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Copper mediated, heterogeneous, enantioselective intramolecular Buchner reactions of α -diazoketones using continuous flow processing

Daniel C. Crowley[†], Denis Lynch[†] and Anita R. Maguire^{‡*}

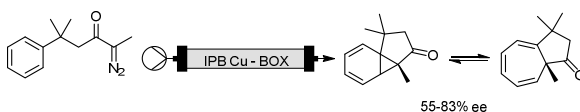
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Abstract

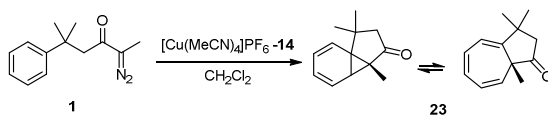
Enantioselective intramolecular Buchner reactions of α -diazoketones can be effected using heterogeneous copper–bis(oxazoline) catalysts in batch or using continuous flow processing in up to 83% ee. The catalyst can be reused up to 7 times without loss of activity. For α -diazoketones **3** and **4**, the enantioselection achieved in flow with the immobilized catalyst was comparable with the standard homogeneous catalyzed process.



Introduction

The intramolecular addition of carbenes to aromatic rings, yielding expanded fused ring systems, has been investigated over many years.¹⁻⁶ The intramolecular Buchner reaction is typically catalyzed by a transition metal to generate an electrophilic carbenoid, which adds to the adjacent aryl ring forming a norcaradiene (NCD) product, which exists in tautomeric equilibrium with a cycloheptatriene (CHT) through reversible electrocyclic ring opening/closing, as evidenced by time averaged signals in ¹H NMR (Scheme 1).^{7,8}

Scheme 1. Intramolecular enantioselective aromatic addition.



Diastereocontrol and enantiocontrol in homogeneous transition metal mediated intramolecular aromatic additions are well documented.⁹⁻¹¹ In particular,

copper–bis(oxazoline) complexes are potent asymmetric catalysts, affording excellent enantioselectivities.^{12,13} Heterogeneous catalysis of the reaction is highly desirable to aid product purification and to enable potential re-use of the catalyst.

In recent years, there has been much interest in designing heterogeneous catalyst systems with bis(oxazoline) ligands that are easily recoverable and reusable.^{14–18} Polymerization of a suitably functionalised bis(oxazoline) ligand, with cross-linkers (co-polymerization) or by itself (homopolymerization), to form insoluble polymer bound (IPB) catalysts is one such method of covalent immobilization.^{19–21} These heterogeneous catalyst systems have been applied to a variety of transformations utilizing carbenoid chemistry, principally for cyclopropanation, but not for the Buchner reaction to date.²²

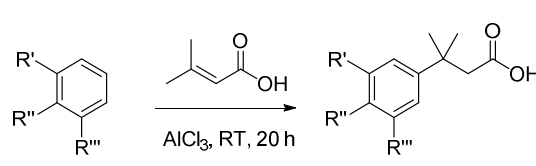
The work herein, focuses on covalently immobilized bis(oxazoline) ligands complexed to copper. During the course of this study, the immobilized copper–bis(oxazoline) was used to perform heterogeneously catalyzed enantioselective, intramolecular Buchner reactions both in batch and on continuous flow processing platforms. Flow chemistry is attractive due to its inherent safety features, such as ease of handling labile and hazardous compounds,^{23–26} including the α -diazoketones used in this study. It has recently been applied to performing homogeneous rhodium catalyzed intermolecular Buchner ring expansions.²⁷ A further feature of continuous flow processing, of which this work aims to take advantage, is the ability to employ packed bed reactors for solid phase catalysts.^{28,29}

Results and discussion

Four α -diazoketones (**1–4**) previously synthesized within our group were selected for investigation of intramolecular Buchner reactions on flow. These α -diazoketones differ with respect to the steric and electronic properties of the substituents on the aromatic ring.³⁰ Substrates **1–3** have previously afforded relatively stable azulenones **23–25**, amenable to isolation and determination of enantiopurity,¹³ while substrate **4** has afforded the highest reported enantioselectivity to date for this process (95% ee).³⁰ Consequently, these α -diazoketones were expected to provide an accurate assessment of homogeneous vs. heterogeneous catalysis and batch conditions vs. continuous flow processing as part of this work. Use of electron donating methoxy substituents was avoided in this study, as the azulenones formed are complicated by further dynamic processes,³¹ while substrates bearing an α -hydrogen are known to generate trienone or tetralone products subsequent to carbenoid insertion and are also vulnerable to epimerisation,² and so were not explored during this work. The synthetic

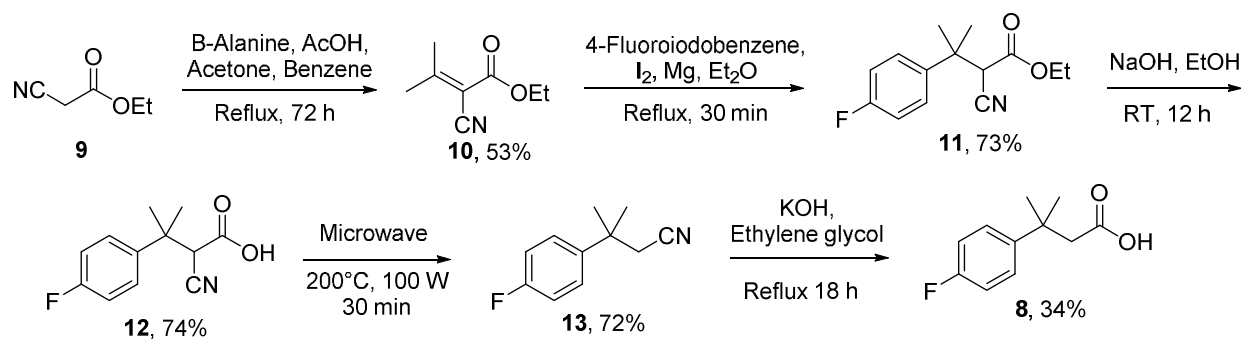
route to α -diazoketones **1**, **2** and **4** began with preparation of their analogous carboxylic acids **5-7** via Friedel–Crafts alkylation (Table 1).

