An efficient, asymmetric organocatalyst-mediated conjugate addition of nitroalkanes to unsaturated cyclic and acyclic ketones

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5-Pyrrolidin-2-yltetrazole is a versatile organocatalyst for the asymmetric conjugate addition of nitroalkanes to enones. Using this catalyst, this transformation requires short reaction times, tolerates a broad substrate scope, and possibly proceeds *via* generation of an iminium species.

Introduction

Nitroalkanes are a particularly useful source of stabilised carbanions for asymmetric addition to electron-poor alkenes. The strongly electron-withdrawing nature of the nitro group (pK_a $MeNO_2 = 10$) facilitates generation of the nitronate anion under mild conditions.[1] In addition, nitroalkanes can be easily prepared and the nitro group is a versatile functionality that can be readily modified, enabling access to a range of products.

There are numerous examples of substrate-controlled asymmetric conjugate additions of nitroalkanes to α,β-unsaturated carbonyls, in which the chirality resides in either the donor or the acceptor.[2] Additionally, a variety of catalyst systems have been developed for the asymmetric conjugate addition of nitroalkanes, and in particular nitromethane, to chalcones. These include chiral crown ethers,[3] chiral Lewis acids,[4] phase-transfer catalysts derived from cinchona alkaloids[5] and cinchona alkaloid-derived thiourea catalysts.[6] Recently, the use of an aluminium-salen catalyst with substrates other than chalcones was reported.[7]

Proline (**1**, Fig. 1) has been used as its rubidium salt in the addition of nitroalkanes to both acyclic and cyclic enones with moderate to good enantioselectivities (41–84%).[8] The use of proline with amine additives for additions to cyclic enones was extensively investigated by Hanessian and Pham. The best results were obtained with piperazine bases.[9] Specifically, *trans*-2,5-dimethylpiperazine gave moderate to excellent enantioselectivities (61–93%), the lower enantioselectivities arising from the addition of the less bulky nitromethane and nitroethane nucleophiles. The use of proline for acyclic systems has yet to be reported.

Imidazoline catalyst **2** has been found to give good enantioselectivities (34–86%) for the conjugate addition of nitroalkanes to acyclic α,β-unsaturated enones.[10] However, only a moderate enantioselectivity (49%) was obtained using cyclohexenone as the acceptor. Reaction times were typically between 4.5 and 12.5 days. In addition, the nitroalkanes were employed as the reaction solvent, and thus were used in approximately 20-fold excess. Very recently, the tetrazole analogue **3** was reported, and led to improved enantioselectivities and rates (3–8 days).[11] Nitroalkanes were still employed as the reaction solvent and the catalyst again performed best for acyclic enones relative to cyclic precursors.

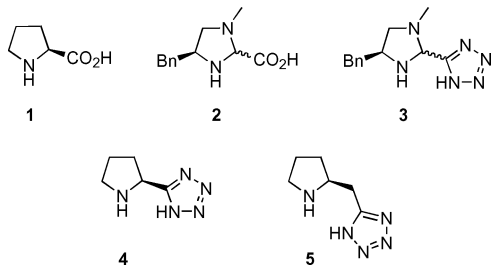

Fig. 1 Proline and related organocatalysts.

Although a range of methods have been developed for the addition of nitroalkanes to enones, none are both broadly applicable and amenable to large-scale organic synthesis. The tetrazole analogue of proline (**4**) had been demonstrated to be a more soluble and effective catalyst than proline itself in a variety of transformations,[12] thus its application in the addition of nitroalkanes to enones was investigated.[13]

Results and discussion

Catalyst screen

Initial investigations into the addition of 2-nitropropane to cyclohexenone (**6**) employed achiral *meso* base *trans*-2,5-dimethylpiperazine (**7**), according to the conditions developed by Hanessian and Pham for the corresponding proline-catalysed transformation.[9] These results were promising, as tetrazole catalyst **4** outperformed proline in chloroform in terms of both product yield and ee (Table 1, entries 1, 2). Reducing the reaction time resulted in a corresponding drop in yield (entry 3). There was only minimal background reaction observed in the absence of base (entry 4), and no background reaction in the absence of catalyst (entry 5).

While homologated tetrazole **5** effectively catalysed the asymmetric Michael addition of ketones to nitro-olefins,[14] in the Michael addition of nitroalkanes to enones it provided the product in only poor yield and enantioselectivity (entry 6). Two of the chiral imidazolidinone catalysts developed by MacMillan and Austin[15] were also screened, but gave none of the expected product under these particular reaction conditions (entries 7, 8).

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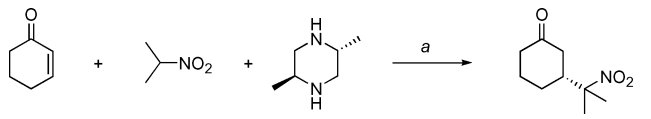
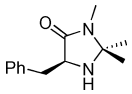
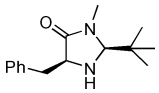
Table 1 Catalyst screen

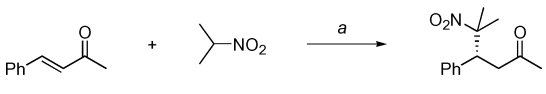


6 7 8

Entry	Catalyst	Base equiv.	Yield (%)[b]	Ee (%)[c]
1	**1**	1	64	89
2	**4**	1	70	98
3	**4**[d]	1	58	99
4	**4**	—	4	53
5	—	1	0	—
6	**5**	1	17	28
7		1	—	—
8		1	—	—

[a] Conditions: **6** (0.5 mmol), 2-nitropropane (1.0 mmol), catalyst (15 mol%), **7** (0.5 mmol), $CHCl_3$ (2 mL), oven-dried glassware, rt, 2 d. [b] Isolated yield. [c] Determined by chiral GC. [d] 1 d.

Table 2 Solvent screen

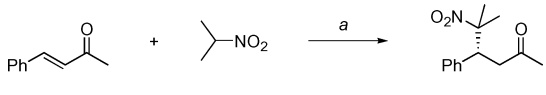


9 10

Entry	Solvent	Yield (%)[b]	Ee (%)[c]
1	$CHCl_3$	27	76
2	$CHCl_3$[d]	49	58
3	CH_2Cl_2	65	72
4	ClH_2CCH_2Cl	33	84
5	THF	10	84
6	Dioxane	5	76
7	THF–CH_2Cl_2 (1 : 1)	28	71
8	MeCN	38	66
9	MeOH	58	7
10	DMSO	39	−4

[a] Conditions: **9** (0.5 mmol), 2-nitropropane (1.0 mmol), **4** (15 mol%), **7** (0.5 mmol), solvent (2 mL), oven-dried glassware, rt, 2.5 d. [b] Isolated yield. [c] Determined by chiral GC. [d] Using proline (**1**, 15 mol%).

Table 3 Further optimisation



9 10

Entry	Conditions[a]	Time/d	Yield (%)[b]	Ee (%)[c]
1	5 mol% **4**	2	55	72
2	1.1 equiv. 2-nitropropane	2	57	71
3	0 °C	4	30	79
4	40 °C	1	68	46
5	0.5 equiv. **7**	2	20	78
6	2 equiv. **7**	1	48	67
7	0.13 M	3	34	75

[a] **9** (0.5 mmol), 2-nitropropane (1.0 mmol), **4** (15 mol%), **7** (0.5 mmol), CH_2Cl_2 (2 mL, 0.25 M), oven-dried glassware, rt, unless otherwise indicated. [b] Isolated yield. [c] Determined by chiral GC.

Solvent screen

With proline tetrazole **4** identified as an effective catalyst for addition to cyclic enones, optimisation of reaction conditions using less reactive acyclic enones ensued. 4-Phenyl-3-buten-2-one (**9**) was chosen as a representative substrate. Using chloroform as the reaction solvent, the product was generated in good ee; however, the isolated yield was low (Table 2, entry 1). Proline gave the product in higher yield but only moderate enantioselectivity (entry 2). An enhanced rate of reaction was observed in dichloromethane, with a 65% isolated yield after 2.5 days (entry 3). Use of 1,2-dichloroethane, THF or dioxane as reaction solvent afforded the product in very good ee, but only poor yield, presumably due to low solubility of the catalyst in these solvents (entries 4–6). Efforts to improve the solubility of **4** in THF by using dichloromethane as a cosolvent led to an improved, but still poor, product yield. Both polar protic and polar aprotic solvents led to almost complete erosion of the enantioselectivity, suggesting that these solvents disrupt interactions necessary for stereocontrol (entries 8–10).

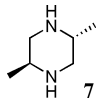
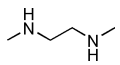
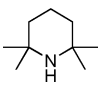
Further optimisation

Reducing the catalyst loading to 5 mol% slowed the reaction but had no detrimental effect on the enantioselectivity (Table 3, entry 1). Similarly, using only 1.1 equiv. of nitroalkane reduced the reaction rate, without decreasing the enantioselectivity (entry 2). Unsurprisingly, lowering the temperature decreased the reaction rate, but improved the product ee (entry 3). In contrast, increasing the temperature led to a large drop in enantioselectivity (entry 4). Varying the loading of **7** revealed that the optimal level of base additive was one equivalent (entries 5, 6). Decreasing the concentration had an effect similar to that of lowering the temperature; the product was generated in lower yield but higher ee (entry 7). Additionally, monitoring the reaction by HPLC over 4 d showed that the reaction did not progress significantly after 3 d.

