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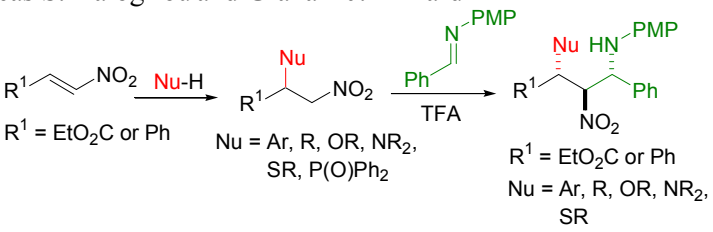

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Conjugate addition nitro-Mannich reaction of carbon and heteroatom nucleophiles to nitroalkenes

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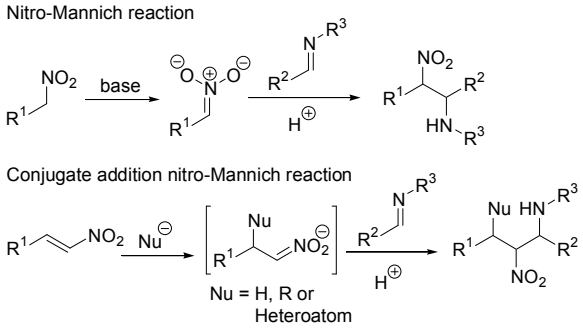
ABSTRACT

The conjugate addition nitro-Mannich reactions of ethyl-β-nitroacrylate (**1**) and β-nitrostyrene (**2**) with electron rich aromatic nucleophiles, stabilized carbanions, alcohols, amines, thiols, and diphenyl phosphine oxide were investigated. The one pot conjugate addition nitro-Mannich reaction was unsuccessful except for the addition of alkoxides to **2** in alcohol as solvent. Isolation of the conjugate addition products followed by deprotonation with ^{n}BuLi and treatment with a simple imine in the presence of TFA led to β-nitroamine derived products. Products derived from **1** spontaneously cyclised in only a few examples and on the whole led to inherently unstable products. Products derived from **2** were isolated as their trifluoroacetamides, gave good yields of single diastereoisomers for aromatic and alkoxide nucleophiles and the structures were verified by single crystal X-ray crystallography. Products derived from amine nucleophiles were isolated in low yields while sulfur nucleophiles gave poor diastereoselectivities.

1. Introduction

The nitro-Mannich reaction has emerged as a powerful method for the construction of C-C bonds with control of up to two contiguous C-N stereocentres in the β-nitroamine products (Scheme 1).[1] The product *β*-nitroamines have emerged as flexible synthetic building blocks due to the complimentary oxidation states of the two nitrogen atoms. They have been used in the synthesis of many nitrogen containing functional groups including *α*-amino carbonyls,[2,3] 1,2-diamines,[4-7] peptidomimetics,[8] natural products[9-15] and many heterocyclic small molecules.[16-29] To address the paucity of structurally diverse nitroalkanes we have developed conjugate addition nitro-Mannich protocols (Scheme 1).[30-32] The use of nitroalkenes (prepared via the Henry reaction) provides easy access to more structurally complex nitro coupling partners, thereby generating β-nitroamines with higher levels of functionality which may be further manipulated to produce a range of useful intermediates. The 1,4-addition of nucleophiles to nitroalkenes generates a nitronate species which can undergo a subsequent nitro-Mannich reaction with a suitable imine. The use of a Hantzsch ester as a hydride source and a simple chiral thiourea organocatalyst to catalyse the reductive nitro-Mannich reaction, gave access to enantio-enriched and structurally diverse β-nitroamines.[32] Enantioselective 1,4-addition of dialkylzincs to nitroalkenes generated zinc nitronates, which when reacted with an imine gave complex β-nitroamines with excellent diastereocontrol over three contiguous stereocentres.[30] Two distinct stereochemical outcomes were possible, dependent upon the choice of solvent, which dictated whether the reaction was homogeneous or heterogeneous. We extended this strategy to the addition of diorganozinc nucleophiles to ethyl-β-nitroacrylate, the products of which spontaneously lactamized *in situ* to give densely substituted pyrrolidin-2-ones.[27] Up to the present time, the conjugate addition nitro-Mannich methodology has been limited to the use of diorganozinc and hydride reagents. We thought that the use of more readily available carbon nucleophiles and especially heteroatom nucleophiles would greatly increase the versatility of the conjugate addition nitro-Mannich reaction.



Scheme 1.

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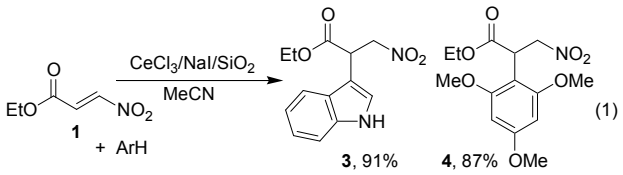
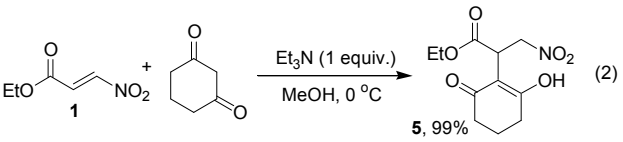
2. Results and Discussion

A number of heteroatom nucleophiles are known to add to nitro-alkenes. Furthermore, possible modification of the Nu group in the final products could enable further applications in target synthesis. From the large number of possible nucleophiles, we concentrated on a representative sample of carbon, oxygen, nitrogen, sulfur and phosphorus nucleophiles. The scope of nitroalkenes that could be used is potentially large, so for this investigation we selected to study the reactions of ethyl-β-nitroacrylate (**1**) and *β*-nitrostyrene (**2**), as we have used both of these extensively in previous studies.[27,30-32]

We investigated the 1,4-addition reactions to nitroacrylate **1** first. The addition of electron rich aromatics such as indole derivatives to **1** is known to be promoted by $CeCl_3$/NaI supported on silica.[33] There also exists an organocatalysed asymmetric protocol.[34] Synthesis of the indole addition product **3** was straightforward (91%) and the literature conditions could also be used with trimethoxybenzene to give **4** in 87% yield (Equation 1).



The attempted addition of some stabilized nucleophiles derived from Meldrum's acid, malononitrile and diethyl malonate under neutral conditions, with a variety of amines and NaH were all unsuccessful. By analogy to an example in the literature though 1,3-cyclohexanedione in the presence of Et_3N led to the addition product **5** in nearly quantitative yield (Equation 2).[35]



The 1,4-addition of oxygen nucleophiles to nitroalkenes is well documented,[36] so the corresponding additions of alcohols to nitroacrylate **1** were investigated (Equation 3). Addition of a solution of MeONa in MeOH (0.10 M) to a solution of nitroacrylate at rt, gave only degradation of the starting material (baseline on TLC). This result was attributed to base-catalysed polymerization. Reversing the addition mode led to the formation of the 1,4-addition product **6** in 62% yield, after quenching with AcOH and aqueous workup (entry 2, Table 1). Performing the same reaction at -78 °C gave **6** in an improved 80% yield (entry 3). Furthermore, when nitroacrylate **1** was refluxed in MeOH for 24 h, **6** was isolated in 85% yield (entry 4). It was found that activation of the nitroacrylate **1** under acidic conditions was ineffective in promoting the conjugate addition of alcohols. Other simple alcohols EtOH and BnOH when refluxed with **1** gave the corresponding addition products **7** and **8** in 89% and 62% yield respectively (entries 5 and 6). Reaction with phenol was unsuccessful (entries 7-10) as was attempts at the 1,4-addition of H_2O/hydroxide ion.

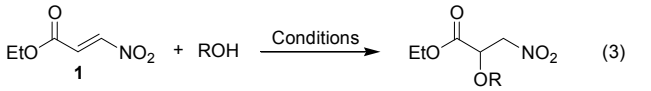


Table 1. 1,4-addition of ROH to nitroacrylate **1**.

Entry	ROH/conditions	Compound	Yield/%[a]
1	MeONa/MeOH added to **1**, rt	-	-
2	**1** added to MeONa/MeOH, rt	**6**	62
3	**1** added to MeONa/MeOH, -78 °C	**6**	80
4	MeOH, reflux	**6**	85
5	EtOH, reflux	**7**	89
6	BnOH, 100 °C	**8**	62
7	PhOH/PhMe, rt	-	-
8	PhOH/PhMe, reflux	-	-
9	PhOH/PhMe, K_2CO_3 (0.3 equiv), rt	-	-
10	PhOH, melt (70 °C)	-	-

[a]Isolated yields.

The 1,4-addition of nitrogen nucleophiles was subsequently investigated. Simply mixing nitroacrylate **1** with simple substituted amines in most cases gave fast and clean reactions (Equation 4, Table 2). Reactions with hydrazine and ammonia were unsuccessful, as was reaction with oxazolidin-2-one, which was surprising as it is known to add to simple nitroalkenes quite readily.[37]

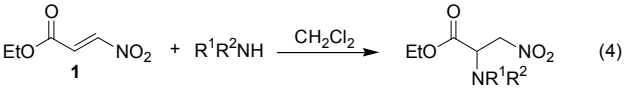
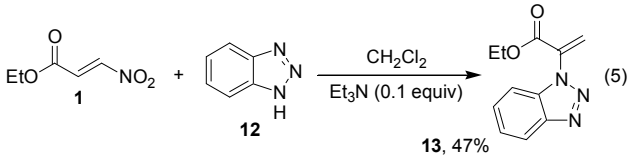


Table 2. 1,4-addition of substituted amines to nitroacrylate **1**.

Entry	R^1R^2NH (equivs.)	T/°C	t/h	Compound	Yield/%[a]
1	*p*-MeOPhNH$_2$ (1.8)	rt	24	**9**	98
2	Morpholine (1.2)	rt	1	**10**	98
3	$BnNH_2$ (1.1)	0	1	**11**	81

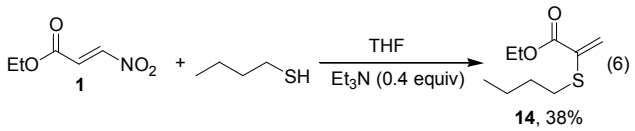
[a]Isolated yields.

In a similar manner the 1,4-addition of 1*H*-benzotriazole (**12**) was attempted, but gave no reaction. In the presence of catalytic Et_3N (0.1 equiv.) product **13**, derived from elimination of HNO_2 from the desired addition product, was isolated in 47% yield (Equation 5). Elimination of HNO_2 from nitroalkanes under basic or acidic conditions has been reported and in this case is exacerbated by the acidifying effect of the ester group.[38]



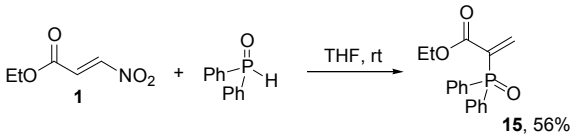
The conjugate addition of a sulfur and a phosphorus nucleophile was also investigated. Despite following the literature precedent with 1-propanethiol,[39] treatment of nitroacrylate **1** with 1-butanethiol in the presence of catalytic Et_3N led to consumption of starting material over 24 h, but

again gave elimination of HNO_2 to give **14** in 38% yield (Equation 6). Repeating the reaction in the absence of base, with 1-butanethiol (1.00 equiv.), in EtOH, at rt, was much faster (consumption of starting material in 10 min), but again failed to provide the desired product. Only a baseline spot was observed on TLC indicating degradation, presumably due to polymerisation.



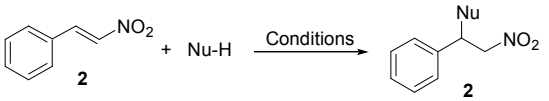
(6)

Simple addition of diphenylphosphine (1.10 equiv.) to a solution of **1** in THF, at rt, led to complete consumption of the starting material in 20 min. It was not possible to isolate any product, due to instability to purification. As phosphines are prone to oxidation we repeated the reaction with diphenylphosphine oxide. The reaction was slower (completed in 17 h), but unfortunately the only product isolated was the eliminated product **15** in 56% yield (Equation 7).



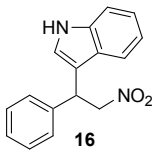
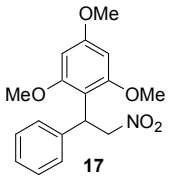
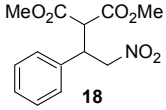
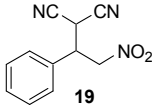
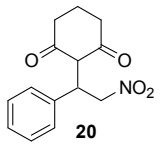
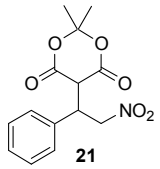
(7)

Investigations into the 1,4-addition of a similar series of nucleophiles to β-nitrostyrene (**2**) were generally more successful. Reaction with electron rich aromatics and stabilized carbon nucleophiles worked well in most cases to give the desired products (Equation 8, Table 3).



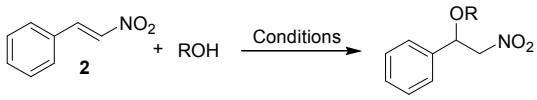
(8)

Table 3. 1,4-additions of carbon nucleophiles to β-nitrostyrene (**2**).

Entry	NuH/conditions	Compound	Yield/%[a]
1	Indole, $CeCl_3$/NaI/SiO_2[33]	 **16**	92
2	2,4,6-$(MeO)_3$Ph, $CeCl_3$/NaI/SiO_2[33]	 **17**	71
3	$CH_2(CO_2Et)_2$, NaH, THF[40]	 **18**	96
4	$CH_2(CN)_2$, NaH, 15-crown-5, THF	-	-
5	$CH_2(CN)_2$, proline, DMF[41]	 **19**	89
6	1,3-cyclohexadione, Et_3N, THF	-	-
7	1,3-cyclohexadione, MeONa, MeOH[42]	 **20**	34
8	Meldrum's acid, Et_3N, CH_2Cl_2[43]	 **21**	96
9	1-phenylvinyl trimethylsilyl ether, TBAF, THF -45 °C[44]	-	-

[a]Isolated yields.

In contrast to the 1,4-addition of simple alcohols to nitroacrylate **1**, reflux of β-nitrostyrene (**2**) in methanol gave no reaction (Equation 9, Table 4, entry 1). Attempts at an acid catalysed 1,4-addition of MeOH were also ineffective (entries 2,3). Addition of MeONa was much more successful with treatment in MeOH giving the highest yield of **22** (entries 4-6).[45] The optimized conditions were then applied to a range of other simple alcohols (entries 7-9). The use of ^{t}BuOH (mp = 23-26 °C) as the solvent required warming to 30 °C which led to a poor yield of 1,4-addition product **26** (entry 10). Using THF as a cosolvent was much more effective giving **26** in 40% yield (entry 14).



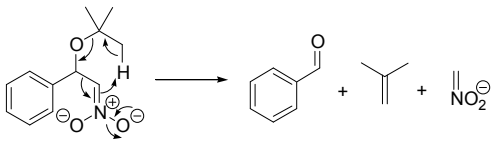
(9)

Table 4. 1,4-addition of ROH to β-nitrostyrene (**2**).[a]

Entry	ROH/conditions	Compound	Yield/%[b]
1	MeOH, reflux, 22 h	-	-
2	MeOH, TFA (10 equiv.)	-	-
3	MeOH, H_2SO_4 (2 equiv.)	-	-
4	MeONa, 15-crown-5, THF	**22**	53
5	MeONa, MeOH, Et_2O	**22**	62
6	MeONa, MeOH	**22**	73
7	EtONa, EtOH	**23**	66
8	BnONa, BnOH	**24**	66
9	^{i}PrONa, ^{i}PrOH	**25**	58
10	^{t}BuONa, ^{t}BuOH	**26**	9
11	^{t}BuONa, ^{t}BuOH, DMF	Degradation[c]	-
12	^{t}BuONa, 18-crown-6, THF	Degradation[c]	-
13	^{t}BuONa, (0.53 M in ^{t}BuOH), THF[d]	**2** and PhCHO	-
14	^{t}BuONa, (0.53 M in ^{t}BuOH), THF	**26**	40

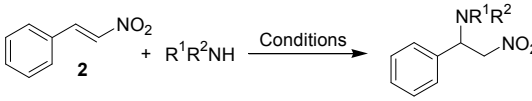
[a]Alkoxide (1 equiv.) and reactions quenched with AcOH (6 equiv.). [b]Isolated yields. [c]baseline by TLC. [d]reaction quenched with satd. aq. NH_4Cl.

For entry 13 (Table 4) although TLC indicated complete consumption of starting material to the 1,4-addition product **26**, after work up with saturated aqueous NH_4Cl only a trace of **26** was observed. Instead there was a complex mixture of degradation products among which we could identify benzaldehyde and β-nitrostyrene (**2**). While the formation of **2** can be readily explained by base catalysed elimination of ^{t}BuOH, the presence of benzaldehyde can be explained by elimination of 2-methylpropene and nitromethane (Equation 10).



