover, the thiophosphoramide has the lowest acidity among these derivatives.

Table 8. Asymmetric conjugate addition of nitromethane (**22**) to 2-cyclohexen-1-one (**24**).[a]



Entry	Catalyst	Solvent	Conv [%][b]	ee [%][c]
1	**13**	$CHCl_3$	35	97
2	**13**	A	97 (82)	97
3	**6**	$CHCl_3$	34	97
4	**6**	A	94 (80)	97

[a] Reaction conditions: 0.03 mmol (10 mol%) catalyst, 0.3 mmol **24**, 3 mmol **22**, 0.5 cm^3 solvent, A: toluene + 0.03 mmol AcOH + 0.06 mmol H_2O, 70 °C, 24 h.
[b] Conversion determined by GC-FID, yield of the isolated product in brackets.
[c] Enantiomeric excesses determined by GC-FID, the absolute configuration of the excess enantiomer was *S*.[20]



Scheme 4. Catalytic cycle of the asymmetric Michael addition of **9** to maleimides promoted by (*S*,*S*)-1,2-diphenylethane-1,2-diamine-derived bifunctional catalysts.

As the latter compound afforded both the highest activities and enantioselectivities in the additions of **9** to maleimides, in these reactions a weaker H-bonding of the Michael acceptor assures a catalytically more efficient interaction. Similar behaviour was observed in the reaction of **9** with **19** using carboxamides *vs* sulfonamides.[22]

The inverse order of the acidity strength of the H-bond donor group as compared to the obtained conversions indicates that this group is not directly involved in the acid-accelerated reversible formation of the enamine (EA) or the hydrolysis of the imine (IM) intermediate formed from iminium species (Scheme 4, TS2). However, the reaction of **9** with **10 a** occurred readily without adding acid, whereas in reactions of ketones acid and water additives improved the conversion.

Besides increasing the rate, the higher *ee* values obtained with the (thio)phosphoramides indicate, that tuning the acidity of the amide group affected the step in which the chiral centre is formed (Scheme 4, step III.). Accordingly, a more stereospecific interaction in the TS1 occurs when the H-bond is weaker. This observation is in contrast with results obtained using thiourea derivatives, which provided high enantioselectivities as a consequence of a double H-bonding of the electrophile.[9] A probable explanation is that the more flexible bond between the thiophosphoramide moiety and the maleimide allows better arrangement of the activated electrophile.

Differences in reactions catalysed by **6** and **13** were observed when we have determined the relative concentrations of the intermediates by electrospray-ionization mass-spectrometry (ESI-MS). A mechanistic study of the reaction of **9** and **10 b** by ESI-MS measurements was published by Kokotos using amino acid catalysts.[23]

Addition of **9** to the solution of **6** or **13** resulted in complete transformation of these amines to the corresponding enamines (M $420+H^+$ and $418+H^+$) in less than one day (for ESI-MS spectra see the Supporting information). Following addition of **10 a** to these solutions the appearance of the imines (IM; M $607+H^+$ and $605+H^+$) was detected after another day. However, the relative abundance of the IM formed from **13** was much lower as compared to that resulted from **6** (14% *vs* 56%, see Figure 5), and these relative concentrations didn't change significantly after another day. Addition of **10 a** to a solution of the organo-catalysts allowed the detection of **13**–**10 a** and **6**–**10 a** molecular associates of low intensities (M $553+H^+$ and $551+H^+$, see the Supporting information). However, the abundance of the former was higher, confirming the stronger H-bonding of the maleimide to the sulfonamide **13** as compared with the phosphoramide **6**. By adding **9** the amounts of IM formed were close to that obtained previously using the opposite addition order (Figure 5, **6**(a)).

The significantly higher amount of IM intermediate accumulated during the reaction catalysed by **6** as compared to **13** indicated a faster C–C bond forming rate in the former reaction. This results in a higher concentration of the intermediate IM which follows to be hydrolysed, a step not affected by the catalyst structure, however influenced by the concentration of the IM intermediate. Thus, these results suggest that the better performance, *i.e.* significantly higher activity, of the thiophosphoramide as compared to sulfonamides may derive from the looser H-bond of the electrophile, as supposed previously.

