Amidine catalysed *O*- to C-carboxyl transfer of heterocyclic carbonate derivatives†

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The structural requirements of amidines necessary to act as efficient *O*- to C-carboxyl transfer agents are delineated and the scope of this process outlined through its application to a range of oxazolyl, benzofuranyl and indolyl carbonates.

Introduction

Bicyclic amidines such as DBU are commonly used in synthesis for a variety of base-mediated transformations including eliminations,[1] esterifications,[2] condensations,[3] and the formation of trichlorocarbinols.[4] A common misconception regarding the reactivity of these species is their low nucleophilicity, however, they have been implicated as nucleophilic catalysts in a number of reactions[5] including ring opening polymerisations,[6] silylation of alcohols,[7] esterifications with dimethyl carbonate,[8] and the acylation of alcohols.[9] Despite their widespread use, only limited applications employing amidines as catalysts for C–C bond forming reactions have been delineated. For example, Zhang and Shi have shown that DBU may be employed in cyanoacylation reactions,[10] while Aggarwal and Mereu have shown that DBU is a versatile catalyst for Baylis–Hillman reactions.[11] Nearly forty years ago Steglich and Höfle showed that both DMAP and 4-(pyrrolidino)pyridine (PPY) could promote the rearrangement of 5-oxazolyl carbonate derivatives **1** to their corresponding 4-carboxyazlactones **2** (Fig. 1).[12] A number of elegant asymmetric approaches to this transformation using catalysts such as **5**–**8** have been developed,[13] and this *O*-to C-carboxyl transfer reaction has been applied to a range of heterocyclic (oxazolyl, indolyl and benzofuranyl) carbonate derivatives in both the racemic and asymmetric series. To date, only limited catalysts other than DMAP or PPY derivatives are known to promote this synthetically useful transformation. Vedejs *et al.* have shown that both achiral and chiral phosphines such as **4** and **6** are catalytically active in this reaction,[13c] while we have shown that N-heterocyclic carbene **3** is an efficient catalyst of this transformation.[14,15]

Despite the vast advances made within this area of research, limitations of the methodology developed to date include the low reactivity of C(4)-α-branched oxazolyl carbonates such as **9** in this reaction, presumably due to steric hindrance,[13c] and the formation of significant quantities (typically >20%) of the parent benzofuranones (±)-**15** and (±)-**16** when employing PEt_3 or PBu_3 **4** upon the rearrangement of benzofuranyl carbonates such as **11** and **12** respectively (Fig. 2).[13c,16] While this product formally corresponds to protonation of the enolate postulated to occur during the catalytic cycle, this product is often present in crude product mixtures prior to work-up and when strictly anhydrous conditions are employed. It has been proposed that this product may arise from an internal proton-transfer pathway due to the presence of potentially acidic C–H bonds adjacent to phosphorus in the intermediate ion pair, although conclusive evidence for this pathway has not been delineated.[16] Furthermore, to the best of our knowledge, the corresponding product arising from the carbonate functionality upon generation of the parent benzofuranone has not been isolated or characterised.

As part of a research programme concerned with the development and applications of nucleophilic organocatalysts,[17] we demonstrate herein that amidines can act as efficient *O*- to C-carboxyl transfer agents and show that the catalytic efficiency and product distributions of these reactions is markedly affected by catalyst structure.[18] The optimal catalyst identified from an initial screen is subsequently applied to the rearrangement of a wide range of oxazolyl, benzofuranyl and indolyl carbonates.

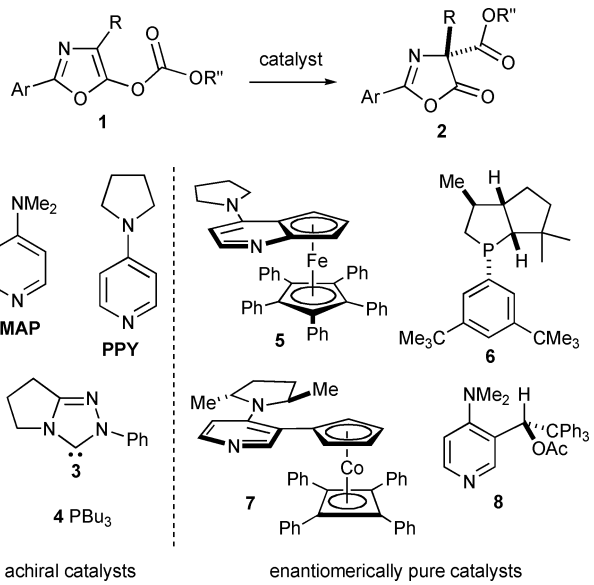

Fig. 1 Catalysts for *O*- to C-carboxyl transfer.

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† Electronic supplementary information (ESI) available: Spectroscopic data (^1H and ^{13}C) for all new products as well as ^1H data for all known compounds prepared by a non-literature procedure. See DOI: 10.1039/b805850d

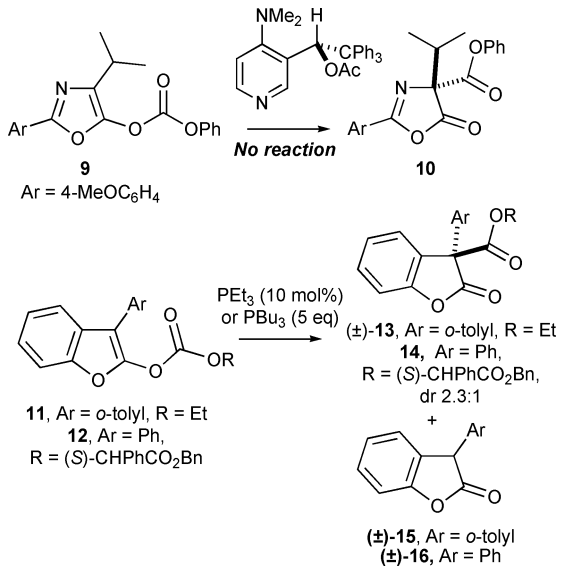


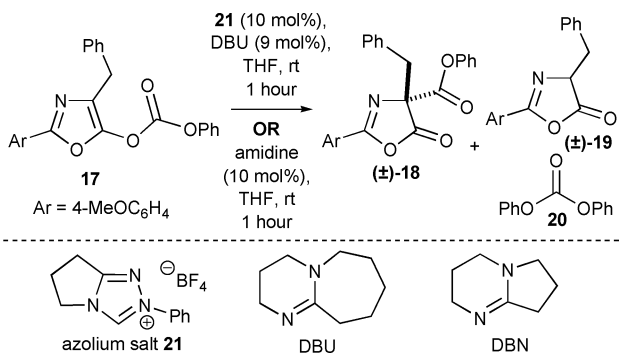
Fig. 2 Limitations of the *O*- to C-carboxyl transfer reaction methodology.