Table 1. Synthesis of carboxylic acids (**5-7**)

	Entry	Acid	R'	R''	R'''	Yield (%)
	1	5	H	H	H	89
	2	6	H	Cl	H	94
	3	7	Me	Me	Me	92

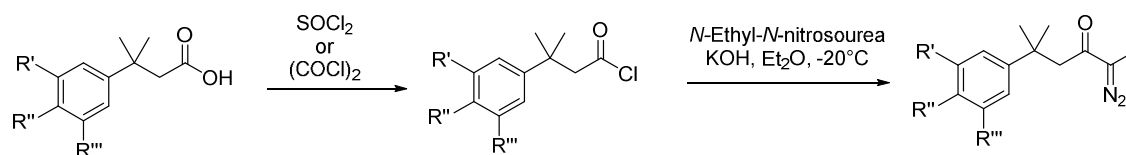
As this method did not provide exclusively the *para*-fluoro acid **8**, it was synthesized instead as shown in Scheme 2.³² Ethyl cyanoacetate (**9**) and acetone were first condensed to form ethyl 2-cyano-3-methylbut-2-enoate (**10**). This product was then reacted with freshly prepared 4-fluoromagnesium bromide to form cyanoester **11** which was hydrolyzed to the corresponding cyanocarboxylic acid **12** and, in turn decarboxylated to 3-methyl-3-(4-fluorophenyl)butanenitrile (**13**). Finally, this nitrile was hydrolyzed to afford acid **8**. While the synthesis requires five steps, synthetically useful amounts of acid **8** can be readily accessed by this sequence.

Scheme 2. Synthesis of carboxylic acid **8**.



Carboxylic acids **5-8** were then transformed to the corresponding acyl chlorides with thionyl chloride (**5**, **6**) or with oxalyl chloride (**7**, **8**). These acyl halides were treated with freshly prepared diazoethane to afford α -diazoketones **1-4** (Table 2).

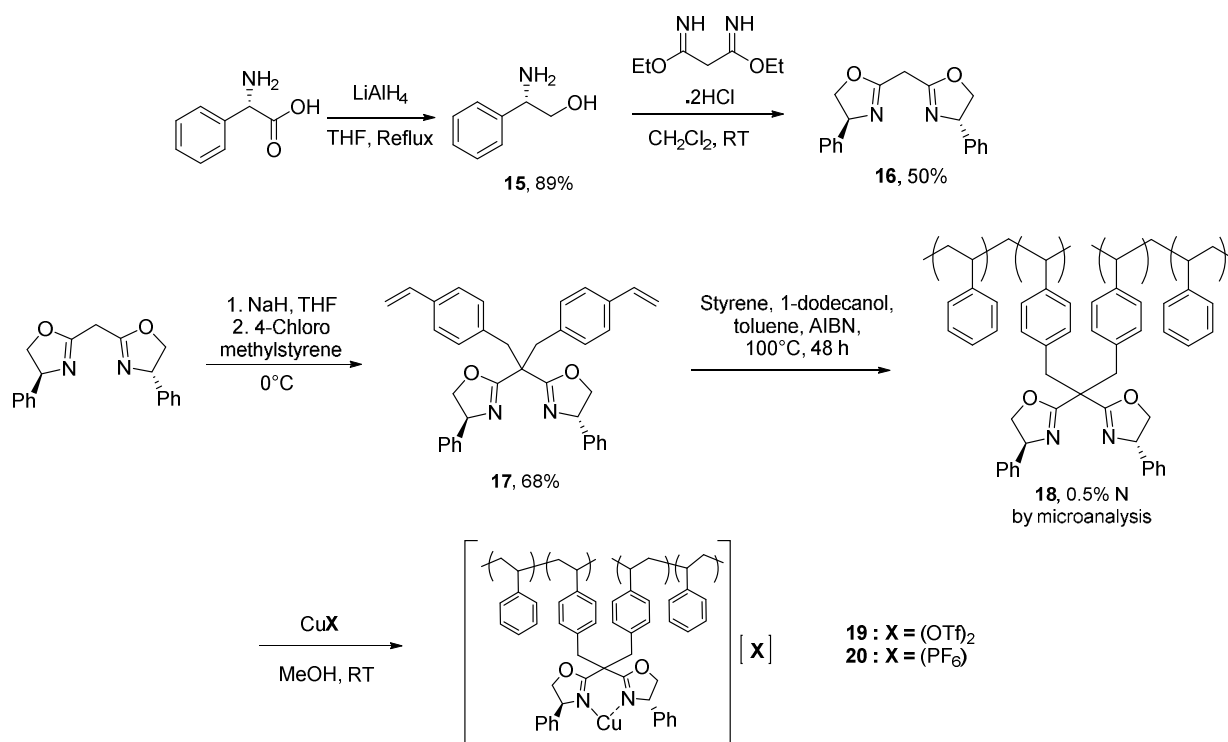
Table 2. Synthesis of α -diazoketones (**1-4**)



Entry	Diazo	R'	R''	R'''	Yield (%)
1	1	H	H	H	83
2	2	H	Cl	H	60
3	3	H	F	H	38 ^a
4	4	Me	Me	Me	67 ^a

^a Isolated yield calculated over two steps from carboxylic acid.

