A sequential enantioselective, organocatalytic route to chiral 1,2-oxazines and chiral pyridazines†

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A sequential, organocatalysed asymmetric reaction to access chiral 1,2-oxazines and chiral pyridazines is reported, which proceeds in moderate to good yields and good to excellent enantioselectivities.

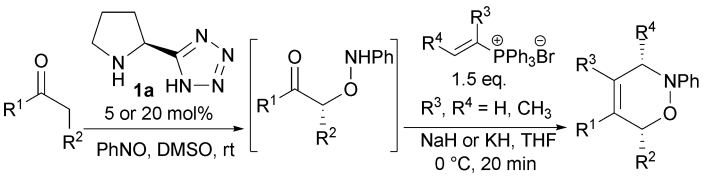
Introduction

The synthetic potential of multicomponent, tandem or domino reactions has been exploited for the efficient and stereoselective construction of a variety of complex structures from simple starting materials.[1] These one-pot sequential transformations avoid lengthy purification or protection procedures and thus greatly reduce both the cost and time taken for chemical syntheses. In recent years, spectacular advances have been made in organocatalytic processes[2] and one significant advantage is their ability to promote several types of reactions through different activation modes.[3] In particular, tandem reactions mediated by organocatalysts can be applied to generate useful enantiomerically pure building blocks in the synthesis of biologically active natural products.[4] It was envisaged that such a process might be used in the preparation of both optically active 1,2-oxazines and 3,6-dihydropyridazines.

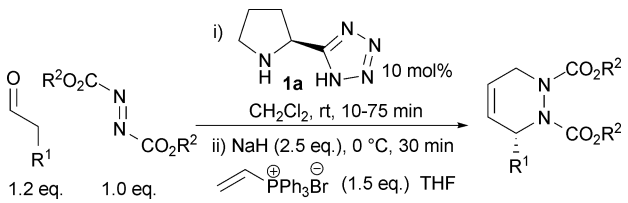
Conventionally, these compounds are prepared by the [4 + 2] cycloaddition of nitroso or azo compounds and dienes,[5] or the ring-closing metathesis of suitable alkene precursors.[6] However, their asymmetric preparation[7] can be difficult to achieve without control induced by chiral substrates[8] or chiral auxiliaries.[9] Therefore, the development of an asymmetric organocatalytic route, which would lead to a variable substitution pattern, was very attractive.

Following optimisation studies, we first demonstrated an efficient new route to enantiopure 1,2-oxazines from commercially available achiral precursors using (*S*)-pyrrolidinyl-tetrazole catalyst **1a** (Scheme 1).[10] The transformation involves an asymmetric organocatalytic α-oxyamination[11] with nitrosobenzene to afford an intermediate, which undergoes base-promoted conjugate addition to a vinylphosphonium salt.[12] The resulting ylide then cyclises to the 1,2-oxazine *via* an intramolecular Wittig process.

Through this new method, by varying any one of the three components, a wide range of potentially useful enantiomerically enriched heterocycles can be accessed. Indeed, by changing the carbonyl component from aldehyde to ketone or varying the vinylphosphonium salt used in the Wittig step, more substituted enantiopure 1,2-oxazines can be obtained. Moreover, alteration of the electrophilic component to provide a related, synthetically useful class of compound has been demonstrated, namely 3,6-dihydropyridazines.[13] In a similar manner, these may be obtained by applying an initial α-amination using an azo compound instead of a nitroso component (Scheme 2).



Scheme 1 Synthesis of chiral 1,2-oxazines from aldehyde and ketone substrates.



Scheme 2 Synthesis of chiral 3,6-dihydropyridazines.

Results and discussion

We have recently demonstrated an efficient new route to enantiopure 1,2-oxazines from commercially available aldehydes[10a] and ketones.[10b] To achieve this, extensive optimisation studies were conducted. Initial work centred on finding conditions most appropriate for the organocatalytic α-oxyamination reaction, while remaining compatible with the subsequent steps in the one-pot procedure. Solvents, temperatures, order of addition, reaction times and equivalents of reagents used, were screened. It was found that conditions similar to those developed by Zhong,[11a] where only a small excess of aldehyde partner in DMSO was required, were optimum for the use of pyrrolidinyl-tetrazole catalyst **1a**. NaH (2 eq.) was needed in the subsequent intramolecular Wittig process in a mixed solvent system (1 : 1, DMSO–THF). Interestingly, increased yields were observed with more substituted aldehydes, suggesting competing homo-aldol reactions (Table 1). In support of this hypothesis is the observed reduction in overall yield as the number of equivalents of aldehyde were increased. The matched/mismatched effect was investigated using citronellal as the chiral aldehyde to create dihydro-1,2-oxazines with pendant chirality (Entries 9 and 10). Although yields

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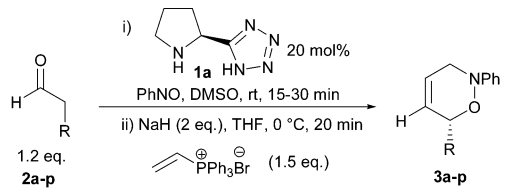
Table 1 Synthesis of 1,2-oxazines from aldehydes



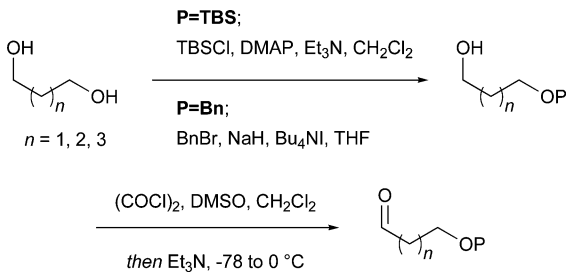
Entry	Aldehyde	1,2-Oxazine	Yield[a] %	Entry	Aldehyde	1,2-Oxazine	Yield[a] %
1	**2a**	**3a**	71 (99 ee)[b]	9	**2i**	**3i**	67 (83 de)[c]
2	**2b**	**3b**	50 (99 ee)[b]	10	**2j**	**3j**	61 (99 de)[c]
3	**2c**	**3c**	45 (99 ee)[b]	11	**2k**	**3k**	<2
4	**2d**	**3d**	39 (99 ee)[b]	12	**2l**	**3l**	7 (98 ee)[b]
5	**2e**	**3e**	44 (99 ee)[b]	13	**2m**	**3m**	31 (98 ee)[b]
6	**2f**	**3f**	50 (99 ee)[b]	14	**2n**	**3n**	32 (99 ee)[b]
7	**2g**	**3g**	40 (99 ee)[b]	15	**2o**	**3o**	38 (96 ee)[d]
8	**2h**	**3h**	82 (99 ee)[b]	16	**2p**	**3p**	33 (98 ee)[b]

[a] Isolated yields of material after chromatography. [b] The ee values were determined directly by chiral HPLC. [c] The de values were determined directly by ^{1}H NMR of crude material. [d] The ee value was determined directly by chiral SFC.

were similar, diastereoselectivity did differ with a diastereomeric excess of only 83% in the mismatched compared with 99% in the matched case (Entry 9).

The use of (*S*)-pyrrolidinyl-tetrazole **1a** as a catalyst for this process was based on its improved properties, especially solubility, when compared, for example, to L-proline. As with other chemistries developed independently by ourselves,[14] Yamamoto *et al.*,[11f,11g,15] Hartikka and Arvidsson[16] and others[17] where **1a** was an especially effective catalyst, it also proved to be the compound of choice in this work.[18]

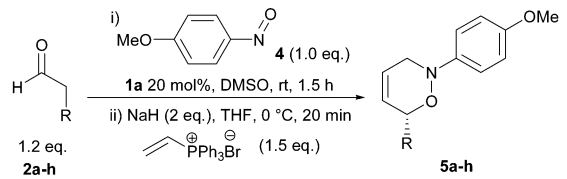
In order to probe the synthetic scope of the method, linear aldehydes with various protecting groups and chain lengths were prepared by oxidising a suitable mono-protected diol (Scheme 3).[19] However, under the optimised reaction conditions although the enantiomeric excesses were still excellent, the yields were no longer as high. Most notably, it was found that only traces of the 1,2-oxazine products **3k** and **3l** from protected β-hydroxyaldehydes were observed (Entries 11–12, Table 1). For reasons which are not entirely clear, this suggests a critical aldehyde chain length of four carbons or more for successful α-oxyamination.