Results and discussion

The identification of an efficient amidine catalysed *O*-to C-carboxyl transfer protocol

Our interest in the ability of amidines to catalyse the rearrangement of oxazolyl carbonates developed from screening a range of organic bases for the generation of the corresponding NHC from triazolium salt **21**.[19] Relatively efficient catalysis of the rearrangement of oxazolyl carbonate **17** to (±)-**18** was noted using DBU as the base for the deprotonation of salt **21** in THF, proceeding to give (±)-**18** in ~85% conversion after 2 hours (Table 1, entry 1). However, background experiments showed that treatment of **17** with DBU (10 mol%) alone in THF promoted 40% conversion to the parent azlactone (±)-**19**, with diphenyl carbonate **20** isolated as a by-product of this transformation (entry 2). Although none of the desired C-carboxyazlactone (±)-**18** was formed in this reaction, the isolation of azlactone (±)-**19** and diphenyl carbonate implied that DBU was involved as a nucleophilic catalyst in this transformation. Treatment of an authentic sample of (±)-**18** with DBU returned only starting material, implying that product (±)-**18** is not an intermediate in the formation of (±)-**19** in this reaction. Simply changing the geometric constraints of the amidine from DBU to DBN showed a remarkable change in product distribution, giving, at full conversion of **17**, an 80 : 20 mixture of the desired C-carboxyazlactone (±)-**18** : azlactone (±)-**19** (entry 3).

Table 1 Identification of amidines as *O*- to C-carboxyl transfer catalysts



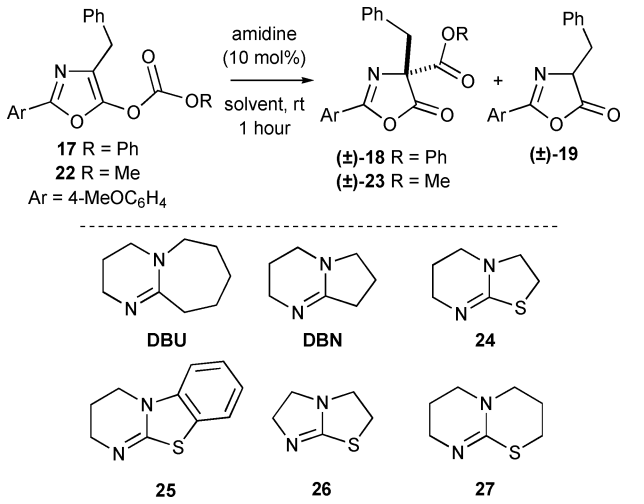
Entry	Salt	Amidine (mol%)	Conversion[a]	Product ratio (±)-**18** : (±)-**19**[a]
1	**21**	DBU (9)	85%	100 : 0
2	—	DBU (10)	40%	0 : 40
3	—	DBN (10)	>98%	80 : 20

[a] All reaction conversions and product distributions were judged by ^{1}H NMR spectroscopic analysis of the crude reaction product.

Cognisant of the recent seminal *O*-acylation studies employing amidine catalysis by both Birman and Okamoto *et al.*,[20] further investigations sought to develop this amidine promoted *O*- to C-carboxyl transfer reaction into a viable synthetic protocol. Systematic variation of the amidine catalyst structure and reaction solvent was investigated in order to minimise the formation of undesired azlactone (±)-**19** and diphenyl carbonate **20** from **17**. The effect of changing the solvent from THF to CH_2Cl_2 was first investigated, with DBU (10 mol%) giving an identical 40% conversion of **17** to (±)-**19** and diphenyl carbonate **20** (Table 2, entry 2), although DBN (10 mol%) in CH_2Cl_2 gave an improved 90 : 10 ratio of (±)-**18** : (±)-**19** (entry 4). The incorporation of a sulfur atom conjugated to the catalytic site was next investigated, with thioamidine **24** and its benzannulated derivative **25** giving essentially exclusive conversion of carbonate **17** to (±)-**18** (>98%), affording (±)-**18** in 63% and 87% isolated yield respectively (entries 5 and 6). Further variation in catalyst ring size using **26** or **27** was investigated, with only starting material returned upon treatment of **17** with imidazo-fused **26** (10 mol%), while **27** (10 mol%) gave an 88 : 12 mixture of (±)-**18** : (±)-**19** (entries 7 and 8). The effect of altering the migrating group showed that methyl carbonates are also tolerated in this reaction. Treatment of methyl carbonate **22** with amidine **24** gave a 90 : 10 mixture of (±)-**23** : (±)-**19**, giving (±)-**23** in 59% isolated yield, while benzannulated amidine **25** again gave full conversion to exclusively (±)-**23**, giving (±)-**23** in 87% isolated yield (entries 9 and 10). Addition of either **26** or **27** to **22** returned only starting material in both cases (entries 11 and 12). These findings indicate the critical importance of the size and substitution of both heterocyclic rings within these amidines in terms of catalyst activity and product distribution and follow a similar trend to the studies of both Birman and Okamoto for alcohol *O*-acylation.[20,21] These results also indicate that benzannulated amidine **25** is the optimal catalyst tested in this initial screen to promote the desired *O*- to C-carboxyl transfer.

The formation of the parent azlactone (±)-**19** and diphenyl carbonate **20** from phenyl carbonate **17** under anhydrous reaction conditions in these reactions is noteworthy, as this is analogous to the formation of benzofuranones upon reaction of benzofuranyl carbonates with phosphine catalysts.[13c,16] The generation of these by-products in variable amounts upon the reaction of carbonate **17** with amidines DBU, DBN, **24**, **26** and **27** indicates that competitive mechanistic pathways are available in these reactions. The formation of the desired C-carboxyazlactone (±)-**18** from **17** presumably follows the established mechanistic pathway of the Steglich rearrangement, with nucleophilic attack of the amidine at the carbonate carbonyl and subsequent collapse of the tetrahedral intermediate **28** generating carboxyl transfer intermediate **29** and enolate **30**. Recombination generates tetrahedral intermediate **31**,