(10)

The 1,4-addition of amines required some investigation, but a number of different substrates could be synthesized (Equation 11, Table 5). While stirring with electron rich 2,4-dimethoxyaniline gave a good yield of 1,4-addition product **27** (70%, Entry 1), the less nucleophilic parent aniline was unreactive (Entry 2). By analogy to the literature, performing the reaction in water worked well (68%, Entry 3).[46] The electron withdrawn *para*-nitroaniline was unreactive under both sets of conditions, but deprotonation with ^{n}BuLi and subsequent addition to nitroalkene **2** gave the desired 1,4-addition product **29** in 45% yield (entry 4). Reaction with morpholine in CH_2Cl_2 at rt gave complete consumption of starting material, but only a small yield (22%) of 1,4-addition product **30** was isolated (entry 5). Performing the reaction in the presence of catalytic $Sm(OTf)_3$ (0.2 equiv.)[47] was much more successful leading to a 94% yield of the addition product **30** (entry 6). The reaction of **2** with hydrazine in MeOH led to degradation. A solution of ammonia in THF gave no addition product, while saturating a solution of **2** with ammonia gas caused degradation. Reaction with benzotriazole (**12**) in CH_2Cl_2 at rt gave isolation of the 1,4-addition product in good 83% yield (entry 7). Reaction with 2-oxazolidinone required deprotonation with ^{t}BuOK and 18-crown-6 (entry 8).[37]



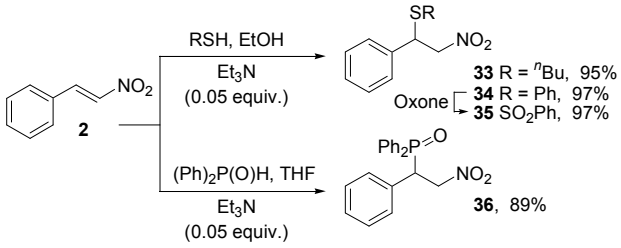
(11)

Table 5. 1,4-addition of amines to β-nitrostyrene (**2**).

Entry	R^1R^2NH/conditions	Compound	Yield/%[a]
1	2,4-diMeOPhNH$_2$ / CH_2Cl_2	**27**	70
2	PhNH$_2$ / CH_2Cl_2	-	-
3	PhNH$_2$ / H_2O	**28**	67
4	4-NO_2PhNH$_2$ / ^{n}BuLi / THF	**29**	45
5	HN(CH_2CH_2)$_2$O / CH_2Cl_2	**30**	22
6	HN(CH_2CH_2)$_2$O / $Sm(OTf)_3$ / CH_2Cl_2	**30**	94
7	**12** / CH_2Cl_2	**31**	83
8	2-oxazolidinone / ^{t}BuOK / 18-C-6 / THF	**32**	90

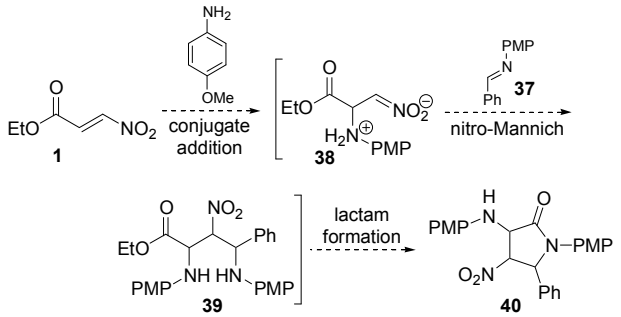
[a]Isolated yields.

The conjugate addition of thiols proceeded by analogy to the literature and gave the sulfides **33** and **34** by the smooth addition of 1-butanethiol and thiophenol respectively (Scheme 2). Sulfide **34** was also oxidized to its corresponding sulfone by Oxone® in MeOH/H_2O[38] to give **35** in 97% yield. Treatment of **2** with diphenylphosphine oxide gave the 1,4 addition product **36** in 89% yield.



Scheme 2.

With a variety of 1,4-addition reactions with ethyl-β-nitroacrylate (**1**) and *β*-nitrostyrene (**2**) characterized for a range of non diorganozinc nucleophiles, we first investigated whether it was feasible to conduct a conjugate addition nitro-Mannich reaction with **1**. Our previous work with diorganozinc nucleophiles to **1** gave products which had spontaneously lactamized *in situ* to give densely substituted pyrrolidin-2-ones.[27] We had shown that *p*-anisidine added directly to **1** (Equation 4, Table 2) and we repeated this reaction in the presence of imine **37** to explore whether the intermediate nitronate species **38** would undergo a nitro-Mannich reaction to give **39** and whether this would cyclise spontaneously or otherwise to **40** (Scheme 3). We hoped that the acidic proton in **38** would be able to protonate imine **37** to facilitate the nitro-Mannich reaction.[4]

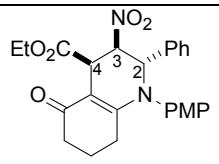
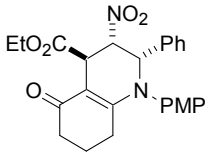
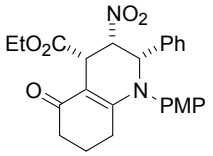
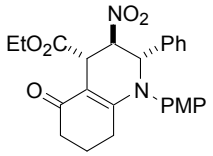


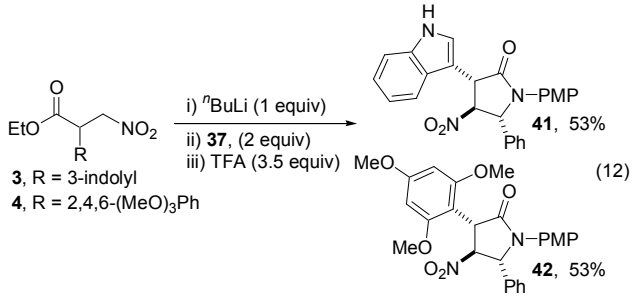
Scheme 3. Investigation of desired reaction (PMP=*p*-methoxyphenyl).

Mixing of the reactants in PhMe only led to isolation of the 1,4-addition product **9** (tautomer of **38**) in 86% yield. Repeating the reaction in CH_2Cl_2 at rt or reflux led to quantitative conversion to **9**. The addition of acid was investigated by mixing the reactants in THF and adding TFA (3 equiv to **1**), but this again gave **9** in 93% yield after 24 h. The use of the more electrophilic *p*-tosylimine and other nucleophiles: morpholine, phenol and 1-butanethiol were all surveyed under a variety of different conditions, but were all unsuccessful.

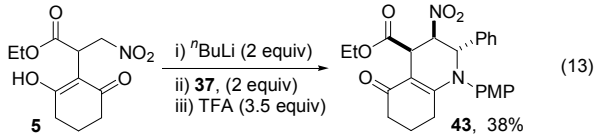
In light of these results we decided to investigate a two step process where the 1,4-addition product was deprotonated with ^{n}BuLi to form a nitronate species, and then imine and acid added. We were pessimistic of this strategy due to perceived problems with β-elimination of the 1,4-addition products. However reaction of **3** and **4** derived from electron rich π carbon nucleophiles gave highly functionalized pyrrolidinones in moderate yields, but as single diastereoisomers (Equation 12).

Table 6. Calculated selected coupling constants and internuclear distances for all diastereoisomers of **43**.

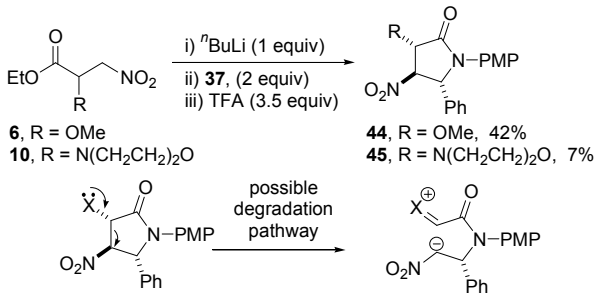
	 **43** *cis/trans*	 *trans/cis*	 *cis/cis*	 *trans/trans*
$J_{H2\text{-}H3}$ (Hz)	10.6	3.4	2.0	10.6
$J_{H3\text{-}H4}$ (Hz)	4.5	12.1	3.9	11.8
H2-H4 (Å)	3.84	3.84	2.45	2.64
H3-H4 (Å)	3.06	3.08	2.41	3.09



It would be highly unlikely for the aromatic side chains in **3** and **4** to β-eliminate. Nitroalkane **5** could eliminate a stabilized anion, but reacted under similar conditions (2.1 equiv. ^{n}BuLi to sequester the enolic proton) to give the 6-membered octahydroquinoline **43** as opposed to the 5-membered lactam (Equation 13).



Investigation of the nitro-Mannich reaction of the remaining 1,4-addition products to ethyl-β-nitroacrylate (**1**) derived from O, N, S or P nucleophiles were not encouraging. The only products isolated were **44** (42%) and **45** (7%), with the other substrates giving a complex mixture of products. Both **44** and **45** were unstable, both degrading after ~30 mins at rt, probably because of the electron donating substituent at C-3 of the pyrrolidinone (Scheme 4).



Scheme 4. Investigation of desired reaction (PMP=*p*-methoxyphenyl).

Like the pyrrolidinones synthesised in our previous work, the lactams here were all isolated as single diastereoisomers. Although we could not obtain a single crystal X-ray structure determination, the J^3 coupling constants between the ring protons are in range with those observed previously. This suggests that the major diastereoisomer formed from the nitro-Mannich reaction is the usual *syn*, *anti*-diastereoisomer and that this is disposed towards favourable cyclisation to a pyrrolidinone product. This tentative stereochemical assignment is supported by the relative stereochemistry of piperidine **43**. One dimensional nOe experiments and analysis of the J^3 coupling constants around the piperidine ring were not definitive. Coupling constant $J_{H2\text{-}H3}$ is large, suggesting a *trans* relationship, while $J_{H3\text{-}H4}$ is of a medium value suggesting a *cis* relationship. This concurs with the large nOe enhancement of 3.2% for H3 upon irradiation of H4. However the small nOe observed at H2 upon irradiation of H4 is ambiguous. Although if H2 and H4 were cis, we would expect a $J_{H3\text{-}H4}$ to be similar to $J_{H2\text{-}H3}$, and a strong nOe enhancement to exist between them. Molecular modelling of each diastereoisomer and calculation of their coupling constants and relevant internuclear distances gave us confidence in assigning the stereochemistry of **43** as drawn (Table 6).[49] The *cis/trans* stereochemistry of **43** was the closest fit to the spectroscopic data.

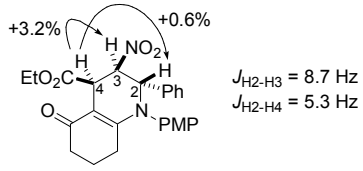


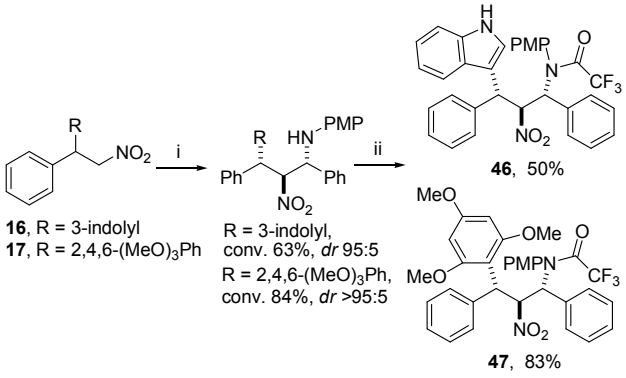
Figure 1. Values of nOe enhancements and coupling constants for **43**.

The stereochemical outcome of the five products formed in this reaction are all tentatively derived from a *syn, anti*-diastereoisomer of the precursor β-nitroamine. As we determined in our previous study of dialkyl zinc additions to **1**,[27] although the other diastereoisomers may form in the nitro-Mannich reaction they are in equilibrium through a retro- re-addition reaction and it is only the *syn, anti*-diastereoisomer that seems to cyclise in a rate determining and irreversible lactamisation.

We then surveyed the use of the 1,4-addition products derived from β-nitrostyrene (**2**) in nitro-Mannich reactions. The 1,4-addition reactions had required many different

reaction protocols and each protocol was tested with a representative nucleophile for *in situ* nitro-Mannich addition reactivity by adding imine **37** and TFA to the reaction mixtures. All except one example of the addition of NaOMe were unsuccessful (vide infra). As above we then investigated the two pot procedure for all of the 1,4-addition products derived from **2**.

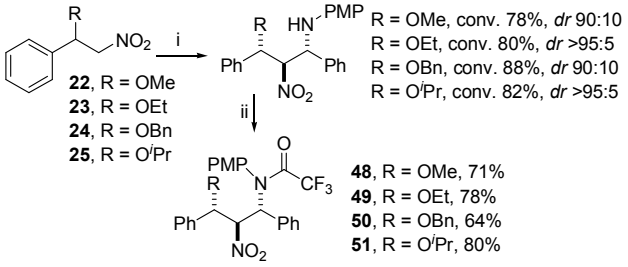
The derivatives derived from electron rich π carbon nucleophiles **16** and **17** were reacted under standard nitro-Mannich conditions with ^{n}Buli, imine **37** and TFA. Upon workup 1H NMR showed good conversion and excellent diastereoselectivity (95:5). These sensitive β-nitroamine products were isolated as their trifluoroacetamides **46** and **47** as single diastereoisomers in 50% and 83% yields respectively (Scheme 5). A single crystal X-ray structure determination of **47** verified the *anti, anti* relative stereochemistry.[50] The indole derivative **46** was not crystalline, but the coupling constants between the alkane C-H protons were similar, so we also assigned that as the *anti, anti*-diastereoisomer.



Scheme 5. Reagents and conditions (i) ^{n}BuLi, THF -78 °C; **37**, TFA; (ii) TFAA, Py, CH_2Cl_2, rt.

In contrast the other 1,4-addition products derived from stabilised carbon nucleophiles did not undergo the nitro-Mannich reaction. Reaction of malonate **18** and the malononitrile **19** gave only recovered starting materials. Cyclohexanedione **20** and Meldrums acid **21** gave only a complicated mixture of degradation products. In these experiments 2 equivalents of ^{n}BuLi were used as **18**-**21** all possess a more or comparably acidic proton to the O_2NC-H proton.

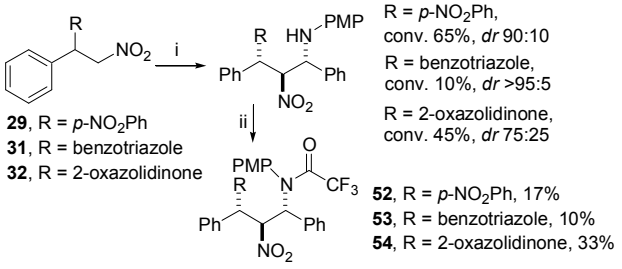
The nitro-Mannich reactions of the alcohol addition products **22**-**25** under the standard conditions gave the desired β-nitroamines in good conversions and diastereoselectivities. After protection, the resultant trifluoroacetamides were isolated in good yields and as single diastereoisomers (Scheme 6). A single crystal X-ray structure determination of **48** confirmed the *anti, anti* relative stereochemistry.[50] All of the ether analogues **48**-**51** exhibited a tight range of coupling constants for the alkane protons; $J_{ROCH\text{-}O2NCH}$ 6.7-8.5 Hz and $J_{O2NCH\text{-}NCH}$ 10.7-11.0 Hz. Due to these close values we assigned **49**-**51** also as the *anti, anti*-diastereoisomers. The ^{t}BuO derivative **26** led to only ~5% of nitro-Mannich product amongst starting materials, β-nitrostyrene (**2**) and ^{t}BuOH from β-elimination of **26** (~65%). Possible steric compression from the large ^{t}butyl group could account for the propensity of this substrate towards elimination.



Scheme 6. Reagents and conditions (i) ^{n}BuLi, THF -78 °C; **37**, TFA; (ii) TFAA, Py, CH_2Cl_2, rt.

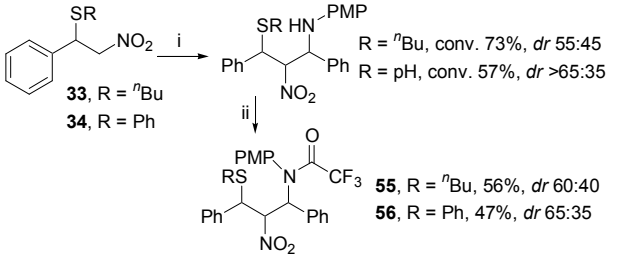
A one pot conjugate addition nitro-Mannich was attempted with NaOMe in MeOH. The solvent MeOH was needed for a high yielding 1,4-addition to **2**, but we had not used this solvent in nitro-Mannich reactions before. Reaction of β-nitrostyrene (**2**) with MeONa in MeOH, followed by addition of solutions of imine **37** and TFA in MeOH and trifluoroacetamide protection of the resultant crude β-nitroamine product, trifluoroacetamide **48** was isolated in 43% yield as a single diastereoisomer. When imine **37** was present from the beginning of the reaction with the nitroalkene, **48** was isolated in 49% yield, which was very close to the overall yield of the two pot procedure (52%). Although other alcohols could be used in this multicomponent procedure, a limitation is the liquidity of the alcohol solvent at the initial temperature of the nitro-Mannich reaction of -78 °C.

The nitro-Mannich reactions of N-substituted nitroalkanes were not as successful as those of the ether series. Electron rich amines **27**, **28** and **30** gave none of the desired β-nitroamine products, instead yielding only parent β-nitrostyrene (**2**) and the free amine which indicated β-elimination. We attribute this to the acid (TFA) added to promote the nitro-Mannich reaction. Quenching of the nitro-Mannich reaction without TFA led to recovery of starting materials. Reduction of the amount of TFA from 3.5 to 1.0 equivalents did not change the result. Nitro-Mannich reaction of the *p*-nitro-aniline derivative **29** gave 65% conversion (*dr* 90:10, Scheme 7), but only led to a 17% yield of protected product **52**. A substantial amount of material degraded during the trifluoroacetamide protection by elimination of the PMP amine trifluoroacetamide under the basic reaction conditions. Quite why this particular substrate is so sensitive to this elimination remains unanswered. The substrates derived from benzotriazole **31** and oxazolidinone **32** gave protected nitro-Mannich products **53** and **54** in similarly modest yields (10% and 33%). In the case of the benzotriazole product **53** a 79% yield of recovered starting material **31** was also isolated. A single crystal X-ray structure determination of **53** and **54** confirmed the *anti, anti* relative stereochemistry.[50] We have tentatively assigned the *p*-nitro-aniline derivative **52** as the *anti, anti*-diastereoisomer, although the alkane coupling constants for **52** are significantly different from those of **53** and **54**. This could be due to the fact that **52** possesses a relatively acidic N-H proton capable of hydrogen bonding internally to the other vicinal amino group, which could substantially alter the conformation compared to **53** and **54**.



