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Organocatalysis with proline derivatives: improved catalysts for the asymmetric Mannich, nitro-Michael and aldol reactions

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Tetrazole and acylsulfonamide organocatalysts derived from proline have been synthesised and applied to the asymmetric Mannich, nitro-Michael and aldol reactions to give results that are superior to the proline-catalysed counterpart.

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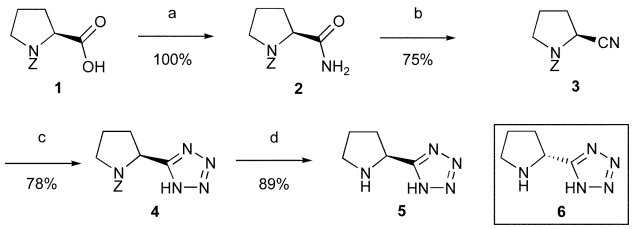
Introduction

The search for asymmetric catalysts that provide high yields and enantioselectivities is an on-going quest for organic chemists. An important area that has been intensively studied over the past few years is that of asymmetric organocatalysis, the primary advantage of which is that it avoids the use of metals, which can be both expensive and toxic. Proline[1] is one example of a versatile organocatalyst, which despite having been used effectively in the Hajos–Parrish–Eder–Sauer–Wiechert[2] reaction in the 1970s has only recently received full attention in synthetic applications, such as aldol[3–6], Mannich[7–9] and nitro-Michael[10,11] reactions. However, there are a number of drawbacks in the use of proline. First, its limited solvent compatibility; often reactions are performed in very polar solvents such as DMSO, MeOH, or H_2O. Secondly a relatively high catalyst loading is usually required to effect the desired reaction in a reasonable timescale; commonly proline is used at levels of around 20 mol%.

Catalyst design

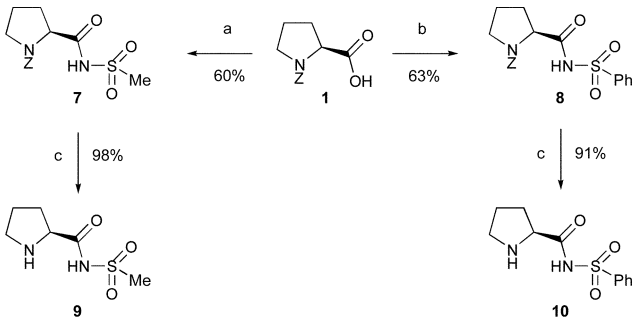
The initial aim in our organocatalyst program was to design several organocatalysts with the intention of overcoming some of these problems; in particular we hoped to design a catalyst which could be used in solvents more commonly used in organic synthesis with highly lipophilic substrates.

Tetrazoles are used in medicinal chemistry as bioisosteres for carboxylic acids due to the similarity in pK_a as well as their increased solubility. It was hoped that replacing the carboxylic acid in proline with a tetrazole unit would give the greater solubility that was desired. This would allow a greater range of solvents to be used with the organocatalyst than it is possible to use with proline. Tetrazole **5** was synthesised according to a modified literature procedure (Scheme 1).[8,12] The enantiomer of this compound was also synthesised by the same route from *Z*-D-proline to give tetrazole **6**.



Scheme 1 *Reagents and conditions*: [a] EDCI, 1-hydroxybenzotriazole, NH_3, THF, rt, 24 h; [b] *p*-TsCl, pyridine, CH_2Cl_2, rt, 72 h; [c] NaN_3, NH_4Cl, DMF, 90–95 °C, 8 h; [d] 10% Pd/C, H_2, AcOH–H_2O, rt, 4 h. EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

We also envisaged that acyl sulfonamides **9** and **10** would have increased solubility and act as alternatives to proline in organocatalytic reactions, owing to the acidity of the sulfonamidic proton.[13,22] The synthesis of these compounds involved the coupling of *Z*-L-proline with the relevant sulfonamide (Scheme 2).



Scheme 2 *Reagents and conditions*: [a] methanesulfonamide, EDCI, DMAP, CH_2Cl_2, rt, 48 h; [b] benzenesulfonamide, EDCI, DMAP, CH_2Cl_2, rt, 48 h; [c] 10% Pd/C, H_2, MeOH, rt, 20 h. DMAP = 4-dimethylaminopyridine.

Results

Asymmetric Mannich-type reaction

The asymmetric Mannich-type addition of a ketone directly into an imine has been the subject of much study over recent years. This reaction thus served as an excellent measure by which to compare these new organocatalysts. The reaction of cyclohexanone into the highly reactive electrophile *N*-PMP-protected α-imino ethyl glyoxalate **12** (synthesised from the condensation of *p*-anisidine with ethyl glyoxalate)[14] was selected as a starting point.[15] For the study various solvents were used to ascertain the solvent scope and to ascertain whether the organocatalysts were, indeed, more soluble than proline itself (Table 1).

Pleasingly, all three organocatalysts catalysed the reaction in high enantioselectivities with good to excellent yields in all solvents investigated. Significantly, these catalysts worked effectively in dichloromethane, whereas L-proline failed to give any product.

Perhaps the most important observation is that tetrazole **5** gives an expeditious reaction at levels of 1 mol%, with no detrimental effect on enantioselectivity. This represents a vast improvement on L-proline, which is commonly used at levels of 20 mol%. When using organocatalyst **9**, levels of 5 mol% maintained enantioselectivity, although a slightly reduced yield was observed. Tetrazole catalyst **5** therefore shows a significant advantage over sulfonamides **9** and **10** in that it can be used

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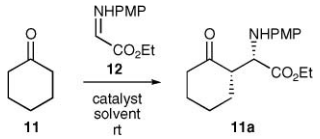
Table 1 Catalyst and solvent screen for the asymmetric Mannich-type reaction



Entry	Cat (mol%)	Solvent	T (h)	Yield (%)[a]	Dr *syn* : *anti*[b]	Ee (%)[c]
1	**5** (5)	CH_2Cl_2	2	65	>19 : 1	>99
2	L-Pro (5)	CH_2Cl_2	2	0	—	—
3	**5** (5)	Wet MeCN	2	49	>19 : 1	>99
4	**5** (5)	Wet THF	2	37	>19 : 1	>99
5	**5** (1)	CH_2Cl_2	16	70	>19 : 1	>99
6	**9** (20)	MeOH	24	74	>19 : 1	95
7	**9** (20)	CH_2Cl_2	24	82	>19 : 1	96
8	**9** (5)	CH_2Cl_2	24	65	>19 : 1	83
9	**9** (1)	CH_2Cl_2	24	53	>19 : 1	40
10	**10** (20)	DMSO	24	87	>19 : 1	>99
11	**10** (20)	THF	24	87	>19 : 1	>99
12	**10** (20)	MeOH	24	69	>19 : 1	95
13	**10** (20)	CH_2Cl_2	24	75	>19 : 1	>99

[a] Based on isolated product. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC.

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in reactions for shorter times, or in lower loading, to achieve similar results.

Also noteworthy is the similarity of the results using the sulfonamide catalysts **9** and **10**, suggesting that the functionality appended to this moiety has little effect on the outcome of this reaction.

Overall, these promising results showed the utility of these organocatalysts and compounds **5** and **9** were used to screen the reaction of the same electrophile with a variety of ketones. Reactions with organocatalyst **5** were conducted at a level of 5 mol% for reasons of practicality and organocatalyst **9** was used at the optimised level of 20 mol% (Table 2).

The enantioselectivities obtained were excellent with the exception of fluoroacetone as the ketone partner (Table 2, entry 9). With this example a bi-phasic mixture occurred, giving little interaction between the ketone and the catalyst, accounting for the low yield. The low enantioselectivity, however, is attributed to fluorine interfering with the hydrogen bonded transition state thought to be necessary to give a rigid chiral environment, as suggested by Houk (Fig. 1).[16]

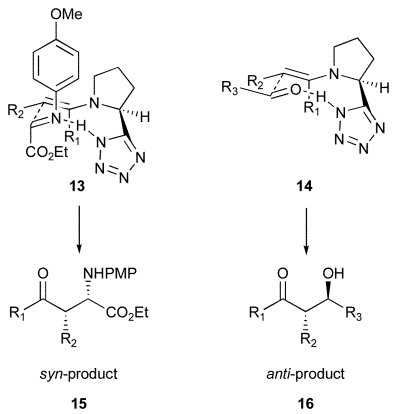


Fig. 1 Major pathways in the Mannich and aldol reactions.

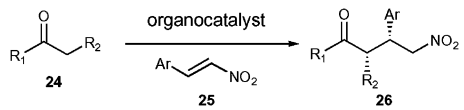
In this model, the imine sits in a position where its groups are axial, avoiding any *gauche* interaction with the tetrazole unit **13** (Fig. 1). This means that although the enamine adopted is the *E*-isomer, the *syn*-product results. This is in contrast to the aldol reaction where the major pathway occurs with large substituents in an equatorial position, delivering predominantly the *anti*-product (Fig. 1).

Tetrazole catalyst **5** was shown to be just as, or more efficient, than L-proline itself. Furthermore, the reaction using this catalyst in dichloromethane appeared to give a more rapid reaction than DL-proline in DMSO as visualised by thin layer chromatography.

In summary, these organocatalysts have been shown to catalyse a Mannich-type reaction in non-polar solvents with either reduced loading or shorter reaction times, thus demonstrating greater versatility than L-proline.

Asymmetric nitro-Michael addition

A further use of the tetrazole catalyst **5** was demonstrated with the addition of a ketone to a nitro-olefin (Scheme 3). [17] Recently, there have also been a number of investigations into nitro-Michael additions using various organocatalysts.[5,10,11,18,19] Proline was one of the first to be studied and it successfully catalysed the reaction both in DMSO and alcoholic solvents. However, in most cases reported the enantioselectivities obtained were low. It was hoped that one of our organocatalysts would successfully catalyse the reaction in more conventional organic solvents and/or with a greater enantioselectivity. The reaction conditions were investigated using the reaction between cyclohexanone and β-nitrostyrene, using a variety of solvents (Table 3).



Scheme 3 General pyrrolidine mediated nitro-Michael reaction.

Although the reaction did not proceed using organocatalysts **9** or **10**, tetrazole **5** gave good to excellent yields and good enantioselectivities. Again, in dichloromethane, L-proline failed to give any product even at reflux and the tetrazole gave more rapid reaction in methanol than literature reports using L-proline.[11] More significantly, reaction with tetrazole **5** in methanol gave the best enantioselectivities and this prompted the screening of the reaction in various mixtures of alcoholic solvents (Table 4).

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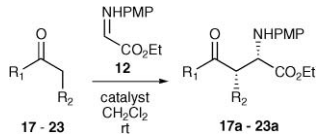
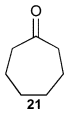
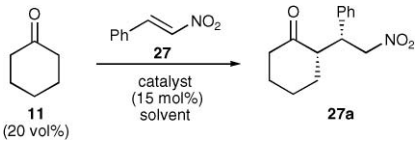
Table 2 Substrate screen



Entry	Carbonyl	Cat (mol%)	T (h)	Yield (%)[a]	Dr *syn* : *anti*[b]	Ee (%)[c]
1	 17	**5** (5)	16	63	>19 : 1	>99
2		**9** (20)[d]	24	60	>19 : 1	>99
3	 18	**5** (5)[e]	8	99	—	>99
4		**9** (20)[d]	24	55	—	96
5	 19	**5** (5)	8	66	>19 : 1	>99
6		**9** (20)[d]	24	77	>19 : 1	97
7	 20	**5** (5)	24	74	>19 : 1	94
8	 21	**5** (5)	8	59	>19 : 1	>99
9	 22	**5** (5)[f]	24	31	—	14
10	 23	**5** (5)	24	75	7 : 1[g]	95[h]

[a] Based on isolated product. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC. [d] Reaction performed in MeOH. [e] Reaction performed in neat acetone. [f] Reaction stopped after 24 h at 55% conversion. [g] Epimerisation on the silica column led to a deterioration of dr. [h] Ee measured on corresponding lactone. *Indicates position of enamine formation.

