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Catalytic enantioselective Steglich rearrangements using chiral *N*-heterocyclic carbenes

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ABSTRACT

The evaluation of a range of enantiomerically pure NHCs, prepared in situ from imidazolinium or triazolium salt precatalysts, to promote the catalytic enantioselective Steglich rearrangement of oxazolyl carbonates to their *C*-carboxyazlactones, is reported. Modest levels of enantioselectivity (up to 66% ee) are observed using oxazolidinone derived NHCs.

1. Introduction

N-Heterocyclic carbenes (NHCs) are versatile and widely used reagents, catalysts and ligands that have been utilised in a variety of synthetic applications. Building upon the classic umpolung reactivity modes observed using NHC mediated catalysis of the Benzoin and Stetter reactions, a number of asymmetric organocatalytic transformations promoted by NHCs have been developed within the last decade.[1] Asymmetric induction within these processes is generally achieved via the formation a C–C, C–H or C–heteroatom bond with one of four main synthetic intermediates that are prepared in situ; three nucleophilic species **1**–**3** that are d^1, d^2 and d^3 synthons (acyl anion,[2] azolium enol or enolate,[3,4] and azolium homoenolate[5,3b] intermediates, respectively) and an electrophilic acylazolium species **4** (Fig. 1).[6]

While asymmetric reactions utilising acyl anion, azolium enolate and azolium homoenolates have been much studied, relatively few asymmetric processes that involve the *direct* preparation of an asymmetric acylazolium species have been developed. In this area, enantiomerically pure NHCs have been used to facilitate asymmetric O-acylation reactions, with applications in kinetic resolution and desymmetrisation processes. For example, Marouka et al. have employed chiral C_2-symmetric imidazolium salt **6** and enol ester **7** to achieve excellent levels of enantioselectivity (*S* up to 80) in the kinetic resolutions of alkyl-aryl carbinols **5** (Fig. 2).[7] Related work by Suzuki et al. has shown that good selectivity (*S* up to 37) in the kinetic resolution of 2-naphthylethanol can be achieved using a related imidazolium salt as a precatalyst and vinyl acetate as the acyl donor.[8]

Alternative approaches to the generation of chiral acylazolium ions have been used by Rovis et al. and Scheidt et al. with applications to desymmetrisation processes. Rovis et al. have applied a

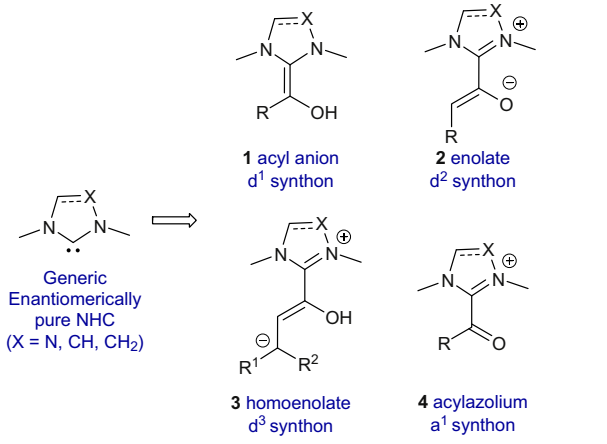

Figure 1. Common synthetic intermediates through which asymmetric organocatalytic processes occur with NHCs.

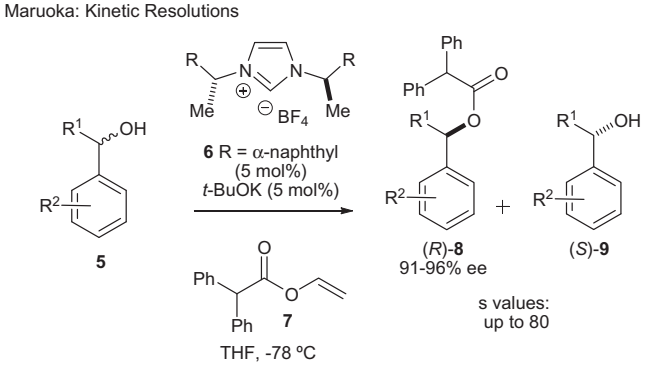

Figure 2. Kinetic resolution of alkyl-aryl carbinols with chiral NHCs.

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redox strategy to generate a chiral acylazolium species from α-haloaldehyde **10** using the NHC derived from precatalyst **12**, allowing the desymmetrisation of *meso*-hydrobenzoin **11** to give ester **13** in good yield and 83% ee.[9] Scheidt et al. have used an in situ hydroxyazolium oxidation strategy to allow the desymmetrisation of diol **14** using chiral triazolium salt **16**, giving mono-ester **17** in 80% ee (Fig. 3).[10]

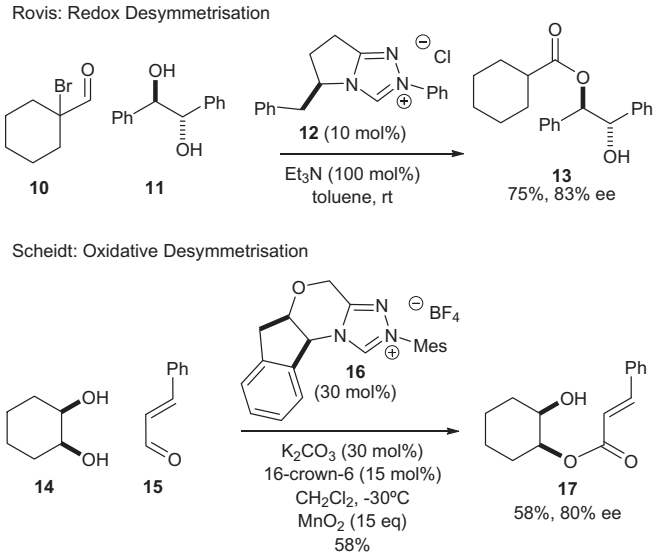


Figure 3. Desymmetrisation strategies using NHCs.

As part of an ongoing research programme to investigate the use of Lewis bases in catalysis, we have extensively probed the ability of achiral NHCs to catalyse the Steglich *O*- to *C*-carboxyl rearrangement[11] of a variety of heterocyclic carbonate derivatives, a reaction that presumably proceeds via the intermediacy of a carboxyazolium ion **22**. For example, the generation of NHC **19** by deprotonation of triazolium salt **18** with a metallated base (typically KHMDS) promotes the rearrangement of oxazolyl carbonates **20** to their *C*-carboxyazlactones **23** with excellent tolerance of structural diversity at either C(4)- or within the carbonate functionality (Fig. 4).[12]

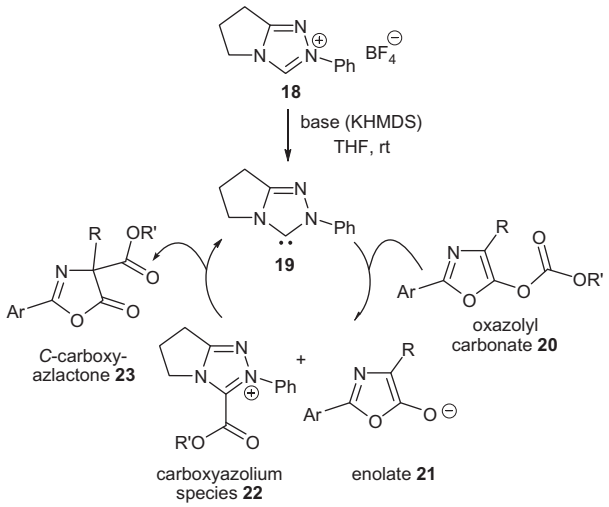


Figure 4. NHC promoted *O*- to *C*-carboxyl transfer of oxazolyl carbonates.

Within the literature, a range of asymmetric Lewis base mediated *O*- to *C*-carboxyl rearrangement processes have been developed,[13] with enantiomerically pure derivatives of PPY and DMAP such as **26**–**29** used by the Fu,[14] Richards,[15] Vedejs[16] and Gotor et al.[17], respectively, to generate enantiomerically enriched *C*-carboxyazlactones.[18] Alternative catalyst motifs such as phosphine **30**,[16a] as well as isothioureas **31**[19] and **32**,[20] have also been used to promote enantioselective carboxyl and acyl transfer processes.[21] Ooi et al. have recently disclosed the ability of chiral ammonium betaine **33** as a highly enantioselective catalyst of this transformation,[22] while Zhang has shown that bicyclic imidazoles such as **34** deliver high asymmetry in this reaction process (Fig. 5).[23] Herein, we report the ability of chiral NHCs to promote the asymmetric *O*- to *C*-carboxyl transfer reaction of oxazolyl carbonates and some preliminary mechanistic investigations regarding this transformation.

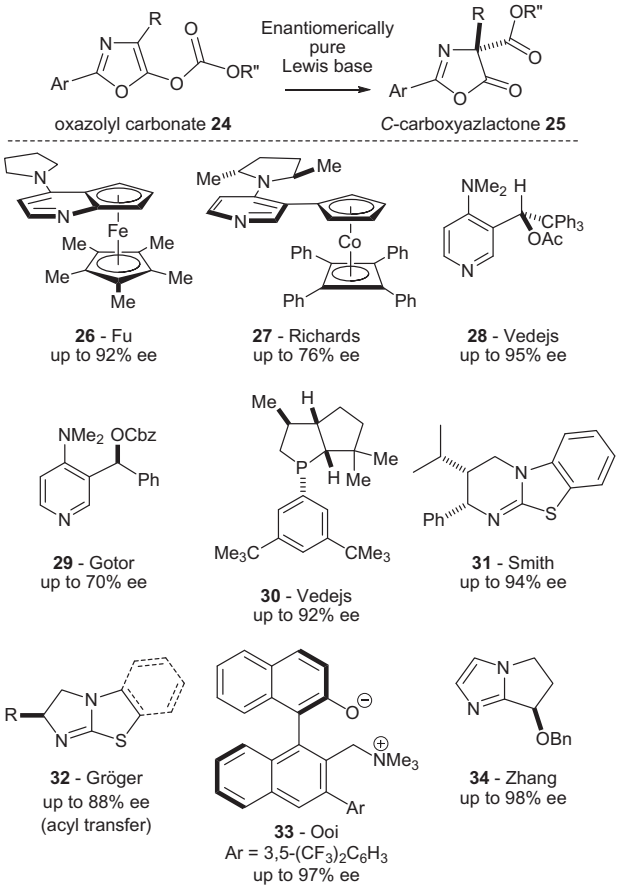


Figure 5. Lewis base catalysts for the asymmetric *O*- to *C*-carboxyl and acyl rearrangement of oxazolyl carbonates and esters.

2. Results and discussion

2.1. Precatalyst and reaction screening and optimisation studies

Initial investigations probed the ability of a range of structurally diverse NHCs **39**–**53** to promote an asymmetric Steglich rearrangement. As our previous work has shown that oxazolyl phenyl carbonates undergo facile NHC promoted *O*- to *C*-carboxyl transfer, the rearrangement of phenyl carbonate **35** to *C*-carboxyazlactone **36** was chosen as a model for optimisation. Variation in the reactivity and enantioselectivity with structural diversity of the parent azolium salt precatalyst (imidazolium, imidazolinium and triazolium derived) and the stereodirecting group(s) within the catalyst were tested, with KHMDS used as the base in each case (Fig. 6). Notably, NHCs derived from either C_2- or C_1-symmetric imidazolium or imidazolinium precatalysts **39**–**43** gave essentially no

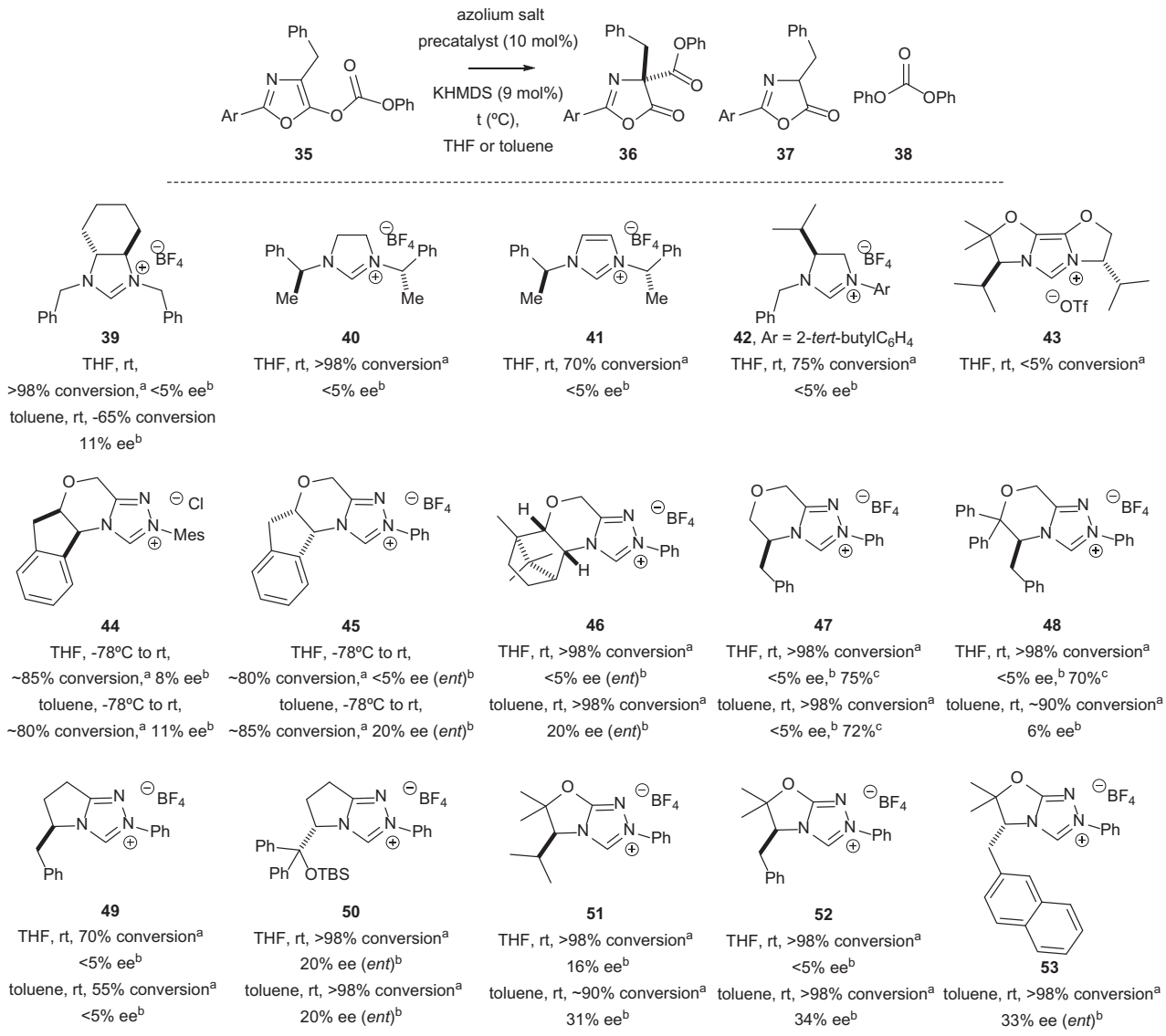


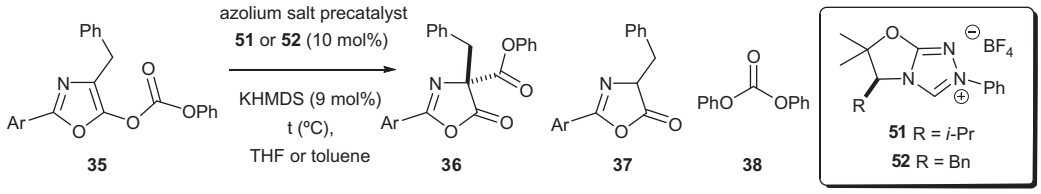
Figure 6. Asymmetric Steglich rearrangements with NHCs (absolute configuration determined by comparison of the specific rotation of **35** and HPLC retention times in comparison to the literature).[19] [a]As shown by ^{1}H NMR spectroscopic analysis of the crude reaction product; the remaining product mass parent azlactone **37** and diphenylcarbonate **38**. [b]Determined by chiral HPLC analysis. [c]Isolated yield of homogeneous product after chromatographic purification.

enantioselectivity (<5% ee) in this protocol but good consumption of **35**, typically giving *C*-carboxyl **36** as the major reaction product and a corresponding quantity of azlactone **37** and diphenylcarbonate **38**. Triazolium precatalysts **44**–**48** with a fused 5;6-skeleton showed consistently good reactivity, essentially giving exclusively **36**, although with poor enantioselectivity observed in THF (<10% ee) and a modest improvement in toluene (up to 20% ee). Alternative triazolium precatalysts **49**–**53** based upon a fused 5;5-skeleton showed generally good reactivity, resulting in good conversion to product **36** (typically >90%), with NHCs prepared from the oxazolidinone derived precatalysts **51**–**53** giving the highest, although still modest, enantioselectivity in this initial screen with toluene as the solvent (31–34% ee).

