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PAPER

Thiourea catalyzed organocatalytic enantioselective Michael addition of diphenyl phosphite to nitroalkenes†

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Bifunctional thiourea catalyzes the enantioselective Michael addition reaction of diphenyl phosphite to nitroalkenes. This methodology provides a facile access to enantiomerically enriched β-nitrophosphonates, precursors for the preparation of synthetically and biologically useful β-aminophosphonic acids. DFT level of computational calculations invoke the attack of the diphenyl phosphite to the nitroolefin by the *Re* face, this give light to this scarcely explored process update in the literature. The computational calculations support the absolute configuration obtained in the final adducts.

Introduction

Due to the immense progress in the scientific community, the claim in the organic synthesis has been shifted to the design and synthesis of more complex structures and important targets making essential the search for new methods and new efficient processes.[1] Organocatalysis has emerged as a powerful tool and as an efficient solution for the rapid and stereoselective construction of significant chiral entities.[2,3] In the last decade, the enantioselective synthesis of α- and β-aminophosphonic acids and their phosphonate esters has received significant attention owing to their biological activities as structurally analogues to α- and β-amino acids.[4,5] It is not surprising that the absolute configuration of the stereogenic α- or β-carbon in these phosphonyl compounds strongly influences their biological properties.[6] In this context, great efforts have been focused toward the development of excellent asymmetric methods for the synthesis of enantiomerically pure α-aminophosphonic acids.[5,7] However, the strategies for the synthesis of β-aminophosphonic acids has been less studied[4] and only a few examples based in organocatalytic protocols have been scarcely investigated to date.[8] The Michael addition of phosphorus compounds to nitroolefins provides a straightforward and convenient method for synthesizing P–C bonds.[9,10] Two interesting and pioneer organocatalytic enantioselective methods concerning Michael addition of diphenyl phosphite have been reported using chiral guanidine **1** and quinine **2** (Fig. 1).[8a,b] Very recently, Rawal and co-workers reported the Michael addition of phosphite to nitroalkenes catalyzed by squaramide **3**.[8c] Therefore, the development of new and efficient catalytic methodologies to obtain β-nitrophosphonates are still of remarked importance. Among the great number of organocatalysts developed until now, thioureas/ureas have attracted a great attention in the scientific community from pioneering examples reported by Curran and co-workers,[11] as suitable catalysts for a great number of efficient processes.[12] Herein, we report the organocatalytic enantioselective Michael addition of diphenyl phosphites to nitroolefins affording β-nitrophosphonates enantiomerically enriched using bifunctional thiourea **4a**. Michael adducts could be further conveniently transformed to chiral β-aminophosphonic acids following the procedures previously reported in the literature.[8a,b]

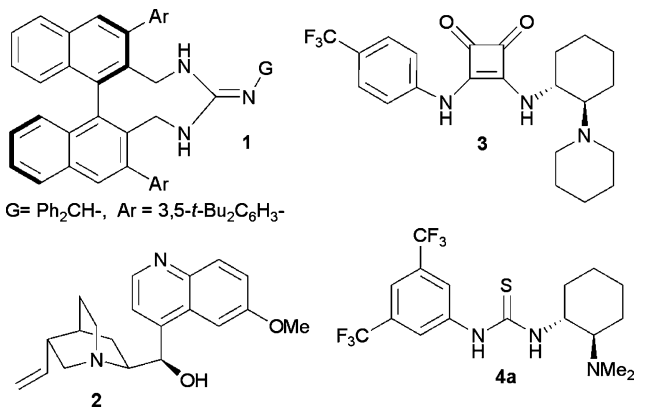

Fig. 1 Catalysts employed in the phospha-Michael addition reaction.

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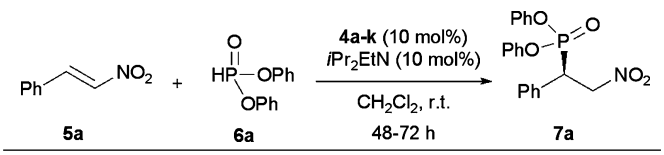
Table 1 Screening of thiourea catalysts **4a–4k**[a]



5a 6a 7a

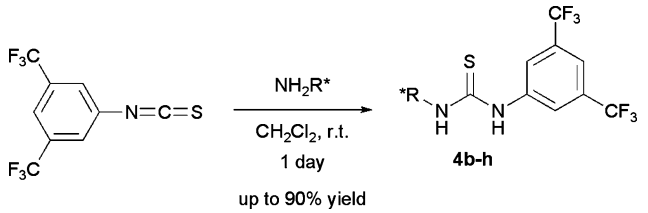
Entry	catalyst	yield (%)[b]	ee (%)[c]
1[d]	**4a**	90	70
2	**4b**	67	5
3	**4c**	67	Rac.[e]
4	**4d**	78	3
5	**4e**	63	Rac.[e]
6	**4f**	50	Rac.[e]
7	**4g**	60	Rac.[e]
8[d]	**4h**	86	9
9	**4i**	45	Rac.[e]
10	**4j**	79	Rac.[e]
11	**4k**	76	Rac.[e]

[a] *Experimental conditions*: To a solution of nitroalkene **5a** (0.4 mmol) and corresponding catalyst **4a–k** (10 mol%) in CH_2Cl_2 (1 mL), iPr_2EtN (10 mol%) and diphenyl phosphite **6a** (0.4 mmol) were added at room temperature. [b] After isolation by column chromatography. [c] Determined by chiral HPLC analysis (Chiralpak IA). [d] Reaction performed in absence of iPr_2EtN. [e] Racemic sample.

Results and discussion

Based on our experience using thiourea catalysts[13] and the demonstrated ability of these molecules activating nitro groups as proposed by several authors,[14,15] we decided to explore and study these structures in the asymmetric phospha-Michael reaction of nitroalkenes (Fig. 2, Table 1). Thioureas **4b–h** were first synthesized following our previously reported procedure, depicted in Scheme 1.[13b,e] This easy method allows access to a great variety of this kind of structures.

These synthesized thioureas (**4b–h**), as well as others commercially available (**4a** and **4i–k**) (Fig. 2) were tested as catalysts in a model hydrophosphonylation reaction using *trans*-β-nitrostyrene (**5a**) as substrate, and the results are summarized in Table 1.



