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Conjugate addition of 1,3-dicarbonyl compounds to maleimides using bifunctional primary amine–(thio)phosphoramide organocatalysts

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ABSTRACT

Asymmetric Michael additions of 1,3-dicarbonyl compounds to *N*-substituted maleimides were carried out using primary amine-(thio)phosphoramide bifunctional chiral organocatalysts derived from optically pure C_2-symmetric 1,2-diamines. The addition of ethyl 2-fluoroacetoacetate using the 1,2-diphenylethane-1,2-diamine derived thiophosphoramide catalyst afforded various succinimides substituted with fluorine bearing quaternary carbon in high yields, good diastereomeric ratios and excellent enantiomeric excesses. Alicyclic β-ketoesters provided the diastereomerically pure Michael adducts in good yields and high enantioselectivities, whereas 2,4-pentanedione afforded products with slightly lower enantiomeric excesses. The bulkiness of the *N*-substituent of the maleimide ring influenced mostly the conversions. The thiophosphoramide catalyst was found also efficient in the addition of ethyl 2-fluoroacetoacetate to β-nitrostyrenes. Unprecedentedly, during this work the highly enantioselective addition of 1,3-dicarbonyl compounds to maleimides were catalyzed by a primary amine–hydrogen-bond donor groups containing bifunctional organocatalyst. These reactions occurred through enamine intermediate, as evidenced by electrospray-ionization mass spectrometry and NMR spectroscopy.

1. Introduction

The stereoselective preparation of enantiomerically pure compounds has become one of the main goal of the synthetic organic chemistry. Among various methods used for this purpose, applications of asymmetric organocatalysts are efficient and economical approaches for obtaining such compounds [1–5]. Fine-tuning of the organocatalysts structure is essential to expand their applicability, as novel derivatives often make possible wider extension of the scope of the chiral compounds used as catalysts. Thus, the exploration of new organocatalyst derivatives brought significant developments in stereoselective preparation of chiral organic building blocks, which became the subject of numerous recent reviews [6–17]. Conjugate additions are outstanding reactions in fine chemical research and industry, due to the wide range of valuable chiral materials obtainable by these reactions. Their reduced toxicity, high efficiency, outstanding stereoselectivity and the applied simple operational procedures make the chiral organocatalysts widely used in the stereoselective Michael additions [18–30].

Maleimides are important Michael acceptors, which have been successfully used in asymmetric organocatalytic transformations [31,32]. The stereoselective Michael addition of various nucleophiles to maleimides affords succinimide derivatives, which are core structural units found in several natural products and clinical drug candidates [33–38]. The first highly efficient organocatalytic enantioselective Michael addition to *N*-substituted maleimides employed 1,3-dicarbonyl compounds as nucleophiles and was catalyzed by natural cinchona alkaloids [31]. Following this, excellent results were achieved in the conjugate addition of aldehydes and ketones to maleimides with chiral primary or secondary amine organocatalysts derived from optically pure 1,2-diamines, diarylprolinols, amino acids and oligopeptides [32, 39–54]. The latter transformations occur through formation of the enamine by reaction of the catalyst with the carbonyl compound, whereas the electrophile is activated by interaction with the hydrogen-bond (Hb) donor group of the bifunctional organocatalyst (Fig. 1(a)).

Since the pioneering report of Bartoli and co-workers [31], several studies were published applying soluble and heterogeneous cinchona alkaloid-based organocatalysts for the stereoselective addition of 1, 3-dicarbonyl compounds to maleimides [32,55–67]. Other types of bifunctional chiral organocatalysts, such as a bicyclic guanidine derivative or a bis(2-aminobenzimidazole) derived from optically pure cyclohexane-1,2-diamine were also found active in the asymmetric

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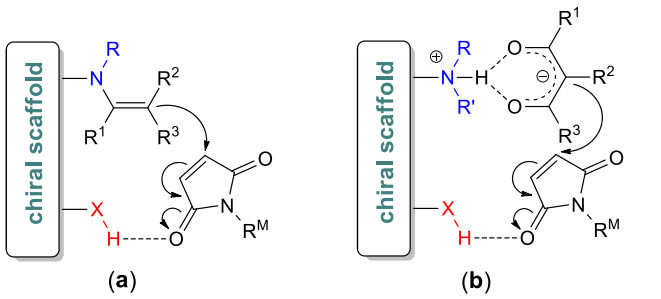


Fig. 1. Activation modes in the asymmetric additions of nucleophiles to maleimides using bifunctional organocatalysts.

addition of various β-ketoesters or β-diketones to maleimides [32, 68–73]. Contrary to the reactions of aldehydes and ketones, the addition of these strong nucleophiles occurs through a deprotonation-type mechanism, with the enolate bonded to the protonated tertiary amine group of the bifunctional organocatalyst, to form a bidentate complex (Fig. 1(b)).

Recently, we have reported the use of (thio)phosphoramide catalysts prepared from C_2-symmetric optically pure 1,2-diamines in the addition of aldehydes and ketones to maleimides [51]. High yields and excellent enantioselectivities were obtained with the 1,2-diphenylethane-1, 2-diamine derivatives, whereas the diastereoselectivities were satisfactory only in reactions of alicyclic ketones. These catalysts also performed well in additions of carbonyl compounds to β-nitrostyrene and in reaction of nitromethane with unsaturated ketones. However, all these reactions take place by covalent activation of the reactants, either as enamine or as iminium ion. In the present work we attempted to use these primary amine-(thio)phosphoramide chiral bifunctional organocatalysts in the enantioselective additions of 1,3-dicarbonyl compounds to *N*-substituted maleimides, which up to now have not been efficiently carried out with primary amine catalysts. In reactions with 2-substituted 1,3-dicarbonyl compounds highly functionalized succinimide derivatives bearing a quaternary chiral center may be prepared by this way, which are valuable building blocks in the pharmaceutical industry.

2. Results and discussions

In our previous study, we have synthesized phosphoramides and thiophosphoramides from optically pure (1*S*,2*S*)-cyclohexane-1,2-diamine (**1**) and (1*S*,2*S*)−1,2-diphenylethane-1,2-diamine (**4**) by one or three-step procedures using (*O,O*-)diethyl (thio)phosphoric chlorides, such as *O,O*-diethyl ((1*S*,2*S*)−2-aminocyclohexyl)phosphoramidothioate (**2**), diethyl ((1*S*,2*S*)−2-aminocyclohexyl)phosphoramidate (**3**), *O,O*-diethyl ((1*S*,2*S*)−2-amino-1,2-diphenylethyl) phosphoramidothioate (**5**) and diethyl ((1*S*,2*S*)−2-amino-1,2-diphenylethyl)phosphoramidate (**6**). These catalysts (Fig. 2) gave excellent results in conjugate additions of aldehydes and ketones to maleimide derivatives [51]. In the followings, we attempted to extend the applicability of these catalysts using 1,3-dicarbonyl compounds as nucleophiles.

2.1. Addition of β-ketoesters to maleimide derivatives

We started our catalytic studies by testing the selected organocatalysts (Fig. 2) in the asymmetric conjugate addition of ethyl 2-fluoroacetoacetate (**8a**) to *N*-ethylmaleimide (**7a**) leading to the succinimide derivative **9aa** (Table 1). The increased nucleophilic character of **8a** motivated our choice, which is due to the additional electron-withdrawing effect of fluorine in the α position. Moreover, fluorine-containing chiral compounds recently receive increasing attention in the pharmaceutical industry, due to beneficial effects of this substituent on the biological activity of the organic compounds [74–78]. In spite of

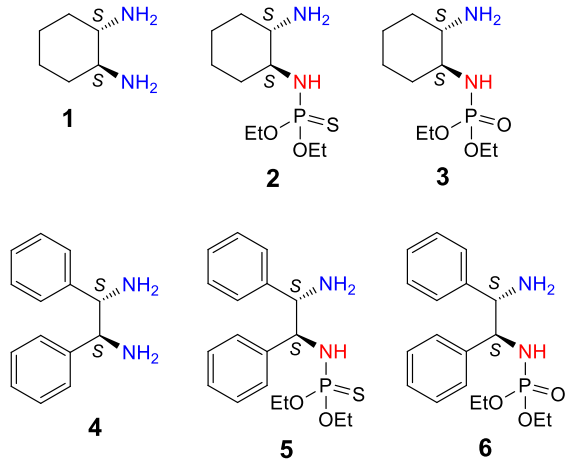
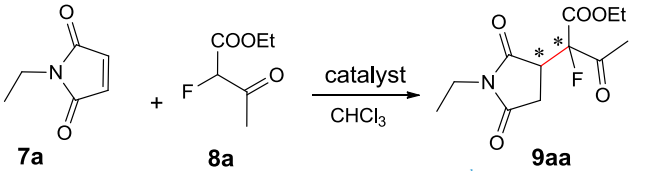


Fig. 2. Structure of the chiral 1,2-diamine-derived (thio)phosphoramides and the parent diamines.

Table 1
Asymmetric Michael addition of ethyl-2-fluoroacetoacetate (**8a**) to *N*-ethylmaleimide (**7a**)[a].

