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Electronic effects of aryl-substituted bis(oxazoline) ligands on the outcome of asymmetric copper-catalysed C–H insertion and aromatic addition reactions

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ABSTRACT

The effect of the modification of bis(oxazoline) ligands on the outcome of copper-catalysed C–H insertion and aromatic addition reactions is described. In general, these reactions display minimum sensitivity in terms of enantiocontrol to variation of the electronic properties of the aryl moiety of the ligand however, some influence is observed for C–H insertions employing naphthyl-substituted bis(oxazolines) and for aromatic addition reactions of biphenyl diazo ketone substrates. The synthesis of the modified bis(oxazolines), which include four novel structures, is also described.

1. Introduction

Catalytic transformations of α-diazocarbonyl compounds have long been utilised for the synthesis of a diverse range of products.[1] The synthetic potential of these versatile compounds was first realised by researchers in the 1970's[2–6] and since this time large advances have been made in controlling the chemo-, regio- and enantioselectivity of these reactive substrates in various metal-catalysed reactions. Early work examining α-diazocarbonyl transformations employed copper-based catalysts, although with the introduction of rhodium(II) acetate in the 1970's,[2] focus switched to rhodium-catalysed processes, which were generally more effective from a synthetic perspective. While the exploration of chiral copper catalysts in cyclopropanation has been described, in general enantioselective catalysis in other C–C bond-forming reactions of α-diazocarbonyls has concentrated almost exclusively on rhodium-based systems.

Recognising that the majority of reports examining asymmetric α-diazocarbonyl reactions have focused on rhodium-catalysed processes, we and others have recently investigated the potential of copper-based catalyst systems for such transformations, offering a more cost-effective and potentially environmentally benign catalytic alternative. In particular, we have examined the application of copper-bis(oxazoline) catalysts for enantioselective C–H insertion and aromatic addition reactions of various diazo ketone substrates, with high levels of enantiocontrol achieved for both processes by a careful choice of the catalytic system.[7–11] Notably, enantioselectivities obtained for these previously reported reactions represent the highest levels of asymmetric induction recorded to date for both copper-catalysed C–H insertion and aromatic addition.[7,9]

In earlier work, a number of key elements of catalyst design were identified. The reaction efficiency and enantioselectivity were found to be particularly sensitive to the nature of the catalyst counterion. The highest levels of asymmetric induction, shortest reaction times and minimal levels of by-product formation were achieved for catalysts generated with additives possessing weakly coordinating counterions such as NaBARF {BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate} and $NaPF_6$.[8,11] The choice of bis(oxazoline) ligand was also found to be important. For C–H insertion reactions of α-diazo-β-keto sulfones leading to cyclopentanones, benzyl- and indane-substituted ligand systems were found to provide the highest levels of enantioselectivity,[10–12] while phenyl-substituted ligands were the most effective in terms of enantiocontrol for C–H insertion reactions of α-diazosulfones forming thiopyrans[9] and aromatic addition reactions of α-diazo ketones.[7] Thus, since the ligand structure clearly had an influence on the stereochemical outcome of the C–H insertion and aromatic addition reactions, we wished to explore the impact of altering the electronic properties of the substituents on the aryl ring of the bis(oxazoline) scaffold on the asymmetric induction in the copper-mediated transformations of α-diazocarbonyls.

Herein we report the synthesis of a range of aryl-substituted bis(oxazoline) ligands based on the structure of the widely employed commercially available phenyl- and benzyl substituted ligands **1** and **2**, respectively (Fig. 1, ligands **3**–**8**). Of the chosen compliment of ligands, bis(oxazolines) **4**, **6**, **7** and **8** are novel while the synthesis of ligands **3** and **5** has been previously described. The effect of the ligand modifications on the outcome of

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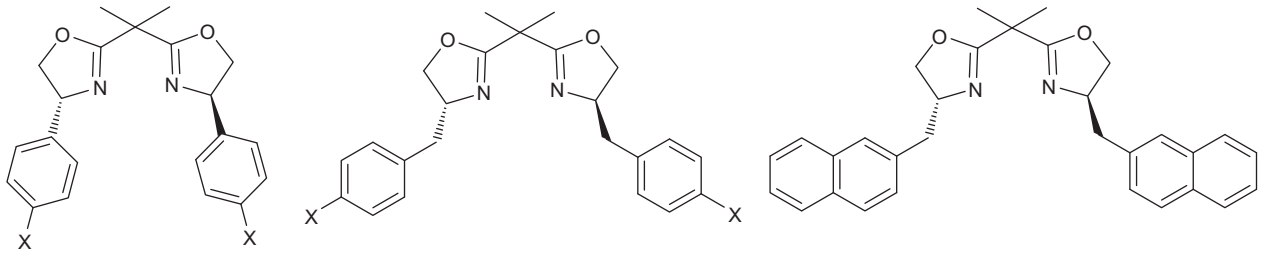


Figure 1. Bis(oxazoline) ligands.

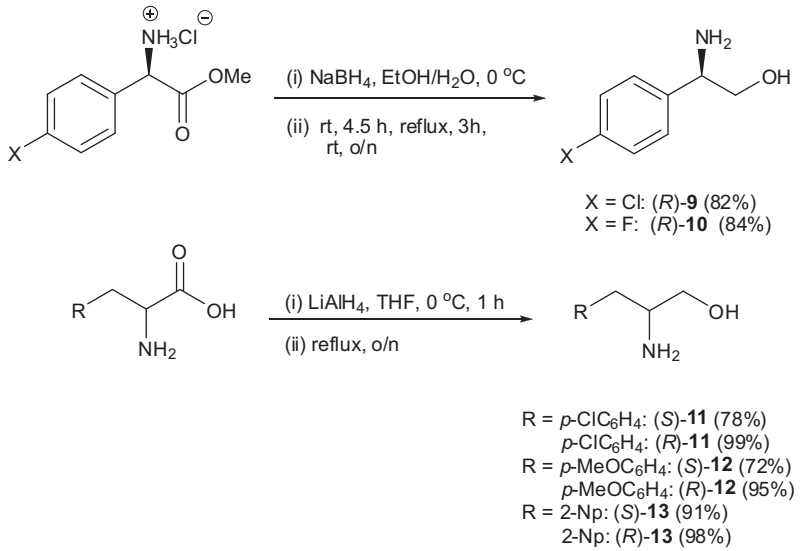
copper-catalysed C–H insertion reactions of α-diazo-β-keto sulfones and aromatic addition reactions of α-diazo ketones is subsequently explored. It should be noted that these novel ligands may also have potential applications in a broad range of bis(oxazoline)-mediated transformations.[13–15]

2. Results and discussion

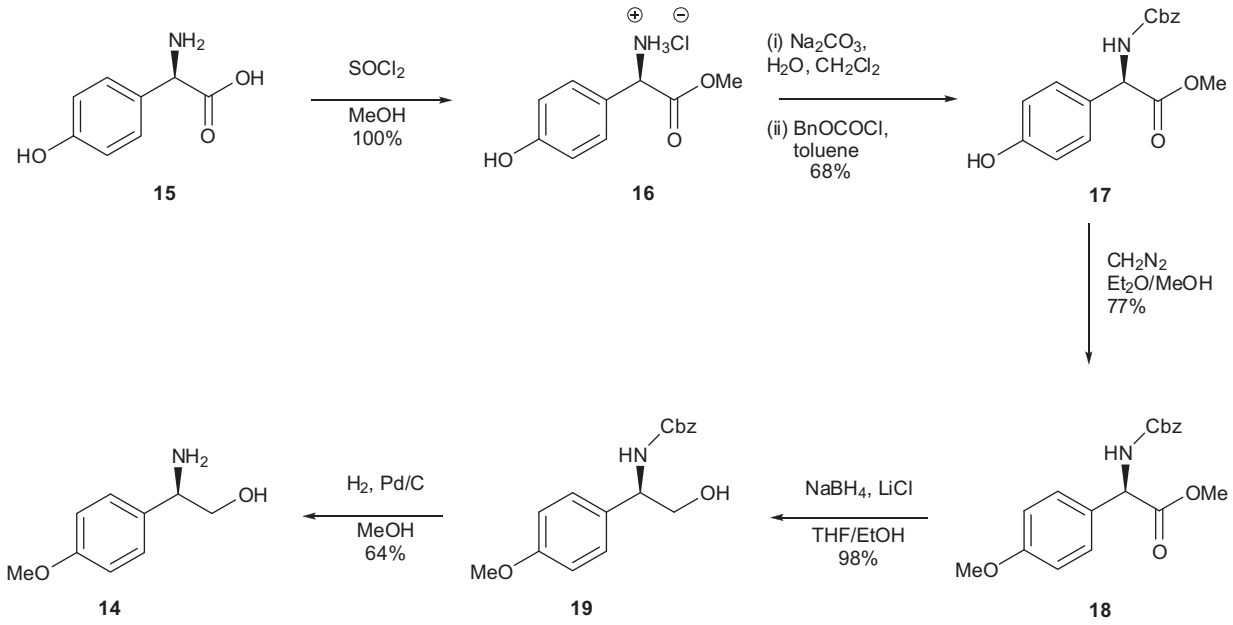
The vast majority of bis(oxazoline) ligands are prepared from optically active amino alcohols. The first challenge in this project was therefore accessing the necessary enantiopure amino alcohols required for the synthesis of **3**–**8**. Commercial precursors to 2-amino-2-(4-chlorophenyl)ethanol **9**, 2-amino-2-(4-fluorophenyl) ethanol **10**, 2-amino-3-(4-methoxyphenyl)propan-1-ol **11**, 2-amino-3-(4-chlorophenyl)propan-1-ol **12** and 2-amino-3-(naphthalene-2-yl)propan-1-ol **13**, required for access to bis(oxazolines) **3**, **4**, **6**, **7** and **8**, respectively, were readily available. Each of the amino alcohols was prepared in a single step in high yield as shown in Scheme 1.[16]

The prerequisite amino alcohol or amino alcohol precursor required for the preparation of ligand **5** was not available from commercial sources, and as a result, the synthesis of the *para*-methoxy-substituted phenylglycinol **14** was necessary. The synthesis of this amino alcohol had been previously described by Evans et al.[17] The route used in earlier work involved four synthetic steps beginning with 4-methoxystyrene. Herein an alternative approach to amino alcohol **14** was explored by starting from commercially available (*R*)-4-hydroxyphenylglycine **15** (Scheme 2). The first step in the synthetic plan involved the generation of (*R*)-4-hydroxyphenylglycine methyl ester hydrochloride **16** following a well established literature procedure,[18,19] followed by carbamate protection of the amine group.[20] The next step in the sequence was the methylation of the aryl hydroxyl group. A method described by Čaplar involving the treatment of **17** with potassium carbonate and methyl iodide in acetone was initially explored for this transformation,[20] however, while satisfactory on a small scale, partial racemisation was observed upon increasing the reaction scale. The desired methylation was instead reproducibly achieved by reaction of **17** with diazomethane,[21] providing an enantiopure sample of the *para*-methoxy derivative **18** in 77% yield after column chromatography. The product ester **18** was finally transformed into the desired amino alcohol **14** by reduction of **18** with sodium borohydride followed by reductive cleavage of the Cbz protecting group of **19**.[22]

With the desired amino alcohols in hand, the preparation of the phenyl-substituted bis(oxazolines) **3**–**5** was next undertaken using a methodology previously described by Evans.[23] Accordingly, acylation of amino alcohols **9**, **10** and **14** was achieved by treatment with dimethylmalonyl chloride to give the analogous bisamides **20**, **21** and **22**, respectively, which subsequently underwent ring-closure in the presence of *para*-tosyl chloride, triethylamine and a catalytic quantity of 4-(dimethylamino)pyridine to provide the desired ligands **3**–**5** in moderate-to-good yields following

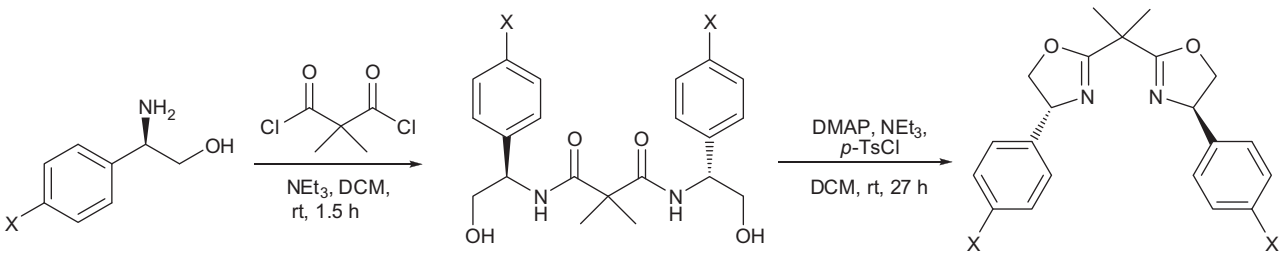


Scheme 1. Synthesis of amino alcohols **9**–**13**.