Effect of amine bases

The relative effectiveness of a variety of amine bases in this transformation was examined. The choice of base was found to have an impact not only on the product yield, but also on the enantioselectivity. Use of the tertiary triethylamine generated the desired product in low yield and ee (Table 4, entry 2). Use of the secondary diethylamine provided the product in higher yield, but lower enantioselectivity relative to **7** (entries 1, 3). Whereas substoichiometric amounts of diethylamine resulted in improved enantioselectivities but diminished yields (entry 4), excess diethylamine resulted in enhanced yields but decreased enantioselectivities (entry 5). Other piperazines were not found to be as effective as 2,5-dimethyl piperazine. Piperazine itself gave the product in a slightly higher ee, but significantly lower yield (entry 6). The latter effect might be due to the low solubility of piperazine under the reaction conditions. However, other more

Table 4 Effect of amine base[a]

Entry	Base	Equiv.	Yield (%)[b]	Ee (%)[c]
1	 **7**	1	65	72
2	Et_3N	2	28	29
3	Et_2NH	1	72	62
4	Et_2NH	0.5	8	80
5	Et_2NH	2	84	60
6		1	30	76
7		1	27	68
8		1	44	67
9		1	63	47
10		2	7	60
11		1	0	—
12		1	86	53
13		2	93	52
14	DBU	1	36	28
15	*i*-Pr_2NH	1	14	67
16		1	30	50
17		2	—	—

[a] Conditions: **9** (0.5 mmol), 2-nitropropane (1.0 mmol), **4** (15 mol%), base, CH_2Cl_2 (2 mL), oven-dried glassware, rt. [b] Isolated yield. [c] Determined by chiral GC.

soluble piperazines also gave the product in low yield (entries 7, 8). Using an acyclic diamine, the product was obtained in comparable yield, but appreciably lower ee (entry 9), suggesting that the ring structure of the piperazines was crucial. Generally, the use of weaker bases resulted in lower yields (entries 10 and 11), whereas stronger bases, such as piperidine, resulted in higher yields (entries 12, 13). An exception was the use of DBU, which afforded the product in poor yield (entry 14). Hindered amines performed poorly in this reaction (entries 15, 16). Finally, the use of pyrrolidine resulted only in significant formation of unidentified side products (entry 17). Thus, the original base choice (**7**) was found to be optimal.

Effect of water

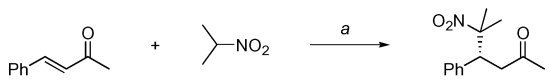
The reaction of certain substrates demonstrated an unexpected sensitivity to water. For example, reactions of **9** that were not run under anhydrous conditions provided the product **10**, in lower yield and higher enantioselectivities than those run under anhydrous conditions (Table 5, entries 1 and 2; 3 and 4). These variations were due to the presence or absence of water, rather than the presence or absence of argon, as there was not a substantial difference between reactions run in oven-dried glassware under standard atmosphere or under inert atmosphere (entries 2 and 5). As further verification, the addition of small amounts of water to the reaction again generated the product in lower yield and higher enantioselectivity (entries 6, 7). The addition of large amounts of water, however, did not result in further enhancement of the product ee, but instead substantially eroded the yield (entry 8). Finally, the reaction did proceed in the presence of molecular sieves, albeit in very poor ee. Although the mechanism for these reactions has not been rigorously established, it is plausible that they proceed *via* the formation of an iminium species, which would necessitate the involvement of water in the catalytic cycle.

Reaction scope: donor

The addition of a variety of nitroalkanes to both cyclic and acyclic enones was examined. Generally, reactions with cyclohexenone provided products in good yield and excellent enantioselectively (Table 6) and did not exhibit the sensitivity to water that those with *trans*-4-phenyl-3-buten-2-one did. Reactions proceeded more quickly in dichloromethane relative to chloroform, but with slightly lower enantioselectivity (Conditions A *vs.* B). The lower yield obtained with nitromethane may be due to further reactions of the product, which contains a reactive primary nitroalkane (entry 4).[16] To circumvent this, the addition of a higher excess of nitromethane was investigated, but led to similar ratios of product to side products as indicated by ^{1}H NMR. Using nitroethane, the high stereoselectivity at the β-position was maintained; however, almost no stereocontrol was observed at the exocyclic stereocentre of the nitroalkyl side chain (entries 6, 7). The high enantioselectivities observed for nitromethane and nitroethane using the tetrazole catalyst are an improvement over the results reported using proline, where poorer selectivity was observed for the addition of these less sterically hindered nucleophiles.[9] Using 1-nitropentane, a mixture of diastereomers again resulted, although pleasingly the products were obtained in good yield and excellent enantioselectivity (entry 8). It should be noted that the poor selectivities generally observed at the acidic γ-position have been proposed to arise from epimerisation under the basic conditions typically required for these reactions.[1] Finally, although the addition of the more hindered nitrocyclohexane nucleophile proceeded more slowly, the products were obtained in good yield and excellent ee (entries 9, 10).

As mentioned above, 4-phenyl-3-buten-2-one (**9**) was less reactive compared to cyclohexenone, and reactions with this substrate did not proceed to completion. Moderate to good yields and good enantioselectivities were obtained in all cases (Table 7). As discussed previously, higher yields but lower enantioselectivities were observed with oven-dried glassware (Conditions A *vs.* B). The addition of 2-nitropropane was also run over 4 d on a 15 mmol scale using 5 mol% catalyst **4**, and product yields and ee values were comparable to those in entry 1. As with cyclohexenone, very good enantioselectivities but poor yields were obtained with nitromethane (entry 3). In this case, however, the addition of 10 equiv. of nitromethane afforded the product in good yield

Table 5 Effect of water

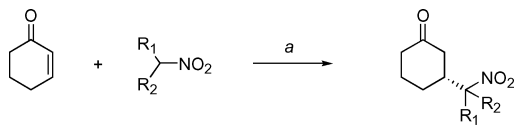


9 10

Entry	Conditions[a]	Yield (%)[b]	Ee (%)[c]
1	Non-oven-dried glassware	50	74
2	Oven-dried glassware, cooled under argon	65	72
3	Non-oven-dried glassware, dried **7**	54	74
4	Oven-dried glassware, dried **7**	63	72
5	Oven-dried glassware, reaction run under Ar	67	71
6	0.25 equiv. H_2O	46	74
7	0.5 equiv. H_2O	38	76
8	2 equiv. H_2O	25	72
9	4 Å MS	59	12

[a] **9** (0.5 mmol), 2-nitropropane (1.0 mmol), **4** (15 mol%), **7** (0.5 mmol), CH_2Cl_2 (2 mL), 3 d, rt. [b] Isolated yield. [c] Determined by chiral GC.

Table 6 Varying the nitroalkane with cyclohexenone

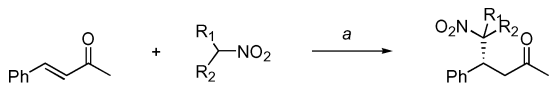


6

Entry	R_1, R_2	Conditions[a]	Yield (%)[b]	Ee (%)[c]
1	$R_1 = R_2 =$ Me	A	84	96
2	$R_1 = R_2 =$ Me	A[d]	84	96
3	$R_1 = R_2 =$ Me	B	70	98
4	$R_1 = R_2 =$ H	A	47	94
5	$R_1 = R_2 =$ H	B	49	95
6	$R_1 =$ H, $R_2 =$ Me	A	84	95/94, dr 1.1 : 1
7	$R_1 =$ H, $R_2 =$ Me	B	74	95, dr 1.2 : 1
8	$R_1 =$ H, $R_2 = (CH_2)_3CH_3$	A	73	94, dr 1.3 : 1
9	$R_1 = R_2 = -(CH_2)_5-$	A	63	94
10	$R_1 = R_2 = -(CH_2)_5-$	B	53	97

[a] Conditions A: **6** (0.5 mmol), nitroalkane (1.0 mmol), **4** (15 mol%), **7** (0.5 mmol), CH_2Cl_2 (2 mL), oven-dried glassware, rt, 1 d. Conditions B: as A, except $CHCl_3$ (2 mL), 2 d. [b] Isolated yield. [c] Determined by chiral GC, ee major/minor diastereomer. [d] Non-oven-dried glassware.

Table 7 Varying the nitroalkane with *trans*-4-phenyl-3-buten-2-one



9

Entry	R_1, R_2	Conditions[a]	Yield (%)[b]	Ee (%)[c]
1	$R_1 = R_2 =$ Me	A	65	72
2	$R_1 = R_2 =$ Me	B	50	74
3	$R_1 = R_2 =$ H	A	45	89
4	$R_1 = R_2 =$ H	A[d]	76	77
5	$R_1 =$ H, $R_2 =$ Me	A	67	80, dr 1.3 : 1
6	$R_1 =$ H, $R_2 =$ Me	B	40	82/80, dr 1.3 : 1
7	$R_1 =$ H, $R_2 = (CH_2)_3CH_3$	A	80	84, dr 1.9 : 1
8	$R_1 = R_2 = -(CH_2)_5-$	A	80	73
9	$R_1 = R_2 = -(CH_2)_5-$	B	59	77

[a] Conditions A: **9** (0.5 mmol), nitroalkane (1.0 mmol), **4** (15 mol%), **7** (0.5 mmol), CH_2Cl_2 (2 mL), oven-dried glassware, rt, 3 d. Conditions B: as A, except non-oven-dried glassware. [b] Isolated yield. [c] Determined by chiral GC, ee major/minor diastereomer. [d] Nitroalkane (5.0 mmol) used.