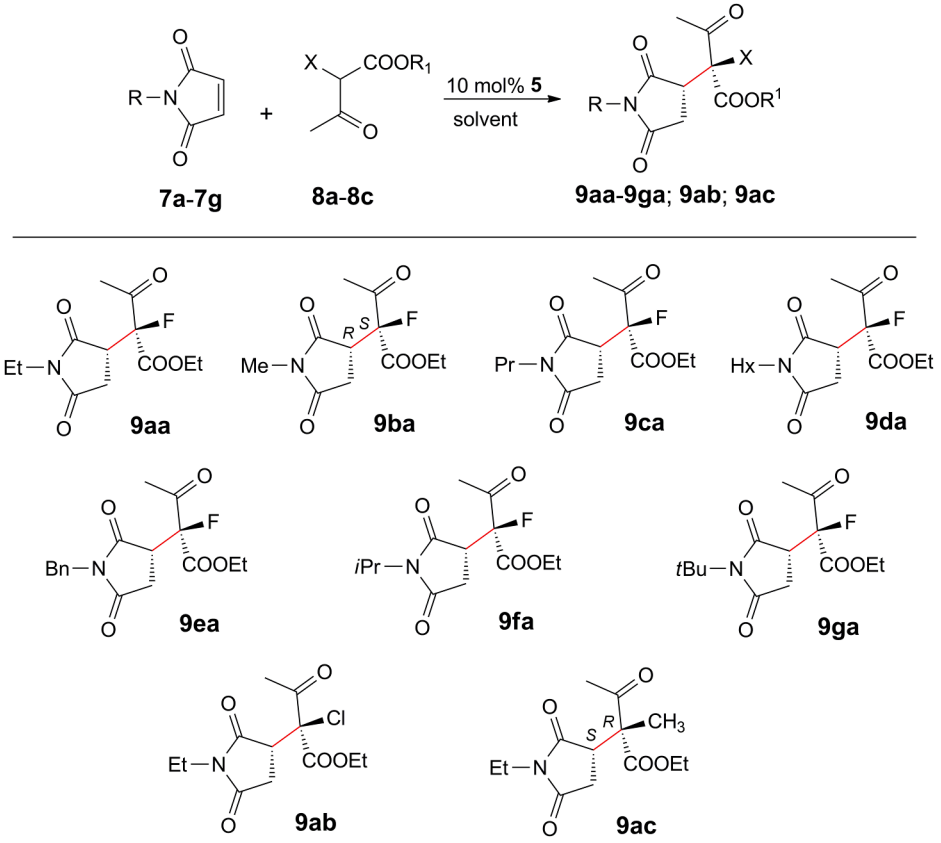


Entry	Catalyst	Temp (°C)	Time (day)	*Conv* (%)[b]	*dr*[c]	*ee* (%)[c]
1	**1**	24	3	51	78/22	*rac.*
2	**2**	24	3	51	91/9	56
3	**3**	24	3	50	89/11	40
4	**4**	70	3	45	84/16	48
5	**5**	24	3	55	96/4	99
6	**5**	24	7	79 (70[d])	94/6	99
7	**5**	50	3	83	93/7	98
8	**5**	70	3	98 (90[d])	92/8	97
9[e]	**5**	70	3	80	91/9	97
10	**5**	70	2	93	91/9	97
11[f]	**5**	70	2	81	93/7	98
12[g]	**5**	70	2	92 (80[d])	91/9	97
13	**6**	70	3	89	93/7	97

[a] *Reaction conditions*: 0.03 mmol (10 mol%) catalyst, 0.3 mmol **7a**, 0.4 mmol **8a**, solvent: 0.5 cm^3 $CHCl_3$.
[b] Conversion (*Conv*) determined by GC-FID.
[c] Diastereomeric ratio (*dr*) and enantiomeric excess (*ee*) of the major enantiomer pair determined by GC-FID.
[d] Yield of the product isolated by flash chromatography.
[e] 0.015 mmol (5 mol%) **5**.
[f] Reaction carried out in toluene ($PhCH_3$).
[g] Reaction carried out in $PhCH_3$ + 0.03 mmol (10 mol%) acetic acid (AcOH).

the potential pharmaceutical importance of the fluorinated optically pure chemicals, only two publications appeared on the asymmetric addition of 2-fluoro-1,3-dicarbonyl compounds to maleimides [59,70]. In the present study initially we have compared the performances of (thio)phosphoramides **2, 3, 5** and **6** with those of the corresponding chiral diamines **1** or **4** (Table 1).

Results summarized in Table 1 show, that the catalyst must contain a Hb-donor group, as both chiral diamines (**1** and **4**) were less efficient than their functionalized derivatives, providing low *ee*, if any (see entries 1, 4). Under the same reaction conditions, *i.e.* at room temperature (rt, 24 °C), using 10 mol% catalyst following 3 days reactions, **2** and **3** having cyclohexane backbone showed similar activity as **5** having diphenylethane backbone (entries 2, 3, 5), however, the diastereomeric ratio (*dr*) and the enantiomeric excess (*ee*) was much higher with the



Scheme 1. Products obtained by asymmetric Michael addition of β-ketoesters to *N*-substituted maleimides.

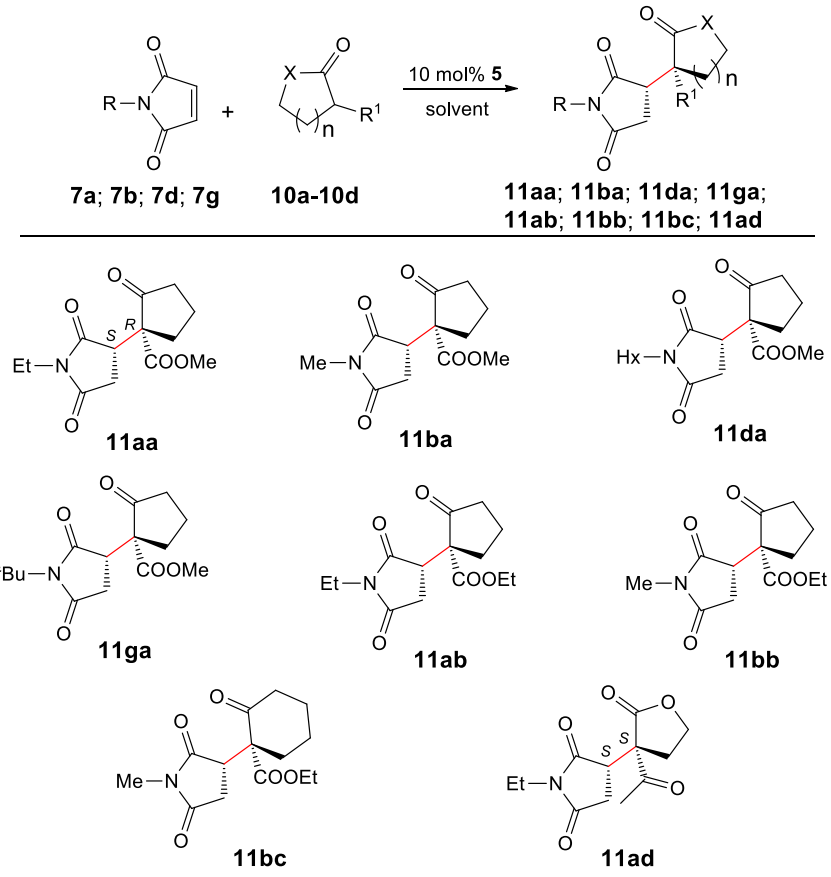
latter (*dr* 96/4, *ee* 99%). Owing to the excellent enantioselectivity obtained using catalyst **5**, this derivative was used in further efforts to increase the conversion (*Conv*) of **7a**. However, prolonging the reaction to one week (entry 6) did not result in complete conversion (79%). Higher value was achieved by increasing the temperature (entries 7, 8). Thus, we reached 98% *Conv* in 3 days in the reaction carried out at 70 °C and we could isolate the product in 90% yield. Under these conditions, we also obtained good *Conv* and high *ee* by applying less, *i.e.* 5 mol%, **5** (entry 9).

Next, we have investigated the effect of the solvent, changing from

Table 2
Michael addition of β-ketoesters **8a-8c** to *N*-substituted maleimides **7a-7g** catalyzed by **5**[a].