Table 3 Catalyst and solvent screen for the asymmetric nitro-Michael reaction



Entry	Cat.	Solvent	T (°C)	Yield (%)[a]	Dr *syn* : *anti*[b]	Ee (%)[c]
1	**5**	DMSO	20	97	>15 : 1	35
2	L-Pro	DMSO	20	93	>15 : 1	35
3	**5**	MeOH	20	61	>15 : 1	53
4	L-Pro	MeOH	20	37	>15 : 1	57
5	**5**	MeOH	50	42	>15 : 1	53
6	**5**	CH_2Cl_2	20	20	>15 : 1	40
7	L-Pro	CH_2Cl_2	20	0	—	—
8	**5**	CH_2Cl_2	40	98	>15 : 1	37
9	L-Pro	CH_2Cl_2	40	0	—	—
10	**5**	THF	20	33	>15 : 1	25
11	**9**[d]	CH_2Cl_2	20	0	—	—
12	**10**[d]	CH_2Cl_2	20	0	—	—

[a] Based on isolated product. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC. [d] 20 mol% used.

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Table 4 Further optimisation studies for the conjugate addition of cyclohexanone (20 vol%) into β-nitrostyrene using 15 mol% of organocatalyst **5**. All reactions conducted for 24 h

Entry	Cat.	Solvent	Cyclohexanone (eq.)	Yield (%)[a,b]	Ee (%)[c]
1	**5**	MeOH	20	61	53
2	**5**	MeOH–IPA (2 : 1)	20	56	53
3	**5**	MeOH–IPA (1 : 1)	20	65	61
4	**5**	MeOH–IPA (1 : 2)	20	76	58
5	**5**	EtOH	20	65	65
6	**5**	EtOH–IPA (2 : 1)	20	80	59
7	L-Pro	EtOH–IPA (1 : 1)	20	78	47
8	**5**	EtOH–IPA (1 : 1)	20	96	62
9	**5**	EtOH–IPA (1 : 2)	20	100	56
10	**5**	IPA	20	80	40
11	L-Pro	EtOH–IPA (1 : 1)	1.5	52	51
12	**5**	EtOH–IPA (1 : 1)	1.5	80	62

[a] Based on isolated product. [b] All drs were >15 : 1 by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC (Daicel Chiralpak AD-H column).

The best overall conditions were shown to be those using equal amounts of ethanol and isopropanol. It was these conditions that were used for further optimisation of the system, where variations in the amount of ketone, and organocatalyst were investigated. The reactions with organocatalysts **9** and **10** were also repeated under the optimised ethanol–isopropanol conditions, but no product was observed.

It is clear that in the case of the alcoholic solvents, reducing the amount of catalyst lowers the yield. In dichloromethane this is not the case. Nevertheless, the decrease in catalyst loading does not seem to effect the enantioselectivities in either case (Table 5, entries 1 and 9). Decreasing the amount of ketone in the reaction lowers the yield of product in the case of the alcoholic solvent system (Table 5, entry 4), but again, this reduction seems to have little effect in dichloromethane (Table 5, entry 11).

In alcoholic solvents, tetrazole outperforms proline, both in terms of product yield and enantioselectivity (**5** provides almost a 20% better yield than L-proline and a 15% improvement in ee. Table 5, entries 7 and 8).

Despite the obvious superiority of yields in dichloromethane, the better enantioselectivities obtained in the alcoholic solvent led to this being the system of choice for further investigations into the scope of this reaction. The best system was that using ethanol–isopropanol (1 : 1) and 1.5 equivalents of ketone. Several nitro-olefins were screened under these conditions using cyclohexanone as the ketone and the results are shown (Table 6). Reactions in dichloromethane are also shown in comparison.

It was found that under these conditions, the yields were generally good and ranged between 47% and 92%. However, the substituent of the nitro-olefin appears to have little effect on the enantioselectivities of the reaction, which range from 55% to 65%. The relative configuration of compound **27a** has been confirmed by X-ray crystallographic methods (Fig. 2).†

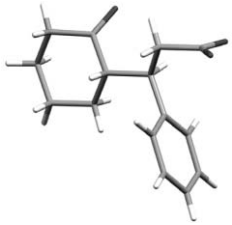

Fig. 2 X-Ray structure of adduct **27a**.

β-3-Dinitrostyrene was found to produce the best result providing an excellent yield and good enantioselectivity (entry 5). It was this Michael acceptor that was used to investigate the scope of ketones within the reaction (Table 7).

The results of this study showed that in general, cyclic ketones performed best, with the exception of 3-pentanone (entry 7) which gave good enantioselectivity. The best example was that using tetrahydrothiopyran-4-one as the ketone which gave the corresponding Michael adduct **34a** in 62% yield and 70% enantiomeric excess (Table 7, entry 2). This is in stark

† CCDC reference number 256659. See http://www.rsc.org/suppdata/ob/b4/b414742a/ for crystallographic data in .cif or other electronic format.

Table 5 Further optimisation of the tetrazole asymmetric organocatalysed reaction using cyclohexanone and β-nitrostyrene

Entry	Cat.	mol%	Cyclohexanone (eq.)	Solvent	T (°C)	Yield (%)[a,b]	Ee (%)[c]
1	**5**	1	20	EtOH–IPA (1 : 1)	20	10	59
2	**5**	5	20	EtOH–IPA (1 : 1)	20	57	60
3	L-Pro	5	20	EtOH–IPA (1 : 1)	20	25	51
4	**5**	15	1.1	EtOH–IPA (1 : 1)	20	69	68
5	**5**	15	1.5	EtOH–IPA (1 : 1)	20	80	62
6	**5**	15	5	EtOH–IPA (1 : 1)	20	84	65
7	**5**	15	20	EtOH–IPA (1 : 1)	20	96	62
8	L-Pro	15	20	EtOH–IPA (1 : 1)	20	78	47
9	**5**	1	20	CH_2Cl_2	Reflux	62	46
10	**5**	5	20	CH_2Cl_2	Reflux	100	44
11	**5**	15	1.1	CH_2Cl_2	Reflux	86	49
12	**5**	15	5	CH_2Cl_2	Reflux	68	51
13	**5**	15	10	CH_2Cl_2	Reflux	64	37

[a] Based on isolated product. [b] All drs were >15 : 1 by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC (Daicel Chiralpak AD-H column).

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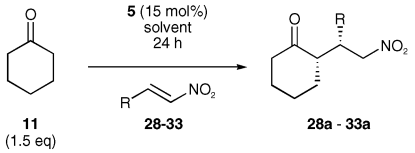
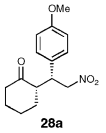
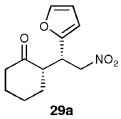
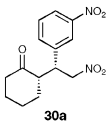
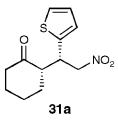
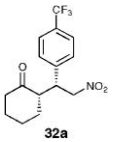
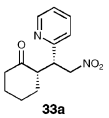
Table 6 Use of various nitro-olefins under optimised conditions



Entry	Product	Solvent (T/°C)	Yield (%)[a,b]	Ee (%)[c]
1	 28a	EtOH–IPA (1 : 1), (20)	83	58
2		CH_2Cl_2, (reflux)	96	37
3	 29a	EtOH–IPA (1 : 1) (20)	59	65
4		CH_2Cl_2, (reflux)	100	23
5	 30a	EtOH–IPA (1 : 1), (20)	92	65
6	 31a	EtOH–IPA (1 : 1), (20)	74	57
7	 32a	EtOH–IPA (1 : 1), (20)	58	55
8	 33a	EtOH–IPA (1 : 1), (20)	47	60

[a] Based on isolated product. [b] All drs were>15 : 1 by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC (Daicel Chiralpak AD-H column).

contrast with L-proline which falls short of the tetrazole-induced enantioselectivity by 30% (Table 7, entry 1). The enantiomeric tetrazole **6** was also applied to this example to give the product of the opposite stereochemistry, in a comparable yield and enantioselectivity (Table 7, entry 3).

The improvement in enantioselectivity of the tetrazole catalysts **5** and **6** over proline, suggests that there is an inherent difference between the two organocatalysts that alters the transition state. On one hand, if the tetrazole participates in a hydrogen bonded framework as is suggested by Enders for proline (Fig. 3),[11] then it would be expected for them to give similar enantioselectivities unless there is an inherent difference in the hydrogen bonding strengths between tetrazole catalyst **5** and L-proline, resulting in a tighter transition state. The hydrogen bonding strength is, of course, affected by the solvent and this would be consistent with the observed range of enantioselectivities in the various solvents investigated.

A second explanation is that the slightly larger tetrazole moiety occupies a larger region of space than a carboxylic acid, thereby providing more of a facial preference for an approaching substrate. This explanation has been used recently to explain the performance of some other organocatalysts in the same reaction (Fig. 3).[18]

In conclusion, tetrazole organocatalysts **5** and **6** have been shown to catalyse the asymmetric addition of a ketone to a nitro-olefin to better yields and enantioselectivities than L-proline itself. This demonstrates the advantages of having an organocatalyst that can be used under a diversity of conditions and in a wider solvent scope than the previously limited L-proline reactions.

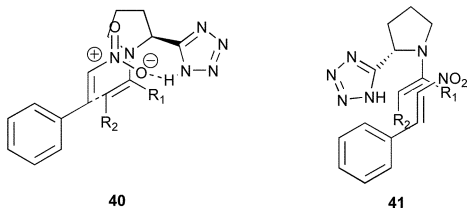


Fig. 3 Potential transition states.

Asymmetric aldol reaction

Following our initial publication of organocatalyst **5**[8], its application in the asymmetric aldol reaction has been studied thoroughly.[19,20,21] Here we report only our investigations with organocatalysts **9** and **10** using a range of ketones with *p*-nitrobenzaldehyde as a test to measure their utility (Table 8).[22]

Firstly, a solvent screen was investigated with **9** and **10** and optimum results were observed in methylene chloride,

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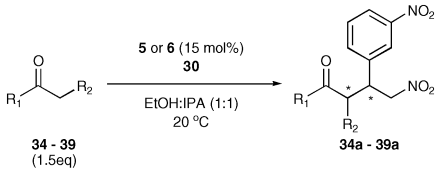
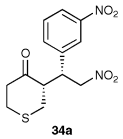
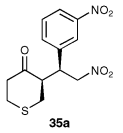
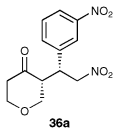
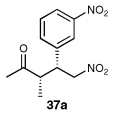
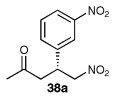
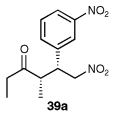
Table 7 Investigation of ketone scope



Entry	Product	Cat.	Time (h)	Yield (%)[a]	Dr (*syn* : *anti*)[b]	Ee (%)[c]
1		L-Pro	24	47	10 : 1	40
2	 **34a**	**5**	24	62	10 : 1	70
3	 **35a**	**6**	24	67	10 : 1	73
4	 **36a**	**5**	24	94	6 : 1	54
5	 **37a**	**5**	24	71	10 : 1	32
6	 **38a**	**5**	48	72	—	33
7	 **39a**	**5**	72	68	>19 : 1	65

[a] Based on isolated product. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC (Daicel Chiralpak AD-H column).

providing excellent enantioselectivity and practical reaction times (Table 8). Alcoholic solvents were observed to give reduced enantioselectivities, consistent with the interruption of a hydrogen bonded transition state (Fig. 1) and also promoted the elimination of the product. Aprotic solvents gave comparably high enantioselectivities, although dichloromethane was shown to give the highest selectivity and reaction rate of the apolar solvents studied, with the sulfonamide catalysts observed to have even greater solubility than the tetrazole catalyst **5**. The excellent enantioselectivity observed in DMSO shows that it is indeed the sulfonamide catalyst that is superior to proline in this asymmetric aldol reaction, not just in solubility, but also in enantioselectivity, (87% with catalyst **9** compared to 76% with L-proline).