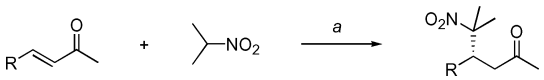
(entry 4). Using nitroethane, good stereoselectivity was obtained at the β-position, but the product was, again, a mixture of diastereomers at the γ-position (entries 5, 6). The relative stereochemistry of the minor diastereoisomer was determined by X-ray crystallography. 1-Nitropentane underwent addition in good yield and enantioselectively, and gave a higher 1.9 : 1 diastereomeric ratio (entry 7). The relative configuration of the minor diastereomer was assigned by analogy to the product of nitroethane addition. The addition of the hindered nitrocyclohexane nucleophile also proceeded in good ee (entries 8, 9).

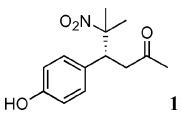
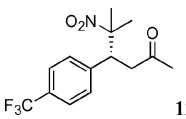
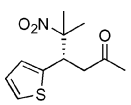
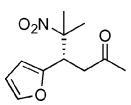
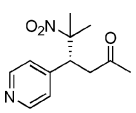
Reaction scope: acceptor

The addition of 2-nitropropane to a variety of linear, aromatic enones was investigated (Table 8). None of the aromatic enones examined demonstrated the sensitivity to water that *trans*-4-phenyl-3-buten-2-one did. The reaction tolerated incorporation of both electron-donating and electron-withdrawing substituents on the phenyl ring of this substrate (entries 1–4). The use of heterocyclic enones provided products in moderate yields and good enantioselectivities (entries 5–10). Pyridine **15** was inseparable from the starting enone, but was generated in excellent conversion and moderate ee (entries 9, 10).

The tetrazole catalyst was also effective for the addition of various nitroalkanes to all other substrates examined, which included α,β-unsaturated ethyl ketones, cyclic enones, non-aromatic enones, and enal substrates (Table 9). Ethyl ketone **16** was formed considerably more slowly than the corresponding methyl ketone and thus required longer reaction times (entries 1, 2). The addition of 2-nitropropane to cyclopentenone gave the product in moderate yield and good enantioselectivity (entries 3, 4). While the addition of bulky 2-nitropropane to sterically congested enone substrates, such as 3-methylcyclohexenone, does not readily occur, excellent ee values were obtained for the addition of nitromethane to this substrate (entries 5, 6). The reaction of (*E*)-methyl-4-oxopent-2-enoate afforded the product **19** in excellent regioselectivity, and good yield and enantioselectivity (entries 7, 8). The aliphatic enone, nonenone, was found to be less reactive, and also gave poorer enantioselectivity (entry 9). The use of 2 equiv. of base, however, gave improved results (entry 10). Reactions of aldehydes proceeded in, at best, modest enantioselectivities and yields: **21** was obtained in 46% ee and cinnamaldehyde gave racemic product **22** (entries 11–13). Further studies on cinnamaldehyde showed significant levels of background reaction with the base additive but no catalyst (data not shown).

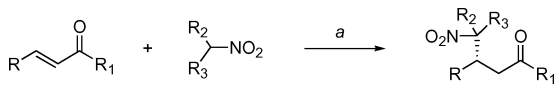
Table 8 Addition of 2-nitropropane to linear, aromatic enones

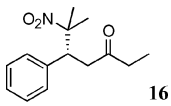
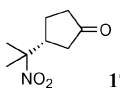
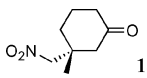
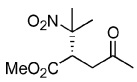
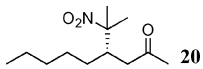
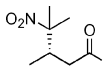
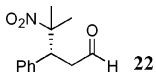


Entry	Product	Conditions[a]	Yield (%)[b]	Ee (%)[c]
1	 **11**	A	72	61
2		B	70	62
3	 **12**	A	73	66
4		B	66	68
5	 **13**	A	61	72
6		B	63	72
7	 **14**	A	53	66
8		B	51	66
9	 **15**	A	96[d]	64
10		B	97[d]	65

[a] Conditions A: enone (0.5 mmol), 2-nitropropane (1.0 mmol), **4** (15 mol%), **7** (0.5 mmol), CH_2Cl_2 (2 mL), oven-dried glassware, rt, 3 d. Conditions B: as A, except non-oven-dried glassware. [b] Isolated yield. [c] Determined by chiral GC/HPLC. [d] Conversion as measured by ^{1}H NMR.

Table 9 Addition of nitroalkanes to various enones



Entry	Product	Conditions[a]	Yield (%)[b]	Ee (%)[c]
1	 **16**	A	21	83
2		A[d]	78	78
3	 **17**	A[e]	62	80
4		B	63	75
5	 **18**	A	64	91
6		C	59	91
7	 **19**	A	88	82
8		C	96	82
9	 **20**	A	23	54
10		A[f]	44	58
11	 **21**	A[e]	40	42
12		C[e]	39	46
13	 **22**	A[e]	67	0

[a] Conditions A: enone (0.5 mmol), nitroalkane (1.0 mmol), **4** (15 mol%), **7** (0.5 mmol), CH_2Cl_2 (2 mL), oven-dried glassware, rt, 3 d. Conditions B: as A, except $CHCl_3$ (2 mL). Conditions C: as A, except non-oven-dried glassware. [b] Isolated yield. [c] Determined by chiral GC. [d] Reaction time 12 d. [e] Reaction time 21 h. [f] **7** (1.0 mmol) used.

Effect of chiral bases

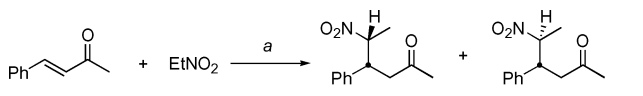
Although the reaction of **9** with nitroethane in the presence of *trans*-2,5-dimethylpiperazine was a highly enantioselective process, the diastereoselectivity was poor. As the base employed was found to influence product enantioselectivity, it was thought that the use of chiral bases might improve the diastereoselectivity of this transformation. A range of chiral non-racemic bases were investigated in this reaction (Table 10). The use of either enantiomer of **27** gave a slightly improved diastereomeric ratio compared to *trans*-2,5-dimethylpiperazine. In both cases, however, the major diastereomer generated was the same (entries 4, 5). Similarly, both enantiomers of **28** favoured formation of the same diastereomer in an improved 1.6 : 1 ratio (entries 6, 7). Interestingly, the major diastereomer was formed with a higher enantioselectivity than the minor diastereomer. As opposite enantiomers of base pairs gave the same diastereoselectivity, the use of asymmetric bases was not investigated further.

Kinetic investigations

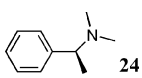
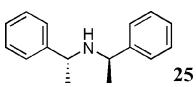
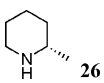
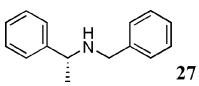
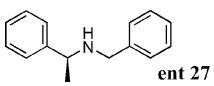
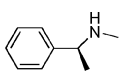
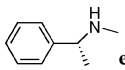
The reaction of nitroethane with enone **9** was monitored every 20 min using ReactIR. Examining the region between 1600 and 1750 cm^{-1} more closely, it was possible to observe the disappearance of the enone (peak under 1700 cm^{-1}) and formation of the product (peak over 1700 cm^{-1}); however, there was no evidence confirming the formation of intermediates (data not shown). The reactions of both enone **9** and cyclohexenone with one equivalent of catalyst were also investigated in methanol. Again, however, no changes in absorption were observed which could be assigned to the formation of a carbon–nitrogen bond.

The reaction was followed by HPLC over 4 d with React Array™ SK233 equipment using stilbene as an internal standard. The data showed that 14% of the starting material was consumed within the first 15 min of the reaction, although only 0.3% of the product had been formed (data not shown). This is consistent with rapid reaction of the catalyst (15 mol% used) with the enone, presumably to form an iminium species, followed by slower reaction with the nitroalkane.

Table 10 Effect of chiral amines



9 **23** **23'**

Entry	Base	Conv. (%)[b]	Dr[b]	Ee (%)[c]
1	 **24**	16	1.1 : 1	66/46
2	 **25**	6	1.3 : 1	58/44
3	 **26**	96	1.3 : 1	76/74
4	 **27**	21	1.5 : 1	62
5	 **ent 27**	11	1.4 : 1	46
6	 **28**	41	1.6 : 1	88/76
7	 **ent 28**	38	1.6 : 1	88/78

[a] Conditions: **9** (0.5 mmol), nitroethane (1.0 mmol), **4** (15 mol%), base (0.5 mmol), CH_2Cl_2 (1 mL), oven-dried glassware, rt. [b] Conversion, measured by ^1H NMR. [c] Determined by chiral GC, ee major/minor diastereomer.