Entry	Product	Solvent	Time (day)	*Conv* (%)[b]	*dr*	*ee* (%)[c]
1	**9aa**	$CHCl_3$	3	98 (90)	92/8	97
2	**9aa**	$PhCH_3$ + AcOH	2	92 (80)	91/9	97
3	**9ba**	$CHCl_3$	1	82 (74)	93/7	97
4	**9ba**	$PhCH_3$ + AcOH	1	85 (75)	91/9	97
5	**9ca**	$CHCl_3$	2	87 (75)	92/8	97
6	**9ca**	$PhCH_3$ + AcOH	2	91 (80)	90/10	98
7	**9da**	$CHCl_3$	2	92 (84)	92/8	98
8	**9da**	$PhCH_3$ + AcOH	2	85 (75)	92/8	98
9	**9ea**	$CHCl_3$	3	99 (90)	90/10	99
10[d]	**9ea**	$CHCl_3$	3	81 (70)	87/13	>99
11[d]	**9ea**	$PhCH_3$ + AcOH	3	91 (80)	89/11	>99
12	**9fa**	$CHCl_3$	3	97 (88)	91/9	97
13	**9fa**	$PhCH_3$ + AcOH	3	97 (87)	90/10	97
14	**9ga**	$CHCl_3$	3	66 (50)	90/10	96
15	**9ga**	$PhCH_3$ + AcOH	3	67 (54)	89/11	96
16[e,f]	**9ab**	$PhCH_3$ + AcOH	7	5 (nd)	98/2	96
17[e]	**9ac**	$CHCl_3$	7	9 (nd)	85/15	66
18[e]	**9ac**	$PhCH_3$ + AcOH	7	55 (44)	94/6	95

[a] *Reaction conditions:* 0.03 mmol (10 mol%) **5**, 0.3 mmol **7a-7g**, 0.4 mmol **8a-8c**, 0.5 cm^3 solvent (10 mol% AcOH, when used), 70 °C, nd: not determined.
[b] Conversion (*Conv*) determined by GC-FID, in brackets are the yields of the purified products; *dr*: diastereomeric ratio.
[c] Enantiomeric excess (*ee*) of the major enantiomer pair determined by GC-FID, the configuration of the excess products are shown in Scheme 1.
[d] 0.015 mmol (5 mol%) **5**.
[e] 0.6 mmol **8b**.
[f] Similar results were obtained in $CHCl_3$ with or without addition of 10 mol% AcOH.



Scheme 2. Products obtained in the asymmetric Michael addition of cyclic β-ketoesters to *N*-substituted maleimides.

$CHCl_3$ to toluene ($PhCH_3$) with or without the addition of 10 mol% acetic acid (AcOH). Previous reports showed that acid additives may increase the *Conv* in the asymmetric addition of carbonyl compounds to maleimides or nitroolefins [45,51,79,80]. Good results were obtained in the $PhCH_3$ + 10 mol% AcOH system, however, in $PhCH_3$ without AcOH lower *Conv* was reached (entries 10–12). Phosphoramide **6** was slightly less active than **5** but provided the same *dr* and *ee* values (entry 13). We would like to highlight, that the results obtained using **5** exceeded those obtained by the previously applied cinchona alkaloid organocatalysts in additions of fluorinated nucleophiles [59].

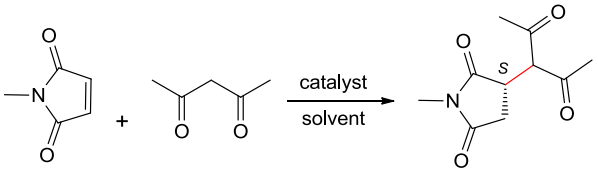
Table 3
Michael addition of cyclic β-ketoesters **10a–10d** to *N*-substituted maleimides catalyzed by **5**[a].

Entry	Product	Time (day)	*Conv* (%)[b]	*dr*[c]	*ee* (%)[c]
1	**11aa**	3	78 (70)	>99/1	96
2	**11ba**	3	96 (88), 71[d]	>99/1	92, 95[e]
3	**11da**	3	84 (75)	99/1	96
4	**11ga**	3	36 (25), 27[d]	99/1	94, 96[e]
5	**11ab**	3	91 (80)	>99/1	94
6	**11bb**	3	95 (82)	99/1	92
7	**11bc**	5	75 (62), 33[d]	>99/1	91, 94[e]
8	**11ad**	7	72 (60)	>99/1	82

[a] *Reaction conditions:* 0.03 mmol (10 mol%) **5**, 0.3 mmol maleimide derivative, 0.4 mmol cyclic β-ketoester, 0.5 cm^3 $CHCl_3$, 70 °C.
[b] Conversion (*Conv*) determined by GC-FID with the yields of the purified products in brackets.
[c] *dr*: diastereomeric ratio and the enantiomeric excess (*ee*) of the major enantiomer pair determined by GC-FID, for the suggested configurations of the products see Scheme 2.
[d] Conversion (*Conv*) obtained in $PhCH_3$ + 10 mol% AcOH.
[e] Enantiomeric excess (*ee*) obtained in $PhCH_3$ + 10 mol% AcOH.

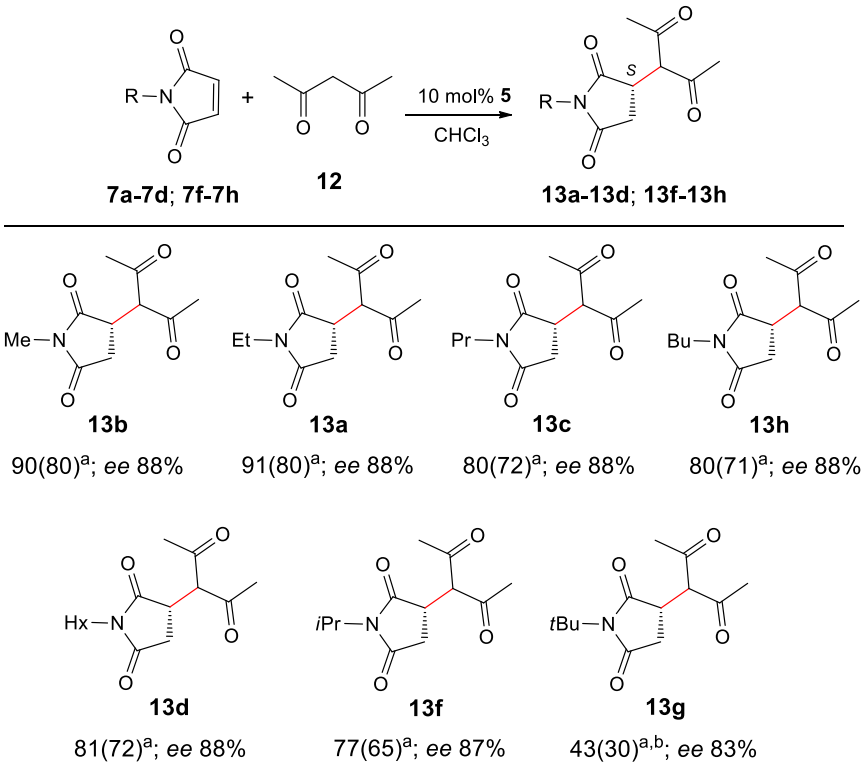
Motivated by the above stereoselectivities (*dr* and *ee*) and yields, reactions of other *N*-substituted maleimides and aliphatic β-ketoesters were examined using **5** as catalyst. Compounds obtained in these

Table 4
Asymmetric Michael addition of acetylacetone (**12**) to *N*-methylmaleimide (**7b**)[a].



Entry	Catalyst	Solvent	*Conv* (%)[b]	*ee* (%)[c]
1	**2**	$CHCl_3$	91	55
2	**3**	$CHCl_3$	78	53
3	**5**	$CHCl_3$	90 (80)[d]	88
4	**6**	$CHCl_3$	70	86
5[e]	**5**	$CHCl_3$	96 (87)[d]	88
6[f]	**5**	$CHCl_3$	62	89
7[g]	**5**	$CHCl_3$	59	91
8	**5**	$PhCH_3$	85	89
9	**5**	$PhCH_3$ + AcOH	89 (80)[d]	87

[a] *Reaction conditions*: 0.03 mmol (10 mol%) catalyst, 0.3 mmol **7b**, 0.6 mmol **12**, 0.5 cm^3 solvent, 70 °C, reaction time: 3 days.
[b] Conversion (*Conv*) determined by GC-FID.
[c] Enantiomeric excess (*ee*) determined by GC-FID.
[d] Yields of the product purified by flash chromatography.
[e] Reaction time: 5 days.
[f] Using 1 cm^3 $CHCl_3$ solvent.
[g] Reaction at rt for 7 days.

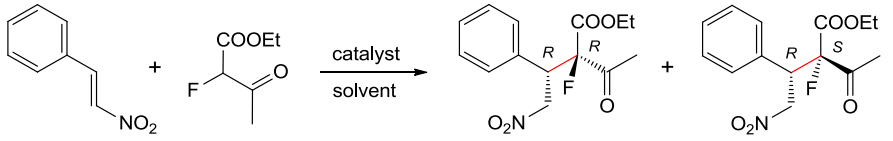


Scheme 3. Results obtained in the Michael addition of **12** to *N*-alkylmaleimides. *Reaction conditions*: 0.03 mmol (10 mol%) **5**, 0.3 mmol *N*-alkylmaleimide, 0.6 mmol **12**, 0.5 cm^3 $CHCl_3$, 70 °C, 3 days. [a] *Conv* (%) determined by GC-FID and yields (%) of the purified products in parenthesis. [b] Reaction time 5 days.

reactions are shown in Scheme 1. Additions of **8c** to **7a** carried out in CH_2Cl_2 at −20 °C using quinine or quinidine as catalysts showed the formation of the same enantiomer pair as major product which was obtained in the reaction promoted by **5**. In this reaction **5** afforded the same enantiomer in excess as resulted in that catalyzed by quinine and the opposite as obtained with quinidine. Based on these observations and reports of Melchiorre and co-workers [31,55] we suppose the formation of ethyl (*R*)−2-((3*S*)−1-ethyl-2,5-dioxopyrrolidin-3-yl)−2-methyl-3-oxobutanoate (*R,S*-**9ac**) enantiomer in excess. Similarly, in reactions of **7b** and **7e** with **8a** the same enantiomers were formed in excess with **5** as were obtained in reactions catalyzed by quinine. Accordingly, with catalyst **5** products with the configurations shown in Scheme 1 were obtained.