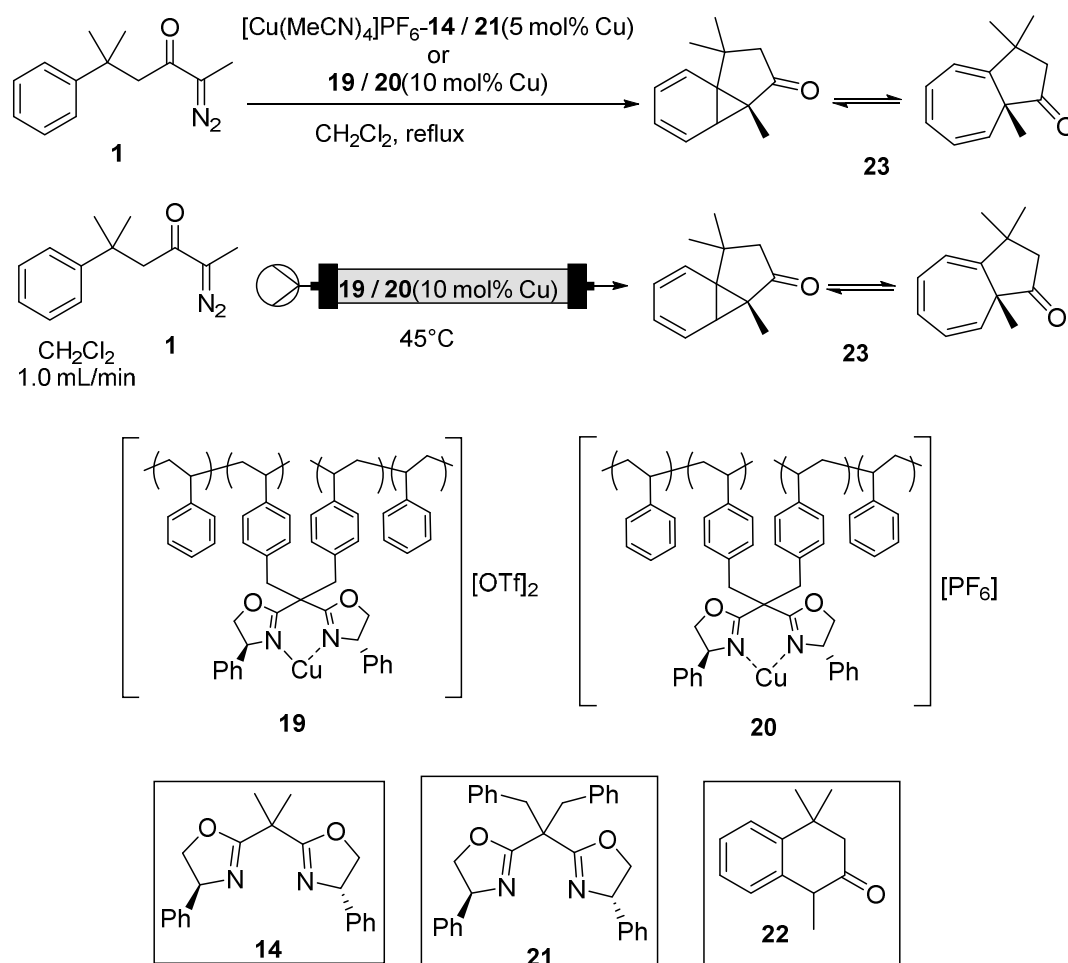
The homogeneous copper catalyst derived from 4-phenyl bis(oxazoline) ligand **14** (Table 3) has afforded the best enantioselectivities for intramolecular aromatic addition, in comparison to other commercially available bis(oxazoline) ligands, and accordingly was selected for immobilization. The suitably functionalized monomer **17** was synthesized using previously reported methods.³³⁻³⁶ Following this, Burguete's methodology for polymerisation and copper triflate complexation was employed to afford IPB catalyst **19** (Scheme 3).³⁷ The same method was extended to form IPB catalyst **20** (Scheme 3) by using [Cu(MeCN)₄]PF₆ in place of Cu(OTf)₂. Thus **19** (TfO⁻) and **20** (PF₆⁻) differ in the counter-ion present – the immobilized ligand is identical in each case. Atomic absorption spectroscopy (AAS) indicated that the copper content of **20** is 0.24 mmol/g of catalyst; based on the elemental analysis result for nitrogen content and assuming all coordination sites of the bis(oxazoline) moieties are available, the copper content was projected to be 0.16 mmol/g of catalyst. Burguete *et al* reported their synthesis of IPB catalyst **19** with a copper content of 0.39 mmol/g.³⁷