Scheme 1 Synthesis of chiral thioureas.

Among all thioureas tested in this process, only **4a** afforded promising results in terms of both reactivity and enantioselectivity (Table 1, entry 1).[16] In the other cases, the addition of an external base was always required in order to observe reactivity,[17] except for catalyst **4h**,[18] which also has a Brønsted base moiety in its structure (Table 1, entry 8). However unfortunately, the final products were obtained with very poor enantioselectivities. On the basis of this observation, it is conceivable that the presence of the Brønsted base and the thiourea moiety placed on the right position in the same molecular structure is crucial for the success of this protocol. Maybe, due to formation of a rigid transition state, leading to higher values of enantioselectivity.

Catalysts **4c**, **4e**, and **4g** were used expecting a bifunctional mode of action of these structures, since the possible bifunctional character of such catalysts has been already proposed when the thiourea moiety and the hydroxy group, which would activate the nucleophile, are present in the same skeleton (Fig. 3).[13b,e] However in this case, the coordination of the nucleophile with the H of the hydroxyl group seems to be neither effective nor efficient enough to promote the reaction in an enantioselective way.

The bifunctional role that catalyst **4h** may play in similar processes has been also previously proposed and discussed.[13d,18] In fact, in the current reaction, catalyst **4h** gave slighlty the second best result, which is in agreement with the importance of having both moeties (the Brønsted base and the thiourea) in the same structure. Furthermore, bis-thiourea catalyst **4d**[19] has been also invoked to react as bifunctional catalyst interacting with both nucleophile and electrophile by hydrogen-bonds. To further explore the viability of this phospha-Michael addition, different

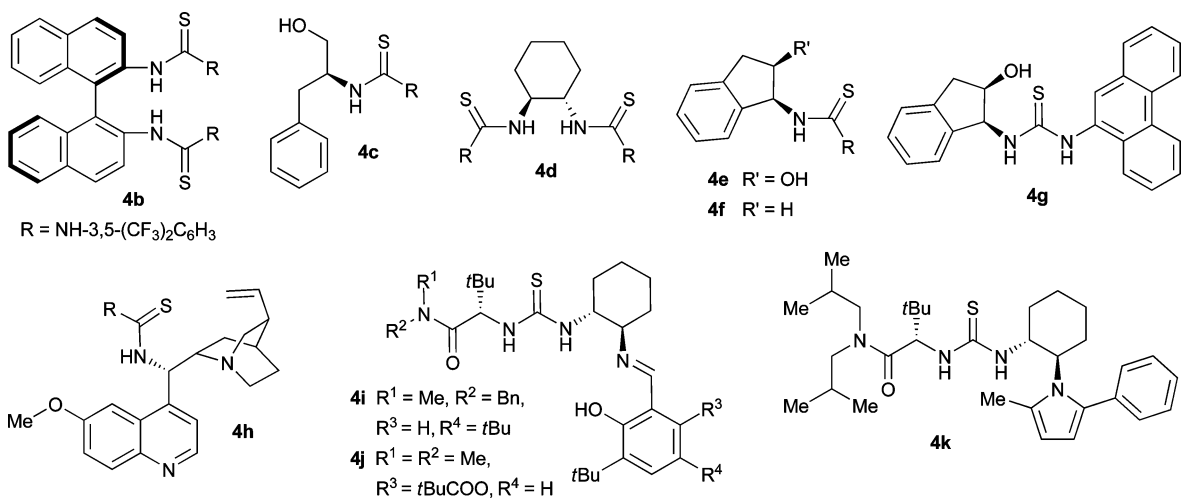
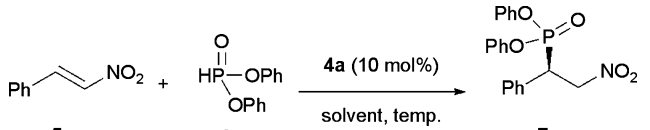


Fig. 2 Thiourea catalysts tested.

Table 2 Screening for the organocatalytic asymmetric Michael addition reaction of phosphite **6a** to *trans*-β-nitrostyrene (**5a**)[a]



5a **6a** **7a**

Entry	solvent (mL)	**4a** (%)	*T*/°C	time (h)	yield (%)[b]	ee (%)[c]
1	Xylene (1)	10	r.t.	10 min	85	58
2	Toluene (1)	10	r.t.	10 min	85	60
3	CH_3CN (1)	10	r.t.	24	25	60
4	CH_2Cl_2 (1)	10	r.t.	72	90	70
5	$CHCl_3$ (1)	10	r.t.	96	26	54
6	THF (1)	10	r.t.	96	n.r.[d]	n.r.[d]
7	Et_2O (1)	10	r.t.	96	n.r.[d]	n.r.[d]
8	CH_2Cl_2 (1)	15	r.t.	72	85	68
9	CH_2Cl_2 (1)	5	r.t.	72	n.d.[e]	66
10	CH_2Cl_2 (2)	10	r.t	72	n.d.[e]	68
11	CH_2Cl_2 (0.5)	10	r.t.	48	85	72
12[f]	CH_2Cl_2 (1)	10	r.t.	12	85	60
13	CH_2Cl_2 (1)	10	−10	120	39	78
14	CH_2Cl_2 (0.5)	10	−10	72	95	76
15	CH_2Cl_2 (1)	20	−10	24	65	72
16[f]	CH_2Cl_2 (1)	20	−10	12	85	72

[a] *Experimental conditions* (unless otherwise specified): To a solution of nitroalkene **5a** (0.4 mmol) and catalyst **4a** (10 mol%) in the corresponding solvent (1 mL), diphenyl phosphite **6a** (0.4 mmol) was added at room temperature. [b] After isolation by column chromatography. [c] Determined by chiral HPLC analysis (Chiralpak IA). [d] No reaction observed. [e] Not determined. [f] 2 equiv. of diphenyl phosphite **6a**.