The additions catalyzed by **5** were carried out at 70 °C in both $CHCl_3$ and $PhCH_3$ + 10 mol% AcOH. Selected results are presented in Table 2. High *Conv* and *ee* values were reached in reactions of the fluorine derivative **8a** (products **9aa**−**9fa**) with the exception of the *N*-*tert*-butyl substituted maleimide **7g**, which was transformed in up to 67% (entries 14, 15) following three days, possibly due to the steric hindrance of the *tert*-butyl group. Although, the other *N*-substituted maleimides (Me, Et, Pr, Hx, Bn, *i*Pr) gave high *Conv*, the steric effect of the *N*-substituent was detected in this series as well. Thus, the *N*-Me compound **7b** needed only one day to reach over 80% *Conv* (entries 3, 4), whereas for the other *n*-alkyl derivatives (**7a, 7c, 7d**) two days were necessary to be transformed in high degrees. The *N*-benzylmaleimide (**7e**) was completely reacted in three days (entry 9), which allowed us to decrease the catalyst amount to

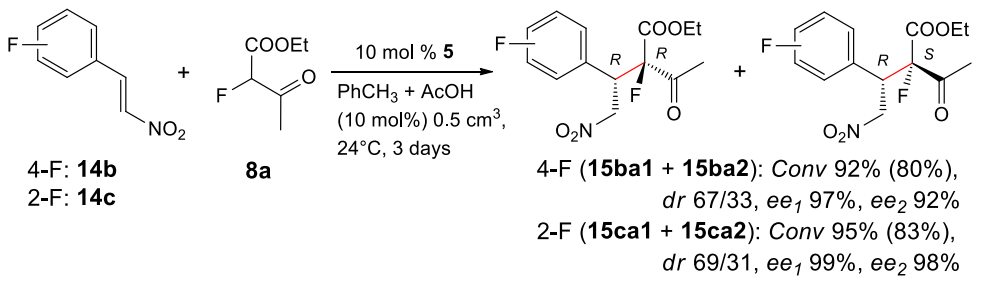
Table 5
Asymmetric Michael addition of **8a** to *trans*-β-nitrostyrene (**14a**) catalyzed by **5**[a].



14a **8a** **15aa1** **15aa2**

Entry	Solvent	Time (day)	*Conv* (%)[b]	*dr*[c]	ee_1; ee_2 (%)[d]
1	$CHCl_3$	4	86	65/35	96; 89
2	$PhCH_3$ + AcOH	4	96 (80)	68/32	98; 94
3	$PhCH_3$ + AcOH	3	95 (80)	68/32	98; 95
4	$PhCH_3$ + AcOH	2	82	67/33	98; 94
5	$PhCH_3$	2	55	68/32	95; 78
6[e]	$PhCH_3$ + AcOH	3	86	56/44	98; 97

[a] *Reaction conditions*: 0.03 mmol (10 mol%) **5**, 0.3 mmol **14a**, 0.4 mmol **8a**, 0.5 cm^3 solvent, 10 mol% AcOH when used, rt.
[b] Conversion (*Conv*) determined by GC-FID, in brackets the yield of the purified products (both diastereomers).
[c] Diastereomeric ratio, *dr*: the (**15aa1**+*ent*-**15aa1**)/(**15aa2**+*ent*-**15aa2**) ratio.
[d] Enantiomeric excesses (ee_1 *and* ee_2) by GC-FID, configurations of the excess enantiomers are assigned based on previous results [88].
[e] Using 0.03 mmol (10 mol%) **6** as catalyst.



Scheme 4. Products obtained by asymmetric Michael addition of **8a** to 4- and 2-fluoro-β-nitrostyrene (**14b, 14c**). *Reaction conditions:* see Table 5, entry 3, 0.3 mmol **14b** or **14c**. *Conv, dr, ee*$_1$ and *ee*$_2$ determined by GC-FID (isolated yields in parenthesis).

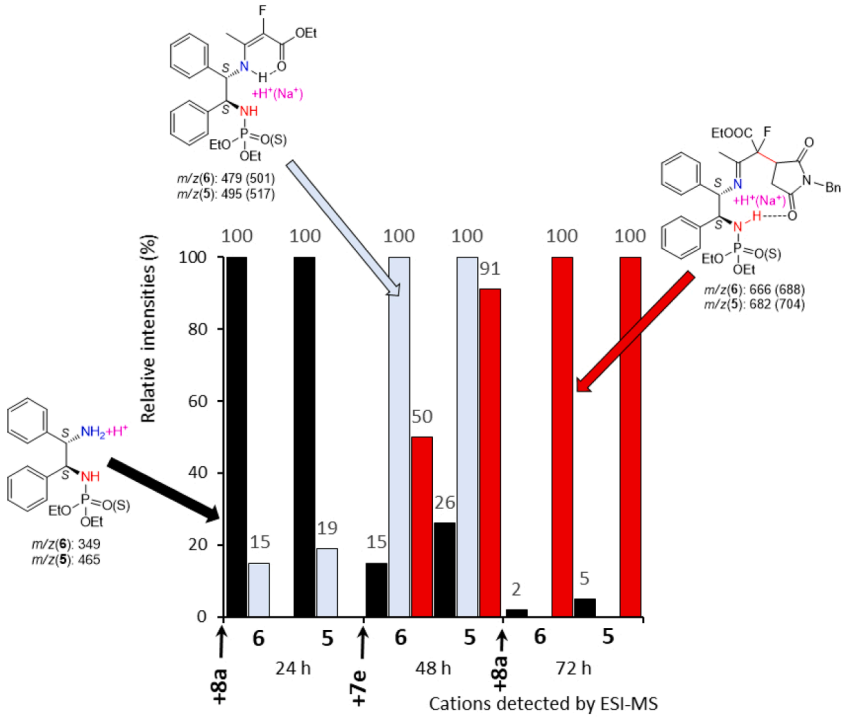


Fig. 3. Relative intensities of species detected by ESI-MS in mixtures of **7e** and **8a** in presence of **6** or **5**. *Conditions:* 0.5 cm^3 $CHCl_3$, 0.015 mmol **6** or **5**, 0.15 mmol **8a**, 24 h; addition of 0.15 mmol **7e**, 48 h; addition of 0.15 mmol **8a**, 72 h; ■: (**6** or **5**)+H^+, ■: enamines+H^+(Na^+), ■: imines+H^+(Na^+).

5 mol%. The α-branched *N*-isopropylmaleimide (**7f**) needed three days to obtain high *Conv* with 10 mol% catalyst. When compared to $CHCl_3$, similar or slightly better *Conv*s were reached in $PhCH_3$ + AcOH solvent (except **7d**).

The *Conv* of **7a** was negligible when ethyl 2-chloroacetoacetate (**8b**) was used as Michael donor, even with two equivalents (eq.) of the nucleophile and after one week reaction (entry 16). We observed a very significant solvent effect in the addition of ethyl 2-methylacetoacetate (**8c**) to **7a**, which needed two eq. **8c** and one-week long reaction. While only 9% of the starting material was converted in $CHCl_3$, the *Conv* reached 55% in $PhCH_3$ + 10 mol% AcOH. In the latter solvent the *ee* was also better (95% *vs* 66%) (entries 17, 18). Reactions with the latter two nucleophiles showed, that the α-substituents have a significant steric influence on the rate of these Michael additions.

According to the above results thiophosphoramide **5** is a highly effective chiral organocatalyst in the addition of the α-fluoro-β-ketoester **8a** to maleimides, however, reactions of the α-chloro and α-methyl derivatives **8b** and **8c** were sluggish. To further explore the applicability of this bifunctional chiral organocatalyst, next, we examined conjugate additions of cyclic β-ketoesters **10a**–**10d** (Scheme 2). Similarly with the reactions of alicyclic β-ketoesters, in reactions of **7a** with **10a** the same enantiomer was formed in excess as obtained with quinine and opposite with that resulted with quinidine. Thus, we suggest that using **5** the methyl (*R*)−1-((3*S*)−1-ethyl-2,5-dioxopyrrolidin-3-yl)−2-oxocyclopentanecarboxylate (*R,S*-**11aa**) is formed in excess. Accordingly, the configurations of the products are those shown in Scheme 2, assuming that the attack of the nucleophiles occur from the same face of the maleimides in each reaction.

We have carried out these reactions in both previously used solvents, however, under identical conditions the *Conv* of the maleimides were higher in $CHCl_3$. Results obtained in these experiments are summarized in Table 3. Although, the *dr* values in the two solvent systems were identically high, in a few reactions the enantioselectivities obtained in $PhCH_3$ + 10 mol% AcOH were better than in $CHCl_3$, accordingly, these results were also included in Table 3.