Scheme 2. Synthesis of amino alcohol **14**.

Table 1
Synthesis of bis(oxazolines) **3**–**5**[a]



Entry	X	Amino alcohol	Bisamide	Yield[b] (%)	Bis(oxazoline)	Yield[c] (%)
1	Cl	**9**	**20**	73	**3**	67
2	F	**10**	**21**	80	**4**	75
3	OMe	**14**	**22**	82	**5**	45

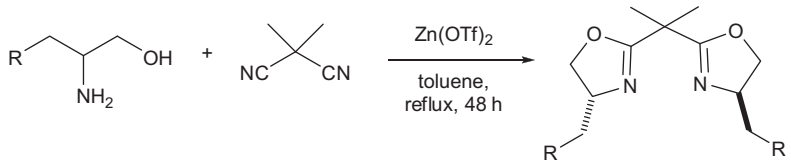
[a] Enantiopurity of the novel bis(oxazoline) **4** was confirmed by chiral HPLC analysis (see supporting information for details). Enantiopurity of bis(oxazolines) **3** and **5** was confirmed by comparison to previously reported specific rotation values.[17]
[b] Yield of bisamide following column chromatography.
[c] Yield of bis(oxazoline) following column chromatography.

chromatographic purification (Table 1, entries 1–3), although notably lower yields were frequently obtained in the ring-closing step.

Accordingly, for the synthesis of the benzyl-substituted ligands **6**–**8**, an alternative synthetic route was sought due to the poor yields and issues with the reproducibility observed during preparation of the phenyl-substituted bis(oxazolines) **3**–**5**. Many routes have been identified in the literature by which amino alcohols can be used for the construction of the bis(oxazoline) framework.[14,15] In 2005, García et al. described an efficient and general one-pot method for the synthesis of chiral bis(oxazoline) ligands involving the zinc triflate-catalysed reaction of chiral β-amino alcohols and 2,2-dimethylmalononitrile.[24] This was an attractive procedure for our desired ligand synthesis as the requirement for bisamide synthesis was circumvented and therefore the synthetic pathway to the final bis(oxazoline) product was shortened by one step. In addition, yields of typically 90% or greater were reported by García for reactions with a wide variety of chiral amino alcohols without the need for product purification via column chromatography. Using this methodology, the desired ligands **6**–**8** were successfully synthesised in one-step from the corresponding amino alcohols (Table 2, entries 1–6). Yields obtained for this procedure were moderate-to-good and, significantly, proved reproducible. In addition, excellent product purity was recorded with purification by recrystallisation required for only two ligand products (Table 2, entries 3 and 5).

The C–H insertions of α-diazo-β-keto sulfones **23**–**28** in the presence of (*R*)-**3**, (*R*)-**4**, (*R*)-**6**, (*R*)-**7** and (*R*)-**8** were next examined (Table 3, entries 1–6) in order to determine the impact of the modified bis(oxazoline) ligands on the stereochemical outcome of this process. Reactions were conducted in refluxing dichloromethane (DCM) using the previously identified optimal catalytic complex for this transformation,[8,10,11] comprising of 5 mol % $CuCl_2$, 6 mol % ligand and 6 mol % NaBARF. Predominant *trans*-cyclopentanone formation **29**–**34** was recorded in each of the reactions

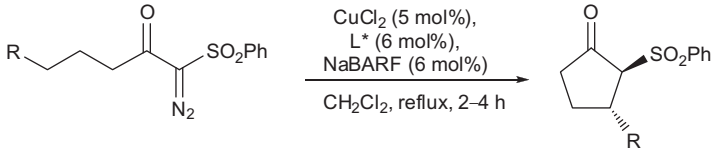
Table 2
Synthesis of bis(oxazolines) **6**–**8**[a]



Entry	R	Amino alcohol	Bis(oxazoline)	Yield (%)
1	*p*-ClC_6H_4	(*S*)-**11**	(*S*)-**6**	70
2	*p*-ClC_6H_4	(*R*)-**11**	(*R*)-**6**	55
3	*p*-$MeOC_6H_4$	(*S*)-**12**	(*S*)-**7**	60[b]
4	*p*-$MeOC_6H_4$	(*R*)-**12**	(*R*)-**7**	74
5	2-Np	(*S*)-**13**	(*S*)-**8**	41[b]
6	2-Np	(*R*)-**13**	(*R*)-**8**	61

[a] Enantiopurity of novel bis(oxazolines) **6**–**8** was confirmed by chiral HPLC analysis.
[b] Yield of bis(oxazoline) following recrystallisation in a 4:1 mixture of hexane:DCM.

Table 3
C–H insertion reactions with modified bis(oxazoline) ligands **3**, **4**, **6**–**8**[a]



Entry	Diazo	CP	R	% ee[b,c] (yield)						
				L*: (*R*)-**1**	(*R*)-**3**	(*R*)-**4**	(*R*)-**2**	(*R*)-**6**	(*R*)-**7**	(*R*)-**8**
1	**23**	**29**	Me	30 (94%)[d]	24 (94%)	31 (98%)	58 (62%)[d]	62 (95%)	61 (98%)	53 (77%)
2	**24**	**30**	Et	29 (97%)[d]	37 (84%)	36 (98%)	62 (70%)[d]	68 (88%)	60 (93%)	56 (87%)
3	**25**	**31**	*i*-Pr	37 (54%)[d]	42 (78%)	42 (62%)	60 (95%)[d]	63 (98%)	56 (93%)	48 (76%)
4	**26**	**32**	*t*-Bu	76 (84%)	77 (90%)	74 (67%)	—	—	—	—
5	**27**	**33**	Ph	57 (69%)	51 (83%)	64 (57%)	81 (88%)	77 (92%)	75 (91%)	70 (95%)
6	**28**	**34**	Bn	28 (57%)[d]	31 (59%)	34 (74%)	57 (54%)[d]	60 (86%)	55 (66%)	42 (69%)

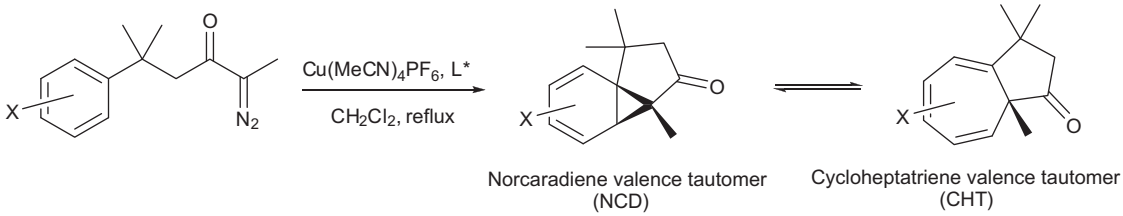
[a] Reactions conducted using the general procedure for copper-catalysed C–H insertion reactions (see Section 4 for details).
[b] Yield of *trans*-cyclopentanone after column chromatography.
[c] Enantiopurity of *trans*-cyclopentanones determined by chiral stationary phase HPLC. Stereochemical assignments for **29**, **30**, **31**, **33** and **34** were made by comparison with previously reported data. [25] Major enantiomer for R = Me and Et was (2*S*,3*R*). Major enantiomer for R = *i*-Pr, *t*-Bu, Ph and Bn was (2*S*,3*S*).
[d] CuCl used instead of $CuCl_2$. Previously published result.[10]

under investigation, however, in some cases, minor amounts of by-products were observed. The commercially available ligands (*R*)-**1** and (*R*)-**2** were also employed to allow us to determine the impact on the enantiocontrol of the aryl substituents on the modified ligand structures.

The inclusion of electron-withdrawing substituents (X = Cl, F) on the phenyl ring of ligands (*R*)-**3** and (*R*)-**4** was found to have minimal effect in the C–H insertion reactions of α-diazo-β-keto sulfones **23**–**28** (Table 3, entries 1–6), with largely comparable results recorded in terms of enantiocontrol for ligands (*R*)-**1**, (*R*)-**3** and (*R*)-**4**. A similar outcome was observed for reactions with the electronically modified benzyl-substituted bis(oxazolines) (*R*)-**6** and (*R*)-**7** in comparison to (*R*)-**2** (Table 3, entries 1–3, 5 and 6). Thus, alteration of the electronic nature of the benzyl-ligand structure was also found to have minimal impact on the enantioselectivity for all of the α-diazo-β-keto sulfone substrates examined. Notably, decreased levels of enantiocontrol were recorded for insertions in the presence of the naphthyl-substituted ligand (*R*)-**8** presumably due to steric effects, although further investigation of the transition states for the insertion reaction is required to validate this finding. Importantly, as no significant electronic impact was observed for ligands **3**, **4**, **6** and **7** it is likely that the steric impact of the ligand is the key determinant in terms of the extent of enantioselection achieved.

