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Asymmetric conjugate addition of nitroalkanes to enones with a chiral α-aminophosphonate catalyst

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ABSTRACT

Chiral diethyl (2*R*)-tetrahydropyrro-2-ylphosphonate is an effective catalyst for the Michael addition of nitroalkanes to α,β-unsaturated ketones. This study revealed that the hydrate salt of this α-aminophosphonate was found to be a better catalytic species. Moderate to high enantioselectivities were achieved in reactions that tolerate various nitroalkanes and enones in the presence of low loading of both catalyst (10 mol %) and bulk base (25 mol %).

1. Introduction

The asymmetric conjugate addition of carbon nucleophiles to electron-poor alkenes is among the most powerful transformations for the formation of carbon–carbon bonds in organic synthesis.[1] Owing to the hydrogen acidity at the α-position, nitroalkanes (pK_a $MeNO_2$ = 10) are a particularly useful source of stabilized carbanions[2] for the asymmetric addition to electron-poor alkenes. In addition, the nitro group represents a versatile functionality allowing further chemical transformations into a variety of functionally useful compounds. Thus, the asymmetric conjugate additions of nitroalkanes to α,β-unsaturated carbonyls remain the subject of intense development. The most general systems reported to date include metal-catalysts, for example, chiral crown ethers[3] and chiral Lewis acids.[4] In addition, Jacobsen et al. have investigated the use of an aluminum–salen catalyst with α,β-unsaturated ketones other than chalcones, in high yields and in good to excellent enantioselectivity.[5] Recently, the field of organocatalysis has been developing rapidly.[6] Good results have been achieved with chiral ammonium salts derived from cinchona alkaloids as phase-transfer catalysts[7] and cinchona alkaloid-derived thiourea catalysts,[8] however, only the reaction of chalcones with nitromethane was explored. Yamaguchi et al. first employed iminium activation in the asymmetric addition of 2-nitropropane to 2-cyclohexenone in the presence of rubidium L-prolinate.[9] Thus, based on this strategy, several pyrrolidine-based catalysts have been successfully applied to the Michael reaction of nitroalkanes (Fig. 1). Extensive investigations revealed that piperazine bases provided the best results when used as bulk bases in the presence of proline **1** for additions to cyclic enones.[10] Specifically, the reaction gave good to excellent enantioselectivities (61–93%), with the lower enantioselectivity arising from the addition of the less bulky nitromethane and nitroethane nucleophiles.

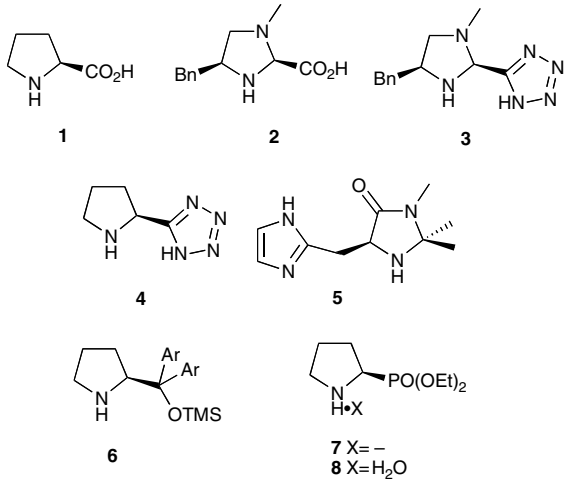

Figure 1. Pyrrolidine-based catalysts.

Jørgensen et al. reported the catalytic asymmetric conjugate addition of nitroalkanes to acyclic α,β-unsaturated enones in the presence of imidazoline catalyst **2** with good enantioselectivities (34–86%).[11] However, only a moderate enantioselectivity (49%) was obtained using cyclohexenone as the acceptor. In addition, reaction times between 4.5 and 12.5 days required the nitroalkanes to be employed as the reaction solvent (~20-fold excess). Later, the same group described the tetrazole analogue **3**, which led to improved enantioselectivities and rates under similar reaction

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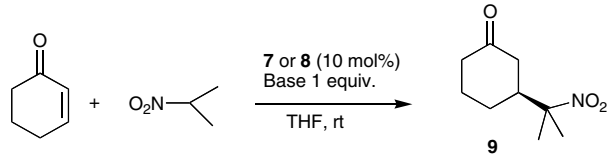
conditions (3–8 days).[12] Interestingly, 4-*trans*-amino-proline-based di- and tetrapeptides, in the presence of *trans*-2,5-dimethylpiperazine, successfully catalyzed the enantioselective conjugate addition of nitroalkanes to cyclic enones with up to 88% ee.[13] The effectiveness of the tetrazole catalyst **4** was demonstrated for the asymmetric addition of a variety of nitroalkanes to both cyclic and acyclic enones using *trans*-2,5-dimethylpiperazine as a stoichiometric base additive. Reactions with **4** provided enantiomeric excesses of up to 98% in relatively short reaction times of 1–3 days.[14]

For α,β-unsaturated aldehydes, Maruoka's chiral phase transfer catalyst was successful in the Michael addition of silyl nitronates.[15] More recently, Arvidsson et al. reported the Michael reaction of enals with nitroalkanes catalyzed by imidazole-containing organocatalyst **5**. The authors' strategy was aimed at incorporating both the iminium-activating function and the base in the catalyst.[16] Later, Hayashi et al. reported a similar reaction using diphenylprolinol silyl ether **6** as an organocatalyst.[17] This reaction expanded upon the previous substrate scope and involves the successful reaction of nitromethane directly with α,β-unsaturated aldehydes. Despite the progress in the asymmetric addition of nitroalkanes to enones, catalysis with proline derivatives requires substantial amounts of base, 1 equiv with respect to enone substrate, and often with a relatively high catalyst loading of 20 mol % to effect the reaction in a reasonable timescale.