Conclusions

As an improvement over other catalyst systems, tetrazole catalyst **4** is a versatile catalyst for the asymmetric addition of a variety of nitroalkanes to both cyclic and acyclic enones using *trans*-2,5-dimethylpiperazine as a stoichiometric base additive. Using **4**, this reaction is scalable, providing enantiomeric excesses of up to 98% in relatively short reaction times of 1–3 d, and using only 2 equiv. of the coupling nitroalkane. The use of chiral amine base additives to improve the diastereoselectivites arising from the conjugate addition of prochiral nitroalkanes was examined, but was unproductive. Finally, kinetic investigations combined with the observed sensitivity of certain substrates to water support a possible mechanism in which this transformation proceeds *via* reaction of the catalyst with the enone to form an iminium species and liberate water.

Experimental

All reactions were carried out in oven-dried test tubes cooled under an atmosphere of argon or non-oven-dried test tubes unless otherwise stated. Dichloromethane, methanol and acetonitrile were distilled from calcium hydride. Tetrahydrofuran was predried over sodium wire and distilled from calcium hydride. Other reagents and solvents were used as received. Flash column chromatography was performed using Merck 60 Kieselgel (230–400 mesh) under pressure. Analytical thin layer chromatography (TLC) was performed on glass plates pre-coated with Merck Kieselgel 60 F254, and visualised by ultra-violet irradiation (254 nm) or by staining with aqueous acidic ammonium hexamolybdate, aqueous acidic potassium permanganate, acidic 2,4-dinitrophenol, cerium ammonium nitrate solutions or iodine, and developed with appropriate heating. Melting points were recorded on a Reichert hot-stage apparatus, and are uncorrected. Optical rotations were acquired on a Perkin-Elmer 343 digital polarimeter using a sodium lamp (589 nm) as the light source. Infra-red spectra were obtained on a Spectrum One FT-IR ATR (Attenuated Total Reflectance) spectrometer, from a thin film deposited on the ATR. Mass spectra were obtained on a Kratos MS890MS, a Kratos Q-TOF or an LCT Premier spectrometer by Waters using Micromass MS software, by electron impact,

fast atom bombardment or electrospray ionisation techniques at the Department of Chemistry, Lensfield Road, Cambridge. ^{1}H NMR spectra were recorded at ambient temperature on Bruker DPX-400 or Bruker DRX-600 spectrometers at 400 or 600 MHz with residual protic solvent $CHCl_3$ as the internal reference ($\delta_H = 7.26$ ppm); chemical shifts (δ) are given in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz). The proton spectra are reported as follows δ/ppm (number of protons, multiplicity, coupling constant J/Hz, assignment). ^{13}C NMR spectra were recorded at ambient temperature on the same spectrometers at 100 or 150 MHz, with the central peak of $CHCl_3$ as the internal reference ($\delta_C = 77.0$ ppm). DEPT135 and two-dimensional (COSY, HMQC, HMBC) NMR spectroscopy were used, where appropriate, to aid the assignments of signals in the ^{1}H and ^{13}C NMR spectra. Where a compound has been characterised as an inseparable mixture of diastereoisomers, the NMR data for the major (maj) and minor (min) isomers have been reported as far as was discernable from the spectrum of the mixture. Where coincident coupling constants have been observed in the ^{1}H NMR spectrum, the apparent multiplicity of the proton resonance concerned has been reported.

General procedure for the addition of nitroalkanes to enones

The enone (0.5 mmol), tetrazole **4** (15 mol%), base **7** (0.5 mmol) and nitroalkane (1 mmol) were stirred in dichloromethane (2 mL) under air at room temperature for the specified time period (unless otherwise indicated). The crude reaction mixture was diluted with dichloromethane (30 mL), and washed with aqueous ammonium chloride (30 mL). The aqueous layer was extracted with dichloromethane (30 mL) and the combined organic fractions were dried ($MgSO_4$) and the solvent removed under reduced pressure. When isolated yields are reported, the products were further purified either by filtration through a pad of silica (eluting with dichloromethane) or by flash column chromatography.

(*R*)-3-(2-Nitropropan-2-yl)cyclohexanone[9] 8. Filtration through a silica pad using dichloromethane as eluent to give the title compound as white prisms (80 mg, 84%). Mp = 61–63 °C; ν_{max} (film)/cm^{-1}: 3003, 2967, 2916, 2878, 1710, 1530, 1348; $[\alpha]_D^{25} = +23.3$ ($c = 0.525$, $CHCl_3$, 96% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42–2.29 [3H, m, C*H*C(NO$_2$), C(=O)C*H*H′CH, C(=O)C*H*HCH$_2$], 2.26–2.17 [1H, m, C(=O)CH*H*CH$_2$], 2.13–2.06 [2H, m, C(=O)CH*H*′CH, C(=O)CH$_2$C*H*H′], 1.80–1.75 (1H, m, CHC*H*H′), 1.62–1.57 [1H, m, C(=O)CH$_2$CH*H*′], 1.55 [3H, s, C(C*H*$_3$)(CH′$_3$)], 1.53 [3H, s, C(CH$_3$)(C*H*′$_3$)], 1.44–1.37 (1H, m, CHCH*H*′). Chiral GC: Chirasil Dex-CB, 140 °C, 25 psi, 17.8 min (4.0 pA s, *S*), 18.1 min (187.6 pA s, *R*) gave 96% ee.

(*R*)-5-methyl-5-nitro-4-phenylhexan-2-one[10] 10. Purification using flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 4) to give the title compound as white prisms (74 mg, 61%). Mp = 51–52 °C; ν_{max} (film)/cm^{-1}: 1703, 1530, 1353; $[\alpha]_D^{25} = -34.1$ ($c = 1$, EtOH, 99% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.26 (3H, m, Ar*H*), 7.20–7.18 (2H, m, Ar*H*), 3.92 (1H, dd, J = 3.5, 10.6 Hz, PhC*H*), 3.08 [1H, dd, J = 10.6, 16.9 Hz, C(=O)C*H*H′], 2.72 [1H, dd, J = 3.5, 16.9 Hz, C(=O)CH*H*′], 2.02 [3H, s, C(=O)C*H*$_3$], 1.55 [3H, s, C(C*H*$_3$)(CH′$_3$)], 1.45 [3H, s, C(CH$_3$)(C*H*′$_3$)]. Chiral GC: Chirasil Dex-CB, 140 °C, 25 psi, 27.3 min (area 504.4 pA s, *R*), 28.1 min (51.3 pA s, *S*) gave 82% ee.

(*R*)-3-(Nitromethyl)cyclohexanone[9]. Purification using flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 2) to give the title compound as a clear oil (40 mg, 49%). ν_{max} (film)/cm^{-1}: 1709, 1543, 1384; $[\alpha]_D^{25} = +8.8$ ($c = 0.635$, $CHCl_3$, 96% ee). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.36 (1H, dd, J = 7.3, 12.1 Hz, C*H*H′NO$_2$), 4.33 (1H, dd, J = 6.6, 12.1 Hz, CH*H*′NO$_2$), 2.67–2.60 (1H, m, C*H*CH$_2$NO$_2$), 2.48 [1H, ddd, J = 2.1, 4.2, 14.2 Hz, C(=O)C*H*H′CH], 2.42 [1H, dd, J = 11.4, 14.8 Hz, C(=O)C*H*H′CH$_2$], 2.31–2.26 [1H, m, C(=O)CH*H*′CH$_2$], 2.18–2.14 [1H, m, C(=O)CH*H*′CH], 2.13–2.09 [1H, m, C(=O)CH$_2$C*H*H′], 1.99–1.97 (1H, m, CHRC*H*H′), 1.77–1.69 [1H, m, C(=O)CH$_2$CH*H*′], 1.54–1.47 (1H, m, CHRCH*H*′). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 208.1, 80.0, 44.4, 40.8, 37.2, 28.2, 24.2. Chiral GC: Chiradex G-TA, 150 °C, 25 psi, 12.9 min (321.5 pA s, *R*), 14.3 min (8.5 pA s, *S*) gave 95% ee.

(1′*R*,3*R*)-3-(1′-Nitroethyl)cyclohexanone[9] and (1′*S*,3*R*)-3-(1′-nitroethyl)cyclohexanone[9]. Filtration through a silica pad using dichloromethane as eluent to give the title compounds as a clear oil (74 mg, 84%), as an inseparable 1.1 : 1 mixture of diastereomers. ν_{max} (film)/cm^{-1}: 1710, 1542, 1358; $[\alpha]_D^{25} = +5.4$ ($c = 0.765$, $CHCl_3$, dr 1.1 : 1, 95/94% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.50–4.42 [1H$_{maj}$ and 1H$_{min}$, m, C*H*C(NO$_2$)], 2.44–2.04 [6H$_{maj}$ and 6H$_{min}$, m, 2 × C(=O)C*H*$_2$CHR, 2 × C(=O)C*H*$_2$CH$_2$, 2 × C*H*C(NO$_2$), 2 × C(=O)CH$_2$C*H*H′], 1.94–1.81 (1H$_{maj}$ and 1H$_{min}$, m, 2 × CHC*H*H′), 1.69–1.57 (1H$_{maj}$ and 1H$_{min}$, m, 2 × COCH$_2$CH*H*′), 1.52 [3H$_{maj}$, d, J = 6.7 Hz, C(NO$_2$)C*H*$_3$], 1.49 [3H$_{min}$, d, J = 6.7 Hz, C(NO$_2$)C*H*$_3$], 1.47–1.38 (1H$_{maj}$ and 1H$_{min}$, m, 2 × CHCH*H*′). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.5 (maj), 208.3 (min), 86.9, 43.6 (min), 43.3 (maj), 42.4 (min), 42.3 (maj), 40.8, 27.5 (maj), 26.9 (min), 24.5 (min), 24.2 (maj), 16.3 (min), 16.1 (maj). Chiral GC: Chiradex G-TA, 160 °C, 25 psi, 7.6 min (189.5 pA s, *R*), 9.0 min (5.3 s pA s, *S*) gave 95% ee for the major diastereomer, 11.4 min (5.9 pA s, *S*), 12.6 min (175.5 pA s, *R*) gave 94% ee for the minor diastereomer.