The influence of ligand modifications on the enantioselectivity was also examined for the aromatic addition reactions of α-diazo ketones. For this purpose, five diazo substrates **35**–**39** were prepared featuring a variety of aromatic substitution patterns. In each case, the norcaradiene obtained is in rapid equilibrium with the corresponding cycloheptatriene valence tautomer.[26] The use of benzyl-substituted bis(oxazolines) **6**–**8** was not examined in this case, as earlier work had shown that the presence of a benzyl group on the ligand scaffold provided poor enantiocontrol for this transformation.[7] As was previously observed for the C–H insertion reactions of α-diazo-β-keto sulfones **23**–**28**, the cyclisation reactions of **35**–**39** were found to be largely insensitive in terms of enantiocontrol to variation of the electronic properties of the bis(oxazoline) structure, with modest levels of enantioselectivity being recorded for each of the ligands examined (Table 4, entries 1–5). Since the yields of the azulenones following chromatography depend on the ease of purification, rather than directly correlating with reaction efficiency, the estimation of the efficiency in the aromatic additions of **35**–**39** is best undertaken through integration of the ^{1}H NMR spectra of the crude product mixtures (comparing the

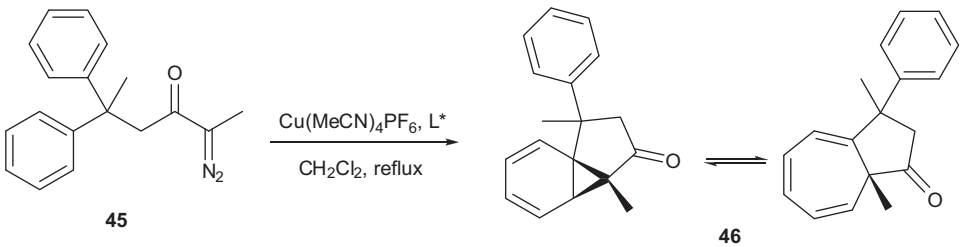
Table 4
Aromatic addition reactions of diazo ketones **35**–**39** with modified bis(oxazoline) ligands **3**–**5**[a,b]



Entry	Diazo	Azulenone	X	L*			
				(*R*)-**1**	(*R*)-**3**	(*R*)-**4**	(*R*)-**5**
				% ee	% ee	% ee	% ee
1	**35**	**40**	4-H	76	76	75	76
2	**36**	**41**	4-Me	80	76	78	84
3	**37**	**42**	4-Cl	60	54	60	60
4	**38**	**43**	4-F	59	60	50	71
5[c]	**39**	**44**	3,4,5-triMe	95	—	92	95

[a] Enantioselectivities for **40**–**43** were determined by chiral shift ^{1}H NMR experiments using (+)-Eu(Hfc)$_3$. As the norcaradiene/cycloheptatriene (NCD/CHT) equilibrium is rapid on the NMR timescale, a time-averaged signal is seen for the system.[26] Enantioselectivities for **44** were determined by chiral HPLC analysis. Major enantiomer for **40**–**44** = (−).
[b] Analysis of the crude product mixtures by ^{1}H NMR showed that reaction efficiencies were > 84% in each case, except for reaction of **38** with ligand (*R*)-**3** (efficiency = 50%).
[c] Reaction performed at room temperature.

Table 5
Aromatic addition reactions of biphenyl diazo ketone **45** with modified bis(oxazoline) ligands **3**–**5**



45 **46**

Entry	L*	Efficiency (%)	dr	ee[a] (%)
1[b]	(*R*)-**1**	87	94: 6	72[c]
2	(*R*)-**3**	88	84: 16	42[c]
3	(*R*)-**4**	93	92: 8	64[c]
4	(*R*)-**5**	96	75: 25	52[c]

[a] Enantioselectivities of major diastereoisomer of **46** as determined by chiral shift ^{1}H NMR experiments using (+)-Eu(Hfc)$_3$.
[b] $CuSbF_6$ was employed as the copper catalyst.
[c] Major enantiomer = (−).

distinctive vinylic protons of the azulenone with aryl signals due to aromatic byproducts). The levels of efficiency for the synthesis of azulenones **40**–**44** were observed to be consistent for all four ligands under investigation.

The only aromatic addition where there was evidence of an electronic effect was the cyclisation of the fluorinated diazo ketone **38**, where the enantioselectivity achieved with the methoxy-substituted ligand (*R*)-**5** was notably higher than that recorded with the other ligands (Table 4, entry 4). This behaviour is presumably electronic in nature and may be due to enhanced CH–π or π–π interactions between the electron rich oxazoline aryl substituent and the electron deficient aryl ring of the substrate, although further investigation of the transition state for the aromatic addition reaction is required to fully understand the factors which assist enantioselection in this process.

The biphenyl diazo ketone **45** also exhibited significant sensitivity to the substituents on the ligand (Table 5, entries 1–4). The basis for the enantioselection in this case due to the reaction at one of the two enantiotopic phenyl rings is distinctly different to that in the cyclisation of diazo ketones **35**–**39** where discrimination between the two enantiotopic faces of the aryl ring is required. In each case, two diastereomers of azulenone **46** were isolated, with one predominating. Despite facilitating highly efficient reactions, the presence of either electron-withdrawing or the electron-donating groups on the ligand results in the formation of azulenone **46** with diminished enantiopurity (⩽64% ee) relative to the reaction with (*R*)-**1** (72% ee). Further work is currently underway in order to fully elucidate the nature of the transition state interactions, which govern enantioselectivity in the aromatic addition process.

3. Conclusion

In conclusion, we have described the synthesis of a range of aryl-substituted bis(oxazolines) **3**–**8**, including four novel ligands. The effect of the ligand modifications was assessed by comparison

to results obtained from the commercially available bis(oxazolines) (*R*)-**1** and (*R*)-**2** for copper-catalysed C–H insertion and aromatic addition reactions. In general, it was observed that the copper-mediated transformations under investigation were largely insensitive in terms of enantiocontrol to electronic modification of the aryl ring on the ligand structure, however, moderately decreased levels of asymmetric induction were recorded for C–H insertions with the naphthyl-substituted ligand (*R*)-**8** and for aromatic addition reactions of the biphenyl diazo ketone **45** with the electronically-modified phenyl-substituted ligands (*R*)-**3**, (*R*)-**4** and (*R*)-**5**. These observations help contribute to our understanding of the nature of the interactions between the bis(oxazoline) ligands and the substituents on the copper-carbene in the transition state for the C–H insertion and aromatic addition processes. The novel ligands synthesised herein may also have potential applications in a broad range of bis(oxazoline)-mediated transformations.

4. Experimental

4.1. General

All solvents were distilled prior to use by the following methods: dichloromethane (DCM) was distilled from phosphorus pentoxide and when used for diazo ketone decompositions was further distilled from calcium hydride; ethyl acetate was distilled from potassium carbonate; toluene was distilled from sodium benzophenone ketyl and stored over 4 Å molecular sieves; hexane was distilled prior to use; ethanol and methanol were distilled from the corresponding magnesium alkoxide (stored over 3 Å molecular sieves) and tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Molecular sieves were dried by heating at >100 °C under vacuum. Organic phases were dried using anhydrous magnesium sulfate. All reactions were carried out under an inert nitrogen atmosphere unless otherwise stated. Infra red (IR) spectra were recorded as thin films on sodium chloride plates for oils or as potassium bromide discs for solids on a 1000 FT-IR spectrometer. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a 300 NMR spectrometer. ^{1}H (400 MHz) NMR spectra were recorded on a 400 NMR spectrometer. All spectra were recorded at 300 K in deuterated chloroform ($CDCl_3$), unless otherwise stated, using tetramethylsilane (TMS) as an internal standard. ^{1}H NMR spectra that were recorded in deuterated dimethylsulfoxide (DMSO-d_6) were assigned using the DMSO peak as the reference peak. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to TMS and coupling constants are expressed in Hertz (Hz). Splitting patterns in ^{1}H NMR spectra are designated as s (singlet), bs (broad singlet), d (doublet), bd (broad doublet), t (triplet), bt (broad triplet), q (quartet), qu (quintet), dd (doublet of doublets), dt (doublet of triplets), dq (doublet of quartets), ddd (doublet of doublet of doublets), td (triplet of doublets), ddt (doublet of doublet of triplets) and m (multiplet). ^{13}C NMR spectra were calibrated using the solvent signals, *i.e.* $CDCl_3$: δ_C 77.0 ppm, DMSO-d_6: δ_C 39.5 ppm, and were assigned with the aid of DEPT experiments. Wet flash column chromatography was carried out using silica gel 60, 0.040–0.063 mm. The enantiopurity of the chiral compounds was determined by chiral stationary phase high performance liquid chromatography (HPLC) performed on a Chiralpak® ASH, Chiralpak® OJ-H or Chiralcel® OD-H column. Low temperature chiral stationary phase HPLC analysis was conducted using an Igloo-Cil® column cooler. Optical rotations were measured on a Perkin-Elmer 141 polarimeter at 589 nm in a 10 cm cell; concentrations (*c*) are expressed in g/100 mL. $[\alpha]_D^T$ is the specific rotation of a compound and is expressed in units of 10^{-1} deg cm^2 g^{-1}. The Microanalysis Laboratory, National University of Ireland, Cork, performed elemental analysis using an Exeter Analytical CE440 elemental analyser. Low resolution mass spectra (LRMS) were recorded on a triple quadrupole instrument in electrospray ionisation (ESI) mode using 50% acetonitrile–water containing 0.1% formic acid as eluent; samples were made up in acetonitrile. High resolution precise mass spectra (HRMS) were recorded on a Tof LC–MS instrument in electrospray ionisation (ESI) mode using 50% acetonitrile–water containing 0.1% formic acid as eluent; samples were prepared in acetonitrile.

4.2. (*R*)-2-Amino-2-(4-chlorophenyl)ethanol 9[27,28]

A solution of (*R*)-4-chlorophenylglycine methyl ester hydrochloride (2.00 g, 8.50 mmol) in aqueous ethanol (50%, 50 mL) was added slowly over 5 min to a solution of sodium borohydride (1.54 g, 40.71 mmol) in aqueous ethanol (50%, 50 mL) at 0 °C. The suspension was stirred at room temperature for 4.5 h, then heated at reflux for 3 h and stirred at room temperature overnight. Water was added to dissolve the remaining solids and the reaction mixture transferred to a separating funnel and extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried, filtered and concentrated under reduced pressure to give the amino alcohol **9** (1.20 g, 82%) as a white solid which was used without further purification, mp 75–76 °C; $[\alpha]_D^{18} = -41.2$ (*c* 0.69, $CHCl_3$), {Lit.,[27] $[\alpha]_D^{18}$ (for the (*S*)-enantiomer) = +39.7 (*c* 0.69, $CHCl_3$)}; ν_{max}/cm^{-1} (KBr) 3422–2708 (OH and NH_2), 1621, 1596, 1499, 1412, 1092, 1040; δ_H (300 MHz) 1.61 (3H, br s, NH_2 and OH), 3.52 [1H, dd, A of ABX, J_{AB} 10.8, J_{AX} 8.1, one of C(1)H_2], 3.72 [1H, dd, B of ABX, J_{AB} 10.8, J_{BX} 4.4, one of C(1)H_2], 4.05 [1H, dd, X of ABX, J_{AX} 8.1, J_{BX} 4.5, C(2)H], 7.22–7.38 (4H, m, aromatic H).

4.3. (*R*)-2-Amino-2-(4-fluorophenyl)ethanol 10[29]

(*R*)-4-Fluorophenylglycine methyl ester hydrochloride (2.00 g, 9.10 mmol), sodium borohydride (1.65 g, 43.61 mmol) and aqueous ethanol (50%, 100 mL) were used following the procedure for **9** to give the amino alcohol **10** (1.05 g, 84%) as a white solid, mp 94–96 °C; $[\alpha]_D^{20} = -47.1$ (*c* 0.79, $CHCl_3$), {Lit.,[29] $[\alpha]_D^{20}$ (for the (*S*)-enantiomer) = +47.0 (*c* 0.78, $CHCl_3$)}; ν_{max}/cm^{-1} (KBr) 3332–2343 (OH and NH_2), 1604, 1513, 1225; δ_H (300 MHz) 1.88 (3H, br s, NH_2 and OH), 3.53 [1H, dd, A of ABX, J_{AB} 10.5, J_{AX} 8.1, one of C(1)H_2], 3.72 [1H, dd, B of ABX, J_{AB} 10.8, J_{BX} 4.5, one of C(1)H_2], 4.06 [1H, dd, X of ABX, J_{AX} 8.1, J_{BX} 4.2, C(2)H], 6.99–7.09 (2H, m, aromatic H), 7.25–7.35 (2H, m, aromatic H).