Herein, we report the use of α-aminophosphonate **7**,[18] in conjunction with an appropriate acid co-catalyst to promote the Michael addition of nitroalkanes to enones. Judicious choice of a proton source has implications for higher reactivity although with marginal effect on the selectivity. With some substrates, the catalytic system (10 mol %) still operates efficiently at catalytic concentration of bulk base.

2. Results and discussion

An initial evaluation of α-aminophosphonate **7** as a catalyst was performed using achiral *meso* base *trans*-2,5-dimethylpiperazine, under conditions similar to those developed earlier by Hanessian and Pham . It was encouraging to see that reacting cyclohexenone with 2-nitropropane (1.5 equiv) in the presence of *trans*-2,5-dimethylpiperazine (1 equiv) and aminophosphonate (10 mol %) at room temperature in THF, afforded the desired product (*R*)-**9** in good yields with enantioselectivities up to 89:11 er (Scheme 1). Interestingly, during these preliminary investigations we noticed a change in the structure of catalyst **7**, which also induced a variation in the reaction rate. Freshly prepared **7** was isolated as a yellow oil that crystallized upon standing. This solid was identified as hydrate product **8** and displayed higher reactivity with similar enantioselectivity (vide infra).



Scheme 1. Michael addition catalyzed by aminophosphonate **7** or **8**.

2.1. Screening for base: investigation of background reaction

Our initial investigation into the Michael addition of 2-nitropropane began with the evaluation of a wide range of bases, provided that the added base could lead to parallel non-selective reactions. Thus, a screening of the base-catalyzed background reaction was carried out, with the objective of finding a strong enough base to deprotonate the nitroalkane yet one that does not catalyze the Michael addition. For comparison with literature data a base concentration of 1 M was used in dichloromethane as the solvent. All reactions were performed at room temperature for 26 h and then quenched with saturated NH_4Cl, and analyzed on chiral GC (Table 1).

Table 1
Base-catalyzed background reaction

Base	Conversion (%)
Piperazine	27
Morpholine	13 (87% amine addition)
TMEDA	0
DMEDA	85
Ethylendiamine	86
Pyrrolidine	100
Triethylamine	5
DBU	100
2,5-*trans*-Dimethylpiperazine	4

Typically, a negligible competitive background reaction was observed when triethylamine, TMEDA, and *trans*-2,5-dimethylpiperazine were used as bases in the absence of catalyst **8**. Surprisingly, piperazine furnished 27% of the background racemic product **9**. In the literature, piperazine and *trans*-2,5-dimethylpiperazine have proven to be the most effective bases for proline and the pyrrolidine-tetrazole catalyst.[10,14] Interestingly, piperazine and *trans*-2,5-dimethylpiperazine in the presence of catalyst **8** provided an er of 82:18 and 84:16, respectively. Herein, morpholine was an exception, and proved to act readily as a Michael donor to yield 87% of the addition product.

2.2. Base concentration

The concerns raised by a measurable background reaction even with the remarkably effective *trans*-2,5-dimethylpiperazine prompted us to question the concentration of bulk base used in the Michael addition of nitroalkanes. The asymmetric Michael addition of nitroalkanes, in most cases, still requires 100–150 mol % of bulk base to achieve good conversion. Hence, the amount of bulk base was varied for the purpose of this study. It is noteworthy that in the addition reaction catalyzed by **8** (10 mol %), base loading was successfully reduced to 25 mol % with respect to the enone substrate and had little effect on the enantioselectivity (see Fig. 2).

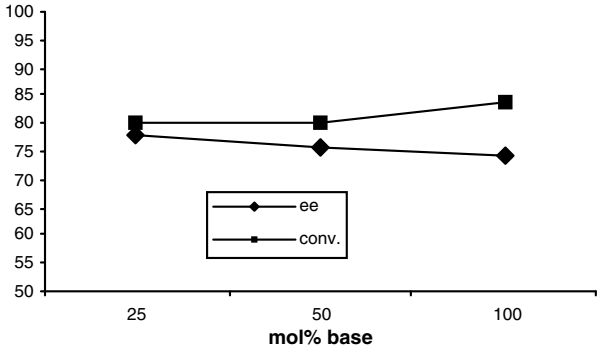
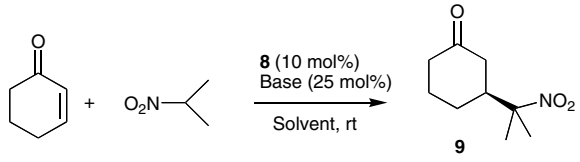


Figure 2. Effect of base concentration.