Table 2 Variation of product distribution with amidine catalyst structure



Entry	Amidine	R	Solvent	Conversion[a]	Product ratio (±)-**18** or (±)-**23** : (±)-**19**[a]
1	**DBU**	Ph	THF	40%	0 : 40
2	**DBU**	Ph	CH_2Cl_2	40%	0 : 40
3	**DBN**	Ph	THF	>98%	80 : 20
4	**DBN**	Ph	CH_2Cl_2	>98%	90 : 10
5	**24**	Ph	CH_2Cl_2	>98%	>98:<2; (63%)[b]
6	**25**	Ph	CH_2Cl_2	>98%	>98:<2; (87%)[b]
7	**26**	Ph	CH_2Cl_2	0	—
8	**27**	Ph	CH_2Cl_2	>98%	88 : 12
9	**24**	Me	CH_2Cl_2	>98%	90 : 10; (59%)[b]
10	**25**	Me	CH_2Cl_2	>98%	>98:<2; (87%)[b]
11	**26**	Me	CH_2Cl_2	0	—
12	**27**	Me	CH_2Cl_2	0	—

[a] All product conversions and distributions were judged by ^{1}H NMR spectroscopic analysis of the crude reaction product. [b] Isolated yield of homogeneous product after aqueous work-up or chromatographic purification.

with elimination of the amidine giving (±)-**18** and regenerating the catalyst (Fig. 3). Although a complete and unambiguous mechanistic hypothesis to account for the formation of diphenyl carbonate **20** and azlactone (±)-**19** in these reactions has yet to be fully developed, it seems reasonable to assume *in situ* formation of phenoxide as a necessity for the formation of **20**. Phenoxide could be generated from a number of sources in the assumed catalytic cycle, including tetrahedral intermediates **28** or **31**, or alternatively from *in situ* hydrolysis of **17**, (±)-**18** or **29** from adventitious water. While not conclusive, preliminary investigations indicate that treatment of **17** with KOPh (1 eq) and 18-crown-6 (1 eq) generates azlactone (±)-**19** and diphenyl carbonate as the major reaction products, while addition of KOPh (10 mol%) and 18-crown-6 (10 mol%) to (±)-**18** returns only starting material. Ongoing investigations are aimed towards developing a full mechanistic understanding of the product distributions of these transformations.

Probing the generality of amidine catalysed *O*- to C-carboxyl transfer: oxazolyl carbonates

Having established benzannulated thioamidine **25** as the optimal catalyst screened, further investigations sought to explore the

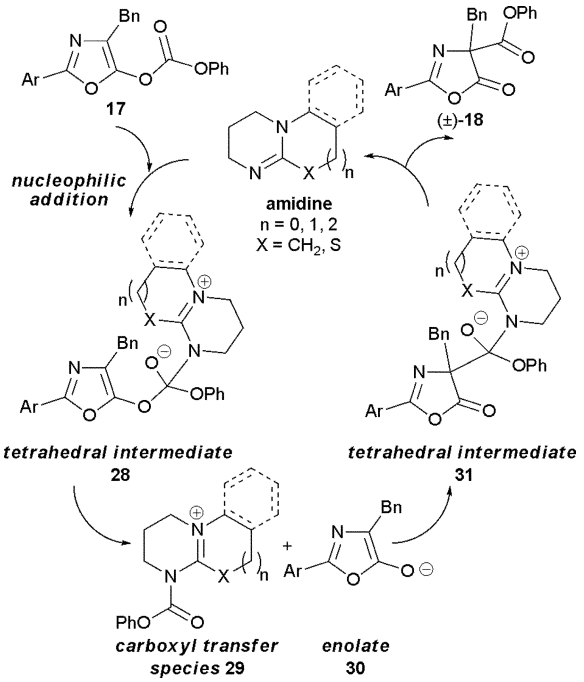
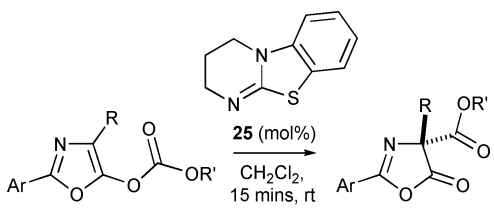


Fig. 3 Plausible mechanistic pathway for the *O*- to C-carboxyl transfer reaction.

scope of this transformation (Table 3). Variation of the carbonate functionality within the oxazole structure was first probed. Treatment of C(4)-benzyl substituted Ph, Me, Bn and $C(Me)_2CCl_3$ carbonate derivatives **17**, **22**, **32** and **33**[22] with amidine **25** (2–10 mol%) gave exclusively the corresponding (±)-C-carboxyazlactones (±)-**18**, (±)-**23**, (±)-**38** and (±)-**39**, isolated in 76–92% yield in each case (entries 1–4). C(4)-Isobutyl substituted carbonates **34**–**37** also readily rearranged upon treatment with **25** (entries 5–8), giving the desired products (±)-**40**–(±)-**43** in 61–93% yield. In both series, rearrangement of the phenyl carbonate derivatives proved the most

Table 3 Variation of carbonate functionality



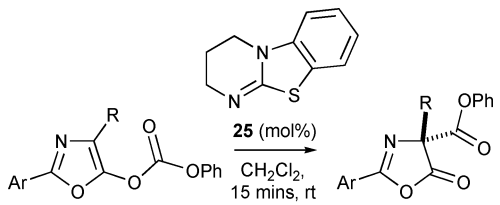
Entry		R	R′	Product	**25** (mol%)	Yield[a]
1	**17**	Bn	Ph	(±)-**18**	2	87%
2	**22**	Bn	Me	(±)-**23**	10	87%
3	**32**	Bn	Bn	(±)-**38**	10	76%
4	**33**	Bn	$C(Me)_2CCl_3$	(±)-**39**	10	92%[b]
5	**34**	*i*-Bu	Ph	(±)-**40**	2	61%
6	**35**	*i*-Bu	Me	(±)-**41**	10	61%
7	**36**	*i*-Bu	Bn	(±)-**42**	10	93%
8	**37**	*i*-Bu	$C(Me)_2CCl_3$	(±)-**43**	10	92%

[a] Isolated yield of homogeneous product after aqueous work-up or chromatographic purification. [b] Reaction time of one hour.

efficient, with catalyst loadings of 2 mol% employed to give full conversion to the corresponding (±)-C-carboxyazlactone within 15 minutes. The catalyst loadings required for the rearrangement of the other carbonate derivatives could also be lowered, but required significantly longer reaction times to achieve reasonable product conversions.