Subsequent optimisation studies for the preparation of **36** from oxazolyl carbonate **35** focused upon the effect of base, solvent and reaction temperature using oxazolidinone-derived precatalysts **51** and **52**. Using KHMDS (9 mol %) as the base, screening of a range of solvents showed that THF allowed good reactivity, almost giving exclusively *C*-carboxyazlactone **36** but with poor enantioselectivity. Toluene or mixtures of solvents containing predominantly toluene, gave the highest product ees. In toluene, improved product enantioselectivities were observed upon cooling but also significant quantities of azlactone **37** and diphenyl carbonate (up to 40%) as by-products were observed. Furthermore, the NHC prepared from precatalyst **51** bearing an *i*-Pr stereodirecting unit proved more reactive than **52** bearing a Bn stereodirecting group, giving acceptable conversions at reaction temperatures down to −50 °C (up to 50% ee). However, long reaction times (typically 16 h) were needed for the reactions to proceed to acceptable conversions at these lower temperatures (Table 1). Further studies using KHMDS in toluene, showed that the ee of the product was also independent of the concentration of the NHC from [0.25 mM] to [50 mM].

Further work studied the effect of varying the base using precatalyst **51** at rt. In general, the use of a metallated base (KHMDS or LiHMDS) gave optimal reactivity, giving excellent conversion to the product, but with only a negligible effect on product ee (Table 2, 32–39% ee). It should be noted that Cs_2CO_3 as well as

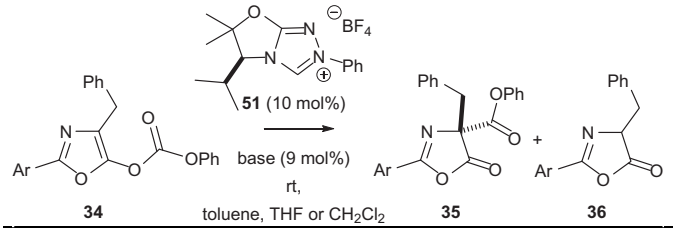
Table 1
Asymmetric Steglich rearrangements with NHCs: solvent optimisation (absolute configuration determined by comparison of the specific rotation of **35** and HPLC retention times in comparison to the literature)[19]



Entry	Precatalyst	t (℃)	solvent	ee (%)[a]	Ratio **36**:**37**[b]
1	**51**	rt	THF	16	>98:2
2	**51**	rt	C_6H_5Cl	8	>98:2
3	**51**	rt	benzene	20	>98:2
4	**51**	rt	20% C_6H_5Cl in toluene	29	>98:2
5	**51**	rt	20% hexane in toluene	32	>98:2
6	**51**	rt	toluene	33	>98:2
7	**51**	−20	toluene	43	80:20
8	**51**	−30	toluene	50	65:35
9	**51**	−30	20% C_6H_5Cl in toluene	48	60:40
10	**51**	−30	20% hexane in toluene	50	60:40
11	**52**	−50	toluene	48	60:40
12	**52**	rt	THF	2	>98:2
13	**52**	rt	Et_2O	27	>98:2
14	**52**	rt	C_6H_5Cl	13	>98:2
15	**52**	rt	benzene	14	>98:2
16	**52**	rt	toluene	34	>98:2
17	**52**	−10	toluene	39	90:10
18	**52**	−15	toluene	43	90:10
19	**52**	−20	toluene	46	80:20
20	**52**	−30	toluene	–	No reaction

[a] Determined by chiral HPLC analysis.
[b] As shown by ^{1}H NMR spectroscopic analysis of the crude reaction product.

Table 2
Asymmetric Steglich rearrangements with NHCs: base optimisation (absolute configuration determined by comparison of the specific rotation of **35** and HPLC retention times in comparison to the literature)[19]



Entry	Solvent	Base	ee[a] (%)	Ratio **35**:**36**[b]
1	Toluene	KHMDS	32	>98:2
2	Toluene	KH	31	80:20
3	Toluene	*t*-BuOK	31	80:20
4	Toluene	NaHMDS	33	70:30
5	Toluene	NaH	5	70:30
6	Toluene	LiHMDS	39	95:5
7	THF	Cs_2CO_3	25	80:20
8	Toluene	Cs_2CO_3	5	75:25
9	CH_2Cl_2	NEt_3	22	90:10

[a] Determined by chiral HPLC analysis.
[b] As shown by ^{1}H NMR spectroscopic analysis of the crude reaction product.

the organic base NEt_3, can also be used to promote the rearrangement, but generate *C*-carboxyazlactone **36** with low ee and with significant quantities (up to 30%) of the azlactone by-product (entries 7–9, <5–25% ee).

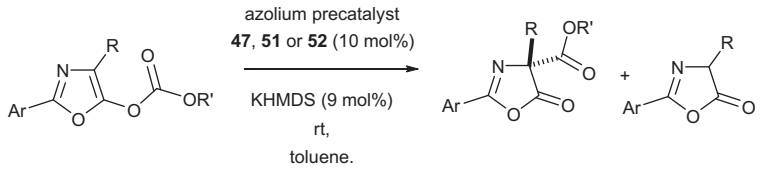
2.2. Reaction generality

After these optimisation studies, the generality of this *O*- to *C*-carboxyl transfer process was studied, using KHMDS as the base and employing toluene as the reaction solvent. In particular, the effect upon changing the carbonate from an aryl functionality to a relatively unreactive alkyl carbonate group, as well as variation of the C(4)-substituent was investigated. Under standardised conditions, the NHCs derived from precatalysts **51** and **52** gave best conversion to the product *C*-carboxyazlactones with reactive aryl carbonates (up to 42% ee). Slightly improved enantioselectivity, but poor reactivity (typically 40–50%, up to 80% conversion), were noted with alkyl carbonates (up to 66% ee), with *i*-Pr substituted precatalyst **51** generally giving better levels of conversion to the *C*-carboxyazlactone product. Given these findings, the reactivity and enantioselectivity of the NHC derived from precatalyst **47** was tested upon a range of substrates, giving excellent levels of reaction conversion in each case, but with disappointing enantioselectivities (up to 31% ee) (Table 3).

2.3. Mechanistic studies: crossover experiments

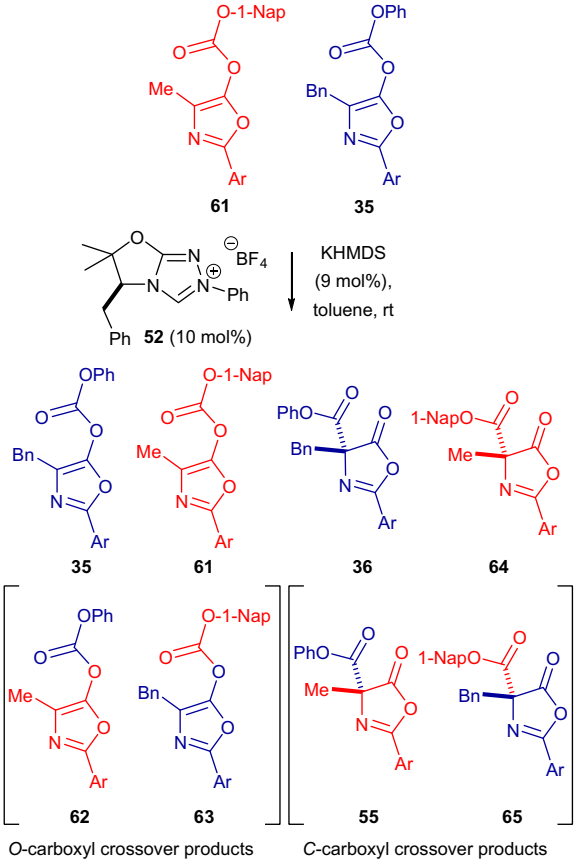
Due to the low enantioselectivities observed within this NHC-catalysed process, simple mechanistic studies were pursued to determine if the low stereoselectivities observed were a consequence of low enantiocontrol in the C–C bond-forming event, or if racemisation was occurring in situ. Control experiments indicated that the *C*-carboxyazlactone products are configurationally stable under the reaction conditions, as retreatment of *C*-carboxyazlactone **36** (20% and 50% ee samples) with the NHC derived from precatalyst **51** returned starting materials with identical enantioselectivities. Furthermore, monitoring the rearrangement of **35** to *C*-carboxyazlactone **36** using the NHC derived from precatalyst **51** showed that the product ee of 50% was independent of conversion and time at −30 °C. Both of these observations are consistent with the C–C bond-forming event in this reaction being irreversible, with the low product enantioselectivities being the

Table 3
Asymmetric Steglich rearrangements with NHCs (absolute configurations determined by comparison of specific rotations and HPLC retention times to the literature)[19]



Entry	Precatalyst	R	R'	Product	Product ratio (%)[a]	ee (%)[b]
1	**51**	Bn	Ph	**36**	>98:<2	32
2	**51**	Bn	Me	**54**	50:0	37
3	**51**	Me	Ph	**55**	>98:<2	19
4	**51**	Me	Me	**56**	0:0	–
5	**52**	Bn	Ph	**36**	>98:<2	34
6	**52**	Bn	Me	**54**	95:5	24
7	**52**	Bn	CMe_2CCl_3	**57**	40:0	8
8	**52**	Me	Ph	**55**	>98:<2	42
9	**52**	Et	Ph	**58**	>98:<2	22
10	**52**	4-$BnOC_6H_4CH_2$	Ph	**59**	>98:<2	8
11	**52**	*i*-Bu	CMe_2CCl_3	**60**	40:0	66
12	**47**	Bn	Ph	**36**	95:5	<5, (72%)[c]
13	**47**	Et	Ph	**58**	90:10	<5, (70%)[c]
14	**47**	Me	Me	**56**	>95:<5	31, (70%)[c]
15	**47**	*i*-Bu	CMe_2CCl_3	**60**	>95:<5	5, (85%)[c]

[a] As shown by ^{1}H NMR spectroscopic analysis of the crude reaction product; reaction conversions indicated by summation of *C*-carboxyl and azlactone product ratios.
[b] Determined by chiral HPLC analysis.
[c] Isolated yield of homogeneous product mixture after purification.



Scheme 1. Asymmetric NHC catalysed *O*- to *C*-carboxyl transfer: crossover experiments.

result of low stereocontrol in the C–C bond-forming event. Further studies probed the mechanism of this reaction by analysis of the product distributions arising from crossover experiments. Treatment of a 50:50 mixture of reactive aryl oxazolyl carbonates **35** and **61** with the NHC derived from precatalyst **52** gave a mixture of eight products after a short reaction time; four oxazolyl carbonates **61**:**35**:**62**:**63** (accounting for ~30% of the product ratio) in an approximate 25:25:25:25 ratio, as well as four *C*-carboxyazlactone products **64**:**36**:**55**:**65** (accounting for ~70% of the product ratio) in an approximate 25:25:25:25 ratio (Scheme 1).

These crossover and product stability experiments are consistent with this *O*- to *C*-carboxyl group transfer process proceeding through a mechanistic pathway involving an initial rapid and reversible *O*-carboxylation process (allowing for crossover in the oxazolyl carbonates), followed by an irreversible C-carboxylation event that occurs with low levels of enantiocontrol with chiral NHCs (Fig. 7). This mechanistic rationale is identical to that observed in this process by both Fu et al. using PPY* **26**[14] and ourselves with achiral NHCs in this reaction manifold.[12f]

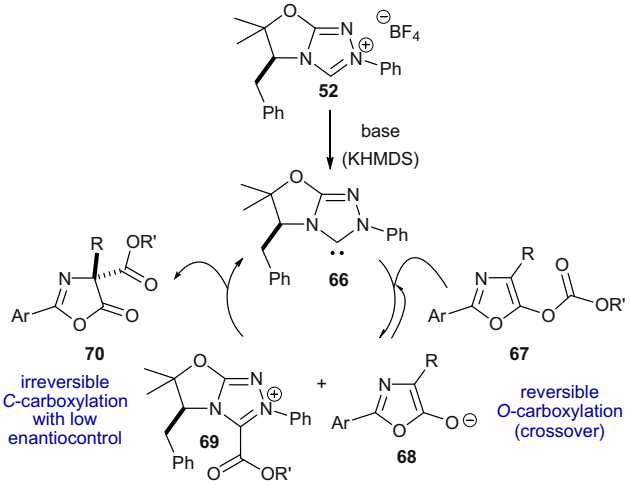


Figure 7. Proposed mechanistic pathway for the chiral NHC catalysed *O*- to *C*-carboxyl transfer reaction.

3. Conclusion

In conclusion, we have demonstrated that a range of chiral NHCs promote the asymmetric Steglich rearrangement of oxazolyl carbonates with modest reactivity and enantioselectivity. Current studies are aimed at developing alternative modes of asymmetric catalysis using enantiomerically pure NHCs.

4. Experimental section

4.1. General information

The ^{1}H NMR Spectra were recorded using a Bruker Avance 400 spectrometer and Bruker Avance 300 spectrometer at 400 and 300 MHz, respectively, using residual protonated solvent as a reference for internal lock. The chemical shift information (δ_H) for each resonance signal are given in units of parts per million (ppm) relative to tetramethylsilane (TMS) where δ_H TMS = 0.00 ppm, or to residual (protonated) solvent. The number of protons (n) for a reported resonance signal are indicated by nH from their integral value and their multiplicity is reported with their coupling constants (J) quoted in Hz. Coupling constants are determined by analysis using iNMR® and Topspin®. The ^{13}C NMR Spectra were recorded using a Bruker Avance 300 and Bruker Avance 400 spectrometer using the PENDANT sequence at 75.5 MHz and 100 MHz, respectively, with internal deuterated solvent lock. The chemical shift information (δ_C) for each resonance signal is given in units of parts per million (ppm) relative to tetramethylsilane (TMS) where δ_C TMS = 0.00 ppm, or to the relevant solvent.