2.3. Effect of solvent

The solvent has proven to be very important for stereoselectivity in organocatalytic reactions. Therefore, using conditions similar

Table 2
Effect of solvent[a]



Solvent	Conversion (%)	er **9** (%)
$CHCl_3$	96	87:13
THF	98	89:11
EtOH	99	57:43
Toluene	98	84:16
DMSO	99	54:46
DMF	93	77:23
DEE	87	85:15
MTBE	96	83:17
Dioxane	90	88:12
DME	85	87:13
Hexane	100	64:36
MeCN	91	83:17
t-amylOH	99	76:24
i-PrOH	100	70:30
MeOH	100	47:53

[a] Standard conditions were used: 10 mol % **8**, 25 mol % *trans*-2,5-dimethylpiperazine and 1.5 equiv nitroalkane in 1 ml solvent, two days.

to those developed earlier for the nitroalkylation of enones, a range of solvents for the reaction was investigated (Table 2). Thus, in each case the desired product was formed with high conversion and the reaction was clearly enantioselective. These results revealed that hydrogen bonding stabilizing solvents such as DMSO, EtOH, and MeOH gave low to moderate enantioselectivities, while the use of *tert*-amylalcohol, hexane, and DMF resulted in a noticeable improvement. This observation suggested competing hydrogen bonding networks in the transition state. Changing the solvent to $CHCl_3$ gave a higher enantioselectivity of 87:13, while maintaining an efficient reaction (Table 2, entry 1). On the other hand, the use of the non-chlorinated solvents, MeCN, DEE, dioxane, MTBE, and THF provided conversions over 90% and similar enantioselectivities with THF proving to be the optimal reaction solvent. The low selectivity encountered with protic solvents may be attributed to their ability to disturb hydrogen-bonds in the transition state. The fact that this effect is minimized with non-polar protic solvents suggests that the transition state is highly polar, as proposed by Hanessian et al.,[10] and the repulsion between solvent and the active complex prevents hydrogen bonding. Surprisingly, hexane, a highly non-polar solvent, only furnished the corresponding product with modest selectivity.

2.4. Effect of water and acidic co-catalyst

During our investigation of the Michael addition of 2-nitropropane to cyclohexenone, we noticed an improved reaction rate for reactions performed with solid catalyst **8**. Indeed, α-aminophosphonate **7** crystallized upon standing when exposed to air. Further, ^1H and ^{13}C NMR analyses revealed spectroscopic data comparable to those of the corresponding hydrochloride salt, which is readily accessible. These observations suggest that hydration of **7** into **8** had occurred upon exposure to moist air for a certain time. Thus, free amine **7** could be regenerated upon treatment of the crystalline compound **8** with NaOH (2 M) and extraction with dichloromethane. While catalyst **8** displayed a threefold increase in the addition reaction rate than the freshly prepared catalyst **7**, there was no change in enantioselectivity.

The observed improvement in the catalytic activity of **8** prompted us to investigate the reactivity of a variety of acidic co-catalysts. In an effort to improve the Michael adduct yield without a loss of the favorable selectivities, we examined a range of proton sources for the formation of complexes **7**·HX as catalysts for the model reaction (Table 3).

Table 3
The effects of proton source and counterion on the model reaction

Entry	Acid[a]	Time	Conversion[b] (%)	er **9** (%)
1	— (**7**)	6 days	98	89:11
2	H_2O (**8**)	2 days	97	87:13
3	*p*-NO_2PhOH (**10**)	22 h	88	89:11
4	HCl (**11**)	5 days	93	90:10
5	HOAc (**12**)	6 days	95	90:10
6	H_3PO_4 (**13**)	11 days	97	92:8
7	*p*-TsOH (**14**)	12 days	99	85:15

[a] Used to form salt with **7**.
[b] Standard conditions were used, that is, 10 mol % **7**, 25 mol % *trans*-2,5-dimethylpiperazine, and 1.5 equiv nitroalkane in 1 ml.

As a general trend there is increased reaction rate with decreasing acidity of the acidic co-catalyst with no dramatic change in enantioselectivity. These observations are in line with a recent report from Gellman et al., on the involvement of proton sources as co-catalysts.[19] Typically, in presence of 4-nitrophenol, the reaction performed six times faster than for the original catalyst (entry 3). Although, phosphoric acid (H_3PO_4) provided an improved enantioselctivity, it also required a much longer reaction time. This could be due to the stronger conjugated base, which could assist in proton transfer in the activated complex. This raises the speculation as to whether the reaction proceeds through a mechanism involving electrophilic activation of the enone via hydrogen bonding.

To further evaluate the sensitivity of the reaction to conditions, we examined the presence of water as an additive at various concentrations (see Table 4). As a confirmation, addition of up to 10 mol % (1.0 equiv to catalyst) of water to catalyst **7** did not affect the reaction dramatically. However, the presence of water at higher concentrations resulted in the steady erosion of the enantioselectivity. These results are in contrast to those reported by Ley et al. who observed no decline in stereoselectivity during the addition of 2-nitropropane to methyl-4-phenyl-3-buten-2-one catalyzed by tetrazole catalyst **4**.[14]

Table 4
Water dependency in a THF system[a]

Water in THF (%)	Water[b] (mol %)	Conversion (%)	er **9** (%)
0	0	90	88:12
0.5	10	95	87:13
2.7	50	99	77:23
5.4	100	94	59:41
10.8	200	89	50:50
21.6	400	86	50:50

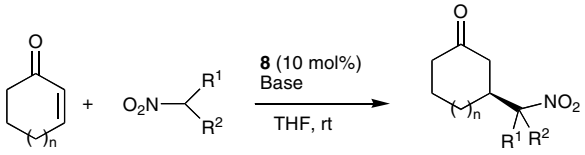
[a] All reagents, solvents, and reaction vessels were dried prior to use. Standard conditions were used, that is, 10 mol % **7**, 25 mol % *trans*-2,5-dimethylpiperazine, and 1.5 equiv nitroalkane in 1 ml. The reaction was run for 5 days.
[b] With respect to cyclohexenone.

Having established that α-aminophosphonate **8** is an effective catalyst for the addition of 2-nitropropane to cyclohexenone, we then considered the extension of this study to a variety of enones and nitroalkanes.