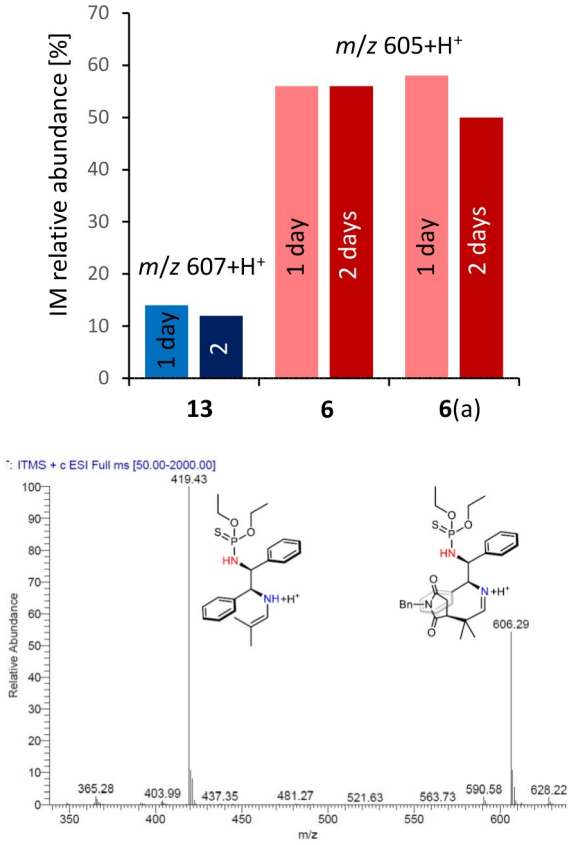


Figure 5. Relative abundances of the imines formed in reactions of **9** with **10a** catalysed by **13** and **6** after 1 and 2 days at rt; below the ESI-MS spectrum recorded after 1 day reaction. Reaction conditions: 0.015 mmol **13** or **6** in 0.5 cm^3 $CHCl_3$, 0.15 mmol **9**, 0.15 mmol **10a** added after 18 h; (a) **10a** was added 18 h before introducing **9**.

The significantly lower activity of the organocatalysts with 1,2-diphenylethane as compared with the 1,2-cyclohexane scaffold revealed the importance of the C_2-symmetric diamine backbone. The steric constraints exerted by phenyl rings decreased the accessibility of the catalyst, as compared with the cyclohexane moiety, however, also ensured higher *ee* values. Nevertheless, opposite order of activities were noted in the reaction of **17a** and **19**, owing to the flexibility of the nitroolefin, as compared with the more rigid cyclic maleimide. The α-unbranched aldehyde **15** reacted much slower than **9** possibly as a consequence of the lower nucleophilicity of the enamine intermediate. However, the similarly high *ee* values reached with **15** indicated that the more appropriate orientation of the maleimides is at the origin of the better stereocontrol reached with the thiophosphoramide (as compared to sulfonamide). This is also confirmed by the high *ee*'s obtained with various *N*-substituted maleimides. In reactions of these derivatives with **9** the substituent influenced mostly the rate, *i.e.* the time necessary to reach close to complete transformations of maleimides, probably by affecting their access to the active sites.

Reactions of ketones and maleimides was sluggish without acid additives possibly due to slow EA formation or IM hydrolysis (Scheme 4, steps I. and V.). Acceleration of these steps by addition of an acid and water led to formation of products in shorter reactions, with the formation of the C–C bond taking over the rate determination. The steric effect of the ketone structure was indicated by the time necessary to obtain high conversion and the diastereomeric ratio obtained with various ketones. This had as a consequence the smaller influence of the catalyst H-bond donor group, *i.e.* lower differences in the *ee*'s obtained with **6** and **13**, especially in reactions of bulkier ketones.