4.4. 2-Amino-3-(4-chlorophenyl)propan-1-ol 11[30–32]

L-4-Chlorophenylalanine (0.50 g, 2.50 mmol) was added slowly, in small portions, to a solution of lithium aluminium hydride (0.50 g, 13.17 mmol) in THF (50 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h then heated at reflux while stirring overnight. The solution was cooled to 0 °C and water (0.5 mL) was carefully added dropwise, followed by aqueous sodium hydroxide (10%, 0.5 mL) and further water addition (1.5 mL). The reaction mixture was stirred at room temperature until a white suspension was observed. The precipitate was filtered, recovered and heated at reflux in THF for 1 h and then re-filtered. The combined THF extracts were concentrated under reduced pressure and the remaining precipitate washed with DCM (50 mL). The combined organic extracts were washed with brine (50 mL), dried, filtered and concentrated under reduced pressure to give amino alcohol (*S*)-**11** (0.10 g, 72%) as a cream solid, (*S*)-**11**: $[\alpha]_D^{20} = -12.4$ (*c* 0.99, CH_2Cl_2). D-4-Chlorophenylalanine (0.76 g, 3.81 mmol), lithium aluminium hydride (0.5 g, 13.17 mmol) and THF (70 mL) were used following the procedure described for (*S*)-**11** to give the amino alcohol (*R*)-**11**

(0.70 g, 99%) as a cream solid, (*R*)-**11**: $[\alpha]_D^{20} = +13.0$ (*c* 0.99, CH_2Cl_2). mp 81–83 °C, ν_{max}/cm^{-1} (KBr) 3353–2343 (OH and NH_2), 1592, 1491, 1354, 1088; δ_H (400 MHz) 1.55 (3H, br s, NH_2 and OH), 2.52 [1H, dd, A of ABX, J_{AB} 13.4, J_{AX} 8.6, one of C(3)H_2], 2.77 [1H, dd, B of ABX, J_{AB} 13.6, J_{BX} 5.6, one of C(3)H_2], 3.05–3.13 [1H, m, C(2)H], 3.36 [1H, dd, A of ABX, J_{AB} 10.7, J_{AX} 7.0, one of C(1)H_2], 3.62 [1H, dd, B of ABX, J_{AB} 10.7, J_{BX} 4.5, one of C(1)H_2], 7.13 (2H, d, *J* 8.4, aromatic H), 7.28 (2H, d, *J* 8.4, aromatic H).

4.5. 2-Amino-3-(4-methoxyphenyl)propan-1-ol 12[20]

L-4-Methoxyphenylalanine (0.15 g, 0.77 mmol), lithium aluminium hydride (0.50 g, 13.17 mmol) and THF (50 mL) were used following the procedure described for **11** to give the amino alcohol (*S*)-**12** (0.10 g, 72%) as a cream solid, (*S*)-**12**: $[\alpha]_D^{20} = -19.0$ (*c* 0.99, CH_2Cl_2), {Lit.[20] $[\alpha]_D^{20} = -15.0$ (*c* 0.99, CH_2Cl_2)}. D-4-Methoxyphenylalanine (1.00 g, 5.12 mmol), lithium aluminium hydride (1.00 g, 26.35 mmol) and THF (100 mL) were used following the procedure described for **11** to give the amino alcohol (*R*)-**12** (0.87 g, 95%) as a cream solid, (*R*)-**12**: $[\alpha]_D^{20} = +17.1$ (*c* 0.99, CH_2Cl_2). Mp 98–100 °C, ν_{max}/cm^{-1} (KBr) 3357–2855 (OH and NH_2), 1612, 1513, 1248, 1036; δ_H (400 MHz) 1.62 (3H, br s, OH and NH_2), 2.48 [1H, dd, A of ABX, J_{AB} 13.2, J_{AX} 8.4, one of C(3)H_2], 2.74 [1H, dd, B of ABX, J_{AB} 13.2, J_{BX} 5.4, one of C(3)H_2], 3.02–3.12 [1H, m, C(2)H], 3.36 [1H, dd, A of ABX, J_{AB} 10.7, J_{AX} 7.0, one of C(1)H_2], 3.63 [1H, dd, B of ABX, J_{AB} 10.7, J_{BX} 4.5, one of C(1)H_2], 3.80 (3H, s, CH_3), 6.85 (2H, d, *J* 9.0, aromatic H), 7.11 (2H, d, *J* 8.4, aromatic H).

4.6. 2-Amino-3-(naphthalene-2-yl)propan-1-ol 13[33]

L-2-Naphthylalanine (0.50 g, 2.32 mmol), lithium aluminium hydride (0.5 g, 13.17 mmol) and THF (50 mL) were used following the procedure described for **11** to give the amino alcohol (*S*)-**13** (0.42 g, 91%) as a cream solid, (*S*)-**13**: $[\alpha]_D^{20} = -15.8$ (*c* 0.99, CH_2Cl_2). D-2-Naphthylalanine (1.00 g, 4.65 mmol), lithium aluminium hydride (1.00 g, 26.35 mmol) and THF (100 mL) were used following the procedure described for **11** to give the amino alcohol (*R*)-**13** (0.92 g, 98%) as a cream solid, (*R*)-**13**: $[\alpha]_D^{20} = +17.6$ (*c* 0.99, CH_2Cl_2). Mp 110–112 °C, ν_{max}/cm^{-1} (KBr) 3353–2362 (OH and NH_2), 1596, 1074; δ_H (400 MHz) 1.55 (3H, br s, NH_2 and OH), 2.70 [1H, dd, A of ABX, J_{AB} 13.6, J_{AX} 8.8, one of C(3)H_2], 2.97 [1H, dd, B of ABX, J_{AB} 13.6, J_{BX} 5.2, one of C(3)H_2], 3.20–3.29 [1H, m, C(2)H], 3.43 [1H, dd, A of ABX, J_{AB} 10.8, J_{AX} 7.2, one of C(1)H_2], 3.68 [1H, dd, B of ABX, J_{AB} 10.8, J_{BX} 4.0, one of C(1)H_2], 7.33 (1H, dd, *J* 1.6/8.4, aromatic H), 7.41–7.49 (2H, m, aromatic H), 7.65 (1H, s, aromatic H), 7.75–7.84 (3H, m, aromatic H).

4.7. (*R*)-4-Hydroxyphenylglycine methyl ester hydrochloride 16[18,19]

Thionyl chloride (1.5 mL, 33.0 mmol) was added dropwise to a suspension of (*R*)-4-hydroxyphenylglycine **15** (5.00 g, 29.91 mmol) in dry methanol (25 mL) while stirring at −15 °C under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred overnight. The yellow solution was then brought to reflux for 30 min. The reaction mixture was concentrated under reduced pressure to give the hydrochloride salt **16** as an off-white solid. The hydrochloride salt **16** was stirred in diethyl ether (15 mL), filtered and washed with diethyl ether (2 × 15 mL) and dried to give the hydrochloride salt **16** (6.50 g, 100%) as a white solid, mp 189–191 °C; $[\alpha]_D^{20} = -120.9$ (*c* 1, 1 M HCl), {Lit.,[34] $[\alpha]_D^{25} = -121.1$ (*c* 1, 1 M HCl)}; ν_{max}/cm^{-1} (KBr) 3339 br, 1740 (CO), 1595; δ_H (300 MHz, DMSO-d_6) 3.68 (3H, s, OCH_3), 5.11 [1H, s, C(2)H], 6.80 (2H, d, *J* 8.5, aromatic H), 7.25 (2H, d, *J* 8.5, aromatic H), 8.70 (3H, br s, NH_3), 9.86 (1H, s, OH).

4.8. (*R*)-*N*-(Benzyloxycarbonyl)-4-hydroxyphenylglycine methyl ester 17[33]

A solution of sodium carbonate (2.39 g, 22.55 mmol) in water (10 mL) was added dropwise over 5 min to a solution of (*R*)-4-hydroxyphenylglycine methyl ester hydrochloride **16** (6.50 g, 29.86 mmol) in water (10 mL) and DCM (60 mL) at −10 °C. A solution of benzyl chloroformate (4.7 mL, 33.0 mmol) (freshly distilled at 50 °C at 0.02 mmHg) in toluene (5 mL) was subsequently added at −10 °C over 20 min. The reaction mixture was slowly brought to room temperature and left stirring overnight. Water (20 mL) was then added and the layers separated. The aqueous layer was extracted with DCM (25 mL). The combined extracts were washed with water (20 mL), dried, filtered and concentrated under reduced pressure to give the crude ester **17** as a white solid (9.02 g). Purification by recrystallisation from a mixture of DCM and hexane gave the pure ester **17** (6.42 g, 68%) as a fluffy white solid, mp 117–118 °C; ν_{max}/cm^{-1} (KBr) 3388, 3336, 3068–2450, 1735 (CO), 1666, 1617, 1519; δ_H (300 MHz) 3.72 (3H, s, OCH_3), 4.97 (1H, s, OH), 5.07 (1H, A of ABq, *J* 12.2, one of OCH_2), 5.12 (1H, B of ABq, *J* 12.2, one of OCH_2), 5.29 [1H, bd, *J* 6.5, C(2)H], 5.79 (1H, d, *J* 7.0, NH), 6.76–6.82 (2H, m, aromatic H), 7.23 (2H, d, *J* 8.5, aromatic H), 7.30–7.40 (5H, m, aromatic H).

4.9. (*R*)-*N*-(Benzyloxycarbonyl)-4-methoxyphenylglycine methyl ester 18[21]

(*R*)-*N*-(Benzyloxycarbonyl)-4-hydroxyphenylglycine methyl ester **17** (2.27 g, 8.07 mmol) in diethyl ether (40 mL) and dry methanol (20 mL) was added dropwise over 45 min to an ether solution of diazomethane, while stirring at −20 °C under nitrogen. The yellow solution was then slowly brought to room temperature and stirred for 18 h. The diethyl ether, methanol and residual diazomethane were evaporated under reduced pressure using a rotary evaporator with an acetic acid trap to give the crude ester **18** (2.49 g) as a viscous, pale yellow oil. Purification by flash chromatography, using ethyl acetate in hexane (30: 70) as eluent, gave the pure ester **18** (2.04 g, 77%) as a white solid, mp 68–70 °C, $[\alpha]_D^{28} = -121.9$ (*c* 0.58, $CHCl_3$), {Lit.[35] $[\alpha]_D^{28} = -106.9$ (*c* 0.58, $CHCl_3$)}; (Found: C, 65.84; H, 5.82; N, 4.08. $C_{18}H_{19}NO_5$ requires C, 65.64; H, 5.81; N, 4.25%); ν_{max}/cm^{-1} (KBr) 3382, 3354, 3033–2840, 1738, 1704, 1611, 1586, 1514; δ_H (300 MHz) 3.72, 3.79 (2 × 3H, 2× s, $COOCH_3$, OCH_3), 5.06 (1H, A of ABq, *J* 12.1, one of OCH_2), 5.12 (1H, B of ABq, *J* 12.2, one of OCH_2), 5.31 [1H, d, *J* 7.1, C(2)H], 5.78 (1H, bd, *J* 7.0, NH), 6.88 (2H, bd, *J* 8.7, aromatic H), 7.23–7.39 (7H, m, aromatic H); δ_C(75.5 MHz) 52.8, 55.3 (2× CH_3, $COOCH_3$, OCH_3), 57.3 [CH, C(2)H], 67.1 (CH_2, OCH_2), 114.3 (CH, aromatic CH), 128.2 (CH, aromatic CH), 128.4 (CH, aromatic CH), 128.5 (CH, aromatic CH), 136.1 (C, aromatic C), 155.3 (C, *C*OOBn), 159.8 (C, *C*OCH_3), 171.5 (C, *C*$OOCH_3$); *m*/*z* (ES+) 352 [$(M+Na)^+$, 31%], 179 [$(M-NHCO_2CH_2Ph)^+$, 6%], 91 [$(PhCH_2)^+$, 7%].