As a first extension of the Michael reaction to other substrates, the optimized reaction conditions were applied to various

nitroalkanes with cyclohexenone. Generally, these reactions performed well although in the presence of only 25 mol % of *trans*-2,5-dimethylpiperazine, and provided products in high yields and good enantioselectivities. However, the results were less satisfactory with nitromethane, while the reaction remained very enantioselective. The low yield of the nitromethane adduct can be attributed to the formation of by-products, presumably from a second addition reaction with another cyclohexenone. Higher concentrations of *trans*-2,5-dimethylpiperazine could allow for shorter reaction times (see Table 5).

Table 5
Michael addition of various nitroalkanes to cyclopentenone and cyclohexenone[a]



Product	*n*	Nitroalkane	Reaction time (h)	Conversion[b] (%)	Yield[c] (%)	dr[b]	er[b]
15	0	$R^1 = R^2 = H$	168	84	15	—	N.R.[d]
16	1	$R^1 = R^2 = H$	149	99	18		90:10
17	0	$R^1 = H$, $R^2 = Me$	57	97	64	52:48	84:16 84:16
18	1	$R^1 = H$, $R^2 = Me$	70	97	85	53:47	88:12 87:13
19	0	$R^1 = H$, $R^2 = Et$	80	97	72	51:49	87:13 87:13
20	1	$R^1 = H$, $R^2 = Et$	70	96	80	51:49	89:11 90:10
21	0	$R^1 = R^2 = Me$	80	100	68	—	86:14
9	1	$R^1 = R^2 = Me$	70	96	78		88:12

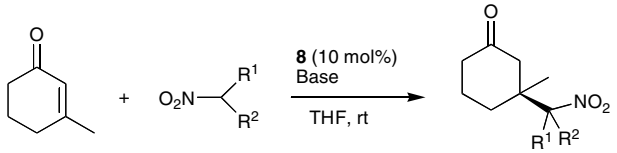
[a] Standard conditions were used, that is, 10 mol % **8**, 25 mol % *trans*-2,5-dimethylpiperazine, and 1.5 equiv nitroalkane in THF.
[b] Determined by chiral GC.
[c] Isolated yield.
[d] Not resolved on chiral GC.

Higher nitroalkanes provided the Michael products in high yield and retained the high stereoselectivity at the β-position, however; virtually no stereocontrol was achieved at the exocyclic stereocenter. The poor selectivities generally observed at the acidic γ-position have been attributed to epimerization under the basic conditions typically required for these reactions. The α-aminophosphonate **8** was also effective for the Michael addition of nitroalkanes to cyclopentanone. Similar to the reaction with cyclohexenone, nitromethane often led to a side reaction at the expense of the target 1,4-addition product. Unfortunately, the enantiomers of 3-nitromethylcyclopentanone could not be separated on chiral GC. In general, with the exception of nitromethane, reactions with cyclopentenone as a Michael acceptor provided the 1,4-addition product in moderate to good yield and good enantioselectivity. However, the diastereoselectivity remains a desirable achievement.

The use of bulkier 3-methylcyclohexenone, a rather uncommon substrate, for the addition of nitroalkanes was particularly tempting. The desired enantioselective nitro-addition would ensue, setting up a new quartenary stereogenic center, a more challenging operation than that for tertiary stereogenic centers (see Table 6).

In contrast to earlier reactions with nitromethane, 3-methylcyclohexenone is free from the drawbacks of side reactions. This is most likely due to the increased steric congestion of the substrate, thus preventing the addition of another 3-methylcyclohexenone. Despite the low reaction rate, good enantioselectivity was obtained and a well-defined diastereoselectivity, whereby the major diastereomer also shows the best enantioselectivity. Unfortunately, no

Table 6
The Michael addition of various nitroalkanes to 3-methylcyclohexenone[a]



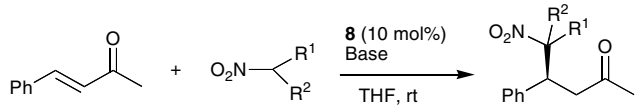
Product	Nitroalkane	Reaction time (days)	Conversion[b] (%)	Yield (%)	dr	er
22	$R = R' = H$	14	61	57	—	86:14
23	$R = H$, $R' = Me$	14	63	54	63:37	88:12 80:20
24	$R = H$, $R' = Et$	14	46	29	72:28	91:9 71:29
25	$R = R' = Me$	14	No reaction	—	—	—

[a] Standard conditions were used, that is, 10 mol % **8**, 25 mol % *trans*-2,5-dimethylpiperazine, and 1.5 equiv nitroalkane in THF.
[b] Determined by chiral GC.

Michael addition was detected with 2-nitropropane and 3-methylcyclohexenone.

A less reactive acceptor in the Michael addition, 4-phenyl-3-buten-2-one, displayed lower enantioselectivity than cyclic substrates. Typically, the reaction of 4-phenyl-3-buten-2-one with 2-nitropropane afforded 98% conversion and 68:32 er over six days (Table 7). By changing the Michael donor to less congested nitroalkanes, we obtained good results both with nitroethane and 1-nitropropane. These reactions provided a slightly improved er of 76:24, and gave a higher 3:2 diastereomeric ratio with 1-nitropropane.

Table 7
The Michael addition of different nitroalkanes to 4-phenyl-3-buten-2-one[a]



Product	Nitroalkane	Reaction time (days)	Conversion[b] (%)	dr[c]	er
26	$R^1 = R^2 = H$	6	92	—	N.R.[d]
27	$R^1 = H$, $R^2 = Me$	6	95	53:47	76:24 76:24
28	$R^1 = H$, $R^2 = Et$	6	97	60:40	76:24 N.R.[d]
29	$R^1 = R^2 = Me$	6	98	—	68:32

[a] Standard conditions were used, that is, 10 mol % **8**, 25 mol % *trans*-2,5-dimethylpiperazine and 1.5 equiv nitroalkane in THF.
[b] Determined by GC and NMR.
[c] Determined by NMR.
[d] Not resolved on chiral GC.