The better performance of the thiophosphoramide derivatives as compared to sulfonamides was also traceable in reaction of carbonyl compounds with β-nitrostyrene, reactions proceeding also through enamine intermediates. The higher flexibility of the nitroolefin **19** as compared with the maleimide cyclic structure may give a reasonable explanation on the slightly lower *ee*'s obtained in these reactions. Hence, these reactions proceed through a similar mechanism via a possible transition state shown in Figure 6(**A**). Significantly improved conversions were obtained with **6** as compared with **13** in the addition of nitromethane to **23** proceeding through iminium ion-type transition state. In these reactions the nucleophile **22**, with negligible steric effect is anchored by H-bonding (Figure 6(**B**)). The origin of the higher activity may also reside in different strengths of the H-bonding with the two catalysts, *i.e.* the flexibility of the nucleophilic species and faster release of the product in reactions catalysed by **6** as compared to **13**. Similarly to the reaction of ketones with maleimides, in these reactions the structure of the ketone had significant effect on the rate, as illustrated by the time necessary to transform **23** and **24**. As in reactions of the latter no difference was observed between the two organocatalysts one may presume the better accessibility of the iminium

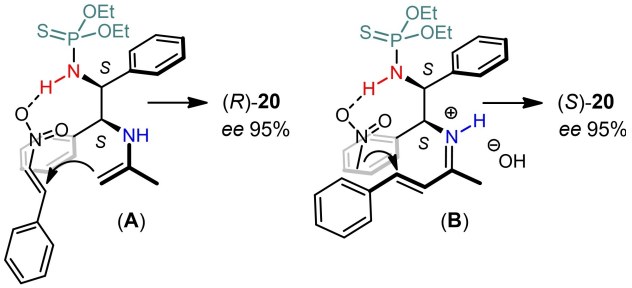


Figure 6. Probable transition states in reactions of **17a** with **19** (**A**) and **22** with **23** (**B**) catalysed by **6**.

ion by the H-bonded **22** in the transition state as compared with **23**.

Conclusions

The present study aimed at tuning the structure of chiral C_2-symmetric diamines derived bifunctional organocatalysts for application in the asymmetric Michael addition of carbonyl compounds to maleimides by using (thio)phosphoramide moieties as hydrogen-bond donor groups. It was found that phosphoramides and especially thiophosphoramides are more efficient in the addition of aldehydes to various *N*-substituted maleimides, as compared with the corresponding sulfonamides. The use of 1,2-diphenylethane-1,2-diamine derived thiophosphoramide, which could be prepared in good yield in a one-step procedure, afforded optically pure products in high yields and also allowed the use of low amount, down to 2.5 mol%, of catalyst. In reactions of ketones and maleimides addition of water and acids was necessary to accelerate the enamine intermediate formation and to obtain the chiral adducts in high yields and enantioselectivities in shorter reactions. The structure of the carbonyl compound influenced the diastereomeric ratios and the time necessary to reach complete conversions.

The applicability of the thiophosphoramide derivative was also investigated in other asymmetric conjugate additions. This organocatalyst proved to be more active and stereoselective in additions of carbonyl compounds to β-nitrostyrene than the corresponding *para*-toluenesulfonamide, whereas in reactions of nitromethane to α,β-unsaturated ketones higher or similar yields and identical enantioselectivities were reached.

The superiority of the chiral thiophosphoramide organocatalysts in Michael additions, as compared with sulfonamides was rationalized suggesting a weaker hydrogen-bonding of the activated olefins to the catalyst using the former derivatives. Besides an increase in the rate this interaction allows a more appropriate arrangement of the activated electrophile.

Experimental Section

Materials and Methods

Optically pure 1,2-diamines: **1**, *ent*-**1**, **2**, *ent*-**2** and **7**; sulfonamides **12**, **13**, *ent*-**13** and **14** and reagents: *O*,*O'*-diethyl chlorophosphate and *O*,*O'*-diethyl chlorothiophosphate were purchased from Sigma-Aldrich and used as received. Carbonyl compounds: **9**, **15**, **17a**–**17f**; *N*-substituted maleimides: **10a**–**10f**, *trans*-β-nitrostyrene (**19**), nitromethane (**22**), *trans*-4-phenylbut-3-en-2-one (**23**) and 2-cyclohexen-1-one (**24**) were commercial products (Sigma-Aldrich) and were used without purification. Solvents, reagents and additives of analytical grades were used in all reactions.