Extensive C(4)-substituent modification within the oxazole skeleton was next investigated using the most reactive phenyl carbonate derivatives (Table 4). Rearrangement of the C(4)-methyl and C(4)-phenyl oxazolyl carbonates **44** and **45** to their corresponding carboxyazlactones (±)-**50** and (±)-**51** using 2 and 5 mol% of amidine **25** respectively proceeded within 15 minutes (entries 3 and 4). Importantly, a C(4)-isopropyl substituent is tolerated (entry 5), a reaction that has previously proven difficult with chiral DMAP derivatives.[13c] This procedure also tolerates heteroatom containing C(4)-substituents with good reaction efficiency (entries 6–8), and allows chemoselective rearrangement of tyrosine derived dicarbonate **48** to give (±)-**54** in 92% isolated yield.

Table 4 Variation of C(4)-substitution within the oxazolyl carbonate

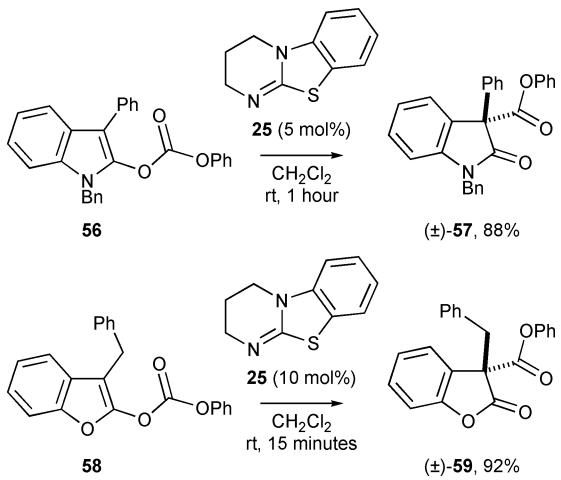


Entry		R	Product	**25** (mol%)	Yield[a]
1	**17**	Bn	(±)-**18**	2	87%
2	**34**	*i*-Bu	(±)-**40**	2	61%
3	**44**	Me	(±)-**50**	2	65%
4	**45**	Ph	(±)-**51**	5	84%
5	**46**	*i*-Pr	(±)-**52**	5	58%
6	**47**	4-BnO$C_6H_4CH_2$	(±)-**53**	2	87%
7	**48**	4-PhO$CO_2C_6H_4CH_2$	(±)-**54**	2	92%
8	**49**	$MeSCH_2CH_2$	(±)-**55**	2	92%

[a] Isolated yield of homogeneous product after aqueous work-up or chromatographic purification.

Amidine catalysed *O*- to C-carboxyl transfer: indolyl and benzofuranyl carbonates

Further studies focused upon extending the substrate scope of this transformation through probing the ability of thioamidine **25** to catalyse the *O*- to C-carboxyl rearrangement of a number of benzofuranyl[23] and indolyl carbonates. Both Fu and Vedejs *et al.* have demonstrated the asymmetric rearrangement of these heterocyclic carbonates, although reactions in the indolyl series typically employ relatively long reaction times (typically 48–96 hours with 5–10 mol% catalyst at rt or 35 °C) for full reaction conversion.[13c,f] While this low reactivity may be countered by the incorporation of an electron withdrawing substituent within the indolyl skeleton, the ability of benzannulated thioamidine **25** to promote this rearrangement at rt upon unactivated indolyl carbonates was tested. Addition of **25** (5 mol%) to *N*-benzyl protected indolyl carbonate **56**, readily prepared in three steps from *N*-benzylisatin, gave good conversion to (±)-**57** within one hour, affording (±)-**57** in 88% isolated yield (Scheme 1). The molecular structure of (±)-**57** was unambiguously proven by X-ray analysis (Fig. 4). This procedure proved equally applicable to benzofuranyl carbonates, as treatment of carbonate **58** with 10 mol% of **25** gave full conversion to (±)-**59** in 15 minutes, affording (±)-**59** in 92% isolated yield.



Scheme 1 Thioamidine promoted rearrangement of indolyl and benzofuranyl carbonates **56** and **58**.

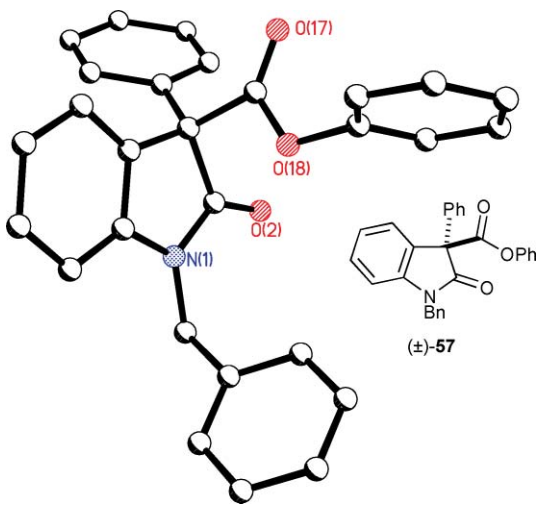


Fig. 4 Molecular representation of the X-ray crystal structure of (±)-**57**.

Conclusion

In conclusion, a number of amidines can promote the rearrangement of oxazolyl carbonates to their corresponding (±)-C-carboxyazlactones, with benzannulated thioamidine **25** proving optimal. Variation of the carbonate functionality and the C(4)-substituent within the oxazole skeleton is readily accommodated and this protocol has also been successfully extended to benzofuranyl and indolyl carbonates. Current studies are focused upon probing fully the mechanism of this transformation and developing applications of enantiomerically pure amidines in asymmetric catalysis.