(1′*R*,3*R*)-3-(1′-Nitropentyl)cyclohexanone[17] and (1′*S*,3*R*)-3-(1′-nitropentyl)cyclohexanone[17]. Purification using flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 4) to give the title compounds as a clear oil (81 mg, 73%), as an inseparable 1.3 : 1 mixture of diastereomers. ν_{max} (film)/cm^{-1}: 2959, 2932, 2873, 1713, 1544, 1362; $[\alpha]_D^{25} = +1.1$ ($c = 0.515$, $CHCl_3$, dr 1.3 : 1, 94% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.41–4.31 (1H$_{maj}$ and 1H$_{min}$, m, 2 × C*H*NO$_2$), 2.49–2.32 [2H$_{maj}$ and 2H$_{min}$, m, 2 × C(=O)C*H*H′CHR, 2 × C(=O)C*H*H′CH$_2$], 2.30–2.03 [4H$_{maj}$ and 4H$_{min}$, m, 2 × C(=O)CH*H*′CHR, 2 × C(=O)CH$_2$C*H*R, 2 × COCH$_2$C*H*H′, 2 × C(=O)CH*H*′CH$_2$], 2.01–1.75 [2H$_{maj}$ and 2H$_{min}$, 2 × C(=O)(CH$_2$)$_2$C*H*H′, 2 × C*H*H′CHNO$_2$], 1.72–1.57 (2H$_{maj}$ and 2H$_{min}$, m, 2 × COCH$_2$CH*H*′, 2 × CH*H*′CHNO$_2$), 1.51–1.20 [5H$_{maj}$ and 5H$_{min}$, m, 2 × C(=O)(CH$_2$)$_2$CH*H*′, 2 × C*H*$_2$CH$_2$CH$_3$, 2 × C*H*$_2$CH$_3$], 0.87 and 0.86 (3H$_{maj}$ and 3H$_{min}$, t, J = 7.0 Hz, 2 × C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.5, 92.6, 43.8 (maj), 43.3 (min), 41.7 (maj), 41.4 (min), 40.8, 30.3, 27.9 (min), 27.7 (maj), 27.6 (min), 27.3 (maj), 24.3 (min), 24.1 (maj), 22.0 (min), 21.9 (maj), 13.6. *m/z* (ESI): found, 214.1441; [MH]$^+$ $C_{11}H_{20}NO_3$ requires, 214.1443. Chiral GC: Chiradex G-TA, 160 °C, 25 psi, 12.9 min (4402.1 pA s, *R*), 14.9 min (125.5 s pA s, *S*) gave 94% ee for the major diastereomer, 15.5 min (165.0 pA s, *S*), 17.8 min (5658.7 pA s, *R*) gave 94% ee for the minor diastereomer, and a diastereomeric ratio of 1 : 1.3.

(*R*)-3-(1-Nitrocyclohexyl)cyclohexanone[9]. Purification using flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 4) to give the title compound as white prisms (60 mg, 53%). Mp = 60–61 °C; ν_{max} (film)/cm^{-1}: 1709, 1524, 1346; $[\alpha]_D^{25}$ = +2.1 (c = 0.515, $CHCl_3$, 97% ee). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.52–2.41 [3H, m, C*H*H′CNO$_2$CH$_2$, CH$_2$CNO$_2$C*H*H′, C(=O)-C*H*H′CHR], 2.40–2.33 [1H, m, C(=O)C*H*H′CH$_2$], 2.24–2.19 [1H, m, C(=O)CH*H*′CH$_2$], 2.17–2.02 [3H, m, C(=O)CH$_2$C*H*H′, C(=O)CH$_2$C*H*R, C(=O)CH*H*′CHR], 1.96–1.89 [1H, m, 2 × C(=O)(CH$_2$)$_2$C*H*H′], 1.71–1.62 [3H, m, C*H*H′CH$_2$CNO$_2$CH$_2$-CH$_2$, CH$_2$CH$_2$CNO$_2$C*H*H′CH$_2$, C*H*H′(CH$_2$)$_2$CNO$_2$], 1.61–1.48 [3H, CH*H*′CNO$_2$CH$_2$, CH$_2$CNO$_2$CH*H*′, C(=O)CH$_2$CH*H*′], 1.39–1.28 [3H, m, CH*H*′CH$_2$CNO$_2$CH$_2$CH$_2$, CH$_2$CH$_2$CNO$_2$-CH*H*′CH$_2$, C(=O)(CH$_2$)$_2$CH*H*′], 1.27–0.81 [1H, m, CH*H*′(CH$_2$)$_2$-CNO$_2$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.5, 93.9, 47.0, 42.5, 40.9, 32.1, 31.4, 25.7, 24.7, 24.5, 22.3, 22.2. Chiral GC: Chiradex G-TA, 170 °C, 25 psi, 21.0 min (19.3 pA s, *S*), 22.1 min (1219.3 pA s, *R*) gave 97% ee.

(*R*)-5-Nitro-4-phenylpentan-2-one[10]. Purification using flash column chromatography (CH_2Cl_2–petroleum ether 40/60, 2 : 1) to give the title compound as white prisms (52 mg, 48%). Mp = 116–117 °C; ν_{max} (film)/cm^{-1}: 1712, 1546, 1383; $[\alpha]_D^{25}$ = −2.8 (c = 0.53, $CHCl_3$, 82% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.24 (3H, m, Ar*H*), 7.22–7.19 (2H, m, Ar*H*), 4.68 [1H, dd, J = 6.9, 12.4 Hz, C*H*H′(NO$_2$)], 4.59 (1H, dd, J = 7.7, 12.4 Hz, CH*H*′NO$_2$), 4.00 (1H, apparent qn, J = 7.1 Hz, PhC*H*), 2.91 [2H, d, J = 7.0 Hz, C(=O)C*H*$_2$], 2.11 [3H, s, C(=O)C*H*$_3$]. Chiral GC: Chiradex G-TA, 150 °C, 25 psi, 23.1 min (area 27.7 pA s, *S*), 23.8 min (278.2 pA s, *R*) gave 82% ee.

(4*R*,5*R*)-5-Nitro-4-phenylhexan-2-one[18] (23) and (4*R*,5*S*)-5-nitro-4-phenylhexan-2-one[18] (23′). Purification using flash column chromatography (EtOAc–petroleum ether 30/40, 1 : 9 → 2 : 3) to give the title compound, **23**, as an oil (41 mg, 36%). ν_{max} (film)/cm^{-1}: 1717, 1543, 1357; $[\alpha]_D^{25}$ = −10.9 (c = 0.54, $CHCl_3$, 80% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.24 (3H, m, Ar*H*), 7.20–7.17 (2H, m, Ar*H*), 4.92 (1H, qd, J = 6.6, 9.9 Hz, C*H*NO$_2$) 3.71 (1H, apparent td, J = 4.3, 9.6 Hz, PhC*H*), 2.96 [1H, dd, J = 9.5, 16.9 Hz, C(=O)C*H*H′], 2.74 [1H, dd, J = 4.3, 17.0 Hz, C(=O)CH*H*′], 2.00 [3H, s, C(=O)C*H*$_3$], 1.32 [3H, d, J = 6.6 Hz, CH(NO$_2$)(C*H*$_3$)]. Chiral GC: Chirasil Dex-CB, 130 °C, 25 psi, 36.5 min (area 29.6 pA s, *R*), 37.4 min (269.5 pA s, *S*) gave 80% ee.

Purification using flash column chromatography (EtOAc–petroleum ether 30/40, 1 : 9 → 2 : 3) to give the title compound, **23′**, as white needles (34 mg, 31%). ν_{max} (film)/cm^{-1}: 1713, 1541, 1357; $[\alpha]_D^{25}$ = −1.4 (c = 0.485, $CHCl_3$, 80% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33–7.24 (3H, m, Ar*H*), 7.15–7.13 (2H, m, Ar*H*), 4.88 (1H, qn, J = 6.6 Hz C*H*NO$_2$), 3.73 (1H, apparent q, J = 6.9 Hz, PhC*H*), 3.04 [1H, dd, J = 6.6, 17.5 Hz, C(=O)C*H*H′], 2.89 [1H, dd, J = 7.6, 17.5 Hz, C(=O)CH*H*′], 2.11 [3H, s, C(=O)C*H*$_3$], 1.48 [3H, d, J = 6.7 Hz, CH(NO$_2$)(C*H*$_3$)]. Chiral GC: Chirasil Dex-CB, 130 °C, 25 psi, 40.9 min (area 228.3 pA s, *R*), 42.6 min (25.0 pA s, *S*) gave 80% ee.