Scheme 3 Preparation of protected hydroxyaldehydes.

An alternative nitroso compound, 4-nitrosoanisole **4** (Table 2),[20] has also been investigated. Under similar reaction conditions, with slow addition of the nitroso compound, generally lower yields but excellent enantioselectivities were observed, in comparison with their nitrosobenzene counterparts (Table 2). It is believed that this

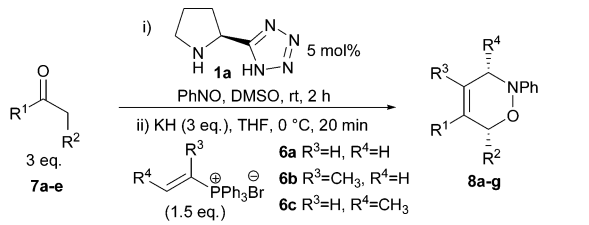
Table 2 Synthesis of 1,2-oxazines from 4-nitrosoanisole[20]



Entry	Aldehyde	1,2-Oxazine	Yield[a] (ee)[b] %
1	**2a**	**5a**	36 (>98)
2	**2h**	**5h**	63 (>98)
3	**2b**	**5b**	<2
4	**2e**	**5e**	<2[c]
5	**2d**	**5d**	<2

[a] Isolated yields of material after chromatography. [b] The ee values were determined directly by chiral HPLC. [c] 6% obtained without NH_4Cl work-up.

Table 3 Synthesis of 1,2-oxazines from ketones



Entry	Ketone	1,2-Oxazine	Yield[a] (ee)[b] %
1	**7a**	**8a**	60 (99)
2	**7b**	**8b**	33 (99)
3	**7c**	**8c**	51 (99)
4	**7d**	**8d**	50 (99)
5	**7e**	**8e**	46[c] (99)
6	**7a**	**8f**	39[d] (99)
7	**7a**	**8g**	65[e] (99)

[a] Isolated yields of material after chromatography. [b] The ee values were determined directly by chiral HPLC. [c] Reaction of 20 eq. **7e** was conducted with 20 mol% of **1a**. [d] Compound **8f** generated using **6b**. [e] Compound **8g** generated using **6c**.

is due to the much more facile dimerisation of the nitroso reagent during the α-oxyamination step caused by the additional electron-donating substituent.

Slight alterations in reaction conditions were required to produce enantiopure 1,2-oxazines from ketone starting materials.[10b] The conditions employed for the α-oxyamination were similar to those used by Yamamoto *et al.*[11g] Crucially, these use a much smaller excess of ketone (3 eq.), such that the subsequent steps may be carried out in a single pot with greatly reduced catalyst loading (5 mol%). The problems from the sequential Wittig process were resolved by the use of KH as a base instead of NaH. Remarkably, an excess of KH did not cause racemisation of the stereogenic centre generated during the α-oxyamination process (99% ee). We were pleased to find that the reaction conditions developed were then applicable to a range of ketones to give moderate to good yields of products with excellent ee's throughout (Table 3).

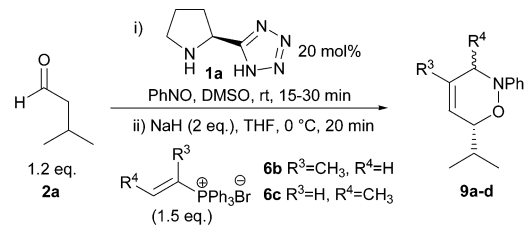
Use of the more substituted vinylphosponium bromide **6b**[21] gave the tri- and tetrasubstituted 1,2-oxazines **9a** (Entry 1, Table 4) and **8f** (Entry 6, Table 3) from aldehyde and ketone starting materials, respectively. When phosphonium salt **6c**[22] was used, a diastereomeric ratio of 6 : 1 was observed in the reaction of isovaleraldehyde, catalysed by (*S*)-pyrrolidinyl-tetrazole **1a**, compared with 4 : 1 when L-proline was used (Entry 2, Table 4) each with **9d** as a by-product.[23] It is also of note that the 1,2-oxazine **8g** from cyclohexanone **7a** was generated with complete diastereoselectivity[24] and excellent enantioselectivity (Entry 7, Table 3).

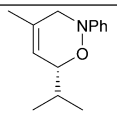
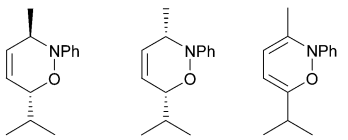
The enantiomer of the pyrrolidinyl-tetrazole catalyst, **1b** was also applied to selected aldehyde and ketone examples to verify its equivalent utility in these transformations. As expected, this was successful in providing the corresponding enantiomeric 1,2-oxazine products (Table 5).

Cleavage of the N–O bond of selected 1,2-oxazines liberated the synthetically useful *cis*-allylic alcohols in high yield using zinc in methanolic HCl, with retention of enantiopurity (Table 6). It is also worth noting that when N–O cleavage of **3a** was performed on a larger scale (3.38 mmol), the yield significantly increased from 83% (1.02 mmol) to 93%, highlighting the practicality of the transformation.

The reactions between nitrosobenzene and activated carbonyl compounds, for example enamines, are known to provide α-oxyamination[11] or α-hydroxyamination[25] products, depending

Table 4 Synthesis of 1,2-oxazines using alternative Wittig reagents



Entry	6	1,2-Oxazine	By-product	Yield[a] (ee) %
1	**6b**	 **9a**		53 (99)[b]
2	**6c**	 **9b** 6:1 **9c** **9d** 8%		59[c] (99)[d]

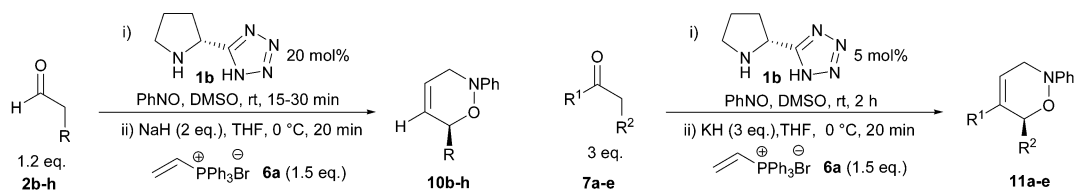
[a] Isolated yields of material after chromatography. [b] The ee was determined directly by chiral GC. [c] 4 : 1 dr obtained when catalysed by L-proline. [d] The ees for both **9b** and **9c** are 99% and were determined directly by chiral HPLC and chiral SFC, respectively.