Under the given conditions all the investigated maleimides reacted with 2-oxocyclopentanecarboxylates **10a** or **10b** providing the corresponding adducts in good yields after three days (entries 1–3, 5, 6), with the exception of **7g**. In the latter reaction (entry 4), the detrimental steric influence of the *tert*-butyl group led to lower conversion, similarly as in the reaction with **8a**. The stereoselectivities of these reactions were excellent. Remarkably, close to the exclusive formation of one

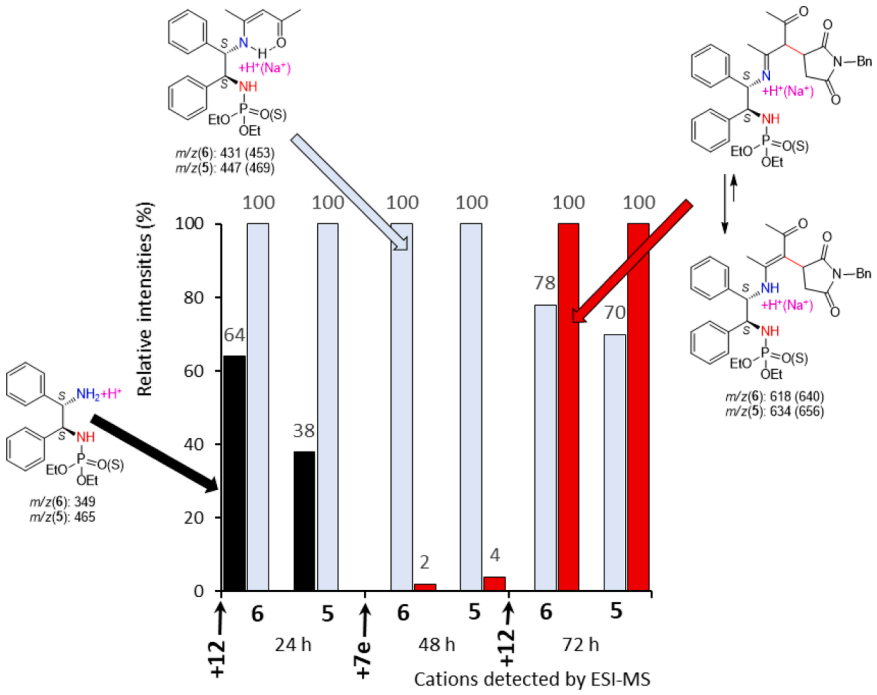


Fig. 4. Relative intensities of species detected by ESI-MS in mixtures of **7e** and **12** in presence of **6** or **5**. *Conditions:* 0.5 cm^3 $CHCl_3$, 0.015 mmol **6** or **5**, 0.15 mmol **12**, 24 h; after 24 h addition of 0.15 mmol **7e**, 48 h; after 48 h addition of 0.15 mmol **12**, 72 h;■: (**6** or **5**)+H^+, : enamines+H^+(Na^+), imines(−enamine) adduct+H^+(Na^+).

enantiomeric pair was detected (*dr* 99/1 or better) and the enantioselectivities were also high (92–96%), the lowest values were obtained in reactions of the *N*-methyl derivative **7b**.

Using ethyl 2-oxocyclohexanecarboxylate (**10c**) as Michael donor longer time was required to reach good *Conv*, nevertheless, the *dr* and

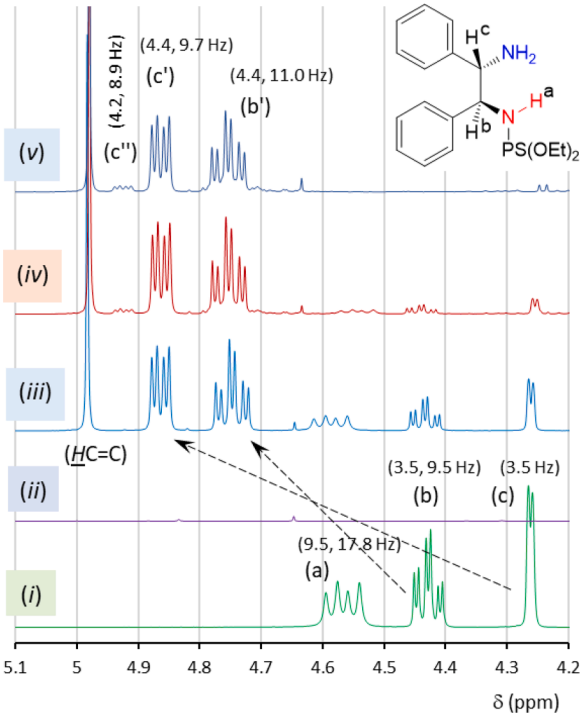


Fig. 5. Selected parts of the ^{1}H-NMR spectra of: 0.03 mmol **5** in 0.5 cm^3 $CDCl_3$ (*i*); 0.033 mmol **12** (*ii*); 0.03 mmol **5** + 1.1 eq. **12** after 24 h (*iii*); + 1.1 eq. **7b** to the previous sample after 24 h (*iv*); further addition of 1.1 eq. **12**, 24 h (*v*); in parenthesis are the coupling constants, *J*.

the *ee* were not affected by the ring size (entry 7). Even less reactive was the α-acetylbutirolactone (**10d**), which gave 72% *Conv* of **7a** in one week, moreover, the product **11ad** was obtained with lower enantioselectivity, though similarly high *dr* (entry 8). Finally, one can see that **5** is an efficient organocatalyst for the asymmetric Michael addition of cyclic β-ketoesters to maleimides, which may provide the corresponding adducts diastereoselectively and in high optical purities, exceeding the *dr* values obtained using cinchona alkaloids and affording similar *ees* without cooling the reactions [31].

2.2. Addition of acetylacetone (2,4-pentanedione) to maleimide derivatives

We continued our study by attempting the use of the primary amine–(thio)phosphoramide bifunctional catalysts (**2, 3, 5, 6**) in the addition of a simple β-diketone, *i.e.* acetylacetone (**12**), to *N*-substituted maleimides. Similarly, with the study using **8a**, initially, we investigated the effect of the catalyst structure and that of the reaction conditions. Selected results obtained in the reaction of **12** with **7b** are summarized in Table 4.

Our initial reactions were carried out under conditions also employed in the addition of **8a** (solvent: $CHCl_3$ 0.5 cm^3, 70 °C, 3 days, entries 1–4). Both thiophosphoramides (**2** and **5**) led to close to complete transformation of **7b**, whereas phosphoramides **3** and **6** afforded lower *Conv*s. Catalysts with cyclohexane backbone (**2** and **3**) were much less enantioselective, compared to those having 1,2-diphenylethane skeleton. Compound **5** afforded the best *ee* (88%, entry 3). Under the same conditions as applied by Chimni and co-workers using dihydroquinine as catalyst [64], we obtained the same enantiomer in excess as with **5**. Thus, we assign the configuration of **13b** to be *S*. By increasing the reaction time (5 days, entry 5) the *Conv* could be improved up to 96% without a change in the *ee*. As the amount of solvent was doubled, the *Conv* decreased without significant modification in the *ee* (entry 6). In the reaction carried out at rt better *ee* was obtained than at 70 °C, however, the *Conv* was low even after 7 days (entry 7). Applying $PhCH_3$ as solvent either in the absence or in the presence of 10 mol% AcOH led

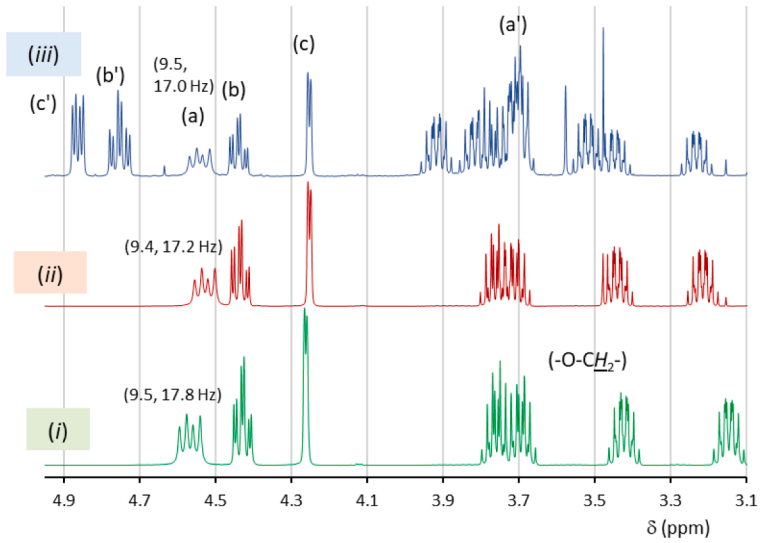


Fig. 6. Selected areas of ^{1}H-NMR spectra of 0.03 mmol **5** in 0.5 cm^3 $CDCl_3$ (*i*); 0.03 mmol **5** + 1.1 eq. **7b** after 24 h (*ii*); and addition of 1.1 eq. **12** to the previous sample after 24 h (*iii*); in parenthesis are coupling constants.