3. Conclusion

In conclusion, we have introduced chiral α-aminophosphonates as a new class of efficient catalysts for the asymmetric Michael addition of nitroalkanes to enones. The reaction provides good results for a range of substrates; the products are isolated in high yields with good to high enantioselectivities. Optimized reaction conditions also allow for catalytic loading (25 mol %) of *trans*-2,5-dimethylpiperazine as a base, using only 1.5 equiv of the nitroalkane. Furthermore, proton sources can be employed as acidic co-catalysts to ensure high reactivity while keeping a high level of enantioselectivity, thus alluding to the involvement of general acid catalysis. Thus, mechanistic studies are underway to develop more efficient aminophosphonate catalysts.

4. Experimental

4.1. General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. All solvents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over Na_2SO4. Thin layer chromatography was performed on aluminum plates coated with 60 F254 silica. Plates were visualized using UV light (254 nm) and phosphomolybdic acid (10% solution in ethanol). Flash column chromatography was performed on Kieselgel 60 silica (230–400 mesh). ^{1}H NMR spectra were recorded on Varian Unity 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from the solvent resonance as the internal standard ($CDCl_3$: 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = single, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on Varian Unity 400 (100 MHz) with complete proton decoupling ($CDCl_3$: 77.23 ppm). Chiral GC separations were performed using a Varian 3400 with a chiral column (Chirasil Dex-CB) using nitrogen as the carrier gas. The racemic samples were prepared by either using racemic proline or DBU as the catalyst. The major enantiomer was assigned by comparison of racemic Michael products with those reported in the literature using L-proline.

4.2. Diethyl (2*R*)-tetrahydropyrro-2-ylphosphonate 4-nitrophenolate 10

Dry catalyst **7** (7.5 mg, 0.036 mmol) was dissolved in THF (0.5 ml) and *p*-nitrophenol (5 mg, 0.036 mmol) was added and left to evaporate in air. The title compound was obtained in quantitative yield as a yellow-green viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (2H, d, J = 8 Hz, NO_2Ar*H*), 6.94 (2H, d, J = 8 Hz, OAr*H*), 4.20 (4H, m, P(=O)OCH_2), 3.52 (1H, m, PC*H*N), 3.17 (2H, m, NCH_2), 2.38–1.95 (4H, m, pyrrol-*H*), 1.36 (6H, t, J = 6.8 Hz, $POCH_2CH_3$).

4.3. Diethyl (2*R*)-tetrahydropyrro-2-ylphosphonate hydrochloride 11

Dry catalyst **7** (29.6 mg, 0.143 mmol) was dissolved in EtOH/HCl (0.5 ml, ~1 M) and left to evaporate in air. A yellow-brown viscous oil was obtained in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.03 (2H, br s, N^+H_2), 4.28 (4H, m, P(=O)OCH_2), 3.90 (1H, m, PC*H*N), 3.50 (2H, m, NCH_2), 2.32–2.07 (4H, pyrrol-*H*), 1.40 (6H, m, $POCH_2CH_3$).

4.4. Diethyl (2*R*)-tetrahydropyrro-2-ylphosphonate acetate 12

Dry catalyst **19** (21.4 mg, 0.103 mmol) was dissolved in AcOH (0.5 ml) and left to evaporate in air. The title compound was obtained in quantitative yield as a yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (2H, br s, NH_2), 4.19 (4H, m, P(=O)OCH_2), 3.58 (1H, m, PC*H*N), 3.15 (2H, m, NCH_2), 2.18–1.87 (4H, m, pyrrol-*H*), 2.08 (3H, s, CH_3C(=O)), 1.35 (6H, t, J = 6.8 Hz, $POCH_2CH_3$).

4.5. Diethyl (2*R*)-tetrahydropyrro-2-ylphosphonate hydrophosphate 13

Dry catalyst **19** (10.46 mg, 0.051 mmol) was dissolved in THF (0.5 ml), and phosphonicacid (5 mg, 0.051 mmol) was added and left to evaporate in air. The title compound was obtained in quantitative yield as a clear viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.23 (4H, m, P(=O)OCH_2), 3.73 (1H, m, PC*H*N), 3.37 (2H, m, NCH_2), 2.28–1.97 (4H, m, pyrrol-*H*), 1.37 (6H, m, $POCH_2CH_3$).

4.6. Diethyl (2*R*)-tetrahydropyrro-2-ylphosphonate *p*-tolulenesulfonate 14

Dry catalyst **19** (28.4 mg, 0.137 mmol) was dissolved in DEE (0.5 ml), and *p*-toluenesulfonicacid *monohydrate* (26 mg, 0.136 mmol) was added and left to evaporate in air. The title compound was obtained in quantitative yield as a yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.89 (1H, br s, N*H*H′), 8.89 (1H, br s, NH*H*′), 7.75 (2H, d, J = 8 Hz, $S(O)_2$Ar*H*), 7.18 (2H, d, J = 8 Hz, CH_3Ar*H*), 4.20 (4H, m, P(=O)OCH_2), 3.93 (1H, m, PC*H*N), 3.51 (2H, m, NCH_2), 2.34 (3H, s, PhCH_3), 2.33–2.01 (4H, m, pyrrol-*H*), 1.32 (6H, m, $POCH_2CH_3$).