Mass spectrometric (m/z) data were acquired by electrospray ionisation (ESI), electron impact (EI) or chemical ionisation (CI), either at the University of St Andrews Mass Spectrometry facility ([A] quoted) or at the EPSRC National Mass Spectrometry Service Centre, Swansea ($[A]^+$ or $[A]^-$ quoted). At the University of St Andrews, low and high resolution ESI MS was carried out on a Micromass LCT spectrometer and low and high resolution EI and CI MS was carried out on a Micromass GCT spectrometer. At the EPSRC National Mass Spectrometry Service Centre, low resolution ESI MS was carried out on a Waters Micromass ZQ4000 spectrometer and low resolution EI and CI MS was carried out on a Micromass Quattro II spectrometer. High resolution ESI and ESI MS were carried out on a Finnigan MAT 900 XLT or a Finnigan MAT 95 XP; a Thermofisher LTQ Orbitrap XL spectrometer was also used to obtain high resolution ESI MS for accurate mass determination but also provided fragmentation data for the characterisation of samples. Values are quoted as a ratio of mass to charge in Daltons. Melting points were determined using an Electrothermal 9100 melting point apparatus and are uncorrected. Optical rotations were determined using a PerkinElmer Model 341 Polarimeter, at 20.0 °C using a Na/Hal lamp tuned to 589 nm. Chiral HPLC was performed on either a Varian ProStar or Gilson apparatus, using a CHIRALPAK OD-H, AD-H or AS-H silica column, 0.46 cm $\phi \times 25$ cm, using hexane and isopropanol as eluents. Analytical thin layer chromatography (TLC) was carried out on pre-coated 0.20 mm Machery–Nagel Polygram SIL G/UV$_{254}$ silica plates. Visualisation was carried out by absorption of ultraviolet light or thermal decomposition after dipping in either an ethanolic solution of phosphomolybdic acid or an aqueous solution of potassium permanganate/sodium hydroxide. Chromatography was performed using Merck Ltd. silica gel 40–63 μm, eluting with solvents supplied under a positive pressure of compressed air. Anhydrous solvents were obtained under the following conditions: dry dichloromethane was distilled from calcium hydride in a recycling still; dry THF was distilled from sodium in a recycling still using benzophenone ketyl as an indicator; dry diethyl ether was distilled from sodium in a recycling still using benzophenone ketyl as an indicator.

From January 2007, anhydrous solvents were obtained from the MBraun SPS-800 solvent purification system. Chemicals were purchased from Acros UK, Sigma–Aldrich UK, Alfa Aeasar UK, Fisher UK or Merck. Brine refers to a saturated aqueous solution of sodium chloride. Reactions involving moisture sensitive reagents were performed under an atmosphere of N_2 or Ar using standard vacuum line techniques and with freshly distilled solvents. All glassware was flame-dried and allowed to cool under vacuum. For known compounds, where certain elements of analytical data are not described in the literature, these data have been reported and are marked §.

4.2. General procedures

4.2.1. Formation of oxazolyl carbonates with triethylamine

4.2.1.1. General procedure A. At first, Et_3N (1.1–1.5 equiv) was added to a stirred solution of the desired azlactone (1 equiv) in THF at 0 °C, followed by the addition of the desired chloroformate (1.06 equiv). The mixture was stirred at 0 °C for 30 min before warming to ambient temperature and stirring over 16 h. The resulting solution was poured into H_2O and the aqueous phase extracted with Et_2O (×3). The organic extracts were combined, washed with 0.1 M HCl(aq), satd $NaHCO_3$(aq) solution, brine, dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by recrystallisation or silica chromatography gave the desired product.

4.2.2. Procedures for Steglich rearrangement

4.2.2.1. General procedure B (standard protocol). To a mixture of azolium salt (x mol %) in solvent (typically THF, ~1 mL per 100 mg of carbonate) was added a solution of base in solvent (0.9x mol %). The mixture was stirred for 20 min then a solution of carbonate (1 equiv) in solvent (typically THF, ~1 mL per 100 mg of carbonate) was added via cannula. The mixture was stirred for y min then concentrated in vacuo and, if necessary, the residue was purified by silica chromatography.

4.2.2.2. General procedure C (low temperature). To a mixture of azolium salt (x mol %) in THF or toluene (~1 mL per 100 mg of carbonate) was added a solution of base in solvent (0.9x mol %). The mixture was stirred for 20 min then cooled to the requisite temperature and a cooled solution of carbonate (1 equiv) in THF or toluene (~1 mL per 100 mg of carbonate) was added via cannula. The mixture was stirred at the requisite temperature for a given period of time then concentrated in vacuo, and, if necessary, the residue was purified by silica chromatography.

4.2.2.3. General procedure D (one-pot). To a mixture of azolium salt (x mol %) and carbonate (1 equiv) in THF or toluene (~1 mL per 100 mg of carbonate) was added a solution of base in solvent (0.9x mol %). The mixture was stirred for y min then concentrated in vacuo and, if necessary, the residue was purified by silica chromatography.

For crossover experiments, 0.5 equiv of both carbonate substrates were combined in the relevant solvent, and following the aforementioned general procedure H (assuming 1 equiv of carbonate substrate is added), a sample of the product mixture was concentrated in vacuo then examined spectroscopically to determine the product distributions.

4.3. (*R*)- and (*S*)-Phenyl 4-benzyl-5-oxo-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylate 36

Following general procedure B, KHMDS (44.8 μL, 22.4 μmol), triazolium salt **39**–**53** (24.9 μmol), THF (1 mL) and oxazolyl carbonate **35** (100 mg, 0.249 mmol) gave, after concentration in va-

cuo, a mixture of unreacted carbonate starting material **35**, the desired *C*-carboxyazlactone **36**, azlactone **37** and diphenyl carbonate **38** in varying proportions. Conversion was determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. Purified samples were obtained by chromatographic purification (20% Et_2O/petrol), obtaining the title compound **36** as a colourless oil. δ_H (300 MHz, $CDCl_3$) 7.92–7.87 (2H, m, MeOAr*H*-2,6), 7.43–7.37 (2H, m, Ph*H*), 7.30–7.19 (6H, m, Ph*H*), 7.15–7.10 (2H, m, Ph*H*), 6.98–6.94 (2H, m, MeOAr*H*-2,6), 3.88 (3H, s, ArOCH_3), 3.75 (1H, ABd, *J* 13.7, CH_AH$_B$Ph) and 3.61 (1H, ABd, *J* 13.7, CH$_A$$H_B$Ph). Spectroscopic data are in accordance with the literature.[16a]

Enantiomeric excesses were determined by HPLC with Chiralcel OD-H column (5% *i*-PrOH/hexane, flow rate = 1.0 mL min^{-1}), t_R(*R*) 13.8 min and t_R(*S*) 18.9 min.

4.4. Optimisation of asymmetric Steglich rearrangement using chiral oxazolidinone-derived triazolium salts

All reactions were carried out according to general procedure B above, at 10 mol % precatalyst loading, with the relevant base and solvent stated (1 mL solvent, 0.249 mM concentration of carbonate substrate), and at the temperature stated. Conversions were determined spectroscopically, and enantiomeric excesses were determined following chromatographic purification (20% Et_2O/petrol).

4.5. Preparation of azolium salts

4.5.1. N^1,N^2-Bis((*S*)-1-phenylethyl)imidazolinium tetrafluoroborate 40

A mixture of aqueous glyoxal (1.13 mL of a 40% w/v solution, 7.80 mmol), (*S*)-α-methylbenzylamine (2.06 mL, 16.0 mmol), $MgSO_4$ (4.00 g, 33.2 mmol) and formic acid (1 drop) was stirred for 15 min at ambient temperature. The suspension was filtered over Celite and the filtrate concentrated in vacuo, redissolved in hexane (15 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to afford the corresponding imine product as an orange oil (2.04 g, 99%). $[\alpha]_D^{20} = -114.1$ (*c* 0.2, $CHCl_3$), lit.[24] −113.9 (*c* 0.72, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.97 (2H, N=C*H*), 7.35–7.10 (10H, m, Ar*H*), 4.32 (2H, q, *J* 6.7, C*H*(CH_3)Ph) and 1.41 (6H, d, *J* 6.7, CH_3). Data are in accordance with the literature.[24]

To a stirred solution of diimine (1.10 g, 4.16 mmol) in THF (6 mL) was added a solution of lithium aluminium hydride (3.12 mL of a 2.0 M solution, 6.24 mmol) in THF at 0 °C. The mixture was warmed to ambient temperature over 16 h, then recooled to 0 °C and ice-cold H_2O added carefully until gas evolution ceased. An aqueous solution of KOH (3 mL of a 3 M solution) was added then the mixture was extracted with EtOAc (10 mL × 3). The organics were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo to afford the diamine product as an orange oil (890 mg, 80%). $[\alpha]_D^{20} = -70.0$ (*c* 0.5, $CHCl_3$), lit.[25] −69.4 (*c* 1.1, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.39–7.09 (10H, m, Ph*H*), 3.67 (2H, q, *J* 6.7, C*H*(CH_3)Ph), 2.50 (2H, br s, N*H*) and 1.36 (6H, d, *J* 6.7, CH_3). Data are in accordance with the literature.[25]

To a solution of diamine (500 mg, 1.87 mmol) in MeOH (5 mL) was added triethyl orthoformate (0.78 mL, 4.69 mmol) and NH_4BF_4 (218 mg, 2.08 mmol). The mixture was heated at reflux (100 °C) for 90 min, the mixture cooled to ambient temperature and then Et_2O added (5 mL), forming an oily precipitate. Exhaustive trituration (Et_2O) gave the title compound **40** as an orange/yellow oil (500 mg, 73%). $[\alpha]_D^{20} = +23.0$ (*c* 0.5, $CHCl_3$), lit.[26] +23, (*c* 0.51, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.42 (1H, s, NC*H*N), 7.28–7.42 (10H, m, Ph*H*), 4.94 (2H, q, *J* 6.9, PhC*H*CH_3), 3.62–3.76 (4H, m, NCH_2) and 1.73 (6H, d, *J* 6.9, CH_3); δ_C[§] (100 MHz, $CDCl_3$) 154.6 (NCHN), 137.5 (PhC-1), 129.3 (PhCH-2,6), 129.2 (PhCH-4), 127.0 (PhCH-3,5), 58.2 (NCHMePh), 46.3 (*C*H_2) and 18.9 (*C*H_3). Data are in accordance with the literature.[26]

4.5.2. N^1,N^2-Bis((*S*)-1-phenylethyl)imidazolium tetrafluoroborate 41

To a solution of (*S*)-α-methylbenzylamine (1.21 g, 10.0 mmol) in toluene (20 mL) was added paraformaldehyde (300 mg, 10.0 mmol) with vigorous stirring and cooling to 10 °C. After 30 min, further (*S*)-α-methylbenzylamine (1.21 g, 10.0 mmol) was added at 0 °C, to which was then added HBF_4(aq) (1.25 mL of an ~8 M solution, 10.0 mmol) dropwise. After stirring for 15 min, the ice-bath was removed and aqueous glyoxal (1.45 mL of a 40% w/v solution, 10.0 mmol) was added dropwise. The mixture was stirred for 30 min at ambient temperature then heated to 40 °C for 12 h. Et_2O (10 mL) and H_2O (10 mL) were added and the mixture extracted with Et_2O (10 mL × 2). The organic fractions were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to afford a viscous brown oil. Exhaustive trituration with Et_2O followed by heating to 50 °C in vacuo for 12 h gave the title compound **41** as a viscous orange oil (2.73 g, 75%). $[\alpha]_D^{20} = +7.8$ (*c* 0.5, $CHCl_3$);[§] δ_H (300 MHz, $CDCl_3$) 11.04 (1H, s, NC*H*N), 7.32–7.28 (2H, m, Ph*H*), 7.26 (2H, s, NC*H*C), 7.24–7.20 (3H, m, Ph*H*), 5.92 (2H, q, *J* 7.2, C*H*CH_3) and 1.91 (6H, d, *J* 7.2, CH_3). Spectroscopic data are in accordance with the literature.[27]

4.5.3. (*S*)-1-Benzyl-3-(2-*tert*-butylphenyl)-5-isopropyl-4,5-dihydro-1*H*-imidazolium tetrafluoroborate 42

L-Valine (6.57 g, 56.1 mmol) and NaOH (2.34 g) were dissolved in H_2O (17 mL). Next, Et_2O (90 mL) was added, and the mixture was cooled to 0 °C and stirred rapidly. Benzoyl chloride (6.58 mL, 56.6 mmol) and a solution of NaOH (2.34 g) in H_2O (6 mL) were added alternatively portionwise over 90 min, then the mixture was warmed to ambient temperature over 16 h. The mixture was then concentrated to half volume in vacuo before concd HCl (5 mL) was added to induce precipitation of the product. The product was collected by filtration and washed with Et_2O (100 mL) and dried to obtain *N*-benzoylvaline as a colourless solid (10.3 g, 83%), which was used immediately without further purification. A suspension of *N*-benzoylvaline (1.50 g, 6.78 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C and *N*-methylmorpholine (0.751 mL, 6.78 mmol) was added before dropwise addition of ethyl chloroformate (0.671 mL, 6.78 mmol). After 20 min, 2-*tert*-butylaniline (1.06 mL, 6.78 mmol) was added to the suspension. The mixture was warmed to ambient temperature over 16 h then quenched with H_2O (30 mL). The mixture was diluted with CH_2Cl_2 (20 mL) and extracted with CH_2Cl_2 (30 mL × 3). The combined organics were washed successively with 4% $NaHCO_3$(aq) (30 mL) and 1 M HCl(aq) (30 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo. The product was triturated with pentane (20 mL) to obtain the diamide product as a colourless solid (1.36 g, 53%), which was used without further purification. To a suspension of diamide (1.00 g, 4.06 mmol) in THF (10 mL) was added a solution of $LiAlH_4$ (9.13 mL, 18.3 mmol) and the mixture heated at reflux for 72 h, then quenched at 0 °C with H_2O (0.69 mL), 40% KOH(aq) (0.69 mL) and further H_2O (2.07 mL), before drying over excess $MgSO_4$ and filtration through Celite. Following concentration in vacuo, chromatographic purification (10% EtOAc/petrol) gave the diamine as a clear colourless oil (790 mg, 60%). $[\alpha]_D^{20} = +0.3$ (*c* 1.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.27–7.22 (4H, m, Ar*H*), 7.20–7.16 (2H, m, Ar*H*), 7.07 (1H, td, *J* 7.6, 1.4, NAr*H*-4), 6.63–6.58 (2H, m, Ar*H*), 4.76 (1H, t, *J* 4.4, ArN*H*), 3.74 (1H, ABd, *J* 12.8, PhCH_AH$_B$), 3.71 (1H, ABd, *J* 12.8, PhCH_AH$_B$), 3.20 (1H, dt, *J* 11.5, 4.4, ArNHCH_AH$_B$), 2.95 (1H, ddd, *J* 11.4, 6.6, 4.4, ArNHCH$_A$$H_B$), 2.65 (1H, td, *J* 6.6, 4.0, BnNHC*H*), 2.03–1.91 (1H, m, C*H*(CH_3)$_2$), 1.37 (9H, s, C(CH_3)$_3$), 0.97 (3H, d, *J* 6.8, CH_3) and 0.90 (3H, d, *J* 6.8, CH_3); δ_C (100 MHz, $CDCl_3$) 147.1 (NHArC-1), 140.5 (PhC-1), 133.5 (NHArC-2), 128.5 (PhCH), 128.4 (PhCH), 127.2 (ArCH), 127.1 (ArCH), 126.2 (ArCH), 116.5 (NHArC-4), 111.5 (NHArC-6), 61.9 (BnNCH), 51.1 (Ph-CH_2), 43.3 (ArNHCH_2), 34.4 (*C*(CH_3)$_3$), 29.9

($C(CH_3)_3$), 29.3 ($CH(CH_3)_2$), 20.0 (CH_3) and 18.4 (CH_3); *m/z* MS (ESI+) 325 (100, $[M+H]^+$); HRMS (ESI+) $C_{22}H_{33}N_2^+$ ($[M+H]^+$) requires 325.2644, found 325.2639 (−1.3 ppm); IR ν_{max} (thin film) /cm^{-1} 3425 (br, N–H), 2958, 2930, 1644, 1504, 1443, 1055, 834, 741 and 697.