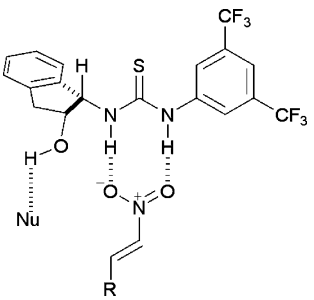
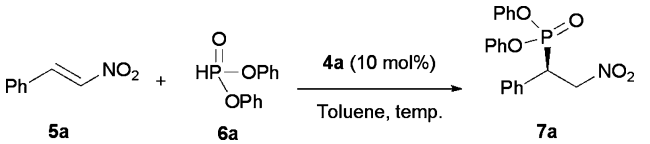


Fig. 3 Bifunctional mode of action.

parameters were investigated using *trans*-β-nitrostyrene (**5a**) as the test substrate and the best catalyst (**4a**) (Table 2).

In an initial screening of solvents at room temperature, while THF and Et_2O showed not to be effective for this reaction (entries 6–7), toluene, xylene, CH_3CN, $CHCl_3$, and CH_2Cl_2 provided the final product with promising values of enantioselectivity (entries 1–5). Finally, CH_2Cl_2 was the solvent of choice for further variations, since it led to the highest yield and enantioselectivity (entry 4), even when longer reaction time was required compared with toluene or xylene (entries 1–2). Variation of the catalyst loading (entries 8–9), dilution of the reaction mixture (entry 10) or the addition of an excess of phosphite (entry 12) had a negative effect on the enantioselectivity and the yield. On the other hand, increasing the concentration accelerated the reaction giving comparable results (entry 11). Lowering the temperature to −10 °C improved the enantioselectivity at the expense of reactivity and yield (entry 13). Thus, the combination of both variations (concentration and cooling down to −10 °C) led to a slight increase

Table 3 Screening of different reaction conditions using toluene as solvent[a]



5a **6a** **7a**

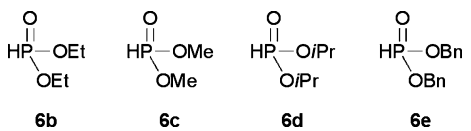
Entry	solvent (mL)	**6a** (eq.)	time (h)	yield (%)[b]	ee (%)[c]
1	2	1	12	62	66
2	2.5	1	120	34	64
3	3	1	120	n.d.[d]	60
4[e]	1	1	72	n.d.[d]	66
5[f]	1	1	12	78	62
6	1	2	5 min	84	62
7	2	2	5 min	80	60
8	2	0.9	12	80	60

[a] *Experimental conditions*: To a solution of nitroalkene (**5a**) (0.4 mmol) and catalyst **4a** (10 mol%) in toluene (1 mL), diphenyl phosphite **6a** (0.4 mmol) was added. [b] After isolation by column chromatography. [c] Determined by chiral HPLC analysis (Chiralpak IA). [d] Not determined. [e] 5 mol% of catalyst **4a**. [f] Reaction performed at 0 °C.

in the asymmetric induction as well as in the the yield, providing finally the best reaction conditions (entry 14). However, due to the interesting short reaction time required when toluene was used (Table 2, entry 2), we could not discard this solvent before further investigations were carried out (Table 3).

Unfortunately, any of the variations performed in the concentration of the solution (entries 1–3,7–8), catalyst loading (entry 4), temperature (entry 5), and amount of diphenyl phosphite (**6a**) (entry 6–8) did not afford better results in comparison with those achieved using CH_2Cl_2 as solvent. We observed the fast precipitation of the final product in the reaction media, due to its insolubility in toluene. This fact accelerates the process but it does not provide better enantioselectivity.

The effect of other different nucleophilic dialkyl phosphites [diethyl phosphite (**6b**), dimethyl phosphite (**6c**), diisopropyl phosphite (**6d**) and dibenzyl phosphite (**6e**)] were also explored in order to improve the enantioselectivity of the Michael reaction (Fig. 4).



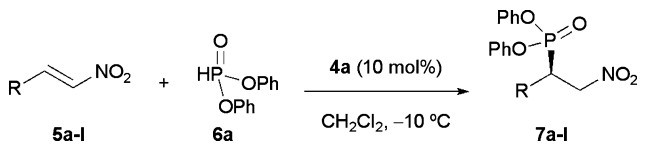
6b **6c** **6d** **6e**

Fig. 4 Dialkyl phosphites tested.

However, under the best reaction conditions, after 3 days, any of these dialkyl phosphites (**6b–e**) were reactive enough. Thus, only diphenyl phosphite (**6a**) furnished the corresponding final product **7a** with good results. The lack of reactivity and the dramatic descent of the reaction rates using these dialkyl phosphites (**6b–e**) might be due to the drastic variation of its pK_a values,[20] as we observed in a previous work.[21]

Having established the optimal reaction conditions, we further explored the scope of this 1,4-Michael addition for various substituted nitroolefines **5b–l**. Corresponding derivatives **7a–l** were furnished with very good yields and good enantioselectivities in CH_2Cl_2 at −10 °C (Table 4).

Table 4 Organocatalytic enantioselective 1,4-Michael addition of phosphite **6a** to nitroalkenes **5a–l** catalyzed by thiourea **4a**[a]



5a-l 6a 7a-l

Entry	*R*	time (days)	yield (%)[b]	ee (%)[c]
1	Ph (**7a**)	3	95	76
2	4-MeC_6H_4 (**7b**)	3	81	74
3	4-MeOC_6H_4 (**7c**)	3	79	78
4	2-MeOC_6H_4 (**7d**)	3	75	73
5	2-$CF_3C_6H_4$ (**7e**)	3	79	76
6	4-ClC_6H_4 (**7f**)	3	87	73
7	4-FC_6H_4 (**7g**)	4	60	72
8	2-furyl (**7h**)	3	67	76
9	4-BrC_6H_4 (**7i**)	3	79	76
10	4-BnOC_6H_4 (**7j**)	3	81	78
11	Cy (**7k**)	3	82	72
12	$PhCH_2CH_2$ (**7l**)	3	60	68

[a] See Experimental Section. [b] After isolation by column chromatography. [c] Determined by chiral HPLC analysis (Chiralpak IA and IB).