Experimental procedures and analytical data

General information

All reactions involving moisture sensitive reagents were performed under an inert atmosphere *via* standard vacuum line techniques and with freshly dried solvents. All glassware was flame dried and allowed to cool under vacuum. Tetrahydrofuran (THF) and dichloromethane were obtained dry from a solvent purification system (MBraun, SPS-800). Petrol is defined as petroleum ether 40–60 °C. All solvents and commercial reagents were used as supplied without further purification unless stated otherwise. Room temperature refers to 20–25 °C. Temperatures of 0 °C were obtained using an ice–water bath and reaction reflux conditions using an oil bath equipped with a contact thermometer. *In vacuo* refers to the use of a Büchi Rotavapor R-2000 rotary evaporator with a Vacubrand CVC_2 vacuum controller or a Heidolph Laborota 4001 rotary evaporator with a vacuum controller. Analytical thin layer chromatography was performed on aluminium sheets coated with 60 F_{254} silica. TLC visualisation was carried out with ultraviolet light (254 nm), followed by staining with 1% aqueous $KMnO_4$ solution. Flash column chromatography was performed on Kieselgel 60 silica in the solvent system stated. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (300 MHz ^1H, 75.4 MHz ^{13}C) or a Bruker Avance II 400 (400 MHz ^1H, 100 MHz ^{13}C) spectrometer and in the deuterated solvent stated. Coupling constants (J) are reported in Hz. Multiplicities are indicated by: s (singlet), d (doublet), dd (doublet of doublets), sept (septet) and m (multiplet). The abbreviation Ar is used to denote aromatic. Infrared spectra (ν_{max}) were recorded on a Perkin-Elmer Spectrum GX FT-IR spectrometer using either thin films on NaCl plates (thin film) or KBr discs (KBr disc) as stated. Only the characteristic peaks are quoted. Microanalyses were carried out on a Carlo Erba CHNS analyser. Melting points were recorded on an Electrothermal apparatus and are uncorrected. Mass spectrometric (m/z) data was acquired by electrospray ionisation (ESI), electron impact (EI) or chemical ionisation (CI), either at the University of St Andrews Mass Spectrometry facility or from the EPSRC National Mass Spectrometry Service Centre, Swansea. At the University of St Andrews, low and high resolution ESI MS were carried out on a Micromass LCT spectrometer and low and high resolution CI MS were carried out on a Micromass GCT spectrometer. At the EPSRC National Mass Spectrometry Service Centre, low resolution CI MS was carried out on a Micromass Quattro II spectrometer and high resolution EI MS on a Finnigan MAT 900 XLT spectrometer.

Literature procedures were used for the preparation of known compounds **24**, **26** and **27**;[24] **32** and **36**;[13a] **17**, **34**, **44**, **45** and **58**;[13b] **22**, **35**, **46** and **49**[15] and **58**,[13c] and all gave spectroscopic data consistent with the literature.

General experimental procedures

General procedure A—rearrangement of carbonates

The selected catalyst was added to a solution of the desired carbonate in CH_2Cl_2 at room temperature. After the specified time, the solution was concentrated *in vacuo* and the desired product was obtained by either an acidic work-up in which the solution was poured into aqueous 0.1 M HCl, extracted with Et_2O and dried ($MgSO_4$) or chromatographic purification (silica).

General procedure B—synthesis of carbonates

Based upon the procedure described by Fu *et al.*,[13a] triethylamine (1.10 eq) was added to a stirred solution of azlactone (1.00 eq) in THF at 0 °C, followed by addition of the desired chloroformate (1.06 eq) and stirred at 0 °C for 30 minutes before warming to room temperature and stirring overnight. The resulting solution was poured into H_2O and the aqueous phase extracted with Et_2O (× 3). The organic extracts were combined, washed with aqueous 0.1 M HCl, saturated aqueous $NaHCO_3$ solution, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo.*

Phenyl 4-benzyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-18

Following general procedure A, oxazolyl carbonate **17**[13b] (0.20 mmol, 81 mg), CH_2Cl_2 (2 mL) and **25** (2 mol%, 0.8 mg) gave, after 15 minutes and an acidic work-up, (±)-**18** (71 mg, 87%) as a colourless oil with spectroscopic data (^1H NMR) in accordance with the literature.[13b]

Phenyl 2-(4-methoxyphenyl)-4-methyl 5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-23

Following general procedure A, oxazolyl carbonate **22**[15] (0.20 mmol, 68 mg), CH_2Cl_2 (2 mL) and **25** (5 mol%, 1.9 mg) gave, after 15 minutes and an acidic work-up, (±)-**23** (59 mg, 87%) as a colourless oil with spectroscopic data (^1H NMR) in accordance with the literature.[15]

3,4-Dihydro-2*H*-pyrimido [2,1-*b*] benzothiazole 25

Following a modified procedure described by Birman *et al.,*[20b] a mixture of aminopropanol (5.30 mmol, 4.00 mL) and 2-chlorobenzothiazole (5.80 mmol, 0.730 mL) was heated at 130 °C overnight. After cooling, toluene (23 mL) and thionyl chloride (11.7 mmol, 0.850 mL) were added and the reaction mixture was refluxed at 120 °C for 4 hours. The cooled mixture was then poured onto ice cold 20% aqueous KOH (10 mL) and extracted with CH_2Cl_2 (× 3). The organic extracts were combined, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated under vacuum. KOH (13.3 mmol, 0.744 g) and methanol (50 mL) were added to the resultant residue and the solution was refluxed for 3 hours. After cooling, the solution was poured into water and extracted with CH_2Cl_2 (× 3). The organic extracts were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated under vacuum. Chromatographic purification (EtOH–CH_2Cl_2 10 : 90) gave the product as an orange solid (0.445 g, 44%) with spectroscopic data (^1H NMR and ^{13}C NMR) in accordance with the literature.[24]

4-Benzyl 2-(4-methoxyphenyl)-oxazol-5-yl 1,1,1-trichloro-2-methylpropan-2-yl carbonate 33

Following general procedure B, triethylamine (3.91 mmol, 0.540 mL), 4-benzyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydro-oxazole (3.55 mmol, 1.00 g) (prepared from DL-leucine following a procedure described in the literature),[13c] THF (30 mL) and

2,2,2-trichloro-1,1-dimethyl chloroformate (3.76 mmol, 0.900 g) gave, after chromatography (petrol–Et_2O 75 : 25), oxazole **33** (1.34 g, 78%) as a colourless solid. Mp 62–64 °C; Found C, 54.51; H, 4.14; N, 2.92%; $C_{22}H_{20}Cl_3NO_5$ requires C, 54.51; H, 4.16; N, 2.89%; υ_{max} (KBr disc)/cm^{-1} 2996 (C–H), 1783 (C=O), 1611 (C=N), 1246 (C–O) and 802 (C–Cl); δ_H (300 MHz, $CDCl_3$) 7.89 (2H, d, *J* 9.0, 4-OMe(2,6)Ar*H*), 7.31–7.29 (5H, m, Ar*H*), 6.93 (2H, d, *J* 9.0, 4-OMe(3,5)Ar*H*), 3.88 (2H, s, CH_2), 3.85 (3H, s, OCH_3) and 1.92 (6H, s, 2 × CH_3); δ_C (75 MHz, $CDCl_3$) 161.5 (C), 155.4 (C), 148.4 (C), 145.7 (C), 137.5 (C), 129.0 (ArH), 128.6 (ArH), 127.8 (ArH), 126.7 (ArH), 123.3 (C), 120.0 (C), 114.2 (ArH), 104.6 (C), 92.3 (C), 55.5 (CH_3), 31.8 (CH_2) and 21.1 (CH_3); *m*/*z* (CI+) 282.0 (100, M − ($COOCMe_2CCl_3$) + H^+), 484.0 (6, (^{35}Cl)M + H^+), 486.0 (6, (^{37}Cl)M + H^+); HRMS (ES+) $C_{22}H_{21}Cl_3NO_5$ requires 484.0477, found 484.0480 (−0.5 ppm).