Gas-chromatographic analysis of the reaction products were carried out using Agilent Techn. 6890N GC-5973 MSD (GC-MSD) equipped with a 30 m long HP-1MS capillary columns for mass spectrometric identification of the products. For quantitative analysis Agilent 7890A GC-FID or Agilent 6890N-FID chromatographs equipped with chiral capillary columns (Cyclosil-B, 30 m × 0.25 mm ID, J&W or Hydrodex g-TBDAc, 25 m × 0.25 ID, Macherey-Nagel) was used. ^{1}H and ^{13}C NMR spectra of the purified products were recorded on Bruker Avance DRX 400 or Bruker Ascend 500 spectrometers using $CDCl_3$ solvent. For identification of the newly prepared organocatalysts and for the mechanistic investigations the ESI-MS spectra were recorded using LCQ Fleet Ion Trap LC/MS (Thermo Sci.) instrument using direct injection. Products were isolated by flash chromatography on silica gel 60, 40–63 µm. The purity of the fractions were checked by thin-layer chromatography on Kieselgel-G (Merck Si 254 F) layers. Optical rotations of the compounds were measured using Perkin-Elmer 341 polarimeter.

Preparation of (thio)Phosphoramides

One-Step Preparation Method

Preparation of *O*,*O*-diethyl[(1*S*,2*S*)-2-amino-1,2-diphenyl-ethyl] phosphoramidothioate (**6**).

In a 100 cm^3 three-necked round bottom glass flask to a solution of 4 mmol (849.2 mg) (1S,2S)-1,2-diphenylethane-1,2-diamine (**2**) in 15 cm^3 dry CH_2Cl_2 4 mmol (0.560 cm^3) Et_3N was added. The flask was flushed with N_2 and the solution was cooled to 0 °C. To this solution 4 mmol (0.630 cm^3) O,O'-diethyl chlorothiophosphate dissolved in 25 cm^3 dry CH_2Cl_2 was added dropwise in 2 h. The solution was let to warm up slowly to room temperature and stirred for another 18 h (total reaction time 20 h). To the resulted slurry 40 cm^3 water was added, the organic phase was separated, the aqueous phase was washed twice with 25 cm^3 CH_2Cl_2 and the unified organic phases were dried over sicc. Na_2SO_4. The crude product obtained following evaporation of the solvent was purified by flash chromatography eluted using CH_2Cl_2/MeOH 25/1 mixture. 1.095 g (yield 75%) of product **6** was obtained as white crystalline material (for spectroscopic data see the Supporting information).

The other compounds obtained via one-step procedure were prepared similarly at 2 or 4 mmol scale using the corresponding diamine and chloro(thio)phosphate; yields: 11% (**3**), 14% (**4**), 72% (**5**), 76% (*ent*-**6**) and 64% (**8**).

Three-Steps Preparation Method

Preparation of *O*,*O*-diethyl[(1*R*,2*R*)-2-aminocyclohexyl]-phosphoramidothioate (**4**).

(1) In a 100 cm^3 two-necked round bottom glass flask 7.5 mmol (1.4267 g) *para*-toluenesulfonic acid monohydrate was dehydrated by refluxing in 40 cm^3 xylene for 2 h using a water separator. The solution was cooled to room temperature, 7.5 mmol (0.8564 g) (1*R*,2*R*)-cyclohexane-1,2-diamine (**1**) and 7.5 mmol (1.1109 g) phthalic anhydride were added and the solution was stirred at 160 °C for 3 h. The mixture was cooled to room temperature and the crystalized material was filtered,

washed with 10 cm^3 cold toluene and dried, to obtain 2.9675 g (yield 95%) *N*-[(1*R*,2*R*)-2-ammoniumcyclohexyl]-phthalimide *para*-toluenesulfonate.