An enantioselectivity/temperature profile showed that in all cases a small improvement on the enantioselectivity was posible after longer reaction time, by running the reactions at –10 °C. As illustrated in Table 4, nitroolefines **5a–l** underwent conjugate addition with diphenyl phosphite **6a** in the presence of catalyst **4a** within 3 reaction days with high yields and good enantiomeric ratio (up to 78%). The steric hindrance and the electronic environment influence only slightly on the enantioselectivity of this process, which was almost independent of the aryl group (entries 1–10). Although with alkyl substituents the enantioselectivity seems to be somewhat lower (entries 11–12). These results are comparable to those previously reported by Wang and co-workers, but shorter reaction times and a less drastic decrease in temperature (–55 °C) were required,[8a] which saves energy and time management. Unfortunately, we could not improve the excellent results reported by Terada,[8b] and Rawal[8c] groups. However, the readily accessible thioureas, compared with the more tedious preparation of their catalysts, reinforces the simplicity and viability of our procedure. The absolute configuration of the Michael adducts **7a–l** was determined by comparison of the optical rotation values with those previously reported in the literature for the same products.[8]

On the basis of the obtained results, we envisioned that catalyst **4a** could act in a bifunctional fashion, as previously proposed in the literature.[22] The activation of nitroolefins by thiourea **4a** has been demonstrated earlier in other processes[16,23] and kinetic studies indicated the bifunctional character of this structure in Michael reactions.[16c] In order to give additional support to this hypothesis we performed calculations at DFT level (B3LYP/6-31+G*).[24] We assumed that the enantioselectivity of the reaction is controlled during the C–P bond formation between the activated nitroalkene and the nucleophile. We have studied the approach of dimethyl phosphite, which has been employed as the model reagent, to both *Re* and *Si* faces of the nitroalkene. For each enantiotopic face, the attack can occur from above or below, leading to four transition states. Among these transition states, those corresponding to the upper attack (**TS-1** and **TS-2**) are lower in energy (Fig. 5). The key proton abstraction from the developing phosphite anion by the dimethylamino group[25] helps in stabilizing the transition states and it is responsible of the enantioselective approach of the nucleophile to the nitroalkene. From the two possible orientations of the double bond, that corresponding to the *Re* attack and leading to (*R*)-isomer, resulted the most stable by 1.39 kcal mol^{-1}, thus being in good qualitative agreement with the experimental results.

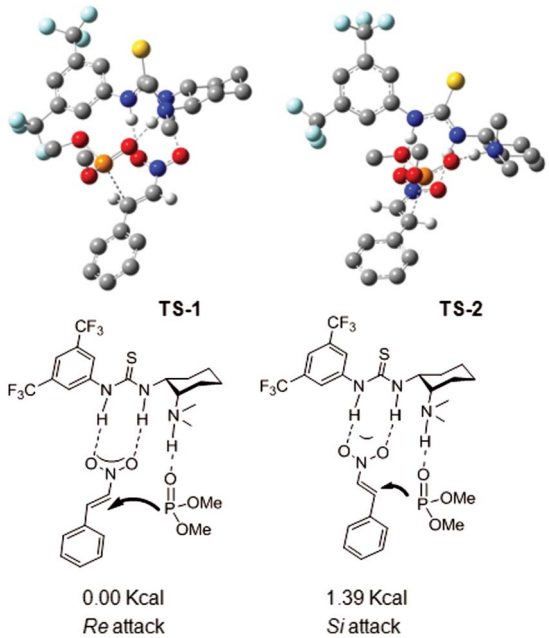


Fig. 5 Transition state models.

In contrast to the *Si*-facial attack, *Re*-facial approach of the phosphite is located at the less sterically demanding upper right-hand quadrant. Therefore, **TS-1** is more stabilized than **TS-2** because a lower steric repulsion between the phosphite nucleophile and the inside-oriented phenyl group of the nitroalkene. These results are also in agreement with similar theoretical studies reported by Papai and co-workers[25a] for the thiourea catalyzed nucleophilic addition of acetylacetone to nitrostyrene. The C–P distances in the transition states were found to be very similar, 2.76 Å and 2.80 Å for **TS-1** and **TS-2**, respectively indicating early transition states in which the electrostatic interaction between the phosphite and the dimethylamino group at the catalyst is crucial for approaching the reagents. The possibility of hydrogen bonding between the nitro group and the thiourea moiety through an only oxygen atom as recently proposed by other authors[26] has also been considered, but in all cases higher energy stationary points have been found in close agreement with previous calculations made by Papai in which it was demonstrated the preference by a substrate binding through bidentate H-bonds with the nitroalkene.[25a] Higher level calculations considering solvent correction are underway in our group to confirm these preliminary results and will be reported in due course.

Conclusions

In summary, we have reported a simple and enantioselective organocatalytic phospha-Michael reaction catalyzed by

commercially available Takemoto's thiourea catalyst **4a**. Thus, this methodology provides a facile access to the corresponding enantiomerically enriched β-nitrophosphonates in good yields. The limited number of catalytic enantioselective methods for the synthesis of β-nitrophosphonates by straightforward hydrophosphonylation of nitroalkenes,[8,27] and the high synthetic versatility of these products make this new approach very attractive for the synthesis of optically active β-aminophosphonic acids. DFT level of computational calculations appeal to the attack of the diphenyl phosphite to the nitroolefin by the *Re* face, this shed light on this process which has been scarcely explored up to now in the literature. We have invoked the importance, efficiency and utility of bifuctional catalysts and we will study the design and synthesis of new bifuncional thioureas. Future research will be carried out concerning the improvement of enanantiocontrol of this process.

Due to the extremely simple operational procedure our methodology is very accessible and it increases the utility and interest of the work in this growing area of the use of thioureas as organocatalysts.

Experimental section

General Information

Purification of reaction products was carried out by flash chromatography using silical gel (0.040–0.063 mm). Analytical thin layer chromatography was performed on 0.25 mm silical gel 60-F plates. ^{1}H-NMR spectra were recorded at 400 MHz; ^{13}C-NMR spectra were recorded at 100 MHz and 75 MHz; $CDCl_3$ as solvent. Chemical shifts were reported in the δ scale relative to residual $CHCl_3$ (7.26 ppm) for ^{1}H-NMR and to the central line of $CDCl_3$ (77.0 ppm) for ^{13}C-NMR.