2-(4-Methoxyphenyl)-4-isobutyloxazol-5-yl 1,1,1-trichloro-2-methylpropan-2-yl carbonate 37

Following general procedure B, triethylamine (4.40 mmol, 0.610 mL), 4-isobutyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole (4.00 mmol, 0.995 g) (prepared from DL-leucine as described in the literature),[13a] THF (30 mL) and 2,2,2-trichloro-1,1-dimethyl chloroformate (4.24 mmol, 1.02 g) gave, after chromatography (petrol–Et_2O 75 : 25), oxazole **37** (1.35 g, 74%) as a colourless solid. Mp 68–70 °C; Found: C, 50.40; H, 5.09; N, 3.13%; $C_{19}H_{22}Cl_3NO_5$ requires C, 50.63; H, 4.92; N, 3.11%; υ_{max} (KBr disc)/cm^{-1} 2960 (C–H), 1781 (C=O), 1613 (C=N), 1242 (C–O) and 802 (C–Cl); δ_H (300 MHz, $CDCl_3$) 7.89 (2H, d, *J* 9.0, 4-OMe(2,6)Ar*H*), 6.93 (2H, d, *J* 9.0, 4-OMe(3,5)Ar*H*), 3.85 (3H, s, OCH_3), 2.34 (2H, d, *J* 6.9, CH_2), 2.05 (1H, sept, *J* 6.9, C*H*), 2.01 (6H, s, (CH_3)$_2$) and 0.96 (6H, s, (CH_3)$_2$); δ_C (75 MHz, $CDCl_3$) 161.4 (C), 155.2 (C), 148.8 (C), 145.9 (C), 127.7 (ArH), 123.6 (C), 120.1 (C), 114.2 (ArH), 104.6 (C), 92.3 (C), 55.5 (CH_3), 34.0 (CH_2), 27.7 (CH), 22.5 (CH_3) and 21.2 (CH_3); *m*/*z* (CI+) 248.1 (100, M − ($COOCMe_2CCl_3$) + H^+), 450.1 (2, (^{35}Cl)M + H^+), 452.1 (2, (^{37}Cl)M + H^+); HRMS (ES+) $C_{19}H_{23}Cl_3NO_5$ requires 450.0636, found 450.0633 (−0.8 ppm).

Benzyl 4-benzyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-38

Following general procedure A, oxazolyl carbonate **32**[13a] (0.20 mmol, 83 mg), CH_2Cl_2 (2 mL) and **25** (10 mol%, 3.8 mg) gave, after 15 minutes and an acidic work-up, (±)-**38** (63 mg, 76%) as a colourless oil with spectroscopic data (^{1}H NMR) in accordance with the literature.[13a]

1,1,1-Trichloro-2-methylpropan-2-yl 4-benzyl 2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-39

Following general procedure A, oxazolyl carbonate **33** (0.20 mmol, 97 mg), CH_2Cl_2 (2 mL) and **25** (10 mol%, 3.8 mg) gave, after 1 hour and an acidic work-up, (±)-**39** (89 mg, 92%) as a colourless oil. υ_{max} (thin film)/cm^{-1} 2933 (C–H), 1821 (C=O), 1760 (C=O), 1642 (C=N), 1262 (C–O) and 793 (C–Cl); δ_H (300 MHz, $CDCl_3$) 7.80 (2H, d, *J* 9.0, 4-OMe(2,6)Ar*H*), 7.21–7.16 (5H, m, Ar*H*), 6.90 (2H, d, *J* 9.0, 4-OMe(3,5)Ar*H*), 3.84 (3H, s, OCH_3), 3.59 (1H, d, *J* 13.8, CH_2), 3.48 (1H, d, *J* 13.8, CH_2), 1.95 (3H, s, CH_3) and 1.93 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 173.7 (C), 163.6 (C), 163.5 (C), 163.5 (C), 133.1 (C), 130.4 (ArH), 130.1 (ArH), 128.3 (ArH), 127.6 (CH), 117.3 (C), 114.3 (ArH), 105.2 (C), 91.0 (C), 78.2 (C), 55.6 (CH_3), 39.1 (CH_2) and 21.3 (CH_3); *m*/*z* (CI+) 282.1 (100, M − ($COOCMe_2CCl_3$) + H^+), 484.0 (5, (^{35}Cl)M + H^+), 486.0 (5, (^{37}Cl)M + H^+); HRMS (ES+) $C_{22}H_{21}Cl_3NO_5$ requires 484.0480, found 484.0478 (−0.3 ppm).

Phenyl 4-isobutyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-40

Following general procedure A, oxazolyl carbonate **34**[13b] (0.20 mmol, 73 mg), CH_2Cl_2 (2 mL) and **25** (2 mol%, 0.8 mg) gave, after 15 minutes and chromatography (petrol–Et_2O 80 : 20), (±)-**40** (45 mg, 61%) as a colourless oil with spectroscopic data (^{1}H NMR) in accordance with the literature.[13b]

Methyl 4-isobutyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-41

Following general procedure A, oxazolyl carbonate **35**[15] (0.20 mmol, 70 mg), CH_2Cl_2 (2 mL) and **25** (10 mol%, 3.8 mg) gave, after 15 minutes and chromatography (petrol–Et_2O 80 : 20), (±)-**41** (43 mg, 61%) as a colourless oil with spectroscopic data (^{1}H NMR) in accordance with the literature.[15]

Benzyl 4-isobutyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-42

Following general procedure A, oxazolyl carbonate **36**[13a] (0.20 mmol, 76 mg), CH_2Cl_2 (2 mL) and **25** (10 mol%, 3.8 mg) gave, after 15 minutes and an acidic work-up, (±)-**42** (70 mg, 92%) as a colourless oil with spectroscopic data (^{1}H NMR) in accordance with the literature.[13a]

1,1,1-Trichloro-2-methylpropan-2-yl 4-isobutyl-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-43