Crystal data: compound 23′. $C_{12}H_{15}NO_3$, M = 221.25, orthorhombic, space group $P2_12_12_1$, a = 5.6440(10), b = 8.4770(2), c = 25.1210(5) Å, V = 1201.89(4) Å^3, Z = 4, D_{calc} = 1.223 Mg m^{-3}, $F(000)$ = 472, μ(Mo-Kα) = 0.088 mm^{-1}, T = 180(2) K, 9256 total reflections measured, 1600 independent reflections measured on a Nonius Kappa CCD diffractometer (R_{int} = 0.0273) using Mo-Kα radiation (λ = 0.71073 Å). Refinement using full-matrix least-squares on F^2. Final residues were R_1 = 0.0312, wR_2 = 0.0752 [for reflections with $I > 2\sigma(I)$], R_1 = 0.0341, wR_2 = 0.0770 for all reflections.

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(4*R*,5*R*)-5-Nitro-4-phenylnonan-2-one and (4*R*,5*S*)-5-nitro-4-phenylnonan-2-one. Purification using flash column chromatography (CH_2Cl_2–toluene, 1 : 2) and repurification using flash column chromatography (Et_2O–petroleum ether 40/60, 1 : 9 → 1 : 4) to give the major diastereomer of the title compound as an oil (47 mg, 36%). ν_{max} (film)/cm^{-1}: 1719, 1548, 1366; $[\alpha]_D^{25}$ = +4.2 (c = 0.515, $CHCl_3$, 84% ee). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 (2H, t, J = 7.5 Hz, Ar$_{ortho}$*H*), 7.26 (1H, t, J = 7.2 Hz, Ar$_{para}$*H*), 7.19 (2H, d, J = 7.4 Hz, Ar$_{meta}$*H*), 4.65 (1H, m, C*H*NO$_2$), 3.68 (1H, app td, J = 3.5, 10.0 Hz, PhC*H*), 2.96 [1H, dd, J = 10.0, 16.7 Hz, C(=O)C*H*H′], 2.67 [1H, dd, J = 3.5, 16.7 Hz, C(=O)CH*H*′], 1.98 [3H, s, C(=O)C*H*$_3$], 1.85–1.80 [1H, m, CH(NO$_2$)C*H*H′], 1.39–1.36 [1H, m, CH(NO$_2$)CH*H*′], 1.24–1.16 [4H, m, (C*H*$_2$)$_2$CH$_3$], 0.77 (3H, t, J = 6.6 Hz, C*H*$_3$). ^{13}C NMR (150 MHz, $CDCl_3$): δ 204.9, 138.6, 129.0, 128.0, 127.8, 92.7, 46.3, 44.7, 31.6, 30.4, 27.8, 21.8, 13.6. m/z (ESI): found, 286.1416; $[M + Na]^+$ $C_{15}H_{21}NaNO_3$ requires, 286.1419. Chiral GC: Chirasil Dex-CB, 130 °C, 25 psi, 89.6 min (area 830.6 pA s, *R*), 91.5 min (70.3 pA s, *S*) gave 84% ee.

Purification using flash column chromatography (CH_2Cl_2–toluene, 1 : 2) and repurification using flash column chromatography (Et_2O–petroleum ether 40/60, 1 : 9 → 1 : 4) to give the minor diastereomer of the title compound as white needles (28 mg, 21%). Mp = 71–73 °C; ν_{max} (film)/cm^{-1}: 2957, 2929, 2862, 1719, 1544, 1370; $[\alpha]_D^{25}$ = −8.6 (c = 0.565, $CHCl_3$, 84% ee). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.31–7.24 (3H, m, Ar*H*), 7.13 (2H, d, J = 7.2 Hz, Ar$_{meta}$*H*), 4.75 (1H, ddd, J = 3.5, 6.8, 10.5 Hz, C*H*NO$_2$), 3.72 (1H, apparent q, J = 7.0 Hz, PhC*H*), 3.02 [1H, dd, J = 6.6, 17.5 Hz, C(=O)C*H*H′], 2.86 [1H, dd, J = 7.4, 17.5 Hz, C(=O)CH*H*′], 2.10 [3H, s, C(=O)C*H*$_3$], 1.92–1.88 [1H, m, CH(NO$_2$)C*H*H′], 1.72–1.67 [1H, m, CH(NO$_2$)CH*H*′], 1.35–1.25 [4H, m, (C*H*$_2$)$_2$CH$_3$], 0.87 (3H, t, J = 7.0 Hz, C*H*$_3$). ^{13}C NMR (150 MHz, $CDCl_3$): δ 205.7, 138.0, 128.7, 128.2, 127.9, 91.5, 45.2, 43.9, 30.8, 30.6, 28.0, 22.1, 13.7. m/z (ESI): found, 286.1416; $[M + Na]^+$ $C_{15}H_{21}NaNO_3$ requires, 286.1419. Chiral GC: Chirasil Dex-CB, 130 °C, 25 psi, 113.8 min (area 45.6 pA s, *S*), 116.2 min (389.7 pA s, *S*) gave approximately (due to incomplete resolution) 80% ee.

(*S*)-4-(1-Nitrocyclohexyl)-4-phenylbutan-2-one[10]. Purification using flash column chromatography (CH_2Cl_2–toluene, 1 : 3) and repurification using preparative TLC (Et_2O–CH_2Cl_2, 1 : 9) to give the title compound as white prisms (112 mg, 80%). Mp = 68–69 °C; ν_{max} (film)/cm^{-1}: 2935, 2856, 1706, 1527, 1336; $[\alpha]_D^{25}$ = +3.7 (c = 0.505, $CHCl_3$, 73% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31–7.25 (3H, m, Ar*H*), 7.11 (2H, dd, J = 2.0, 5.9 Hz, Ar*H*), 3.65 (1H, dd, J = 4.3, 9.6 Hz, PhC*H*), 3.02 [1H, dd, J = 9.6, 17.3 Hz, C(=O)C*H*H′], 2.92 [1H, dd, J = 4.3, 17.3 Hz, C(=O)CH*H*′], 2.52 (1H, dd, J = 2.3, 14.1 Hz, C*H*H′CNO$_2$CH$_2$), 2.32 (1H, dd, J = 2.4, 14.2 Hz, CH$_2$CNO$_2$C*H*H′), 2.01 [3H, s, C(=O)C*H*$_3$], 1.68–1.08 [8H, m, CH*H*′(C*H*$_2$)$_3$ CH*H*′]. HPLC: Daicel Chiralpak® AD-H. Hexane–*i*-PrOH, 90 : 10, 215 nm: t_R (major) = 7.9 min; t_R (minor) = 13.2 min.

(*R*)-4-(4-Hydroxy-phenyl)-5-methyl-5-nitro-hexan-2-one[10] 11. Purification using flash column chromatography (Et_2O–CH_2Cl_2, 1 : 49) to give the title compound as a white solid (90 mg, 72%). ν_{max} (film)/cm^{-1}: 3272, 1699, 1612, 1594, 1532, 1517, 1451, 1410, 1397, 1370, 1354, 1305, 1274, 1232, 1200, 1179, 1140, 1111, 1067, 1029, 965, 851, 805; $[\alpha]_D^{25} = +26.8$ ($c = 4.50$, CH_3CN, 62% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02, 2H, d, $J = 8.5$ Hz, Ar*H*), 6.68 (2H, d, $J = 8.5$ Hz, Ar*H*), 5.78 (1H, *br* s, O*H*), 3.85 (1H, dd, $J = 11.1$, 3.4 Hz, C*H*ArOH), 3.04 (1H, dd, $J = 16.6$, 11.1 Hz, C*H*H′COCH$_3$), 2.67 (1H, dd, $J = 16.6$, 3.4 Hz, CH*H*′COCH$_3$), 2.04 (3H, s, COC*H*$_3$), 1.54 [3H, s, C*H*$_3$C(CH′$_3$)NO$_2$], 1.47 [3H, s, CH$_3$C(C*H*′$_3$)NO$_2$]. ^{13}C NMR [100 MHz, $(CD_3)_2SO$]: δ 205.7, 156.6, 130.1, 127.9, 114.9, 91.6, 47.7, 43.0, 30.2, 23.5, 23.0. *m*/*z* (ES+): found, 274.1074; [MNa]$^+$ $C_{13}H_{17}NO_4Na$ requires, 274.1055. HPLC: Daicel Chiralpak AD-H. Hexane–*i*-PrOH, 95 : 5, 1 mL min^{-1}, 280 nM: t_R (major) = 52 min; t_R (minor) = 47 min.