Materials. All commercially available solvents and reagents were used as received. Chiral thioureas catalysts were obtained following the literature procedure: **4b**,[28] **4c**,[13e] **4d**,[18a] **4e–g**,[13e] and **4h**.[29] The ^{1}H and ^{13}C-NMR spectra for the compounds **7a–d**,**h–i**,**k**,l are consistent with values previously reported in the literature.[8]

Representative experimental procedure for enantioselective 1,4-addition reaction of diphenyl phosphite (6a) with nitroalkenes (5a–l) catalyzed by thiourea 4a. To a solution of nitroalkene (**5a–l**) (0.4 mmol) and catalyst **4a** (10 mol%) in CH_2Cl_2 (0.5 mL), in a test tube, diphenyl phosphite (**6a**) (0.4 mmol) was added. After the appropriate reaction time, at –10 °C, the residue was purified by silica gel chromatography (SiO_2, hexane–EtOAc 7 : 3) to afford the adducts **7a–l** as white solid. Yields and spectral and analytical data for compounds **7a–l** are as follows:

(*R*)-Diphenyl 2-nitro-1-phenylethylphosphonate (7a). Following the general procedure, compound **7a** was obtained after 3 days at –10 °C as a white solid in 95% yield. M.p. 154–160 °C. The ee of the product was determined by HPLC using a Daicel Chiralpak IA column (n-hexane/*i*-PrOH = 60 : 40, flow rate 0.5, mL min^{-1}, λ = 254 nm): τ_{major} = 18.7 min; τ_{minor} = 21.0 min. HRMS calcd for $C_{20}H_{18}NNaO_5P$ 406.0820; found 406.0812 [M$^+$ + Na]. $[\alpha]_D^{22}$ = –1.24 (*c* 1.0, $CHCl_3$, 76% ee). The ^{1}H and ^{13}C NMR spectra are consistent with values previously reported in the literature.[8a,b]

(*R*)-Diphenyl 2-nitro-1-*p*-tolylethylphosphonate (7b). Following the general procedure, compound **7b** was obtained after 3 days at –10 °C as a white solid in 81% yield. M.p. 116–119 °C. The ee of the product was determined by HPLC using a Daicel Chiralpak IB column (n-hexane/*i*-PrOH = 90 : 10, flow rate 1 mL min^{-1}, λ = 254 nm): τ_{major} = 22.1 min; τ_{minor} = 15.3 min. HRMS calcd for $C_{21}H_{20}NNaO_5P$ 420.0977; found 420.0964 [M$^+$ + Na]. $[\alpha]_D^{22}$ = –3.92 (*c* 1.0, $CHCl_3$, 74% ee). The ^{1}H and ^{13}C NMR spectra are consistent with values previously reported in the literature.[8b]

(*R*)-Diphenyl 1-(4-methoxyphenyl)-2-nitroethylphosphonate (7c). Following the general procedure, compound **7c** was obtained after 3 days at –10 °C as a white solid in 79% yield. M.p. 133–137 °C. The ee of the product was determined by HPLC using a Daicel Chiralpak IB column (n-hexane/*i*-PrOH = 90 : 10, flow rate 1 mL min^{-1}, λ = 254 nm): τ_{major} = 28.2 min; τ_{minor} = 22.9 min. HRMS calcd $C_{21}H_{20}NNaO_6P$ 436.0926; found 436.0920 [M$^+$ + Na]. $[\alpha]_D^{22}$ = –0.48 (*c* 1.0, $CHCl_3$, 78% ee). The ^{1}H and ^{13}C NMR spectra are consistent with values previously reported in the literature.[8a,b]

(*R*)-Diphenyl 1-(2-methoxyphenyl)-2-nitroethylphosphonate (7d). Following the general procedure, compound **7d** was obtained after 3 days at –10 °C as a white solid in 75% yield. M.p. 85–88 °C. The ee of the product was determined by HPLC using a Daicel Chiralpak IB column (n-hexane/*i*-PrOH = 90 : 10, flow rate 1 mL min^{-1}, λ = 254 nm): τ_{major} = 17.6 min; τ_{minor} = 13.3 min. HRMS calcd for C $C_{21}H_{20}NNaO_6P$ 436.0926; found 436.0929 [M$^+$ + Na]. $[\alpha]_D^{22}$ = +10.5 (*c* 1.0, $CHCl_3$, 73% ee). The ^{1}H and ^{13}C NMR spectra are consistent with values previously reported in the literature.[8a,b]

(*R*)-Diphenyl 2-nitro-1-(2-trifluoromethyl)phenyl)ethylphosphonate (7e). Following the general procedure, compound **7e** was obtained after 3 days at –10 °C as a viscous yellow liquid in 79% yield. The ee of the product was determined by HPLC using a Daicel Chiralpak IB column (n-hexane/*i*-PrOH = 90 : 10, flow rate 1 mL min^{-1}, λ = 254 nm): τ_{major} = 14.1 min; τ_{minor} = 10.5 min. HRMS calcd for $C_{21}H_{17}F_3NNaO_5P$ 474.0694; found 474.0684 [M$^+$ + Na]. $[\alpha]_D^{22}$ = +10.3 (*c* 1.0, $CHCl_3$, 76% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (ddd, $^2J_{H-P}$ = 24.3, $^3J_{H-H}$ = 9.6, $^3J_{H-H}$ = 5.3 Hz, 1H, CH), 5.02–5.10 (m, 1H, CH_2), 5.19–5.26 (m, 1H, CH_2), 6.64–6.65 (m, 1H, Ar), 6.65–6.67 (m, 1H, Ar), 7.01–7.06 (m, 1H, Ar), 7.09–7.16 (m, 4H, Ar), 7.17–7.22 (m, 1H, Ar), 7.30–7.35 (m, 2H, Ar), 7.42–7.47 (m, 1H, Ar), 7.53–7.57 (m, 1H, Ar), 7.72–7.74 (m, 1H, Ar), 7.82–7.84 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.8 (d, *J* = 143.4 Hz), 75.4 (d, *J* = 2.3 Hz), 119.7 (d, *J* = 4.6 Hz), 120.4 (d, *J* = 4.1 Hz), 123.8 (qd, *J* = 274.4, 1.4 Hz), 125.3 (d, *J* = 1.2 Hz), 125.9 (d, *J* = 1.2 Hz), 127.1 (m), 128.9 (d, *J* = 3.5 Hz), 129.6, 129.6, 129.7 (d, *J* = 4.8 Hz), 129.8 (qd, *J* = 30.0, 8.2 Hz), 130.0 (d, *J* = 1.2 Hz), 132.5 (d, *J* = 3.5 Hz), 147.8 (d, *J* = 9.8 Hz), 148.1 (d, *J* = 9.3 Hz).