A mixture of diamine (186 mg, 0.573 mmol), NH_4BF_4 (60.1 mg, 0.573 mmol), triethyl orthoformate (0.23 mL) and MeOH (1.6 mL) were heated at 80 °C for 16 h then concentrated in vacuo before dissolution in CH_2Cl_2 and filtration to remove excess NH_4BF_4. The mixture was concentrated in vacuo after which chromatographic purification (10% MeOH/CH_2Cl_2) gave the title product **42** as a clear colourless oil (225 mg, 93%). $[\alpha]_D^{20} = -0.7$ (*c* 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.01 (1H, s, NC*H*N), 7.36 (1H, dd, *J* 8.1, 1.3, ArC*H*-6), 7.27–7.21 (6H, m, ArC*H*), 7.17–7.13 (2H, m, ArC*H*), 4.87 (1H, ABd, *J* 14.6, PhCH_AH_B), 4.44 (1H, ABd, *J* 14.6, PhCH_AH_B), 4.32–4.26 (1H, m, Me_2CHCH), 4.11 (1H, app t, *J* 11.6, ArNCH_AH_B), 3.81 (1H, ABX, J_{BA} 11.6, J_{BX} 9.9, ArNCH_AH_B), 2.34–2.23 (1H, m, C*H*Me_2), 1.21 (9H, s, $C(CH_3)_3$), 0.93 (3H, d, *J* 6.8, CH_3) and 0.80 (3H, d, *J* 7.0, CH_3); δ_C (100 MHz, $CDCl_3$) 158.8 (NCHN), 147.0 (NAr*C*-1), 134.0 (NAr*C*-2), 132.2 (Ph*C*), 130.6 (Ar*C*H), 130.0 (Ar*C*H), 129.5 (Ph*C*H), 129.3 (Ph*C*H), 129.0 (Ar*C*H), 128.8 (Ar*C*H), 128.3 (Ar*C*H), 65.0 (N*C*H(*i*-Pr)), 54.9 (ArNCH_2), 50.2 (Ph–CH_2), 35.7 ($C(CH_3)_3$), 32.0 ($C(CH_3)_3$), 26.6 ($CHMe_2$), 18.0 (CH_3) and 14.4 (CH_3); *m/z* MS (ESI+) 335 (100, $[M-BF_4]^+$); HRMS (ESI+) $C_{23}H_{31}N_2^+$ ($[M-BF_4]^+$) requires 335.2487, found 335.2479 (−2.4 ppm); IR ν_{max} (thin film)/ cm^{-1} 3389, 3069, 2957, 2924, 2850, 1635 (C=N), 1457, 1366, 1259, 1086, 1057, 1036, 753 and 703.

4.5.4. (3*S*,7*S*)-3,7-Diisopropyl-2,3,7,8-tetrahydroimidazo[4,3-*b*:5,1-*b*′]bis(oxazole)-4-ium trifluoromethanesulfonate 43

To a suspension of sodium borohydride (6.92 g, 183 mmol) in THF (200 mL) was added L-valine (8.90 g, 76.0 mmol) in one portion. The mixture was cooled to 0 °C before addition of a solution of iodine (19.3 g, 76.0 mmol) in THF (50 mL) dropwise over 30 min. Once hydrogen gas evolution ceased, the mixture was heated at reflux (80 °C) for 18 h then cooled to ambient temperature. MeOH was added cautiously until the mixture became clear and was stirred for a further 30 min, upon which time the mixture was concentrated in vacuo to afford a colourless paste, which was redissolved in 20% KOH(aq) with stirring over 4 h. The mixture was extracted with CH_2Cl_2 (150 mL × 3), the organics combined, dried (Na_2SO_4), filtered and concentrated in vacuo to afford the crude product as a colourless semi-solid. Purification by distillation (117–120 °C/57 mm) afforded (*S*)-valinol as a colourless oil (6.66 g, 85%). $[\alpha]_D^{20} = +17.1$ (*c* 0.5, EtOH), lit.[28] +17.0 (*c* 10.0, EtOH); δ_H (300 MHz, $CDCl_3$) 3.60 (1H, ABX, J_{AB} 12.0, J_{AX} 1.9, OCH_AH_B), 3.26 (1H, ABX, J_{BA} 12.0, J_{BX} 11.0, OCH_AH_B), 2.56–2.47 (1H, m, C*H*NH_2), 2.21 (2H, br s, NH_2), 1.52 (1H, *J* 6.9, C*H*$(CH_3)_2$) and 0.85 (6H, d, *J* 6.9, CH(CH_3)$_2$). Data are in accordance with the literature.[28,29]

To a solution of (*S*)-valinol (1.00 g, 9.69 mmol) in toluene (35 mL) was added diethyl oxalate (0.64 mL, 4.73 mmol) and the mixture heated at reflux (110 °C) for 5 h. The mixture was then cooled to ambient temperature and hexane (35 mL) was added, forming a colourless precipitate of the product. Trituration with hexane (20 mL) gave the purified diamide as a colourless solid (1.00 g, 81%); mp 171–174 °C, lit.[30] 172–174 °C; $[\alpha]_D^{20} = -28.4$ (*c* 0.5, MeOH), lit.[30] −27.7 (*c* 1.5, MeOH); δ_H (300 MHz, DMSO-d_6) 8.13 (2H, d, *J* 9.5, N*H*), 4.64 (2H, br s, O*H*), 3.41–3.57 (6H, m, CH_2 and NC*H*), 1.82 (2H, sept d, *J* 6.9, 6.7, C*H*Me_2), 0.85 (6H, d, *J* 6.5, CH_3) and 0.82 (6H, d, *J* 6.4, CH_3). Data are in accordance with the literature.[30]

To a suspension of bis(hydroxymethyl)oxalamide (900 mg, 3.46 mmol) in toluene (15 mL) was added thionyl chloride (0.560 mL, 7.64 mmol) and the mixture was heated to 90 °C for 4 h. The mixture was cooled to ambient temperature then poured onto ice-cold 20% KOH(aq) (7.4 mL) and extracted with CH_2Cl_2 (20 mL × 3). The organics were combined, washed with satd $NaHCO_3$(aq) (10 mL), dried ($MgSO_4$) and concentrated in vacuo to afford the dichloride as a colourless solid (960 mg, 93%); mp 130–132 °C, lit.[31] 131–132 °C; $[\alpha]_D^{20} = -71.0$ (*c* 0.5, $CHCl_3$), lit.[31] −68.8 (*c* 2, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 5.56 (2H, d, *J* 9.0, N*H*), 4.33–4.21 (2H, m, C*H*N), 3.72 (2H, ABX, J_{AB} 11.1, J_{AX} 4.2, CH_AH_BCl), 3.63 (2H, ABX, J_{BA} 11.1, J_{BX} 4.2, CH_AH_BCl), 1.62–1.54 (6H, m, C*H*Me_2), 0.99 (6H, d, *J* 6.3, CH_3) and 0.96 (6H, d, *J* 6.4, CH_3). Data are in accordance with the literature.[31]

A mixture of dichloride (957 mg, 3.22 mmol) and KOH (452 mg, 8.05 mmol) in MeOH (30 mL) was heated at reflux (70 °C) for 3 h, with KCl precipitation occurring throughout. The mixture was cooled to ambient temperature, poured into H_2O (40 mL) and extracted with CH_2Cl_2 (20 mL × 3). The organics were combined, washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford the bisoxazoline as a pale yellow oil which solidified on standing to a pale cream solid (601 mg, 83%); mp 58–60 °C, lit.[32] 50 °C; $[\alpha]_D^{20} = -157.9$ (*c* 0.53, $CHCl_3$), lit.[32] −158.8 (*c* 0.97, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 4.44–4.30 (2H, m, H_A-5), 4.11–3.97 (4H, m, *H*-4 and H_B-5), 1.79 (2H, sept d, *J* 6.7, 1.6, C*H*$(CH_3)_2$), 0.92 (6H, d, *J* 6.7, CH_3) and 0.84 (6H, d, *J* 6.7, CH_3). Data are in accordance with the literature.[32]

To a suspension of silver(I) triflate (415 mg, 1.62 mmol) in CH_2Cl_2 (5 mL) was added chloromethyl pivalate (243 mg, 1.62 mmol) and the resulting suspension stirred for 45 min. The supernatant was transferred to the bisoxazoline (250 mg, 1.12 mmol) and the mixture stirred at 40 °C in the dark in a sealed Schlenk tube for 24 h. After cooling to ambient temperature, the reaction was quenched with MeOH (5 mL) and the mixture was concentrated in vacuo to afford a brown oil. Chromatographic purification (5% MeOH/CH_2Cl_2) and subsequent recrystallisation from CH_2Cl_2/Et_2O gave the title compound **43** as a colourless solid (264 mg, 61%). $[\alpha]_D^{20} = +54.6$ (*c* 0.5, CH_2Cl_2), lit.[33] +55.0 (*c* 1.0, CH_2Cl_2); mp[§] 155–157 °C; δ_H (400 MHz, $CDCl_3$) 8.73 (1H, s, NC*H*N), 5.07 (2H, dd, *J* 9.0, 7.9, CH_2O), 4.98–4.93 (2H, m, C*H*CH_2O), 4.83 (2H, dd, *J* 9.0 and 4.1, CH_2O), 2.35–2.31 (2H, m, C*H*CH_3), 1.03 (6H, d, *J* 6.9, CH_3), 0.99 (6H, d, *J* 6.9, CH_3); δ_C (100 MHz, $CDCl_3$) 125.6 (N*C*O), 120.6 (q, *J* 321, *C*F_3), 116.3 (N*C*HN), 79.1 (CH_2), 63.9 ($CHCH_2$), 31.1 ($CHCH_3$), 17.6 (CH_3) and 16.7 (CH_3); ^{19}F NMR (273 MHz, $CDCl_3$) −78.6 (CF_3). Data are in accordance with the literature.[33]

4.5.5. (5a*R*,10b*S*)-2-Phenyl-4,5a,6,10b-tetrahydroindeno[2,1-*b*][1,2,4]triazolo[4,3-*d*][1,4]-oxazinium tetrafluoroborate 45

Sodium hydride (60% wt in mineral oil, 273 mg, 6.84 mmol) was suspended in hexane (10 mL) and then left to stand for 5 min before removal of the supernatant via cannula. This procedure was repeated two times and then THF (100 mL) was added. The mixture was cooled to 0 °C then (1*S*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol (500 mg, 3.35 mmol) was added. The mixture was stirred for 15 min and then further aminoindanol (500 mg, 3.35 mmol) was added. The mixture was heated to 70 °C for 40 min and then cooled to 0 °C before ethyl chloroacetate (0.732 mL, 6.84 mmol) was added slowly. The mixture was stirred for 30 min and then heated at reflux for 2 h. After cooling to ambient temperature, the solution was washed with brine (20 mL × 2) and the aqueous layers combined and back-extracted with EtOAc (10 mL × 2). The combined organics were dried ($MgSO_4$) with vigorous stirring over 16 h then filtered and concentrated in vacuo to afford a pale orange/brown solid. Hexane (30 mL) was added to the crude solid and the heterogeneous mixture heated at reflux for 2 h, cooled to ambient temperature and then the hexanes removed by filtration. Final trituration with cold (−78 °C) EtOAc (10 mL) gave the morpholinone as a colourless solid (799 mg, 63%); mp[§] 198–200 °C decomp; $[\alpha]_D^{20§} = +55.2$ (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.86 (1H, br d, *J*

4.4, NH), 7.39–7.24 (4H, m, ArH), 4.78 (1H, t, J 4.4, H-4a), 4.54 (1H, t, J 4.4, H-9a), 4.17 (2H, s, CH_2-2), 3.23 (1H, dd, J 17.0 and 4.4, H_A-9) and 3.10 (1H, d, J 17.0, H_B-9); δ_C[§] (100 MHz, $CDCl_3$) 169.8 (C=O), 140.7 (C-8a), 139.2 (C-4b), 128.3 (CH-8), 127.4 (CH-6), 125.1 (CH-7), 123.9 (CH-5), 76.1 (CH-9a), 66.4 (CH_2-2), 58.6 (CH-4a) and 37.6 (CH_2-9). IR[§] ν_{max} (KBr)/cm^{-1} 3425 (br, H-bonded NH), 3183 (free NH), 2934 (C–H), 2928, 2843, 1641 (C=O), 1462 (C–H), 1372 (C–H) and 1103 (C–O). Spectroscopic data (^{1}H NMR) are in accordance with the literature.[34]

Trimethyloxonium tetrafluoroborate (213 mg, 1.44 mmol) was added to a solution of morpholinone (250 mg, 1.32 mmol) in CH_2Cl_2 (8 mL) and the mixture was stirred at ambient temperature for 16 h. Phenylhydrazine (0.130 mL, 1.32 mmol) was added and stirred for 48 h before concentration in vacuo. The residue was dissolved in MeOH (1 mL) and triethyl orthoformate (3 mL) and heated at reflux for 16 h at 100 °C. The precipitate was filtered and recrystallised from MeOH to afford the title compound **45** as a colourless solid (250 mg, 50%); mp[§] 205–207 °C; $[\alpha]_D^{20} = +300.4$ (c 0.5, MeCN), lit.[35] +294.4 (c unspecified, MeCN); δ_H (400 MHz, CD_3OD) 11.10 (1H, s, NCHN), 7.93–7.86 (2H, m, NPhH-2,6), 7.65–7.55 (3H, m, NPhH-3,4), 7.52 (1H, dd, J 7.1 and 1.4, H-7), 7.33–7.22 (3H, m, H-8,9,10), 5.91 (1H, d, J 4.0, H-10b), 5.13 (1H, ABd, J 16.4, H_A-4), 4.97 (1H, ABd, J 16.4, H_B-4), 4.89 (1H, app t, J 4.3, H-5a), 3.36 (1H, ABX, J_{AB} 17.2, J_{AX} 4.9, H_A-6) and 3.17 (1H, obscured AB d, J ~17, H_B-6). Data are in accordance with the literature.[35]

4.5.6. (5a*S*,6*R*,9*S*,9a*R*)-6,11,11-Trimethyl-2-phenyl-5a,6,7,8,9,9[a]-hexahydro-4*H*-6,9-methano-benzo[*b*][1,2,4]triazolo[4,3-*d*][1,4]oxazin-2-ium tetrafluoroborate 46

To a cooled (−40 °C) solution of potassium *tert*-butoxide (18.4 g, 103 mmol) in Et_2O (125 mL) was added D-camphor (12.5 g, 82.0 mmol) in Et_2O (40 mL) dropwise over 25 min. Once the addition was complete the mixture was stirred at ambient temperature for 1 h, recooled to −40 °C and isoamyl nitrite (22.0 mL, 164 mmol) was added dropwise over 30 min. The bright orange solution was warmed to ambient temperature over 16 h and then extracted with H_2O (50 mL × 3). The combined aqueous phases were acidified to pH 2 with concd HCl (~8 mL) and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed successively with satd $NaHCO_3$(aq) (20 mL), H_2O (20 mL) and brine (20 mL) then dried ($MgSO_4$), filtered and concentrated in vacuo to give the crude oxime as a yellow solid (19.9 g, 84%) as a ~2:1 mixture of *E*/*Z*-diastereomers which was used immediately without further purification. To a cooled (0 °C) solution of oxime (12.1 g, 66.8 mmol) in THF (30 mL) was added $LiAlH_4$ (50.0 mL of a 1 M solution in THF, 100 mmol) dropwise over 30 min. After H_2 evolution had ceased, the solution was heated at reflux (80 °C) for 30 min. The solution was allowed to cool to ambient temperature, diluted with Et_2O (65 mL) and quenched with H_2O (4 mL), NaOH (10% w/v, 4 mL) and H_2O (12 mL). The mixture was filtered through Celite and the filtrate was concentrated in vacuo to give the crude *syn*-amino alcohol product (~8:1 dr) as a colourless solid (10.6 g, 94%), which was used immediately without further purification. To a cooled (0 °C) solution of the amino alcohol (2.30 g, 13.6 mmol) and Et_3N (3.02 mL, 21.7 mmol) in CH_2Cl_2 (60 mL) was added chloroacetyl chloride (1.19 mL, 14.9 mmol) dropwise over 30 min. The solution was warmed to ambient temperature over 16 h then recooled to 0 °C and a solution of potassium *tert*-butoxide (6.40 g, 57.0 mmol) in isopropanol (50 mL) was added over 30 min. The mixture was allowed to warm to ambient temperature and stirred for 18 h before concentration in vacuo. The brown residue was taken up in EtOAc (20 mL) and H_2O (30 mL) added. The product was extracted with EtOAc (20 mL × 3) and the combined organic fraction was dried (Na_2SO_4), filtered and concentrated in vacuo to give a brown solid. Chromatographic purification (50% EtOAc/petrol) gave the morpholinone as a pale yellow solid (640 mg, 44%). $[\alpha]_D^{20} = +96.1$ (c 1.0, $CHCl_3$), lit.[36] +95.0 (c 1.0, $CHCl_3$); mp[§] 94–97 °C; δ_H (400 MHz, $CDCl_3$) 5.93 (1H, br s, NH), 4.12 (1H, d, J 15.4, CH_AH_B-2), 3.78 (1H, d, J 15.4, CH_AH_B-2), 3.65 (1H, d, J 6.8 CH-8a), 3.37 (1H, d, J 6.8, CH-4a), 1.62–1.54 (4H, m, CH-5, CH_2-7 and CH_AH_B-6), 1.13 (3H, s, (CH_3)C-8), 1.08–1.02 (1H, m, CH_AH_B-6), 0.99 (3H, s, CH_3) and 0.85 (3H, s, CH_3). Data are in accordance with the literature.[36]