A range of ketones were then explored and the results summarised in Table 8. Excellent enantioselectivities were observed for straight chain and cyclic ketones, although the diastereomeric ratios observed with cyclic ketones remain an unsolved problem. Noteworthy examples include that of **19b** with an observed enantioselectivity of 77% compared to that of L-proline 59% and **11b** where an enantioselectivities of 90% and 68% (entries 17 and 28) are observed for the *anti* and *syn* products respectively with catalyst **10**, compared with 63% and 36% for L-proline. Excellent yields and enantioselectivities were also produced for the *syn* and *anti* aldol products from the reaction of cyclobutanone **20** (entries 13 and 14). Only cyclopentanone **42** proved a disappointing substrate in this reaction, providing moderate enantioselectivities.

A possible rationale of these marked increases in enantioselectivity through a hydrogen bonded Houk transition state (Fig. 1) is through the increased pK_a of the sulfonamide proton giving a stronger hydrogen bond to the carbonyl moiety and subsequently a more tightly bound transition state, leading to greater selectivity. It is hard to envisage a steric argument for the differences between proline and the sulfonamide catalysts **9** and **10**, as well as between the sulfonamide catalysts themselves, as the relevant groups are too distant from the point of chiral induction. The differences between the sulfonamide catalysts **9** and **10** can also be rationalised by the opposing electron donating and withdrawing nature of the methyl and phenyl substituents, consistent with **10** having the lowest pK_a and giving predominantly the best enantioselectivities.

The effect of changing DMSO for methylene chloride could also be a factor in the strength of hydrogen bonding in the transition state (supported by the difference in enantioselectivity shown for example **18a**, Table 8) as DMSO is likely to alter the pK_a of the sulfonamidic proton, effecting the enantioselectivity as previously discussed.

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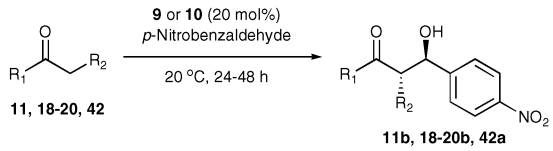
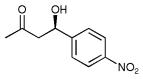
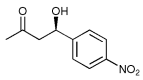
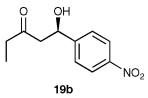
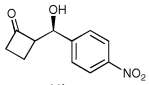
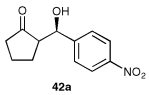
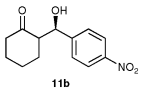
Table 8 Scope of the asymmetric aldol reaction using sulfonamide organocatalysts



Entry	Product	Cat.	Solvent	Yield (%)[a] *syn* (*anti*)	Ee (%)[c] *syn* (*anti*)
1	 18b	**9**	DMSO	52	87
2		**9**	CH_2Cl_2	78	79
3		**9**	MeOH	49	49
4		**9**	$CHCl_3$	67	78
5		**9**	IPA–EtOH	57	44
6	 18b	**10**	CH_2Cl_2	49	84
7		**10**	MeOH	42	61
8		**10**	$CHCl_3$	62	65
9		**10**	IPA–EtOH	39	75
10		**10**	Acetone	100	92
11	 19b	**9**	CH_2Cl_2	42[c]	76
12		**10**	CH_2Cl_2	48[c]	77
13	 20b	**9**	CH_2Cl_2	24 (46)	78 (84)
14		**10**	CH_2Cl_2	21 (43)	86 (94)
15	 42a	**9**	CH_2Cl_2	30 (55)	41 (36)
16		**10**	CH_2Cl_2	30 (54)	33 (23)
17	 11b	**9**	CH_2Cl_2	29 (51)	74 (78)
18		**10**	CH_2Cl_2	35 (53)	63 (90)

[a] Based on isolated product. [b] Determined by chiral HPLC. [c] Reaction stirred for 7 days.

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Conclusions

New tetrazole and sulfonamide derivatised proline catalysts have been shown to give good to excellent yields and enantioselectivities in a range of important transformations. In all cases studied these new catalysts gave superior or equivalent results in terms of enantioselectivity, catalyst loading, solvent tolerance and reaction times, when compared with proline itself.

We are currently investigating rational design of new catalysts for enamine derived reactions and the application to combinatorial and multi-step synthesis, the results of which will be published in due course.

Experimental

All reactions were carried out in freshly distilled solvent under an atmosphere of Argon unless otherwise stated. Dichloromethane, toluene, methanol and tetrahydrofuran were distilled from calcium hydride. All other solvents were anhydrous grade and used as received. All other reagents were used as received. Flash column chromatography was carried out 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, or aqueous acidic potassium permanganate solutions as appropriate. Melting points were performed on a Reichert hot-stage apparatus, and are uncorrected. Optical rotations were recorded 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 and accurate mass data were obtained on a Micromass Platform LC-MS, Kratos MS890MS, Kratos Concept IH, Micromass Q-TOF, or Bruker BIOAPEX 4.7 T FTICR spectrometer, by electron ionisation, chemical ionisation or fast atom/ion bombardment techniques at the Department of Chemistry, Lensfield Road, Cambridge. ^{1}H NMR spectra were recorded at ambient temperature on Bruker DPX-400, Bruker DRX-500 or Bruker DRX-600 spectrometers at 400, 500 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 temperatures on the same spectrometers at 100, 125 or 150 MHz, with the central peak of $CHCl_3$ as the internal reference ($\delta_C = 77.0$ ppm). Where rotamers are apparent, peaks for major and minor rotamers are reported, when resolved. DEPT135 and two dimensional (COSY, HMQC, HMBC) NMR spectroscopy were used where appropriate, to aid the assignment 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 isomer has 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. Evaporation refers to the removal of solvent under reduced pressure.

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(2*S*)-2-Carbamoyl-pyrrolidine-1-carboxylic acid benzyl ester[21] 2

To a solution of *Z*-L-proline (4.00 g, 16.1 mmol, 1 eq.) in THF (80 mL) were added 1-hydroxybenzotriazole (3.26 g, 24.1 mmol, 1.5 eq.) and EDCI (3.08 g, 16.1 mmol, 1 eq.). The resulting mixture was stirred at room temperature for 30 min whereupon aqueous ammonia (11 mL) was added slowly by syringe. The resulting mixture was allowed to stir for 24 h. After this time, saturated aqueous ammonium chloride (100 mL) was added and the aqueous phase extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give a pale yellow oil, which was purified by flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 4) to give the *title compound* as a clear colourless oil (3.98 g, 100%). $[\alpha]_D = -82.8°$ ($c = 0.50$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.28$ (5H, m, Ar*H*), 6.71 (1H, s, N*H*H′), 5.80 (1H, s, NH*H*′), 5.19 (1H, d, $J = 12$ Hz, ArC*H*H′), 5.15 (1H, d, $J = 12$ Hz, ArCH*H*′), 4.39 (1H, m, NC*H*C(O)), 3.59–3.45 (2H, m, NCH_2), 2.40–1.90 (4H, m, CH_2CH_2).

(2*S*)-2-Cyano-pyrrolidine-1-carboxylic acid benzyl ester[12] 3

To a solution of (2*S*)-2-carbamoyl-pyrrolidine-1-carboxylic acid benzyl ester **2** (3.98 g, 16.1 mmol, 1 eq.) in dichloromethane (40 mL) at room temperature was added pyridine (6.49 mL, 80.2 mmol, 5 eq.) followed by neat tosyl chloride (6.13 g, 32.1 mmol, 2 eq.). The resulting mixture was allowed to stir for 72 h after which time, saturated aqueous ammonium chloride (30 mL) was added. The aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a yellow oil which was purified by flash column chromatography (EtOAc–petroleum ether 40/60, 7 : 3) to give the *title compound* as a pale yellow oil (2.80 g, 75%). $[\alpha]_D = -89.0°$ ($c = 1.00$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.42$–7.31 (5H, m, Ar*H*), 5.22–5.14 (2H, m, $ArCH_2$), 4.61–4.54 (1H, dd, $J = 26.4$, 5.5 Hz, NC*H*CO), 3.60–3.57 (1H, m, NC*H*H′), 3.46–3.39 (1H, m, NCH*H*′), 2.39–2.04 (4H, m, CH_2CH_2).

(2*S*)-2-(1*H*-Tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester[12] 4

To a solution of (2*S*)-2-cyano-pyrrolidine-1-carboxylic acid benzyl ester **3** (1.50 g, 6.52 mmol, 1 eq.) in DMF (15 mL) were added sodium azide (440 mg, 6.78 mmol, 1.04 eq.) and ammonium chloride (380 mg, 7.17 mmol, 1.1 eq.). The resulting mixture was heated to 90 °C for 8 h. After this time, the reaction was allowed to cool to room temperature and acidified to pH 2 with 1 M aqueous HCl. The aqueous layer was extracted with chloroform (3 × 25 mL) and the combined organic layers were washed with saturated aqueous lithium chloride (50 mL). The organic layer was then dried ($MgSO_4$), filtered and evaporated *in vacuo* to give the *title compound* analytically pure as a clear colourless residue (1.39 g, 78%). $[\alpha]_D = -85.7°$ ($c = 1.18$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.35$ (5H, m, Ar*H*), 7.06 (1H, s, N*H*), 5.40–4.98 (3H, m, $ArCH_2$ and NC*H*CN), 3.66–3.45 (2H, m, NCH_2), 2.62–1.86 (4H, m, CH_2CH_2).

(2*S*)-5-Pyrrolidin-2-yl-1*H*-tetrazole[12] 5

(2*S*)-2-(1*H*-Tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester **4** (1.40 g, 5.08 mmol, 1 eq.) and 10% Pd/C (279 mg) in acetic acid–water (9 : 1, 75 mL) were stirred under an atmosphere of hydrogen at room temperature for 4 h. After this time the mixture was filtered through Celite® and the filtrate evaporated *in vacuo*. The residue was azeotroped using toluene to aid removal of acetic acid. The resulting solid was recrystallised with a mixture of toluene and methanol to give the *title compound* as an off-white solid (590 mg, 89%). $[\alpha]_D = +1.2°$ ($c = 0.5$, H_2O). ^{1}H NMR (400 MHz, CD_3COOD) $\delta = 4.95$ (1H, t, $J = 8.1$ Hz, NHC*H*CN), 3.45 (2H, m, $NHCH_2$), 2.60–2.16 (4H, m, CH_2CH_2).

(2*R*)-2-Carbamoyl-pyrrolidine-1-carboxylic acid benzyl ester[23]

Synthesised in the same way as described above for **2** from *Z*-D-proline (8.00 g, 32.1 mmol). Purified by flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 4) to give the *title compound* as a white solid (5.43 g, 68%). Mp = 289–291 °C, $[\alpha]_D = -82.8°$ ($c = 0.50$, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 7.34$ (5H, m, Ar*H*), 6.70 (1H, s, N*H*, major rot), 6.04 (1H, broad, s, N*H*, minor rot), 5.87 (1H, broad, s, N*H*, minor rot) 5.80 (1H, broad, s, N*H*, major rot), 5.15 (1H, d, $J = 12.3$ Hz, ArC*H*H′), 5.15 (1H, d, $J = 12.3$ Hz, ArCH*H*′), 4.35 (1H, m, NC*H*C(O)), 3.53–3.44 (2H, m, NCH_2), 2.31–1.89 (4H, m, CH_2CH_2).

(2*R*)-2-Cyano-pyrrolidine-1-carboxylic acid benzyl ester. (ent-3)

Synthesised in the same way as described above for **3** from (2*R*)-2-carbamoyl-pyrrolidine-1-carboxylic acid (5.43 g, 21.8 mmol) to yield the *title compound* as a pale yellow oil (3.22 g, 64%). ν_{max} (film)/cm^{-1} 2959, 2883, 1701, 1405, 1355, 1118, 1091. $[\alpha]_D = +89.2°$ ($c = 0.47$, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 7.42$–7.31 (5H, m, Ar*H*), 5.22–5.14 (2H, m, $ArCH_2$), 4.61–4.54 (1H, m, NC*H*CN), 3.60–3.57 (1H, m, NC*H*H′), 3.46–3.39 (1H, m, NCH*H*′), 2.39–2.04 (4H, m, CH_2CH_2). ^{13}C NMR (150 MHz, $CHCl_3$) (major and minor rotamers) $\delta = 154.3$, 153.6, 136.1, 136.0, 128.5, 128.2, 128.1, 118.9, 118.7, 67.8, 67.6, 47.5, 47.0, 46.3, 45.9, 31.7, 30.8, 30.3, 24.6, 23.7. *m/z* (ES) found 231.1134 ($[MH]^+$ $C_{13}H_{15}N_2O_2$ requires 231.1128).