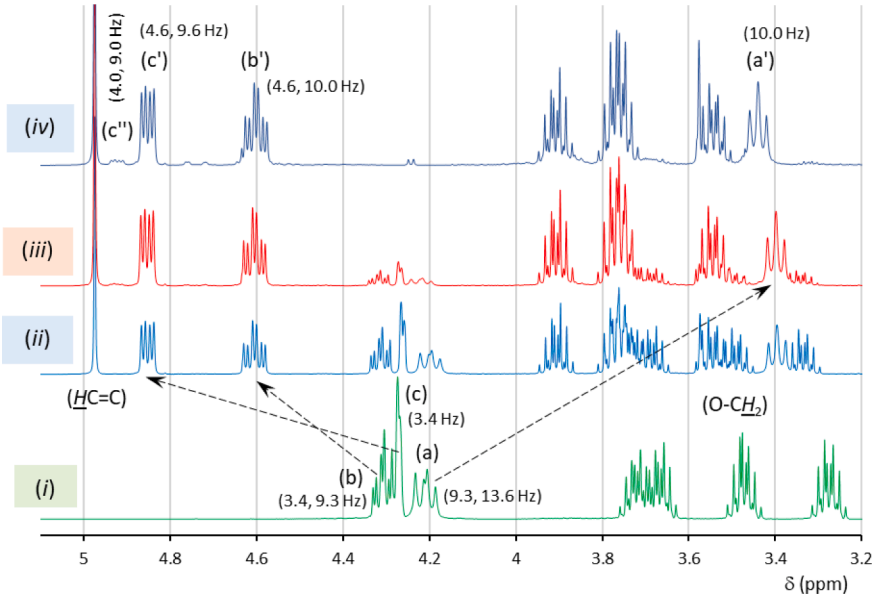


Fig. 7. Selected parts of ^{1}H-NMR spectra of 0.03 mmol **6** in 0.5 cm^3 $CDCl_3$ (*i*); 0.03 mmol **6** + 1.1 eq. **12** after 24 h (*ii*); + 1.1 eq. **7b** to the previous sample after 24 h (*iii*); and further addition of 1.1 eq. **12** and standing 24 h (*iv*); in parenthesis are coupling constants.

to similar results as obtained in $CHCl_3$ (entries 8, 9).

Based on these observations, reactions of **12** with other *N*-substituted maleimides (**7a-7d, 7f-7h**) using catalyst **5** were performed in $CHCl_3$ (Scheme 3). It is reasonable to assume that in all these reactions the *S* enantiomers were formed in excess. For comparison, reactions carried out in toluene + 10 mol% AcOH were also examined (see supplementary material (SM), Table SM1), however, similar or somewhat lower *Conv*s were obtained, whereas the *ee* values were close to those reached in $CHCl_3$. Increase in the length of the *N*-alkyl substituent from Me or Et to longer chain such as Pr, Bu, Hx led to a decrease in the *Conv* with about 10%, however, all these derivatives gave the products with equally good enantioselectivities (*ee* 88%). Further decrease in *Conv* was detected in reactions of maleimides substituted with α-branched alkyl groups. The presence of the *i*Pr group slightly decreased the degree of the transformation of the maleimide **7f** without significantly altering the *ee*, whereas the *tert*-butyl substituted **7g** was converted in a much lower amount (43%) after 5 days and the *ee* also decreased to 83%.

The above results obtained using acetylacetone as nucleophile confirmed that the thiophosphoramide derivative of 1,2-diphenylethane-1,2-diamine is an efficient organocatalyst for the asymmetric Michael addition of a β-diketone as well. However, similar to the reactions of β-ketoesters, bulky *N*-substituents may have detrimental steric effects both on the *Conv* and the stereoselectivities.

2.3. Addition of ethyl 2-fluoroacetoacetate (**8a**) to β-nitrostyrene derivatives

Owing to the practical importance of the functionalized optically pure nitroalkanes, which are versatile pharmaceutical intermediates [81–83], and the special properties of fluorine-containing compounds, next we examined the catalytic performance of **5** and **6** in the asymmetric Michael addition of ethyl 2-fluoroacetoacetate (**8a**) to

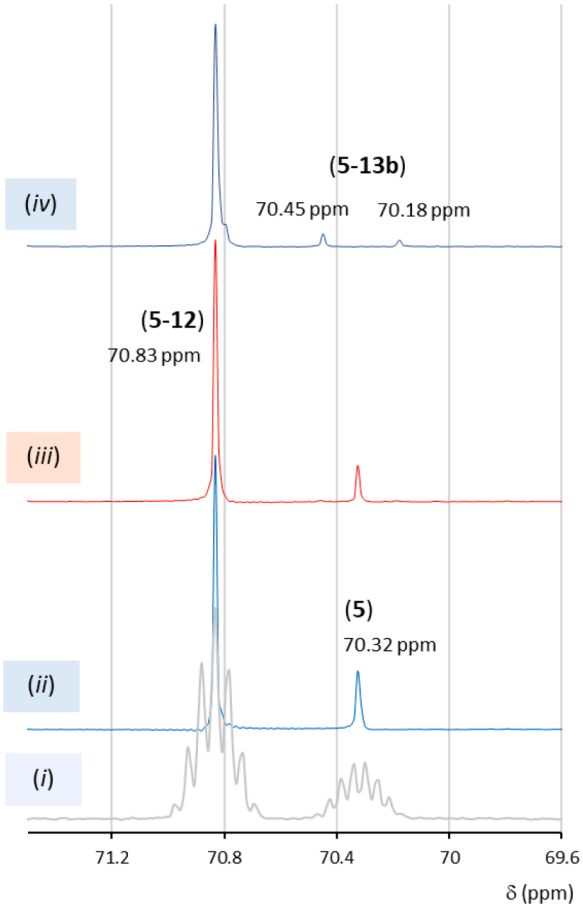


Fig. 8. ^{31}P-NMR spectra of 0.03 mmol **5** and 0.033 mmol **12** in 0.5 cm^3 $CDCl_3$ after 24 h (*i*); and the ^{1}H decoupled spectrum (*ii*); the ^{1}H decoupled spectrum of the sample obtained by addition of 0.033 mmol **7b** to the previous sample, 24 h (*iii*); and by further addition of 0.033 mmol **12**, 24 h (*iv*).

trans-β-nitrostyrene (**14a**). The organocatalytic asymmetric addition of 1,3-dicarbonyl compounds to **14a** also requires bifunctional catalysts bearing both Hb donor and acceptor groups [18,81]. The few enantioselective additions of 2-fluoro-1,3-dicarbonyl compounds to nitrostyrenes reported until now (with one exception) used chiral organocatalysts bearing tertiary amine basic groups [84–90]. It was reported that primary amines also catalyze the addition of 1,3-dicarbonyl compounds to nitrostyrene through the deprotonation-based mechanism, as a non-selective, competing bypass to that occurring stereoselectively through enamine intermediate [91]. Due to the fast formation of the enamine intermediate in the above examined reactions, we hoped that these catalysts may be efficient in transformations of nitrostyrenes as well.

To our delight, thiophosphoramide **5** performed well in the reaction of **8a** with **14a**. Selected results obtained in our short optimization study are summarized in Table 5. At rt the *Conv* of **14a** was higher in $PhCH_3$ + 10 mol% AcOH compared to $CHCl_3$ (entries 1, 2), in the former solvent 95% and over 80% conversions were achieved in 3 and 2 days, respectively (entries 3, 4). The *dr* and the *ee* values also increased in $PhCH_3$ + 10 mol% AcOH compared to $CHCl_3$. Increasing the temperature had detrimental effect on the *ee* (not shown), whereas without the addition of AcOH both the *Conv* and the *ee* decreased (entry 5). Phosphoramide **6** was less active compared to **5**, in addition lower *dr* was obtained (entry 6).

The optimized catalytic system, *i.e.* 10 mol% **5**, $PhCH_3$ + 10 mol% AcOH, rt, also proved to be effective in the transformation of two fluorine substituted β-nitrostyrenes, **14b** and **14c** (Scheme 4). Michael additions of **8a** to these derivatives gave the expected **15ba** and **15ca** products in high yields, and similar *dr* and *ee*s, as were reached in the reaction of the unsubstituted **14a**. Thus, the stereoselective synthesis of chiral nitro compounds having ~~a~~ fluorine substituted quaternary carbon atom and additionally bearing fluorine substituted phenyl moieties was also possible.