4.10. (*R*)-*N*-(Benzyloxycarbonyl)-4-methoxyphenylglycinol 19

(*R*)-*N*-(Benzyloxycarbonyl)-4-methoxyphenylglycine methyl ester **18** (2.04 g, 6.19 mmol) in THF (19 mL) was added to a mixture of sodium borohydride (0.59 g, 15.49 mmol) and lithium chloride (0.66 g, 15.49 mmol) in ethanol (12 mL) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. The reaction was subsequently filtered and water (30 mL) was added to the filtrate. The reaction solution was evaporated until just the water remained. Ethyl acetate (30 mL) was added followed by saturated aqueous ammonium chloride solution (30 mL) at 0 °C. The layers were separated and the aqueous was washed with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water (50 mL), brine (50 mL) dried and concentrated under

reduced pressure to give the crude alcohol **19** as an off-white solid, mp 114–116 °C; (Found: C, 67.31; H, 6.29; N, 4.40. $C_{17}H_{19}NO_4$ requires C, 67.76; H, 6.36; N, 4.65); ν_{max}/cm^{-1} (KBr) 3305 br, 3030–2837, 1684, 1611, 1554, 1513; δ_H (300 MHz) 3.77–3.87 [5H, m containing s at 3.79 due to OCH_3, C(1)H_2], 4.74–4.85 [1H, bm, C(2)H], 5.07 (1H, A of ABq, *J* 12.2, one of OCH_2), 5.12 (1H, B of ABq, *J* 12.2, one of OCH_2), 5.47 (1H, bd, *J* 6.6, NH), 6.83–6.89 (2H, m, aromatic H), 7.21 (2H, bd, *J* 8.7, aromatic H), 7.34 (5H, br s, aromatic H); δ_C(75.5 MHz) 55.3 (CH_3, OCH_3), 56.6 br [CH, C(2)H], 66.5 br [CH_2, C(1)H_2], 67.0 (CH_2, OCH_2), 114.2 (CH, aromatic CH), 127.7 (CH, aromatic CH), 128.2 (CH, aromatic CH), 128.5 (CH, aromatic CH), 136.2 (C, aromatic C), 156.4 (C, *C*OOBn), 159.2 (C, aromatic C); HRMS (ES+): Exact mass calculated for $C_{17}H_{20}NO_4$ [(M+H)$^+$], 302.1392. Found 302.1391. *m*/*z* (ES+) 324 [(M+Na)$^+$, 100%], 91 [($PhCH_2$)$^+$, 31%].

4.11. (*R*)-2-Amino-2-(4-methoxyphenyl)ethanol 14[27]

A mixture of (*R*)-*N*-(benzyloxycarbonyl)-4-methoxyphenylglycinol **19** (0.32 g, 1.06 mmol) and palladium on carbon (10%, 0.18 g) in methanol (15 mL) was shaken under hydrogen at 30 psi for 12 h at room temperature. The crude reaction mixture was filtered through a short column of silica gel using ethyl acetate as eluent to remove the hydrogenation catalyst. Concentration of the solution gave the crude alcohol **14** (0.11 g, 61%) as an off-white solid, mp 96–98 °C; $[\alpha]_D^{18} = -38.5$ (*c* 0.46, $CHCl_3$), {Lit.,[27] $[\alpha]_D^{18}$ (for the (*S*)-enantiomer) = +38.3 (*c* 0.43, $CHCl_3$)}; ν_{max}/cm^{-1} (KBr) 3348 br, 3287, 2894–2837, 1615, 1518; δ_H (300 MHz) 2.05 (3H, br s, NH_2, OH), 3.53 [1H, dd, A of ABX, J_{AB} 10.7, J_{AX} 8.4, one of C(1)H_2], 3.70 [1H, dd, B of ABX, J_{AB} 10.6, J_{BX} 4.4, one of C(1)H_2], 3.80 (3H, s, OCH_3), 3.95–4.07 [1H, bm, X of ABX, C(2)H], 6.86–6.92 (2H, m, aromatic H), 7.22–7.28 (2H, m, aromatic H).

4.12. *N*,*N*′-bis[(*R*)-2-Hydroxy-1-(4-chlorophenyl)ethyl]-2,2-dimethylmalonamide 20

Dimethylmalonyl chloride (0.50 g, 2.92 mmol), in DCM (3 mL) was added dropwise to a heterogeneous solution of (*R*)-2-amino-2-(4-chlorophenyl)ethanol **9** (1.00 g, 5.83 mmol) and triethylamine (2.0 mL, 14.6 mmol) in DCM (6 mL) at 0 °C. The homogeneous reaction mixture was removed from the bath and stirred for 40 min. Aqueous hydrochloric acid (10%, 10 mL) was added to the reaction mixture and the biphasic mixture was stirred for 15 min. The layers were separated and the aqueous layer was washed with DCM (2 × 10 mL). The combined organic layer was washed with saturated aqueous sodium bicarbonate (15 mL). The aqueous layer was back extracted with DCM (2 × 10 mL). The combined organic extracts were dried, filtered and concentrated under reduced pressure to give the bisamide **20** as a pale yellow solid. Purification by recrystallisation from a mixture of DCM and hexane gave the pure bisamide **20** (0.96 g, 73%) as a white solid, mp 186–189 °C, (Found: C, 56.93; H, 5.42; Cl, 16.30; N, 6.37. $C_{21}H_{24}Cl_2N_2O_4$ requires C, 57.14; H, 5.51; Cl, 16.14; N, 6.38%); ν_{max}/cm^{-1} (KBr) 3650–3061 (OH and NH), 1656 (C=O), 1508, 1077; δ_H (300 MHz, CD_3OD-d_4) 1.48 [6H, s, C(CH_3)$_2$], 3.64–3.82 [4H, m, 2× C(2)H_2], 4.91 (4H, br s, 2× OH and 2× NH), 5.00 [2H, dd, *J* 7.5/5.4, 2× C(1)H], 7.20–7.33 (8H, m, aromatic H); δ_C(75.5 MHz, CD_3OD-d_4) 24.9 [CH_3, C(CH_3)$_2$], 52.3 [C, *C*(CH_3)$_2$], 57.4 [CH, 2× C(1)H], 66.4 [CH_2, 2× C(2)H_2], 130.3 (CH, 4× aromatic CH), 134.9 (C, 2× aromatic C), 140.6 (C, 2× aromatic C), 176.5 (C, 2× CO); HRMS (ES+): Exact mass calculated for $C_{21}H_{25}Cl_2N_2O_4$ [(M+H)$^+$], 439.1191. Found 439.1187. *m*/*z* (ES+) 439 [(M+H)$^+$, 100%].

4.13. *N*,*N*′-bis[(*R*)-2-Hydroxy-1-(4-fluorophenyl)ethyl]-2,2-dimethylmalonamide 21

(*R*)-2-Amino-2-(4-fluorophenyl)ethanol **10** (1.50 g, 9.67 mmol), dimethylmalonyl chloride (0.82 g, 4.83 mmol), triethylamine (3.4 mL, 24.2 mmol) and DCM (14 mL) were used following the procedure described for **21** to give the bisamide **21** as a white solid, mp 156–158 °C, (Found: C, 61.90; H, 5.94; F, 9.27; N, 6.68. $C_{21}H_{24}F_2N_2O_4$ requires C, 62.06; H, 5.95; F, 9.35; N, 6.89); ν_{max}/cm^{-1} (KBr) 3630–3080 (OH and NH), 1651 (C=O), 1511; δ_H (300 MHz, CD_3OD- d_4) 1.47 [6H, s, C(CH_3)$_2$], 3.68–3.82 [4H, m, 2× C(2)H_2], 4.90 (4H, br s, 2× OH and 2× NH), 5.02 [2H, dd, *J* 7.5/5.1, 2× C(1)H], 6.96–7.05 (4H, m, aromatic H), 7.25–7.32 (4H, m, aromatic H); δ_C(75.5 MHz, CD_3OD) 24.3 [CH_3, C(CH_3)$_2$], 51.6 [C, *C*(CH_3)$_2$], 56.7 [CH, 2× C(1)H], 65.9 [CH_2, 2× C(2)H_2], 116.2 (CH, d, $^2J_{CF}$ 21, 2× aromatic CH), 129.8 (CH, d, $^3J_{CF}$ 8, 2× aromatic CH), 137.1 (C, d, $^4J_{CF}$ 3, 2× aromatic C), 163.6 (C, $^1J_{CF}$ 244, 2× aromatic C), 175.8 (C, 2× CO); HRMS (ES+): Exact mass calculated for $C_{21}H_{25}F_2N_2O_4$ [(M+H)$^+$], 407.1782. Found 407.1775. *m*/*z* (ES+) 407 [(M+H)$^+$, 100%].

4.14. *N*,*N*′-Bis[(*R*)-2-hydroxy-1-(4-methoxyphenyl)ethyl]-2,2-dimethylmalonamide 22

(*R*)-2-Amino-2-(4-methoxyphenyl) ethanol **14** (0.65 g, 3.86 mmol), dimethylmalonyl chloride (0.33 g, 1.93 mmol), triethylamine (1.4 mL, 9.7 mmol) and DCM (10 mL) were used following the procedure described for **20** to give the bisamide **22** as a pale yellow solid. Purification by recrystallisation from a mixture of DCM and hexane gave the pure bisamide **22** (681 mg, 82%) as a white solid, mp 95–97 °C; [Found: (with carbon catalyst) C, 63.75; H, 7.07; N, 6.43. $C_{23}H_{30}N_2O_6$ requires C, 64.17; H, 7.02; N, 6.51%]; ν_{max}/cm^{-1} (KBr) 3423 br, 3315 br, 1645 (CO), 1515; δ_H (300 MHz) 1.49 [6H, s, C(CH_3)$_2$], 1.78 (2H, br s, 2× OH), 3.74 [2H, dd, A of ABX, J_{AB} 11.5, J_{AX} 7.3, 2× one of C(2)H_2], 3.78 (6H, s, 2× OCH_3), 3.88 [2H, dd, B of ABX, J_{AB} 11.5, J_{BX} 4.0, 2× one of C(2)H_2], 5.07 [2H, t of d, X of ABX, J_{AX} 7.5, J_{BX} 4.0, 2× C(1)H], 6.81–6.87 (4H, m, aromatic H), 7.06 (2H, br d, *J* 7.7, 2× NH), 7.13–7.20 (4H, m, aromatic H); δ_C(75.5 MHz) 23.6 [CH_3, C(CH_3)$_2$], 49.9 [C, *C*(CH_3)$_2$], 55.2 [CH, 2× C(1)H], 55.3 (CH_3, 2× OCH_3), 66.2 [CH_2, 2× C(2)H_2], 114.2 (CH, 2× aromatic CH), 127.9 (CH, 2× aromatic CH), 130.4 (C, 2× aromatic C), 159.1 (C, 2× aromatic C), 174.0 (C, 2× CO); *m*/*z* (ES−) 430 (M$^-$, 100%), 430 [(M−H)$^-$, 100%].