(*R*)-Diphenyl 1-(4-chlorophenyl)-2-nitroethylphosphonate (7f). Following the general procedure, compound **7f** was obtained after 3 days at –10 °C as a white solid in 87% yield. M.p. 134–137 °C. The ee of the product was determined by HPLC using a Daicel Chiralpak IB column (n-hexane/*i*-PrOH = 90 : 10, flow rate 1 mL min^{-1}, λ = 254 nm): τ_{major} = 28.9 min; τ_{minor} = 17.8 min. HRMS calcd for $C_{20}H_{17}ClNNaO_5P$ 440.0431; found 440.0430 [M$^+$ + Na]. $[\alpha]_D^{22}$ = –6.2 (*c* 1.0, $CHCl_3$, 73% ee). The ^{1}H and ^{13}C NMR spectra are consistent with values previously reported in the literature.[8a]

(*R*)-Diphenyl 1-(4-fluorophenyl)-2-nitroethylphosphonate (7g). Following the general procedure, compound **7g** was obtained after 4 days at −10 °C as a white solid in 60% yield. M.p. 130–134 °C. The ee of the product was determined by HPLC using a Daicel Chiralpak IB column (n-hexane/*i*-PrOH = 90 : 10, flow rate 1 mL min^{-1}, λ = 254 nm): τ_{major} = 26.7 min; τ_{minor} = 15.0 min. HRMS calcd for $C_{20}H_{17}FNNaO_5P$ 424.0726; found 424.0724 [M$^+$ + Na]. $[\alpha]_D^{22}$ = +0.23 (*c* 1.0, $CHCl_3$, 72% ee). The ^{1}H and ^{13}C NMR spectra are consistent with values previously reported in the literature.[8a]

(*S*)-Diphenyl 1-(furan-2-yl)-2-nitroethylphosphonate (7h). Following the general procedure, compound **7h** was obtained after 3 days at −10 °C as a white solid in 67% yield. M.p. 82–85 °C. The ee of the product was determined by HPLC using a Daicel Chiralpak IB column (n-hexane/*i*-PrOH = 90 : 10, flow rate 1 mL min^{-1}, λ = 254 nm): τ_{major} = 21.8 min; τ_{minor} = 12.1 min. HRMS calcd for $C_{18}H_{16}NNaO_6P$ 396.0613; found 396.0620 [M$^+$ + Na]. $[\alpha]_D^{22}$ = −9.0 (*c* 1.0, $CHCl_3$, 76% ee). The ^{1}H and ^{13}C NMR spectra are consistent with values previously reported in the literature.[8a,b]

(*R*)-Diphenyl 1-(4-bromophenyl)-2-nitroethylphosphonate (7i). Following the general procedure, compound **7i** was obtained after 3 days at −10 °C as a white solid in 79% yield. M.p. 134–137 °C. The ee of the product was determined by HPLC using a Daicel Chiralpak IB column (n-hexane/*i*-PrOH = 90 : 10, flow rate 1 mL min^{-1}, λ = 254 nm): τ_{major} = 30.6 min; τ_{minor} = 21.0 min. HRMS calcd for $C_{20}H_{17}BrNNaO_5P$ 483.9925; found 483.9960 [M$^+$ + Na]. $[\alpha]_D^{22}$ = −8.7 (*c* 1.0, $CHCl_3$, 76% ee). The ^{1}H and ^{13}C NMR spectra are consistent with values previously reported in the literature.[8a,b]

(*R*)-Diphenyl 1-(4-(benzyloxy)phenyl)-2-nitroethylphosphonate (7j). Following the general procedure, compound **7j** was obtained after 3 days at −10 °C as a yellow solid in 81% yield. M.p. 122–126 °C. The ee of the product was determined by HPLC using a Daicel Chiralpak IB column (n-hexane/*i*-PrOH = 90 : 10, flow rate 1 mL min^{-1}, λ = 254 nm): τ_{major} = 40.2 min; τ_{minor} = 28.1 min. HRMS calcd for $C_{27}H_{24}NNaO_6P$ 512.1239; found 512.1242 [M$^+$ + Na]. $[\alpha]_D^{22}$ = −1.0 (*c* 1.0, $CHCl_3$, 78% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (ddd, $^2J_{H-P}$ = 24.5, $^3J_{H-H}$ = 11.1, $^3J_{H-H}$ = 4.6 Hz, 1H, CH), 5.00–5.10 (m, 1H, CH_2), 5.04 (s, 2H, OCH_2), 5.13–5.19 (m, 1H, CH_2), 6.75–6.77 (m, 2H, Ar), 6.95–6.95 (m, 2H, Ar), 7.07–7.10 (m, 3H, Ar), 7.15–7.20 (m, 3H, Ar), 7.28–7.43 (m, 9H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.7 (d, *J* = 141.9 Hz), 70.1, 75.2 (d, *J* = 5.9 Hz), 115.6 (d, *J* = 2.2 Hz), 115.8, 120.2 (d, *J* = 4.4 Hz), 120.4 (d, *J* = 4.4 Hz), 122.5 (d, *J* = 8.1 Hz), 125.5, 125.6 (d, *J* = 24.2 Hz), 127.5, 128.1, 128.7, 129.7, 130.0, 136.6, 130.5 (d, *J* = 6.6 Hz), 149.9 (d, *J* = 10.2 Hz), 150.0 (d, *J* = 9.5 Hz), 159.2 (d, *J* = 2.9 Hz).