2.4. Examination of the reaction intermediates

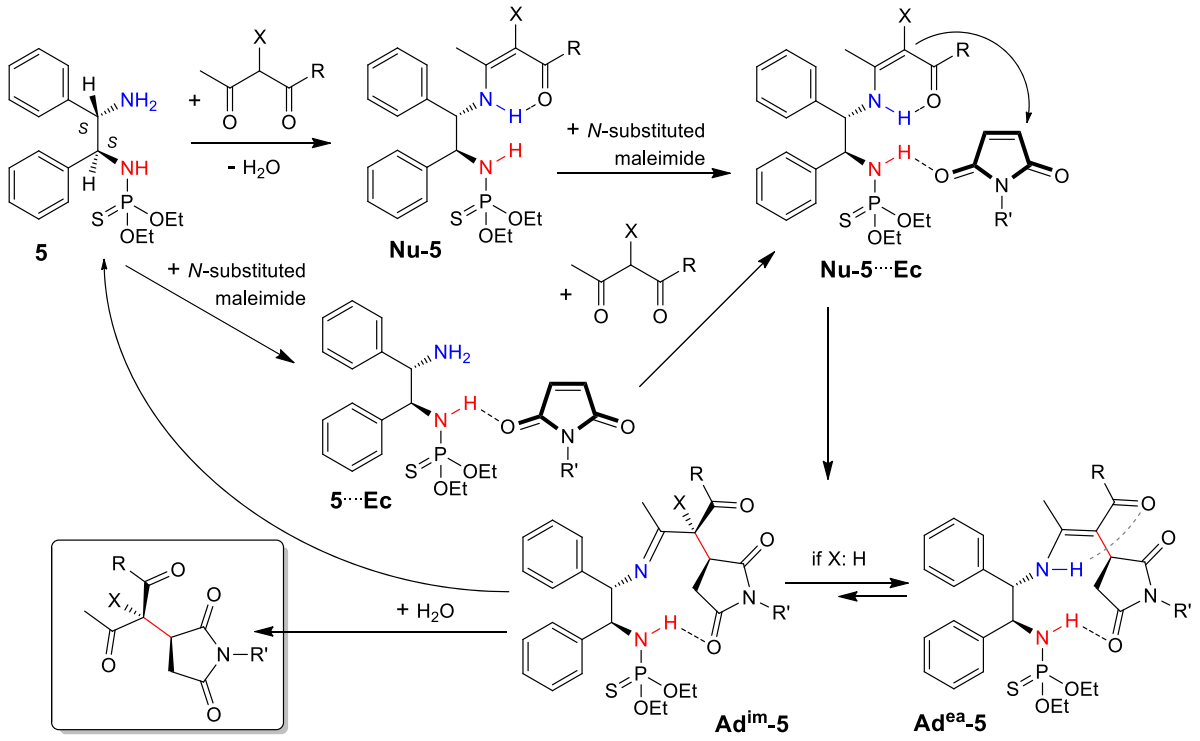
The Michael additions of aldehydes and ketones studied using primary amine–(thio)phosphoramides occur through enamine intermediates, evidenced by detecting the catalyst-aldehyde enamine by electrospray-ionization mass spectrometry (ESI-MS) [51]. However, the asymmetric Michael additions of malonates, β-ketoesters or β-diketones to activated olefins are catalyzed by tertiary or secondary amines through deprotonation-based mechanisms [18,31,32]. In their report, Portnoy and co-workers suggested that the moderate *ee* obtained in the addition of β-ketoesters or β-diketones to β-nitrostyrene catalyzed by primary amine bifunctional catalysts is due to both mechanistic pathways being active [91]. In order to investigate the intermediates through which the addition of these nucleophiles react with maleimides using the organocatalysts applied in this study, we examined the species formed in mixtures of **5** or **6** with **8a** or **12** and **7e** by ESI-MS measurements. The obtained spectra are presented in Figs. SM1-SM14, and the results are summarized in Figs. 3 and 4.

Both catalysts (**5** and **6**) were transformed in low amounts to enamines in the presence of **8a** following 24 h (Fig. 3). The addition of the maleimide **7e** to these solutions after another 24 h resulted in low amounts of catalysts remained unreacted, instead, the enamine and the imine intermediates were detected. Although the remaining amount of **5** was higher than that of **6**, the intensity of the imine formed with the former was almost twice compared to **6**. In another 24 h following addition of **8a** (72 h) the enamines were completely consumed and the imine intermediates were obtained.

In contrast, the addition of **12** to **5** or **6** resulted in the formation of enamines in high proportions following 24 h, especially in the case of the thiophosphoramide **5** (Fig. 4). Addition of the maleimide **7e** to these solutions following another 24 h resulted in the consumption of the catalysts, however, only small amounts of imines were formed. It should be noted, that in reactions of **12**, the equilibrium of the possible imine-enamine isomerization is probably shifted to the latter intermediates. Following another day and repeated addition of **12**, the catalyst-bonded adducts were more abundant compared to the enamines, although, in contrast with **8a**, the latter were also detected in significant relative abundances. Again, the enamine formed with **5** was transformed in imine–enamine adduct in a slightly higher proportion compared to **6**.

Accordingly, these reactions occur through enamine intermediates using these primary amine bifunctional organocatalysts. Correlation between the rate of transformation of the enamines to imine(–adduct enamine) intermediates detected by ESI-MS and the reactivity of the 1,3-dicarbonyl compound in the Michael addition was also observed. However, we still could not rule out the deprotonation-type pathway, as the addition of acid necessary to detect cations by ESI-MS measurements may obscure the observation of weaker interactions. To gain more insight on interactions occurring between substrates with catalysts and to identify the intermediates, we carried out an NMR spectroscopic study using close to one equivalent of the simplest reactants **12** and **7b** in mixtures with either **5** or **6**. Parts of the ^{1}H-NMR spectra obtained in this study using the bifunctional catalyst **5** are shown in Fig. 5 (full spectra were included in the SM, Figs. SM20-SM25). Identification of signals in the ^{1}H-NMR spectrum of **5** was aided by 2D NMR spectroscopy (see Figs. SM15-SM19).

Addition of **12** to the solution of **5** resulted in the shift of a significant ratio of signals (a: dd 4.57 ppm, b: dtr 4.43 ppm and c: d 4.26 ppm; dd: double doublet, dtr: double triplet, d: doublet) corresponding to hydrogens P-N*H*, *H*C—NP and *H*C—NH_2. The shifted signals were denoted as b' (4.75 ppm) and c' (4.86 ppm). The a' (~3.73 ppm) is not shown in



Scheme 5. Probable reaction pathways and reaction intermediates in the asymmetric Michael addition of 1,3-dicarbonyl compounds to maleimides catalyzed by the bifunctional catalyst **5** (**Nu**: nucleophile, **Ec**: electrophile, **Ad^{im}** and **Ad^{ea}** the imine and enamine form of the adduct intermediate).

Fig. 5, as it was found superimposed with the OC*H*$_2$ signals, however, its presence is indicated by the integral values. According to the spectrum of **12**, the enol/keto ratio in $CDCl_3$ solution was 85/15. The signal of the enolic –OH (broad singlet at 15.45 ppm) in the presence of **5** disappeared and a doublet at 11.51 ppm developed (Figs. SM21, SM25) having identical integral value with signals b' and c' and coupled with c' (J = 9.7 Hz). Moreover, the singlet corresponding to *H*C═C (5.50 ppm) decreased and a singlet equal with the b' or c' signals appeared at 4.98 ppm. Based on these changes the new set of signals may be assigned to a compound formed by reaction of **12** with **5**, *i.e.* the enamine **5**–**12**. The ratio of **5**–**12**/**5** was 74/26 after 24 h (Fig. 5 (*iii*) and Fig. SM21). Both OC*H*$_2$ and the C*H*$_3$ signals were also shifted to higher δ values and changes in the aromatic region were also detected in the spectrum of **5**–**12** compared to that of **5**.

The addition of **7b** to the above solution led to more extensive transformation of **5** following an additional 24 h, as shown by the 89/11 ratio of the b'/b or c'/c signals (Fig. 5(*iv*) and Figs. SM22, SM24). A small amount of another product also appeared, indicated by the well-resolved c" dd (c"/c' 7/93). This is suggested to be the enamine **5**–**13b**, as a new doublet, possibly corresponding to enamine-N*H* at 13.17 ppm coupled with c" (J = 8.9 Hz) also appeared. The addition of another 1.1 eq. **12** after 24 h led to the complete disappearance of **5**, increase in the c"/c' ratio to 11/89 along with increase in the intensity of the enamine-N*H* signal at 13.17 ppm (Fig. 5(*v*) and Figs. SM23-SM25).

Similar to the ESI-MS results, these spectra showed the formation of enamines **5**–**12** and **5**–**13b**, however, other interactions between the reactants and catalyst were not detected. In our attempt to further investigate weak interactions, we examined the spectrum obtained by mixing initially **5** and **7b** (Fig. 6 and Figs. SM26, SM27). In this solution slight shift of the signal (a) from 4.57 ppm to 4.53 ppm and to 4.54 ppm following addition of **12** was detected. Moreover, the $^3J_{HP}$ coupling constant also slightly changed (from 17.8 to 17.2 and 17.0 Hz, respectively). This indicates that the *H*N-P interacts with the maleimide, possibly by Hb-ing. The supposed interaction is confirmed by the shifted signals corresponding to the POC*H*$_2$– hydrogens to higher δ values. Addition of **12** to the above solution led to a similar transformation of **5** to enamine, as was detected previously, however, in a lesser amount (**5**–**12**/**5** 57/43). Thus, the presence of the maleimide affected the formation rate of the enamine, which may be due to the above-suggested Hb-ing to the catalyst.