Scheme 7. Reagents and conditions (i) ^{n}BuLi, THF -78 °C; **37**, TFA; (ii) TFAA, Py, CH_2Cl_2, rt.

Finally, the nitro-Mannich reactions of the sulphur and phosphorus 1,4-addition products were investigated. Nitro-Mannich reaction of both ^{n}butyl sulfide **33** and phenyl sulfide **34** derivatives gave reasonable conversions (73% and 57%), but were poorly diastereoselective. Subsequent trifluoroacetamide protection led to the protected β-nitroamines **55** and **56** in moderate isolated yields and similarly disappointing diastereoselectivites (Scheme 8). Despite **56** being isolated as a solid, suitable crystals for X-ray analysis could not be obtained and coupled with the fact that each diastereomeric pair of products **55** and **56** possessed very similar alkane coupling constants, we could not substantiate any relative stereochemistry with confidence.



Scheme 8. Reagents and conditions (i) ^{n}BuLi, THF -78 °C; **37**, TFA; (ii) TFAA, Py, CH_2Cl_2, rt.

Reactions of sulfone **35** and phosphine oxide **36** 1,4-addition products were unsuccessful, in both cases returning unreacted starting materials. As the O_2NC-H proton is expected to be the most acidic based on the pK_a of simple compounds (pK_a's in DMSO α to NO_2 ~17, α to $P(O)R_2$ ~25 and α to SO_2Ph ~24)[51] and there is at least one example each of β-nitrophopshonate[52] and β-nitrosulfone[53] reacting α to NO_2 (all be it in a conjugate addition reaction), this result was unexpected. Perhaps the electron withdrawing nature of both the β-substituents renders the nitronate species too unreactive for the nitro-Mannich reaction.

The sense of diastereoselectivity for the aryl, alkoxy and amino conjugate addition derivatives are all profoundly *anti, anti* as drawn. This is in direct contrast to our previous work were dialkylzinc addition to **1** or a variety of nitro styrenes led to predominantly the *syn, anti*-diastereoisomer or for the latter case in certain solvents the *syn, syn*-diastereoisomer.[27,30] The *anti*-diastereoselectivity for the nitro-Mannich reaction is by far the most common diastereoselectivity exhibited by this reaction and most probably arises through a closed Zimmerman-Traxler like transition state.[4,7] In this work it is of interest that we obtained the *anti*-diastereoselectivity between the stereocentre derived from the 1,4-addition and the nitro stereocentre from the nitro-Mannich reaction. To explain our earlier results we accepted that the control of the diastereoselectivity from the initial conjugate addition step was dictated by the energetics of electrophilic addition adjacent to an α-stereocentre. Houk had calculated that the trajectory of an electrophilic addition adjacent to an α-stereocentre, ignoring any stereoelectronic effects that normally arise from polar substituents on the directing centre, is energetically most favourable from a Felkin-Anh like reactive conformation.[54] If we assume for the cases of **46** and **47** that the indole substituent and especially the trimethoxyphenyl substituent are the largest substituents of that chiral centre, then the most reactive conformation (**A**, Figure 2) will have those groups perpendicular to the nitronate anion. This model would correctly predict the major *anti*-diastereoselectivity observed in both additions.

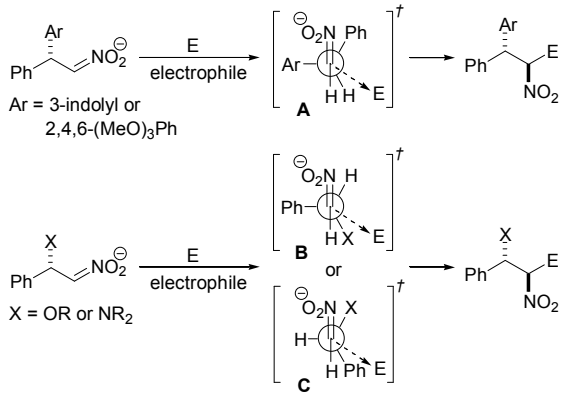


Figure 2. Houk-type analysis of electrophilic attack adjacent to an α-stereocentre.

A complication arises when we consider the more polar alkoxy and amino substituents, which also gave *anti*-diastereoselectivity. In the Felkin-Anh model for nucleophilic addition to carbonyl groups, a more polar substituent favours the perpendicular position so that it can lower the LUMO of the carbonyl π* orbital by overlap with its low lying $\sigma^*_{C\text{-}X}$ orbital. By contrast electrophilic addition favours an electron donor perpendicular to the π-orbital to maximize the energy of the π HOMO. To account for the same sense of facial addition the Ph or H groups, as electron donors, would have to be placed perpendicular to the nitronate π-orbital leading to conformer **B** or **C** (Figure 2). Houk carried out further calculations which suggested that the most reactive conformation for a chiral centre containing an electron withdrawing group (O substituent) adjacent to an alkene reacting with an electrophile, would be the *inside* conformer **C**. However in this case there would be severe buttressing between the developing C-electrophile bond and the phenyl group, which suggests conformer **B** would be more favourable. The sulfur derivatives are neither very electron withdrawing or sterically bulky, so their corresponding diastereoselectivity is low.

3. Conclusion

The investigation of the conjugate addition nitro-Mannich reaction of non-zinc nucleophiles to ethyl-β-nitroacrylate (**1**) and *β*-nitrostyrene (**2**) was described. A diverse range of nucleophiles including electron rich aromatic nucleophiles, stabilized carbanions, alcohols, amines, thiols, and phosphines were surveyed. Each set of nucleophiles had their own particular reaction protocols for a successful 1,4-addition reaction and the main complication with a subsequent in situ nitro-Mannich addition reaction was the compatibility of reagents and conditions. The one pot conjugate addition nitro-Mannich reaction with **1** was unsuccessful for all nucleophiles investigated. The one pot procedure with **2** was found to work with MeONa in MeOH and then adding imine **37** and TFA, which gave after protection, the desired β-nitroamine trifluoroacetamide as a single diastereoisomer. This reaction could also be performed by adding NaOMe to a mixture of **2** and **37** and then adding TFA. The β-nitroamine was again isolated as its trifluoroacetamide as a single diastereoisomer in a yield comparable to the 2 step procedure also investigated (~50%). A limitation to this method is that the alcohol solvent has to remain liquid at the initial temperature of the nitro-Mannich reaction of -78 °C. Other types of nucleophiles were

unsuccessful with the one pot conjugate addition nitro-Mannich reaction with **2**.

More success was found with the two-pot procedures. The 1,4-addition products from nitroacrylate **1** were isolated in good yields (81-99%). Subsequent deprotonation with ^{n}BuLi and reaction with imine **37** and TFA, gave stable pyrrolidine products with only the indole and 2,4,6-trimethoxyphenyl derivatives. The methoxide and morpholine pyrrolidine derivatives, although isolable, were unstable over time. The 1,3-cyclohexanedione derivative gave a piperidine product in 38% yield. These few highly functionalized products were all isolated as single diastereoisomers. The conjugate addition of the same range of nucleophiles to *β*-nitrostyrene (**2**) gave variable yields of 1,4-addition products (45-97%). After deprotonation and nitro-Mannich reaction, the isolated *β*-nitroamines were protected as their trifluoroacetamides so they could be purified. The reaction of the aromatic derivatives was successful, whereas the derivatives of nucleophilic methylene nucleophiles were mostly ineffective. Nitro-Mannich reactions of alcohol derivatives gave good yields of trifluoroacetamide protected β-nitroamines, except for the ^{t}butanol derivative. Reaction of amine derivatives was mostly ineffective, with only small yields of products being isolated in limited cases. Thiol derivatives gave the desired trifluoroacetamides in medium yields, but uncharacteristically poor diastereoselectivities, while adducts of phosphines were unreactive.

Limitations do exist for the conjugate addition nitro-Mannich methodology presented here. Problems with β-elimination of the nucleophile from the 1,4-addition product on formation of the nitronate species may account for the failue of the stabilized carbon nucleophile derivatives in the nitro-Mannich reaction. The stabilized nucleophiles also make relatively good leaving groups. The 1,4-addition products derived from amines participated poorly in the nitro-Mannich reaction. This is probably due to the basic amine being protonated by the acid required to promote the nitro-Mannich reaction, leading to β-elimination. Less basic, but more electron withdrawn amines while less likely to be protonated are themselves better leaving groups and again performed poorly. Certain nucleophiles, particularly the electron rich aromatics or alcohols, on the whole did not suffer from this degradation and gave good yields of products as single diastereoisomers. The high levels of *anti, anti*-diastereoselectivity with nitro-Mannich reactions of derivatives from **2** is in contrast to the addition of dialkyl zinc nucleophiles which routinely gives *syn, anti*- or *syn, syn*-diastereoselectivity. These densely functionalized diastereomerically pure products could potentially serve as useful building blocks for target synthesis.

4. Experimental section

4.1. General

Melting points are uncorrected and were recorded on a Reichert Melting Point Apparatus. All ^{1}H and ^{13}C NMR data were recorded using Bruker AVANCE III 400 MHz and Bruker AVANCE III 600 MHz machines at 400 and 600 MHz for ^{1}H and 100 and 150 MHz for ^{13}C respectively. ^{19}F NMR data were recorded on a Bruker AMX 300 MHz machine at 282 MHz. Samples were made as dilute solutions of $CDCl_3$ and spectra recorded at 298 K, unless otherwise stated. Data were manipulated directly using Bruker XwinNMR (version 2.6) or Top Spin (version 2.1). All chemical shifts (δ) are reported in parts per million (ppm), relative to residual solvent peaks δ = 7.26 for ^{1}H NMR and δ = 77.1 for ^{13}C NMR. Multiplicities for ^{1}H coupled signals are denoted as s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet. Coupling constants (*J*) are reported in Hertz (Hz). ^{13}C multiplicities were assigned using a DEPT sequence. Where appropriate, HMQC, COSY, HMBC, NOE experiments were carried out to aid assignment. Mass spectroscopy data were collected on Thermo Finnigan Mat900xp (EI/CI) VG-70se (FAB) and Waters LCT Premier XE (ES) instruments. Infrared data were collected using Perkin-Elmer 100 FTIR spectrometer as a thin film. Elemental analysis was performed on an Exeter Analytical Inc. EA440 horizontal load analyser. Optical rotations were obtained using a Perkin-Elmer 343 model polarimeter. X-ray crystallography was carried out using a AFC12 goniometer, equipped with an enhanced sensitivity (HG) Saturn724+ detector mounted at the window of an FR-E+ SuperBright molybdenum rotating anode generator with HF Varimax optics (100µm focus).

For all non-aqueous chemistry, glassware was rigorously flame-dried and an inert (N_2) atmosphere maintained throughout. All solvents and chemicals were used as received unless stated. Chromatographic separations were performed using Merck Geduran® silica gel 60. Petroleum ether with a boiling range 40-60 ºC was used. Commercial solvents and reagents were used as supplied or purified in accordance to standard procedures. The dry solvents Diethyl Ether (Et_2O), Tetrahydrofuran (THF), Dichloromethane (DCM), Toluene and Hexane were obtained from a solvent tower, where degassed solvents were passed through two columns of activated alumina and a 7 micron filter under 4 bar pressure. Benzaldehyde was distilled from calcium hydride under an atmosphere of nitrogen, and stored at 5 ^{o}C. All solutions of organolithium reagents were kept under a Nitrogen atmosphere at 5 ^{o}C and standardised with Salicylaldehyde Phenylhydrazone.[55]

4.2. 1,4-Additions to nitroacrylate 1

*4.2.1. Ethyl 2-(1H-indol-3-yl)-3-nitropropanoate (**3**).*[33] To a preformed mixture of $CeCl_3$·NaI·SiO_2 (11:2.5:1, 339 mg) was added MeCN (4 mL) followed by indole (69 mg, 0.59 mmol) and nitroacrylate **1** (85 mg, 0.59 mmol). The mixture was stirred for 30 min, the solvent removed *in vacuo* and the residue stirred for 24 h. Addition of Et_2O (30 mL), filtration through celite,® evaporation *in vacuo* and purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **3** (140 mg, 89%) as a yellow oil; R_f 0.23 (Petrol:EtOAc 4:1); ^{1}H NMR (600 MHz) δ 1.24 (t, *J* = 7.1, 3H), 4.20 (m, 2H), 4.65 (dd, *J* = 14.5, 5.0, 1H), 4.76 (dd, *J* = 9.8, 4.9, 1H), 5.22 (dd, *J* = 14.4, 9.9, 1H), 7.12 (app. d, *J* = 2.6, 1H), 7.19 (m, 1H), 7.26 (m, 1H), 7.39 (app. d, *J* = 8.2, 1H), 7.68 (app. d, *J* = 8.0, 1H), 8.34 (br s, 1H), in agreement with that reported.[34]

*4.2.2. Ethyl 2-(2,4,6-trimethoxyphenyl)-3-nitropropanoate (**4**).*[33] Procedure identical to above, 1,3,5-trimethoxybenzene (84 mg, 0.50 mmol) and nitroacrylate **1** (73 mg, 0.50 mmol) gave after purification by flash column chromatography (Petrol:Et_2O 1:1) **4** (140 mg, 89%) as white crystals, mp. 107-108 ^{o}C; R_f 0.27 (Petrol:Et_2O 1:1); IR υ_{max} (thin film) 2952, 2843, 1732, 1609, 1594, 1554, 1500, 1459, 1420, 1378, 1344, 1329, 1226, 1203, 1152, 1119, 1058, 1029, 951, 815 cm^{-1}; ^{1}H NMR (600 MHz) δ 1.18 (t, *J* = 7.1, 3H), 3.79 (s, 6H), 3.82 (s, 3H), 4.10-4.21 (m, 2H), 4.29 (dd, *J* = 13.5, 5.2, 1H), 5.05 (dd, *J* = 8.8, 5.2, 1H), 5.12 (dd, *J* = 13.5, 8.8, 1H), 6.12 (s, 2H); ^{13}C NMR (150 MHz) δ 14.1(CH_3), 38.0 (CH), 55.3 (CH_3), 55.7 (CH_3), 61.1 (CH_2), 74.3 (CH_2), 90.6 (CH), 103.8 (Cq), 158.6 (Cq), 161.3 (Cq), 171.6 (Cq); m/z (CI^{+}) 314 (M+H^{+}, 73%), 267

($M+H^+-NO_2$, 100%), 240 (40%); HRMS: found 314.12450, $C_{14}H_{20}NO_7$ requires 314.12398.

*4.2.3. Ethyl 3-nitro-2-(2,6-dioxocyclohexyl)propanoate (**5**).*[35] To a solution of 1,3-cyclohexanedione (62 mg, 0.55 mmol) in MeOH (3 mL) was added Et_3N (77 µL, 0.55 mmol) at 0 °C, followed by a solution of nitroacrylate **1** (80 mg, 0.55 mmol) in MeOH (2 mL). The mixture was warmed to rt and stirred until complete consumption of the nitroacrylate (TLC, 2 h). A solution of HCl 0.5 M (10 mL) was then added and the mixture extracted with CH_2Cl_2 (3×10 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification by flash column chromatography (Petrol:Me_2CO 1:1) gave nitroalkane **5** (140 mg, 99%) as a white solid, mp. 91-92 °C; R_f 0.47 (Petrol:Me_2CO 1:1); IR υ_{max} (thin film) 3420, 2981, 1710, 1584, 1557, 1382, 1282, 1248, 1192, 1031, 1012, 678 cm^{-1}; ^1H NMR (600 MHz) δ 1.23 (m, 3H), 2.01 (m, 2H), 2.52 (m, 4H), 4.16 (m, 2H), 4.36 (m, 1H), 4.72 (m, 1H), 5.02 (dd, *J* = 13.7, 8.4, 1H), 8.62 (br s, 1H); ^{13}C NMR (150 MHz) δ 13.9 (CH_3), 20.3 (CH_2), 32.5 (CH_2), 37.5 (CH), 61.9 (CH_2), 73.7 (CH_2), 110.1 (Cq), 171.8 (Cq), 188.6 (Cq); m/z (CI^+) 178 ($M+H^+$, 30%), 211 (20%), 180 (27%), 165 (100%); HRMS: found 258.09712, $C_{11}H_{16}NO_6$ requires 258.09776.

*4.2.4. Ethyl 2-methoxy-3-nitropropanoate **6**.* A solution of nitroacrylate **1** (80 mg, 0.55 mmol) in MeOH (5 mL) was stirred at reflux until complete consumption of the starting material (24 h). The solvent was then evaporated *in vacuo* and the residue purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **6** (83 mg, 85%) as a colourless oil; R_f 0.44 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 2984, 1937, 1751, 1736, 1557, 1379, 1193, 1129, 1038, 1017 cm^{-1}; ^1H NMR (600 MHz) δ 1.31 (t, *J* = 7.2, 3H), 3.53 (s, 3H), 4.27 (m, 2H), 4.45 (dd, *J* = 8.1, 3.5, 1H), 4.65 (dd, *J* = 13.9, 8.2, 1H), 4.72 (dd, *J* = 13.9, 3.6, 1H); ^{13}C NMR (150 MHz) δ 14.0 (CH_3), 59.5 (CH_3), 62.1 (CH_2), 75.8 (CH_2), 76.6 (CH), 168.4 (Cq); m/z (EI^+) 178 (M^+, 100%); HRMS: found 178.07170, $C_6H_{11}NO_5$ requires 178.07155; Anal. Cald. For $C_6H_{11}NO_5$: C, 40.68, H, 6.26, N, 7.91. Found C, 40.38, H, 6.29, N, 7.57%.