(2*R*)-2-(1*H*-Tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester. (ent-4)

Synthesised in the same way as described above for **4** from (2*R*)-2-cyano-pyrrolidine-1-carboxylic acid benzyl ester (3.22 g, 14.0 mmol) to yield the *title compound* analytically pure (3.12 g, 82%). ν_{max} (film)/cm^{-1} 2957, 2919, 2851, 1663, 1411, 1355, 1120, 1099, 696. $[\alpha]_D = +89.0°$ ($c = 0.96$, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.35$ (5H, m, Ar*H*), 7.06 (1H, s, N*H*), 5.40–4.98 (3H, m, $ArCH_2$ and NC*H*CN), 3.66–3.45 (2H, m, NCH_2), 2.62–1.86 (4H, m, CH_2CH_2). ^{13}C NMR (100 MHz, $CHCl_3$) $\delta = 156.3$, 135.7, 128.6, 128.3, 127.8, 68.0, 52.6, 51.4, 47.0, 33.0, 24.6. *m/z* (ES) found 274.1304 ($[MH]^+$ $C_{13}H_{16}N_5O_2$ requires 274.1299).

(2*R*)-5-Pyrrolidin-2-yl-1*H*-tetrazole 6

Synthesised in the same way as described above for **5** from (2*R*)-2-(1*H*-tetrazol-5-yl)-pyrrolidine-1-carboxylic acid benzyl ester (3.12 g, 11.4 mmol) to yield the *title compound* as an off white solid (1.37 g, 84%). Mp = 272–274 °C. ν_{max} (film)/cm^{-1} 2940, 2580, 2460, 1627, 1456, 1420, 1396, 1046, 1012, 954. $[\alpha]_D = -0.8°$ ($c = 1.00$, H_2O). ^{1}H NMR (400 MHz, CD_3COOD) $\delta = 4.95$ (1H, t, $J = 8.1$ Hz, NHC*H*), 3.45 (2H, m, $NHCH_2$), 2.60–2.16 (4H, m, CH_2CH_2). ^{13}C NMR (100 MHz, CD_3COOD) $\delta = 156.5$, 54.7, 46.6, 30.3, 23.6. *m/z* (EI) found 139.0856 ($[M]^+$ $C_5H_9N_5$ requires 139.0858).

(2*S*)-2-Methanesulfonylaminocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester 7

To a stirred solution of *Z*-L-proline (5.00 g, 20.1 mmol, 1 eq.) in dichloromethane (150 mL) were added methanesulfonamide (2.10 g, 22.1 mmol, 1.1 eq.), DMAP (380 mg, 3.11 mmol, 0.15 eq.) and EDCI (3.85 g, 20.1 mmol, 1 eq.) respectively. The resulting mixture was stirred at room temperature for 2 days. The reaction was concentrated to half the volume *in vacuo* and the resulting mixture was partitioned between EtOAc (250 mL) and 1 M aqueous HCl (100 mL). The organic layer was washed with half-saturated brine (50 mL), dried ($NaSO_4$) and concentrated *in vacuo*. The crude product was purified by flash column chromatography (dichloromethane–EtOAc, 7 : 3) to give the *title compound* as a clear colourless residue (3.92 g, 60%). The crude product may be used directly in the next step.

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ν_{max} (film)/cm^{-1} 3207, 2963, 1674, 1416, 1336, 1121, 969, 697. $[a]_D = -86.4°$ ($c = 2.10$, $CHCl_3$). ^{1}H NMR (500 MHz $CDCl_3$, major rotamer) $\delta = 10.1$ (1H, broad, s, N*H*), 7.36 (5H, m, Ar*H*), 5.21 (1H, d, $J = 12.2$ Hz, C*H*H′Ar), 5.15 (1H, d, $J = 12.2$ Hz, CH*H*′Ar), 4.36 (1H, m, NHC*H*), 3.46 (2H, m, NHCH_2), 3.25 (3H, s, CH_3), 2.46 (1H, s, CHC*H*H′), 1.94 (3H, m, CH_2CHH′). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 170.2$, 157.2, 135.7, 128.6, 128.5, 128.2, 68.2, 61.1, 47.3, 41.3, 26.9, 24.5. *m/z* (ES) found 327.1018 ([MH]$^+$ $C_{14}H_{19}N_2O_5S$ requires 327.1015).

(2*S*)-2-Benzenesulfonylaminocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester 8

To a stirred solution of *Z*-L-proline (5.00 g, 20.1 mmol, 1 eq.) in dichloromethane (150 mL) were added benzenesulfonamide (3.16 g, 20.1 mmol, 1 eq.), DMAP (400 mg, 3.28 mmol, 0.16 eq.) and EDCI (3.85 g, 20.1 mmol, 1 eq.) respectively. The resulting mixture was stirred at room temperature for 2 days before being partitioned between EtOAc (250 mL) and 1 M aqueous HCl (100 mL). The organic layer was washed with half-saturated brine, dried ($NaSO_4$) and concentrated *in vacuo*. The residue was treated with dichloromethane and the resulting white solid was filtered-off. Following evaporation *in vacuo* the crude product was purified by flash column chromatography (dichloromethane–EtOAc 7 : 3) to give the *title compound* as an off white solid (4.92 g, 63%). The crude product may be used directly in the next step. Mp = 196–197 °C, ν_{max} (film)/cm^{-1} 3063, 2955, 2882, 1673, 1448, 1416 1351, 1185, 1174, 1123, 1084, 686. $[a]_D = -87.5°$ ($c = 0.24$, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, major rotamer) $\delta = 10.5$ (1H, broad, s, N*H*), 8.06 (2H, d, $J = 7.4$ Hz, SO_2Ar*H*), 7.65 (1H, t, $J = 7.4$ Hz, SO_2Ar*H*), 7.54 (2H, t, $J = 7.4$ Hz, SO_2Ar*H*), 7.42 (5H, m, CH_2Ar*H*), 5.24 (2H, s, CH_2Ar), 4.32 (1H, d, $J = 6.8$ Hz, NC*H*), 3.42 (2H, m, NCH_2), 2.45 (1H, d, $J = 8.2$ Hz, CH_2CH_2C*H*H′), 1.90 (3H, m, CH_2CH_2CHH′). ^{13}C NMR (125 MHz, $CDCl_3$) $\delta = 168.7$, 157.5, 138.7, 135.8, 133.8, 128.9, 128.7, 128.5, 128.4, 128.3, 68.3, 60.8, 47.2, 26.8, 24.4. *m/z* (ES) found 389.1171 ([MH]$^+$ $C_{19}H_{21}N_2O_5S$ requires 389.1171).

(2*S*)-*N*-(2-Pyrrolidine-2-carbonyl)-methanesulfonamide 9

To a solution of (*S*)-2-methanesulfonylaminocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester **7** (1.00 g, 3.06 mmol, 1 eq.) in MeOH (100 mL) was added 10% Pd/C (180 mg). The mixture was stirred at room temperature for 20 hours under an atmosphere of hydrogen. The reaction was filtered through Celite® and 1 cm of silica gel and the filtrate concentrated *in vacuo*. The crude product was purified by flash column chromatography (dichloromethane–MeOH, 8 : 2) to give the *title compound* as a white solid (576 mg, 98%). Mp 214–216 °C; ν_{max} (film)/cm^{-1} 3096, 1575, 1253, 1109, 834. $[a]_D = -42.6°$ ($c = 1.03$, DMSO). ^{1}H NMR (500 MHz, DMSO) $\delta = 8.55$ (2H, broad, s, CH_2N*H*, SO_2N*H*), 3.82 (1H, dd, $J = 7.0$, 8.3 Hz, C*H*C(O)), 3.21 (1H, m, NHC*H*H′), 3.06 (1H, m, NHCH*H*′), 2.79 (3H, s, CH_3), 2.12–1.74 (4H, m, CH_2CH$_2$). ^{13}C NMR (125 MHz, DMSO) $\delta = 23.5$, 29.3, 40.2, 45.4, 62.0, 172.0. *m/z* (ES) found 193.0643 ([MH]$^+$ $C_6H_{13}N_2O_3S$ requires 193.0647).

(2*S*)-*N*-(2-Pyrrolidine-2-carbonyl)-benzenesulfonamide 10

To a solution of (*S*)-2-benzenesulfonylaminocarbonyl-pyrrolidine-1-carboxylic acid benzyl ester **8** (5.85 g, 15.0 mmol) in MeOH (300 mL) was added 10% Pd/C (900 mg). The mixture was stirred at room temperature for 20 h under an atmosphere of hydrogen. The reaction was filtered through Celite® and 1 cm of silica gel, and the filtrate was concentrated *in vacuo* to give a white solid. The crude product was purified by flash column chromatography (dichloromethane–MeOH 8 : 2) to give the *title compound* as a white solid (2.01 g, 91%). Mp 237–239 °C; $[a]_D = -21.1°$ ($c = 1.00$, DMSO). ν_{max} (film)/cm^{-1} 3066, 1623, 1576, 1256, 1130, 1083, 831, 690. ^{1}H NMR (500 MHz, DMSO) $\delta = 8.51$ (2H, broad, s, N*H*), 7.78 (2H, dd, $J = 10.4$, 2.7 Hz, Ar*H*), 7.41 (3H, m, Ar*H*), 3.82 (1H, dd, $J = 6.8$, 8.3 Hz, C*H*C(O)), 3.14 (1H, m, NHC*H*H′), 3.03 (1H, m, NHCH*H*′), 2.10–1.67 (4H, m, CH_2CH$_2$). ^{13}C NMR (125 MHz, DMSO) $\delta = 23.4$, 29.1, 45.3, 62.0, 126.9, 127.8, 130.3, 145.3, 171.4. *m/z* (ES) found 255.0815 ([MH]$^+$ $C_{11}H_{15}N_2O_3S$ requires 255.0803).

N-*p*-Methoxybenzyl-α-iminoglyoxalate[14] 12

Methyl glyoxalate (8.14 mL, 50% sol in toluene, 40 mmol) was dissolved in dichloromethane (150 mL) and a solution of *p*-anisidine (4.92 g, 40 mmol) in dichloromethane (50 mL) was added slowly. The reaction mixture was stirred at room temperature for 30 min and pre-activated 4 Å molecular sieves were added. After stirring for an additional 1 h, the mixture was filtered and the filtrate evaporated *in vacuo* to give the *title compound*, analytically pure, as a yellow oil (8.20 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.95$ (1H, s, *H*C(N)), 7.38 (2H, d, $J = 8.8$ Hz, Ar*H*), 6.92 (2H, d, $J = 8.8$ Hz, Ar*H*), 4.42 (2H, q, $J = 6.9$ Hz, CH_2CH$_3$), 3.84 (3H, s, OCH_3), 1.41 (3H, t, $J = 6.9$ Hz, CH$_2$CH_3).

General procedure for the addition of a carbonyl-containing compound to *N*-*p*-methoxybenzyl-α-iminoglyoxalate 12

N-*p*-Methoxybenzyl-α-iminoglyoxalate **12** (93.5 mg, 0.5 mmol) was dissolved in dichloromethane (4 mL). Carbonyl-containing compound (1 mL, 20 vol%) was added to this solution followed by 5-pyrrolidin-2-(*S*)-yl-1*H*-tetrazole **5** (3.5 mg, 5 mol%) or *N*-((*S*)-pyrrolidine-2-carbonyl)-benzenesulfonamide (25.5 mg, 20 mol%) and the resulting mixture stirred for 2–24 h. After this time, the mixture was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (2 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a residue, which was purified by flash column chromatography using varying mixtures of ethyl acetate and petroleum ether 40/60 as eluent.