(*R*)-5-Methyl-5-nitro-4-(4-trifluoromethylphenyl)hexan-2-one 12. Purification using flash column chromatography (EtOAc–hexane, 3 : 17) to give the title compound (101 mg, 66%). ν_{max} (film)/cm^{-1}: 2989, 2348, 1720, 1621, 1538, 1460, 1425, 1399, 1375, 1347, 1324, 1163, 1114, 1070, 1017, 959, 912, 850, 803; $[\alpha]_D^{25} = +23.2$ ($c = 5.03$, $CHCl_3$, 68% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (2H, d, $J = 8.2$ Hz, Ar*H*), 7.32 (2H, d, $J = 8.1$ Hz, Ar*H*), 3.99 (1H, dd, $J = 10.5$, 3.3 Hz, C*H*ArCF$_3$), 3.09 (1H, dd, $J = 17.5$, 10.6 Hz, C*H*H′COCH$_3$), 2.80 (1H, dd, $J = 17.5$, 3.4 Hz, CH*H*′COCH$_3$), 2.05 (3H, s, COC*H*$_3$), 1.55 [3H, s, C*H*$_3$C(CH′$_3$)NO$_2$], 1.50 [3H, s, CH$_3$C(C*H*′$_3$)NO$_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.4, 142.0 (d, $J = 1.3$ Hz), 130.1 (q, $J = 32.5$ Hz), 129.5, 125.4 (q, $J = 3.8$ Hz), 125.2, 90.5, 48.4, 43.8, 30.2, 25.5, 22.8. *m*/*z* (ES+): found, 326.0981; [MNa]$^+$ $C_{14}H_{16}F_3NO_3Na$ requires, 326.0974. Chiral GC: Chirasil Dex-CB, 150°, 25 psi, 18.4 min (417.0 pA s, *R*), 19.1 min (78.8 pA s, *S*) gave 68% ee.

(*S*)-5-Methyl-5-nitro-4-(thiophen-2-yl)hexan-2-one[10] 13. Purification using flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 9) to give the title compound. ν_{max} (film)/cm^{-1}: 2920, 1717, 1537, 1345, 850, 703; $[\alpha]_D^{25} = +26.4$ ($c = 1.242$, $CHCl_3$, 66% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (1H, d, $J = 4.6$ Hz, Ar*H*), 6.90–6.93 (2H, m, Ar*H*), 4.29 [1H, dd, $J = 10.8$, 2.9 Hz, C*H*C(CH$_3$)$_2$NO$_2$], 3.01 [1H, dd, $J = 16.9$, 10.9 Hz, C(=O)C*H*H′], 2.65 [1H, dd, $J = 16.9$, 3.0 Hz, C(=O)CH*H*′], 2.05 [3H, s, C(=O)C*H*$_3$], 1.62 [3H, s, (C*H*$_3$)(CH′$_3$)CNO$_2$], 1.52 [3H, s, (CH$_3$)(C*H*′$_3$)CNO$_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.4, 140.3, 127.5, 126.9, 126.3, 91.0, 45.6, 44.3, 30.3, 25.6, 22.5.

(*S*)-4-(Furan-2-yl)-5-methyl-5-nitrohexan-2-one[10] 14. Purification using flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 9) to give the title compound. ν_{max} (film)/cm^{-1}: 1719, 1538, 1346, 1014, 746; $[\alpha]_D^{25} = +22.4$ ($c = 0.905$, $CHCl_3$, 72% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (1, s, Ar*H*), 6.27 (1H, m, Ar*H*), 6.15 (1H, d, $J = 3.1$ Hz, Ar*H*), 4.09 [1H, dd, $J = 10.9$, 3.0 Hz, C*H*C(CH$_3$)$_2$NO$_2$], 3.06 [1H, dd, $J = 16.9$, 10.9 Hz, C(=O)C*H*H′], 2.51 [1H, dd, $J = 16.9$, 3.30 Hz, C(=O)CH*H*′], 2.04 [3H, s, C(=O)C*H*$_3$], 1.55 [3H, s, (C*H*$_3$)(CH′$_3$)CNO$_2$], 1.48 [3H, s, (CH$_3$)(C*H*′$_3$)CNO$_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.6, 151.3, 142.2, 110.5, 109.1, 90.5, 42.5, 42.1, 30.0, 25.6, 22.4. Chiral GC: Chiraldex G-TA, 130°, 25 psi, 23.4 min (*S*), 24.2 min (*R*) gave 66% ee.

(*R*)-5-Methyl-5-nitro-4-(pyridin-4-yl)hexan-2-one 15. Purification using flash column chromatography (petroleum ether 40/60–EtOAc, 1 : 4) to give the title compound. ν_{max} (film)/cm^{-1}: 2920, 1717, 1537, 1345, 850, 703; $[\alpha]_D^{25} = +21.2$ ($c = 0.51$, $CHCl_3$, 65% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (2H, d, $J = 5.8$ Hz, Ar*H*), 7.12 (2H, d, $J = 5.9$ Hz, Ar*H*), 3.91 [1H, dd, $J = 10.5$, 3.2 Hz, C*H*C(CH$_3$)$_2$NO$_2$], 3.07 [1H, dd, $J = 17.7$, 10.5 Hz, C(=O)C*H*H′], 2.80 [1H, dd, $J = 17.7$, 3.3 Hz, C(=O)CH*H*′], 2.07 [3H, s, C(=O)C*H*$_3$], 1.56 [3H, s, (C*H*$_3$)(CH′$_3$)CNO$_2$], 1.40 [3H, s, (CH$_3$)(C*H*′$_3$)CNO$_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.1, 150.0, 147.0, 124.3, 90.1, 48.0, 43.5, 30.3, 35.7, 22.9. *m*/*z* (ES): found, 237.1237; [MH]$^+$ $C_{12}H_{17}N_2O_3$ requires, 237.1239. HPLC: Daicel Chiralcel OD-H. Hexane–*i*-PrOH, 80 : 20, 1 mL min^{-1}, 254 nM: t_R (minor) = 14 min; t_R (major) = 16 min.

(*R*)-6-Methyl-6-nitro-5-phenylheptan-3-one[10] 16. Purification using flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 24) to give the title compound as a colorless oil (67 mg, 78%). ν_{max} (film)/cm^{-1}: 2980, 1717, 1536, 1456, 1397, 1373, 1344, 1112, 849; $[\alpha]_D^{25} = +6.81$ ($c = 3.34$, $CHCl_3$, 78% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18–7.32 (5H, m, Ar*H*), 3.95 (1H, dd, $J = 10.6$, 3.4 Hz, C*H*Ar), 3.07 (1H, dd, $J = 16.8$, 10.6 Hz, C*H*H′COCH$_2$CH$_3$), 2.69 (1H, dd, $J = 16.8$, 3.4 Hz, CH*H*′COCH$_2$CH$_3$), 2.32–2.42 (1H, m, COC*H*H′CH$_3$), 2.18–2.28 (1H, m, COCH*H*′CH$_3$), 1.55 [3H, s, C*H*$_3$C(CH′$_3$)NO$_2$], 1.49 [3H, s, CH$_3$C(C*H*′$_3$)NO$_2$], 0.91 (3H, t, $J = 7.3$ Hz, COCH$_2$C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.8, 137.8, 129.1, 128.5, 127.8, 91.1, 48.9, 42.9, 36.4, 25.9, 22.5, 7.5. *m*/*z* (ES+): found, 272.2195; [MNa]$^+$ $C_{14}H_{19}NO_3Na$ requires, 272.1263. Chiral GC: Chirasil Dex-CB, 150 °C, 25 psi, 22.9 min (173.8 pA s, *R*), 23.6 min (21.5 pA s, *S*) gave 78% ee.

(*R*)-3-(2-Nitropropan-2-yl)cyclopentanone[9] 17. Purification using flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 9) to give the title compound as a colorless oil (53 mg, 62%). ν_{max} (film)/cm^{-1}: 2986, 1738, 1528, 1473, 1400, 1374, 1338, 1281, 1252, 1241, 1225, 1208, 1191, 1164, 1120, 1079, 1000, 980, 946, 918, 900, 853, 839, 819; $[\alpha]_D^{25} = +80.8$ ($c = 2.64$, $CHCl_3$, 80% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.85 [1H, m, C*H*C(CH′$_3$)$_2$NO$_2$], 2.19–2.44 (3H, m, C*H*$_2$COC*H*H′), 2.02–2.14 (2H, m, CH$_2$COCH*H*′ and cpent-*H*), 1.64–1.73 (1H, m, cpent-*H*), 1.62 [3H, s, C*H*$_3$C(CH′$_3$)NO$_2$], 1.61 [3H, s, CH$_3$C(C*H*′$_3$)NO$_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.4, 89.4, 45.6, 40.1, 38.5, 24.4, 23.6, 23.3. Chiral GC: Chiradex G-TA, 150 °C, 25 psi, 10.4 min (43.0 pA s, *S*), 10.8 min (392.9 pA s, *R*) gave 80% ee.

(*R*)-3-Methyl-3-(2-nitropropan-2-yl)cyclohexanone 18. Purification using flash column chromatography (EtOAc–hexane, 1 : 4) to give the title compound as a colorless oil (55 mg, 64%). ν_{max} (film)/cm^{-1}: 2953, 1708, 1544, 1462, 1430, 1378, 1297, 1229, 1193, 1146, 1080, 1051, 932, 886; $[\alpha]_D^{25} = +1.5$ ($c = 2.73$, $CHCl_3$, 91% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29 (2H, dd, $J = 19.7$, 10.7 Hz, C*H*$_2$NO$_2$), 2.24–2.44 (4H, m, C*H*$_2$COCC*H*$_2$), 1.58–2.03 (4H, m, chex-*H*), 1.12 (3H, s, C*H*$_3$CCH′$_2$NO$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.7, 84.9, 50.8, 40.5, 39.8, 33.5, 23.2, 21.3. *m*/*z* (ES+): found, 194.0435; [MNa]$^+$ $C_8H_{13}NO_3Na$ requires, 194.0793. Chiral GC: Chirasil Dex-CB, 150 °C, 25 psi, 8.8 min (286.6 pA s, *R*), 9.3 min (13.6 pA s, *S*) gave 91% ee.