*4.2.5. Ethyl 2-ethoxy-3-nitropropanoate (**7**).* In an identical procedure as to the preparation of **6**, nitroacrylate **1** (100 mg, 0.69 mmol) in EtOH (7 mL) after purification by flash column chromatography (Petrol:Et_2O 9:1) gave nitroalkane **7** (117 mg, 89%) as a colourless oil; R_f 0.33 (Petrol:Et_2O 9:1); IR υ_{max} (thin film) 2923, 1753, 1736, 1559, 1379, 1200, 1130, 1052, 1019, 559 cm^{-1}; ^1H NMR (600 MHz) δ 1.21 (t, *J* = 7.1, 3H), 1.31 (t, *J* = 7.2, 3H), 3.56 (m, 1H), 3.84 (m, 1H), 4.26 (m, 2H), 4.57 (dd, *J* = 3.5, 8.4, 1H), 4.64 (dd, *J* = 8.5, 13.6, 1H), 4.71 (dd, *J* = 8.5, 13.5, 1H); ^{13}C NMR (150 MHz) δ 14.1 (CH_3), 14.9 (CH_3), 62.0 (CH_2), 67.7 (CH_2), 75.1 (CH), 76.1 (CH_2), 168.8 (Cq); no M+ peak on mass spec; Anal. Cald. For $C_7H_{13}NO_5$: C, 43.98, H, 6.85, N, 7.33. Found C, 44.24, H, 6.86, N, 7.58%.

*4.2.6. Ethyl 2-(benzyloxy)-3-nitropropanoate (**8**).* A solution of nitroacrylate **1** (73 mg, 0.50 mmol) in BnOH (1 mL) was stirred at 100 °C until complete consumption of the starting material (24 h). The solvent was then evaporated *in vacuo* and the residue purified byflash column chromatography (Petrol:CH_2Cl_2 1:1) gave nitroalkane **8** (79 mg, 62%) as a colourless oil; R_f 0.46 (Petrol: CH_2Cl_2 1:1); IR υ_{max} (thin film) 2922, 2852, 1745, 1559, 1456, 1378, 1274, 1203, 1131, 1020 cm^{-1}; ^1H NMR (600 MHz) δ 1.32 (t, *J* = 7.1, 3H), 4.28 (m, 2H), 4.60 (d, *J* = 11.2, 1H), 4.68 (m, 3H), 4.87 (d, *J* = 11.2, 1H), 7.30-7.38 (m, 5H); ^{13}C NMR (150 MHz) δ 14.1(CH_3), 62.1 (CH_2), 73.7 (CH_2), 74.2 (CH), 76.0 (CH_2), 128.3 (CH), 128.4 (CH), 128.5 (CH), 136.2 (Cq), 168.6 (Cq); m/z (CI^+) 254 ($M+H^+$, 13%) (HRMS analysis failed), 181 ($M+H^+$-COOEt, 100%).

*4.2.7. Ethyl 2-((4-methoxyphenyl)amino)-3-nitropropanoate (**9**).* To a stirred solution of nitroacrylate **1** (201 mg, 1.39 mmol) in CH_2Cl_2 (14 mL) was added at rt *para*-anisidine (307 mg, 2.50 mmol) and the mixture was stirred until complete consumption of the nitroacrylate (TLC, 24 h). The mixture was then evaporated and purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **9** (364 mg, 98%) as an orange solid; mp. 74-75 °C; R_f 0.40 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 3387, 3010, 2956, 2917, 2836, 1732, 1546, 1515, 1317, 1250, 1233, 1210, 1186, 1152, 1031, 829, 806 cm^{-1}; ^1H NMR (600 MHz) δ 1.29 (t, *J* = 7.1, 3H), 3.75 (s, 3H), 4.26 (br. s, 1H), 4.27 (m, 2H), 4.55 (t, *J* = 5.0, 1H), 4.76 (dd, *J* = 13.7, 4.8, 1H), 4.82 (dd, *J* = 13.7, 5.1, 1H), 6.68 (app d, *J* = 8.9, 2H), 6.80 (app. d, *J* = 8.9, 2H); ^{13}C NMR (150 MHz) δ 14.0 (CH_3), 55.6 (CH_3), 56.3 (CH), 62.5 (CH_2), 75.8 (CH_2), 114.9 (CH), 115.9 (CH), 139.2 (Cq), 153.6 (Cq), 169.7 (Cq); m/z (EI^+) 268 (M^+, 20%), 149 (100%), 134 (46%); HRMS: found 268.10592, $C_{12}H_{16}N_2O_5$ requires 268.10686; Anal. Cald. For $C_{12}H_{16}N_2O_5$: C, 53.73, H, 6.01, N, 10.44. Found C, 53.74, H, 6.00, N, 10.15%.

*4.2.8. Ethyl 2-morpholino-3-nitropropanoate (**10**).* In an identical procedure as to the preparation of **9**, nitroacrylate **1** (80 mg, 0.55 mmol) in wet CH_2Cl_2 (5 mL) and morpholine (54 µL, 0.66 mmol) gave after purification by flash column chromatography (Petrol:EtOAc 4:1) nitroalkane **10** (125 mg, 98%) as an orange oil; R_f 0.33 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 2965, 2858, 1729, 1557, 1383, 1187, 1116, 1023, 855 cm^{-1}; ^1H NMR (600 MHz) δ 1.31 (t, *J* = 7.2, 3H), 2.50 (m, 2H), 2.80 (m, 2H), 3.62 (m, 4H), 4.03 (dd, *J* = 8.9, 6.4, 1H), 4.23 (m, 2H), 4.61 (dd, *J* = 13.5, 9.0, 1H), 4.67 (dd, *J* = 13.6, 6.4, 1H); ^{13}C NMR (150 MHz) δ 14.3 (CH_3), 49.9 (CH_2), 61.4 (CH_2), 64.5 (CH), 67.1 (CH_2), 73.3 (CH_2), 168.1 (Cq); m/z (EI^+) 232 (M^+, 7%), 159 (M^+-COOEt, 53%), 113 (M^+-NO_2-COOEt, 100%); HRMS: found 232.10474, $C_9H_{16}N_2O_5$ requires 232.10537.

*4.2.9. Ethyl 2-(benzylamino)-3-nitropropanoate (**11**).* To a stirred solution of nitroacrylate **1** (80 mg, 0.55 mmol) in CH_2Cl_2 (5 mL) was added at 0 °C benzylamine (72 µL, 0.66 mmol) and the mixture was stirred at this temperature until complete consumption of **1** (TLC, 1 h). The mixture was then evaporated and purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **11** (112 mg, 81%) as an orange oil; R_f 0.59 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 3340, 3030, 2982, 2931, 1735, 1557, 1379, 1196, 1020, 739, 699 cm^{-1}; ^1H NMR (600 MHz) δ 1.31 (t, *J* = 7.1, 3H), 2.27 (br. s, 1H), 3.81 (d, *J* = 13.3, 1H), 3.85 (dd, *J* = 6.1, 5.0, 1H), 3.96 (d, *J* = 13.3, 1H), 4.26 (m, 2H), 4.63 (dd, *J* = 13.5, 4.9, 1H), 4.67 (dd, *J* = 13.5, 6.0, 1H), 7.28 (m, 1H), 7.31-7.36 (m, 4H); ^{13}C NMR (150 MHz) δ 14.0 (CH_3), 52.0 (CH_2), 57.7 (CH), 62.0 (CH_2), 76.7 (CH_2), 127.4 (CH), 128.2 (CH), 128.5 (CH), 138.8 (Cq), 170.8 (Cq); m/z (CI^+) 253 ($M+H^+$, 4%), 179 (9%), 133 (M^+-NO_2-COOEt, 17%), 106 ($PhCH=NH_2^+$, 20%), 91 ($PhCH_3^+$, 100%); HRMS: found 253.11934, $C_{12}H_{17}N_2O_4$ requires 253.11883.

*4.2.10. Ethyl 2-(1H-benzo[d][1,2,3]triazol-1-yl)acrylate (**13**).* To a solution of nitroacrylate **1** (72 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) was added 1*H*-benzo[d][1,2,3]triazole (**12**, 65 mg, 0.55 mmol) and the mixture was stirred at rt until complete consumption of **1** (TLC, 2 days). The mixture was then evaporated *in vacuo* and purification of the residue by flash column chromatography (Petrol:Et_2O 7:3) gave acrylate **13** (62 mg, 47%) as a colourless oil; R_f 0.38 (Petrol:Et_2O 7:3); IR υ_{max}

(thin film) 2984, 1729, 1635, 1455, 1378, 1276, 1240, 1178, 1074, 1055, 1018, 785, 747 cm^{-1}; ^1H NMR (600 MHz) δ 1.32 (t, *J* = 7.2, 3H), 4.36 (q, *J* = 7.2, 2H), 6.30 (s, 1H), 6.74 (s, 1H), 7.41 (app. t, *J* = 7.8, 1H), 7.44 (app. d, *J* = 8.4, 1H), 7.52 (app. t, *J* = 7.4, 1H), 8.10 (d, *J* = 8.3, 1H); ^{13}C NMR (150 MHz) δ 14.0 (CH_3), 62.5 (CH_2), 110.6 (CH), 120.1 (CH), 124.2 (CH), 125.2 (CH_2), 128.2 (Cq), 133.1 (Cq), 134.4 (Cq), 145.8 (Cq), 161.6 (Cq); m/z (CI^+) 218 ($M+H^+$, 100%), 161 (26%), 133 (98%); HRMS: found 218.09295, $C_{11}H_{12}N_3O_2$ requires 218.09247; Anal. Cald. For $C_{11}H_{11}N_3O_2$: C, 60.82, H, 5.10, N, 19.34. Found C, 60.53, H, 5.21, N, 19.63%.

*4.2.11. Ethyl 2-(butylthio)acrylate (**14**).* To a stirred solution of nitroacrylate **1** (60 mg, 0.41 mmol) in THF (2 mL) at rt was added 1-butanethiol (180 μL, 1.24 mmol) and triethylamine (24 μL, 0.17 mmol), and the mixture was stirred overnight until complete consumption of **1** (TLC, 22 h). The mixture was then evaporated *in vacuo* and purification of the residue by flash column chromatography (Petrol: Et_2O 9:1) gave acrylate **14** (29 mg, 38%) as a colourless oil, which was found to be unstable and could not be completely characterised, R_f 0.38 (Petrol:Et_2O 9:1); IR υ_{max} (thin film) 2959, 1719, 1583, 1465, 1385, 1277, 1248, 1117, 1025 cm^{-1}; ^1H NMR (600 MHz) δ 1.33 (m, 3H), 1.47 (m, 2H), 1.66 (m, 2H), 2.72 (m, 2H), 4.27 (m, 2H), 5.40 (s, 1H), 6.35 (s, 1H); ^{13}C NMR (150 MHz) δ 13.6 (CH_3), 14.1 (CH_3), 22.2 (CH_2), 29.7 (CH_2), 31.1 (CH_2), 61.7 (CH_2), 118.5 (CH_2), 137.9 (Cq), 164.6 (Cq); m/z (EI^+) 188 (M^+, 30%), 107 (100%); HRMS: found 188.08600, $C_9H_{16}O_2S$ requires 188.08655.

*4.2.12. Ethyl 2-(diphenylphosphoryl)acrylate (**15**).* To a stirred solution of the nitroacrylate **1** (65 mg, 0.45 mmol) in dry THF (5 mL) at rt was added diphenylphosphine oxide (100 mg, 0.500 mmol) and the mixture was stirred at rt overnight, until complete consumption of **1** (TLC, 16 h). After completion, the mixture was evaporated and purification of the residue by flash column chromatography gave acrylate **15** (75 mg, 56%) as a yellow oil; R_f 0.29 (Petrol:Me_2CO 3:2); IR υ_{max} (thin film) 3058, 2981, 1721, 1438, 1250, 1184, 1118, 1098, 1019, 728, 695 cm^{-1}; ^1H NMR (600 MHz) δ 1.05 (t, *J* = 7.1, 3H), 4.10 (q, *J* = 7.1, 2H), 6.30 (dd, ^{P-H}J = 17.4, ^2J = 1.4, 1H), 7.25 (dd, ^{P-H}J = 33.6, ^2J = 1.4, 1H), 7.40-7.60 (m, 6H), 7.85 (m, 4H); ^{13}C NMR (150 MHz) δ 13.7 (CH_3), 61.4 (CH_2), 128.4 (d, *J* = 12.6, CH), 131.2 (d, *J* = 108.6, Cq), 131.8 (d, *J* = 10.1, CH), 132.0 (d, *J* = 2.8, CH), 137.3 (d, *J* = 95.5, Cq), 144.6 (d, *J* = 4.9, CH_2), 164.3 (d, *J* = 14.1, Cq); ^{31}P NMR (300 MHz) δ 26.0; m/z (ESI^+) 301 ($M+H^+$, 100%), 243 (55%), 215 (40%); HRMS: found 301.0996, $C_{17}H_{18}O_3P$ requires 301.0994.

4.3. 1,4-Additions to β-nitrostyrene 2

*4.3.1. 3-(2-nitro-1-phenylethyl)-1H-indole (**16**).*[33] In a manner identical to the preparation of **3** indole (59 mg, 0.50 mmol) was added to β-nitrostyrene (**2**, 74 mg, 0.50 mmol) and purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **16** (123 mg, 92%) as a colourless oil; R_f 0.43 (Petrol:EtOAc 4:1); ^1H NMR (600 MHz) δ 4.96 (dd, *J* = 12.4, 8.4, 1H), 5.09 (dd, *J* = 12.4, 7.7, 1H), 5.21 (t, *J* = 8.1, 1H), 7.04 (d, *J* = 2.3, 1H), 7.10 (app. t, *J* = 7.5, 1H), 7.22 (app. t, *J* = 7.5, 1H), 7.29 (m, 1H), 7.35 (m, 5H), 7.47 (d, *J* = 7.9, 1H), 8.09 (br. s, 1H); ^{13}C NMR (150 MHz) δ 41.5 (CH), 79.5 (CH_2), 111.4 (CH), 114.4 (Cq), 118.9 (CH), 119.9 (CH), 121.6 (CH), 122.7 (CH), 126.0 (Cq), 127.5 (CH), 127.7 (CH), 128.9 (CH), 136.4 (Cq), 139.1 (Cq). Data in agreement with that reported.[56]

*4.3.2. 1,3,5-Trimethoxy-2-(2-nitro-1-phenylethyl)benzene (**17**).*[33] In a manner identical to the preparation of **3** 1,3,5-trimethoxybenzene (84 mg, 0.50 mmol) was added to β-nitrostyrene (**2**, 74 mg, 0.50 mmol) and purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **17** (113 mg, 71%) as a colourless oil, R_f 0.43 (Petrol:EtOAc 4:1); ^1H NMR (600 MHz) δ 3.80 (s, 3H), 3.81 (s, 6H), 5.14 (dd, *J* = 12.8, 7.6, 1H), 5.26 (dd, *J* = 12.7, 8.1, 1H), 5.51 (t, *J* = 7.9, 1H), 6.14 (s, 2H), 7.19 (t, *J* = 7.3, 1H), 7.27 (t, *J* = 7.4, 2H), 7.33 (d, *J* = 7.6, 2H); ^{13}C NMR (150 MHz) δ 38.5 (CH), 55.2 (CH_3), 55.7 (CH_3), 78.3 (CH_2), 91.0 (CH), 108.5 (Cq), 126.5 (CH), 127.5 (CH), 128.2 (CH), 140.4 (Cq), 158.9 (Cq), 160.5 (Cq). Data in agreement with that reported.[57]

*4.3.3. Diethyl 2-(2-nitro-1-phenylethyl)malonate (**18**).*[40] To a solution of diethyl malonate (0.15 mL, 1.0 mmol) in THF (3 mL) was added NaH (24 mg, 1.0 mmol, 95%) and the mixture stirred at rt for 15 min. A solution of β-nitrostyrene (**2**, 74 mg, 0.50 mmol) in THF (2 mL) was then added and the mixture stirred at rt until complete consumption of the nitroalkene (TLC, 15 min). The mixture was then quenched with addition of saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3×10 mL), the combined organics were then washed with brine (10 mL), dried ($MgSO_4$), evaporated in vacuo and purification of the crude residue by flash column chromatography (Hexane:Et_2O 7:3) gave nitroalkane **18** (148 mg, 96%) as a colourless oil; R_f 0.30 (Hexane:Et_2O 7:3); ^1H NMR (600 MHz) δ 1.05 (t, *J* = 7.1, 3H), 1.27 (t, *J* = 7.1, 3H), 3.83 (d, *J* = 9.4, 1H), 4.02 (q, *J* = 7.2, 2H), 4.27 (m, 3H), 4.85 (dd, *J* = 13.1, 9.4, 1H), 4.95 (dd, *J* = 13.1, 4.8, 1H), 7.23-7.34 (m, 5H); ^{13}C NMR (150 MHz) δ 13.7 (CH_3), 14.0 (CH_3), 42.9 (CH), 54.9 (CH), 61.9 (CH_2), 62.2 (CH_2), 77.6 (CH_2), 128.0 (CH), 128.4 (CH), 128.9 (CH), 136.1 (Cq), 166.8 (Cq), 167.5 (Cq). Data in agreement with that reported.[58]