Following general procedure A, oxazolyl carbonate **37** (0.20 mmol, 90 mg), CH_2Cl_2 (2 mL) and **25** (10 mol%, 3.8 mg) gave, after 15 minutes and an acidic work-up, (±)-**43** (83 mg, 92%) as a colourless solid. Mp 64–66 °C; υ_{max} (KBr disc)/cm^{-1} 2958 (C–H), 1818 (C=O), 1762 (C=O), 1647 (C=N), 1261 (C–O) and 791 (C–Cl); δ_H (300 MHz, $CDCl_3$) 7.96 (2H, d, *J* 9.0, 4-OMe(2,6)Ar*H*), 6.97 (2H, d, *J* 9.0, 4-OMe(3,5)Ar*H*), 3.87 (3H, s, OCH_3), 2.36 (1H, dd, *J* 14.4, 5.7, CH_2), 2.03 (1H, dd, *J* 14.4, 7.5, CH_2), 1.90 (3H, s, CH_3), 1.87 (3H, s, CH_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); δ_C (75 MHz, $CDCl_3$) 175.1 (C), 163.7 (2 × C), 163.2 (C), 130.2 (ArH), 117.7 (C), 114.4 (ArH), 105.2 (C), 90.8 (C), 77.1 (C), 55.6 (CH_3), 41.5 (CH_2), 24.7 (CH), 23.9 (CH_3), 23.1 (CH_3) and 21.2 (CH_3); *m*/*z* (CI+) 248.1 (100, M − ($COOCMe_2CCl_3$) + H^+), 450.1 (7, (^{35}Cl)M + H^+), 452.1 (7, (^{37}Cl)M + H^+); HRMS (ES+) $C_{19}H_{23}Cl_3NO_5$ requires 450.0636, found 450.0631 (−1.1 ppm).

4-((4-Benzyloxy)benzyl)-2-(4-methoxyphenyl)-oxazolyl-5-yl phenyl carbonate 47

Following general procedure B, triethylamine (2.84 mmol, 0.400 mL), 4-((4-benzyloxy)benzyl)-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole (2.58 mmol, 1.00 g) (prepared from DL-tyrosine following a procedure described in the literature),[13a] THF

(30 mL) and phenyl chloroformate (2.71 mmol, 0.310 mL) gave **47** as a colourless solid after recrystallisation with Et_2O (1.10 g, 84%), mp 116–117 °C; υ_{max} (KBr disc)/cm^{-1} 3033 (Ar-H), 2911 (Alk-H), 1800 (C=O), 1613 (C=N) and 1214 (C–O); δ_H (400 MHz, $CDCl_3$) 7.96 (2H, d, *J* 9.0, 4-OMe(2,6)Ar*H*), 7.48–7.30 (10H, m, 2 × Ph*H*), 7.25 (2H, m, 4-OBn(3,5)Ar*H*), 6.95 (4H, d, 4-OMe(3,5)Ar*H* and 4-OBn(2,6)Ar*H*), 5.07 (2H, s, CH_2), 3.93 (2H, s, CH_2) and 3.90 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 161.5 (C), 157.7 (C), 155.5 (C), 150.8 (C), 150.1 (C), 145.6 (C), 137.2 (C), 130.1 (ArH), 129.8 (ArH), 128.7 (ArH), 128.0 (ArH), 127.9 (ArH), 127.5 (ArH), 126.9 (ArH), 123.8 (C), 120.6 (ArH), 119.9 (C), 115.0 (ArH), 114.2 (ArH), 70.1 (CH_2), 55.5 (CH_3) and 31.1 (CH_2); *m*/*z* (ES+) 530.2 (100, M + Na), HRMS (ES+) $C_{31}H_{25}NO_6Na$ requires 530.1580, found 530.1584 (+0.9 ppm).

2-(4-Methoxyphenyl)-4-((4-phenoxycarbonyloxy)benzyl)oxazolyl-5-yl phenyl carbonate 48

Triethylamine (14.0 mmol, 1.94 mL) was added to a stirred solution of DL-*N*-(4-methoxybenzoyl)tyrosine (3.17 mmol, 1.00 g) (prepared from DL-tyrosine following a procedure described in the literature)[13a] followed by the addition of phenyl chloroformate (13.8 mmol, 1.50 mL) and stirred at room temperature overnight. The resulting solution was poured into aqueous 1 M HCl and the aqueous phase extracted with Et_2O (× 3). The organic extracts were combined, washed with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), filtered and concentrated *in vacuo.* Chromatographic purification (petrol–Et_2O 80 : 20) afforded the oxazole **48** (1.46 g, 86%) as a colourless solid. Mp 71–74 °C; υ_{max} (KBr disc)/cm^{-1} 3065 (Ar-H), 2934 (Alk-H), 1798 (C=O), 1779 (C=O), 1614 (C=N) and 1235 (C–O); δ_H (300 MHz, $CDCl_3$) 7.92 (2H, d, *J* 9.0, 4-OMe(2,6)Ar*H*), 7.45–7.21 (14H, m, Ar*H*), 6.95 (2H, d, *J* 9.0, 4-OMe(3,5)Ar*H*), 3.93 (2H, s, CH_2) and 3.85 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 161.6 (C), 155.7 (C), 152.1 (C), 151.1 (C), 150.8 (C), 150.1 (C), 149.8 (C), 145.8 (C), 135.7 (C), 130.1 (ArH), 129.9 (ArH), 129.7 (ArH), 127.96 (ArH), 126.4 (ArH), 126.4 (ArH), 126.4 (ArH), 123.0 (C), 121.0 (CH), 120.6 (ArH), 119.8 (C), 114.3 (ArH), 55.5 (CH_3) and 31.0 (CH_2); *m*/*z* (CI+) 538.1 (62, M + H$^+$), 418.1 (17, M − (COOPh) + H$^+$); HRMS (ES+) $C_{31}H_{23}NO_8Na$ requires 560.1321, found 560.1323 (+0.2 ppm).