(2*S*,1′*S*)-Ethyl-2-(*p*-methoxyphenylamino)-2-(2′-oxocyclohex-1′-yl)-acetate[15] 11a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 3) to give the *title compound* as a yellow oil (99.1 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta =$ **6.72** (2H, d, $J = 8.8$ Hz, Ar*H*), **6.72** (2H, d, $J = 8.8$ Hz, Ar*H*), 4.25 (1H, d, $J = 5.3$ Hz, C*H*NH), 4.12 (2H, q, $J = 6.9$ Hz, OCH_2CH$_3$), 3.73 (3H, s, OCH_3), 2.81 (1H, m, C*H*CHNH), 2.48–1.64 (8H, m, chex-H), 1.21 (3H, t, $J = 6.9$ Hz, CH$_2$CH_3). HPLC: Daicel Chiralpak AS. Hexane–*i*-PrOH, 94 : 6, 0.7 mL min^{-1}, 254 nm: tR (major) = 22 min; tR (minor) = 27 min.

(2*S*,3*S*)-Ethyl-2-(*p*-methoxyphenylamino)-3-methyl-4-oxo-hexanoate[15] 17a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 3) to give the *title compound* as a yellow oil (91.7 mg, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 6.70$ (2H, d, $J = 8.8$ Hz, Ar*H*), 6.58 (2H, d, $J = 8.8$ Hz, Ar*H*), 4.20 (1H, m, CHC*H*N), 4.08 (2H, q, $J = 6.9$ Hz, OCH_2CH$_3$), 3.69 (3H, s, OCH_3), 2.95 (1H, m, C*H*CHN), 2.44 (2H, m, C(O)CH_2), 1.18 (6H, m, C(O)CH$_2$CH_3 and CHCH_3), 0.98 (3H, t, $J = 6.9$ Hz, OCH$_2$CH_3). HPLC: Daicel Chiralpak AS. Hexane–*i*-PrOH, 96 : 4, 0.7 mL min^{-1}, 254 nm: tR (major) = 42 min; tR (minor) = 34 min.

(2*S*)-Ethyl-2-(*p*-methoxyphenylamino)-4-oxo-pentanoate[15]18a. To a solution of *N*-*p*-methoxybenzyl-α-iminoglyoxalate **12** (93.5 mg, 0.5 mmol) in acetone (4 mL) was added (2*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole **5** (3.45 mg, 5 mol%) or (2*S*)-*N*-(-pyrrolidine-2-carbonyl)-benzenesulfonamide **10** (25.5 mg, 20 mol%) and the resulting mixture was stirred for 8 h. After this time, the mixture was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (2 × 25 mL). The combined organic layers were dried over

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$MgSO_4$, filtered and evaporated *in vacuo*. Purification using flash column chromatography (EtOAc–petroleum ether 40/60, 7 : 13) gave the *title compound* as a yellow oil (133 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.78 (2H, d, J = 8.8 Hz, Ar*H*), 6.65 (2H, d, J = 8.8 Hz, Ar*H*), 4.19–4.09 (3H, m, C*H*NH and CH_2CH_3), 3.73 (3H, s, OCH_3), 2.97 (2H, m, CH_2CH), 2.19 (3H, s, $CH_3C(O)$), 1.25 (3H, m, CH_2CH_3). HPLC: Daicel Chiralcel AS. Hexane–*i*-PrOH, 99 : 1, 1 mL min^{-1}, 254 nm: tR (major) = 26 min; tR (minor) = 21 min.

(2*S*,3*S*)-Ethyl-2-(*p*-methoxyphenylamino)-3-methyl-4-oxo-pentanoate[15] 19a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 2) to give the *title compound* as a yellow oil (107 mg, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.77 (2H, d, J = 8.9 Hz, ArH), 6.64 (2H, d, J = 8.9 Hz, Ar*H*), 4.30 (1H, s, C*H*NH), 4.16 (2H, dq, J = 1.9, 7.1 Hz, CH_2CH_3), 3.85 (1H, s, N*H*), 3.74 (3H, s, OCH_3), 3.03 (1H, m, C*H*CHNH), 2.23 (3H, s, $CH_3C(O)$), 1.25 (6H, m, $CHCH_3$, CH_2CH_3). HPLC: Daicel Chiralpak AS. Hexane–*i*-PrOH, 96 : 4, 0.5 mL min^{-1}, 254 nm: tR (major) = 44 min; tR (minor) = 64 min.

(2*S*,1′*S*)-Ethyl-2-(*p*-methoxyphenylamino)-2-(2′-oxocyclobut-1′-yl)-acetate 20a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 2 : 3) to give the *title compound* as a yellow oil (102 mg, 74%). ν_{max} (film)/cm^{-1} 2961, 1781, 1732, 1513, 1238, 1035. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.70 (2H, d, J = 8.8 Hz, Ar*H*), 6.65 (2H, d, J = 8.8 Hz, Ar*H*), 4.20 (1H, m, C*H*CHNH), 4.13 (3H, m, OCH_2CH_3, CHC*H*NH), 3.75 (3H, s, OCH_3), 3.12–2.85 (2H, m, $CH_2C(O)$), 2.15–1.90 (2H, m, $CH_2CHC(O)$), 1.16 (3H, t, J = 6.9 Hz, CH_2CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) (major and minor rotamers). δ = 208.0, 207.6, 183.1, 178.5, 172.1, 171.6, 153.2, 140.7, 140.6, 131.8, 125.7, 120.2, 116.5, 115.7, 114.9, 114.8, 114.5, 61.6, 61.3, 58.1, 57.5, 55.7, 45.6, 45.5, 14.1, 13.0. *m*/*z* (EI) found 277.1313 ([M]$^+$ $C_{15}H_{19}NO_4$ requires 277.1313). HPLC: Daicel Chiralcel OD. Hexane–*i*-PrOH, 95 : 5, 1 mL min^{-1}, 254 nm: tR (major) = 14 min; tR (minor) = 19 min.

(2*S*,1′*S*)-Ethyl-2-(*p*-methoxyphenylamino)-2-(2′-oxocyclohept-1′-yl)-acetate 21a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 2) to give the *title compound* as a yellow solid (94.0 mg, 59%). Mp 103–105 °C; ν_{max} (film)/cm^{-1} 3367, 2931, 2855, 1728, 1698, 1510, 1455, 1237, 1183, 1034, 820. $[\alpha]_D$ = −85.4° (c = 0.26, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.68 (2H, d, J = 8.8 Hz, Ar*H*), 6.57 (2H, d, J = 8.8 Hz, Ar*H*), 4.21 (1H, m, C*H*NH), 4.07 (2H, m, OCH_2CH_3), 3.66 (3H, s, OCH_3), 2.82 (1H, m, C*H*CHNH), 2.55–1.15 (10H, m, chept-*H*), 1.12 (3H, t, J = 6.9 Hz, CH_2CH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 214.3, 173.1, 153.1, 140.1, 116.0, 114.8, 61.2, 60.6, 55.7, 55.2, 43.8, 29.8, 29.2, 27.2, 24.2, 14.1. *m*/*z* (ES) found 319.1783 ([MH]$^+$ $C_{18}H_{25}NO_4$ requires 319.1705). HPLC: Daicel Chiralpak AS. Hexane–*i*-PrOH, 94:6, 0.7 mL min^{-1}, 254 nm: tR (major) = 18 min; tR (minor) = 24 min.

(2*S*)-Ethyl-5-fluoro-2-(*p*-methoxy-phenylamino)-4-oxopentanoate[9] 22a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 2 : 3) to give the *title compound* as a yellow oil (43.8 mg, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.72 (2H, d, J = 8.8 Hz, Ar*H*), 6.60 (2H, d, J = 8.8 Hz, Ar*H*), 4.75 (2H, d, J = 50 Hz, CH_2F), 4.37 (1H, t, J = 5.7 Hz, C*H*N), 4.13 (2H, q, J = 6.9 Hz, OCH_2CH_3), 3.69 (3H, s, OCH_3), 3.01 (2H, m, CH_2CHN), 1.19 (3H, t, J = 6.9 Hz, CH_2CH_3). HPLC: Daicel Chiralpak AS. Hexane–*i*-PrOH, 85 : 15, 1 mL min^{-1}, 254 nm: tR (major) = 16 min; tR (minor) = 22 min.

(2*S*,3*S*)-Ethyl-3-formyl-2-(*p*-methoxy-phenylamino)-4-methyl-pentanoate[4] 23a. Purified using flash column chromatography (EtOAc–petroleum ether 40–60, 2 : 3) to give the *title compound* as a yellow oil (110 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.78 (1H, d, J = 3.0 Hz, C*H*(O)), 6.77 (2H, d, J = 9.2 Hz, Ar*H*), 6.66 (2H, d, J = 9.2 Hz, Ar*H*), 4.31 (1H, m, C*H*NH), 4.16 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.82 (1H, broad, s, CHN*H*), 3.74 (3H, s, OCH_3), 2.55 (1H, m, C*H*CHNH), 2.31 (1H, m, $CH(CH_3)_2$), 1.22 (3H, t, J = 7.1, OCH_2CH_3) 1.16 (3H, d, J = 6.9 Hz, $CH(CH_3)(CH_3)$), 1.03 (3H, d, J = 6.9, $CH(CH_3)(CH_3)$).

(3*S*,4*S*)-4-Isopropyl-3-(*p*-methoxy-phenylamino)-dihydro-furan-2-one. A solution of crude 3-formyl-2-(4-methoxy-phenylamino)-4-pentanoic acid ethyl ester **23a** in EtOH (2 ml) was added to a suspension of $NaBH_4$ (14.1 mg, 0.37 mmol, 0.75 eq.) in EtOH (1 mL) at 0 °C. The reaction was stirred at 0 °C for 1 h and quenched with saturated aqueous ammonium chloride (5 mL). The aqueous phase was extracted with ethyl acetate (2 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo* and the resulting residue was purified by flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 4) to yield the *title compound* as a yellow oil (52.1 mg, 42% *over 2 steps*). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.84 (2H, d, J = 8.8 Hz, Ar*H*), 6.68 (2H, d, J = 8.8 Hz, Ar*H*), 4.40 (2H, CH_2O), 4.10 (1H, m, C*H*NH), 4.05 (1H, m, N*H*), 3.79 (3H, s, OCH_3), 2.79 (1H, m, C*H*CHN), 2.00 (1H, m, $CH(CH_3)_2$), 1.02 (3H, d, J = 6.9 Hz, $CH(CH_3)(CH_3)$), 0.88 (3H, d, J = 6.9 Hz, $CH(CH_3)(CH_3)$). HPLC: Daicel Chiralpak AS. Hexane–*i*-PrOH, 94 : 6, 0.7 mL min^{-1}, 254 nm: tR (major) = 57 min; tR (minor) = 43 min.

General procedure for the conjugate addition of a ketone to a nitro-olefin

To a suspension of 5-pyrrolidin-2-yl-1*H*-tetrazole **5** or **6** (10.5 mg, 15 mol%) and nitro-olefin (0.5 mmol) in isopropanol–ethanol (1 : 1, 4 mL) was added the relevant ketone (0.75 mmol). The resulting mixture was allowed to stir at room temperature for 24 h, whereupon the reaction was quenched with saturated aqueous ammonium chloride (25 mL) and the aqueous layer extracted with ethyl acetate (2 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated *in vacuo* to give an oil which was purified by flash column chromatography using varying amounts of ethyl acetate and petroleum ether 40/60 as eluent.

(2*S*,1′*R*)-2-[1′-Phenyl-2′-nitro-ethyl]-cyclohexanone[24] 27a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 3 : 7) to give the *title compound* as a white solid (119 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.24 (3H, m, Ar*H*), 7.16 (2H, d, J = 7.0 Hz, Ar*H*), 4.93 (1H, dd, J = 12.5, 4.5 Hz, C*H*H′NO$_2$), 4.60 (1H, dd, J = 12.5, 9.9 Hz, CH*H*′NO$_2$), 3.76 (1H, m, C*H*Ar), 2.69 (1H, m, C*H*C(O)), 2.50–2.35 (2H, m, chex-*H*), 2.07 (1H, m, chex-*H*), 1.81–1.52 (4H, m, chex-*H*), 1.24 (1H, m, chex-*H*). HPLC: Daicel Chiralpak AS. Hexane–*i*-PrOH, 80 : 20, 1 mL min^{-1}, 230 nm: tR (major) = 23 min; tR (minor) = 17 min.