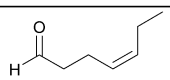
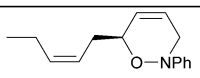
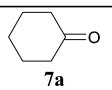
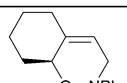
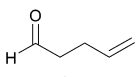
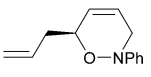
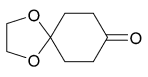
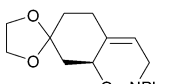
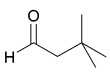
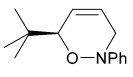
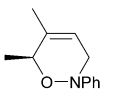
on the catalyst used. Maruoka and co-workers have recently developed an axially chiral secondary amine catalyst **14** (Table 7) to direct enantioselective hydroxyamination of aldehydes.[25]

By applying catalyst **14**, the α-hydroxyaminated intermediate can be generated chemoselectively. Following base-promoted conjugate addition to a vinylphosphonium salt, intramolecular Wittig cyclisation thus yields dihydro-1,2-oxazines with the stereogenic centre alpha to nitrogen (Table 7). This illustrates that regioisomers of these compounds can be generated by simply changing the catalyst used.[26]

It has also been shown that an organocatalytic α-amination,[27] to provide α-hydrazinocarbonyl compounds, can furnish 3,6-dihydropyridazines by a similar route.[13] Reaction conditions similar to those developed by Jørgensen *et al.*[27a] where dichloromethane was used as the solvent of choice, were chosen to facilitate the sequential Wittig process. Importantly, a reduced excess of aldehyde (1.2 eq.) was found to give good yields, further aiding the following intramolecular Wittig step by minimising side reactions. Using isovaleraldehyde and diethyl azodicarboxylate (DEAD, **17a**, Table 8) as our model system, it was found that the use of a mixed solvent system (1 : 1, CH_2Cl_2–THF) was optimum, and also provided for an easier work-up. Comparison of the catalytic activity of L-proline **1c** and (*S*)-pyrrolidinyl-tetrazole **1a** shows that although the ee values were very similar, the yields varied significantly (Entries 3–6, Table 8). (*S*)-Pyrrolidinyl-tetrazole demonstrated much higher activity leading to significantly reduced reaction times, especially when low catalyst loadings were applied (Entries 5–8, Table 8). The reaction scope was then evaluated by examining a variety of aldehydes and azodicarboxylates under these optimised reaction conditions (Table 9) and indeed a selection of aldehydes reacted with DEAD **17a** giving the 3,6-dihydropyridazines **18a-18k** in good to excellent yields and enantioselectivities. These results further support our homo-aldol coupling hypothesis, with unbranched aldehydes showing lower yields and surprisingly lower selectivities (Entries 3–5, Table 9). The study has also indicated that the reaction can successfully be scaled up (Entry 1, Table 9). Notably, the 3,6-dihydropyridazine product **18k** can be obtained

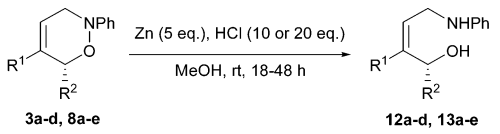
Table 5 Synthesis of 1,2-oxazines catalysed by (*R*)-pyrrolidinyl-tetrazole from aldehydes and ketones

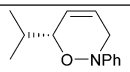
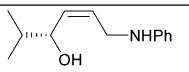
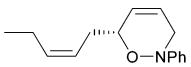
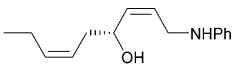
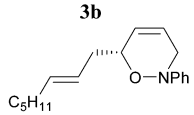
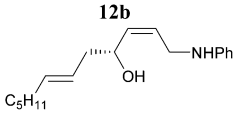
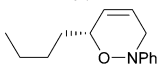
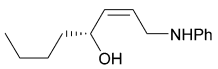
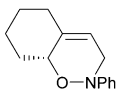
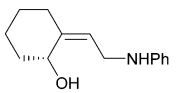
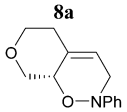
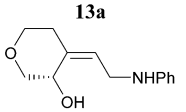
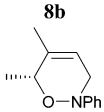
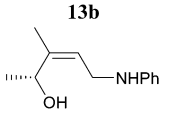


Entry	Aldehyde	1,2-Oxazine	Yield[a] (ee)[b] %	Entry	Ketone	1,2-Oxazine	Yield[a] (ee)[b] %
1	 **2b**	 **10b**	44 (99)	4	 **7a**	 **11a**	57 (99)
2	 **2e**	 **10e**	38 (99)	5	 **7d**	 **11d**	54 (99)
3	 **2h**	 **10h**	78 (99)	6	 **7e**	 **11e**	38 (99)

[a] Isolated yields of material after chromatography. [b] The ee values were determined directly by chiral HPLC.

Table 6 Synthesis of *cis*-allylic alcohols through N–O bond cleavage



Entry	1,2-Oxazine	Alcohol	Yield[a] (ee)[b] %
1	 **3a**	 **12a**	83[c] (99) 93[d] (99)
2	 **3b**	 **12b**	92 (99)
3	 **3c**	 **12c**	83 (99)
4	 **3d**	 **12d**	96 (99)
5	 **8a**	 **13a**	83 (99)
6	 **8b**	 **13b**	Quant. (99)
7	 **8e**	 **13e**	88 (99)

[a] Isolated yields of material after chromatography. [b] The ee values were determined directly by chiral HPLC. [c] Reaction carried out on 1.02 mmol scale. [d] Reaction carried out on 3.38 mmol scale.

from the TBS-protected β-silyloxypropanal **2k** (Entry 8, Table 9). This indicates that no critical aldehyde chain length exists as it does in the α-oxyamination case. Interestingly, with L-proline as catalyst, elimination product **19** (Fig. 1) was obtained as the sole reaction product.

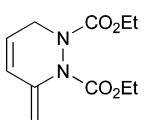
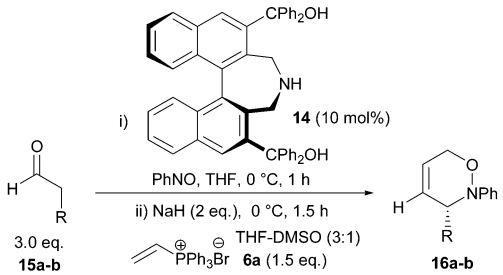


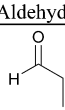
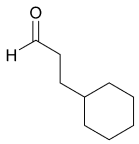
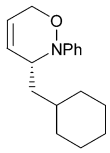
Fig. 1 Elimination product **19**.

Using both enantiomers of citronellal as the chiral aldehyde, although yields were similar, this mismatched case showed not only lower diastereoselectivity, but also a much longer reaction time (compare Entry 6 with Entry 7, Table 9).

A comparison of azodicarboxylates was carried out using isovaleraldehyde under the optimised reaction conditions (Table 10). It was found that the di-*tert*-butyl derivative (Entry 1) provided an improved ee whilst the benzyl analogue (Entry 2) gave

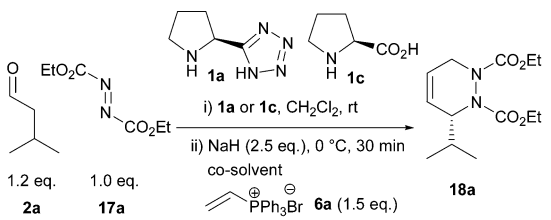
Table 7 Synthesis of 1,2-oxazines from aldehydes catalysed by the Maruoka catalyst



Entry	Aldehyde	1,2-Oxazine	Yield[a] (ee)[b] %
1	 **15a**	 **16a**	33 (99)
2	 **15b**	 **16b**	45 (99)

[a] Isolated yields of material after chromatography. [b] The ee values were assigned according to Maruoka's values at the hydroxyamination stage[25] assuming no epimerisation in the following steps as found in all previous reactions.

Table 8 Catalyst and solvent screening

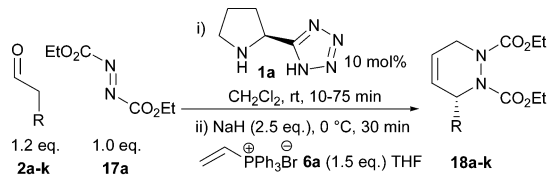


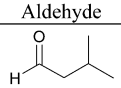
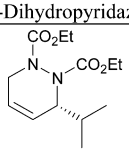
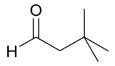
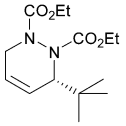
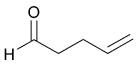
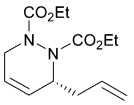
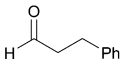
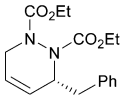
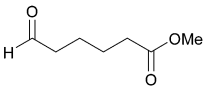
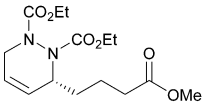
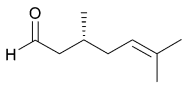
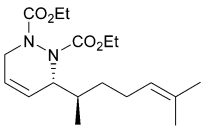
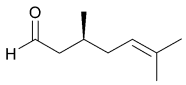
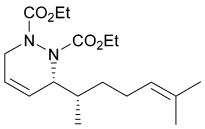
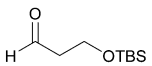
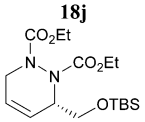
Entry	Co-solvent	Catalyst (mol%)	Time[a] (min)	Yield[b] (ee)[c] %
1	DMSO	**1c** (10)	70	89 (94)
2	DMSO	**1a** (10)	12	82 (95)
3	THF	**1c** (10)	70	67 (94)
4	THF	**1a** (10)	11	89 (94)
5	THF	**1c** (5)	95	73 (95)
6	THF	**1a** (5)	16	77 (95)
7	THF	**1c** (2)	360	No reaction
8	THF	**1a** (2)	35	68 (92)