*4.3.4. 2-(2-Nitro-1-phenylethyl)malononitrile (**19**).*[41] To a solution of *L*-Proline (11.5 mg, 10 mol%) in DMF (1 mL) was added malononitrile (66 mg, 1.0 mmol) followed by β-nitrostyrene (149 mg, 1.00 mmol) and the mixture was stirred at rt until complete consumption of the nitroalkene (TLC, 20 h). Water (10 mL) was then added, the mixture extracted with Et_2O (3×10 mL), dried ($MgSO_4$), evaporated *in vacuo* and purified by flash column chromatography (CH_2Cl_2) gave nitroalkane **19** (192 mg, 89%) as a yellow oil; R_f 0.49 (DCM); ^1H NMR (600 MHz) δ 4.09 (m, 1H), 4.43 (d, *J* = 6.0, 1H), 4.90 (dd, *J* = 14.2, 6.2, 1H), 4.97 (dd, *J* = 14.3, 7.9, 1H), 7.30-7.48 (m, 5H); ^{13}C NMR (150 MHz) δ 27.6 (CH), 43.7 (CH), 74.9 (CH_2), 110.3 (Cq), 110.4 (Cq), 127.7 (CH), 129.9 (CH), 130.4 (CH), 131.8 (Cq). Data in agreement with that reported.[41]

*4.3.5. 3-Hydroxy-2-(2-nitro-1-phenylethyl)cyclohex-2-enone (**20**).*[42] To a solution of 1,3-cyclohexanedione (560 mg, 5.00 mmol) in methanol (1 mL) was added a solution of sodium (25 mg, 1.1 mmol) in methanol (2 mL) and the mixture stirred for 1 min at rt. The mixture was then cooled to 0 °C, a solution of β-nitrostyrene (745 mg, 5.00 mmol) in methanol (2 mL) was added and the mixture stirred at this temperature for 30 min, then at rt until complete consumption of the starting material (TLC, 5 h). The mixture was poured into ice-water, neutralised with 10% HCl, filtered and recrystallised from methanol to give pure nitroalkane **20** (440 mg, 34%, lit.[42] 68%) as a white solid; mp. 142-143 °C (lit. 144-146 °C); R_f 0.35 (Petrol:Me_2CO 1:1); ^1H NMR (600 MHz) δ 1.86 (m, 2H), 2.37 (m, 4H), 5.08 (m, 2H), 5.19 (m, 1H), 7.19-7.34 (m, 5H), 9.91 (br. s, 1H); ^{13}C NMR (150 MHz) δ 20.4 (CH_2), 33.0 (CH_2), 35.2 (CH_2), 38.2 (CH), 77.3 (CH_2), 114.4 (Cq), 126.9 (CH), 127.8 (CH), 128.4 (CH), 138.8 (Cq), 139.7 (Cq), 197.4 (Cq). Data in agreement with that reported.[42]

*4.3.6. 2,2-Dimethyl-5-(2-nitro-1-phenylethyl)-1,3-dioxane-4,6-dione (**21**).*[43] To a solution of Meldrum's acid (144 mg, 1.00 mmol) in CH_2Cl_2 (7 mL) was added Et_3N (130 μL, 1.00 mmol) and the mixture stirred at rt for 30 min before β-nitrostyrene (**2**, 149 mg, 1.00 mmol) was added in one batch and the mixture stirred at rt until complete consumption of the starting material (TLC, 1 h). The mixture was acidified to pH = 2 with addition of 10% HCl, extracted with CH_2Cl_2 (3×10 mL), dried ($MgSO_4$) and evaporated in vacuo to give pure nitroalkane **21** (280 mg, 96%, lit.[43] 88%) as a white solid; mp. 92-94 °C (lit.[43] 93-95 °C); R_f 0.49 (DCM:MeOH 10:1); ^{1}H NMR (600 MHz) δ 1.39 (s, 3H), 1.71 (s, 3H), 4.04 (d, *J* = 3.2, 1H), 4.64 (m, 1H), 5.02 (dd, *J* = 14.0, 6.5, 1H), 5.40 (dd, *J* = 14.0, 9.0, 1H), 7.30-7.35 (m, 5H); ^{13}C NMR (150 MHz) δ 27.6 (CH_3), 28.1 (CH_3), 41.8 (CH), 48.5 (CH), 75.9 (CH_2), 105.9 (Cq), 128.8 (CH), 128.9 (CH), 129.2 (CH), 135.1 (Cq), 164.0 (Cq), 164.4 (Cq). Data in agreement with that reported.[43]

*4.3.7. (1-Methoxy-2-nitroethyl)benzene (**22**).*[45] A 1.5 M solution of MeONa in MeOH (670 μL, 1.00 mmol) was added at rt to a solution of β-nitrostyrene (**2**, 149 mg, 1.00 mmol) in MeOH (10 mL). The mixture was stirred at rt until no more nitroalkene was observed on TLC (15 min). Acetic acid (400 μL, 6.00 mmol) was then added and the mixture stirred for 5 min and then poured into H_2O (20 mL). The mixture was extracted with CH_2Cl_2 (3×10 mL), the combined organics washed with brine (10 mL), dried ($MgSO_4$) and purification of the crude residue by flash column chromatography (Petrol:Et_2O 9:1) gave nitroalkane **22** (133 mg, 73%, lit.[45] 60%) as a colourless oil, R_f 0.63 (Petrol:Et_2O 9:1); ^{1}H NMR (600 MHz) δ 3.28 (s, 3H), 4.41 (dd, *J* = 12.8, 3.3, 1H), 4.62 (dd, *J* = 12.7, 10.1, 1H), 4.97 (dd, *J* = 10.2, 3.4, 1H), 7.36-7.45 (m, 5H); ^{13}C NMR (150 MHz) δ 57.1 (CH_3), 80.0 (CH), 80.4 (CH_2), 126.8 (CH), 129.0 (CH), 129.1 (CH), 135.9 (Cq). Data in agreement with that reported.[45]

*4.3.8. (1-Ethoxy-2-nitroethyl)benzene (**23**).*[45] In an identical manner as for the preparation of **22**, but with EtONa in EtOH gave nitroalkane **23** (129 mg, 66%, lit.[45] 6%) as a colourless oil; R_f 0.49 (Petrol:Et_2O 9:1); ^{1}H NMR (600 MHz) δ 1.16 (t, *J* = 7.3, 3H), 3.39 (m, 2H), 4.39 (dd, *J* = 12.8, 3.4, 1H), 4.61 (dd, *J* = 12.8, 10.3, 1H), 5.06 (dd, *J* = 10.0, 3.3, 1H), 7.35-7.42 (m, 5H); ^{13}C NMR (150 MHz) δ 14.9 (CH_3), 62.9 (CH_2), 78.2 (CH), 80.5 (CH_2), 126.7 (CH), 128.9 (CH), 129.0 (CH), 136.7 (Cq). Data in agreement with that reported.[45]

*4.3.9. (1-(Benzyloxy)-2-nitroethyl)benzene (**24**).*[45] In an identical manner as for the preparation of **22**, but with BnONa in BnOH gave nitroalkane **24** (171 mg, 66%, lit.[45] 30%) as a colourless oil; R_f 0.39 (Petrol:Et_2O 9:1); ^{1}H NMR (600 MHz) δ 4.34 (d, *J* = 11.6, 1H), 4.42 (dd, *J* = 12.8, 3.4, 1H), 4.52 (d, *J* = 11.5, 1H), 4.70 (dd, *J* = 12.8, 10.1, 1H), 5.16 (dd, *J* = 10.2, 3.4, 1H), 7.23-7.41 (m, 9H); ^{13}C NMR (150 MHz) δ 70.9 (CH_2), 77.5 (CH), 80.3 (CH_2), 127.0 (CH), 127.9 (CH), 128.0 (CH), 128.4 (CH), 129.2 (CH), 129.2 (CH), 136.0 (Cq), 136.9 (Cq). Data in agreement with that reported.[45]

*4.3.10. (1-Isopropoxy-2-nitroethyl)benzene (**25**).*[45] In an identical manner as for the preparation of **22**, but with ^{i}PrONa in ^{i}PrOH gave nitroalkane **25** (121 mg, 58%) as a colourless oil; R_f 0.51 (Petrol:Et_2O 9:1); IR υ_{max} (thin film) 2974, 1553, 1494, 1454, 1418, 1379, 1336, 1224, 1143, 1122, 1095, 1062, 1029, 976, 762, 717, 699 cm^{-1}; ^{1}H NMR (600 MHz) δ 1.07 (d, *J* = 6.2, 3H), 1.13 (d, *J* = 6.2, 3H), 3.56 (sept, *J* = 6.1, 1H), 4.36 (dd, *J* = 12.7, 3.3, 1H), 4.57 (dd, *J* = 12.6, 10.3, 1H), 5.17 (dd, *J* = 10.2, 3.2, 1H), 7.35 (m, 1H), 7.40 (m, 4H); ^{13}C NMR (150 MHz) δ 20.8 (CH_3), 23.2 (CH_3), 70.4 (CH), 75.8 (CH), 80.8 (CH_2), 126.7 (CH), 128.8 (CH), 128.9 (CH), 137.5 (Cq); m/z (CI^+) 210 ($M+H^+$, 6%), 162 (M^+-HNO_2, 24%), 149 (M^+-CH_2NO_2, 61%), 107 (PhCHO+H^+, 100%), 104 (PhCH=CH_2^+, 72%); HRMS: found 210.11276, $C_{11}H_{16}NO_3$ requires 210.11302.

*4.3.11. (1-(tert-Butoxy)-2-nitroethyl)benzene (**26**).* A 0.53 M solution of ^{t}BuONa in ^{t}BuOH (1.90 mL, 1.00 mmol) was added to a solution of β-nitrostyrene (**2**, 149 mg, 1.00 mmol) in THF (10 mL) at rt. The mixture was stirred at this temperature for 5 min and then acetic acid (4.00 μL, 6.00 mmol) was added, the mixture stirred for 5 min and then poured into H_2O (20 mL). The mixture was extracted with CH_2Cl_2 (3×10 mL), the combined organics washed with brine (10 mL), dried ($MgSO_4$), evaporated *in vacuo* and purification of the crude residue by flash column chromatography (Petrol:Et_2O 9:1) gave nitroalkane **26** (89 mg, 40%) as a white solid; mp. 45-46 °C; R_f 0.57 (Petrol:Et_2O 9:1); IR υ_{max} (thin film) 2977, 1555, 1455, 1379, 1190, 1092, 1066, 963, 765, 722, 701 cm^{-1}; ^{1}H NMR (600 MHz) δ 1.10 (s, 9H), 4.32 (dd, *J* = 12.0, 3.3, 1H), 4.49 (dd, *J* = 12.0, 10.2, 1H), 5.27 (dd, *J* = 10.1, 3.2, 1H), 7.31-7.41 (m, 5H); ^{13}C NMR (150 MHz) δ 28.3 (CH_3), 72.0 (OCH), 75.5 (Cq), 81.9 (CH_2), 126.2 (CH), 128.3 (CH), 128.7 (CH), 140.2 (Cq); m/z (CI^+) 224 ($M+H^+$, 6%), 163 ($M+H^+$-CH_3NO_2, 65%), 150 ($M+H^+$-^{t}BuOH, 26%), 107 (PhCHO+H^+, 100%); HRMS: found 224.12912, $C_{12}H_{18}NO_3$ requires 224.12867; Anal. Cald. For $C_{12}H_{17}NO_3$: C, 64.55, H, 7.67, N, 6.27. Found C, 64.76, H, 7.79, N, 6.07%.

*4.3.12. 2,4-Dimethoxy-N-(2-nitro-1-phenylethyl)aniline (**27**).* To a solution of β-nitrostyrene (**2**, 149 mg, 1.00 mmol) in dry CH_2Cl_2 (5 mL) was added 2,3-dimethoxyaniline (184 mg, 1.20 mmol) at rt and the mixture was stirred overnight until no more nitroalkene was observed (TLC, 19 h). The mixture was then evaporated in vacuo and purification by flash column chromatography (Petrol:EtOAc 4:1) gave the nitroalkane **27** (212 mg, 70%) as a yellow oil; R_f 0.38 (Petrol:EtOAc 4:1); ^{1}H NMR (600 MHz) δ 3.72 (s, 3H), 3.85 (s, 3H), 4.66 (br. s, 1H), 4.70 (dd, *J* = 12.3, 5.5, 1H), 4.73 (dd, *J* = 12.2, 8.3, 1H), 5.13 (dd, *J* = 8.0, 5.9, 1H), 6.31 (dd, *J* = 8.8, 2.6, 1H), 6.45 (d, *J* = 2.5, 2H), 7.32 (m, 1H), 7.39 (m, 4H); ^{13}C NMR (150 MHz) δ 55.6 (CH_3), 55.6 (CH_3), 57.2 (CH_3), 80.1 (CH_2), 99.2 (CH), 103.5 (CH), 111.9 (CH), 126.5 (CH), 128.5 (CH), 129.2 (CH), 129.6 (Cq), 138.1 (Cq), 148.3 (Cq), 152.8 (Cq). Data in agreement with that reported.[59]

*4.3.13. N-(2-Nitro-1-phenylethyl)aniline (**28**).*[46] A mixture of β-nitrostyrene (**2**, 149 mg, 1.00 mmol), aniline (110 μL, 1.20 mmol) and H_2O (4 mL) was stirred vigorously for 2 h. The mixture was then extracted with CH_2Cl_2 (3×10 mL), dried ($MgSO_4$) and evaporated in vacuo. Purification by flash column chromatography (Petrol:Et_2O 9:1) gave nitroalkane **28** (163 mg, 67%) as a yellow oil, R_f 0.28 (Petrol:Et_2O 9:1); ^{1}H NMR (600 MHz) δ 4.44 (d, *J* = 6.6, 1H), 4.73 (d, *J* = 6.7, 2H), 5.21 (q, *J* = 6.9, 1H), 6.65 (d, *J* = 8.0, 2H), 6.78 (t, *J* = 7.4, 1H), 7.18 (t, *J* = 7.9, 2H), 7.36 (m, 1H), 7.42 (m, 4H); ^{13}C NMR (150 MHz) δ 56.5 (CH), 79.9 (CH_2), 113.8 (CH), 118.8 (CH), 126.4 (CH), 128.6 (CH), 129.2 (CH), 129.3 (CH), 137.6 (Cq), 145.6 (Cq). Data in agreement to that reported.[60]

*4.3.14. 4-Nitro-N-(2-nitro-1-phenylethyl)aniline (**29**).* A solution of ^{n}BuLi (400 μL, 2.5 M, 1.00 mmol) in hexane was added to a solution of *para*-nitroaniline (138 mg, 1.00 mmol) in dry THF (10 mL) at -78 °C and the mixture stirred for 10 min before a solution of β-nitrostyrene (**2**, 149 mg, 1.00 mmol) in dry THF (2 mL) was added dropwise. The mixture was stirred at this temperature for 10 min and then warmed to rt and stirred until complete consumption of the starting nitroalkene (TLC, 1.5 h). Saturated aqueous $NaHCO_3$ solution

(10 mL) was then added and the mixture extracted with CH_2Cl_2 (3×10 mL), dried ($MgSO_4$) and evaporated in vacuo. Purification by flash column chromatography (Petrol:EtOAc 4:1) gave nitroalkane **29** (129 mg, 45%) as a yellow oil; R_f 0.21 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 3365, 3065, 2922, 1596, 1551, 1503, 1476, 1378, 1302, 1277, 1184, 1110, 833, 752, 698 cm^{-1}; ^1H NMR (600 MHz) δ 4.79 (m, 2H), 5.28 (m, 1H), 5.40 (d, *J* = 6.5, 1H), 6.59 (app. d, *J* = 8.9, 2H), 7.36-7.44 (m, 5H), 8.05 (app. d, *J* = 8.9, 2H); ^{13}C NMR (150 MHz) δ 56.0 (CH), 79.6 (CH_2), 112.5 (CH), 126.2 (CH), 126.2 (CH), 129.2 (CH), 129.2 (CH), 129.6 (CH), 135.9 (Cq), 139.3 (Cq), 151.0 (Cq); m/z (EI^+) 287 (M^+, 25%), 227 (85%), 181 (17%), 138 (24%), 104 (100%); HRMS: found 287.09031, $C_{14}H_{13}N_3O_4$ requires 287.09005.