Crystal data:† compound 27a. $C_{14}H_{17}NO_3$, M = 247.29, orthorhombic, space group $P2_12_12_1$, a = 5.5369(4), b = 8.5297(8), c = 27.769(3) Å, V = 1311.5(2) Å^3, Z = 4, D_{calc} = 1.252 Mg m^{-3}, $F(000)$ = 528, μ(Mo–Kα) = 0.088 mm^{-1}, T = 180(2) K, 4884 total reflections measured, 1661 independent reflections measured on a Nonius Kappa CCD diffractometer (R_{int} = 0.0685) using Mo–Kα radiation (λ = 0.71073 Å). Refinement using SHELXL-97. Final residues were $R1$ = 0.0649, $\omega R2$ = 0.1626 (for reflections with $I > 2\sigma(I)$), $R1$ = 0.0855, $\omega R2$ = 0.1726 for all reflections.

(2*S*,1′*R*)-2-[1′-(*p*-Methoxy-phenyl)-2′-nitro-ethyl]-cyclohexanone[25] 28a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 3 : 7) to give the *title compound* as a white solid (99.0 mg, 83%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.25 (1H, t, J = 7.4 Hz, Ar*H*), 7.15 (2H, d, J = 7.4 Hz, Ar*H*), 4.90 (1H, dd, J = 12.6, 4.5 Hz, C*H*H′NO$_2$), 4.60 (1H, dd, J = 12.4, 9.9 Hz, CH*H*′NO$_2$), 3.78 (3H, s, OCH_3), 3.71

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(1H, m, C*H*Ar), 2.65 (1H, m, C*H*CO), 2.48 (1H, m, chex-*H*), 2.32 (2H, m, chex-*H*), 2.09 (1H, m, chex-*H*), 1.70 (4H, m, chex-*H*), 1.21 (1H, m, chex-*H*). HPLC: Daicel Chiralpak AD-H. Hexane–*i*-PrOH, 95 : 5, 1 mL min^{-1}, 230 nm: tR (major) = 25 min; tR (minor) = 19 min.

(2*S*,1′*R*)-2-[2′-Nitro-1′-(*o*-furanyl)-ethyl]-cyclohexanone[26] 29a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 3 : 17) to give the *title compound* as a yellow solid (69.9 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 (1H, d, J = 1.1 Hz, Ar*H*), 6.28 (1H, dd, J = 2.8, 1.1 Hz, Ar*H*), 6.17 (1H, d, J = 2.8 Hz, Ar*H*), 4.78 (1H, dd, J = 12.5, 4.8 Hz, C*H*H′NO$_2$), 4.67 (1H, dd, J = 12.5, 9.3 Hz, CH*H*′NO$_2$), 3.99 (1H, m, C*H*Ar), 2.77 (1H, m, C*H*C(O)), 2.51–2.35 (2H, m, chex-*H*), 2.15 (1H, m, chex-*H*), 1.95–1.62 (4H, m, chex-*H*), 1.35 (1H, m, chex-*H*). HPLC: Daicel Chiralpak AD-H. Hexane–*i*-PrOH, 95 : 5, 0.5 mL min^{-1}, 230 nm: tR (major) = 25 min; tR (minor) = 32 min.

(2*S*,1′*R*)-2-[2′-Nitro-1′-(*m*-nitro-phenyl)-ethyl]-cyclohexanone[24] 30a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 3) to give the *title compound* as a yellow solid (135 mg, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.12 (1H, d, J = 7.9 Hz, Ar*H*), 8.07 (1H, s, Ar*H*), 7.55 (1H, d, J = 7.7 Hz, Ar*H*), 7.50 (1H, m, Ar*H*), 4.99 (1H, dd, J = 13.1, 4.4 Hz, C*H*H′NO$_2$), 4.71 (1H, dd, J = 13.1, 10.2 Hz, CH*H*′NO$_2$), 3.92 (1H, m, C*H*Ar), 2.74 (1H, m, C*H*C(O)), 2.46 (1H, m, chex-*H*), 2.40 (1H, m, chex-*H*), 2.09 (1H, m, chex-*H*), 1.80 (1H, m, chex-*H*), 1.76–1.55 (3H, m, chex-*H*), 1.24 (1H, m, chex-*H*). HPLC: Daicel Chiralpak AD. Hexane–*i*-PrOH, 95 : 5, 0.5 mL min^{-1}, 230 nm: tR (major) = 99 min; tR (minor) = 82 min.

(2*S*,1′*R*)-2-[2′-Nitro-1′-(*o*-thiophenyl)-ethyl]-cyclohexanone[27] 31a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 3 : 17) to yield the *title compound* as a white solid (94.0 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.21 (1H, d, J = 4.9 Hz, Ar*H*), 6.93 (1H, dd, J = 5.1, 3.6 Hz, Ar*H*), 6.87 (1H, d, J = 3.0 Hz, Ar*H*), 4.89 (1H, dd, J = 12.6, 4.8 Hz, C*H*H′NO$_2$), 4.67 (1H, dd, J = 12.6, 9.3 Hz, CH*H*′NO$_2$), 4.15 (1H, m, C*H*Ar), 2.71 (1H, m, C*H*C(O)), 2.58–2.35 (2H, m, chex-*H*), 2.12 (1H, m, chex-*H*), 1.97–1.82 (2H, m, chex-*H*), 1.76–1.55 (2H, m, chex-*H*), 1.35 (1H, m, chex-*H*). HPLC: Daicel Chiralpak AD. Hexane–*i*-PrOH, 95 : 5, 1 mL min^{-1}, 230 nm: tR (major) = 20 min; tR (minor) = 23 min.

(2*S*,1′*R*)-2-[2′-Nitro-1′-(*p*-trifluoromethylphenyl)-ethyl]-cyclohexanone 32a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 1 : 4) to yield the *title compound* as a white solid (91.4 mg, 58%). Mp = 92–94 °C, ν_{max} (film)/cm^{-1}: 2944, 1707, 1551, 1258, 1216, 1162. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.31–7.15 (4H, dd, J = 19.8, 8.8 Hz, Ar*H*), 4.92 (1H, dd, J = 12.8, 4.8 Hz, C*H*H′NO$_2$), 4.63 (1H, dd, J = 12.4, 9.9 Hz, CH*H*′NO$_2$), 3.82 (1H, m, C*H*Ar), 2.69 (1H, m, C*H*C(O)), 2.46 (1H, m, chex-*H*), 2.38 (1H, m, chex-*H*), 2.09 (1H, m, chex-*H*), 1.83–1.56 (4H, m, chex-*H*), 1.26 (1H, m, chex-*H*). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 211.8, 149.1, 136.9, 130.0, 121.7, 121.7, 78.9, 52.9, 43.7, 43.1, 33.5, 28.8, 25.5. m/z (FAB$^+$) found 354.0924 ([MNa]$^+$ $C_{15}H_{16}NO_4F_3Na$ requires 354.0924). HPLC: Daicel Chiralpak AD. Hexane–*i*-PrOH, 95 : 5, 1 mL min^{-1}, 230 nm: tR (major) = 17 min; tR (minor) = 26 min.

(2*S*,1′*R*)-2-[2′-Nitro-1′-(*o*-pyridinyl)-ethyl]-cyclohexanone 33a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 13 : 7) to yield the *title compound* as a yellow oil (58.5 mg, 47%). ν_{max} (film)/cm^{-1} 2944, 1705, 1548, 1428, 1378, 1130, 716. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.53–8.45 (2H, m, Ar*H*), 7.55 (1H, dt, J = 7.8, 1.8 Hz, Ar*H*), 7.27 (1H, m, Ar*H*), 4.92 (1H, dd, J = 12.8, 4.4 Hz, C*H*H′NO$_2$), 4.69 (1H, dd, J = 12.8, 9.9 Hz, CH*H*′NO$_2$), 3.80 (1H, m, C*H*Ar), 2.72 (1H, m, C*H*C(O)), 2.46 (2H, m, chex-*H*), 2.11 (1H, m, chex-*H*), 1.83–1.43 (4H, m, chex-*H*), 1.25 (1H, m, chex-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 211.4, 150.3, 149.7, 136.0, 134.0, 124.1, 78.5, 52.6, 43.1, 42.0, 33.5, 28.7, 25.5. m/z (ES) found 249.1246 ([MH$^+$] $C_{13}H_{17}N_2O_3$ requires 249.1239. HPLC: Daicel Chiralpak AD. Hexane–*i*-PrOH, 88 : 12, 1 mL min^{-1}, 254 nm: tR (major) = 26 min; tR (minor) = 35 min.

(3*S*,1′*R*)-3-(2′-Nitro-1′-(*m*-nitrophenyl)-ethyl)-tetrahydro-thiopyran-4-one 34a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 3 : 7) to yield the *title compound* as a white solid (96.1 mg, 62%). ν_{max} (film)/cm^{-1} 2925, 1701, 1558, 1525, 1347, 734, 686. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.19 (2H, m, Ar*H*), 7.60 (2H, m, Ar*H*), 4.82 (1H, m, C*H*H′NO$_2$), 4.68 (1H, m, CH*H*′NO$_2$), 4.18 (1H, m, C*H*Ar), 3.10 (1H, m, C*H*CHAr), 2.99 (2H, m, C(O)C*H*$_2$), 2.84 (2H, m, C(O)CH$_2$C*H*$_2$), 2.58 (1H, m, CHC*H*H′S), 2.48 (1H, m, CHCH*H*′S). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 208.4, 148.2, 139.0, 134.6, 130.4, 123.4, 123.0, 77.9, 54.7, 44.6, 43.3, 35.0, 31.5. m/z (EI) found 310.0613 ([M]$^+$ $C_{13}H_{14}N_2O_5S$ requires 310.0623). HPLC: Daicel Chiralpak AD-H. Hexane–*i*-PrOH, 90 : 10, 1 mL min^{-1}, 254 nm: tR (major) = 51 min; tR (minor) = 28 min.

(3*R*,1′*S*)-3-(2′-Nitro-1′-(*m*-nitrophenyl)-ethyl)-tetrahydro-thiopyran-4-one 35a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 3 : 7) to yield the *title compound* as a white solid (104 mg, 67%). ν_{max} (film)/cm^{-1} 2925, 1701, 1558, 1525, 1347, 734, 686. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.19 (2H, m, Ar*H*), 7.60 (2H, m, Ar*H*), 4.82 (1H, m, C*H*H′NO$_2$), 4.68 (1H, m, CH*H*′NO$_2$), 4.18 (1H, m, C*H*Ar), 3.10 (1H, m, C*H*CHAr), 2.99 (2H, m, C(O)C*H*$_2$), 2.84 (2H, m, C(O)CH$_2$C*H*$_2$), 2.58 (1H, m, CHC*H*H′S), 2.48 (1H, m, CHCH*H*′S). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 208.4, 148.2, 139.0, 134.6, 130.4, 123.4, 123.0, 77.9, 54.7, 44.6, 43.3, 35.0, 31.5. m/z (EI) found 310.0613 ([M]$^+$ $C_{13}H_{14}N_2O_5S$ requires 310.0623). HPLC: Daicel Chiralpak AD-H. Hexane–*i*-PrOH, 90 : 10, 1 mL min^{-1}, 254 nm: tR (major) = 29 min; tR (minor) = 51 min.