4.7. General procedure: nitroalkane Michael addition to enones

Catalyst **8** (0.033 mmol, 10 mol %), *trans*-2,5-dimethylpiperazine (0.0825 mmol, 25 mol %), enone (0.33 mmol), and nitroalkane (0.5 mmol) were added to a vial together with THF (270 μl). The mixture was stirred at rt and monitored with chiral GC. Samples were quenched by adding ethylacetate (2 ml) and $NH_4Cl_{(sat)}$ (1 ml). The aqueous phase was extracted with additional ethylacetate (1 ml). The organic phases were combined and dried with Na_2SO_4, and the solvent removed under reduced pressure. Column chromatography on silica gel afforded pure product.

4.8. (*S*)-3-(Nitromethyl)cyclopentanone 15[10b]

The reaction mixture was quenched after 168 h. Purification using column chromatography (EtOAc–heptane 1:2) gave the title compound as a colorless oil (7.0 mg, 0.049 mmol, 15%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.48 (2H, d, J = 7.2 Hz, NO_2CH_2), 3.06–2.98 (1H, m, $CHCH_2NO_2$), 2.58–2.52 (1H, m, C(=O)C*H*H′CHR), 2.46–2.23 (3H, m, C(=O)CH*H*′CHR, C(=O)CH_2CH_2), 2.06–1.98 (1H, m), 1.76–1.58 (2H, m). Chiral GC: Chirasil Dex-CB could not resolve enantiomers.

4.9. (*S*)-3-(Nitromethyl)cyclohexanone 16[14a]

The reaction mixture was quenched after 149 h. Purification using column chromatography (EtOAc–heptane 1:3) gave the title compound as a colorless oil (9.4 mg, 0.0599 mmol, 18%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.36 (2H, m, CH_2NO_2), 2.66 (1H, m, $CHCH_2NO_2$), 2.48 (1H, m, C(=O)C*H*H′CH), 2.42 (1H, m, C(=O)C*H*H′CH_2) 2.34–2.26 (1H, m, C(=O)C*H*′HCH_2), 2.20–2.14 (1H, m, C(=O)C*H*′HCH), 2.16–2.10 (1H, m, C(=O)CH_2C*H*H′), 2.01–2.97 (1H, m, CHRC*H*H′), 1.78–1.69 (1H, m, C(=O)CH_2CH*H*′), 1.57–1.47 (1H, m, CHRCH*H*′). Chiral GC: Chirasil Dex-CB, 125 °C, 56.9 min (major), 57.9 min (minor) gave 90:10 er.

4.10. (1′*R*,3*S*)-3-(Nitroethyl)cyclopentanone and (1′*S*,3*S*)-3-(nitroethyl)cyclopentanone 17[10b]

The reaction mixture was quenched after 57 h. Purification using column chromatography (EtOAc–heptane 1:2) gave the title compound as a colorless oil (33.2 mg, 0.210 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.52 (1H, m, $CHNO_2$), 2.78–2.68 (1H, m, NO_2CHCH) 2.48–2.37 (2H, m, C(=O)CH_2CH_2), 2.31–2.15 (2H, m, C(=O)CH_2CHR), 2.13–2.04 ($1H_{maj}$, m, C(=O)CH_2H′), 1.98–1.91 ($1H_{min}$, m, C(=O)CH_2H′), 1.77–1.64 (1H, m, C(=O)CH_2H′), 1.63 ($3H_{min}$, d, J = 6.4 Hz, NO_2CHCH_3), 1.60 ($3H_{maj}$, d, J = 6.8 Hz, NO_2CHCH_3). Chiral GC: Chirasil Dex-CB, 120 °C, major diastereoisomer: 33.7 min (major), 34.9 min (minor); minor

diastereoisomer: 36.8 min (major), 37.5 min (minor) gave 52:48 dr and 84:16/84:16 er.

4.11. (1′*R*,3*R*)-3-(1′-Nitroethyl)cyclohexanone and (1′*S*,3*R*)-3-(1′-nitroethyl)cyclohexanone 18[14a]

The reaction mixture was quenched after 70 h. Purification using column chromatography (EtOAc–heptane 1:3) gave the title compound as a colorless oil (47.7 mg, 0.279 mmol, 84.5%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.51 (1H, m, C*H*NO_2), 2.49–2.42 (2H, m, C(=O)CH_2CH), 2.37–2.23 (2H, m, C(=O)CH_2CH_2), 2.18–2.09 (2H, m, C(=O)CH$_2$C*H*H′ CH$_2$C*H*R), 1.97–1.87 (1H, m, CHC*H*H′), 1.72–1.66 (1H, m, C(=O)CH$_2$CH*H*′), 1.62–1.42 (5H, m, C(NO_2)HCH_3, CH$_2$CH_2CH). Chiral GC: Chirasil Dex-CB, 120 °C, major diastereoisomer: 40.9 min (minor), 41.4 min (major); minor diastereoisomer: 46.2 min (major), 47.8 min (minor) gave 53:47 dr and 88:12/87:13 er.