4.15. 2,2-Bis{2-[4(*R*)-(4-chlorophenyl)-1,3-oxazolinyl]}propane 3[17,23]

Triethylamine (0.6 mL, 0.4 mmol) was added dropwise to a solution of *N*,*N*′-bis[(*R*)-2-hydroxy-1-(4-chlorophenyl)ethyl]-2,2-dimethylmalonamide **20** (0.44 g, 1.00 mmol) and 4-(dimethylamino) pyridine (12.2 mg, 0.10 mmol) in DCM (10 mL) over 2 min. The flask was placed in a room temperature water bath after which a solution of *p*-toluenesulfonyl chloride (0.38 g, 1.99 mmol) in DCM (10 mL) was added dropwise over 5 min. The yellow solution was then stirred at room temperature for 27 h. Saturated aqueous ammonium chloride (10 mL) was then added to the solution and the biphasic mixture was stirred for a further 15 min. The layers were separated and the aqueous layer was washed with DCM (3 × 15 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (15 mL). Once again the aqueous layer was washed with DCM (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried, filtered and concentrated under reduced pressure to give the crude bis(oxazoline) **3** as a light yellow oily solid. Purification by column chromatography, employing 75% diethyl ether in hexane as eluent, gave the pure bis(oxazoline) **3** as a white solid (0.27 g, 67%), mp

89–92 °C, $[\alpha]_D^{20} = +133.0$ (*c* 0.37, CH_2Cl_2), {Lit.,[17] $[\alpha]_D^{20}$ (for the (*S*)-enantiomer) = −141.0 (*c* 7.4, CH_2Cl_2)}; ν_{max}/cm^{-1} (KBr) 3061–2895, 1655, 1492; δ_H (300 MHz) 1.66 [6H, s, C(CH_3)$_2$], 4.11 (2H, dd, A of ABX, J_{AB} 8.4, J_{AX} 7.7, 2× one of OCH_2), 4.66 (2H, dd, B of ABX, J_{BX} 10.2, J_{AB} 8.4, 2× one of OCH_2), 5.21 (2H, dd, X of ABX, J_{BX} 10.1, J_{AX} 7.6, 2× C=NCH), 7.17–7.22 (4H, m, aromatic H), 7.27–7.32 (4H, m, aromatic H).

4.16. 2,2-Bis{2-[4(*R*)-(4-fluorophenyl)-1,3-oxazolinyl]}propane 4

N,*N*′-Bis[(*R*)-2-hydroxy-1-(4-fluorophenyl)ethyl]-2,2-dimethylmalonamide **21** (0.85 g, 2.09 mmol), triethylamine (1.3 mL, 9.3 mmol), 4-(dimethylamino) pyridine (25.6 mg, 0.21 mmol), *p*-toluenesulfonyl chloride (0.80 g, 4.20 mmol) and DCM (50 mL) were used following the procedure described for **3** to give the crude bis(oxazoline) **4** as a cream solid. Purification by column chromatography, employing 75% diethyl ether in hexane as eluent, gave the pure bis(oxazoline) **4** (0.63 g, 75%) as a white solid, mp 81–84 °C, $[\alpha]_D^{20} = +125.7$ (*c* 0.30, $CHCl_3$); (Found: C, 67.91; H, 5.75; F, 10.58; N, 7.38. $C_{21}H_{20}F_2N_2O_2$ requires C, 68.10; H, 5.44; F, 10.26; N, 7.56); ν_{max}/cm^{-1} (KBr) 3066–2908, 1656 s, 1605; δ_H (300 MHz) 1.67 [6H, s, C(CH_3)$_2$], 4.12 (2H, dd, A of ABX, J_{AB} 8.4, J_{AX} 7.6, 2× one of OCH_2), 4.67 (2H, dd, B of ABX, J_{BX} 10.1, J_{AB} 8.4, 2× one of OCH_2), 5.22 (2H, dd, X of ABX, J_{BX} 10.1, J_{AX} 7.6, 2× C=NCH), 6.95–7.05 (4H, m, aromatic H), 7.19–7.29 (4H, m, aromatic H); δ_C(75.5 MHz) 24.4 [CH_3, C(CH_3)$_2$], 38.9 [C, *C*(CH_3)$_2$], 68.8 (CH, 2× C=*N*CH), 75.5 (CH_2, 2× OCH_2), 115.5 (CH, d, $^2J_{CF}$ 21, 4× aromatic CH), 128.3 (CH, d, $^3J_{CF}$ 8, 4× aromatic CH), 138.1 (C, d, $^4J_{CF}$ 3, 2× aromatic C), 162.2 (C, $^1J_{CF}$ 246, 2× aromatic C), 170.4 (C, 2× *C*=N); HRMS (ES+): Exact mass calculated for $C_{21}H_{21}F_2N_2O_2$ [(M+H)$^+$], 371.1571. Found 371.1574. *m*/*z* (ES+) 372 [(M+2H)$^+$, 32%], 371 [(M+H)$^+$, 100%].

4.17. 2,2-Bis{2-[4(*R*)-(4-methoxyphenyl)-1,3-oxazol inyl]}propane 5[17]

N,*N*′-Bis[(*R*)-2-hydroxy-1-(4-methoxyphenyl)ethyl]-2,2-dimethylmalonamide **22** (0.83 g, 1.93 mmol), triethylamine (1.2 mL, 8.5 mmol), 4-(dimethylamino)pyridine (23.6 mg, 0.19 mmol) and DCM (12 mL) were used following the procedure described for **3** to give the crude bis(oxazoline) **5** (0.84 g) as an orange/brown oil. Purification by flash chromatography, using diethyl ether as eluent, gave the bis(oxazoline) **5** (0.34 g, 45%) as a viscous, clear oil, which solidified after standing at −20 °C for 12 h, mp 68–69 °C; $[\alpha]_D^{25} = +183.2$ (*c* 0.50, $CHCl_3$), {Lit.,[17] $[\alpha]_D^{20}$ (for the (*S*)-enantiomer) = −170 (*c* 0.32, $CHCl_3$)}; ν_{max}/cm^{-1} (KBr) 2906, 1655, 1610, 1582, 1513; δ_H (300 MHz) 1.66 [6H, s, C(CH_3)$_2$], 3.79 (6H, s, 2× OCH_3), 4.14 (2H, dd, A of ABX, J_{AB} 8.3, J_{AX} 7.5, 2× one of OCH_2), 4.64 (2H, dd, B of ABX, J_{BX} 10.0, J_{AB} 8.3, 2× one of OCH_2), 5.18 [2H, dd, X of ABX, J_{BX} 10.0, J_{AX} 7.5, 2× C=NCH), 6.82–6.88 (4H, m, aromatic H), 7.15–7.21 (4H, m, aromatic H).

4.18. 2,2′-(Propane-2,2-diyl)bis[4-(4-chlorobenzyl)-4,5-dihydrooxazole] 6

A mixture of 2,2-dimethylmalononitrile (0.11 g, 1.17 mmol) and zinc triflate (0.42 g, 1.16 mmol) in toluene (50 mL) was stirred for 5 min at room temperature. (*S*)-2-Amino-3-(4-chlorophenyl)propan-1-ol **11** (0.44 g, 2.37 mmol) was then added in small portions to the stirring solution. The reaction mixture was heated at reflux for 48 h, then the resulting brown solution was washed with brine (3 × 20 mL) and aqueous sodium bicarbonate (3 × 20 mL), dried, filtered and concentrated under reduced pressure to give the bis(oxazoline) **6** as a white solid, mp 75–80 °C. (*S*)-**6**: 70% yield, 96% ee, $[\alpha]_D^{20} = -46.0$ (*c* 0.30, $CHCl_3$). (*R*)-**6**: 55% yield [from (*R*)-**11**], 100% ee, $[\alpha]_D^{20} = +53.5$ (*c* 0.30, $CHCl_3$). ν_{max}/cm^{-1} (KBr) 1655, 1492; δ_H (400 MHz) 1.44 [6H, s, C(CH_3)$_2$], 2.69 (2H, dd, A of ABX, J_{AB} 13.8, J_{AX} 7.4, 2× one of CH_2Ph), 2.96 (2H, dd, B of ABX, J_{AB} 13.8, J_{BX} 5.0, 2× one of CH_2Ph), 3.94 (2H, dd, A of ABX, J_{AB} 8.4, J_{AX} 6.8, 2× one of OCH_2), 4.18 (2H, dd appears as t, *J* 8.6, 2× one of OCH_2), 4.32–4.42 (2H, m, 2× C=NC*H*), 7.12 (4H, d, *J* 8.0, aromatic *H*), 7.25 (4H, d, *J* 8.0, aromatic *H*); δ_C(75.5 MHz) 24.2 [CH_3, C(CH_3)$_2$], 38.5 [C, *C*(CH_3)$_2$], 40.5 (CH_2, 2× CH_2Ph), 66.7 (CH, 2× *C*HN), 71.8 (CH_2, 2× OCH_2), 128.5 (CH, 4× aromatic CH), 130.9 (CH, 4× aromatic CH), 132.3 (C, 2× aromatic C), 136.0 (C, 2× aromatic C), 169.5 (C, 2× NCO); *m*/*z* (ES+) 431.1 [(M+H)$^+$, 100%]; HRMS (ES+): exact mass calculated for $C_{23}H_{24}Cl_2N_2O_2$ (M+H)$^+$ 431.1297. Found 431.1299 (M+H)$^+$.

4.19. 2,2′-(Propane-2,2-diyl)bis[4-(4-methoxybenzyl)-4,5-dihydrooxazole] 7

(*R*)-2-Amino-3-(4-methoxyphenyl)propan-1-ol **12** (0.87 g, 4.80 mmol), 2,2-dimethylmalononitrile (0.23 g, 2.44 mmol), zinc triflate (0.87 g, 2.39 mmol) and toluene (80 mL) were used following the procedure described for **6** to give the bis(oxazoline) **7** as a light yellow oil. (*S*)-**7**: 60% yield, 99% ee, $[\alpha]_D^{20} = -33.5$ (*c* 0.30, $CHCl_3$). (*R*)-**7**: 74% yield [from (*R*)-**12**], 100% ee, $[\alpha]_D^{20}$ = +25.7 (*c* 0.30, $CHCl_3$). ν_{max}/cm^{-1} (film) 1656, 1613, 1513, 1248; δ_H (400 MHz) 1.46 [6H, s, C(CH_3)$_2$], 2.60 (2H, dd, A of ABX, J_{AB} 14.0, J_{AX} 8.4, 2× one of CH_2Ph), 3.01 (2H, dd, B of ABX, J_{AB} 13.6, J_{BX} 4.8, 2× one of CH_2Ph), 3.78 (6H, s, 2× OCH_3), 3.98 (2H, dd, A of ABX, J_{AB} 8.4, J_{AX} 6.8, 2× one of OCH_2), 4.16 (2H, dd appears as t, *J* ~8.4, 2× one of OCH_2), 4.31–4.40 (2H, m, 2× C=NC*H*), 6.82 (4H, d, *J* 8.4, aromatic *H*), 7.11 (4H, d, *J* 8.8, aromatic *H*); δ_C(75.5 MHz) 24.2 [CH_3, C(CH_3)$_2$], 38.5 [C, *C*(CH_3)$_2$], 40.4 (CH_2, 2× CH_2Ph), 55.3 (CH_3, 2× OCH_3), 67.1 (CH, 2× *C*HN), 72.0 (CH_2, 2× OCH_2), 113.9 (CH, 4× aromatic CH), 129.7 (C, 2× aromatic C), 130.4 (CH, 4× aromatic CH), 158.3 (C, 2× aromatic C), 169.4 (C, 2× NCO); *m*/*z* (ES+) 423.2 [(M+H)$^+$, 100%]; HRMS (ES+): exact mass calculated for $C_{25}H_{30}N_2O_4$ (M+H)$^+$ 423.2286. Found 423.2284 (M+H)$^+$.