To a solution of morpholinone (200 mg, 0.956 mmol) in CH_2Cl_2 (20 mL) was added trimethyloxonium tetrafluoroborate (169 mg, 1.14 mmol) and the mixture was stirred for 16 h at ambient temperature. Phenylhydrazine (94.1 μL, 0.956 mmol) was added and the solution was stirred for 24 h. The mixture was then concentrated in vacuo and the residue triturated with Et_2O (10 mL) to give a light brown solid that was dissolved in chlorobenzene (1 mL) and triethyl orthoformate (5 mL) and then heated at reflux (125 °C) for 12 h. The mixture was concentrated in vacuo then triturated with Et_2O (10 mL) to afford the title product **46** as a colourless solid (75.9 mg, 20%). $[\alpha]_D^{20} = +28.8$ (c 0.5, $CHCl_3$), lit.[36] +29.4 (c 1.0, $CHCl_3$); mp[§] 191–192 °C; δ_H (300 MHz, $CDCl_3$) 10.28 (1H, s, NCHN), 7.91–7.89 (2H, m, ArH), 7.55–7.52 (3H, m, ArH), 5.07 (1H, d, J 15.1, CHO), 4.67 (1H, d, J 15.1, CHN), 4.48 (1H, d, J 7.0 CH), 4.08 (1H, d, J 7.0, CH_2), 2.66 (1H, d, J 4.5 CH_2), 1.96–1.84 (1H, m, CH_2), 1.68–1.58 (1H, m, CH_2), 1.39–1.24 (1H, m, CH_2), 1.03 (3H, s, CH_3), 0.88 (3H, s, CH_3) and 0.66 (3H, s, CH_3). Data are in accordance with the literature.[36]

4.5.7. (*S*)-5-Benzyl-2-phenyl-6,8-dihydro-5*H*-[1,2,4]triazolo[3,4-*c*][1,4]oxazin-2-ium tetrafluoroborate 47

To a mixture of sodium borohydride (2.60 g, 68.8 mmol) in THF (80 mL) was added L-phenylalanine (5.00 g, 30.2 mmol). The mixture was cooled to 0 °C and a solution of iodine (7.67 g, 30.2 mmol) in THF (20 mL) was added dropwise over 40 min. After gas evolution had ceased, the reaction was heated at reflux (80 °C) for 18 h. When the reaction had cooled to ambient temperature, MeOH was slowly added until the solution became clear. The mixture was then stirred for a further 30 min. The mixture was concentrated in vacuo to afford a colourless paste, which was redissolved in KOH(aq) (20% w/v, 100 mL) with stirring over 4 h. The mixture was extracted with CH_2Cl_2 (150 mL × 2), the organic layers were combined, dried (Na_2SO_4), filtered and concentrated in vacuo to afford the crude product as a colourless solid. Recrystallisation from Et_2O gave the product (*S*)-phenylalaninol as a colourless solid (2.49 g, 55%); mp 88–90 °C, lit.[37] 86–88 °C; $[\alpha]_D^{20} = -22.3$ (c 1.01, $CHCl_3$), lit.[37] −21.7 (c 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.36–7.18 (5H, m, PhH), 3.66 (1H, ABX, J_{AB} 10.6, J_{AX} 3.9, CH_AH_BOH), 3.41 (1H, ABX, J_{BA} 10.6, J_{BX} 7.2, CH_AH_BOH), 3.18–3.11 (1H, m, $CHNH_2$), 2.82 (1H, ABX, J_{AB} 13.5, J_{AX} 5.2, $PhCH_AH_B$), 2.55 (1H, ABX, J_{BA} 13.5, J_{BX} 8.6, $PhCH_AH_B$) and 1.79 (2H, br s, NH_2). Data are in accordance with the literature.[37]

To a cooled (0 °C) solution of (*S*)-phenylalaninol (500 mg, 3.31 mmol) and Et_3N (1.38 mL, 9.92 mmol) in CH_2Cl_2 (10 mL) was added chloroacetyl chloride (0.28 mL, 3.47 mmol) dropwise. The mixture was warmed to ambient temperature over 16 h then satd $NaHCO_3$(aq) (10 mL) was added and the mixture extracted with CH_2Cl_2 (20 mL × 3). The organics were combined and washed with 1 M H_2SO_4(aq) (10 mL), H_2O (10 mL) and brine (10 mL), then dried (Na_2SO_4), filtered and concentrated in vacuo to afford the crude amide intermediate as a brown oil which was used immediately in the subsequent step. The product was redissolved in THF (10 mL) and cooled to 0 °C before addition of potassium *tert*-butoxide (405 mg, 3.61 mmol). The mixture was warmed to ambient temperature over 90 min then concentrated in vacuo then partitioned between EtOAc (10 mL) and brine (10 mL). The aqueous fraction was extracted with EtOAc (10 mL × 2), then the combined organic fractions were dried ($MgSO_4$), filtered and concentrated in vacuo to afford the crude

morpholinone product. Chromatographic purification (40% EtOAc/petrol) gave the morpholinone as a colourless solid (420 mg, 66%); mp 85–87 °C, lit.[38] 86–87 °C; $[\alpha]_D^{20} = +4.2$ (*c* 1.0, MeOH), lit.[38] +4.0 (*c* 0.66 MeOH); δ_H (400 MHz, $CDCl_3$) 7.33–7.16 (5H, m, Ph*H*), 5.89 (1H, br s, N*H*), 4.22 (1H, ABd, *J* 17.8, OC*H*$_A$H$_B$CO), 4.19 (1H, ABd, *J* 17.8, OCH$_A$*H*$_B$CO), 3.88 (1H, ABX, J_{AB} 11.5, J_{AX} 3.8, OC*H*$_A$H$_B$CH), 3.77 (1H, ddd, *J* 9.2, 5.8, 3.8, NHC*H*), 3.46 (1H, ABX, J_{BA} 11.5, J_{BX} 5.8, OCH$_A$*H*$_B$CH), 2.85 (1H, ABX, J_{AB} 13.5, J_{AX} 5.8, C*H*$_A$H$_B$Ph) and 2.70 (1H, ABX, J_{BA} 13.5, J_{BX} 9.2, CH$_A$*H*$_B$Ph). Data are in accordance with the literature.[38]

To a solution of lactam (400 mg, 2.09 mmol) in CH_2Cl_2 (12 mL) was added trimethyloxonium tetrafluoroborate (337 mg, 2.28 mmol) and the mixture was stirred for 16 h. To the mixture was then added phenylhydrazine (0.206 mL, 2.09 mmol) and the mixture was stirred for 20 h. The mixture was then concentrated in vacuo and redissolved in MeOH (1.5 mL) and triethyl orthoformate (4.5 mL). The mixture was heated at reflux (110 °C) for 16 h then cooled to ambient temperature, whereby the product had precipitated.[†] The product was collected by filtration and washed with cold (−78 °C) EtOAc (~5 mL) to afford the title product **47** as a pale peach solid (230 mg, 29%); mp 190–195 °C; $[\alpha]_D^{20} = -18.1$ (*c* 0.8, MeOH); δ_H (400 MHz, DMSO-d_6) 10.91 (1H, s, NC*H*N), 7.90–7.88 (2H, m, Ph*H*), 7.76–7.71 (2H, m, Ph*H*), 7.71–7.65 (1H, m, Ph*H*-4), 7.43–7.40 (2H, m, NPh*H*-2), 7.36–7.32 (3H, m, NPh*H*), 5.23 (1H, ABd, *J* 16.2, OC*H*$_A$H$_B$), 5.15 (1H, ABd, *J* 16.2, OCH$_A$*H*$_B$), 4.85 (1H, app dq, *J* 9.7, 5.9, BnC*H*), 4.01–3.93 (2H, m, OC*H*$_2$CHBn), 3.50 (1H, ABX, J_{AB} 13.6, J_{AX} 5.9, PhC*H*$_A$H$_B$) and 3.18 (1H, ABX, J_{BA} 13.6, J_{BX} 9.7, PhCH$_A$*H*$_B$); δ_C (100 MHz, DMSO-d_6) 149.9 (NCHN), 135.1 (N=*C*), 134.9 (NAr*C*-1), 134.9 (CH$_2$Ph*C*-1), 130.8 (Ar*C*H-4), 130.4 (Ar*C*H), 129.5 (Ar*C*H), 129.0 (Ar*C*H), 127.5 (Ar*C*H), 120.7 (Ar*C*H), 65.1 (O*C*H$_2$), 61.5 (O*C*H$_2$), 56.3 (N*C*H) and 37.5 (Ph–*C*H$_2$); *m/z* MS (ESI+) 292 (100, $[M-BF_4]^+$); HRMS (ESI+) $C_{18}H_{18}ON_3^+$ ($[M-BF_4]^+$) requires 292.1444, found 292.1443 (−0.4 ppm); IR ν_{max} (KBr)/cm^{-1} 3337, 3141, 3060 (Ar C–H), 3026, 2987, 2969, 1585 (C=N), 1536, 1497 (Ar C=C), 1469, 1118 (C–O) and 1054 (br).

4.5.8. (*S*)-5-Benzyl-2,6,6-triphenyl-6,8-dihydro-5*H*-[1,2,4]triazolo[3,4-*c*][1,4]oxazin-2-ium tetrafluoroborate 48

4.5.8.1. Free basification of methyl ester. A solution of L-phenylalanine methyl ester hydrochloride (5.00 g, 23.2 mmol) was dissolved in Et_2O (25 mL) and NaOH(aq) (25.0 mL of 1 M solution, 25.0 mmol) was added. The product was extracted with Et_2O (25 mL × 2), dried ($MgSO_4$), filtered and concentrated in vacuo to afford the free base as a colourless oil (2.50 g, 60%).

4.5.8.2. Conversion to the diphenyl alcohol. The free base (2.50 g, 13.9 mmol) was dissolved in Et_2O (25 mL). Phenylmagnesium bromide (16.3 mL of a 3.0 M in Et_2O, 48.9 mmol) was added dropwise and then the mixture was heated at reflux (60 °C) for 18 h. The reaction was quenched with ice-cold H_2O (60 mL), then extracted with CH_2Cl_2 (50 mL × 2). The organic phases were combined, washed with brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed in vacuo to give a pale yellow solid. Recrystallisation from EtOAc gave the alcohol product as a colourless solid (2.58 g, 61%); mp 138–139 °C, lit.[39] 134–136 °C; $[\alpha]_D^{20} = -90.0$ (*c* 1.0, $CHCl_3$), lit.[39] −86.0 (*c* 1.53, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.69–7.66 (2H, m, Ar*H*), 7.65–7.62 (2H, m, Ar*H*), 7.37–7.30 (6H, m, Ar*H*), 7.27–7.20 (5H, m, Ar*H*), 4.21 (1H, ABX, J_{XB} 10.8, J_{XA} 2.5, C*H*NH$_2$), 2.68 (1H, ABX, J_{AB} 13.9, J_{AX} 2.5, PhC*H*$_A$H$_B$) and 2.49 (1H, ABX, J_{BA} 13.9, J_{BX} 10.8, PhCH$_A$*H*$_B$). Data are in accordance with the literature.[39]

[†] In the event of no precipitation, the mixture was concentrated in vacuo, redissolved in EtOAc (5 mL) and then Et_2O (1 drop) was added to induce precipitation.

To a cooled (0 °C) solution of tertiary alcohol (1.00 g, 3.30 mmol) and Hünig's base (0.575 mL, 3.30 mmol) in CH_2Cl_2 (10 mL) was added chloroacetyl chloride (0.262 mL, 3.30 mmol) dropwise. The mixture was warmed to ambient temperature over 16 h then satd $NaHCO_3$(aq) (10 mL) was added and the mixture extracted with EtOAc (30 mL × 3). The organics were combined and washed with 1 M H_2SO_4(aq) (10 mL), H_2O (10 mL) and brine (10 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo to afford the crude amide intermediate as a cream solid, which was used immediately without further purification. The product was redissolved in THF (10 mL) and cooled to 0 °C before the addition of potassium *tert*-butoxide (404 mg, 3.60 mmol), and allowed to warm to ambient temperature over 90 min before concentration in vacuo and partitioning between EtOAc (10 mL) and brine (10 mL). The aqueous fraction was extracted with EtOAc (15 mL × 2), then the organic fractions were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to afford the desired morpholinone product (970 mg, 86%); mp 187–188 °C; $[\alpha]_D^{20} = +15.0$ (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.42–7.21 (13H, m, Ph*H*), 7.11–7.09 (2H, m, Ph*H*), 5.96 (1H, br d, *J* 3.7, N*H*), 4.42–4.36 (2H, m, NHC*H* and OC*H*$_A$H$_B$), 3.94 (1H, ABd, *J* 17.2, OCH$_A$*H*$_B$), 2.73 (1H, ABX, J_{AB} 13.4, J_{AX} 11.2, PhC*H*$_A$H$_B$) and 2.42 (1H, ABX, J_{BA} 13.4, J_{BX} 2.7, PhCH$_A$*H*$_B$); δ_C (75 MHz, $CDCl_3$) 168.3 (N*C*O), 143.3 (OCPh*C*-1), 140.3 (OCPh*C*-1), 137.8 (Ph*C*-1CH$_2$), 129.5, 128.9, 128.5, 127.9, 127.6, 127.2, 126.8, 125.4, 80.1 (Ph$_2$*C*), 63.9 (CO*C*H$_2$), 57.0 (BnCH) and 39.2 (Ph-*C*H$_2$); *m/z* MS (ESI+) 344 (100, $[M+H]^+$); HRMS (ESI+) $C_{23}H_{22}O_2N^+$ ($[M+H]^+$) requires 344.1645, found 344.1647 (+0.4 ppm); IR ν_{max} (KBr)/cm^{-1} 3175 (NH), 3120, 3060, 6027, 2953, 2917, 2896, 1682 (C=O), 1603 (Ar C=C), 1493, 1448, 1413, 1323 and 1098 (C–O).