[a] α-Amination reaction time. [b] Isolated yields of material after chromatography. [c] The ee values were determined directly by chiral SFC.

notably reduced selectivity. An alternative aminating agent, *N*-phenyltriazoline dione (PTAD, **17d**) was also investigated (Entry 3) and the reagent was completely consumed in only 20 minutes in the α-amination step, despite its rather low solubility in dichloromethane. However, a much longer reaction time (4 h) was required in the sequential cyclisation step, which could be due

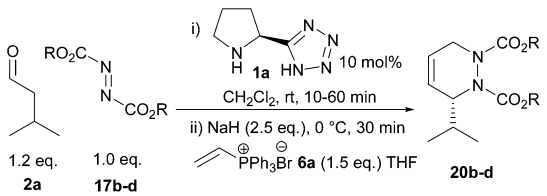
Table 9 Synthesis of 3,6-dihydropyridazines from aldehydes

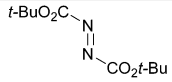
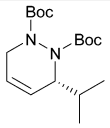
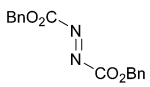
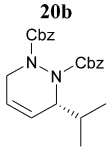
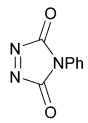
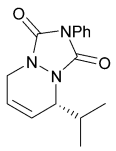


Entry	Aldehyde	3,6-Dihydropyridazine	Yield[a] %
1	 **2a**	 **18a**	89 (94 ee)[b] 86[c] (93 ee)[b]
2	 **2h**	 **18h**	84 (99 ee)[b]
3	 **2e**	 **18e**	69 (90 ee)[b]
4	 **2g**	 **18g**	58 (79 ee)[b]
5	 **2f**	 **18f**	67[d] (69 ee)[b]
6	 **2i**	 **18i**	75[e] (>60 de)[f]
7	 **2j**	 **18j**	84[g] (>85 de)[f]
8	 **2k**	 **18k**	65[h] (87 ee)[b]

[a] Isolated yields of material after chromatography. [b] The ee values were determined directly by chiral SFC. [c] Reaction carried out on 5 mmol scale. [d] 20 mol% of catalyst used. [e] 330 min required for α-amination. [f] Determining the de values directly by ^{1}H NMR of crude material was difficult due to the number of rotameric forms present in the spectra. [g] 83 min required in α-amination. [h] The product obtained was **19** when catalysed by L-proline.

Table 10 Alternative aminating agents



Entry	Aminating agent	3,6-Dihydropyridazine	Yield[a] (ee)[b] %
1	 **17b**	 **20b**	81 (99)
2	 **17c**	 **20c**	75 (82) 63 (89)[c]
3	 **17d**	 **20d**[d]	45 (56)[e]

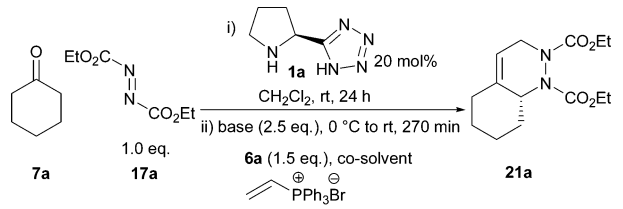
[a] Isolated yields of material after chromatography. [b] The ee values were determined directly by chiral SFC. [c] Complete reaction sequence carried out at 0 °C. [d] The relative stereochemistry was confirmed by X-ray crystallography: CCDC reference number 649830. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b708646f, see the ESI† for details. [e] A 4 h reaction time was required for the cyclisation step.

to the increased steric bulk of the reagent and might explain the reduced enantioselectivity.

Following the successful synthesis of chiral 3,6-dihydropyridazines from aldehyde starting materials, application to ketone precursors did not initially prove very effective. α-Amination was firstly investigated using cyclohexanone and DEAD in dichloromethane. Compared with the literature values (79% ee, 11 h)[27b] using L-proline as catalyst, (*S*)-pyrrolidinyl-tetrazole **1a** provided a definite improvement in both enantioselectivity (84% ee) and reaction time (5.5 h). An optimisation study was then centred on the tandem Wittig process. The optimum conditions were with KH as the base in a mixed solvent system (1 : 1 : 1, CH_2Cl_2–DMSO–THF) where a reduced amount of ketone (1.2 eq.) was key in minimising intermolecular Wittig side reactions (Entry 4, Table 11).

With this information in hand, the scope of the ketone substrates was then examined (Table 12). It was pleasing to find that the reaction conditions developed were indeed applicable to a range of ketones (1.2 eq.) using (*S*)-pyrrolidinyl-tetrazole catalyst (20 mol%) to give generally moderate yields of product and good enantioselectivities. In only one case (Entry 5, Table 12), that of the linear butan-2-one substrate, was it necessary to use a higher excess of ketone (5 eq.) and higher catalyst loading (30 mol%). A mixture of regioisomers was obtained with this substrate. Interestingly, a better ratio of 10 : 1 was achieved using L-proline whilst (*S*)-pyrrolidinyl-tetrazole gave only 2 : 1.

Table 11 Optimisation study of ketone substrates



Entry	Co-solvent[a]	Base	Eq. of **7a**	Yield[b] (ee)[c] %
1	THF	NaH	1.5	35 (58)
2	THF	NaH	1.2	42 (58)
3	DMSO	NaH	1.2	39 (71)
4	DMSO−THF	KH	1.2	52 (76)

[a] Co-solvents used in a 1 : 1 ratio with CH_2Cl_2. [b] Isolated yields of material after chromatography. [c] The ee values were determined directly by chiral SFC.

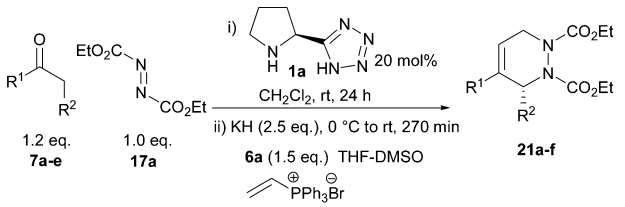
Conclusions

A sequential one-pot synthesis of chiral 1,2-oxazines from achiral aldehyde and ketone starting materials has been developed. A range of molecular decoration can be successfully achieved by varying the substitution pattern of the reagents involved. Similarly, chiral pyridazines can be prepared by applying α-amination instead of α-oxyamination in the first part of the transformation. The 1,2-oxazine products undergo facile N–O bond cleavage to provide *cis*-allylic alcohols, which are synthetically useful building blocks. Further efforts to evaluate the use of these methods and their application to natural product synthesis and related processes are underway.