4.20. 2,2′-(Propane-2,2-diyl)bis[4-(naphthalen-2-ylmethyl)-4,5-dihydrooxazole] 8

2-Amino-3-(naphthalene-2-yl)propan-1-ol **13** (0.42 g, 2.09 mmol), 2,2-dimethylmalononitrile (0.10 g, 1.06 mmol), zinc triflate (0.38 g, 1.05 mmol) and toluene (40 mL) were used following the procedure described for **6** to give the bis(oxazoline) **8** as a light yellow solid, mp 128–131 °C. (*S*)-**8**: 41% yield, 100% ee, $[\alpha]_D^{20} = -34.7$ (*c* 0.30, $CHCl_3$). (*R*)-**8**: 61% yield [from (*R*)-**13**], 100% ee, $[\alpha]_D^{20}$ = +33.7 (*c* 0.30, $CHCl_3$). ν_{max}/cm^{-1} (KBr) 3416, 2979, 1654, 1460; δ_H (400 MHz) 1.46 [6H, s, C(CH_3)$_2$], 2.82 (2H, dd, A of ABX, J_{AB} 13.6, J_{AX} 8.4, 2× one of CH_2Ph), 3.22 (2H, dd, B of ABX, J_{AB} 14.0, J_{BX} 4.8, 2× one of CH_2Ph), 3.99 (2H, dd, A of ABX, J_{AB} 8.6, J_{AX} 6.8, 2× one of OCH_2), 4.13 (2H, dd, B of ABX, J_{AB} 8.4, J_{BX} 9.2, 2× one of OCH_2), 4.44–4.54 (2H, m, 2× C=NC*H*), 7.32 (2H, dd, *J* 8.4/1.6, aromatic H), 7.39–7.46 (4H, m, aromatic H) 7.61 (2H, s, aromatic H), 7.74–7.82 (6H, m, aromatic H); δ_C(75.5 MHz) 24.2 [CH_3, C(CH_3)$_2$], 38.6 [C, *C*(CH_3)$_2$], 41.4 (CH_2, 2× CH_2Ph), 66.9 (CH, 2× CHN), 72.0 (CH_2, 2× OCH_2), 125.5 (CH, 2× aromatic CH), 126.0 (CH, 2× aromatic CH), 127.5 (CH, 2× aromatic CH), 127.6 (CH, 2× aromatic CH), 127.9 (CH, 2× aromatic CH), 127.9 (CH, 2× aromatic CH), 128.0 (CH, 2× aromatic CH), 132.2 (C, 2× aromatic C), 133.5 (C, 2× aromatic C), 135.2 (C, 2× aromatic C), 169.5 (C, 2× NCO); *m*/*z* (ES+) 463.3 [(M+H)$^+$, 100%]; HRMS (ES+): exact mass calculated for $C_{31}H_{30}N_2O_2$ (M+H)$^+$ 463.2386. Found 463.2390 (M+H)$^+$.

4.21. General procedure for the C–H insertion reactions of α-diazo-β-keto sulfones 23–28

The $CuCl_2$-L*-NaBARF catalyst was generated *in situ* from a mixture of $CuCl_2$ (5 mol %), bis(oxazoline) ligand (6 mol %) and NaBARF (6 mol %) in DCM (15 mL). This catalytic mixture was stirred under nitrogen at 40 °C for 1.5 h. Next, α-diazo-β-keto sulfone **23–28** (150 mg, 1 equiv) was added dropwise in DCM (15 mL) over 0.5 h to the refluxing solution. The progress of the reaction was monitored by IR spectroscopy, where reaction completion was indicated by the disappearance of the characteristic diazo peak at 2110–2126 cm^{-1}. Upon reaction completion, evaporation of the reaction solvent at reduced pressure gave the crude product. Purification by flash chromatography on silica gel, employing ethyl acetate in hexane as eluent, gave the pure cyclopentanone products **29–34**.

4.21.1. *trans*-2-Phenylsulfonyl-3-methylcyclopentanone 29[25]

White solid, mp 123–125 °C; ν_{max}(KBr)/cm^{-1} 1744 (C=O), 1305, 1141 (SO_2); δ_H (400 MHz) 1.29 (3H, d, *J* 6.8, CH_3), 1.45–1.59 [1H, m, one of C(4)H_2], 2.25–2.40 [3H, m, C(5)H_2, one of C(4)H_2], 2.95–3.04 [1H, m, C(3)*H*CH_3] 3.34 [1H, d, *J* 8.0, C(2)*H*SO_2], 7.56–7.60 (2H, m, aromatic H), 7.66–7.71 (1H, m, aromatic H), 7.87–7.90 (2H, m, aromatic H).

4.21.2. *trans*-2-Phenylsulfonyl-3-ethylcyclopentanone 30[25]

White solid, mp 79–81 °C; ν_{max}(KBr)/cm^{-1} 1743 (C=O), 1308, 1147 (SO_2); δ_H (300 MHz) 0.98 (3H, t, *J* 7.5, CH_3), 1.39–1.60 [2H, m, one of C*H*$_2$$CH_3$, one of C(4)$H_2$], 1.74–1.88 (1H, m, one of C*H*$_2$$CH_3$), 2.28–2.50 [3H, m, C(5)H_2, one of C(4)H_2], 2.82–2.94 [1H, m, C(3)H], 3.39 [1H, d, *J* 6.9, C(2)*H*SO_2], 7.54–7.61 (2H, m, aromatic H), 7.65–7.72 (1H, m, aromatic H), 7.85–8.00 (2H, m, aromatic H).

4.21.3. *trans*-2-Phenylsulfonyl-3-*iso*-propylcyclopentanone 31

White solid, (Found C, 63.06; H, 6.79. $C_{14}H_{18}O_3S$ requires C, 63.13; H, 6.81%); mp 96–98 °C; ν_{max}(KBr)/cm^{-1} 1746 (C=O), 1302, 1140 (SO_2), δ_H (400 MHz) 0.91 [3H, d, *J* 6.8, one of CH(C*H*$_3$)$_2$], 0.97 [3H, d, *J* 6.8, one of CH(C*H*$_3$)$_2$], 1.65–1.76 [1H, m, one of C(4)H_2], 1.85–1.97 [1H, sym m, *J* 6.7, C*H*(CH$_3$)$_2$], 2.19–2.36 [2H, m, one of C(4)H_2, one of C(5)H_2], 2.44–2.54 [1H, m, one of C(5)H_2], 2.86–2.94 [1H, sym m, *J* 6.7, C(3)*Hi*-Pr], 3.51 [1H, d, *J* 5.2, C(2)*H*SO_2], 7.56–7.62 (2H, m, aromatic H), 7.66–7.72 (1H, m, aromatic H), 7.84–7.88 (2H, m, aromatic H); δ_C(75.5 MHz) 18.1 [CH_3, one of CH(*C*H$_3$)$_2$], 20.5 [CH_3, one of CH(*C*H$_3$)$_2$], 22.1 [CH_2, C(4)H_2], 31.0 [CH, *C*H(CH$_3$)$_2$], 38.4 [CH_2, C(5)H_2], 43.2 (CH, *C*H*i*-Pr), 73.0 (CH, *C*HSO_2Ph), 129.1 (CH, 4× aromatic CH), 134.1 (CH, aromatic CH), 134.0 (C, aromatic C), 207.6 (C, CO); *m*/*z* (ES+) 267.0 [(M+H)$^+$, 100%], 284.1 [(M+H_2O)$^+$, 72%], 552.4 (89%).

4.21.4. *trans*-2-Phenylsulfonyl-3-tert-butylcyclopentanone 32

White solid, (Found C, 64.21; H, 7.27. $C_{15}H_{20}O_3S$ requires C, 64.26; H, 7.19%); mp 93–96 °C; ν_{max}(KBr)/cm^{-1} 1743 (C=O), 1306, 1142 (SO_2); δ_H (300 MHz) 0.89 [9H, s, 3× C(C*H*$_3$)], 1.87–1.99 [1H, m, one of C(4)H_2], 2.20–2.36 [2H, m, one of C(4)H_2, one of C(5)*H*$_2$], 2.55–2.71 [1H, m, one of C(5)H_2], 2.86–2.94 [1H, m, C(3)H], 3.55 [1H, bd, *J* 3.6, C(2)H], 7.55–7.63 (2H, m, aromatic H), 7.66–7.30 (1H, m, aromatic H), 7.82–7.88 (2H, m, aromatic H); δ_C(75.5 MHz) 21.5 [CH_2, C(4)H_2], 27.1 (CH_3, 3× CH_3), 33.6 [C, C(CH$_3$)$_3$], 37.9 [CH_2, C(5)H_2], 46.3 [CH, C(3)H], 73.0 [CH, C(2)H], 129.0 (CH, aromatic CH), 129.18 (CH, aromatic CH), 129.39 (CH, aromatic CH), 134.20 (CH, aromatic CH), 137.7 (C, aromatic C), 208.6 (C, CO); *m*/*z* (ES+) 281.2 [(M+H)$^+$, 43%].

4.21.5. *trans*-2-Phenylsulfonyl-3-phenylcyclopentanone 33[25]

White solid, mp 96–99 °C; ν_{max}(KBr)/cm^{-1} 1743 (C=O), 1306, 1150 (SO_2); δ_H (400 MHz) 1.92–2.07 [1H, m, one of C(4)H_2], 2.49–2.70 [3H, m, C(5)H_2, one of C(4)H_2], 3.91 [1H, d, *J* 7.5, C(2)*H*SO_2], 4.05–4.14 [1H, m, C(3)*H*Ph], 7.12–7.16 (2H, m, aromatic H), 7.20–7.32 (3H, m, aromatic H), 7.47–7.53 (2H, m, aromatic H), 7.59–7.65 (1H, m, aromatic H), 7.77–7.83 (2H, m, aromatic H).