To a solution of lactam (0.500 g, 1.46 mmol) in CH_2Cl_2 (5 mL) was added trimethyloxonium tetrafluoroborate (235 mg, 1.57 mmol) and the mixture stirred for 16 h. To the mixture was then added phenylhydrazine (0.143 mL, 1.46 mmol) and the mixture stirred for 20 h. The mixture was then concentrated in vacuo and redissolved in MeOH (1 mL) and triethyl orthoformate (4 mL). The mixture was heated at reflux (110 °C) for 18 h then cooled to ambient temperature and concentrated in vacuo. The dark brown oil was redissolved in MeOH/Et_2O (1:20) and was cooled to −78 °C to induce precipitation. The mixture was filtered rapidly and washed with cold (−78 °C) Et_2O (5 mL) to afford the title product **48** as a brown solid (250 mg, 32%); mp 120 °C; $[\alpha]_D^{20} = +3.0$ (*c* 0.5, MeOH); δ_H (300 MHz, $CHCl_3$) 9.04 (1H, s, NC*H*N), 7.53–7.30 (6H, m, Ph*H*), 7.36–7.16 (12H, m, Ph*H*), 6.98 (2H, d, *J* 6.7, Ph*H*), 6.19 (1H, ABX, J_{XA} 9.7, J_{XB} 6.0, PhCH$_2$C*H*), 5.34 (1H, ABX, J_{AB} 17.1, J_{AX} 9.7, PhC*H*$_A$H$_B$), 4.77 (1H, ABX, J_{BA} 17.1, J_{BX} 6.0, PhCH$_A$*H*$_B$) and 2.85–2.74 (2H, d, *J* 8.4, OCH$_2$); δ_C (75 MHz, $CHCl_3$) 148.7 (NCHN), 140.5 (N–*C*), 137.0 (N–*C*), 134.6 (Ph*C*), 134.4 (Ph*C*), 131.3 (Ph*C*H), 130.6 (Ph*C*H), 130.5 (Ph*C*H), 130.2 (Ph*C*H), 130.1 (Ph*C*H), 130.0 (Ph*C*H), 129.8 (Ph*C*H), 129.21 (Ph*C*H), 129.16 (Ph*C*H-4), 128.4 (Ph*C*H-4), 127.3 (*p*-Ph*C*H), 120.3 (Ph*C*H), 81.8 (*C*Ph$_2$), 60.9 (Bn*C*H), 57.5 (O*C*H$_2$) and 38.1 (Ph-*C*H$_2$); *m/z* MS (ESI+) 444 (100, $[M-BF_4]^+$); HRMS (ESI+) $C_{30}H_{26}N_3O^+$ ($[M-BF_4]^+$) requires 444.2070, found 444.2067 (−0.6 ppm); IR ν_{max} (KBr) /cm^{-1} 3116, 3059 (Ar CH), 3028, 2920, 1597, 1576 (C=N), 1530, 1496 (Ar C=C), 1450, 1406, 1279, 1259, 1233, 1204, 1158, 1083 (br), 1052, 1031, 972, 758, 719, 703 and 680.

4.5.9. (*R*)-5-Benzyl-2-phenyl-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoroborate 49

At first, Boc_2O (52.6 g, 0.241 mol) was added dropwise to a stirred solution of L-phenylalanine (34.7 g, 0.210 mol) in 1 M NaOH(aq) (210 mL) and *t*-BuOH (140 mL). The reaction mixture was stirred at ambient temperature for 24 h then acidified to

~pH 1 with 1 M $KHSO_4$(aq) and extracted with Et_2O (250 mL × 3). The organic extracts was combined, washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford Boc-L-phenylalanine as a colourless oil (57.9 g, 85%). $[\alpha]_D^{20} = +24.0$ (*c* 1.03, EtOH), lit.[40] +24.7 (*c* 1.50, EtOH); δ_H (400 MHz, $CDCl_3$) 8.35 (1H, br s, COO*H*), 7.32–7.18 (5H, m, Ph*H*), 4.94 (1H, d, *J* 7.9, N*H*), 4.61 (1H, app q, *J* 6.5, C*H*COOH), 3.21 (1H, ABX, J_{AB} 13.8, J_{AX} 5.4, PhCH_AH$_B$), 3.09 (1H, ABX, J_{BA} 13.8, J_{BX} 6.5, PhCH$_A$H$_B$), 1.42 (6H, s, C(CH_3)$_3$) and 1.28 (3H, s, C(CH_3)$_3$). Data are in accordance with the literature.[40]

To a solution of Boc-L-phenylalanine (15.7 g, 53.2 mmol) in CH_2Cl_2 (200 mL) was added 2,2-dimethyl-1,3-dioxane-4,6-dione (7.61 g, 52.7 mmol) and DMAP (8.78 g, 71.9 mmol). The mixture was cooled to −5 °C, and then a solution of DCC (10.9 g, 52.7 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 1 h, after which the mixture was stirred for 20 h at −5 °C. The mixture was warmed to ambient temperature, after which the precipitate was removed by filtration. The filtrate was then washed with $KHSO_4$(aq) (5% w/v, 100 mL × 4) and brine (100 mL) and dried ($MgSO_4$) at +5 °C (refrigerator) over 18 h. The solution was concentrated in vacuo to ~200 mL and the crude product was used immediately without further purification. To the solution of crude ketomalonate (assumed ~53.2 mmol) in CH_2Cl_2 (200 mL) was added glacial AcOH (30 mL) and the mixture cooled to −5 °C. $NaBH_4$ (4.63 g, 115 mmol) was added portionwise over 3 h at −5 °C, then the reaction mixture was stirred at -5 °C for a further 20 h. The reaction mixture was washed with H_2O (100 mL × 2), brine (100 mL × 2), dried ($MgSO_4$), filtered and concentrated in vacuo to afford a pale yellow oil, and the malonate product was crystallised from Et_2O as a colourless solid (10.2 g, 56% from L-phenylalanine); mp 120–121 °C, lit.[41] 111–113 °C; $[\alpha]_D^{20\S} = +4.5$ (*c* 1.0, MeOH); δ_H (300 MHz, $CDCl_3$) 7.38–7.23 (5H, m, Ph*H*), 4.52–4.49 (1H, m, N*H*), 4.32–4.24 (1H, m, C*H*NH), 3.96 (1H, td, *J* 2.0, 0.5, C*H*C(O)), 2.90 (2H, d, *J* 6.4, PhCH_2), 2.36–2.14 (2H, m, CH_2CHC(O)), 1.82 (3H, s, CH_3), 1.78 (3H, s, CH_3) and 1.40 (9H, s, C(CH_3)$_3$). Data are in agreement with the literature.[41,42]

A solution of malonate derivative (8.76 g, 23.2 mmol) in toluene (100 mL) was heated at 110 °C for 5 h, then the mixture was concentrated in vacuo to afford the crude protected pyrrolidinone product as a brown oil (7.09 g, quantitative yield), which was used immediately without further purification. To a cooled (0 °C) solution of pyrrolidinone (3.00 g, 10.9 mmol) in CH_2Cl_2 (100 mL) was added TFA (1.86 mL, 24.1 mmol) dropwise. The reaction was allowed to warm to ambient temperature and stirred for 4 h. The reaction was quenched slowly with sat $NaHCO_3$(aq) (100 mL) and extracted with CH_2Cl_2 (50 mL). The combined organic fraction was washed with H_2O (100 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford the crude pyrrolidinone as a yellow solid (1.91 g, quantitative) which was used immediately without further purification. To a solution of pyrrolidinone (1.00 g, 5.71 mmol) in CH_2Cl_2 (40 mL) was added trimethyloxonium tetrafluoroborate (0.930 g, 6.29 mmol) and the reaction stirred for 16 h at ambient temperature. To the solution was added phenylhydrazine (0.620 mL, 6.29 mmol) and stirred for a further 16 h. The mixture was concentrated in vacuo then redissolved in MeOH (2 mL) and triethyl orthoformate (20 mL) and heated to 80 °C for 16 h. The mixture was concentrated in vacuo and the product precipitated from EtOAc to give a yellow solid. Recrystallisation from MeOH gave the title product **49** as a golden crystalline solid (1.03 g, 50%); mp 191–192 °C, lit.[2b] 195.1–196.5 °C; $[\alpha]_D^{20} = +8.7$ (*c* 1.04, MeCN), lit.[2b] +9.1 (*c* unspecified, MeCN); δ_H (300 MHz, $CDCl_3$) 10.02 (1H, s, NC*H*N), 7.86–7.80 (2H, m, Ph*H*), 7.60–7.53 (3H, m, Ph*H*), 7.38–7.22 (5H, m, Ph*H*), 5.41–5.32 (1H, m, BnC*H*N), 3.54 (1H, ABX, J_{AB} 13.5, J_{AX} 5.0, PhCH_AH$_B$), 3.23–3.17 (1H, m, CH_AH$_B$-7), 3.15 (1H, ABX, J_{BA} 13.5, J_{BX} 8.8, PhCH$_A$H$_B$), 3.04–2.88 (2H, m, CH_AH$_B$-6 and CH$_A$H$_B$-7) and 2.70–2.59 (1H, m, CH$_A$H$_B$-6); Data are in accordance with the literature.[2b]

4.5.10. (*S*)-5-((*tert*-Butyldimethylsilyloxy)diphenylmethyl)-2-phenyl-2,5,6,7-tetrahydropyrrolo[2,1-*c*][1,2,4]triazolium tetrafluoroborate 50

To a solution of (*S*)-pyroglutamic acid (10.0 g, 77.5 mmol) in MeOH (250 mL) at −15 °C was added thionyl chloride (6.23 mL, 85.7 mmol) dropwise. The mixture was stirred at −15 °C for 30 min and then warmed to ambient temperature before concentration in vacuo to afford the crude ester product as a viscous yellow oil (11.1 g, quantitative). The product was used without further purification. To a cooled (−78 °C) solution of the pyroglutamate (5.00 g, 34.9 mmol) in THF (40 mL) was added phenylmagnesium bromide (40.0 mL of a 3 M solution in Et_2O, 120 mmol) over 30 min. The mixture was warmed to −40 °C for 15 min then warmed to 0 °C for 30 min, then the reaction was quenched with 5% HCl(aq) (~30 mL). The product was extracted with CH_2Cl_2 (50 mL × 5). The organic extracts were combined, dried ($MgSO_4$), filtered through Celite, concentrated in vacuo and the residue was recrystallised from Et_2O to afford the desired tertiary alcohol product as a colourless solid (5.02 g, 54%); mp 189–190 °C, lit.[43] 191–192 °C; $[\alpha]_D^{20} = -81.2$ (*c* 1.0, $CHCl_3$), lit.[43] −80.8 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.46–7.17 (10H, m, Ph*H*), 4.58 (1H, br s, N*H*), 4.70–4.64 (1H, dd, *J* 8.2, 4.8, NHC*H*), 3.87 (1H, br s, O*H*), 2.36–2.28 (1H, m, C(O)CH_AH$_B$), 2.26–2.17 (1H, m, C(O)CH$_A$H$_B$), 2.12–2.04 (1H, m, C(O)CH$_2$CH_AH$_B$) and 1.95–1.87 (1H, m, C(O)CH$_2$CH$_A$H$_B$). Data are in agreement with the literature.[43]

To a cooled (0 °C) solution of alcohol (1.50 g, 5.59 mmol) and Et_3N (1.01 mL, 7.29 mmol) in CH_2Cl_2 (30 mL) was added TBSOTf (1.70 mL, 7.29 mmol). The reaction mixture was warmed to ambient temperature over 5 h. Another portion of TBSOTf (0.850 mL, 3.65 mmol) and Et_3N (0.495 mL, 3.65 mmol) were added and the mixture stirred for 2 h at ambient temperature. The reaction mixture was quenched with H_2O (12 mL) and extracted with CH_2Cl_2 (30 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Chromatographic purification (30% EtOAc:petrol) gave the product as a colourless solid (2.04 g, 96%); mp[§] 138–140 °C; $[\alpha]_D^{20} = -63.0$ (*c* 0.5, $CHCl_3$), lit.[44] −65.0 (*c* 1.01, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.38–7.28 (10H, m, Ph*H*), 5.83 (1H, br s, N*H*), 4.66 (1H, dd, *J* 8.2, 3.3, NHC*H*), 2.19–2.09 (2H, m, COCH_2), 1.91–1.80 (1H, m, COCH$_2$-CH_AH$_B$), 1.10–0.89 (1H, m, COCH$_2$CH$_A$H$_B$), 0.92 (9H, s, SiC(CH_3)$_3$), −0.34 (3H, s, SiCH_3) and −0.39 (3H, s, SiCH_3). Data are in accordance with the literature.[44]

To a solution of lactam (1.00 g, 2.62 mmol) in CH_2Cl_2 (16 mL) was added trimethyloxonium tetrafluoroborate (426 mg, 2.88 mmol) and the mixture stirred for 16 h. To the solution was added phenylhydrazine (0.258 mL, 2.62 mmol) and stirred for 24 h. The mixture was then concentrated in vacuo and the residue redissolved in MeOH (1.18 mL) and triethyl orthoformate (6.35 mL) and heated at reflux (100 °C) for 16 h. The mixture was cooled to ambient temperature and concentrated in vacuo then triturated with Et_2O (~20 mL) to afford the title product **60** as a brown solid (606 mg, 41%); mp 208–210 °C, lit.[4a] 210–211 °C; $[\alpha]_D^{20} = -108.4$ (*c* 0.5, MeCN), lit.[4a] −112.4 (*c* 0.5, MeCN); δ_H (300 MHz, $CDCl_3$) 9.07 (1H, s, NC*H*N), 7.73–7.69 (2H, m, Ph*H*), 7.55–7.45 (5H, m, Ph*H*), 7.45–7.35 (4H, m, Ph*H*), 7.00 (2H, t, *J* 7.3, NPh*H*-3,5), 6.95 (2H, app br s, NPh*H*-2,6), 6.11 (1H, d, *J* 8.3, C*H*-5), 3.25–3.14 (1H, m, CH_AH$_B$-7), 3.00–2.88 (1H, m, CH$_A$H$_B$-7), 2.87–2.62 (1H, m, CH_AH$_B$-6), 1.77–1.65 (1H, m, CH$_A$H$_B$-6), 0.96 (9H, s, Si(CH_3)$_3$), −0.32 (3H, s, SiCH_3) and −0.35 (3H, s, SiCH_3). Data are in accordance with the literature.[4a]

4.5.11. (*S*)-6,6-Dimethyl-2-phenyl-5-isopropyl-5,6-dihydrooxazolo[2,3-*c*] [1,2,4]triazol-2-ium tetrafluoroborate 51

To a cooled (0 °C) suspension of L-valine (20.0 g, 171 mmol) in MeOH (200 mL) was added thionyl chloride (36.5 mL, 502 mmol) dropwise, after which the reaction was stirred at ambient temperature for 16 h. The reaction mixture was then concentrated in vacuo to give a pale yellow solid, which was washed with Et_2O (100 mL) to afford the ester hydrochloride as a colourless solid (28.6 g, quantitative); mp 164–165 °C, lit.[45] 169–170 °C; $[\alpha]_D^{20} = +24.2$ (*c* 1.0, MeOH), lit.[46] +22.3 (*c* 2.0, MeOH); δ_H (300 MHz, D_2O) 4.01 (1H, d, *J* 4.7, C*H*NH), 3.83 (3H, s, OCH_3), 2.42–2.25 (1H, m, C*H*Me$_2$), 0.92 (3H, d, *J* 4.4, CH(CH_3)$_A$) and 0.90 (3H, d, CH(CH_3)$_B$). Data are in accordance with the literature.[45,46]

To a suspension of (*S*)-valine methyl ester hydrochloride (20.0 g, 119 mmol) in EtOH (60 mL) was added $NaHCO_3$ (26.1 g, 310 mmol) and Boc_2O (29.6 g, 136 mmol). The mixture was stirred for 48 h at ambient temperature then the colourless suspension was filtered through Celite and the filtrate concentrated in vacuo to afford the carbamate product as a pale yellow oil (27.5 g, quantitative) which was used without further purification. $[\alpha]_D^{20} = -4.0$ (*c* 0.5, AcOH), lit.[47] −6.3 (*c* 1, AcOH); δ_H (400 MHz, $CDCl_3$) 5.05 (1H, d, *J* 8.7, CHN*H*), 4.17 (1H, ABX, J_{XA} 8.7, J_{XB} 4.8, C*H*NH), 3.68 (3H, s, OCH_3), 2.16–1.98 (1H, m, C*H*Me$_2$), 1.51–1.34 (9H, m OC(CH_3)$_3$), 0.90 (3H, d, *J* 6.9, CH(CH_3)$_A$) and 0.85 (3H, d, *J* 6.9, CH(CH_3)$_B$). Data are in accordance with the literature.[47]