4.12. (1′*R*,3*S*)-3-(1′-Nitropropyl)cyclopentanone and (1′*S*,3*S*)-3-(1′-nitropropyl)cyclopentanone 19

The reaction mixture was quenched after 80 h. Purification using column chromatography (EtOAc–heptane 1:3) gave the title compound as a colorless oil (40.7 mg, 0.236 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.34 (1H, dt, J = 9.6, 3.2 Hz, NO_2C*H*), 2.73 (1H, m, NO_2CHC*H*), 2.49–2.35 (2H, m, C(=O)CH_2CH_2), 2.30–2.20 (1H, C(=O)C*H*H′CHR), 2.18–1.92 (3H, m, C(=O)CH*H*′CHR, C(=O)CH$_2$C*H*H′), 1.85–1.59 (3H, m, C(=O)CH$_2$CH*H*′, NO_2CHCH_2), 1.01 (3H$_{min}$, t, J = 7.4 Hz, CH$_2$CH_3), 1.00 (3H$_{maj}$, t, J = 7.4 Hz, CH$_2$CH_3). Chiral GC: Chirasil Dex-CB gave 49:51 dr and 87:13/87:13 er.

4.13. (1′*R*,3*S*)-3-(1′-Nitropropyl)cyclohexanone and (1′*S*,3*S*)-3-(1′-nitropropyl)cyclohexanone 20[10b]

The reaction mixture was quenched after 70 h. Purification using column chromatography (EtOAc–heptane 1:3) gave the title compound as a colorless oil (48.6 mg, 0.262 mmol, 79.4%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.38–4.27 (1H, m, C*H*NO_2), 2.52–2.40 (2H, m, C(=O)CH_2CH), 2.33–2.23 (3H, m, C(=O)CH_2CH$_2$, C(=O)CH$_2$C*H*H′), 2.16–2.07 (1H, m, C*H*H′CH$_3$), 2.05–1.93 (1H, m, C(=O)CH$_2$C*H*R′), 1.88–1.78 (2H, m, CH$_2$CH_2CHR), 1.69–1.42 (2H, m, CH*H*′CH$_3$, C(=O)CH$_2$CH*H*′), 0.99–0.95 (3H, m, CH_3). Chiral GC: Chirasil Dex-CB, 125 °C, major diastereoisomer: 38.2 min (major), 38.9 min (minor); minor diastereoisomer: 42.5 min (major), 43.3 min (minor) gave 51:49 dr and 89:11/90:10 er.

4.14. (*S*)-3-(2-Nitropropane-2-yl)cyclopentanone 21[14a]

The reaction mixture was quenched after 80 h. Purification using column chromatography (EtOAc–heptane 1:3) gave the title compound as a colorless oil (38.3 mg, 0.223 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.86 (1H, m, C*H*C$(CH_3)_2NO_2$), 2.45–2.20 (3H, m, CH_2C(=O)C*H*H′), 2.14–2.03 (2H, m, C(=O)CH*H*′, C(=O)CH$_2$C*H*H′), 1.74–1.60 (1H, m, C(=O)CH$_2$CH*H*′), 1.63 (3H, s, CH_3), 1.62 (3H, s, CH_3). Chiral GC: Chirasil Dex-CB gave 86:14 er.

4.15. (*S*)-3-(2-Nitropropane-2-yl)cyclohexanone 9[14a]

The reaction mixture was quenched after 70 h. Purification using column chromatography (EtOAc–heptane 1:3) gave the title compound as white crystals (47.6 mg, 0.256 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45–2.36 (3H, m, C*H*CNO_2, C(=O)C*H*H′CH$_2$, C(=O)C*H*H′CH), 2.26–2.21 (1H, m, C(=O)CH*H*′CH$_2$), 2.16–2.09 (2H, m, C(=O)CH*H*′CH, C(=O)CH$_2$C*H*H′), 1.82–1.79 (1H, m, CHRC*H*H′CH$_2$), 1.64 (1H, m, C(=O)CH$_2$CH*H*′), 1.58 (3H, s, CH_3), 1.57 (3H, s, C*H*′$_3$), 1.47–1.40 (1H, m, CHRCH*H*′CH$_2$). Chiral GC: Chirasil Dex-CB, 130 °C, 35.5 min (major), 36.7 min (minor) gave 88:12 er.

4.16. (*S*)-3-Methyl-3-(nitromethyl)cyclohexanone 22[14a]

The reaction mixture was quenched after 14 days. Purification using column chromatography (EtOAc–heptane 1:6) gave the title compound as a colorless oil (27.7 mg, 0.187 mmol, 57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.30 (2H, dd, J = 20.0, 10.8 Hz, CH_2NO_2), 2.45–2.05 (4H, m, CH_2C(=O)CH_2), 2.06–1.71 (4H, m, C(=O)CH$_2$CH_2CH$_2$), 1.13 (3H, s, CH_3). Chiral GC: Chirasil Dex-CB, 125 °C, 32.8 min (major), 34.3 min (minor) gave 86:14 er.

4.17. (1′*R*,3*S*)-3-Methyl-3-(nitroethyl)cyclohexanone and (1′*S*,3*S*)-3-methyl-3-(nitroethyl)cyclohexanone 23

The reaction mixture was quenched after 14 days. Purification using column chromatography (EtOAc–heptane 1:8) gave the title compound as a colorless oil (33.4 mg, 0.179 mmol, 54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.52 (1H, q, J = 7.2 Hz, C*H*NO_2), 2.54–1.98 (5H, m, CH_2C(=O)CH_2, C(=O)CH$_2$C*H*H′), 1.89–1.63 (3H, m, C(=O)CH$_2$CH*H*′, CH$_2$CH_2CHR), 1.52 (3H$_{min}$, d, J = 6.4 Hz, CHNO_2CH_3), 1.51 (3H$_{maj}$ d, J = 6.8 Hz, CHNO_2CH_3), 1.02 (3H$_{maj}$, s, CRCH_3), 1.00 (3H$_{min}$, s, CRCH_3). Chiral GC: Chirasil Dex-CB, 125 °C, major diastereoisomer: 33.8 min (major), 35.4 min (minor); minor diastereoisomer: 38.2 min (major), 41.6 min (minor) gave 63:37 dr and 88:12/80:20 er.