Scheme 3. Synthesis of catalysts **19** and **20**

For the purposes of this work, α -diazoketone **1** was selected as a test substrate for intramolecular aromatic additions catalyzed heterogeneously with **20** in a batch process (Table 3). The reaction was monitored by infrared spectroscopy; complete disappearance of the diazo band (2066 cm^{-1}) was typically seen immediately after addition of the α -diazoketone was complete. Interestingly, IR monitoring indicates that the heterogeneously catalyzed reaction proceeds within the same time frame as the homogeneously catalyzed reaction with no noticeable impact on the rate of the reaction. Notably, the recovered catalyst changed from its distinctive green colour to dull brown when recovered at the end of the reaction. However, stirring in tetrahydrofuran returned the catalyst to its initial appearance. The recovered catalyst, once dry, could then be re-used (Table 3, entry 3). The heterogeneously catalyzed reaction, when conducted in a flask with the immobilized catalyst, afforded **23** with similar efficiencies and yields (Table 3, entries 2 and 3) to that previously reported with the related homogeneous catalyst (Table 3, entry 1). Differences in yield between run 1 and run 2 are associated with losses during chromatography. Examination of the ^1H NMR spectra of the crude products showed that azulenone **23**, isolated as a rapidly equilibrating mixture of tautomeric norcaradiene and cycloheptatriene structures, is the predominant product.³⁸ This equilibration does not impact on the enantioselectivity of the carbenoid

insertion process as the absolute stereochemistry at C-8a is fixed during the carbenoid addition and is retained during the subsequent rapid equilibration between the norcaradiene and cycloheptatriene structures. The efficiency of the aromatic addition is only marginally reduced relative to the homogeneously catalyzed reaction, as evidenced by the ratio of azulene signals to aromatic by-product signals.³⁹

Table 3 Results for the intramolecular aromatic addition of 1 to form azulene 23 under batch and flow conditions.



Entry	Catalyst	Method	Run ^a	Flow rate (mL/min)	Efficiency (%) ^b	Yield (%) ^c	% ee ^d
1	[Cu(MeCN) ₄]PF ₆ - 14	Batch	-	-	85 ¹³	74 ¹³	78 ¹³
2	20	Batch	1	-	80	53	62
3	20	Batch	2	-	82	65	64
4	20	Flow	3	0.175	78	62	61
5	20	Flow	4	0.200	73	50	64
6	20	Flow	5	0.250	75	55	62
7	20	Flow	6	0.300	78	60	61
8	20	Flow	7	0.300	78	65	60
9	20	Flow	8	0.300	76	41	55
10	20	Flow	1	1.000	75	68	65
11	20	Batch ^e	1	-		55	40
12	20	Flow ^e	1	0.060	55	33	32
13	[Cu(MeCN) ₄]PF ₆ - 21	Batch	-	-	-	75	76
14	19	Batch	1	-	-	-	-
15	19	Batch	2	-	66	55	65
16	19	Batch	3	-	75	74	66

^a Run refers to use in a single reaction in batch or on flow. ^b Determined by integration of the aromatic by-product signals against those of the azulene in the ¹H NMR spectrum of the crude product. ^c Purified by column chromatography. ^d Determined from chiral shift ¹H NMR experiments using (+)-Eu(hfc)₃. ^e BME used as solvent.

Notably, use of heterogeneous IPB catalyst **20** afforded **23** with an enantioselectivity of 62% ee, reduced from 78% ee with the homogeneous catalyst (Table 3, entries 1 and 2). Significantly however, when reused under the same conditions, catalyst **20** produced a similar enantioselectivity (Table 3, entry 3) to its first use. The decreased enantioselection on immobilization can be rationalized by the altered environment of the bis(oxazoline) ligand in

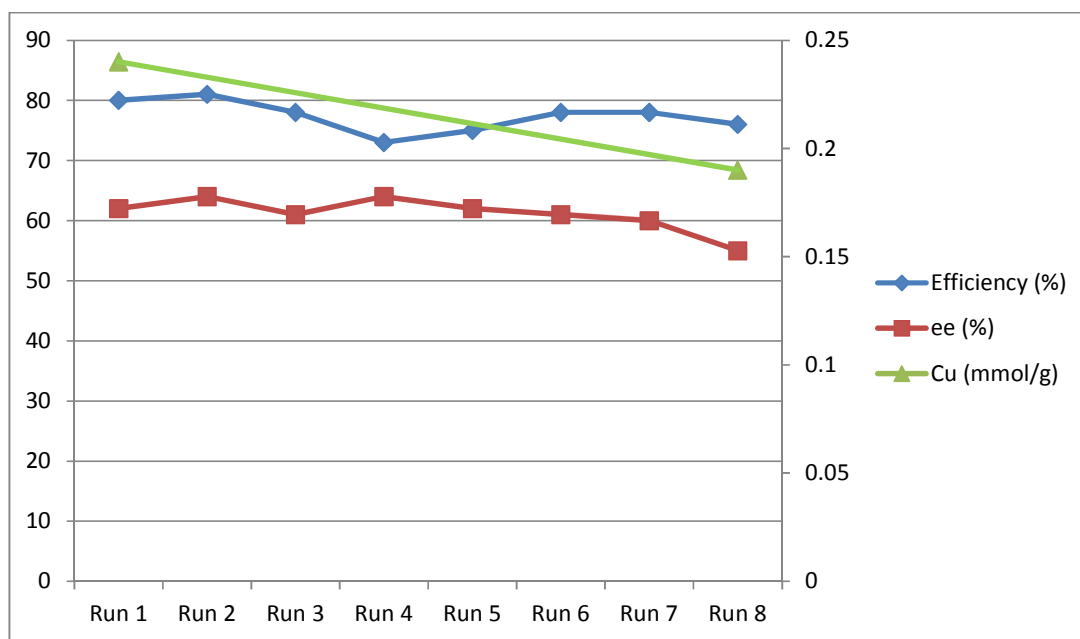
the polymer matrix. To explore this further, a bis(oxazoline) ligand **21** with benzyl groups on the methylene bridge, structurally similar to **20**, was prepared. $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ and ligand **21** were used to homogeneously catalyze the transformation of **1** to azulenone **23**. A small reduction in enantioselectivity (Table 1, entry 13) was noted, albeit to a lesser extent than with the heterogeneous catalyst, indicating that incorporation of the bis(oxazoline) in the polymer has a detrimental effect on enantioselectivity.