To a cooled (0 °C) solution of Boc-L-valine methyl ester (10.0 g, 43.2 mmol) in Et_2O (100 mL) was added methylmagnesium bromide (46.0 mL of a 3.0 M solution in THF, 138 mmol) dropwise at ambient temperature. The reaction was stirred for 48 h, quenched with ice-cold H_2O (~30 mL) and filtered through Celite. The filtrate was extracted with CH_2Cl_2 (50 mL × 2) and the combined organic phase was washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford the crude alcohol as a colourless oil (8.34 g, 83%) which was used without further purification. $[\alpha]_D^{20} = +11.5$ (*c* 1.0, CH_2Cl_2), lit.[48] +9.1 (*c* 0.01, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 4.85 (1H, d, *J* 10.2, CHN*H*), 3.36 (1H, dd, *J* 10.2, 2.7, C*H*NH), 2.12–2.03 (1H, m, C*H*Me$_2$), 1.43–1.40 (9H, m, OC(CH_3)$_3$), 1.24 (3H, s, C(CH_3)$_A$), 1.20 (3H, s, C(CH_3)$_B$), 0.95 (3H, d, *J* 6.8, CH(CH_3)$_A$) and 0.91 (3H, d, *J* 6.8, CH(CH_3)$_B$). Data are in accordance with the literature.[48]

To a cooled (0 °C) solution of alcohol (3.00 g, 13.0 mmol) in THF (60 mL) was added potassium *tert*-butoxide (1.60 g, 14.3 mmol). The solution was warmed to ambient temperature over 16 h and concentrated in vacuo then redissolved in EtOAc (50 mL) and washed with 0.5 M HCl (aq) (40 mL) and brine (50 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated in vacuo to give a clear yellow oil. Chromatographic purification (25% EtOAc:petrol) gave the oxazolidinone as a colourless solid (1.94 g, 95%); mp 85–87 °C, lit.[50] 87–89 °C; $[\alpha]_D^{20} = +24.1$ (*c* 1.0, $CHCl_3$), lit.[50] +21.3 (*c* 0.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.06 (1H, s, N*H*), 3.18 (1H, dd, *J* 8.6, 6.7, NHC*H*), 1.88–1.79 (1H, m, C*H*Me$_2$), 1.49 (3H, s, OC(CH_3)$_A$), 1.38 (3H, s, OC(CH_3)$_B$), 0.99 (3H, d, *J* 6.6, CH(CH_3)$_A$) and 0.92 (3H, d, *J* 6.6, CH(CH_3)$_B$).

To a solution of oxazolidinone (1.86 g, 11.8 mmol) in CH_2Cl_2 (50 mL) was added trimethyloxonium tetrafluoroborate (1.93 g, 13.0 mmol) and the mixture was stirred for 16 h. Phenylhydrazine (1.16 mL, 11.8 mmol) was added and the solution was stirred for a further 24 h. The mixture was then concentrated in vacuo and the residue dissolved in triethyl orthoformate (28 mL) and MeOH (6 mL) and heated at reflux (100 °C) for 18 h. The solution was concentrated to approximately half volume in vacuo and the product precipitated upon addition of Et_2O (~1 mL). The precipitate was collected by filtration and washed with ice-cold EtOAc to afford the title product **51** as a pale brown solid (2.04 g, 50%); mp 112–118 °C, lit.[4m] 179–180 °C; $[\alpha]_D^{20} = -5.0$ (*c* 1.0, MeCN), lit. -7.0 (*c* 0.5, MeCN); δ_H (300 MHz, DMSO-d_6) 9.54 (1H, s, NC*H*N), 7.99–7.54 (5H, m, Ph*H*), 4.63 (1H, d, *J* 7.5, *i*-PrC*H*N), 2.50–2.35 (1H, m, *i*-PrC*H*), 2.02 (3H, s, C(CH_3)$_A$), 1.82 (3H, s, C(CH_3)$_B$), 1.22 (3H, d, *J* 6.6, CH(CH_3)$_A$) and 1.12 (3H, d, *J* 6.6, CH(CH_3)$_B$). Data are in accordance with the literature.[4m]

4.5.12. (*S*)-5-Benzyl-6,6-dimethyl-2-phenyl-5,6-dihydrooxazolo[2,3-*c*][1,2,4]triazol-2-ium tetrafluoroborate 52

To a suspension of L-phenylalanine methyl ester hydrochloride (20.0 g, 97.2 mmol) in EtOH (60 mL) was added Na_2CO_3 (30.1 g, 284 mmol) and Boc_2O (24.5 g, 112 mmol). The suspension was stirred for 48 h at ambient temperature. The colourless suspension was filtered through Celite and the filtrate concentrated in vacuo to afford Boc-L-phenylalanine methyl ester as a clear yellow oil (27.2 g, 91%). $[\alpha]_D^{20} = +49.2$ (*c* 1.0, CH_2Cl_2), lit.[49] +46.9 (*c* 3.4, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 7.06–7.03 (5H, m, Ar*H*), 5.37 (1H, br d, *J* 8.3, N*H*), 4.47 (1H, app q, *J* 7.2, C*H*NH), 3.52 (3H, s, OCH_3), 3.01 (1H, ABX, J_{AB} 13.7, J_{AX} 5.6, PhCH_AH$_B$), 2.90 (1H, ABX, J_{BA} 13.7, J_{BX} 7.0, PhCH$_A$$H_B$) and 1.42–1.30 (9H, m, C(CH_3)$_3$). Data are in accordance with the literature.[49]

To a cooled (0 °C) solution of Boc-L-phenylalanine methyl ester (10.0 g, 35.8 mmol) in Et_2O (100 mL) was added methylmagnesium bromide (37.0 mL of a 3.0 M solution in THF, 111 mmol) slowly via cannula. The mixture was stirred for 16 h at ambient temperature, quenched with ice-cold H_2O (~30 mL), then filtered through Celite. The (partially aqueous) filtrate was extracted with CH_2Cl_2 (50 mL × 2) and the combined organics were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford the crude alcohol product as a pale yellow solid (7.32 g, 73%) which was used immediately without further purification. To a cooled (0 °C) solution of the crude alcohol (5.00 g, 17.9 mmol) in THF (50 mL) was added potassium *tert*-butoxide (2.21 g, 19.7 mmol). The mixture was stirred for 16 h at ambient temperature and then concentrated in vacuo to afford a viscous yellow oil. The oil was dissolved in EtOAc (100 mL) and washed with brine (100 mL) and the aqueous phase extracted with EtOAc (20 mL × 2). The combined organics were dried ($MgSO_4$), filtered and concentrated in vacuo to give a clear yellow oil. Chromatographic purification (25% EtOAc:petrol) gave the oxazolidinone as a yellow oil (3.51 g, 79%); $[\alpha]_D^{20} = -108.2$ (*c* 1.0, $CHCl_3$), lit.[50] −103.5 (*c* 0.6, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.37–7.15 (5H, m, Ar*H*), 4.79 (1H, br s, N*H*), 3.74–3.65 (1H, m, C*H*NH$_2$), 2.84 (1H, ABX, J_{AB} 13.3, J_{AX} 3.7, PhCH_AH$_B$), 2.67 (1H, ABX, J_{BA} 13.3, J_{BX} 10.8, PhCH$_A$$H_B$), 1.49 (3H, s, C$H_3$) and 1.46 (3H, s, C$H_3$). Data are in accordance with the literature.[50]

To a solution of oxazolidinone (1.86 g, 9.06 mmol) in CH_2Cl_2 (30 mL) was added trimethyloxonium tetrafluoroborate (1.48 g, 10.0 mmol) and then the mixture was stirred for 16 h. Phenylhydrazine (0.902 mL, 9.06 mmol) was added and the solution was stirred for a further 24 h. The mixture was concentrated in vacuo and the residue dissolved in triethyl orthoformate (20 mL) and MeOH (4 mL) and heated at reflux (100 °C) for 18 h. The resultant precipitate was collected by filtration and washed with cold EtOAc to obtain the purified title product **52** as a light brown solid (2.02 g, 57%); mp 178–180 °C, lit. 177–179 °C; $[\alpha]_D^{20} = -73.0$ (*c* 0.5, MeCN), lit.[4m] −76.4 (*c* 1.0, MeCN); δ_H (300 MHz, $CDCl_3$) 9.03 (1H, s, NC*H*N), 7.64–7.25 (10H, m, Ar*H*), 5.28 (1H, t, *J* 8.1, CH_2C*H*N), 3.40 (1H, ABd, *J* 14.0, PhCH_AH$_B$), 3.19 (1H, ABd, *J* 14.0, PhC$H_A$$H_B$), 1.71 (3H, s, C$H_3$) and 1.58 (3H, s, C$H_3$). Data are in accordance with the literature.[4m]

4.5.13. (*R*)-Methyl 4-benzyl-5-oxo-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylate 54

Following general procedure B, KHMDS (90.0 μL of a 0.5 M solution in toluene, 45.0 μmol), triazolium salt (50.0 μmol), THF (2 mL) and phenylalanine-derived methyl carbonate (170 mg, 0.500 mmol) gave, after chromatographic purification (15%

Et_2O:petrol), the title compound (*R*)-**54** as a colourless oil (129 mg, 76%). δ_H (300 MHz, $CDCl_3$) 7.85–7.80 (2H, m, MeOAr*H*-3,5), 7.20–7.14 (5H, m, Ph*H*), 6.94–6.89 (2H, m, MeOAr*H*-2,6), 3.85 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.63 (1H, ABd, *J* 13.7, CH_AH$_B$Ph) and 3.48 (1H, ABd, *J* 13.7, CH$_A$$H_B$Ph). Spectroscopic data are in accordance with the literature.[12a] Enantiomeric excesses (37% and 24% ee) were determined by HPLC with Chiralcel OD-H column (2% *i*-PrOH/hexane, flow rate = 1.0 mL min^{-1}), t_R(*R*) 15.7 min and t_R(*S*) 19.9 min.

4.5.14. (*R*)-Phenyl methyl-5-oxo-2-(4-methoxyphenyl)-4,5-dihydro-oxazole-4-carboxylate 55

Following general procedure B, alanine-derived phenyl carbonate (100 mg, 0.308 mmol), KHMDS (55.4 μL, 27.7 μmol), triazolium salt (30.8 μmol) and toluene (1 mL) gave, after 60 min and chromatographic purification (20% Et_2O/petrol), the product (*R*)-**55** as a colourless oil. δ_H (300 MHz, $CDCl_3$) 7.97–7.92 (2H, m, MeOAr*H*-3,5), 7.34–7.25 (2H, m, Ph*H*-2,6), 7.19–7.13 (1H, m, Ph*H*-4), 7.05–6.99 (2H, m, Ph*H*-3,5), 6.95–6.90 (2H, m, MeOAr*H*-2,6), 3.81 (3H, s, OCH_3) and 1.80 (3H, s, CH_3). Spectroscopic data are in accordance with the literature.[12a] Enantiomeric excess (19% and 42% ee) was determined by HPLC with Chiralcel OD-H column (2% *i*-PrOH/hexane, flow rate = 1.0 mL min^{-1}), t_R(*R*) 14.8 min and t_R(*S*) 18.1 min.

4.5.15. (*R*)-Phenyl 4-ethyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (*R*)-58

Following general procedure D, 4-ethyl-2-(4-methoxyphenyl)oxazol-5-yl phenyl carbonate (68.0 mg, 0.200 mmol), THF (0.7 mL), triazolium salt (20.0 μmol) and KHMDS (36.0 μL, 18.0 μmol) gave, after 60 min and chromatographic purification (20% Et_2O:petrol), the title product (*R*)-**58** as a colourless oil (47.6 mg, 70%). δ_H (400 MHz, $CDCl_3$) 8.04 (2H, d, *J* 9.2, MeOAr*H*-3,5), 7.40–7.09 (5H, m, Ph*H*), 7.01 (2H, d, *J* 9.2, MeOAr*H*-2,6), 3.90 (3H, s, OCH_3), 2.44 (1H, dq, *J* 14.2, 7.2, CH_AH$_B$), 2.36 (1H, dq, *J* 14.0, 7.2, CH$_A$$H_B$) and 1.01 (3H, t, *J* 7.2, CH_3). Spectroscopic data are in accordance with the literature.[19] Enantiomeric excess (22% and <5% ee) was determined by HPLC with Chiralcel OD-H column (5% *i*-PrOH/hexane, flow rate = 1.0 mL min^{-1}), t_R(*R*) 9.2 min and t_R(*S*) 11.6 min.

4.5.16. 4-Benzyl-2-(4-methoxyphenyl)oxazol-5-yl naphthalen-1-yl carbonate 63

Following general procedure E, Et_3N (0.594 mL, 4.27 mmol), phenylalanine-derived azlactone **37** (1.00 g, 3.56 mmol), CH_2Cl_2 (10 mL) and 1-naphthyl chloroformate (0.660 mL, 4.09 mmol), gave the crude product as a yellow oil. Crystallisation (Et_2O/hexane) gave the product **63** as a colourless solid (828 mg, 51%); mp 86–88 °C; δ_H (400 MHz, $CDCl_3$) 7.95–7.89 (4H, m, MeOAr*H*-3,5 and Nap*H*), 7.80 (1H, d, *J* 8.3, Nap*H*), 7.57 (2H, dt, 6.7, 3.0, Ar*H*), 7.49 (1H, t, *J* 8.0, Ar*H*), 7.39–7.31 (5H, m, Ar*H*), 7.27–7.24 (1H, m, Ar*H*), 6.95 (2H, d, *J* 8.8, MeOAr*H*-2,6), 3.97 (2H, s, PhCH_2) and 3.85 (3H, s, OCH_3); δ_C (100 MHz, $CDCl_3$) 161.7 (MeOAr*C*-1), 155.7 (Ar*C*), 150.2 (Ar*C*), 146.6 (Ar*C*), 145.9 (Ar*C*), 137.6 (Ar*C*), 134.8 (Ar*C*), 129.1 (Ar*C*H), 128.8 (Ar*C*H), 128.3 (Ar*C*H), 128.0 (Ar*C*H), 127.2 (Ar*C*H), 127.2 (Ar*C*H), 127.1 (Ar*C*H), 126.9 (Ar*C*H), 126.1 (Ar*C*), 125.4 (Ar*C*H), 123.5 (Ar*C*), 120.9 (Ar*C*H), 119.9 (Ar*C*), 117.3 (Ar*C*H), 114.4 (Ar*C*H), 55.6 (OCH_3) and 31.9 (CH_2); *m/z* MS (ESI+) 469 (100, [M+NH$_4$]$^+$), HRMS (ESI+) $C_{28}H_{25}N_2O_5^+$ ([M+NH$_4$]$^+$) requires 469.1758, found 469.1758 (+0.0 ppm); IR ν_{max} (KBr) /cm^{-1} 3052 (Ar C–H), 3027, 2970, 2913, 2835, 1792 (C=O), 1667 (Ar C=C), 1617 (C=N), 1603 (Ar C=C), 1459, 1502, 1455, 1434, 1393, 1307, 1258 (C–O), 1213 (C–O) and 1180 (C–O).

4.5.17. (*R*)-1,1,1-Trichloro-2-methylpropan-2-yl 4-benzyl-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate 57

Following the general procedure B, trichlorodimethylethyl oxazolyl carbonate (200 mg, 0.413 mmol), THF (2 mL), triazolium salt **62** (41.3 μmol) and KHMDS (74.4 μL of a 0.5 M in toluene, 37.2 μmol) gave, after 1 h and chromatographic purification (20% Et_2O:petrol), the product (*R*)-**57** as a colourless oil (60.0 mg, 30%). δ_H (300 MHz, $CDCl_3$) 7.82 (2H, d, *J* 8.8, MeOAr*H*-3,5), 7.23–7.18 (5H, m, Ph*H*), 6.89 (2H, d, *J* 8.8, MeOAr*H*-2,6), 3.86 (3H, s, OCH_3), 3.59 (1H, ABd, *J* 13.6, CH_AH$_B$), 3.48 (1H, ABd, *J* 13.6, CH$_A$$H_B$), 1.95 (3H, s, C$H_3$) and 1.91 (3H, s, C$H_3$). Spectroscopic data are in accordance with the literature.[19] Enantiomeric excess for the reaction (8% ee) was determined by derivatisation (see below). Absolute configuration assigned by analogy with the absolute configuration of related products.