(*S*)-Methyl 2-(2-nitropropan-2-yl)-4-oxopentanoate[10] 19. Purification using flash column chromatography (EtOAc–hexane, 1 : 4) to give the title compound as a white solid (105 mg, 96%). ν_{max} (film)/cm^{-1}: 2959, 1736, 1715, 1541, 1438, 1401, 1372, 1346, 1288, 1221, 1198, 1178, 1163, 1133, 1095, 1047, 977, 956, 907, 851; $[\alpha]_D^{25} = +38.1$ (c = 3.81, $CHCl_3$, 82% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.71 (3H, s, OCH_3), 3.67 (1H, dd, J = 11.1, 2.9 Hz, CHCO$_2$CH$_3$), 3.04 (1H, dd, J = 17.8, 11.1 Hz, CHH′COCH$_3$), 2.43 (1H, dd, J = 17.8, 2.8 Hz, CHH′COCH$_3$), 2.16 (3H, s, COCH_3), 1.61 [3H, s, CH_3C(CH′$_3$)NO$_2$], 1.59 [3H, s, CH$_3$C(CH′$_3$)NO$_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.8, 171.3, 88.2, 52.3, 48.2, 41.3, 29.7, 25.4, 23.0. m/z (ES+): found, 240.0828; [MNa]$^+$ $C_9H_{15}NO_5Na$ requires, 240.0848. Chiral GC: Chirasil Dex-CB, 130 °C, 25 psi, 10.9 min (257.2 pA s, *S*), 11.3 min (26.2 pA s, *R*) gave 82% ee.

(*S*)-4-(2-Nitropropan-2-yl)nonan-2-one 20. Purification using flash column chromatography (Et$_2$O–petroleum ether 40/60, 1 : 9 → 3 : 7) to give the title compound as a clear oil (49 mg, 44%). ν_{max} (film)/cm^{-1}: 1718, 1535, 1348; $[\alpha]_D^{25} = +12.6$ (c = 0.495, $CHCl_3$, 58% ee). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.75–2.71 [1H, m, C(NO$_2$)CH], 2.50 [1H, dd, J = 4.4, 18.0 Hz, C(=O)CHH′], 2.32 [1H, dd, J = 6.2, 18.0 Hz, C(=O)CHH′], 2.15 [3H, s, C(=O)CH_3], 1.50 [3H, s, C(NO$_2$)(CH_3)(CH′$_3$)], 1.49 [3H, s, C(NO$_2$)(CH$_3$)(CH′$_3$)], 1.41–1.34 (1H, m, CHRCHH′), 1.24–1.16 [6H, m, –(CH_2)$_3$–], 1.08–1.03 (1H, m, CHRCHH′), 0.84 (3H, t, J = 7.1 Hz, CH$_2$CH_3). ^{13}C NMR (600 MHz, $CDCl_3$): δ 206.1, 91.6, 45.0, 41.3, 31.8, 31.2, 30.0, 27.5, 23.9, 23.7, 22.4, 13.9. m/z (ESI): found, 252.1573; [MNa]$^+$ $C_{12}H_{23}NO_3Na$ requires, 252.1576. Chiral GC: Chirasil Dex-CB, 130 °C, 25 psi, 19.9 min (148.5. pA s, *S*), 20.7 min (39.5 pA s, *R*) gave 58% ee.

(*S*)-3,4-Dimethyl-4-nitropentanal 21. Purification using flash column chromatography (CH_2Cl_2–petroleum ether 40/60, 2 : 3 → 3 : 2) to give the title compound as a clear oil of approximately 90% purity (30 mg, 39%). ν_{max} (film)/cm^{-1}: 1723, 1533, 1349; $[\alpha]_D^{25}$ = +1.0 (c = 0.355, $CHCl_3$, 46% ee). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.73 (1H, m, CHO), 2.90–2.82 [1H, m, C(NO$_2$)CH], 2.46 [1H, ddd, J = 0.7, 2.9, 17.1 Hz, C(=O)CHH′], 2.28 [1H, ddd, J = 2.3, 10.2, 17.2 Hz, C(=O)CHH′], 1.56 [3H, s, C(CH_3)(CH′$_3$)], 1.54 [3H, s, C(CH$_3$)(CH′$_3$)], 0.98 (3H, d, J = 6.3 Hz, CHRCH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 199.7, 91.2, 46.2, 35.9, 23.9, 22.5, 15.3. m/z (ESI): found, 182.0791; [MNa]$^+$ $C_7H_{13}NO_3Na$ requires, 182.0793. Chiral GC: Chirasil Dex-CB, 130 °C, 25 psi, 5.6 min (100.1 pA s, *S*), 5.9 min (37.3 pA s, *R*) gave 46% ee.

(*R*)-4-Methyl-4-nitro-3-phenylpentanal 22. Purification using flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 23) to give the title compound as a white solid. ν_{max} (film)/cm^{-1}: 2998, 2836, 2732, 1723, 1532, 1495, 1455, 1397, 1374, 1344, 1292, 1218, 1134, 1092, 1060, 1019, 910, 846. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (1H, d, J = 1.8 Hz, COCH), 7.20–7.35 (5H, m, ArH), 4.00 (1H, dd, J = 11.1, 3.7 Hz, CHAr), 3.06 (1H, ddd, J = 17.2, 11.1, 2.3 Hz, CHH′COH), 2.71 (1H, dd, J = 17.2, 3.6 Hz), 1.58 [3H, s, CH_3C(CH′$_3$)NO$_2$], 1.49 [3H, s, CH$_3$C(CH′$_3$)NO$_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.0, 136.8, 129.3, 128.7, 128.1, 91.0, 47.6, 43.9, 25.5, 22.2. m/z (ES+): found, 244.1225; [MNa]$^+$ $C_{12}H_{15}NO_3Na$ requires, 244.0950. Chiral GC: Chiradex G-TA, 130 °C, 25 psi, 56.8 min (256.9 pA s), 59.5 min (253.7 pA s) gave 0% ee

Kinetic investigations using ReactIR

Reactions were run using a Mettler Toledo ReactIR 4000 instrument with a SiComp probe. (*E*)-4-Phenyl-3-buten-2-one (**9**) (72 mg, 0.49 mmol), *trans*-2,5-dimethylpiperazine (**7**) (67 mg, 0.50 mmol), and tetrazole **4** (10 mg, 0.074 mmol) were dissolved in dichloromethane (0.75 mL). Nitroethane (70 μL, 74 mg, 0.98 mmol) was added and the reaction monitored every 20 min for 50 h.

Tetrazole **4** (35 mg, 0.26 mmol) was dissolved in methanol (4 mL) in a test tube. The ReactIR side arm was fitted, and five spectra were acquired (1 spectrum min^{-1}). Cyclohexenone (**6**) (25 mL, 25 mg, 0.26 mmol) was added and the reaction monitored every minute for 2 h. No changes were observed in the region 1600–1800 cm^{-1}.

Tetrazole **4** (75 mg, 0.55 mmol) was dissolved in methanol (4 mL) in a 10 mL round-bottomed flask under argon. The ReactIR side arm was fitted, and two spectra were acquired (2 spectra min^{-1}). (*E*)-4-Phenyl-3-buten-2-one (**9**) (80 mg, 0.55 mmol) was added and the reaction monitored every 2 min for 5 h. No changes were observed in the region 1600–1800 cm^{-1}.

Kinetic investigations using a React Array™

Reactions were performed using a React Array™ SK233 automated workstation subjected to in-line HPLC analysis on a Hewlett Packard HP1100 instrument. Column: Supercosil™ ABZ$^+$ 3.3 cm × 4.6 mm, 3 μm. Eluent: A: water, 0.1% TFA; B: 95% acetonitrile, 5% water, 0.05% TFA. Flow rate: 1 mL min^{-1}. Method: gradient 10–95% B in A over 7 min, run time 10 min.

All reactions were performed in air in 5 mL vessels. 50 μL aliquots were sampled at specified intervals. The aliquots were dispensed into 1.5 mL vials, quenched with acetonitrile (1 mL) and mixed [75% by volume (aspirated and dispensed at 10 mL min^{-1})]. 100 μL of these solutions were transferred to clean 1.5 mL vials, diluted with acetonitrile (1 mL) and mixed as described previously to give analytical samples ready for HPLC analysis (20 μL injected).

(*E*)-4-Phenyl-3-buten-2-one (**9**) (148 mg, 1.01 mmol), *trans*-2,5-dimethylpiperazine (**7**) (114 mg, 1.00 mmol), the internal standard *trans*-stilbene (16 mg, 0.09 mmol) and 2-nitropropane (200 μL, 198 mg, 2.22 mmol) were dissolved in dichloromethane (4 mL). The SK233 was initiated, the tetrazole **4** (19 mg, 0.14 mmol) added and the timer started. The reactions were sampled at t = 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 48, 54, 60, 66, 72, 78 and 84 h.

The HPLC trace areas were normalised with respect to the internal standard (*trans*-stilbene). The HPLC trace areas were then extrapolated back to their respective concentrations using the calibration curves. Percentages of (*E*)-4-phenyl-3-buten-2-one (**9**) remaining in solution and (*R*)-5-methyl-5-nitro-4-phenylhexan-2-one (**10**) formed were calculated and plotted against the reaction time.

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