Examination of the interaction of **6** with **12** led to similar results as that of **5**, as shown in Fig. 7 (see also Figs. SM28-SM32). Fortunately, in these experiments, the signal (a') was sufficiently resolved, thus, we could determine the shift and couplings of the *H*N-P in the formed enamine. The triplet at 3.40–3.44 ppm shows modifications of the coupling constants of this hydrogen with both the *H*C—NP (b') and phosphorus, which indicates a distortion of the H–C–N–H dihedral angel. After 24 h in the solution of **6** and **12** the enamine was formed in lower amount compared to **5**, as calculated from the (b'+c')/(b + c) ratio, 58/42 (used because the b and c signals were slightly merged). The appearance of the enamine formed with the participation of the adduct is also detected (Fig. 7(*iv*)), shown by the c" and *H*N—C=C at 13.22 ppm signals coupled with J = 9.0 Hz. However, the c"/c' ratio was slightly smaller (8/92), than that obtained in the corresponding experiment using **5**.

Transformations of the bifunctional catalysts **5** and **6** were also evidenced by the ^{31}P-NMR spectra recorded during the above investigations (see Fig. 8 and Figs. SM33-SM38). The multiplet appeared at 70.83 ppm in the ^{31}P-NMR spectrum of the mixture of **5** and **12** following 24 h is assigned to the phosphorus atom in the **5**–**12** enamine (*i*), which also appears as a sharp singlet in the ^{1}H-decoupled spectrum (*ii*). Decrease or disappearance of the signal at 70.32 ppm and the relative increase of that at 70.83 ppm after 48 or 72 h (Fig. 8 (*iii*) and (*iv*)), showed the transformation of **5**. After 72 h additional peaks appeared at 70.45 and 70.18 ppm, due to the formation of the C–C coupled imine-enamine **5**–**13b**. Similarly, using **6** the formation of the enamine was also detected though in lower ratio as in experiments applying **5**, as indicated by the shift of the ^{31}P signal from 7.59 to 7.12 ppm (Figs. SM36-SM38), in accordance with the results of the ^{1}H-NMR experiments.

According to the above ESI-MS and NMR investigations, the catalyst is transformed to the corresponding enamine by reaction with the nucleophile (Scheme 5, **Nu-5**). The rate of formation of this intermediate depends on the structure of the 1,3-dicarbonyl compound, **12** was faster converted compared to **8a**. We could not detect the presence of intermediates resulted by protonation of the amine by the nucleophiles, which should form according to the deprotonation-type mechanism. However, both the enamine and the phosphoramide groups may act as Hb donors. Judging from the acidity order of these groups, the formation of Hb shown in structure **Nu-5** is probable, being similar with the intramolecular Hb that stabilizes the enol form of **12**. In the mixture of the maleimide and the catalyst, a hydrogen-bonded catalyst-electrophile complex (**5**···**Ec**) was detected. Accordingly, the formation of this intermediate may precede that of the enamine, which is further transformed to **Nu-5**···**Ec**. The nucleophilicity of the enamine will determine the rate of formation of the C−C bond leading to the imine-(adduct-enamine) intermediate. Thus, the transformation of the **8a**-**5**···**Ec** involves the attack of a stronger nucleophile compared to **12**–**5**···**Ec** and as a result reactions of **8a** are faster than those of **12**. This is well illustrated by the relative intensities detected by ESI-MS. The direction of this attack probably is not influenced by the structure of the 1,3-dicarbonyl compound, always occurring from the same face of the anchored maleimide. However, steric effects may play a significant role in determining the rate of C−C bond formation, as shown by the lower rates obtained in reactions of **8b**. The difference in the performance of the two catalysts, **5** and **6**, could be due to the acidity-difference of the phosphoramide compared to the thiophosphoramide group, the latter affording a more strongly activated olefin, due to its higher acidity (which is evidenced by the difference in the δ value of the *H*N-P hydrogens of the two compounds in the ^{1}H-NMR spectra). Finally, hydrolysis of the imine intermediate (Scheme 5, **Ad^{im}-5**) leads to the formation of the product and regeneration of the organocatalyst.

3. Conclusions

The recently reported chiral primary amine−(thio)phosphoramide bifunctional organocatalysts obtained from optically pure 1,2-diamines, used in the asymmetric addition of aldehydes and ketones to maleimides, were tested in the Michael addition of 1,3-dicarbonyl compounds. By optimizing the reaction conditions using ethyl 2-fluoroacetylacetate and *N*-ethylmaleimide high enantioselectivities, conversions and yields were reached accompanied by good diastereoselectivities using the 1,2-diphenylethane-1,2-diamine derived thiophosphoramide. The scope of the reaction was extended on the Michael addition of this β-ketoester to various *N*-substituted maleimides. The use of cyclic β-ketoesters as Michael donors afforded the products in excellent diastereoselectivities, without significantly altering the enantioselectivity of the reactions, though needed slightly longer times to reach high conversions. Longer reactions were necessary to transform *N*-substituted maleimides in reactions with acetylacetone. Should be stressed out that higher enantioselectivities were obtained in most reactions than with the often used tertiary amine cinchona alkaloid organocatalysts without decreasing the reaction temperature below ambient values. The (thio)phosphoramides were also used in the addition of ethyl 2-fluoroacetylacetate to nitrostyrene derivatives, affording high yields and enantioselectivities, accompanied by moderate diastereoselectivities.

The interpretation of the results obtained in these reactions was aided by ESI-MS and NMR investigation of reactants and catalyst mixtures, which showed that these occur through enamine formation. This reaction path and the lack of the concurrent path by deprotonation ensures high stereoselectivities in reactions catalyzed by the bifunctional primary amine organocatalysts. Differences in the reactivities of the nucleophiles were interpreted by the rate of formation of the adduct bonded to the catalyst as imine or enamine, which diverge from the rate of formation of the catalyst-nucleophile enamine intermediate. According to the results of these investigations, we suggested a plausible reaction path, through which these reactions occur. Most important, the obtained results showed that the asymmetric Michael additions of 1,3-dicarbonyl compounds may be catalyzed efficiently by primary amine−hydrogen bond donor bifunctional organocatalysts, unprecedented yet in reactions of *N*-substituted maleimides.

4. Experimental

4.1. Materials

Optically pure 1,2-diamines (**1, 4**) were purchased from Sigma-Aldrich, their derivatives (**2, 3, 5** and **6**) were prepared as described in our previous publication [51]. *N*-substituted maleimides were either commercial products (**7a, 7b, 7e**, 7 g) or were prepared by a slightly modified literature procedure (**7c, 7d, 7f**, 7 h), as described in SM [92]. 1,3-Dicarbonyl compounds (**8a** – **8c, 10a** – **10d, 12**) and β-nitrostyrene derivatives (**14a** – **14c**) were used as received from the supplier (Sigma-Aldrich). Analytical grade solvents, reagents and additives were obtained from commercial sources and used without further purification.

Reaction products were analyzed by gas-chromatography using Agilent Techn. 6890 N GC – 5973 MSD equipped with a 30 m HP-1MS column for mass spectrometric identification of the Michael adducts and Agilent 7890A GC–FID chromatograph equipped with chiral capillary columns (Cyclosil-B, 30 m, J&W or Hydrodex g-TBDAc, 25 m, Macherey-Nagel). Reaction products were isolated by flash chromatography on silica gel 60 (40–63 μm) using Kieselgel-G (Merck Si 254 F) thin-layer to check the purity of fractions. NMR spectra of the isolated products and that of the mixtures used to examine the intermediates were acquired on a Bruker Ascend 500 spectrometer in $CDCl_3$. The ESI-MS investigations were carried out using LCQ Fleet Ion Trap LC/MS (Thermo Sci.) instrument with direct injection of samples diluted and acidified with acetic acid.

4.2. Asymmetric Michael additions: general procedure

The Michael additions were carried out in 4 cm^3 closed vials immersed in a pre-heated oil bath. In a typical run, the organocatalyst was dissolved in the given amount of solvent (0.5 cm^3 unless otherwise noted) followed by the addition of 0.3 mmol *N*-substituted maleimide and the required amount of 1,3-dicarbonyl compound (0.4 or 0.6 mmol). The vial was immersed in the oil bath and the solution was stirred magnetically (600 rpm). Following the given reaction time the reaction was quenched by addition of 1 cm^3 saturated aqueous NH_4Cl, the organic phase was separated, the aqueous phase was washed three times with 1 cm^3 $CHCl_3$ or ethyl acetate (depending on the solvent used in the reaction), the unified organic phases were dried over Na_2SO_4 and the solution was analyzed by GC-MSD and GC-FID using *n*-decane as internal standard. Conversions (*Conv* (%)), diastereomeric ratios (*dr*) and enantiomeric excesses (*ee* (%)) were calculated based on relative concentrations determined by GC-FID using the formulae given in SM. The solvent was evaporated and the products purified by flash chromatography for determination of the yields as indicated in SM. The purified products were characterized by NMR spectroscopy. Configurations of the products were assigned based on GC-FID analysis of products obtained in reactions using quinine, quinidine or their dihydro-derivatives as organocatalysts under conditions given in literature reports [31,55,64,88].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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