Interestingly, the aromatic addition of **1** using catalyst **19** with the triflate counterion did not yield azulenone **23** (Table 3, entry 14). Unexpectedly, the corresponding tetralone **22** was isolated, presumably via acid mediated rearrangement of the initially formed azulenone **23**,² due to the presence of either $\text{Cu}(\text{OTf})_2$ or triflic acid. It was interesting to note, however, that when catalyst **19** was recovered and reused under the same conditions, azulenone **23** was isolated with a yield of 55% and with 65% ee while **22** was not formed (Table 3, entry 15). When the catalyst was recovered and used for a third time, azulenone **23** was isolated with a yield of 74% and with 66% ee again without formation of tetralone **22** (Table 3, entry 16). An unused portion of catalyst **19** was heated to reflux in tetrahydrofuran for 12 hours. When it was collected by filtration and dried, this material was used to catalyze the formation of azulenone **23** affording it in a yield of 69% and with 64% ee on its first use, with no evidence for transformation of **23** to tetralone **22** observed. Heating of catalyst **19** in tetrahydrofuran appears sufficient to remove any uncoordinated copper(II) triflate or trace quantities of triflic acid, generating a catalyst which behaves identically to **20** in terms of efficiency and enantioselectivity produced.

After the initial promising results from the heterogeneous batch reaction, the process was implemented on a continuous flow platform. A range of experiments were performed investigating the optimum flow rate and solvent. The use of *tertiary* butyl methyl ether (*t*BME) was investigated as an alternative solvent as dichloromethane caused the polymeric catalyst to swell leading to high system pressures. While *t*BME ameliorated the problem of the IPB catalyst (**19**, **20**) swelling, it did not prove to be an efficient solvent with regards to yield and enantioselectivity in either batch or flow (Table 3, entries 11 and 12) and so dichloromethane remained the preferred reaction solvent. In our experience, hexane and acetonitrile are not effective solvents for the Buchner reaction, while use of solvents such as THF, toluene or xylene was not feasible due to potential competing reactions with the carbenoid. Ultimately, the increased pressures caused by swelling of the polymer with dichloromethane were overcome by inclusion of glass wool with the polymer in the column,

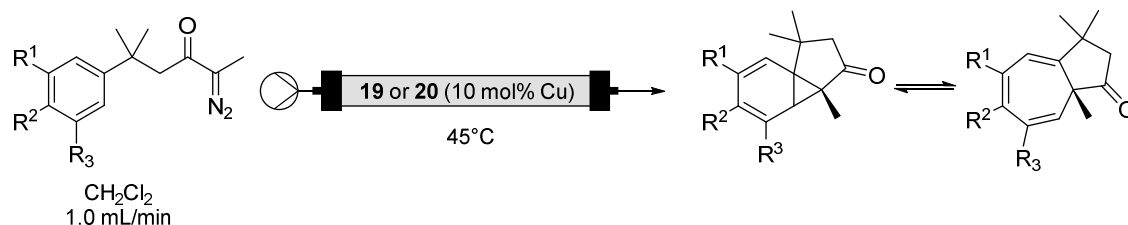
thereby accommodating expansion without increased pressure. Flow rate did not appear to impact efficiency, yield or enantioselectivity, with comparable results achieved at a flow rate as high as 1 mL/min (Table 3, entries 4–10). For an optimised reaction, a CH₂Cl₂ solution (0.0338 M) of α -diazoketone **1** was pumped through a packed bed reactor loaded with catalyst **19** (10 mol % copper relative to the portion of diazoketone employed in each run) at 45°C (Table 3, entry 10). After the experiment, tetrahydrofuran was pumped through the column (at 1 mL/min for 15 min at room temperature) in order to recover the catalyst which was used in subsequent reactions. The yields and enantioselectivities afforded by the transformation on flow (Table 3, entry 4) are comparable to the results from the heterogeneously catalysed batch reaction. One portion of catalyst **20** was utilised and recovered in eight separate reaction runs. It was used twice in batch and six times on flow. The catalyst exhibited excellent reusability up to its seventh use, between batch and flow processes (Table 3, entries 2–8). However, the performance of the catalyst subsequently dropped, with a lower yield and enantioselectivity recorded for azulene **23** on run 8 (Table 3, entry 9). Freshly prepared catalyst **20** has a copper content of 0.24 mmol/g of catalyst, as determined by atomic absorption spectroscopy. The catalyst that was recovered after run 8, however, had a reduced copper content of 0.19 mmol/g of catalyst, consistent with slow leaching of the copper over time. The performance of catalyst **20** in comparison with its copper content is illustrated in Figure 1.