4.21.6. *trans*-2-Phenylsulfonyl-3-benzylcyclopentanone 34[25]

White solid, mp 83–85 °C; ν_{max}(KBr)/cm^{-1} 1750 (C=O), 1307, 1142 (SO_2); δ_H (400 MHz) 1.57–1.68 [1H, m, one of C(4)H_2], 2.10–2.27 [1H, m, one of C(4)H_2], 2.28–2.42 [2H, m, C(5)H_2], 2.78 [1H, dd, H_A of ABC, *J* 13.6, 8.8, one of C*H*$_2$Ph], 3.06 [1H, dd, H_B of ABC, *J* 13.2, 5.2, one of C*H*$_2$Ph], 3.14–3.24 [1H, m, H_C of ABC, C(3)*H*Bn], 3.49 [1H, d, *J* 7.2, C(2)*H*SO_2], 7.14–7.20 (2H, m, aromatic H), 7.22–7.34 (3H, m, aromatic H), 7.54–7.61 (2H, m, aromatic H), 7.65–7.71 (1H, m, aromatic H), 7.82–7.88 (2H, m, aromatic H).

4.22. General procedure for the aromatic addition reactions of α-diazo ketone 35–39 and 45

Diazo ketone **35–39** and **45** (100 mg, 1 equiv) in DCM (75 mL) was added dropwise over 1 h to a refluxing solution of [Cu(MeCN)$_4$]PF_6 (6 mol %) and bis(oxazoline) ligand (6 mol %) in DCM (75 mL). The progress of the reaction was monitored by TLC and was found generally to be complete upon diazo ketone addition. Evaporation of the solvent at reduced pressure gave the crude product. A ^{1}H NMR spectrum of the crude material was recorded in order to determine the efficiency of the cyclisation. Purification by flash chromatography on silica gel employing ethyl acetate in hexane as eluent, gave the pure azulenones **40–44**, **46**.

4.22.1. 3,8a-Dihydro-3,3,8a-trimethylazulen-1(2*H*)-one 40[7]

Pale yellow oil; ν_{max}/cm^{-1} (film) 1748 (CO), 1716 (CO); δ_H (300 MHz) 0.75 [3H, s, C(8a)CH_3], 1.14, 1.31 [2 × 3H, 2× s, C(3)(C*H*$_3$)$_2$], 2.20 [1H, A of ABq, J_{AB} 17.3, one of C(2)H_2], 2.28 [1H, B of ABq, J_{AB} 17.3, one of C(2)H_2], 4.15 [1H, d, *J* 7.9, C(8)H], 6.10 [1H, overlapping dd appears as t, *J* 7.6, 7.6, C(7)H], 6.21–6.44 [3H, m, C(4)H, C(5)H, C(6)H].

4.22.2. 3,8a-Dihydro-3,3,6,8a-tetramethylazulen-1(2*H*)-one 41

Clear oil; ν_{max}/cm^{-1} (film) 1749 (CO), 1716 (CO); δ_H (300 MHz) 0.68 [3H, s, C(8a)CH_3], 1.08, 1.26 [2 × 3H, 2× s, C(3)(C*H*$_3$)$_2$], 1.95 [3H, apparent d, *J* 0.8, C(6)CH_3], 2.08 [1H, A of ABq, J_{AB} 17.3, one of C(2)H_2], 2.16 [1H, B of ABq, J_{AB} 17.3, one of C(2)H_2], 3.49 [1H, d, *J* 6.8, C(8)H], 5.82 [1H, dq, *J* 7.0, 1.1, C(7)H], 6.15–6.20 [2H, m, C(4)H, C(5)H]; δ_C(75.5 MHz) 8.8 [CH_3, C(8a)*C*H_3], 22.2 [CH_3, C(6)*C*H_3], 27.1 [CH_3, one of C(3)(*C*H$_3$)$_2$], 27.8 [CH_3, one of C(3)(*C*H$_3$)$_2$], 35.1, 38.0 [2× C, C(3), C(8a)], 48.9 [CH_2, C(2)H_2], 66.9 br [CH, C(8)H], 84.7 [C, C(3a)], 120.9, 122.6, 127.8 [C(4)H, C(5)H, C(6)H, C(7)H], 134.5 [C, C(6)], 218.0 (C, CO); HRMS (ES+): Exact mass calculated for $C_{14}H_{19}O$ [(M+H)$^+$], 203.1436. Found 203.1434. *m*/*z* (ES+) 203 [(M+H)$^+$, 100%].

4.22.3. 3,8a-Dihydro-6-chloro-3,3,8a-trimethylazulen-1(2*H*)-one 42

Pale yellow oil; ν_{max}/cm^{-1} (film) 1750 (CO), 1720 (CO); δ_H (300 MHz) 0.86 [3H, s, C(8a)CH_3], 1.14, 1.33 [2 × 3H, 2× s, C(3)(C*H*$_3$)$_2$], 2.21 [1H, A of ABq, J_{AB} 17.3, one of C(2)H_2], 2.39 [1H, B of ABq, J_{AB} 17.3, one of C(2)H_2], 4.54 [1H, d, *J* 8.9, C(8)H], 6.14 [1H, dd, *J* 9.0, 1.4, C(7)H], 6.23 [1H, d, *J* 7.9, C(4)H], 6.52 [1H, dd, *J* 8.0, 1.6, C(5)H]; δ_C(75.5 MHz) 13.7 [CH_3, C(8a)*C*H_3], 28.9 [CH_3, one of C(3)(*C*H$_3$)$_2$], 29.7 [CH_3, one of C(3)(*C*H$_3$)$_2$], 38.7, 44.9 [2× C, C(3), C(8a)], 50.7 [CH_2, C(2)H_2], 101.4 [CH, C(8)H], 118.9 (CH), 123.3 [C, C(3a)], 125.6, 127.4 (2 x CH), 131.8 [C, C(6)], 217.0 (C, CO); HRMS (ES+): Exact mass calculated for $C_{13}H_{16}OCl$ [(M+H)$^+$], 222.0811. Found 222.0809.

4.22.4. 3,8a-Dihydro-6-fluoro-3,3,8a-trimethylazulen-1(2*H*)-one 43

Pale yellow oil; ν_{max}/cm^{-1} (film) 1752 (CO), 1720 (CO); δ_H (300 MHz) 0.91 [3H, s, C(8a)CH_3], 1.15, 1.37 [2 × 3H, 2× s, C(3)$(CH_3)_2$], 2.24 [1H, A of ABq, J_{AB} 17.1, one of C(2)H_2], 2.51 [1H, B of ABq, J_{AB} 17.1, one of C(2)H_2], 5.12 [1H, dd, J_{HH} 10.0, J_{HF} 5.1, C(8)H], 6.00–6.11 [1H, m, C(7)H], 6.14–6.24 [2H, m, C(4)H, C(5)H]; δ_C(75.5 MHz) 15.5 [CH_3, C(8a)CH_3], 29.3 [CH_3, one of C(3)$(CH_3)_2$], 30.9 [CH_3, one of C(3)$(CH_3)_2$], 38.9, 48.7 [2× C, C(3), C(8a)], 51.2 [CH_2, C(2)H_2], 111.0 [CH, d, $^2J_{CF}$ 28, C(5)H or C(7)H], 115.5–116.0 [CH, m, C(8)H], 116.1 [CH, $^3J_{CF}$ 11, C(4)H], 117.6 [CH, d, $^2J_{CF}$ 34, C(5)H or C(7)H], 135.3 [C, C(3a)], 159.7 [C, d, $^1J_{CF}$ 242, C(6)], 217.7 (C, CO); HRMS (ES+): Exact mass calculated for $C_{13}H_{16}FO$ [$(M+H)^+$], 207.1185. Found 207.1182. *m*/*z* (ES+) 207 [$(M+H)^+$, 100%].

4.22.5. 3,8a-Dihydro-3,3,5,6,7,8a-hexamethylazulen-1(2*H*)one 44

Cream solid, mp 65–67 °C; ν_{max}/cm^{-1} (KBr) 1709 (CO); δ_H (300 MHz) 0.55 [3H, s, C(8a)CH_3], 1.02, 1.19 [2 × 3H, 2× s, C(3)$(CH_3)_2$], 1.85 [1H, A of ABq, J_{AB} 17.3, one of C(2)H_2], 1.86 (3H, s, CH_3), 1.89 (3H, s, CH_3), 1.96 (3H, apparent d, *J* 1.1, CH_3), 2.08 [1H, B of ABq, J_{AB} 17.3, one of C(2)H_2], 2.47 [1H, s, C(8)H], 5.80 [1H, br s, C(4)H]; δ_C (75.5 MHz) 4.9 [CH_3, C(8a)CH_3], 14.6, 20.4, 21.3 [3× CH_3, C(5)CH_3, C(6)CH_3, C(7)CH_3], 24.9, 26.6 [2× CH_3, C(3)$(CH_3)_2$], 28.1 (C), 37.7 (C), 43.7 [CH, C(8)H], 47.5 [CH_2, C(2)H_2], 54.7 (C), 116.4 [CH, C(4)H], 127.8, 129.0, 135.8 [3× C, C(5), C(6), C(7)], 217.8 (C, CO); HRMS (ES+): Exact mass calculated for $C_{16}H_{23}O$ [$(M+H)^+$], 231.1749. Found 231.1745. *m*/*z* (ES+) 231 [$(M+H)^+$, 100%].

4.22.6. *trans*-(3*S**,8a*R**)-3,8a-Dihydro-3,8a-dimethyl-3-phenylazulen-1(2*H*)-one and *cis*-(3*R**,8a*R**)-3,8a-dihydro-3,8a-dimethyl-3-phenyl-azulen-1(2*H*)-one 46

Cream solid, mp 65–67 °C (dr 93:7); (Found: C, 86.01; H, 7.31. $C_{18}H_{18}O$ requires C, 86.36; H, 7.25%); ν_{max}/cm^{-1} (KBr) 1742 (CO), 1713 (CO). **46a** (major diastereomer): δ_H (300 MHz) 0.79 [3H, s, C(8a)CH_3], 1.64 [3H, s, C(3)CH_3], 2.53 [1H, A of ABq, J_{AB} 17.3, C(2)H_2], 2.59 [1H, B of ABq, J_{AB} 17.7, C(2)H_2], 3.45 [1H, d, *J* 6.8, C(8)H], 6.08–6.19, 6.23–6.45 [2 × 2H, 2× m, C(4)H, C(5)H, C(6)H, C(7)H], 7.08–7.40 (5H, m, aromatic H); δ_C(75.5 MHz) 8.4 [CH_3, C(8a)CH_3], 29.0 [CH_3, C(3)CH_3], 50.3 [CH_2, C(2)H_2], 64.3–64.9 br [CH, C(8)H], 123.2 (CH), 124.9 (CH), 125.4 (CH), 126.4 (CH), 126.5 {CH), 128.4 (CH), 147.0 (C, aromatic C), 217.0 [C, C(1)], signals for C(3a) and C(8a) were not observed. **46b** (minor diastereomer): δ_H (300 MHz) 0.82 [3H, s, C(8a)CH_3], 1.62 [3H, s, C(3)CH_3], 2.46 [1H, A of ABq, J_{AB} 17.5, C(2)H_2], 2.83 [1H, B of ABq, J_{AB} 17.7, C(2)H_2], 4.21 [1H, d, *J* 7.9, C(8)H], 5.87 [1H, d, *J* 6.9, C(4)H]. Signals for C(4)H, C(5)H, C(6)H, C(7)H and aromatic H, are masked by signals for the major diastereomer **46a**; δ_C(75.5 MHz) (partial assignment) 11.2 [CH_3, C(8a)CH_3], 32.6 [CH_3, C(3)CH_3], 51.5 [CH_2, C(2)H_2], 122.1 (CH), 125.0 (CH), 126.6 (CH), 126.8 (CH), 127.2 (CH), 128.6 (CH).

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