Experimental

Solvents: diethyl ether and tetrahydrofuran were distilled from sodium calcium hydride and lithium aluminium hydride (tetrahydrofuran using triphenylmethane as indicator); chloroform, dichloromethane, methanol and toluene from calcium hydride prior to use. Anhydrous dimethylsulfoxide was used as supplied. Petrol refers to petroleum ether b.p. 40–60 °C, and ether to diethyl ether, which were distilled before use. Reagents: all reactions were performed under an argon atmosphere unless otherwise stated. Reagents: were used as supplied or purified using standard procedures as necessary. Chromatography: flash column chromatography was carried out using silica gel 60 (0.040–0.063 mm) 230–400 mesh under pressure unless otherwise indicated. Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kieselgel 60 F254) and visualised by ultraviolet radiation (254 nm), acidic ceric ammonium molybdate, or basic potassium permanganate solutions as appropriate. Data collection: melting points were performed on a Reichert hot-stage apparatus, and are uncorrected. Optical rotations were measured on a Perkin Elmer 343 digital polarimeter using a sodium lamp (589 nm) as the light source, $[\alpha]_D$ values are reported in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded as thin films on a Perkin Elmer Spectrum One FT-IR 1600 spectrometer fitted with an ATR sampling accessory. ^{1}H NMR spectra were recorded at

Table 12 Synthesis of pyridazines from ketones



Entry	Ketone	Pyridazine	Yield[a] (ee)[b] %
1	**7a**	**21a**	52 (76)
2	**7b**	**21b**	25 (84)
3	**7c**	**21c**	40 (83)
4	**7d**	**21d**	50 (76)
5	**7e**	**21e** 2:1 **21f**	58[c] (65)

[a] Isolated yields of material after chromatography. [b] The ee values were determined directly by chiral SFC. [c] 67% with ratio of 10 : 1, **21e**–**21f** obtained when L-proline used.

400, 500 and 600 MHz on Bruker Advance DPX-400, Bruker Advance DRX-500 (cryoprobe) and Bruker Advance DRX-600 spectrometers, respectively with residual protic solvent $CDCl_3$ as the internal reference (δ_H = 7.26 ppm) and are reported as follows: chemical shift δ/ppm (number of protons, multiplicity, coupling constant J/Hz, assignment). ^{13}C NMR spectra were recorded at 100, 125 and 150 MHz on Bruker Advance DPX-400, Bruker Advance DRX-500 (cryoprobe) and Bruker Advance DRX-600 spectrometers, respectively. The resonance of $CDCl_3$ (δ_C = 77.0 ppm, t) was used as an internal reference. ^{13}C DEPT-135 and two-dimensional (COSY, HMQC, HMBC and NOESY) NMR experiments were used where appropriate, to support the assignment of signals in the ^{1}H and ^{13}C spectra. Two-dimensional NOESY experiments were performed on a Bruker Advance

DPX-700 spectrometer at 700 MHz to assign through-space correlation where appropriate. NMR resolution enhancement was also used to assist coupling assignment in most ^{1}H NMR spectra. The ^{31}P NMR spectrum was recorded on a Bruker Advance DPX-400 spectrometer at 162 MHz. Mass spectra and accurate mass data were obtained on an LCT Premier spectrometer by Waters using a Micromass MS software at the Department of Chemistry, University of Cambridge. The enantiomeric excesses (ee) were determined by high performance liquid chromatography (HPLC), performed on Hewlett–Packard Agilent 1100 chromatographs, or by supercritical fluid chromatography (SFC) on a Berger Minigram using a Chiralpak AD (0.46 × 25 cm), Chiralpak AD-H (0.46 × 25 cm), Chiralcel OD (0.46 × 25 cm) or Chiralcel OD-H (0.46 × 25 cm) column as noted, or gas chromatography (GC), performed on an Agilent 6890N chromatograph using an Astec Chiraldex column. The diastereomeric excesses (de) were determined by ^{1}H NMR spectroscopy of crude products. The racemic materials were prepared using DL-proline or a 50 : 50 mixture of (2*S*) and (2*R*)-5-pyrrolidin-2-yl-1*H*-tetrazoles as catalyst in the same procedure as their corresponding optically active compounds. In the experimental section, compounds are divided according to general reaction type, rather than table by table.

For full experimental data of compounds **3a–3j**, **9a** and **12a–12d** see[10a]: http://pubs3.acs.org/acs/journals/supporting_information.page?in_manuscript=ol051577u. General experimental procedures and full characteristic data of representative compounds of each class are supplied here. Full experimental and characteristic details of all compounds featured in this article can be found in the ESI†.

General procedure for the synthesis of 1,2-oxazines from aldehydes

To a stirred solution of the appropriate aldehyde (1.2 eq.) in DMSO (5 ml per 1 mmol of nitrosobenzene) was added (2*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole (20 mol%). The resulting suspension was stirred vigorously for 1 min before addition of nitrosobenzene (1.0 eq.). The bright green reaction mixture was stirred at room temperature until the reaction was determined to be complete by TLC and the disappearance of green colour, resulting in a yellow solution. The reaction mixture was then cooled to 0 °C and THF (1 ml per ml of DMSO) was added. Vinyltriphenylphosphonium bromide (1.5 eq.) was added, followed by sodium hydride (2.0 eq.). After stirring for 20 min at 0 °C, the reaction mixture was quenched using saturated aqueous NH_4Cl (2 ml per ml of reaction volume) and extracted with ether (3 × 2 ml per ml of reaction volume). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (solvents noted) to provide the title compounds.

(6*R*)-6-(2-(Benzyloxy)ethyl)-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (3n). Prepared according to the general procedure from 4-(benzyloxy)butanal (0.22 g, 1.21 mmol) to provide the title compound as a yellow oil (94 mg, 32%, 99% ee) after flash column chromatography (20 : 1, petrol–EtOAc). R_f 0.58 (3 : 1, petrol–EtOAc); $[\alpha]_D^{25}$ +43.6 (*c* 0.39 in $CHCl_3$); ν_{max} (film) 2859, 1598, 1491, 1454, 1363, 1212, 1093, 1029, 1005, 888, 753, 690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.96 (1H, dddd, *J* 14.3, 8.2, 6.3, 4.3 Hz, C*H*H′CH$_2$OCH$_2$Ph), 2.05 (1H, app ddt, *J* 14.3, 8.9, 5.2 Hz, CH*H*′CH$_2$OCH$_2$Ph), 3.65 (1H, ddd, *J* 9.4, 6.3, 5.2 Hz, CH$_2$C*H*H′OCH$_2$Ph), 3.72–3.88 (3H, m, PhNC*H*$_2$CH=CHCH$_2$CH*H*′O), 4.55 (1H, d, *J* 12.0 Hz, OC*H*H′Ph), 4.58 (1H, d, *J* 12.0 Hz, OCH*H*′Ph), 4.76–4.82 (1H, m, PhNCH$_2$CH=CHC*H*CH$_2$), 5.89–5.97 (2H, m, PhNCH$_2$C*H*=C*H*), 6.97 (1H, tt, *J* 7.3, 1.2 Hz, Ph*H*-*para*), 7.06 (2H, dd, *J* 8.8, 1.2 Hz, 2 × Ph*H*-*ortho*), 7.28 (2H, dd, *J* 8.8, 7.3 Hz, 2 × Ph*H*-*meta*), 7.32–7.38 (5H, m, 5 × OCH$_2$Ph*H*); δ_C (100 MHz, $CDCl_3$) 33.7 (*C*H$_2$CH$_2$OCH$_2$Ph), 51.7 (PhN*C*H$_2$CH=CH), 66.7 (CH$_2$*C*H$_2$OCH$_2$Ph), 73.1 (O*C*H$_2$Ph), 75.1 (PhNCH$_2$CH=CH*C*H), 115.4 (2 × Ph*C*-*ortho*), 121.9 (Ph*C*-*para*), 123.0 (PhNCH$_2$*C*H=CH), 127.6, 127.7, 128.4 (5 × OCH$_2$Ph*C*), 128.8 (2 × Ph*C*-*meta*), 129.9 (PhNCH$_2$CH=*C*H), 138.5 (OCH$_2$Ph*C*-*ipso*), 150.6 (Ph*C*-N); *m*/*z* (ES) found 296.1645 ([M+H]$^+$ $C_{19}H_{22}NO_2$), requires 296.1651; HPLC (Chiralpak AD-H, 99 : 1, hexane–^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(major) 19.9 min, t_R(minor) 23.0 min.