Figure 1 Comparison of efficiencies and enantioselectivities of heterogeneous aromatic addition with copper content of catalyst **20**



Following these results, the substrate scope was expanded to α -diazoketones **2**, **3** and **4** (Table 4). Unlike **23**, azulenes **24** and **25** were afforded with comparable enantioselectivity to the analogous homogeneously catalyzed batch reaction, albeit with reduced efficiency (Table 4, entries 4 and 5). Performing this reaction on flow, with the heterogeneous catalyst did not have a deleterious effect on enantioselectivity. Notably, azulenes **24**, **25** and **26** were afforded with the same enantioselectivity from reactions catalyzed by homogeneous $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ -**14** catalyst or heterogeneous catalyst **20** in either batch or flow (Table 4, entries 4–10). As the trimethyl substituted azulene **26** is highly labile, the transformation was carried out at room temperature and the product was not isolated. Instead, it was immediately trapped with a dienophile, 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD), to give a stable cycloadduct **27** whose enantioselectivity was determined by chiral HPLC (Scheme 4). As with the unsubstituted azulene **23**, there was a decrease in enantioselectivity observed for the reaction to form **26** (from 95% ee to 83–85% ee) when catalyzed heterogeneously in either batch or flow (Table 4, entries 3, 6 and 10). It is interesting to note that the efficiency of formation of the labile azulene **26** using the heterogeneous catalyst **20** is notably higher when conducted in flow than in batch (63 vs 25%, Table 4, entries 6 and 10); this is rationalised by decreased degradation of the labile azulene due to removal from the copper catalyst as it is formed.

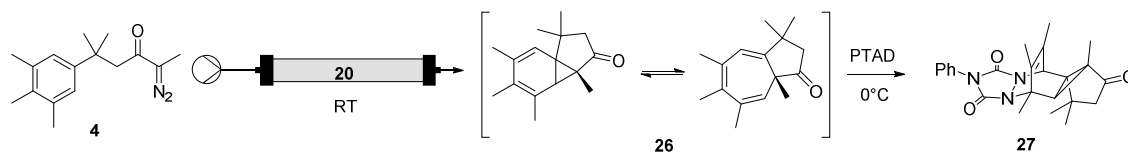
Table 4. Comparison of heterogeneously catalyzed aromatic additions on flow and batch with homogeneously catalyzed aromatic additions in batch.



Entry	Method	Diazo ketone	R ¹	R ²	R ³	Azulenone	Catalyst	Yield (%) ^a	Efficiency (%) ^b	% ee
1	Batch	2	H	Cl	H	24	[Cu(MeCN) ₄]PF ₆ -14	63 ¹³	95 ¹³	62 ¹³
2	Batch	3	H	F	H	25	[Cu(MeCN) ₄]PF ₆ -14	74 ¹³	81 ¹³	56 ¹³
3	Batch ^c	4	Me	Me	Me	26	[Cu(MeCN) ₄]PF ₆ -14	-	-	95 ^{12,30}
4	Batch	2	H	Cl	H	24	20	65	-	65 ^d
5	Batch	3	H	F	H	25	20	55	-	52 ^d
6	Batch ^c	4	Me	Me	Me	26	20	-	25	85 ^e
7	Flow	2	H	Cl	H	24	20	65	70	64 ^d
8	Flow	3	H	F	H	25	19	52	65	57 ^d
9	Flow	3	H	F	H	25	20	49	56	56 ^d
10	Flow ^c	4	Me	Me	Me	26	20	-	63	83 ^e

^a Purified by column chromatography. ^b Determined by integration of the aromatic by-product signals against those of the azulene in the ¹H NMR spectrum of the crude product. ^c Reaction carried out at room temperature. ^d Determined from chiral shift ¹H NMR experiments using (+)-Eu(hfc)₃. ^e Enantioselectivity of PTAD cycladduct determined by chiral HPLC.

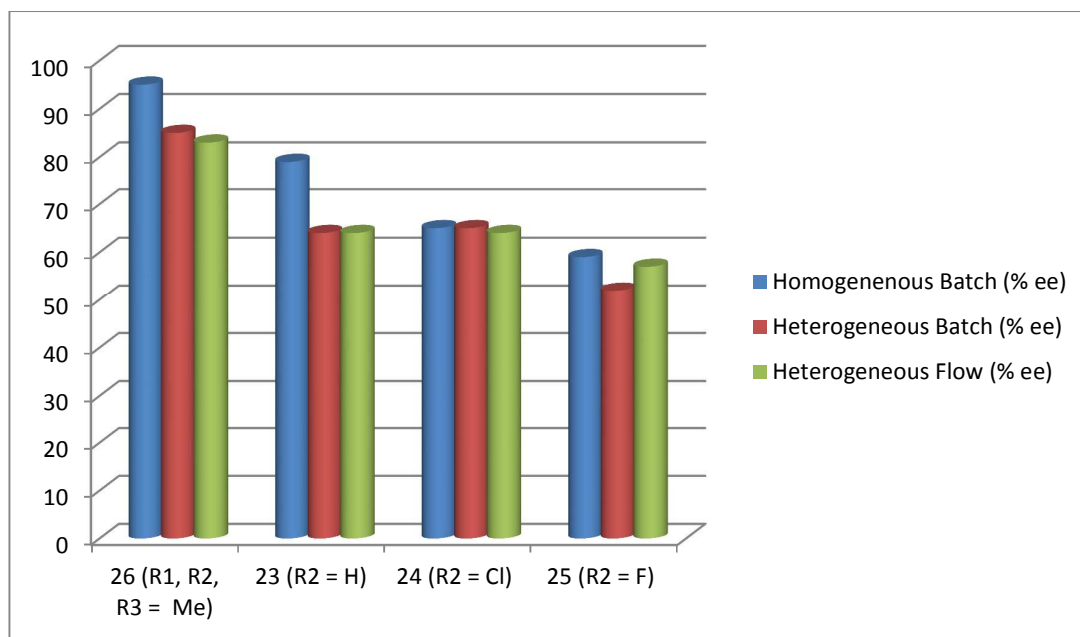
Scheme 4. Synthesis of PTAD cycladduct



The enantioselectivities achieved with the heterogeneous catalyst in both batch and flow for the four azulenes (**23-26**) are compared in Figure 2 with the enantioselectivities previously reported for the homogeneously catalyzed transformations in batch. Importantly, Figure 2 illustrates that enantioselectivity of the reaction is not affected by the performing the process

on flow. The reduced enantioselectivity observed for azulenones **23** and **26** appears to be as a result of using an immobilized catalyst.