(2) 4 mmol (1.666 g) of the material obtained in the previous step was suspended in 30 cm^3 sat. Na_2CO_3 aqueous solution and stirred for 2 h at rt. The aqueous solution was washed three times with 20 cm^3 EtOAc, the unified organic solutions were dried over sicc. Na_2SO_4 and the solvent was evaporated. The material was identified by GC-MSD analysis and was used in the following step without further purification. The obtained material was reacted with diethyl chlorothiophosphate as described in the one-step procedure. It was dissolved in 15 cm^3 dry CH_2Cl_2 followed by addition of 4 mmol (0.560 cm^3) Et_3N. The flask was flushed with N_2 and the solution was cooled to 0 °C. To this solution 4 mmol (0.630 cm^3) *O*,*O*′-diethyl chlorothiophosphate dissolved in 25 cm^3 dry CH_2Cl_2 was added dropwise in 2 h. The solution was let to warm up slowly to room temperature and stirred for another 18 h. To the resulted slurry 40 cm^3 water was added, the organic phase was separated, the aqueous phase was washed twice with 25 cm^3 CH_2Cl_2 and the unified organic phases were dried over sicc. Na_2SO_4. The crude product obtained following evaporation of the solvent was purified by flash chromatography eluted with hexane/ethyl acetate (EtOAc) 1/5 mixture. 1.110 g (yield 70%) of a pale yellow viscous oil was obtained.

(3) The material obtained in the previous step (2.8 mmol) was dissolved in 15 cm^3 EtOH in a 50 cm^3 flask and 1 cm^3 hydrazine hydrate was added. The solution was refluxed for 2 h, cooled to room temperature, the precipitate was dissolved in 20 cm^3 $CHCl_3$, filtered and washed twice with 20 cm^3 $CHCl_3$. From the unified organic phases the solvent was evaporated and the crude product was purified by flash chromatography eluted with $CHCl_3$/MeOH 20/1 mixture. 0.619 g of **4** (yield 83%) was obtained as light beige crystals (see the Supporting information). The overall yield of **4** following three-steps was 55%.

Compound *ent*-**3** was also prepared using the three-step procedure from *ent*-**1** and diethyl chlorophosphate in 52% overall yield.

Michael Additions: General Procedure

The reactions were carried out in 4 cm^3 closed glass vials. The solutions were stirred magnetically (600 rpm) immersed in an oil bath set to the desired temperature. In a typical reaction the given amount of catalyst was dissolved in the corresponding solvent, additives were added if needed followed by introducing the given amounts of maleimide derivative (or other activated olefin) and finally the carbonyl compound. The vial was closed and was introduced in the oil bath (except when the experiments were carried out at rt). Following the given reaction time 1 cm^3 saturated aq. NH_4Cl was added, the organic phase was separated and the aqueous phase was washed three times with 1 cm^3 organic solvent. The unified organic phases were dried on sicc. $MgSO_4$ and analysed by gas-chromatography following filtration and addition of 25 mm^3 *n*-decane internal standard (GC-MSD and GC-FID). The solvent was evaporated and the adducts were purified by flash chromatography using hexane/EtOAc mixtures for determination of the yields and characterization. Reactions at 1 mmol scale were carried out similarly using 8 cm^3 vials and the amounts given in Figure 4 or Table 5, entry 3. For analytical data, ^1H and ^{13}C NMR spectra, GC-MSD spectra and GC-FID chromatograms of the obtained products see the Supporting information.

Conversions (*Conv* [%]), diastereomeric ratios (*syn*/*anti*, where applicable) and enantioselectivities (as enantiomeric excess, *ee* [%]) were calculated based on the relative concentrations determined by gas-chromatography (see the Supporting Information). The absolute configuration of the excess enantiomers were assigned based on chromatographic analysis of products resulted in reactions using catalysts described in the literature.

Acknowledgements

Financial support of the Ministry of Human Capacities, Hungary through grants 20391-3/2018/FEKUSTRAT and NTP-NFTÖ-19 (V. Kozma) is acknowledged.

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