(*R*)-Diphenyl 1-cyclohexyl-2-nitroethylphosphonate (7k). Following the general procedure, compound **7k** was obtained after 3 days at −10 °C as a white solid in 82% yield. M.p. 108–111 °C. The ee of the product was determined by HPLC using a Daicel Chiralpak IB column (n-hexane/*i*-PrOH = 90 : 10, flow rate 1 mL min^{-1}, λ = 254 nm): τ_{major} = 7.5 min; τ_{minor} = 6.7 min. HRMS calcd for $C_{20}H_{24}NNaO_5P$ 412.1290; found 412.1290 [M$^+$ + Na]. $[\alpha]_D^{22}$ = −8.27 (*c* 1.0, $CHCl_3$, 72% ee). The ^{1}H and ^{13}C NMR spectra are consistent with values previously reported in the literature.[8b]

(*R*)-Diphenyl 1-nitro-4-phenylbutan-2-ylphosphonate (7l). Following the general procedure, compound **7l** was obtained after 3 days at −10 °C as a white solid in 60% yield. M.p. 70–75 °C. The ee of the product was determined by HPLC using a Daicel Chiralpak IA column (n-hexane/*i*-PrOH = 95 : 5, flow rate 1 mL min^{-1}, λ = 254 nm): τ_{major} = 43.1 min; τ_{minor} = 47.1 min. HRMS calcd for $C_{22}H_{22}NNaO_5P$ 434.1133; found 434.1145 [M$^+$ + Na]. $[\alpha]_D^{22}$ = +4.70 (*c* 1.0, $CHCl_3$, 68% ee). The ^{1}H and ^{13}C NMR spectra are consistent with values previously reported in the literature.[8c]

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Notes and references

1 *Asymmetric Synthesis: The Essentials*, 2nd edition (Ed.: M. Christmann, S. Bräse), Wiley-VCH, Weinheim, Germany, 2007.
2 For selected reviews on organocatalysis, see for example: (*a*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138; (*b*) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Whiley-VHC, Weinheim, Germany, 2004; (*c*) *Acc. Chem. Res.*, 2004, **37**(8)special issue on organocatalysis; (*d*) J. Seayed and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719; (*e*) *Enantioselective Organocatalysis* (Ed.: P. I. Dalko), Whiley-VCH, Weinheim, Germany, 2007; (*f*) *Chem. Rev.*, 2007, **107**(12)special issue on organocatalysis; (*g*) A. Dondoni and A. Massi, *Angew. Chem., Int. Ed.*, 2008, **47**, 4638; (*h*) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem., Int. Ed.*, 2008, **47**, 6138; (*i*) A. Mielgo and C. Palomo, *Chem.–Asian J.*, 2008, **3**, 922; (*j*) *Asymmetric Phase Transfer Catalysis* (Ed.: K. Maruoka), Wiley-VCH, Weinheim, 2008; (*k*) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178.
3 For applications of organocatalysis in the synthesis of natural products and non-natural biologically active molecules, see: (*a*) R. M. de Figueiredo and M. Christmann, *Eur. J. Org. Chem.*, 2007, 2575; (*b*) E. Marqués-López, R. P. Herrera and M. Christmann, *Nat. Prod. Rep.*, 2010, **27**, 1138.
4 For a recent review about β-aminophosphonic acids, see: M. Ordóñez, H. Rojas-Cabrera and C. Cativiela, *Tetrahedron*, 2009, **65**, 17.
5 For a review on α-aminophosphonic acids, see: F. Palacios, C. Alonso and J. M. de los Santos, *Chem. Rev.*, 2005, **105**, 899.
6 For the biological activity of α-aminophosphonic acids, see: *Aminophosponic and aminophosphinic acids: Chemistry and Biological Activity* (Eds.: V. P. Kukhar, H. R. Hudson), Wiley, NY, 2000.
7 For reviews about enantioselective synthesis of α-aminophosphonate derivatives, see: (*a*) J.-A. Ma, *Chem. Soc. Rev.*, 2006, **35**, 630; (*b*) P. Merino, E. Marqués-López and R. P. Herrera, *Adv. Synth. Catal.*, 2008, **350**, 1195.
8 (*a*) J. Wang, L. D. Heikkinen, H. Li, L. Zu, W. Jiang, H. Xie and W. Wang, *Adv. Synth. Catal.*, 2007, **349**, 1052; (*b*) M. Terada, T. Ikehara and H. Ube, *J. Am. Chem. Soc.*, 2007, **129**, 14112. This work was published during the preparation of this manuscript: (*c*) Y. Zhu, J. P. Malerich and V. H. Rawal, *Angew. Chem., Int. Ed.*, 2010, **49**, 153.
9 For a recent review of phospha-Michael reaction with electron deficient alkenes, see: D. Enders, A. Saint-Dizier, M.-I. Lannou and A. Lenze, *Eur. J. Org. Chem.*, 2006, 29.
10 For organocatalytic enantioselective Michael addition reactions of other phosphorus nucleophiles using electron deficient alkenes, see: (*a*) G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, A. Mazzanti, L. Sambri and P. Melchiorre, *Chem. Commun.*, 2007, 722; (*b*) A. Carlone, G. Bartoli, M. Bosco, L. Sambri and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2007, **46**, 4504; (*c*) I. Ibrahem, R. Rios, J. Vesely, P. Hammar, L. Eriksson, F. Himo and A. Córdova, *Angew. Chem., Int. Ed.*, 2007, **46**, 4507; (*d*) E. Maerten, S. Cabrera, A. Kjaersgaard and K. A. Jørgensen,

J. Org. Chem., 2007, **72**, 8893; (*e*) S. Wen, P. Li, H. Wu, F. Yu, X. Liang and J. Ye, *Chem. Commun.*, 2010, **46**, 4806; (*f*) T. S. Pham, L. Balázs, I. Petneházy and Z. Jászay, *Tetrahedron: Asymmetry*, 2010, **21**, 346. For 1,4-addition reaction of nitroalkenes with dialkyl phosphites catalyzed by achiral guanidine derivatives, see: (*g*) Z. Jiang, Y. Zhang, W. Ye and C.-H. Tan, *Tetrahedron Lett.*, 2007, **48**, 51.

11 (*a*) D. P. Curran and L. H. Kuo, *J. Org. Chem.*, 1994, **59**, 3259; (*b*) D. P. Curran and L. H. Kuo, *Tetrahedron Lett.*, 1995, **36**, 6647.