(3*S*,1′*R*)-3-[2′-Nitro-1′-(*m*-nitrophenyl)-ethyl]-tetrahydro-pyran-4-one 36a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 4 : 6) to yield the *title compound* as a yellow solid (138 mg, 94%). ν_{max} (film)/cm^{-1} 2865, 1706, 1549, 1531, 1344. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.19 (1H, dt, J = 7.2, 1.8 Hz, Ar*H*), 8.11 (1H, s, Ar*H*), 7.57 (2H, m, Ar*H*), 5.01 (1H, dd, J = 13.2, 4.4 Hz, C*H*H′NO$_2$), 4.71 (1H, dd, J = 13.2, 10.3 Hz, CH*H*′NO$_2$), 4.20 (1H, m, C*H*CH$_2$C(O)), 3.98 (1H, m, C*H*Ar), 3.80–3.66 (2H, m, C*H*C(O)C*H*H′CH$_2$), 3.28 (1H, dd, J = 11.4, 9.4 Hz, C(O)CH*H*′CH$_2$), 2.95 (1H, C*H*C(O)), 2.71 (1H, m, C*H*H′C(O)), 2.58 (1H, m, CH*H*′C(O)). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 206.3, 149.0, 138.7, 134.3, 130.32, 123.4, 122.7, 78.0, 71.3, 69.0, 52.8, 43.0, 41.0. m/z (EI) found 294.0861 ([M]$^+$ $C_{13}H_{14}N_2O_6$ requires 294.0861). HPLC: Daicel Chiralpak AD-H. Hexane–*i*-PrOH, 90 : 10, 1 mL min^{-1}, 254 nm: tR (major) = 50 min; tR (minor) = 33 min.

(3*S*,4*R*)-3-Methyl-5-nitro-4-(*m*-nitrophenyl)-pentan-2-one 37a. Purified using flash column chromatography (EtOAc–petroleum ether 40–60, 3 : 7) to yield the *title compound* as a white solid (94.4 mg, 71%). ν_{max} (film)/cm^{-1} 2865, 1706, 1549, 1531, 1344, 689. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.17 (1H, m, Ar*H*), 8.08 (1H, s, Ar*H*), 7.54 (2H, d, J = 5.1 Hz, Ar*H*), 4.70 (2H, m, C*H*$_2$NO$_2$), 3.85 (1H, m, C*H*Ar), 3.03 (1H, m, C*H*C(O)), 2.27 (3H, s, C*H*$_3$C(O)), 1.01 (3H, d, J = 7.2 Hz, C*H*$_3$CH). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 209.7, 148.6, 139.9, 134.5, 130.1, 123.1, 122.8, 77.8, 48.6, 45.4, 29.2, 16.0. m/z (ES) found 267.0975 ([MH]$^+$ $C_{12}H_{15}N_2O_5$ requires 267.0975). HPLC: Daicel Chiralpak AD-H. Hexane–*i*-PrOH, 90 : 10, 1 mL min^{-1}, 254 nm: tR (major) = 16 min; tR (minor) = 13 min.

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(4*R*)-5-Nitro-4-(*m*-nitrophenyl)-pentan-2-one 38a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 4 : 6) to yield the *title compound* as a yellow oil (100 mg, 72%). ν_{max} (film)/cm^{-1} 2980, 1715, 1550, 1526, 1348, 1164. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.13 (1H, d, J = 8.2 Hz, Ar*H*), 8.10 (1H, s, Ar*H*), 7.60 (1H, d, J = 7.7 Hz, Ar*H*), 7.52 (1H, t, J = 8.0 Hz, Ar*H*), 4.76 (1H, dd, J = 12.9, 6.3 Hz, C*H*H′NO$_2$), 4.65 (1H, dd, J = 12.9, 8.3 Hz, CH*H*′NO$_2$), 4.15 (1H, m, C*H*Ar), 2.98 (2H, dd, J = 7.0, 4.1 Hz, CH_2C(O)), 2.16 (3H, s, CH_3C(O)). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 204.4, 157.0, 141.1, 134.2, 130.1, 123.0, 122.1, 78.7, 45.7, 38.5, 30.2. *m*/*z* (EI) found 252.0753 ([M]$^+$ $C_{11}H_{12}N_2O_5$ requires 252.0753). HPLC: Daicel Chiralpak AD-H. Hexane–*i*-PrOH, 90 : 10, 1 mL min^{-1}, 254 nm: tR (major) = 22 min; tR (minor) = 21 min.

(4*S*,5*R*)-4-Methyl-6-nitro-5-(*m*-nitrophenyl)-hexan-3-one 39a. Purified using flash column chromatography (EtOAc–petroleum ether 40/60, 3 : 7) to yield the *title compound* as a yellow oil (95.2 mg, 68%). ν_{max} (film)/cm^{-1} 2976, 1710, 1553, 1529, 1350, 1102. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.17 (1H, m, Ar*H*), 8.08 (1H, s, Ar*H*), 7.54 (2H, m, Ar*H*), 4.69 (2H, m, CH_2NO$_2$), 3.86 (1H, m, C*H*Ar), 3.03 (1H, m, C*H*CH$_3$), 2.67 (1H, m, C*H*H′C(O)), 2,45 (1H, m, CH*H*′C(O)), 1.10 (3H, t, J = 7.3 Hz, CH$_2$CH_3), 1.00 (3H, d, J = 7.2 Hz, CHCH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 212.5, 152.8, 140.0, 134.5, 130.0, 123.1, 122.7, 77.7, 47.8, 45.6, 35.5, 16.3, 7.6. *m*/*z* (EI) found 280.1072 ([M]$^+$ $C_{13}H_{16}N_2O_5$ requires 280.1059). HPLC: Daicel Chiralpak AD-H. Hexane–*i*-PrOH, 90 : 10, 1 mL min^{-1}, 254 nm: tR (major) = 12 min; tR (minor) = 11 min.

General procedure for the sulfonamide catalysed aldol reaction

To a solution of *p*-nitrobenzaldehyde (151 mg, 1 mmol, 1 eq.) in dichloromethane (8 mL) was added the relevant ketone (2 mL, 20 vol%) and *N*-(pyrrolidin-2-(*S*)-carbonyl)-methylsulfonamide **9** (38.6 mg, 0.2 mmol, 20 mol%) or *N*-(pyrrolidin-2-(*S*)-carbonyl)-benzenesulfonamide **10** (51.0 mg, 0.2 mmol, 20 mol%) respectively. The solution was stirred at room temperature and evaporated *in vacuo* after the time reported. The resulting yellow/orange residue was purified by flash column chromatography using varying amounts of ethyl acetate and petroleum ether 40/60 as eluent.

(4*R*)-4-Hydroxy-4-(*p*-nitrophenyl)-butan-2-one[6] 18b. To a solution of *p*-nitrobenzaldehyde (151 mg, 1 mmol, 1 eq.) in acetone (10 mL) was added *N*-(pyrrolidin-2-(*S*)-carbonyl)-benzenesulfonamide **10** (25.5 mg, 0.2 mmol, 20 mol%) and the resulting solution stirred for 24 h. After this time, the mixture was quenched with saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (2 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated *in vacuo*. Purification using flash column chromatography (EtOAc–petroleum ether 40/60, 3 : 7) gave the *title compound* as a yellow oil (209 mg, 100%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.21 (2H, d, J = 8.7 Hz, Ar*H*), 7.54 (2H, d, J = 8.7 Hz, Ar*H*), 5.26 (1H, m, CHC*H*OH), 3.61 (1H, s, O*H*), 2.87–2.83 (2H, m, CH_2CHOH), 2.23 (3H, s, CH_3C(O)). HPLC: Daicel Chiralcel AS. Hexane–*i*-PrOH, 85:15, 1 mL min^{-1}, 254 nm: tR (major) = 26 min; tR (minor) = 39 min.

(1*R*)-Hydroxy-1-(4-nitrophenyl)-pentan-3-one[6] 19b. Purification using flash column chromatography (EtOAc–petroleum ether 40/60, 3 : 7) gave the *title compound* as a yellow oil (40.7 mg, 48%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.20 (2H, d, J = 8.5 Hz, Ar*H*), 7.54 (2H, d, J = 8.5 Hz, Ar*H*), 5.27 (1H, m, CH$_2$C*H*OH), 3.64 (1H, s, CH$_2$CHO*H*), 2.86–2.81 (2H, m, CH_2CHOH), 2.48 (2H, s, CH$_3$CH_2C(O)), 1.08 (3H, t, J = 7.3 Hz, CH_3CH$_2$C(O)). HPLC: Daicel Chiralpak AS. Hexane–*i*-PrOH, 85 : 15, 1 mL min^{-1}, 254 nm: tR (major) = 18 min; tR (minor) = 36 min.

(2*R*,1′*R*)-2-[1′-Hydroxy-(4-nitrophenyl)-methyl]-cyclobutanone 20b. (2*S*,1′*R*)-[Hydroxy-(4-nitrophenyl)-methyl]-cyclobutanone 20b. Reaction performed using *p*-nitrobenzaldehyde (26.0 mg, 0.17 mmol, 1 eq.) under standard conditions. *Syn* and *anti* diastereomers were separated by flash column chromatography (EtOAc–petroleum ether 40/60, 3 : 17) to yield the *title compounds* as white solids (*syn* 8.0 mg, 21%). Mp = 101–103 °C, ν_{max} (film)/cm^{-1} 3401, 1769, 1518, 1352, 1094, 860. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.21 (2H, d, J = 8.7 Hz, Ar*H*), 7.54 (2H, d, J = 8.7 Hz, Ar*H*), 5.26 (1H, m, CHC*H*OH), 3.68 (1H, s, C*H*CHOH), 3.08–2.93 (2H, m, CH_2C(O)), 2.32 (1H, s, CHCHO*H*), 2.24–1.90 (2H, m, CH_2CH_2(O)). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 208.7, 149.0, 147.5, 126.5, 123.8, 69.8, 66.6, 45.5, 11.3. *m*/*z* (ES) found 222.0766 ([MH]$^+$ $C_{11}H_{12}NO_4$ requires 222.0761). HPLC: Daicel Chiralpak AD-H. Hexane–*i*-PrOH, 85 : 15, 1 mL min^{-1}, 254 nm: tR (major) = 22 min; tR (minor) = 33 min. (*anti* 16.3 mg, 43%). Mp = 97–99 °C, ν_{max} (film)/cm^{-1} 3490, 1759, 1517, 1349, 1055, 864. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.22 (2H, d, J = 8.6 Hz, Ar*H*), 7.53 (2H, d, J = 8.6 Hz, Ar*H*), 4.99 (1H, d, J = 7.8 Hz, CHC*H*OH), 3.61 (1H, m, C*H*CHOH), 3.16–2.96 (2H, m, CH_2C(O)), 2.98 (1H, m, CHCHO*H*), 2.14–1.90 (2H, m, CH_2CH_2(O)). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 209.1, 148.3, 147.7, 127.0, 123.8, 73.0, 66.0, 45.2, 14.1. *m*/*z* (ES) found 222.0766 ([MH]$^+$ $C_{11}H_{12}NO_4$ requires 222.0761). HPLC: Daicel Chiralpak AD-H. Hexane–*i*-PrOH, 80 : 20, 1 mL min^{-1}, 254 nm: tR (major) = 23 min; tR (minor) = 17 min.

(2*R*,1′*R*)-[Hydroxy-(4-nitrophenyl)-methyl]-cyclopentanone 42a. (2*S*,1′*R*)-[Hydroxy-(4-nitrophenyl)-methyl]-cyclopentanone[6] 42a. *Syn* and *anti* diastereomers were separated by flash column chromatography (dichloromethane) to yield the *title compounds* as white solids (*syn* 35.8 mg, 30%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.20 (2H, d, J = 8.7 Hz, Ar*H*), 7.53 (2H, d, J = 8.7 Hz, Ar*H*), 4.84 (1H, d, J = 9.1 Hz, CHC*H*OH), 4.72 (1H, s, CHCHO*H*), 2.48–2.23 (2H, m, CH_2C(O), 2.37 (1H, m, C*H*CHOH), 2.03–1.51 (4H, m, CH_2CH_2). HPLC: Daicel Chiralpak AS. Hexane–*i*-PrOH, 80 : 20, 1 mL min^{-1}, 254 nm: tR (major) = 20 min; tR (minor) = 16 min. (*anti* 65.6 mg, 55%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.18 (2H, d, J = 8.7 Hz, Ar*H*), 7.51 (2H, d, J = 8.7 Hz, Ar*H*), 5.41 (1H, s, CHC*H*OH), 2.94 (1H, m, CHCHO*H*), 2.46 (1H, m, C*H*CHOH), 2.37 (1H, m, C*H*H′(O)), 2.15 (1H, m, CH*H*′(O)), 2.03–1.67 (4H, m, CH_2CH_2). HPLC: Daicel Chiralpak AS. Hexane–*i*-PrOH, 70 : 30, 1 mL min^{-1}, 254 nm: tR (major) = 10 min; tR (minor) = 27 min.