General procedure for the synthesis of 1,2-oxazines using 4-nitrosoanisole

To a stirred solution of (2*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole (28 mg, 0.20 mmol, 20 mol%) in DMSO (2 ml) was added a solution of 4-nitrosoanisole (0.15 g, 1.00 mmol, 1.0 eq.) and the appropriate aldehyde (1.20 mmol, 1.2 eq.) in DMSO (3 ml) dropwise *via* syringe over 1 h. The mixture was allowed to stir for further 1 h and then cooled to 0 °C and THF (5 ml) was added. Vinyltriphenylphosphonium bromide (0.57 g, 1.50 mmol, 1.5 eq.) was added, followed by sodium hydride (0.08 g, 2.00 mmol, 2.0 eq.). After stirring for 20 min at 0 °C, the reaction mixture was quenched using saturated aqueous NH_4Cl (20 ml) and extracted with ether (3 × 20 ml). The combined organic layers were washed with saturated aqueous LiCl (20 ml) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (solvents noted) to provide the title compounds.

(6*R*)-6-Isopropyl-2-(4-methoxyphenyl)-3,6-dihydro-2*H*-1,2-oxazine (5a). Prepared according to the general procedure from isovaleraldehyde (0.13 ml, 1.20 mmol) to provide the title compound as a pale yellow solid (84 mg, 36%, >98% ee) after flash column chromatography (10 : 1, petrol–EtOAc). R_f 0.55 (3 : 1, petrol–EtOAc); m.p. 54–55 °C; $[\alpha]_D^{25}$ +11.5 (*c* 0.48 in $CHCl_3$); ν_{max} (film) 3676, 2971, 2902, 1505, 1463, 1385, 1245, 1210, 1175, 1066, 1037, 991, 867, 832, 726, 714, 659 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6.8 Hz, (C*H*$_3$)(CH′$_3$)CH), 1.03 (3H, d, *J* 6.8 Hz, (CH$_3$)(C*H*′$_3$)CH), 1.94 (1H, app oct, *J* 6.8 Hz, (CH$_3$)(CH′$_3$)C*H*), 3.67 (1H, app ddt, *J* 15.7, 5.0, 1.7 Hz, ArNC*H*H′CH=CH), 3.74–3.80 (1H, m, ArNCH*H*′CH=CH), 3.78 (3H, s, OC*H*$_3$), 4.31–4.34 (1H, m, (CH$_3$)$_2$CHC*H*CH=CH), 5.92–5.98 (2H, m, (CH$_3$)$_2$CHCHC*H*=C*H*), 6.86 (2H, d, *J* 9.0 Hz, 2 × Ar*H*-*ortho*), 7.10 (2H, d, *J* 9.0 Hz, 2 × Ar*H*-*meta*); δ_C (150 MHz, $CDCl_3$) 18.3 ((*C*H$_3$)(CH′$_3$)CH), 18.4 ((CH$_3$)(*C*H′$_3$)CH), 31.5 ((CH$_3$)(CH′$_3$)*C*H), 52.7 (ArN*C*H$_2$CH=CH), 55.5 (O*C*H$_3$), 82.4 ((CH$_3$)$_2$CH*C*HCH=CH), 114.1 (2 × Ar*C*-*ortho*), 117.7 (2 × Ar*C*-*meta*), 123.8 (ArNCH$_2$*C*H=CH), 128.5 (ArNCH$_2$CH=*C*H), 144.6 (Ar*C*N), 155.3 (Ar*C*O); *m*/*z* (ES) found 234.1490 ([M+H]$^+$ $C_{14}H_{20}NO_2$), requires 234.1494; HPLC (Chiralcel OD-H, 99 : 1,

hexane–^{i}PrOH, 1.0 ml min^{-1}, 254 nm) t_R(minor) 6.9 min, t_R(major) 9.3 min.

General procedure for the synthesis of 1,2-oxazines from ketones

To a stirred solution of (2*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole (7 mg, 0.05 mmol, 5 mol%) and the appropriate ketone (3.00 mmol, 3.0 eq.) in DMSO (3 ml) was added a solution of nitrosobenzene (0.11 g, 1.00 mmol, 1.0 eq.) in DMSO (2 ml) dropwise *via* syringe over 1 h. The reaction mixture was allowed to stir for a further 1 h, then vinyltriphenylphosphonium bromide (0.57 g, 1.50 mmol, 1.5 eq.) was added. The resulting solution was added to a stirred suspension of KH (0.40 g, 30% in mineral oil, washed with hexane, 3.00 mmol, 3.0 eq.) in THF (5 ml) at 0 °C. After 2 h of vigorous stirring at 0 °C, the reaction mixture was quenched using saturated aqueous NH_4Cl (20 ml), extracted with ether (3 × 30 ml), and washed with saturated aqueous LiCl (20 ml). The combined organic phase was dried using $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (solvent noted) to provide the oxazine products.

(8a*R*)-2-Phenyl-3,5,6,7,8,8a-hexahydro-2*H*-benzo[*e*][1,2]oxazine (8a). Prepared according to the general procedure from cyclohexanone (0.32 ml, 3.00 mmol) to provide the title compound as an orange solid (0.13 g, 60%, 99% ee) after flash column chromatography (20 : 1, petrol–EtOAc). R_f 0.64 (3 : 1, petrol–EtOAc); m.p. 51–53 °C; $[\alpha]_D^{25}$ +133.3 (*c* 0.73 in $CHCl_3$); ν_{max} (film) 3059, 2934, 2854, 2818, 1597, 1486, 1445, 1437, 1361, 1342, 1220, 1193, 1180, 1149, 1093, 1064, 1014, 993, 921, 880, 860, 835, 820, 785, 751, 722, 689 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.25–1.33 (1H, m, CH=CCH$_2$C*H*H′), 1.36–1.48 (2H, m, CH=C(CH$_2$)$_2$CH*H*′C*H*H′), 1.76–1.80 (1H, m, CH=CCH$_2$CH*H*′), 1.85–1.89 (1H, m, CH=C(CH$_2$)$_2$C*H*H′), 2.02–2.09 (1H, m, CH=CCH*H*′(CH$_2$)$_3$), 2.14–2.18 (1H, m, CH=C(CH$_2$)$_3$CH*H*′), 2.38 (1H, dddd, *J* 14.2, 4.2, 2.1, 2.1 Hz, CH=CC*H*H′(CH$_2$)$_3$), 3.72 (1H, app dq, *J* 15.4, 2.7 Hz, PhNC*H*H′CH=C), 3.88 (1H, dddd, *J* 15.4, 5.1, 2.5, 2.5 Hz, PhNCH*H*′CH=C), 4.49–4.54 (1H, m, PhNOC*H*(CH$_2$)$_4$), 5.58–5.60 (1H, m, PhNCH$_2$C*H*=C), 6.98 (1H, tt, *J* 7.3, 1.0 Hz, Ph*H*-*para*), 7.14 (2H, dd, *J* 8.7, 1.0 Hz, 2 × Ph*H*-*ortho*), 7.30 (2H, dd, *J* 8.7, 7.3 Hz, 2 × Ph*H*-*meta*); δ_C (150 MHz, $CDCl_3$) 23.9 (CH=C(CH$_2$)$_2$*C*H$_2$CH$_2$), 26.8 (CH=CCH$_2$*C*H$_2$(CH$_2$)$_2$), 31.4 (CH=C(CH$_2$)$_3$*C*H$_2$), 32.2 (CH=C*C*H$_2$(CH$_2$)$_3$), 52.1 (PhN*C*H$_2$CH=C), 78.3 (NO*C*H(CH$_2$)$_4$), 114.8 (PhNCH$_2$*C*H=C), 115.9 (2 × Ph*C*-*ortho*), 122.0 (Ph*C*-*para*), 128.7 (2 × Ph*C*-*meta*), 140.3 (PhNCH$_2$CH=*C*), 150.6 (Ph*C*-N); *m*/*z* (ES) found 216.1380 ([M+H]$^+$ $C_{14}H_{18}NO$), requires 216.1388; HPLC (Chiralpak AD–H, 99 : 1, hexane–^{i}PrOH, 0.5 ml min^{-1}, 254 nm) t_R(major) 10.1 min, t_R(minor) 10.8 min.