*4.3.15. N-(2-Nitro-1-phenylethyl)morpholine (**30**).*[47] To a solution of β-nitrostyrene (**2**, 149 mg, 1.00 mmol) in CH_2Cl_2 (5 mL) was added morpholine (87 µL, 1.0 mmol) followed by $Sm(OTf)_3$ (1 mg, 0.2 mol%) and the mixture was stirred at rt overnight until the nitroalkene was consumed (TLC, 24 h). CH_2Cl_2 (10 mL) was then added, the mixture washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated in vacuo to give nitroalkane **30** (222 mg, 94%) as a red oil, which was used without further purification; R_f 0.46 (Petrol:EtOAc 4:1); ^1H NMR (600 MHz) δ 2.36 (m, 2H), 2.52 (m, 2H), 3.64 (m, 4H), 4.34 (dd, *J* = 9.5, 5.8, 1H), 4.57 (dd, *J* = 12.3, 5.8, 1H), 4.99 (dd, *J* = 12.3, 9.5, 1H), 7.20 (m, 2H), 7.37 (m, 3H); ^{13}C NMR (150 MHz) δ 49.8 (CH_2), 66.9 (CH_2), 66.9 (CH), 79.6 (CH_2), 128.3 (CH), 128.6 (CH), 129.3 (CH), 133.6 (Cq). Data in agreement to that reported.[47]

*4.3.16. 1-(2-Nitro-1-phenylethyl)-1H-benzo[d][1,2,3]triazole (**31**).* To a solution of β-nitrostyrene (**2**, 74 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) was added 1*H*-benzo[d][1,2,3]triazole (**12**, 65 mg, 0.55 mmol) followed by Et_3N (6 µL, 10 mol%) and the mixture was stirred at rt until complete consumption of the nitroalkene (TLC, 19 h). The mixture was then evaporated in vacuo and purification of the residue by flash column chromatography (Petrol:Et_2O 7:3) gave nitroalkane **31** (111 mg, 83%) as a colourless oil; R_f 0.45 (Petrol:Et_2O 7:3); ^1H NMR (600 MHz) δ 5.16 (dd, *J* = 14.8, 4.8, 1H), 5.95 (dd, *J* = 14.6, 9.8, 1H), 6.60 (dd, *J* = 9.8, 4.8, 1H), 7.36 (m, 2H), 7.43 (m, 3H), 8.07 (d, *J* = 8.4, 1H); ^{13}C NMR (150 MHz) δ 59.7 (CH), 76.5 (CH_2), 109.3 (CH), 120.1 (CH), 124.5 (CH), 126.8 (CH), 128.0 (CH), 129.5 (CH), 129.7 (CH), 132.6 (Cq), 133.9 (Cq), 146.1 (Cq). Data in agreement with that reported.[61]

*4.3.17. 3-(2-Nitro-1-phenylethyl)oxazolidin-2-one (**32**).*[37] To a mixture of 2-oxazolidinone (87 mg, 1 mmol), ^{t}BuOK (112 mg, 1 mmol) and 18-crown-6 (264 mg, 1.00 mmol) was added dry THF (5 mL) and the mixture was stirred at rt for 1 h. The mixture was then cooled to -78 °C and a solution of β-nitrostyrene (**2**, 149 mg, 1.00 mmol) in THF (5 mL) was added and the mixture stirred at this temperature until complete consumption of the starting material (TLC, 30 min). A saturated aqueous solution of NH_4Cl (20 mL) was then added and the mixture warmed to rt and extracted with Et_2O (3x20 mL), dried ($MgSO_4$), evaporated in vacuo and purification of the residue by flash column chromatography (Petrol:Me_2CO 7:3) gave nitroalkane **32** (213 mg, 90%) as a colourless oil, R_f 0.50 (Petrol:Me_2CO 3:2); IR υ_{max} (thin film) 2976, 2925, 1740, 1553, 1482, 1419, 1380, 1248, 1111, 1076, 1047, 761, 733, 699 cm^{-1}; ^1H NMR (600 MHz) δ 3.36 (dt, *J* = 8.0, 8.8, 1H), 3.61(m, 1H), 4.29 (m, 2H), 4.86 (dd, *J* = 5.4, 13.0, 1H), 5.28 (dd, *J* = 10.3, 13.0, 1H), 5.58 (dd, *J* = 5.4, 10.3, 1H), 7.31-7.35 (m, 2H), 7.37-7.43 (m, 3H); ^{13}C NMR (150 MHz) δ 42.0 (CH_2), 55.7 (CH), 62.2 (CH_2), 74.5 (CH_2), 127.3 (CH), 129.3 (CH), 133.6 (Cq), 157.6 (Cq), one CH peak missing; m/z (CI^+) 237 ($M+H^+$, 100%), 176 (M^+-CH_3NO_2, 67%); HRMS: found 237.08724, $C_{11}H_{13}N_2O_4$ requires 237.08753; Anal. Cald. For $C_{11}H_{12}N_2O_4$: C, 55.93, H, 5.12, N, 11.86. Found C, 56.19, H, 5.23, N, 11.60%.

*4.3.18. Butyl(2-nitro-1-phenylethyl)sulfane (**33**).*[39] To a stirred solution of β-nitrostyrene (**2**, 74 mg, 0.50 mmol) in EtOH (1 mL) was added 1-butanethiol (53 µL, 0.50 mmol) at rt followed by Et_3N (4 µL, 5 mol%) when the mixture was instantly decolorized and after 5 min of stirring the mixture was evaporated to give pure nitroalkane **33** (114 mg, 95%) as a colourless oil, which was used without further purification; R_f 0.63 (Petrol:Et_2O 9:1); IR υ_{max} (thin film) 2959, 2930, 2873, 1555, 1455, 1376, 747, 699 cm^{-1}; ^1H NMR (600 MHz) δ 0.87 (t, *J* = 7.4, 3H), 1.35 (m, 2H), 1.53 (quint., *J* = 7.6, 2H), 2.45 (t, *J* = 7.4, 2H), 4.56 (t, *J* = 7.9, 1H), 4.76 (d, *J* = 7.8, 2H), 7.30-7.38 (m, 5H); ^{13}C NMR (150 MHz) δ 13.5 (CH_3), 21.8 (CH_2), 31.1 (CH_2), 31.3 (CH_2), 46.5 (CH), 79.3 (CH_2), 127.6 (CH), 128.4 (CH), 129.0 (CH), 137.4 (Cq); m/z (CI^+) 240 ($M+H^+$, 100%), 193 (M^+-NO_2, 56%), 179 (69%), 150 (M^+-BuS, 67%); HRMS: found 240.10582, $C_{12}H_{18}NO_2S$ requires 240.10617; Anal. Cald. For $C_{12}H_{17}NO_2S$: C, 60.22, H, 7.16, N, 5.85. Found C, 60.32, H, 7.21, N, 5.92%.

*4.3.19. (2-Nitro-1-phenylethyl)(phenyl)sulfane (**34**).*[39] In an identical manner as for the preparation of **33**, thiophenol (51 µL, 0.50 mmol) gave nitroalkane **34** (125 mg, 97%) as a colourless oil, used without further purification; R_f 0.67 (Petrol:Et_2O 9:1); ^1H NMR (600 MHz) δ 4.73 (dd, *J* = 12.8, 6.0, 1H), 4.86 (m, 1H), 4.91 (m, 1H), 7.27-7.44 (m, 10H); ^{13}C NMR (150 MHz) δ 49.7 (CH), 78.4 (CH_2), 127.6 (CH), 128.5 (CH), 128.7 (CH), 128.9 (CH), 129.3 (CH), 131.7 (Cq), 133.7 (CH), 136.2 (Cq). Data in agreement with that reported.[62]

*4.3.20. (2-Nitro-1-(phenylsulfonyl)ethyl)benzene (**35**).*[48] To a solution of sulfide **34** (259 mg, 1.00 mmol) in MeOH (5 mL), cooled to 0 °C, was added Oxone® (923 mg, 1.50 mmol) in H_2O (10 mL) and the resulting suspension was stirred for 1 h, then left to warm to rt and stirred overnight (22 h). After completion H_2O (10 mL) was added and the mixture extracted with CH_2Cl_2 (3×10 mL). The combined organics were then washed with brine (10 mL), dried ($MgSO_4$) and evaporated in vacuo to give pure sulfone **35** (301 mg, 97%) as a white solid which was used without further purification; mp. 180-181 °C; R_f 0.49 (Petrol:Et_2O 4:1); IR υ_{max} (thin film) 3068, 3009, 2956, 1553, 1496, 1447, 1417, 1374, 1360, 1298, 1280, 1143, 1080, 852, 760, 727, 700, 688 cm^{-1}; ^1H NMR (600 MHz) δ 4.99 (dd, *J* = 10.1, 4.7, 1H), 5.10 (dd, *J* = 14.0, 10.0, 1H), 5.37 (dd, *J* = 14.0, 4.6, 1H), 7.14 (m, 2H), 7.29 (m, 2H), 7.36 (m, 1H), 7.45 (m, 2H), 7.55 (m, 2H), 7.63 (m, 1H); ^{13}C NMR (150 MHz) δ 67.9 (CH), 72.7 (CH_2), 128.7 (Cq), 129.0 (CH), 129.1 (CH), 129.1 (CH), 129.4 (CH), 130.0 (CH), 134.5 (CH), 135.8 (Cq); m/z (CI^+) 292 (M^+, 30%), 251 (11%), 186 (13%), 150 (100%); HRMS: found 292.06466, $C_{14}H_{13}NO_4S$ requires 292.06435; Anal. Cald. For $C_{14}H_{13}NO_4S$: C, 57.72, H, 4.50, N, 4.81. Found C, 57.71, H, 4.40, N, 4.72%.

*4.3.21. (2-Nitro-1-phenylethyl)diphenylphosphine oxide (**36**).* To a solution of β-nitrostyrene (**2**, 74 mg, 0.50 mmol) in THF (2 mL) at rt was added diphenylphosphine oxide (101 mg, 0.50 mmol) followed by Et_3N (4 µL, 5 mol%) and the mixture was stirred at rt until the nitroalkene was consumed (TLC, 24 h). After completion, the mixture was evaporated and purification by flash column chromatography (Petrol:Me_2CO 1:1) gave phosphine oxide **36** (157 mg, 89%) as a white solid; mp. 206-207 °C (lit.[62] 208-209 °C); R_f 0.61 (Petrol:Me_2CO 1:1); ^1H NMR (600 MHz) δ 4.42 (m, 1H), 4.76 (m, 1H), 5.12 (m, 1H),

7.21-7.28 (m, 7H), 7.39-7.44 (m, 3H), 7.62 (m, 3H), 7.99 (m, 2H); ^{13}C NMR (150 MHz) δ 45.8 (d, *J* = 64.0, CH), 72.7 (d, *J* = 5.9, CH_2), 128.2 (d, *J* = 2.5, CH), 128.3 (d, *J* = 12.3, CH), 128.7 (d, *J* = 1.7, CH), 129.3 (d, *J* = 11.6, CH), 129.4 (d, *J* = 5.1, CH), 129.6 (d, *J* = 8.6, Cq), 130.3 (Cq), 130.9 (d, *J* = 9.2, CH), 131.1 (d, *J* = 8.8, CH), 131.6 (d, *J* = 5.6, Cq), 132.0 (d, *J* = 2.8, CH), 132.7 (d, *J* = 2.8, CH). Data in agreement to that reported.[63]

4.4. Nitro-Mannich reaction of nitroacrylate adducts.

General procedure A for the synthesis of pyrrolidin-2-ones. A solution of nitroalkane (0.50 mmol) in THF (5 mL), was cooled to -78 °C and ^{n}BuLi (0.55 mmol, of a 2.5 M solution in hexanes, 1.1 equiv.) was added dropwise. The orange mixture was stirred at this temperature for 10 min before the imine **37** (1.00 mmol, 2.0 equiv.) in THF (2 mL) was added *via* cannula. The mixture was stirred for 20 min, before TFA (1.75 mmol, 3.5 equiv.) in THF (0.5 mL) was added *via* cannula. The mixture was stirred at this temperature for a further 1 h before being warmed to rt for 16 h. Saturated aqueous $NaHCO_3$ (20 mL) and Et_2O (20 mL) were then added and the layers separated. The aqueous phase was extracted with Et_2O (3x20 mL), and the combined organics washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to leave the crude pyrrolidinone. which was purified by column chromatography.

4.4.1. (3S,4S*,5R*)-3-(1H-Indol-3-yl)-1-(4-methoxyphenyl)-4-nitro-5-phenylpyrrolidin-2-one (**41**).* Prepared by general procedure A. Nitroalkane **3** (153 mg, 0.620 mmol), ^{n}BuLi (0.680 mmol), imine **37** (260 mg, 1.24 mmol) and TFA (2.17 mmol) after purification by flash column chromatography (Petrol:EtOAc 3:2) gave pyrrolidinone **41** (140 mg, 53%, 79% based on recovered starting material) as an orange solid; mp. 196-197 °C; R_f 0.34 (Petrol:EtOAc 3:2); IR υ_{max} (thin film) 3329, 2960, 1701, 1555, 1512, 1364, 1250, 743 cm^{-1}; ^{1}H NMR (600 MHz) δ 3.74 (s, 1H), 4.92 (d, *J* = 7.9, 1H), 5.27 (dd, *J* = 7.8, 6.5, 1H), 5.73 (d, *J* = 6.3, 1H), 6.85 (m, 3H), 7.21 (m, 2H), 7.23-7.36 (m, 7H), 7.64 (m, 1H), 8.70 (br s, 1H); ^{13}C NMR (150 MHz) δ 46.5 (CH), 55.3 (CH_3), 65.9 (CH), 92.4 (CH), 108.5 (Cq), 112.0 (CH), 114.2 (CH), 118.1 (CH), 120.2 (CH), 122.5 (CH), 124.3 (CH), 125.4 (CH), 125.4 (Cq), 126.9 (CH), 129.2 (CH), 129.2 (Cq), 129.3 (CH), 136.2 (Cq), 136.6 (Cq), 157.7 (Cq), 170.8 (Cq); m/z (EI$^+$) 427 (M^+, 20%), 380 (M^+-HNO_2, 100%), 351 (M+H$^+$-Ph, 17%), 230 (10%), 210 (17%); HRMS: found 427.15312, $C_{18}H_{20}N_3O_4$ requires 427.15266.

4.4.2. (3S,4S*,5R*)-1-(4-Methoxyphenyl)-4-nitro-5-phenyl-3-(2,4,6-trimethoxyphenyl)pyrrolidin-2-one (**42**).* Prepared by general procedure A. Nitroalkane **4** (126 mg, 0.400 mmol), ^{n}BuLi (0.40 mmol), imine **37** (170 mg, 0.800 mmol) and TFA (1.40 mmol) after purification by flash column chromatography (Petrol:Me_2CO 7:3) gave pyrrolidinone **42** (102 mg, 53%) as a white solid; mp. 96-97 °C; R_f 0.28 (Petrol:Me_2CO 7:3); IR υ_{max} (thin film) 3003, 2940, 2839, 1713, 1611, 1595, 1553, 1512, 1457, 1364, 1249, 1205, 1152, 1118, 1033, 835, 817, 701 cm^{-1}; ^{1}H NMR (600 MHz) δ 3.72 (s, 3H), 3.77 (br. s, 3H), 3.82 (s, 3H), 3.95 (br. s, 3H), 5.12 (d, *J* = 9.5, 1H), 5.26 (dd, *J* = 9.6, 7.5, 1H), 5.70 (d, *J* = 7.5, 1H), 6.18 (m, 2H), 6.78 (app. d, *J* = 9.1, 2H), 7.24 (app. d, *J* = 9.1, 1H), 7.26-7.32 (m, 5H); ^{13}C NMR (150 MHz) δ 44.2 (CH), 55.3, 55.4, 55.8 and 56.0 (CH_3), 65.0 (CH), 90.9 and 91.4 (CH), 92.2 (CH), 104.1 (Cq), 114.0 (CH), 125.0 (CH), 127.1 (CH), 128.9 (CH), 129.0 (CH), 129.7 (Cq), 137.4 (Cq), 157.1 (Cq), 158.6 (Cq), 159.7 (Cq), 161.6 (Cq), 170.0 (Cq); m/z (EI$^+$) 479 (M+H$^+$, 100%), 432 (M+H$^+$-NO_2, 70%), 264 (30%); HRMS: found 479.1808, $C_{18}H_{20}N_3O_4$ requires 479.1818; Anal. Cald. For $C_{26}H_{27}N_2O_7$: C, 65.26, H, 5.48, N, 5.85. Found C, 65.39, H, 5.78, N, 5.59%.

4.4.3. (2S,3R*,4R*)-Ethyl 1-(4-methoxyphenyl)-3-nitro-5-oxo-2-phenyl-1,2,3,4,5,6,7,8-octahydroquinoline-4-carboxylate (**43**).* Prepared by general procedure A, except 2.1 equiv. of ^{n}BuLi was used. Nitroalkane **5** (36 mg, 0.14 mmol), ^{n}BuLi (0.28 mmol), imine **37** (59 mg, 0.28 mmol) and TFA (0.49 mmol) after purification by flash column chromatography (Petrol:Me_2CO 7:3) gave quinoline **43** (24 mg, 38%) as a yellow oil; R_f 0.17 (Petrol:Me_2CO 7:3); IR υ_{max} (thin film) 2932, 1730, 1557, 1508, 1396, 1247, 1181, 1027, 841, 733, 702 cm^{-1}; ^{1}H NMR (600 MHz) δ 1.28 (t, *J* = 7.2, 3H), 1.92 (m, 2H), 2.22 (m, 2H), 2.40 (m, 2H), 3.74 (s, 3H), 4.22 (m, 2H), 4.43 (d, *J* = 5.3, 1H), 5.19 (dd, *J* = 8.7, 5.3, 1H), 5.24 (d, *J* = 8.8, 1H), 6.40-6.90 (br, 4H), 7.15 (m, 2H), 7.26 (m, 3H); ^{13}C NMR (150 MHz, at 60 °C) δ 14.0 (CH_3), 21.3 (CH_2), 28.9 (CH_2), 35.8 (CH_2), 39.6 (CH), 55.3 (CH_3), 61.8 (CH_2), 63.7 (CH), 85.5 (CH), 104.2 (Cq), 114.6 (CH), 128.2 (CH), 28.9 (CH), 129.1 (CH), 130.1 (CH), 134.7 (Cq), 135.3 (Cq), 158.9 (Cq), 161.3 (Cq), 171.0 (Cq), 193.8 (Cq); m/z (EI$^+$) 450 (M^+, 32%), 404 (M^+-NO_2, 86%), 330 (M^+-HNO_2-COOEt, 100%), 254 (M^+-NO_2-COOEt -Ph, 35%); HRMS: found 450.17902, $C_{25}H_{26}N_2O_6$ requires 450.17854.