(2*R*,1′*R*)-[Hydroxy-(4-nitrophenyl)-methyl]-cyclohexanone 11b. (2*S*,1′*R*)-2-[1′-Hydroxy-(4-nitrophenyl)-methyl]-cyclohexanone[6] 11b. *Syn* and *anti* diastereomers were separated by flash column chromatography (EtOAc–petroleum ether 40/60, 3 : 17) to yield the *title compounds* as white solids (*syn* 43.4 mg, 35%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.20 (2H, d, J = 8.7 Hz, ArH), 7.51 (2H, d, J = 8.7 Hz, ArH), 4.90 (1H, m, CHC*H*OH), 4.06 (1H, d, J = 3.2 Hz, CHCHO*H*), 2.59 (1H, m, C*H*CHOH), 2.52–2.33 (2H, m, CH_2C(O), 2.13–1.37 (6H, m, chex-*H*). HPLC: Daicel Chiralpak OD. Hexane–*i*-PrOH, 85 : 15, 1 mL min^{-1}, 254 nm: tR (major) = 15 min; tR (minor) = 12 min. (*anti* 66.0 mg, 53%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.20 (2H, d, J = 8.7 Hz, Ar*H*), 7.49 (2H, d, J = 8.7 Hz, Ar*H*), 5.49 (1H, m, CHC*H*OH), 3.15 (1H, d, J = 3.3 Hz, CHCHO*H*), 2.62 (1H, m, C*H*CHOH), 2.50–2.37 (2H, m, CH_2C(O), 2.14–1.52 (6H, m, chex-*H*). HPLC: Daicel Chiralpak AS. Hexane–*i*-PrOH, 85 : 15, 1 mL min^{-1}, 254 nm: tR (major) = 22 min; tR (minor) = 29 min.

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References

1 (*a*) M. Movassaghi and E. N. Jacobsen, *Science*, 2002, **298**, 1904; (*b*) B. List, *Tetrahedron*, 2002, **58**, 5573; (*c*) B. List, *Synlett*, 2001, 1675; (*d*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2001, **40**, 3726.

2 (*a*) Z. G. Hajos and D. R. Parrish, *Angew. Chem., Int. Ed. Engl.*, 1974, **39**, 1615; (*b*) U. Eder, R. Wiechert and G. Sauer: German Patent DE 2014757, 1971; (*c*) U. Eder, G. Sauer and R. Wiechert, *J. Org. Chem.*, 1971, **10**, 496; (*d*) Z. G. Hajos and D. R. Parrish: German Patent DE 2102623, 1971.

3 (*a*) S. Bahmanyar, K. N. Houk, H. J. Martin and B. List, *J. Am. Chem. Soc.*, 2003, **125**, 2475; (*b*) A. Bogevig, N. Kumaragurubaran and K. A. Jorgensen, *Chem. Commun.*, 2002, 620; (*c*) V. Chan, J. G. Kim, C. Jimeno, P. J. Carroll and P. J. Walsh, *Org. Lett.*, 2004, **6**, 2051; (*d*) A. Cordova, W. Notz and C. F. Barbas III, *Chem. Commun.*, 2002, 3024; (*e*) Y. Hayashi, W. Tsuboi, M. Shoji and N. Suzuki, *Tetrahedron Lett.*, 2004, **45**, 4353; (*f*) L. Hoang, S. Bahmanyar, K. N. Houk and B. List, *J. Am. Chem. Soc.*, 2003, **125**, 16; (*g*) J. Kofoed, J. Nielsen and J. L. Reymond, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2445; (*h*) P. Kotrusz, I. Kmentova, B. Gotov, S. Toma and E. Solcaniova, *Chem. Commun.*, 2002, 2510; (*i*) B. List, R. A. Lerner and C. F. Barbas III, *J. Am. Chem. Soc.*, 2000, **122**, 2395; (*j*) B. List, P. Pojarliev and C. Castello, *Org. Lett.*, 2001, **3**, 573; (*k*) B. List, L. Hoang and H. J. Martin, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5839; (*l*) T. P. Loh, L. C. Feng, H. Y. Yang and J. Y. Yang, *Tetrahedron Lett.*, 2002, **43**, 8741; (*m*) H. J. Martin and B. List, *Synlett*, 2003, 1901; (*n*) M. Nakadai, S. Saito and H. Yamamoto, *Tetrahedron*, 2002, **58**, 8167; (*o*) A. B. Northrup and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 6798; (*p*) A. B. Northrup, I. K. Mangion, F. Hettche and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2004, **43**, 2152; (*q*) Y. Y. Peng, Q. P. Ding, Z. C. Li, P. G. Wang and J. P. Cheng, *Tetrahedron Lett.*, 2003, **44**, 3871; (*r*) C. Pidathala, L. Hoang, N. Vignola and B. List, *Angew. Chem., Int. Ed.*, 2003, **42**, 2785; (*s*) S. Saito, M. Nakadai and H. Yamamoto, *Synlett*, 2001, 1245; (*t*) Y. Sekiguchi, A. Sasaoka, A. Shimomoto, S. Fujioka and H. Kotsuki, *Synlett*, 2003, 1655; (*u*) Z. Tang, F. Jiang, L. T. Yu, X. Cui, L. Z. Gong, A. Q. Mi, Y. Z. Jiang and Y. D. Wu, *J. Am. Chem. Soc.*, 2003, **125**, 5262; (*v*) Z. Tang, F. Jiang, X. Cui, L. Z. Gong, A. Q. Mi, Y. Z. Jiang and Y. D. Wu, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5755.

4 A. Cordova and C. F. Barbas III, *Tetrahedron Lett.*, 2002, **43**, 7749.

5 N. Mase, F. Tanaka and C. F. Barbas III, *Angew. Chem., Int. Ed.*, 2004, **43**, 2420.

6 K. Sakthivel, W. Notz, T. Bui and C. F. Barbas III, *J. Am. Chem. Soc.*, 2001, **123**, 5260.

7 (*a*) B. List, *J. Am. Chem. Soc.*, 2000, **122**, 9336; (*b*) A. Cordova, *Acc. Chem. Res.*, 2004, **37**, 102; (*c*) W. Notz, F. Tanaka, S. Watanabe, N. S. Chowdari, J. M. Turner, R. Thayumanavan and C. F. Barbas III, *J. Org. Chem.*, 2003, **68**, 9624; (*d*) P. Pojarliev, W. T. Biller, H. J. Martin and B. List, *Synlett*, 2003, 1903; (*e*) N. S. Chowdari, D. B. Ramachary and C. Barbas III, *Synlett*, 2003, 1906; (*f*) A. Cordova, *Synlett*, 2003, 1651; (*g*) Y. Hayashi, W. Tsuboi, M. Shoji and N. Suzuki, *J. Am. Chem. Soc.*, 2003, **125**, 11208; (*h*) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji and K. Sakai, *Angew. Chem., Int. Ed.*, 2003, **42**, 3677; (*i*) A. Cordova and C. F. Barbas III, *Tetrahedron Lett.*, 2003, **44**, 1923; (*j*) S. Watanabe, A. Cordova, F. Tanaka and C. F. Barbas III, *Org. Lett.*, 2002, **4**, 4519; (*k*) A. Cordova and C. F. Barbas III, *Tetrahedron Lett.*, 2002, **43**, 7749; (*l*) A. Cordova, S. Watanabe, F. Tanaka, W. Notz and C. F. Barbas III, *J. Am. Chem. Soc.*, 2002, **124**, 1866; (*m*) B. List, P. Pojarliev, W. T. Biller and H. J. Martin, *J. Am. Chem. Soc.*, 2002, **124**, 827; (*n*) W. Notz, K. Sakthivel, T. Bui, G. F. Zhong and C. F. Barbas III, *Tetrahedron Lett.*, 2001, **42**, 199.

8 A. J. A. Cobb, D. M. Shaw and S. V. Ley, *Synlett*, 2004, 558.

9 A. Cordova, W. Notz, G. F. Zhong, J. M. Betancort and C. F. Barbas III, *J. Am. Chem. Soc.*, 2002, **124**, 1842.

10 B. List, P. Pojarliev and H. J. Martin, *Org. Lett.*, 2001, **3**, 2423.

11 D. Enders and A. Seki, *Synlett*, 2002, 26.

12 R. G. Almquist, C. Jenningswhite, W. R. Chao, T. Steeger, K. Wheeler, J. Rogers and C. Mitoma, *J. Med. Chem.*, 1985, **28**, 1062.

13 We thank Steve Challenger (Pfizer Inc) for the suggestion of the acyl sulfonamide functionality as an acid surrogate.

14 M. S. Manhas, M. Ghosh and A. K. Bose, *J. Org. Chem.*, 1990, **55**, 575.

15 W. Notz, F. Tanaka and C. F. Barbas III, *Acc. Chem. Res.*, 2004, **37**, 580.

16 (*a*) L. Hoang, S. Bahmanyar, K. N. Houk and B. List, *J. Am. Chem. Soc.*, 2003, **125**, 16; (*b*) S. Bahmanyar and K. N. Houk, *J. Am. Chem. Soc.*, 2001, **123**, 12911; (*c*) S. Bahmanyar, K. N. Houk, H. J. Martin and B. List, *J. Am. Chem. Soc.*, 2003, **125**, 2475.

17 A. J. A. Cobb, D. A. Longbottom, D. M. Shaw and S. V. Ley, *Chem. Commun.*, 2004, 1808.

18 J. M. Betancort, K. Sakthivel, R. Thayumanavan, F. Tanaka and C. F. Barbas III, *Synthesis*, 2004, 1509.

19 (*a*) T. Ishii, S. Fujioka, Y. Sekiguchi and H. Kotsuki, *J. Am. Chem. Soc.*, 2004, **126**, 9558; (*b*) H. Li, Y. Wang, L. Tang and L. Deng, *J. Am. Chem. Soc.*, 2004, **126**, 9906.

20 H. Torii, M. Nakadai, K. Ishihara, S. Saito and H. Yamamoto, *Angew. Chem., Int. Ed.*, 2004, **43**, 1983.

21 A. Hartikka and P. I. Arvidsson, *Tetrahedron: Asymmetry*, 2004, **15**, 1831.

22 Note added in proof:since submission an aldol reaction has been reported with related acyl sulfonamides; (*a*) A. Berkessel, B. Koch and J. Lex, *Adv. Synth. Catal.*, 2004, 1141; a sulfonamide catalyst has been employed in Mannich and a-aminoxylation reactions; (*b*) W. Wang, J. Wang, H. Li and L. X. Liao, *Tetrahedron Lett.*, 2004, **45**, 7235; (*c*) W. Wang, J. Wang and H. Li, *Tetrahedron Lett.*, 2004, **45**, 7243.

23 K. Morikawa, M. Honda, K. I. Endoh, T. Matsumoto, K. I. Akamatsu, H. Mitsui and M. Koizumi, *J. Pharm. Sci.*, 1991, **80**, 837.

24 S. J. Blarer, W. B. Schweizer and D. Seebach, *Helv. Chim. Acta.*, 1982, **65**, 1637.

25 D. Seebach and M. A. Brook, *Helv. Chim. Acta.*, 1985, **68**, 319.

26 D. Seebach, I. M. Lyapkalo and R. Dahinden, *Helv. Chim Acta.*, 1999, **82**, 1829.

27 D. Enders and T. Otten, *Synlett*, 1999, 747.

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