General procedure for the synthesis of 1,2-oxazines catalysed by the Maruoka catalyst

To a stirred solution of the Maruoka catalyst (4 mg, 0.006 mmol, 10 mol%) in THF (0.5 ml) was added nitrosobenzene (7 mg, 0.060 mmol, 1.0 eq.) in one portion at 0 °C. The resulting solution was stirred vigorously for 10 min before dropwise addition of the appropriate aldehyde (0.180 mmol, 3.0 eq.). The reaction mixture was stirred at 0 °C for 1 h until the reaction was determined to be complete by TLC. Vinyltriphenylphosphonium bromide (34 mg, 0.090 mmol, 1.5 eq.) was added, followed by additional THF (0.2 ml), DMSO (0.3 ml) and sodium hydride (5 mg, 0.132 mmol, 2.2 eq.). After 1.5 h of stirring at 0 °C, the reaction mixture was quenched using saturated aqueous NH_4Cl (5 ml) and extracted with ether (3 × 5 ml). The combined organic layers were washed with saturated aqueous LiCl (10 ml), then H_2O (10 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (solvents noted) to provide the title compounds.

(3*R*)-3-Methyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine (16a). Prepared according to the general procedure from propionaldehyde (0.13 µl, 0.180 mmol) to provide the title compound as a yellow oil (4 mg, 33%) after flash column chromatography (3 : 1, petrol–CH_2Cl_2). R_f 0.72 (3 : 1, petrol–EtOAc); $[\alpha]_D^{25}$ + 183.3 (*c* 0.06 in $CHCl_3$); ν_{max} (film) 2959, 2928, 2859, 1726, 1599, 1492, 1460, 1379, 1268, 1121, 1072, 1057, 958, 878, 754, 693 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.6 Hz, C*H*$_3$CHCH=CH), 4.09–4.14 (1H, m, CH$_3$C*H*CH=CH), 4.37 (1H, dddd, *J* 15.6, 3.2, 1.8, 1.8 Hz, CH=CHC*H*H′O), 4.57 (1H, app dq, *J* 15.6, 1.8 Hz, CH=CHCH*H*′O), 5.89 (1H, dddd, *J* 10.0, 3.2, 1.8, 1.8 Hz, CH=C*H*CH$_2$O), 5.94 (1H, dddd, *J* 10.0, 4.1, 1.8, 1.8 Hz, C*H*=CHCH$_2$O), 6.98 (1H, tt, *J* 7.3, 1.1 Hz, Ph*H*-*para*), 7.09 (2H, dd, *J* 8.7, 1.1 Hz, 2 × Ph*H*-*ortho*), 7.30 (2H, dd, *J* 8.7, 7.3 Hz, 2 × Ph*H*-*meta*); δ_C (150 MHz, $CDCl_3$) 14.6 (*C*H$_3$CHCH=CH), 55.5 (CH$_3$*C*HCH=CH), 68.7 (CH=CH*C*H$_2$O), 116.8 (2 × Ph*C*-*ortho*), 122.0 (Ph*C*-*para*), 124.9 (CH=*C*HCH$_2$O), 128.8 (2 × Ph*C*-*meta*), 129.4 (*C*H=CHCH$_2$O), 148.8 (Ph*C*-N); *m*/*z* (ES) found 176.1078 ([M+H]$^+$ $C_{11}H_{14}NO$), requires 176.1075.

General procedure for the synthesis of *cis*-allylic alcohols through N–O cleavage

To a stirred solution of the 1,2-oxazine (1 eq.) in MeOH was added zinc powder (5 eq.) and 3N aqueous HCl (20 eq.). The resulting suspension was stirred vigorously at room temperature until the reaction was determined to be complete by TLC. The reaction mixture was quenched using saturated aqueous $NaHCO_3$, diluted with H_2O and extracted with EtOAc three times. The combined organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (solvents noted) to provide the desired compound.

(*R*,*Z*)-2-(2-(Phenylamino)ethylidene)cyclohexanol (13a). Prepared according to the general procedure from (6*R*)-2-phenyl-3,5,6,7,8,8a-hexahydro-2*H*-benzo[*e*][1,2]oxazine (19 mg, 0.084 mmol) for 48 h to provide the title compound as a brown solid (15 mg, 83%, 99% ee) after flash column chromatography (3 : 1, petrol–EtOAc with 1% triethylamine). R_f 0.28 (3 : 1, petrol–EtOAc with 1% triethylamine); m.p. 56–57 °C; $[\alpha]_D^{25}$ −48.4 (*c* 0.55 in $CHCl_3$); ν_{max} (film) 3675, 3257, 2930, 2901, 2808, 1601, 1522, 1497, 1439, 1408, 1301, 1251, 1234, 1146, 1089, 1060, 1037, 986, 914, 857, 749, 691 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 1.37 (1H, m, CH=CCH$_2$C*H*H′(CH$_2$)$_2$), 1.49–1.61 (2H, m, CH=C(CH$_2$)$_2$C*H*H′C*H*H′), 1.69–1.90 (3H, m, CH=CCH$_2$CH*H*′CH*H*′CH*H*′), 2.00 (1H, app dt, *J* 13.5, 4.2 Hz,

CH=CC*H*H′$(CH_2)_3$), 2.39–2.46 (1H, m, CH=CCH*H*′$(CH_2)_3$), 3.73–3.82 (2H, m, PhNHCH_2CH=C), 4.70 (1H, t, *J* 3.7 Hz, CH=CC*H*OH), 5.38–5.42 (1H, m, PhNHCH_2C*H*=C), 6.64 (2H, dd, *J* 8.6, 1.1 Hz, 2 × Ph*H-ortho*), 6.73 (1H, tt, *J* 7.3, 1.1 Hz, Ph*H-para*), 7.18 (2H, dd, *J* 8.6, 7.3 Hz, 2 × Ph*H-meta*); δ_C (125 MHz, $CDCl_3$) 20.8 (CH=C$(CH_2)_2$ *C*H_2CH_2), 27.8 (CH=CCH_2*C*$H_2(CH_2)_2$), 32.7 (CH=C*C*$H_2(CH_2)_3$), 34.6 (CH=C$(CH_2)_3$*C*H_2), 40.9 (PhNH*C*H_2), 65.5 (CH=C*C*HOH), 113.4 (2 × Ph*C-ortho*), 118.0 (Ph*C-para*), 120.9 (PhNHCH_2-*C*H=C), 129.2 (2 × Ph*C-meta*), 144.3 (PhNHCH_2CH=*C*), 147.9 (Ph*C*–N); *m/z* (ES) found 240.1365 ([M+Na]$^+$ $C_{14}H_{19}NONa$), requires 240.1364; HPLC (Chiralcel OD-H, 90 : 10, hexane–^{i}PrOH, 1.0 ml min^{-1}, 254 nm) t_R(minor) 28.6 min, t_R(major) 35.1 min.

General procedure for the synthesis of 3,6-dihydropyridazines from aldehydes

To a stirred solution of the appropriate aldehyde (1.2 eq.) and aminating agent (1.0 eq.) in CH_2Cl_2 (3 ml per mmol of the aminating agent) was added (2*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole catalyst (10 mol%). The resulting suspension was stirred at room temperature until the yellow colour of the azodicarboxylate or the red colour of the *N*-phenyltriazolinedione, respectively, disappeared. The mixture was then cooled to 0 °C, THF (1 ml per ml of CH_2Cl_2) added. Vinyltriphenylphosphonium bromide (1.5 eq.) was added, followed by NaH (2.5 eq.). After 45 min of stirring at 0 °C, the reaction mixture was quenched using saturated aqueous NH_4Cl (2 ml per ml reaction volume) and extracted with CH_2Cl_2 (3 × 1 ml per ml reaction volume). The combined organic layers were washed with brine (2 ml per ml reaction volume) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (solvents noted) to provide the title compounds.