Phenyl 2-(4-methoxyphenyl)-4-methyl-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-50

Following general procedure A, oxazolyl carbonate **44**[13b] (0.20 mmol, 66 mg), CH_2Cl_2 (2 mL) and **25** (2 mol%, 0.8 mg) gave, after 15 minutes and chromatography (petrol–Et_2O 80 : 20), (±)-**50** (43 mg, 65%) as a colourless oil with spectroscopic data (^{1}H NMR) in accordance with the literature.[13b]

Phenyl 2-(4-methoxyphenyl)-5-oxo-4-phenyl-4,5-dihydrooxazole-carboxylate (±)-51

Following general procedure A, oxazolyl carbonate **45**[13b] (0.20 mmol, 74 mg), CH_2Cl_2 (2 mL) and **25** (5 mol%, 1.9 mg) gave, after 15 minutes and an acidic work-up, (±)-**51** (62 mg, 83%) as a colourless oil with spectroscopic data (^{1}H NMR) in accordance with the literature.[13b]

Phenyl 2-(4-methoxyphenyl)-5-oxo-4-isopropyl-4,5-dihydrooxazole-4-carboxylate (±)-52

Following general procedure A, oxazolyl carbonate **46**[15] (0.20 mmol, 70 mg), CH_2Cl_2 (2 mL) and **25** (5 mol%, 1.9 mg) gave, after 15 minutes and chromatography (petrol–Et_2O 80 : 20), (±)-**52** (41 mg, 58%) as a colourless oil with spectroscopic data (^{1}H NMR) in accordance with the literature.[15]

Phenyl 4-(4-(benzyloxy)benzyl)-2-(4-methoxyphenyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-53

Following general procedure A, oxazolyl carbonate **47** (0.20 mmol, 101 mg), CH_2Cl_2 (2 mL) and **25** (2 mol%, 0.8 mg) gave, after 15 minutes and an acidic work-up, (±)-**53** (88.0 mg, 87%) as a yellow oil with spectroscopic data (^{1}H NMR) in accordance with the literature.[15]

Phenyl 2-(4-methoxyphenyl)-5-oxo-4-(4-phenoxy-carbonyloxy)benzyl)-4,5-dihydrooxazole-4-carboxylate (±)-54

Following general procedure A, oxazolyl carbonate **48** (0.20 mmol, 108 mg), CH_2Cl_2 (2 mL) and **25** (2 mol%, 0.8 mg) gave, after 15 minutes and an acidic work-up, (±)-**54** (99.0 mg, 92%) as a yellow oil with spectroscopic data (^{1}H NMR) in accordance with the literature.[15]

Phenyl 2-(4-methoxyphenyl)-4-(2-(methylthio)ethyl)-5-oxo-4,5-dihydrooxazole-4-carboxylate (±)-55

Following general procedure A, oxazolyl carbonate **49**[15] (0.20 mmol, 77 mg), CH_2Cl_2 (2 mL) and **25** (2 mol%, 0.8 mg) gave, after 15 minutes and an acidic work-up, (±)-**55** (72 mg, 93%) as a colourless oil with spectroscopic data (^{1}H NMR) in accordance with the literature.[15]

1-Benzyl-3-phenylindole-2-yl phenyl carbonate 56

Following general procedure B, triethylamine (0.77 mL, 5.52 mmol), *N*-benzyl-3-phenyloxindole[24] (1.50 g, 5.02 mmol) and phenyl chloroformate (0.67 mL, 5.32 mmol) in THF (23 mL) gave, after recrystallisation (CH_2Cl_2–MeOH), carbonate **56** (1.82 g, 87%) as a pale yellow solid. Mp 116–118 °C; υ_{max} (KBr disc)/cm^{-1} 3060 (C–H), 3033 (C–H), 2925 (C–H), 1793 (C=O), 1620 (C=C) and 1228 (C–O); δ_H (300 MHz; $CDCl_3$) 7.80–7.74 (1H, m, Ar*H*), 7.63–7.59 (2H, m, Ar*H*), 7.44–7.38 (2H, m, Ar*H*), 7.28–7.09 (12H, m, Ar*H*), 6.77–6.72 (2H, m, Ar*H*) and 5.30 (2H, s, CH_2Ph); δ_C (75 MHz; $CDCl_3$) 150.7 (C), 150.2 (C), 138.7 (C), 136.6 (C), 132.9 (C), 132.4 (C), 129.6 (ArH), 128.9 (2 × ArH), 128.4 (ArH), 127.8 (ArH), 126.9 (ArH), 126.6 (ArH), 126.5 (ArH), 125.0 (C), 122.6 (ArH), 120.9 (ArH), 120.5 (ArH), 119.8 (ArH), 110.0 (ArH), 103.8 (C) and 46.2 (CH_2); *m*/*z* (CI) 420.2 (100, M + H$^+$); HRMS (CI) $C_{28}H_{22}NO_3$ requires 420.1600, found 420.1589 (−2.5 ppm).

Phenyl 1-benzyl 2-oxo-3-phenyl-2,3-dihydroindole-3-carboxylate (±)-57

Following general procedure A, indole **56** (0.20 mmol, 84 mg), CH_2Cl_2 (2 mL) and **25** (5 mol%, 1.9 mg) gave, after 1 hour and an acidic work-up, (±)-**57** (74 mg, 88%) as a yellow solid. Mp 85–87 °C; υ_{max} (KBr disc)/cm^{-1} 3061 (C–H), 3032 (C–H), 2936

(C–H), 1768 (C=O), 1714 (C=O), 1608 (C=C) and 1189 (C–O); δ_H (300 MHz; $CDCl_3$) 7.65–7.61 (1H, m, Ar*H*), 7.54–7.19 (15H, m, Ar*H*), 7.09–7.05 (2H, m, Ar*H*), 6.87–6.84 (1H, m, Ar*H*), 5.15 (1H, ABq, *J* 15.8, CH_AH_BPh) and 4.86 (1H, ABq, *J* 15.8, CH_AH_BPh); δ_C (75 MHz; $CDCl_3$) 172.7 (C), 167.8 (C), 150.6 (C), 143.7 (C), 135.4 (2 × C), 130.0 (ArH), 129.5 (ArH), 128.9 (ArH), 128.8 (ArH), 128.6 (ArH), 128.2 (ArH), 127.8 (ArH), 127.2 (ArH), 126.7 (C), 126.3 (ArH), 126.0 (ArH), 123.3 (ArH), 121.2 (ArH), 110.2 (ArH), 64.4 (C) and 44.2 (CH_2); *m/z* (ESI+) 442.1 (100, M + Na^+) HRMS (ESI+) $C_{28}H_{21}NO_3Na$ requires 442.1419, found 442.1422 (+0.7 ppm).‡

Phenyl 3-benzyl-2-oxo-2,3-dihydrobenzofuran-3-carboxylate (±)-59

Following general procedure A, benzofuran **58**[13c] (0.20 mmol, 69 mg), CH_2Cl_2 (2 mL) and **25** (10 mol%, 3.8 mg) gave, after 15 minutes and an acidic work-up, (±)-**59** (64 mg, 92%) as a yellow oil with spectroscopic data (^{1}H NMR) in accordance with the literature.[13c]

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