4.5.18. 1,1,1-Trichloro-2-methylpropan-2-yl 2-benzyl-2-(4-methoxybenzamido)-3-oxo-3-(((*S*)-1-phenylethyl)amino) propanoate

To a solution of (racemic) rearrangement product **57** (100 mg, 0.206 mmol) in CH_2Cl_2 (2 mL) was added DMAP (2.52 mg, 20.6 μmol) followed by (*S*)-α-methylbenzylamine (26.6 μL, 0.206 mmol). The mixture was stirred for 16 h then diluted with CH_2Cl_2 (5 mL) and quenched with NH_4Cl(aq) (8 mL). The product was extracted with EtOAc (5 mL × 3) and the organic fractions combined, dried ($MgSO_4$), filtered and concentrated in vacuo to afford the crude product. In the case of the reaction with the racemic *C*-carboxyazlactone, chromatographic purification (30% EtOAc/petrol) gave the product as a pale yellow oil (88.7 mg, 71%) as a 50:50 mixture of diastereomers. δ_H (300 MHz, $CDCl_3$) 7.73 (2H, d, *J* 2.5, MeOAr*CH*-3,5), 7.70 (2H, d, *J* 2.5, MeOAr*CH*-3,5), 7.58 (1H, s, CON*H*), 7.49 (1H, s, CON*H*), 7.46–7.38 (5H, m, Ph*H*), 7.36–7.25 (9H, m, Ph*H*), 7.17–7.13 (3H, m, Ph*H*), 7.08–7.03 (2H, m, Ph*H*), 6.90–6.95 (4H, m, MeOAr*CH*-2,6), 6.79–6.76 (2H, m, Ph*H*), 6.54 (1H, d, *J* 8.0, CON*H*), 6.47 (1H, d, *J* 7.8, CON*H*), 5.22–5.10 (2H, m, PhC*H*(Me)), 4.03 (1H, ABd, *J* 14.1, PhCH_AH$_B$), 3.95 (1H, ABd, *J* 14.1, PhCH$_A$$H_B$), 3.88 (6H, s, OC$H_3$), 3.54 (1H, ABd, *J* 14.1, PhCH_AH$_B$), 3.39 (1H, ABd, *J* 14.1, PhCH$_A$$H_B$), 2.04 (3H, s, C(C$H_3$)$_2CCl_3$), 2.02 (3H, s, C(C$H_3$)$_2CCl_3$), 1.90 (3H, s, C(C$H_3$)$_2CCl_3$), 1.79 (3H, s, C(C$H_3$)$_2CCl_3$), 1.65 (3H, d, *J* 7.0, CH(CH_3)) and 1.57 (3H, d, *J* 6.9, CH(CH_3)); δ_C (75 MHz, $CDCl_3$) 168.0 (*C*=O), 166.04 (MeOAr*C*-1), 166.00 (MeOAr*C*-1), 164.8 (*C*=O), 164.6 (*C*=O), 162.5 (*C*=O), 142.0 (CH(Me)Ph*C*-1), 141.8 (CH(Me)Ph*C*-1), 134.9 (Ph*C*-1), 134.5 (Ph*C*-1), 130.2 (Ar*C*H), 130.1 (Ar*C*H), 129.1 (Ar*C*H), 128.9 (Ar*C*H), 128.4 (Ar*C*H), 128.2 (Ar*C*H), 128.0 (Ar*C*H), 127.5 (Ar*C*H), 127.2 (Ar*C*H), 126.8 (Ar*C*H), 126.3 (Ar*C*H), 126.2 (MeOAr*C*-4), 113.9 (MeOAr*C*H-2,6), 105.9 (*C*Cl$_3$), 90.8 (O*C*Me$_2$), 90.6 (O*C*Me$_2$), 67.6 (*C*R$_2$(CO)$_2$), 67.5 (*C*R$_2$(CO)$_2$), 55.5 (OCH_3), 50.1 (Ph*C*H(Me)), 49.8 (Ph*C*H(Me)), 39.2 (Ph-*C*H$_2$), 39.0 (Ph-*C*H$_2$), 21.2 (*C*H$_3$), 21.1 (*C*H$_3$), 21.0 (*C*H$_3$) and 20.8 (*C*H$_3$); *m/z* MS (ESI+) 605 (100, ([{^{35}Cl$_3$}M+H]$^+$), 607 (97, [{^{35}Cl$_2$^{37}Cl}M+H]$^+$), 609 (30, [{^{35}Cl^{37}Cl$_2$}M+H]$^+$) and 611 (4, ([{^{37}Cl$_3$}M+H]$^+$); HRMS (ESI+) $C_{30}H_{32}Cl_3N_2O_5^+$ ([{^{35}Cl$_3$}M+H]$^+$) expected 605.1371, found 605.1369 (−0.3 ppm); IR ν_{max} (thin film) /cm^{-1} 3375, 3087, 3064, 3031, 2975, 2930, 1741 (br d, C=O),1685 (br d, C=O), 1654 (d, C=O), 1607 (Ar C=C), 1522, 1477,1257 (C–O) and 705 (C–Cl).

4.5.18.1. Determination of the enantiomeric excess of (*R*)-57. The above experimental procedure was followed, and ^{1}H NMR spectroscopic analysis (400 MHz) of the crude diastereomeric product mixture was used to determine the ee of the rearrangement product (8% ee) using chiral triazolium salt **62**, assuming full stereochemical integrity was retained.

To a solution of enantiomerically enriched rearrangement product **57** (50.0 mg, 0.103 mmol) in CH_2Cl_2 (1 mL) was added DMAP (1.26 mg, 10.3 μmol) followed by (*S*)-α-methylbenzylamine (13.3 μL, 0.103 mmol). The mixture was stirred for 16 h then diluted with CH_2Cl_2 (5 mL) and quenched with NH_4Cl(aq) (5 mL). The product was extracted with EtOAc (5 mL × 3) and

the organic fractions combined, dried ($MgSO_4$), filtered and concentrated in vacuo to afford the crude product, which was inspected spectroscopically.

4.5.19. Naphthalen-1-yl 4-benzyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate 65

Following general procedure B, phenylalanine-derived naphthyl carbonate **63** (100 mg, 0.221 mmol), KHMDS (39.8 μL, 19.9 μmol), triazolium salt **18** (6.03 mg, 22.1 μmol) and THF (1 mL), gave, after chromatographic purification (20% EtOAc:petrol), the product as a colourless oil (232 mg, 70%). δ_H (400 MHz, $CDCl_3$) 7.96–7.90 (1H, m, MeOAr*H*-3,5), 7.88–7.83 (2H, m, Nap*H*), 7.76 (1H, br d, *J* 8.1, Ar*H*), 7.54–7.48 (2H, m, Ar*H*), 7.45 (1H, t, *J* 8.2, Ar*H*), 7.33–7.17 (6H, m, Ar*H*), 6.97–6.63 (2H, m, MeOAr*H*-2,6), 3.86 (3H, s, OCH_3), 3.81 (1H, ABd, *J* 13.7, PhCH_AH$_B$) and 3.68 (1H, ABd, *J* 13.7, PhCH$_A$$H_B$); δ_C (100 MHz, $CDCl_3$) 174.0 (*C*-2), 164.6 (MeOAr*C*-1), 163.7 (*C*OOAr), 163.5 (Ar*C*), 151.9 (Ar*C*), 146.0 (Ar*C*), 134.6 (Ar*C*), 132.8 (Ar*C*), 130.5 (Ar*C*H), 130.3 (Ar*C*H), 128.4 (Ar*C*H), 128.0 (Ar*C*H), 127.7 (Ar*C*H), 126.9 (Ar*C*H), 126.8 (Ar*C*H), 126.7 (Ar*C*H), 126.3 (Ar*C*H), 125.2 (Ar*C*H), 121.0 (Ar*C*H), 117.1 (Ar*C*), 114.3 (MeOAr*C*-2,6), 77.9 (*C*-4), 55.6 (OCH_3) and 40.1 (CH_2); *m/z* MS (ESI+) 451 (42, $[M+H]^+$), 407 (100, $[M+MeOH-Ph]^+$); HRMS (ESI+) $C_{23}H_{22}O_2N$ ($[M+H]^+$) requires 344.1645, found 344.1647 (+0.4 ppm); IR ν_{max} (KBr) /cm^{-1} 3063, 3033, 2965, 2937, 2841, 1822 (C=O), 1770 (C=O), 1645 (C=N), 1606 (Ar C=C), 1575, 1512, 1495 (Ar C=C), 1442, 1426, 1390, 1307, 1263 (C–O), 1212 (C–O) and 1173 (C–O).

4.5.20. Naphthalen-1-yl 2-(4-methoxyphenyl)-4-methyl-5-oxo-4,5-dihydrooxazole-4-carboxylate 64

Following general procedure B, alanine-derived naphthyl carbonate **61** (83.0 mg, 0.221 mmol), KHMDS (39.8 μL, 19.9 μmol), triazolium salt **18** (6.03 mg, 22.1 μmol) and THF (1 mL), gave after chromatographic purification (20% Et_2O:petrol) the product **64** as a colourless oil (58.1 mg, 70%). δ_H (400 MHz, $CDCl_3$) 8.10–8.06 (2H, m, MeOAr*H*-3,5), 7.88–7.83 (2H, m, Nap*H*-5,8), 7.75 (1H, br d, *J* 8.3, Nap*H*-4), 7.52–7.48 (2H, m, Nap*H*-6,7), 7.44 (1H, t, *J* 7.9, Nap*H*-3), 7.28 (1H, dd, *J* 7.6, 1.0, Nap*H*-2), 7.04–7.01 (2H, m, MeOAr*H*-2,6), 3.90 (3H, s, OCH_3) and 1.95 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 175.5 (*C*OOCR$_2$), 165.0 (*C*OOAr), 164.0 and 163.8 (MeOAr*C*-1 and *C*=N), 146.1 (Nap*C*-1), 134.7 (Nap*C*-4a), 130.5 (MeOAr*C*H-3,5), 128.1 (Nap*C*H-5), 127.0 (Nap*C*H), 126.9 (Nap*C*H), 126.8 (Nap*C*H), 126.4 (Nap*C*-8a), 125.3 (Nap*C*H-3), 121.0 (Nap*C*H-8), 117.9 (Nap*C*H-2), 117.5 (MeOAr*C*-4), 114.6 (MeOAr*C*H-2,6), 73.2 (Me*C*(COOAr)), 55.7 (OCH_3) and 20.6 (CH_3); *m/z* MS (ESI+) 408 (100, $[M+MeOH-H]^+$); HRMS (ESI+) $C_{23}H_{22}NO_6^+$ ($[M+MeOH+H]^+$) requires 408.1442, found 408.1440 (−0.5 ppm); IR ν_{max} (thin film) /cm^{-1} 3057, 3009, 2937, 2842, 1826 (C=O), 1772 (C=O), 1645 (C=N), 1608, 1308, 1262 (C–O) and 1221 (C–O).

4.5.21. (*R*)-Phenyl 4-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (*R*)-59

Following general procedure B, tyrosine-derived phenyl carbonate (100 mg, 0.197 mmol), triazolium salt **52** (7.75 mg, 19.7 μmol), KHMDS (35.4 μL, 17.7 μmol) and THF (1 mL) gave, after 1 h and chromatographic purification (10% Et_2O/petrol), the enantioenriched product (*R*)-**59** as a colourless oil (74.9 mg, 75%); δ_H (300 MHz, $CDCl_3$) 7.84–7.78 (2H, m, MeOAr*H*-3,5), 7.33–7.21 (7H, m, Ar*H*), 7.20–7.14 (1H, m, Ar*H*), 7.14–7.07 (2H, m, Ar*H*), 7.04–7.00 (2H, m, Ar*H*), 6.89–6.84 (2H, m, MeOAr*H*-2,6), 6.77–6.71 (2H, m, BnOAr*H*-2,6), 4.89 (2H, s, PhCH_2), 3.78 (3H, s, OCH_3), 3.59 (1H, ABd, *J* 13.8, BnOArCH_AH$_B$) and 3.47 (1H, ABd, *J* 13.8, BnOArCH_AH$_B$); δ_C (100 MHz, $CDCl_3$) 173.8 (*C*OOCR$_2$), 164.7 (*C*OOPh), 163.8 and 163.3 (MeOAr*C*-1 and *C*=N), 158.4 (BnOAr*C*-1), 150.4 (OPh*C*-1), 137.0 (CH$_2$Ph*C*-1), 131.8 (Ar*C*H), 130.4 (Ar*C*H), 129.7 (Ar*C*H), 128.7 (Ar*C*H), 128.1 (Ar*C*H), 127.6 (Ar*C*H), 126.7 (Ar*C*H), 125.2 (MeOAr*C*-4), 121.3 (Ar*C*H), 117.4 (BnOAr*C*-4), 114.8 (OAr*C*H-2,6), 114.5 (OAr*C*H-2,6), 77.8 (*C*-3), 70.0 (OCH_2), 55.7 (OCH_3) and 39.7 (BnOAr-CH_2); *m/z* MS (ESI+) 508 (10, $[M+H]^+$), 135 (38, Ar*C*≡O$^+$) and 95 (100); HRMS (ESI+) $C_{31}H_{26}NO_6$ ($[M+H]^+$) requires 508.1763, found 508.1760 (+0.6 ppm); IR ν_{max} (thin film)/cm^{-1} 3064 (CH), 3035 (CH), 2935 (CH), 2841 (CH), 1823 (C=O), 1766 (C=O), 1647, 1609, 1512, 1493, 1325, 1307 and 1262 (C–O). Enantiomeric excess (8% ee) was determined by HPLC with Chiralcel OD-H column (10% *i*-PrOH/hexane, flow rate = 1.0 mL min^{-1}), t_R(*R*) 22.5 min and t_R(*S*) 29.8 min.

4.5.22. (*R*)-1,1,1-Trichloro-2-methylpropan-2-yl 4-isobutyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate 60

Following general procedure B, leucine-derived phenyl carbonate (100 mg, 0.222 mmol), triazolium salt **52** (8.73 mg, 22.2 μmol), KHMDS (40.0 μL, 20.0 μmol) and THF (2 mL) gave, after 6 h and chromatographic purification (10% Et_2O/petrol), the enantioenriched product (*R*)-**60** as a colourless solid (31.0 mg, 31%); mp 64–66 °C, lit.[19] 68–70 °C (for racemate); $[\alpha]_D^{20} = +40.4$ (*c* 0.2, $CHCl_3$, 66% ee), lit.[19] +60.6 (*c* 0.6, $CHCl_3$, 91.2% ee); δ_H (300 MHz, $CDCl_3$) 7.96 (2H, d, *J* 9.0, MeOAr*H*-3,5), 6.97 (2H, d, *J* 9.0, MeOAr*H*-2,6), 3.87 (3H, s, OCH_3), 2.36 (1H, ABX, J_{AB} 14.4, J_{AX} 5.7, CH*H*), 2.03 (1H, ABX, J_{BA} 14.4, J_{BX} 7.5, CH$_A$$H_B$), 1.90 (3H, s, C$H_3$), 1.87 (3H, s, C$H_3$), 1.71 (1H, sept, *J* 6.6, C*H*), 0.94 (3H, d, *J* 6.6, CH_3) and 0.89 (3H, d, *J* 6.6, CH_3). Data are in accordance with the literature.[19] Enantiomeric excess (66% ee) was determined by HPLC with Chiralcel OD-H column (1% *i*-PrOH/hexane, flow rate = 1.0 mL min^{-1}), t_R(*R*) 5.8 min and t_R(*S*) 6.9 min.

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