4.4.4. (3S,4R*,5R*)-3-Methoxy-1-(4-methoxyphenyl)-4-nitro-5-phenylpyrrolidin-2-one (**44**).* Prepared by general procedure A. Nitroalkane **6** (75 mg, 0.42 mmol), ^{n}BuLi (0.460 mmol), imine **37** (134 mg, 0.640 mmol) and TFA (0.850 mmol) after purification by flash column chromatography (Petrol:EtOAc 7:3) gave pyrrolidinone **44** (60 mg, 42%) as an orange oil that was unstable (degradation was observed after 30 min at rt); R_f 0.35 (Petrol:EtOAc 7:3); IR υ_{max} (thin film) 2958, 2925, 1713, 1555, 1511, 1367, 1248, 1106, 1030, 834, 700 cm^{-1}; ^{1}H NMR (600 MHz) δ 3.72 (s, 1H), 3.75 (s, 1H), 4.74 (d, *J* = 6.0, 1H), 5.02 (t, *J* = 5.8, 1H), 5.48 (d, *J* = 5.7, 1H), 6.78 (app d, *J* = 9.1, 2H), 7.20 (app d, *J* = 9.1, 2H), 7.21-7.40 (m, 5H); ^{13}C NMR (150 MHz) δ 55.3 (CH_3), 59.6 (CH_3), 64.1 (CH), 81.2 (CH), 91.1 (CH), 114.2 (CH), 125.3 (CH), 127.1 (CH), 128.4 (Cq), 129.3 (CH), 129.4 (CH), 135.9 (Cq), 157.9 (Cq), 167.2 (Cq); m/z (EI$^+$) 342 (M^+, 100%), 266 (M^+-Ph+H, 23%), 147 (17%); HRMS: found 342.12084, $C_{18}H_{18}N_2O_5$ requires 342.12102.

4.4.5. (3S,4R*,5R*)-1-(4-Methoxyphenyl)-3-morpholino-4-nitro-5-phenylpyrrolidin-2-one (**45**).* Prepared by general procedure A. Nitroalkane **10** (105 mg, 0.450 mmol), ^{n}BuLi (0.500 mmol), imine **37** (143 mg, 0.680 mmol) and TFA (0.990 mmol) after purification by flash column chromatography (Petrol:EtOAc 3:2) gave pyrrolidinone **45** (12 mg, 7%) as an orange oil that was unstable (degradation was observed after 30 min at rt); R_f 0.31 (Petrol:EtOAc 3:2); IR υ_{max} (thin film) 2961, 2853, 1709, 1557, 1512, 1249, 1115, 1031, 835 cm^{-1}; ^{1}H NMR (600 MHz) δ 2.87 (m, 4H), 3.73 (s, 3H), 3.78 (m, 4H), 4.46 (d, *J* = 7.4, 1H), 5.10 (dd, *J* = 7.4, 6.2, 1H), 5.50 (d, *J* = 6.2, 1H), 6.79 (app d, *J* = 8.9, 2H), 7.15-7.35 (m, 7H); ^{13}C NMR (150 MHz) δ 49.3 (CH_2), 55.3 (CH_3), 64.2 (CH), 66.8 (CH_2), 70.4 (CH), 87.3 (CH), 114.2 (CH), 125.0 (CH), 126.6 (CH), 128.8 (Cq), 129.3 (CH), 129.4 (CH), 136.4 (Cq), 157.7 (Cq), 167.0 (Cq); m/z (CI$^+$) 398 (M+H$^+$, 7%), 310 (M^+-C_4H_5NO, 11%), 266 (M+H$^+$- C_4H_5NO-NO_2, 18%), 227 (72%), 105 (100%); HRMS: found 398.17131, $C_{21}H_{24}N_3O_5$ requires 398.17160.

4.5 Nitro-Mannich reaction to β-nitrostyrene adducts

General procedure B for the synthesis of β-nitroamides. A solution of nitroalkane (0.500 mmol) in THF (5 mL), was cooled to -78 °C and ^{n}BuLi (0.550 mmol, of a 2.5 M solution

in hexanes, 1.1 equiv.) was added dropwise. The orange mixture was stirred at this temperature for 10 min, before the imine **37** (1.00 mmol, 2.0 equiv.) in THF (2 mL) was added via cannula. The mixture was stirred for 10 min before a 1:1 vol. mixture of TFA:THF (TFA 1.75 mmol, 3.5 equiv.) was added dropwise. The mixture was stirred at this temperature for a further 1 h, then warmed to rt over 5 min and quenched with saturated aqueous $NaHCO_3$ (10 mL) extracted with Et_2O (3×10 mL), dried ($MgSO_4$), concentrated *in vacuo* to give crude β-nitroamine. A sample was taken for ^1H NMR analysis and the rest of the crude product was dissolved in CH_2Cl_2 (6 mL), cooled to -78 °C and pyridine (140 µL, 1.50 mmol) and trifluoroacetic anhydride (240 µL, 1.50 mmol) were added. The mixture was then warmed to rt and stirred for a further 3 h. The mixture was then washed with aqueous HCl 2 M (3×10 mL) and brine (10 mL), dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography to give the trifluoroacetamide protected β-nitroamine.

4.5.1. N-((1R,2S*,3R*)-3-(1H-Indol-3-yl)-2-nitro-1,3-diphenylpropyl)-2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide (**46**).* Prepared by general procedure B. Nitroalkane **16** (123 mg, 0.460 mmol), ^{n}BuLi (184 µL, 2.5 M, 0.460 mmol), imine **37** (194 mg, 0.920 mmol) and TFA (123 µL, 1.61 mmol) gave after TFA-protection and purification by flash column chromatography (Petrol:Et_2O 1:1) **46** (133 mg, 50%) as a colourless oil; R_f 0.34 (Petrol:Et_2O 1:1); IR υ_{max} (thin film) 3420, 3063, 3034, 2927, 2840, 1691, 1606, 1555, 1510, 1497, 1456, 1414, 1367, 1301, 1255, 1206, 1180, 1157, 1033, 840, 756, 734, 699 cm^{-1}; ^1H NMR (600 MHz) δ 3.74 (s, 3H), 4.91 (d, *J* = 6.7, 1H), 5.92 (dd, *J* = 8.9, 2.8, 1H), 6.25 (d, *J* = 9.2, 1H), 6.40 (dd, *J* = 6.6, 9.2, 1H), 6.49 (dd, *J* = 8.8, 3.0, 1H), 6.63 (dd, *J* = 8.8, 3.0, 1H), 6.79 (dd, *J* = 8.7, 2.7, 1H), 6.92 (dd, *J* = 8.2, 1.1, 2H), 7.01-7.34 (m, 9H), 7.41 (m, 3H), 6.92 (d, *J* = 2.5, 1H), 8.25 (br. s, 1H); ^{13}C NMR (150 MHz) δ 43.9 (CH), 55.3 (CH_3), 62.8 (CH), 89.1 (CH), 111.2 (CH), 113.4 (CH), 113.6 (CH), 114.7 (Cq), 116.1 (q, *J* = 289.0), 118.8, 120.0, 122.3, 122.6, 127.7, 128.4, 128.6, 128.7, 129.3, 129.6, 131.1 and 132.5 (CH), 126.4, 126.9, 132.8, 136.0 and 138.3 (Cq), 158.3 (q, *J* = 35.5, Cq), 160.1 (Cq); ^{19}F NMR (282 MHz) δ -67.60 (3F, s, CF_3); m/z (EI^+) 573 (M^+, 27%), 308 (M^+-NO_2-PMP-NH-TFA, 100%), 206 ($PhCH^+$-(Indole), 32%); HRMS: found 573.18730, $C_{32}H_{26}F_3N_3O_4$ requires 573.18699.

4.5.2. 2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1R,2S*,3R*)-2-nitro-1,3-diphenyl-3-(2,4,6-trimethoxyphenyl)propyl)acetamide (**47**).* Prepared by general procedure B. Nitroalkane **17** (113 mg, 0.360 mmol), ^{n}BuLi (144 µL, 2.5 M, 0.360 mmol), imine **37** (150 mg, 0.720 mmol) and TFA (96 µL, 1.26 mmol) gave after TFA-protection and purification by flash column chromatography (Petrol:Et_2O 4:1) **47** (185 mg, 83%) as a white solid, mp. 185-186 °C; R_f 0.13 (Petrol:Et_2O 4:1); IR υ_{max} (thin film) 3031, 2939, 2841, 1696, 1605, 1590, 1550, 1510, 1495, 1455, 1203, 1180, 1150, 1122, 1059, 1035, 814, 735, 699 cm^{-1}; ^1H NMR (600 MHz) δ 3.30 (br. s, 3H), 3.72 (s, 3H), 3.77 (s, 3H), 4.05 (br. s, 3H), 5.14 (d, *J* = 11.5, 1H), 5.70-6.20 (br. s, 2H), 5.78 (d, *J* = 6.8, 1H), 6.01 (dd, *J* = 9.0, 2.9, 1H), 6.35 (dd, *J* = 9.0, 3.1, 1H), 6.73 (d, *J* = 7.6, 2H), 6.76 (dd, *J* = 8.8, 2.9, 1H), 7.01 (app. t, *J* = 7.6, 2H), 7.04 (m, 1H), 7.13 (dd, *J* = 11.5, 6.8, 1H), 7.15-7.19 (m, 4H), 7.46 (app. d, *J* = 7.6, 2H); ^{13}C NMR (150 MHz) δ 41.2 (CH), 55.3 (CH_3), 65.2 (CH), 87.0 (CH), 90.0 (CH), 107.3 (Cq), 112.9 (CH), 113.4 (CH), 116.1 (CF_3, q, *J* = 288.7), 126.7 and 127.4 (CH), 127.7 (Cq), 127.9, 128.2, 128.3 and 131.6 (CH), 131.6 (Cq), 131.7 and 132.7 (CH), 140.1 (Cq), 157.5 (O=CCF_3, q, *J* = 35.6), 159.5 and 160.6 (Cq); ^{19}F NMR (282 MHz) δ -67.74 (3F, s, CF_3); m/z (ES^+) 647 (M+Na^+, 20%), 625 (M+H^+, 15%), 578 (M^+-NO_2, 15%), 457 (25%), 378 (15%), 359 (M^+-NO_2-PMP-NH-TFA, 70%), 257 ($(OMe)_3C_6H_3CH^+Ph$, 100%); HRMS: found 647.2003, $C_{33}H_{31}F_3N_2O_7Na$ requires 647.1981; Anal. Cald. For $C_{33}H_{31}F_3N_2O_7$: C, 63.46, H, 5.00, N, 4.48. Found C, 63.36, H, 4.96, N, 4.44%.

4.5.3. 2,2,2-Trifluoro-N-((1R,2R*,3S*)-3-methoxy-2-nitro-1,3-diphenylpropyl)-N-(4-methoxyphenyl)acetamide (**48**).* Prepared by general procedure B. Nitroalkane **22** (44 mg, 0.24 mmol), ^{n}BuLi (96 µL, 2.5 M, 0.24 mmol), imine **37** (101 mg, 0.480 mmol) and TFA (64 µL, 0.840 mmol) gave after TFA-protection and purification by flash column chromatography (Petrol:Et_2O 4:1) **48** (83 mg, 71%) as a white solid; mp. 69-70 °C; R_f 0.32 (Petrol:Et_2O 4:1); IR υ_{max} (thin film) 2937, 2837, 1692, 1557, 1509, 1254, 1203, 1182, 1151, 1096, 1026, 842, 754, 733, 699, 659 cm^{-1}; ^1H NMR (600 MHz) δ 3.24 (s, 3H), 3.82 (s, 3H), 5.06 (d, *J* = 8.4, 1H), 5.38 (dd, *J* = 10.9, 8.5, 1H), 6.01 (dd, *J* = 8.8, 2.6, 1H), 6.54 (dd, *J* = 8.8, 3.0, 1H), 6.89 (d, *J* = 11.0, 1H), 6.92 (m, 2H), 7.00 (dd, *J* = 8.7, 3.0, 1H), 7.16 (app t, *J* = 7.7, 2H), 7.25 (m, 1H), 7.36-7.44 (m, 5H), 7.73 (dd, *J* = 8.8, 2.6, 1H); ^{13}C NMR (150 MHz) δ 55.4 (CH_3), 57.0 (CH_3), 61.7 (CH), 84.7 (CH), 89.5 (CH), 113.5 (CH), 113.6 (CH), 116.6 (q, *J* = 290.1, CF_3), 126.8 (Cq), 127.7 (CH), 128.4 (CH), 128.7 (CH), 129.3 (CH), 129.3 (CH), 129.5 (CH), 131.4 (CH), 132.9 (Cq), 133.5 (CH), 135.6 (CH), 157.9 (q, *J* = 35.7, C=OCF_3), 160.1 (Cq); ^{19}F NMR (282 MHz) δ -67.82 (3F, s, CF_3); m/z (EI^+) 488 (M^+, 5%), 219 (PMPNHTFA$^+$, 8%), 149 (14%), 121 (PhCH-OMe^+, 100%); HRMS: found 488.15642, $C_{25}H_{23}F_3NO_5$ requires 488.15535; Anal. Cald. For $C_{25}H_{23}F_3NO_5$: C, 61.47, H, 4.75, N, 5.74. Found C, 61.60, H, 5.05, N, 5.63%.

4.5.4. N-((1R,2R*,3S*)-3-Ethoxy-2-nitro-1,3-diphenylpropyl)-2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide (**49**).* Prepared by general procedure B. Nitroalkane **23** (110 mg, 0.560 mmol), ^{n}BuLi (224 µL, 2.5 M, 0.560 mmol), imine **37** (236 mg, 1.12 mmol) and TFA (150 µL, 1.96 mmol) gave after TFA-protection and purification by flash column chromatography (Petrol:Et_2O 4:1) **49** (219 mg, 78%) as a yellow oil; R_f 0.36 (Petrol:Et_2O 4:1); IR υ_{max} (thin film) 2977, 1694, 1556, 1510, 1457, 1300, 1254, 1203, 1182, 1152, 1092, 1075, 1032, 843, 783, 755, 733, 699 cm^{-1}; ^1H NMR (600 MHz) δ 1.17 (t, *J* = 7.1, 3H), 3.40 (m, 2H), 3.82 (s, 3H), 5.13 (d, *J* = 8.4, 1H), 5.38 (dd, *J* = 10.9, 8.5, 1H), 6.01 (dd, *J* = 9.1, 2.4, 1H), 6.55 (dd, *J* = 8.9, 3.1, 1H), 6.83 (d, *J* = 10.9, 1H), 6.92 (m, 2H), 7.00 (dd, *J* = 8.8, 3.0, 1H), 7.16 (m, 2H), 7.25 (m, 2H), 7.38 (m, 5H), 7.74 (dd, *J* = 8.7, 2.5, 1H); ^{13}C NMR (150 MHz) δ 14.6 (CH_3), 55.4 (CH_3), 61.7 (CH), 65.2 (CH_2), 83.2 (CH), 89.9 (CH), 113.5 (CH), 113.6 (CH), 116.4 (q, *J* = 288.5, CF_3), 126.8 (Cq), 127.6 (CH), 128.4 (CH), 128.7 (CH), 129.2 (CH), 129.3 (CH), 131.7 (CH), 133.4 (Cq), 133.5 (CH), 136.4 (Cq), 157.7 (q, *J* = 35.0, Cq), 160.2 (Cq); ^{19}F NMR (282 MHz) δ -67.31 (3F, s, CF_3); m/z (CI^+) 502 (M^+, 27%), 410 (M^+-EtOH-NO_2, 24%), 135 (100%); HRMS: found 502.17064, $C_{26}H_{25}F_3N_2O_5$ requires 502.17101.

4.5.5. N-((1R,2R*,3S*)-3-(Benzyloxy)-2-nitro-1,3-diphenylpropyl)-2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide (**50**).* Prepared by general procedure B. Nitroalkane **24** (160 mg, 0.620 mmol), ^{n}BuLi (248 µL, 2.5 M, 0.620 mmol), imine **37** (262 mg, 1.24 mmol) and TFA (166 µL, 2.17 mmol) gave after TFA-protection and purification by flash column chromatography (Petrol:Et_2O 9:1) **50** (224 mg, 64%) as a yellow oil; R_f 0.26 (Petrol:Et_2O 9:1); IR υ_{max} (thin film) 3035, 1696, 1557, 1510, 1254, 1206, 1183, 1169, 1156, 1069, 912, 734, 700 cm^{-1}; ^1H NMR (600 MHz) δ 3.78 (s, 3H), 4.33 (d, *J* = 10.9, 1H), 4.53 (d, *J* = 10.9, 1H), 5.22 (d, *J* = 6.7, 1H), 5.50

(dd, *J* = 11.0, 6.8, 1H), 5.96 (dd, *J* = 8.8, 2.5, 1H), 6.50 (dd, *J* = 8.8, 3.0, 1H), 6.70 (d, *J* = 11.0, 1H), 6.82 (dd, *J* = 8.8, 3.0, 1H), 6.94 (d, *J* = 7.4, 2H), 7.17 (m, 2H), 7.25 (m, 2H), 7.30 (m, 5H), 7.47 (m, 3H), 7.52 (m, 2H); ^{13}C NMR (150 MHz) δ 55.3 (CH_3), 61.0 (CH), 71.5 (CH_2), 81.7 (CH), 90.0 (CH), 113.3 and 113.6 (CH), 116.1 (q, *J* = 288.7, CF_3), 126.4 (Cq), 127.9, 128.2, 128.4, 128.4, 128.7, 128.9, 129.0, 129.3, 129.6, 131.4 and 133.2 (CH), 133.4, 135.4 and 136.3 (Cq), 157.8 (q, *J* = 35.2, Cq), 160.1 (Cq); ^{19}F NMR (282 MHz) δ -67.47 (3F, s, CF_3); m/z (CI^+) 564 (M^+, 100%), 410 (M^+-BnOH-NO_2, 57%), 197 (28%); HRMS: found 564.18742, $C_{31}H_{27}F_3N_2O_5$ requires 564.18666.