Figure 2 Comparison of enantioselectivities of the heterogeneously catalyzed aromatic additions in flow and batch conditions with the homogeneously catalyzed aromatic additions in batch conditions.



In conclusion, enantioselective intramolecular Buchner reactions can be effected using immobilized copper–bis(oxazoline) catalysts in batch or continuous flow; efficiencies and reaction rates are comparable to the analogous homogeneous reactions, and, while for some substrates the enantioselectivity was somewhat decreased, this appears to be solely due to catalyst immobilization and not affected in any way by use of continuous flow. For α -diazoketones **2** and **3**, the enantioselectivities were comparable to those seen under homogeneous conditions. Critically, reuse of the heterogeneous catalysts up to 7 times without deterioration in efficiency and enantioselection has been demonstrated. While generation of the azulenone in flow does not offer any direct synthetic benefit, in terms of yield and stereoselectivity, over the batch reaction, one key advantage is that the enantioselective IPB catalyst can be easily reused in multiple reactions on flow. Furthermore, in recent years we have demonstrated the safe and efficient generation of diazo compounds in continuous flow.^{40,41} Clearly, the potential to couple the synthesis of the diazo precursors using this methodology with the asymmetric copper catalyzed transformation would enable use of the synthetic power of α -diazocarbonyl chemistry without handling the hazardous

precursors at any point. Use of continuous flow processing for reactions of potentially hazardous reagents such as α -diazoketones offers clear safety advantages, particularly for scale-up.

Experimental Section

General Procedures

Solvents were distilled prior to use as follows: dichloromethane was distilled from phosphorus pentoxide and when used for diazoketone reactions was further distilled from calcium hydride, ethyl acetate was distilled from potassium carbonate, hexane was distilled prior to use. Organic phases were dried using anhydrous magnesium sulfate. All commercial reagents were used without further purification unless otherwise stated.

^1H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker Avance 300 MHz NMR spectrometer. ^1H (400 MHz) and ^{13}C (100.6 MHz) NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. All spectra were recorded at 300 K in deuterated chloroform (CDCl_3) unless otherwise stated, using tetramethylsilane (TMS) as internal standard. 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 ^1H 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. NMR signal assignments were confirmed with the support of DEPT spectra and correlations detected using COSY, HETCOR, HSQC and HMBC experiments.

Infrared spectra were measured using a Perkin Elmer FTIR UATR2 spectrometer, or as potassium bromide discs (for solids) or were recorded as thin films on sodium chloride plates (for liquids) on a Perkin-Elmer Paragon 1000 FT-IR spectrometer.

Wet flash column chromatography was carried out using Kieselgel silica gel 60, 0.040-0.063 mm (Merck). Thin layer chromatography (TLC) was carried out on pre-coated silica gel plates (Merck 60 PF254). Visualisation was achieved by UV (254 nm) light absorption.

Elemental analysis was carried out by Microanalysis Laboratory, National University of Ireland, Cork, using Perkin-Elmer 240 and Exeter Analytical CE440 elemental analysers. Low resolution mass spectra (LRMS) were recorded on a Waters Quattro Micro triple quadrupole instrument in electrospray ionization (ESI) mode using 50% acetonitrile–water containing 0.1% formic acid as eluent. High resolution (precise) mass spectra (HRMS) were recorded on a Waters LCT Premier ToF LC-MS instrument in electrospray ionization (ESI) mode using 50% acetonitrile–water containing 0.1% formic acid as eluent, or on a Kratos Profile HV-4 double focusing high resolution mass spectrometer (EI). Samples were prepared for either LRMS or HRMS by employing acetonitrile as solvent.

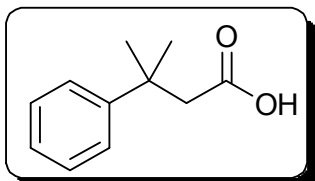
Atomic absorption spectroscopy was performed on an Agilent 240 AA instrument.

Melting points were obtained using a uni-melt Thomas Hoover Capillary melting point apparatus and are uncorrected. Microwave assisted synthesis was achieved using the CEM Discover Labmate Synthesiser in conjunction with ChemDriver software (Version 3.5.0) and the CEM Discover S-Class Synthesiser in conjunction with Synergy software. Microwave temperatures are monitored by a non contact infrared temperature control system. All continuous processes were performed using a Vapourtec R-Series flow reactor consisting of four pumps and a glass reactor manifold containing a temperature controlled glass Omnifit[®] column. To prepare the reactor for operation, pumps were purged with dichloromethane prior to use. All reaction tubing, coils, inlets and connections were also purged thoroughly in a similar manner. Enantiopurity of chiral compounds was determined by chiral stationary phase high performance liquid chromatography (HPLC) performed on a Chiralcel[®] OD-H column. HPLC analysis was performed on a Waters alliance 2690 separations module. Chiral stationary phase HPLC analysis of *PTAD* adduct **27** was performed using a Chiralcel[®] OD-H column at room temperature with isopropanol:hexane (10:90) as eluent, using a flow rate of 0.5 mL/min and the detector set at λ 229 nm. Samples were prepared at a concentration of approximately 1 mg/mL in IPA and an injection volume of 25 μ L was used. Under these conditions, (+)-**27** elutes at 19.0 min and (–)-**27** elutes at 21.6 min. All chiral columns were purchased from Daicel Chemical Industries Limited. Low temperature chiral stationary phase HPLC analysis was conducted using an Igloo-Cil[®] column cooler. Optical rotations were measured at 589 nm in a 10 cm cell on a Perkin-Elmer 141 polarimeter or on a Rudolph Autopol V Plus polarimeter; concentrations (*c*) are expressed in g/100 mL. [α] is the specific rotation of a compound and is expressed in units of 10^{–1} deg cm² g^{–1}.