(3*R*)-3-Isopropyl-3,6-dihydro-pyridazine-1,2-dicarboxylic acid diethyl ester (18a). Prepared according to the general procedure from isovaleraldehyde (130 µl, 103 mg, 1.2 mmol) and diethyl azodicarboxylate (97% purity, 162 µl, 179 mg, 1.0 mmol). Purification by gradient flash column chromatography (10 : 1 → 2 : 1, petrol–EtOAc) gave the title compound as a colourless oil (241 mg, 89%, 94% ee). R_f 0.45 (3 : 1, petrol–EtOAc); $[\alpha]_D^{25}$ −98.3 (*c* 1.00 in $CHCl_3$); ν_{max} (film) 2961, 2872, 1705, 1467, 1407, 1378, 1337, 1287, 1211, 1173, 1111, 1059, 1024, 926, 872, 826, 755, 707 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.95–1.02 (3H, m, CH(C*H*$_3$)(CH′$_3$)), 1.06 (2.25H, d, *J* 6.6 Hz, CH(CH$_3$)(C*H*′$_3$) of major rotamer), 1.11 (0.75H, d, *J* 6.6 Hz, CH(CH$_3$)(C*H*′$_3$) of minor rotamer), 1.19–1.33 (6H, m, 2 × CH_2CH_3), 1.71–1.85 (1H, m, C*H*$(CH_3)_2$), 3.62–3.95 (1H, m, NC*H*H′), 4.02–4.30 (5H, m, NC*H* and 2 × $CO_2CH_2CH_3$), 4.30–4.40 (1H, m, NCH*H*′), 5.66–5.82 and 5.83–5.95 (2H, m, C*H*=C*H*); δ_C (100 MHz, $CDCl_3$) 14.5 and 14.6 (CH_2CH_3), 19.1 and 20.1 (CH(*C*H$_3$)$_2$), 32.2 (*C*H$(CH_3)_2$), 42.5 (N*C*H$_2$), 60.7 (N*C*H), 62.0 and 62.3 (2 × $CO_2CH_2CH_3$), 122.8 and 127.1 (*C*H=*C*H), 155.4 (2 × $CO_2CH_2CH_3$); *m/z* (ESI) found 293.1476 ([M+Na]$^+$ $C_{13}H_{22}N_2O_4Na$), requires 293.1477; SFC (Chiralcel OD-H, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 200 nm) t_R(major) 6.0 min, t_R(minor) 4.9 min.

Diethyl 3-methylenepyridazine-1,2(3*H*,6*H*)-dicarboxylate (19). Prepared according to the general procedure from 3-(*tert*-butyldimethylsilyloxy)propanal (226 mg, 1.2 mmol) and diethyl azodicarboxylate (97% purity, 162 µl, 179 mg, 1.0 mmol) and proline as a catalyst. Reaction time for the α-amination was 48 h. Purification by gradient flash column chromatography (10 : 1 → 2 : 1, hexane–EtOAc) gave the title compound as a colourless oil (105 mg, 44%). R_f 0.50 (3 : 1, hexane–EtOAc); ν_{max} (film) 2983, 2937, 2910, 1713, 1646, 1600, 1466, 1398, 1372, 1327, 1282, 1257, 1207, 1172, 1127, 1090, 1037, 1022, 952, 910, 872, 754 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 1.13–1.31 (6H, m, 2 × $CO_2CH_2CH_3$), 3.67–3.95 (1H, m, NC*H*H′), 4.04–4.31 (4H, m, 2 × $CO_2CH_2CH_3$), 4.37–4.67 (1H, m, NCH*H*′), 4.93 (1H, s, C=C*H*H′), 5.21–5.56 (1H, m, C=CH*H*′), 5.85 (1H, br s, C*H*=CHC=CH_2), 6.06 (1H, d, CH=C*H*C=CH_2); δ_C (150 MHz, $CDCl_3$) 14.4 (2 × $CO_2CH_2CH_3$), 43.8 (N*C*H$_2$), 62.5 and 62.6 (2 × $CO_2CH_2CH_3$), 108.0 (CH=CHC=*C*H$_2$), 124.5 and 125.0 (*C*H=*C*HC=CH_2), 137.2 (CH=CH*C*=CH_2), 155.7 (2 × $CO_2CH_2CH_3$); *m/z* (ESI) found 263.1000 ([M+Na]$^+$ $C_{11}H_{16}N_2O_4Na$), requires 263.1008.

General procedure for the synthesis of pyridazines from ketones

To a stirred solution of the appropriate ketone (1.2 eq.) and diethyl azodicarboxylate (1.0 eq.) in CH_2Cl_2 (5 ml per mmol of diethyl azodicarboxylate) was added (2*S*)-5-pyrrolidin-2-yl-1*H*-tetrazole catalyst (20 mol%). The reaction mixture was stirred at room temperature for 24 h. DMSO (1 ml per ml of CH_2Cl_2) and vinyltriphenylphosphonium bromide (1.5 eq.) were added. The solution was cooled to 0 °C and then added in one portion *via* syringe to a suspension of KH (2.5 eq., 30%, in mineral oil, washed with hexane (2 × 3 ml)) in THF (1 ml per ml of CH_2Cl_2) at 0 °C. The reaction mixture was slowly allowed to warm to room temperature and quenched after 270 min with saturated aqueous NH_4Cl (2 ml per ml reaction volume) and extracted with CH_2Cl_2 (2 × 1 ml per ml reaction volume). The combined organic layers were washed with saturated aqueous LiCl (2 ml per ml reaction volume), brine (2 ml per ml reaction volume) and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (solvents noted) to provide the title compounds.

(8a*R*)-3,5,6,7,8,8a-Hexahydrocinnoline-1,2-dicarboxylic acid diethyl ester (21a). Prepared according to the general procedure from cyclohexanone (124 µl, 118 mg, 1.2 mmol) to provide the title compound as a colourless oil (147 mg, 52%, 76% ee) after flash column chromatography (5 : 1, petrol–EtOAc). R_f 0.62 (2:1, petrol–EtOAc); $[\alpha]_D^{25}$ −101.2 (*c* 2.00 in $CHCl_3$); ν_{max} (film) 2933, 2856, 2295, 1704, 1415, 1382, 1342, 1298, 1240, 1216, 1172, 1141, 1115, 1094, 1070, 1047, 1026, 960, 884, 799, 755 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.08–1.35 (7H, m, one of (C*H*$_2$)$_4$ and 2 × CH_2CH_3), 1.38–1.52 (2H, m, two of (C*H*$_2$)$_4$), 1.71–1.90 (2H, m, two of (C*H*$_2$)$_4$), 1.91–2.10 (2H, m, two of (C*H*$_2$)$_4$), 2.20–2.32 (1H, m, one of (C*H*$_2$)$_4$), 3.55–3.90 (1H, m, NC*H*H′), 4.15–4.22 (4H, m, 2 × $CO_2CH_2CH_3$), 4.22–4.46 (2H, m, NC*H* and NCH*H*′), 5.42 (1H, br s, C=C*H*); δ_C (100 MHz, $CDCl_3$) 14.9 and 15.0 (2 × $CO_2CH_2CH_3$); 25.5, 28.1, 32.6 and 35.1 ((*C*H$_2$)$_4$), 43.2 (N*C*H$_2$), 57.1 (N*C*H), 62.3 and 62.5 (2 × $CO_2CH_2CH_3$), 114.4 (C=*C*H), 139.5 (*C*=CH), 155.7 and 156.0 (2 × $CO_2CH_2CH_3$); *m/z* (ESI) found 305.1486 ([M+Na]$^+$ $C_{14}H_{22}N_2O_4Na$), requires 305.1477; SFC (Chiralcel OD-H, 10% ^{i}PrOH in CO_2, 1.0 ml min^{-1}, 100 bar, 200 nm) t_R(major) 9.2 min, t_R(minor) 7.9 min.

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