4.5.6. 2,2,2-Trifluoro-N-((1R,2R*,3S*)-3-isopropoxy-2-nitro-1,3-diphenylpropyl)-N-(4-methoxyphenyl)acetamide **(51)**.* Prepared by general procedure B. Nitroalkane **25** (95 mg, 0.45 mmol), ^{n}BuLi (180 µL, 2.5 M, 0.450 mmol), imine **37** (190 mg, 0.900 mmol) and TFA (121 µL, 1.58 mmol) gave after TFA-protection and purification by flash column chromatography (Petrol:Et_2O 4:1) **51** (186 mg, 80%) as a yellow oil; R_f 0.36 (Petrol:Et_2O 4:1); IR υ_{max} (thin film) 2976, 1695, 1556, 1510, 1254, 1203, 1168, 1153, 1120, 1090, 1067, 1034, 843, 757, 733, 700 cm^{-1}; ^{1}H NMR (600 MHz) δ 1.16 (d, *J* = 6.2, 6H), 3.53 (m, 2H), 3.83 (s, 3H), 5.24 (d, *J* = 7.7, 1H), 5.43 (dd, *J* = 10.7, 7.7, 1H), 6.07 (d, *J* = 8.7, 1H), 6.58 (dd, *J* = 8.9, 3.0, 1H), 6.75 (d, *J* = 10.8, 1H), 6.95 (m, 2H), 6.99 (dd, *J* = 8.8, 3.0, 1H), 7.17 (m, 2H), 7.26 (m, 2H), 7.38 (m, 5H), 7.70 (m, 1H); ^{13}C NMR (150 MHz) δ 19.6 (CH_3), 23.0 (CH_3), 55.4 (CH_3), 61.1 (CH), 69.3 (CH), 80.2 (CH), 90.4 (CH), 113.5 (CH), 113.6 (CH), 116.3 (q, *J* = 288.7, CF_3), 126.8 (Cq), 127.6 (CH), 128.4 (CH), 128.8 (CH), 129.1 (CH), 129.3 (CH), 129.3 (CH), 131.7 (CH), 133.5 (CH), 133.7 (Cq), 136.5 (Cq), 157.5 (q, *J* = 35.4, Cq), 160.2 (Cq); ^{19}F NMR (282 MHz) δ -67.24 (3F, s, CF_3); m/z (CI^+) 516 (M^+, 32%), 410 (M^+-IPA-NO_2, 100%), 308 (24%); HRMS: found 516.18577, $C_{27}H_{27}F_3N_2O_5$ requires 516.18666.

4.5.7. 2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1R,2S*,3S*)-2-nitro-3-((4-nitrophenyl)amino)-1,3-diphenylpropyl)acetamide **(52)**.* Prepared by general procedure B. Nitroalkane **29** (114 mg, 0.400 mmol), ^{n}BuLi (160 µL, 2.5 M, 0.400 mmol), imine **37** (169 mg, 0.800 mmol) and TFA (31 µL, 0.400 mmol) gave after TFA-protection and purification by flash column chromatography (Petrol:Me_2CO 4:1) **52** (40 mg, 17%) as a yellow solid; mp. 141-142 °C, R_f 0.30 (Petrol:Me_2CO 4:1); IR υ_{max} (thin film) 3332, 1693, 1595, 1558, 1510, 1287, 1258, 1209, 1180, 1160, 1109, 1038, 838, 754, 733, 698 cm^{-1}; ^{1}H NMR (600 MHz) δ 3.77 (s, 3H), 5.33 (dd, *J* = 9.4, 3.1, 1H), 5.75 (dd, *J* = 10.8, 3.1, 1H), 5.97 (app d, *J* = 8.8, 1H), 6.18 (d, *J* = 9.4, 1H), 6.34 (app d, *J* = 8.8, 1H), 6.37 (d, *J* = 10.8, 1H), 6.54 (dd, *J* = 8.8, 3.0, 1H), 6.67 (app d, *J* = 9.1, 1H), 6.72 (dd, *J* = 8.8, 3.1, 1H), 7.00 (m, 2H), 7.24 (app t, *J* = 7.3, 2H), 7.33 (app t, *J* = 7.5, 1H), 7.40-7.48 (m, 5H), 8.09 (app d, *J* = 9.1, 2H); ^{13}C NMR (150 MHz) δ 55.5 (CH_3), 58.0 (CH), 60.4 (CH), 90.0 (CH), 112.5 (CH), 113.4 (CH), 113.7 (CH), 116.0 (q, *J* = 288.3, CF_3), 126.3, 127.0, 128.7, 128.9, 129.6, 129.6, 129.8, 130.1 and 132.5 (CH), 133.2 (Cq), 135.0 (Cq),139.6 (Cq), 150.8 (Cq), 158.8 (q, *J* = 35.8, C=OCF_3), 160.4 (Cq); ^{19}F NMR (282 MHz) δ -67.41 (3F, s, CF_3); m/z (EI⁻) 593 (M-H^+, 75%), 547 (M-HNO_2^+, 100%); HRMS: found 593.1653, $C_{30}H_{24}F_3N_4O_6$ requires 593.1648; Anal. Cald. For $C_{30}H_{25}F_3N_4O_6$: C, 60.61, H, 4.24, N, 9.42. Found C, 60.33, H, 4.21, N, 9.39%.

4.5.8. N-((1R,2R*,3S*)-3-(1H-Benzo[d][1,2,3]triazol-1-yl)-2-nitro-1,3-diphenylpropyl)-2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide **(53)**.* Prepared by general procedure B. Nitroalkane **31** (111 mg, 0.410 mmol), ^{n}BuLi (164 µL, 2.5 M, 0.410 mmol), imine **37** (173 mg, 0.820 mmol) and TFA (110 µL, 1.44 mmol) gave after TFA-protection and purification by flash column chromatography (Petrol:Et_2O 9:1) **53** (23 mg, 10%, 47% based on recovered starting material) as a colourless oil; R_f 0.13 (Petrol:Et_2O 9:1); IR υ_{max} (thin film) 2958, 2926, 2856, 1694, 1557, 1510, 1455, 1300, 1254, 1207, 1180, 1163, 1036, 841, 775, 744, 734, 701 cm^{-1}; ^{1}H NMR (600 MHz) δ 3.74 (s, 3H), 5.87 (d, *J* = 6.3, 1H), 6.02 (dd, *J* = 8.8, 2.4, 1H), 6.08 (d, *J* = 10.7, 1H), 6.39 (dd, *J* = 8.8, 2.9, 1H), 6.75 (d, *J* = 7.7, 2H), 6.80 (dd, *J* = 8.8, 2.9, 1H), 7.16 (m, 3H), 7.32 (m, 1H), 7.39 (m, 7H), 7.52 (s, 2H), 8.01 (d, *J* = 8.3, 1H); ^{13}C NMR (150 MHz) δ 55.3 (CH_3), 63.0 (CH), 63.9 (CH), 86.0 (CH), 109.1 (CH), 113.2 (CH), 113.8 (CH), 115.9 (q, *J* = 288.6, CF_3), 120.2 (CH), 124.4 (CH), 126.9 (CH), 127.2 (Cq), 127.9 (CH), 128.4 (CH), 129.0 (CH), 129.2 (CH), 129.6 (CH), 129.8 (Cq), 129.9 (CH), 130.2 (CH), 131.4 (CH), 131.7 (CH), 132.2 (Cq), 132.6 (CH), 132.5 (Cq), 145.8 (Cq), 158.2 (q, *J* = 35.9, O=CCF_3), 159.9 (Cq); ^{19}F NMR (282 MHz) δ -67.86 (3F, s, CF_3); m/z (EI^+) 575 (M^+, 18%), 410 (M^+-$C_6H_4N_3$-HNO_2, 25%), 357 (M^+-PMP-N-TFA, 100%), 282 (39%), 180 (65%); HRMS: found 575.17786, $C_{30}H_{24}F_3N_5O_4$ requires 575.17749.

4.5.9. 2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1R,2R*,3S*)-2-nitro-3-(2-oxooxazolidin-3-yl)-1,3-diphenylpropyl)acetamide **(54)**.* Prepared by general procedure B. Nitroalkane **32** (134 mg, 0.570 mmol), ^{n}BuLi (248 µL, 2.5 M, 0.620 mmol), imine **37** (240 mg, 1.14 mmol) and TFA (153 µL, 2.00 mmol) gave after TFA-protection and purification by flash column chromatography (Petrol:EtOAc 4:1) **54** (101 mg, 33%) as a white solid; mp. 202-203 °C; R_f 0.21 (Petrol:EtOAc 4:1); IR υ_{max} (thin film) 2926, 1748, 1695, 1557, 1511, 1412, 1252, 1207, 1181, 1034, 734, 703 cm^{-1}; ^{1}H NMR (600 MHz, 60 °C) δ 3.22 (dt, *J* = 8.2, 7.3, 1H), 3.78 (s, 3H), 3.82 (ddd, *J* = 12.2, 8.3, 3.9, 1H), 4.25 (ddd, *J* = 12.8, 9.1, 4.0, 1H), 4.32 (dt, *J* = 9.5, 8.6, 1H), 5.56 (d, *J* = 10.3, 1H), 5.77 (d, *J* = 7.8, 1H), 6.55 (dd, *J* = 9.9, 7.9, 1H), 6.66 (dd, *J* = 8.9, 2.8, 1H), 6.71 (m, 1H), 6.80 (dd, *J* = 8.9, 2.9, 1H), 7.04 (app. d, *J* = 7.6, 2H), 7.09 (app. d, *J* = 8.1, 1H), 7.21 (app. t, *J* = 7.7, 2H), 7.31 (m, 1H), 7.37 (m, 5H); ^{13}C NMR (150 MHz) δ 42.5 (CH_2), 55.4 (CH_3), 59.1 (CH), 62.4 (CH_2), 67.2 (CH), 85.8 (CH), 113.4 (CH), 114.4 (CH), 116.0 (q, *J* = 288.9, CF_3), 128.3 (CH), 128.5 (CH), 128.5 (Cq), 129.1 (CH), 129.5 (CH), 129.8 (CH), 130.3 (CH), 131.5 (CH), 131.7 (Cq), 131.9 (CH), 132.5 (Cq), 158.2 (Cq), 158.6 (q, *J* = 35.9, O=CCF_3), 160.1 (Cq); ^{19}F NMR (282 MHz) δ -67.63 (3F, s, CF_3); m/z (ESI^+) 544 (M+H^+, 55%), 497 (M^+-NO_2, 100%), 325 (M^+-PMPNTFA, 40%), 308 (PhCHN(TFA)PMP, 40%); HRMS: found 544.1682, $C_{27}H_{25}F_3N_3O_6$ requires 544.1695; Anal. Cald. For $C_{27}H_{24}F_3N_3O_6$: C, 59.67, H, 4.45, N, 7.73. Found C, 59.43, H, 4.51, N, 7.44%.

4.5.10. N-((1R,2R*)-3-(Butylthio)-2-nitro-1,3-diphenylpropyl)-2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide **(55)**.* Prepared by general procedure B. Nitroalkane **33** (92 mg, 0.39 mmol), ^{n}BuLi (156 µL, 2.5 M, 0.390 mmol), imine **37** (163 mg, 0.780 mmol) and TFA (105 µL, 1.37 mmol) gave after TFA-protection and purification by flash column chromatography (Petrol:Et_2O 9:1) **55** (118 mg, 56%) as a yellow oil, R_f 0.44 (Petrol:Et_2O 9:1); diastereoisomer ratio (60:40) calculated by CHS signal, δ major = 4.49, δ minor = 4.44; IR υ_{max} (thin film) 2960, 1697, 1557, 1510, 1255, 1208, 1181, 1165, 1035, 840, 734, 700 cm^{-1}; ^{1}H NMR (600 MHz) δ 0.86 (t, *J* = 7.4, 3H), 1.31-1.57 (m, 4H), 2.32 (t, *J* = 7.4, 2H), 3.82 (s, 3H), 4.49 (d, *J* = 6.2, 1H), 5.64 (dd, *J* = 10.4, 6.2, 1H), 6.04 (dd, *J* = 8.8, 2.7, 1H), 6.40 (d, *J* = 10.3, 1H), 6.56 (dd, *J* = 8.8, 2.9, 1H), 6.93-7.44 (m, 10H); ^{13}C NMR (150 MHz) δ 13.5

(CH_3), 21.8, 30.5, 31.7 (CH_2), 49.5 (CH), 55.4 (CH_3), 62.0 (CH), 89.8 (CH), 113.7, 113.8 (CH), 116.4 (q, J = 288.4, CF_3), 126.7 (Cq), 128.1, 128.5, 128.7, 128.8, 128.9, 128.9, 129.3, 129.6, 131.2, 132.9 (CH), 133.0, 136.0, 137.4 (Cq), 158.3 (q, J = 35.6, O=CCF_3), 160.2 (Cq); ^{19}F NMR (282 MHz) δ -67.71 (3F, s, CF_3); m/z (EI^+) 547 ($M+H^+$, 4%), 500 (M^+-NO_2, 52%), 457 (M^+-BuS, 100%), 193 (38%); HRMS: found 547.18784, $C_{28}H_{30}F_3N_2O_4S$ requires 547.18833; Anal. Cald. For $C_{28}H_{29}F_3N_2O_4S$: C, 61.53, H, 5.35, N, 5.13. Found C, 61.14, H, 5.48, N, 5.33%.

Minor diastereomer: ^{1}H NMR (600 MHz) δ 0.84 (t, J = 7.4, 3H), 1.31-1.57 (m, 4H), 2.45 (td, J = 7.1, 2.5, 2H), 3.82 (s, 3H), 4.44 (d, J = 4.6, 1H), 5.59 (br. d, J = 9.6, 1H), 6.24 (dd, J = 10.4, 4.6, 1H), 6.63 (d, J = 8.6, 1H), 6.74 (dd, J = 8.8, 2.9, 1H), 6.83 (dd, J = 8.8, 3.0, 1H), 6.93-7.44 (m, 9H); ^{13}C NMR (150 MHz) δ 13.5 (CH_3), 22.0, 31.0, 32.4 (CH_2), 49.9 (CH), 55.4 (CH_3), 67.9 (CH), 92.4 (CH), 113.3, 114.6 (CH), 116.2 (q, J = 288.4, CF_3), 128.5, 128.7, 129.3, 129.6, 130.6, 130.7 (CH), 133.5 (Cq), 158.3 (q, J = 35.6, O=CCF_3), 160.1 (Cq), 6 CH and 3 Cq peaks missing; ^{19}F NMR (282 MHz) δ -67.73 (3F, s, CF_3).

4.5.11. 2,2,2-Trifluoro-N-(4-methoxyphenyl)-N-((1R,2R*)-2-nitro-1,3-diphenyl-3-(phenylthio)propyl)acetamide* ***(56)***. Prepared by general procedure B. Nitroalkane **34** (125 mg, 0.480 mmol), ^{n}BuLi (192 µL, 2.5 M, 0.480 mmol), imine **37** (203 mg, 0.920 mmol) and TFA (129 µL, 1.68 mmol) gave after TFA-protection and purification by flash column chromatography (Petrol:Et_2O 4:1) **56** (129 mg, 47%) as an orange solid, mp. 51-52 ^{o}C; R_f 0.25 (Petrol:Et_2O 9:1); diastereoisomer ratio (65:35) calculated by CHS signal, δ major = 4.76, δ minor = 4.70; IR υ_{max} (thin film) 3063, 3032, 2964, 2840, 1695, 1557, 1509, 1301, 1254, 1208, 1180, 1166, 1033, 840, 733, 699 cm^{-1}; ^{1}H NMR (600 MHz) δ 3.79 (s, 3H), 4.76 (d, J = 5.1, 1H), 5.69 (d, J = 9.8, 1H), 6.35 (dd, J = 9.8, 5.1, 1H), 6.65-7.40 (m, 19H); ^{13}C NMR (150 MHz) δ 54.0 (CH), 55.4 (CH_3), 67.9 (CH), 92.2 (CH), 113.4 and 114.5 (CH), 116.1 (q, J = 288.6 and 288.3, CF_3), 126.7 (Cq), 127.7, 128.0, 128.5, 128.7, 128.8, 128.8, 128.9, 129.2, 129.4, 129.5, 129.7, 129.8, 130.5, 130.8, 130.9, 131.2, 132.9 and 134.2 (CH), 132.0, 133.1, 133.8, 135.5, 135.6 and 137.0 (Cq), 158.4 (q, J = 35.6 and 35.8, O=CCF_3), 160.1 (Cq); ^{19}F NMR (282 MHz) δ -67.84 (3F, s, CF_3); m/z (EI^+) 566 (M^+, 10%), 457 (M^+-PhS, 38%), 308 (64%), 301 (M^+-NO_2-PMP-NH-TFA, 100%), 199 (44%); HRMS: found 566.14870, $C_{30}H_{25}F_3N_2O_4S$ requires 566.14816.

Minor diastereomer: ^{1}H NMR (600 MHz) δ 3.80 (s, 3H), 4.70 (d, J = 6.1, 1H), 5.79 (dd, J = 10.0, 6.0, 1H), 6.01 (dd, J = 8.8, 2.0, 1H), 6.43 (d, J = 10.0, 1H), 6.53 (dd, J = 8.8, 2.9, 1H), 6.65-7.40 (m, 17H); ^{13}C NMR (150 MHz) δ 52.9 (CH), 55.4 (CH_3), 62.0 (CH), 88.8 (CH), 113.7 and 113.8 (CH), 116.3 (q, J = 288.6 and 288.3, CF_3), 158.4 (q, J = 35.6 and 35.8, O=CCF_3), 160.2 (Cq), the rest of the ^{13}C peaks could not be distinguished between the two diastereomers; ^{19}F NMR (282 MHz) δ -67.58 (3F, s, CF_3).

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