4.18. (1′*R*,3*S*)-3-Methyl-3-(nitropropyl)cyclohexanone and (1′*S*,3*S*)-3-methyl-3-(nitropropyl)cyclohexanone 24

The reaction mixture was quenched after 14 days. Purification using column chromatography (EtOAc–heptane 1:10) gave the title compound as a colorless oil (19.1 mg, 0.097 mmol, 29%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.27 (1H, dt, J = 9.2, 1.8, C*H*NO_2), 2.58–2.12 (4H, m, CH_2C(=O)CH_2), 2.11–1.98 (2H, m, C(=O)CH$_2$C*H*H′, CHNO_2C*H*H′), 1.88–1.73 (3H, m, C(=O)CH$_2$CH*H*′, CHNO_2CH*H*′, CH$_2$C*H*H′C(CH_3)R), 1.72–1.57 (1H, m, CH$_2$C*H*H′C(CH_3)R), 1.05 (3H$_{maj}$, s, CRCH_3), 1.01 (3H$_{min}$, s, CRCH_3), 0.96 (3H, t, J = 7.0, CH$_2$CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.52, 99.69 (min), 98.48 (maj), 50.50 (maj), 48.89 (min), 41.98 (maj), 41.43 (min), 40.83, 33.19 (min), 33.04 (maj), 21.54, 21.34, 20.73, 11.18. Chiral GC: Chirasil Dex-CB, 130 °C, major diastereoisomer: 30.1 min (major), 32.2 min (minor); minor diastereoisomer: 35.3 min (major), 37.3 min (minor) gave 72:28 dr and 91:9/71:29 er.

4.19. (4*S*)-5-Nitro-4-phenylpenta-2-one 26[14a]

The reaction mixture was quenched after six days. NMR analysis showed the title compound in 91% compared to other species. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.21 (5H, m, Ar*H*), 4.70 (1H, dd, NO_2C*H*H′), 4.60 (1H, dd, NO_2CH*H*′), 4.01 (1H, m, PhC*H*), 2.93 (2H, dd, J = 6.8 Hz, C(=O)CH_2CHPhR), 2.13 (2H, s, CH_3C(=O)). Chiral GC: Chirasil Dex-CB could not resolve enantiomers.

4.20. (4*S*,5*R*)-5-Nitro-4-phenylhexan-2-one and (4*S*,5*S*)-5-nitro-4-phenylhexan-2-one 27[14a]

The reaction mixture was quenched after six days. NMR analysis showed the title compound in 92% compared to other species with 53:47 dr. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.13 (5H, m, Ar*H*), 4.89 (1H$_{min}$, m, NO_2C*H*), 4.76 (1H$_{maj}$, m, NO_2C*H*), 3.72 (1H, m, PhC*H*), 3.09–2.72 (2H, m, C(=O)CH_2CHPhR), 2.13 (3H$_{min}$, s, CH_3C(=O)), 2.02 (3H$_{maj}$, s, CH_3C(=O)), 1.49 (3H$_{min}$, d, J = 6.8 Hz, NO_2CHCH_3), 1.33 (3H$_{maj}$, d, J = 6.4 Hz, NO_2CHCH_3). Chiral GC: Chirasil Dex-CB, 130 °C, major diastereoisomer: 28.9 min (major),

29.6 min (minor); minor diastereoisomer: 32.7 min (major), 33.6 min (minor) gave 76:24/76:24 er.

4.21. (4*S*,5*R*)-5-Nitro-4-phenylheptan-2-one and (4*S*,5*S*)-5-nitro-4-phenylheptan-2-one 28

The reaction mixture was quenched after six days. NMR analysis showed the title compound in 94% compared to other species with 60:40 dr. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.13 (5H, m, Ar*H*), 4.70 (1H$_{min}$, m, NO_2CH), 4.58 (1H$_{maj}$, m, NO_2CH), 3.77–3.67 (1H, m, PhC*H*), 3.06–2.65 (2H, m, C(=O)C*H*$_2$CHPhR), 2.11 (3H$_{min}$, s, C*H*$_3$C(=O)), 1.99 (3H$_{maj}$, s, C*H*$_3$C(=O)), 1.94–1.75 (2H, m, NO_2CHCH_2), 0.96 (3H$_{min}$, t, J = 7.2 Hz, CH_2CH_3), 0.84 (3H$_{min}$, t, J = 7.2 Hz, CH_2CH_3). Chiral GC: Chirasil Dex-CB, 125 °C, major diastereoisomer: 41.0 min (minor), 41.6 min (major) gave 76:24 er and could not resolve the second diastereomer at 49.8 min.

4.22. (*S*)-5-Methyl-5-nitro-4-phenylhexan-2-one 29[14a]

The reaction mixture was quenched after six days. NMR analysis showed the title compound in 95% compared to other species. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.19 (5H, m, Ar*H*), 3.95 (1H, dd, J = 3.2, 10.8 Hz, PhC*H*), 3.09 (1H, dd, J = 11.2, 17.2 Hz, C(=O)C*H*H′), 2.72 (1H, dd, J = 3.6, 17.2 Hz, C(=O)CH*H*′), 2.04 (3H, s, C(=O)C*H*$_3$), 1.56 (3H, s, C(NO_2)C*H*$_3$), 1.49 (3H, s, C(NO_2)C*H*$_3$). Chiral GC: Chirasil Dex-CB, 140 °C, 22.2 min (major), 22.7 min (minor) gave 68:32 er.

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