12 (*a*) P. R. Schreiner, *Chem. Soc. Rev.*, 2003, **32**, 289; (*b*) Y. Takemoto, *Org. Biomol. Chem.*, 2005, **3**, 4299; (*c*) S. J. Connon, *Chem.–Eur. J.*, 2006, **12**, 5418; (*d*) M. S. Taylor and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2006, **45**, 1520; (*e*) A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713; (*f*) Z. Zhang and P. R. Schreiner, *Chem. Soc. Rev.*, 2009, **38**, 1187; (*g*) E. Marqués-López and R. P. Herrera, *An. Quim.*, 2009, **105**, 5.

13 (*a*) G. Dessole, R. P. Herrera and A. Ricci, *Synlett*, 2004, 2374; (*b*) R. P. Herrera, V. Sgarzani, L. Bernardi and A. Ricci, *Angew. Chem., Int. Ed.*, 2005, **44**, 6576; (*c*) D. Pettersen, R. P. Herrera, L. Bernardi, F. Fini, V. Sgarzani, R. Fernández, J. M. Lassaletta and A. Ricci, *Synlett*, 2006, 239; (*d*) L. Bernardi, F. Fini, R. P. Herrera, A. Ricci and V. Sgarzani, *Tetrahedron*, 2006, **62**, 375; (*e*) R. P. Herrera, D. Monge, E. Martín-Zamora, R. Fernández and J. M. Lassaletta, *Org. Lett.*, 2007, **9**, 3303.

14 For the recognition of the nitro group by urea moieties, see: (*a*) M. C. Etter and T. W. Panunto, *J. Am. Chem. Soc.*, 1988, **110**, 5896; (*b*) M. C. Etter, Z. Urbañczyk-Lipkowska, M. Zia-Ebrahimi and T. W. Panunto, *J. Am. Chem. Soc.*, 1990, **112**, 8415; (*c*) T. R. Kelly and M. H. Kim, *J. Am. Chem. Soc.*, 1994, **116**, 7072.

15 For selected examples, see: (*a*) J. Wang, H. Li, W. Duan, L. Zu and W. Wang, *Org. Lett.*, 2005, **7**, 4713; (*b*) H. Huang and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2006, **128**, 7170; (*c*) D. A. Yalalov, S. B. Tsogoeva and S. Schmatz, *Adv. Synth. Catal.*, 2006, **348**, 826; (*d*) Z. Zhang and P. R. Schreiner, *Synthesis*, 2007, 2559; (*e*) Z.-H. Zhang, X.-Q. Dong, D. Chen and C.-J. Wang, *Chem.–Eur. J.*, 2008, **14**, 8780.

16 For the first examples using catalyst **4a**, see: (*a*) T. Okino, Y. Hoashi and Y. Takemoto, *J. Am. Chem. Soc.*, 2003, **125**, 12672; (*b*) T. Okino, S. Nakamura, T. Furukawa and Y. Takemoto, *Org. Lett.*, 2004, **6**, 625; (*c*) T. Okino, Y. Hoashi, T. Furukawa, X. Xu and Y. Takemoto, *J. Am. Chem. Soc.*, 2005, **127**, 119.

17 In absence of $i\mathrm{Pr}_2\mathrm{EtN}$ we did not observe the final adduct after 3 days of reaction.

18 For examples of use of **4h** as bifunctional catalyst, see: (*a*) D. Pettersen, F. Piana, L. Bernardi, F. Fini, M. Fochi, V. Sgarzani and A. Ricci, *Tetrahedron Lett.*, 2007, **48**, 7805; (*b*) H. S. Rho, S. H. Oh, J. W. Lee, J. Y. Lee, J. Chin and C. E. Song, *Chem. Commun.*, 2008, 1208; (*c*) D. R. Li, A. Murugan and J. R. Falck, *J. Am. Chem. Soc.*, 2008, **130**, 46.

19 (*a*) Y. Sohtome, A. Tanatani, Y. Hashimoto and K. Nagasawa, *Tetrahedron Lett.*, 2004, **45**, 5589; (*b*) Y. Zhang, Y.-K. Liu, T.-R. Kang, Z.-K. Hu and Y.-C. Chen, *J. Am. Chem. Soc.*, 2008, **130**, 2456.

20 For the pK_a's values of different phosphorus nucleophiles, see: J.-N. Li, L. Liu, Y. Fu and Q.-X. Guo, *Tetrahedron*, 2006, **19**, 2335.

21 R. P. Herrera, D. Roca-López and G. Navarro-Moros, *Eur. J. Org. Chem.*, 2010, 1450.

22 For reviews about thioureas as bifunctional organocatalysts, see: (*a*) H. Miyabe and Y. Takemoto, *Bull. Chem. Soc. Jpn.*, 2008, **81**, 785; (*b*) S. J. Connon, *Chem. Commun.*, 2008, 2499.

23 Y. Hoashi, T. Okino and Y. Takemoto, *Angew. Chem., Int. Ed.*, 2005, **44**, 4032.

24 All calculations were carried out with the Gaussian 09 suite of programs: *Gaussian 09, Revision A.1*, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

25 (*a*) A. Hamza, G. Schubert, T. Soós and I. Pápai, *J. Am. Chem. Soc.*, 2006, **128**, 13151; (*b*) R. Zhu, D. Zhang, J. Wu and C. Liu, *Tetrahedron: Asymmetry*, 2006, **17**, 1611; (*c*) P. Hammar, T. Marcelli, H. Hiemstra and F. Himo, *Adv. Synth. Catal.*, 2007, **349**, 2537.

26 B.-L. Li, Y.-F. Wang, S.-P. Luo, A.-G. Zhong, Z.-B. Li, X.-H. Du and D.-Q. Xu, *Eur. J. Org. Chem.*, 2010, 656.

27 For the single enantioselective Michael addition reaction of dialkyl phosphites to nitroalkenes catalyzed by aluminium lithiumbis(binaphthoxide), see: V. Rai and I. N. N. Namboothiri, *Tetrahedron: Asymmetry*, 2008, **19**, 2335.

28 E. M. Fleming, T. McCabe and S. J. Connon, *Tetrahedron Lett.*, 2006, **47**, 7037.

29 B. Vakula, S. Varga, A. Csámpai and T. Soós, *Org. Lett.*, 2005, **7**, 1967.