Homogeneous catalysis of azulenone formation using a copper–bis(oxazoline) system was carried out in accordance with literature precedent.^{12,30}

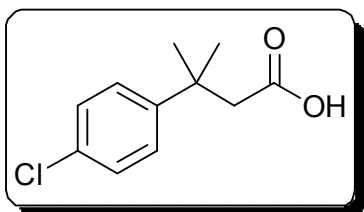
Synthesis of precursors

3-Methyl-3-phenylbutanoic acid (**5**)⁴²



Benzene (100 mL) was added to a 1 L two-neck flask that was then placed in an ice bath and then charged with dimethylacrylic acid (5.00 g, 49.9 mmol) while stirring. Aluminium trichloride (12.50 g, 93.8 mmol) was added very slowly. The ice bath was removed and the mixture was stirred at room temperature for 48 h. The reaction was quenched by adding it into a 250 mL conical flask containing aq. 10% HCl (25 mL) and ice (100 g). The yellow organic layer was removed and the aqueous layer was washed with diethyl ether (2 x 35 mL). The combined organic layers were washed with 20% aq. NaOH (2 x 50 mL). The aqueous layer was then acidified to pH 1 with conc. aq. HCl and washed with diethyl ether (3 x 40 mL). The organic layers were collected and washed with brine, dried, filtered and solvent removed under reduced pressure to yield the *acid 5* as a pale yellow solid (5.88 g, 66%). m.p. 54-56°C (Lit.,⁴² 57-58°C); $\nu_{\text{max}}/\text{cm}^{-1}$ (ATR) 2978 br (OH), 1700 (CO), 1498, 1440, 1409, 1317; δ_{H} (400 MHz) 1.47 [6H, s, C(3)CH₃, C(4)H₃], 2.56 [2H, s, C(2)H₂], 7.18-7.37 (5H, m, Ar H). $\delta_{\text{C}}\{^1\text{H}\}$ (75.5 MHz) 28.8 [CH₃, C(3)CH₃, C(4)H₃], 37.0 [C, C(3)], 48.0 [CH₂, C(2)H₂], 125.4, 126.1, 128.3 {3 x CH, [C(2')H, C(6')H, C(3')H, C(5')H and C(4')H]}, 148.0 [C, C(1')], 178.0 [C, C(1)=O].

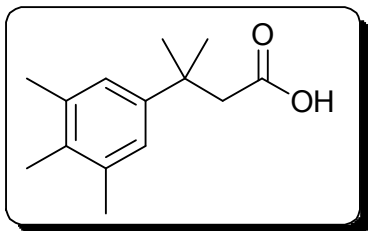
3-Methyl-3-(4-chlorophenyl)butanoic acid (**6**)⁴²



This compound was prepared, using the procedure outlined for 3-methyl-3-phenylbutanoic acid, from chlorobenzene (150 mL), dimethylacrylic acid (7.50 g, 74.9 mmol) and aluminium trichloride (18.75 g, 140.6 mmol) to yield the *acid 6* as a pale yellow solid (14.98 g, 94%). m.p. 64-66°C (Lit.,⁴³ 66-67°C); $\nu_{\text{max}}/\text{cm}^{-1}$ (ATR) 2973 br (OH), 1699 (CO), 1494, 1438, 1321; δ_{H} (400 MHz) 1.43 [6H, s, C(3)CH₃, C(4)H₃], 2.62 [2H, s, C(2)H₂], 7.20-7.35 (4H, m, Ar H). $\delta_{\text{C}}\{^1\text{H}\}$ (75.5 MHz) 28.9 [CH₃, C(3)CH₃, C(4)H₃], 36.8 [C, C(3)], 47.8 [CH₂, C(2)H₂], 127.0,

128.3 {2 x CH, [C(2')H, C(6')H and C(3')H, C(5')H]}, 131.8 [C, C(1')], 146.4 [C, C(4')Cl], 177.6 [C, C(1)=O].

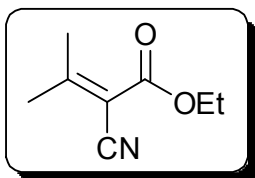
*3-Methyl-3-(3,4,5-trimethylphenyl)butanoic acid (7)*⁴⁴



This compound was prepared, using the procedure outlined for 3-methyl-3-phenylbutanoic acid, from 1,2,3-trimethylbenzene (20 mL, 148.8 mmol), dimethylacrylic acid (3.11 g, 31.1 mmol) and aluminium trichloride (8.22 g, 61.6 mmol) to yield the *acid 7* as a pale brown solid (6.33 g, 92%). m.p 101-108°C (Lit.,⁴⁴ 112-113°C); $\nu_{\max}/\text{cm}^{-1}$ (ATR)

2957 br (OH), 1703 (CO), 1644 1415; δ_{H} (300 MHz) 1.43 [6H, s, C(3)CH₃, C(4)H₃], 2.14 [3H, s, C(4')CH₃], 2.28 [6H, s, C(3')CH₃, C(5')CH₃], 2.63 [2H, s, C(2)H₂], 7.00 [2H, s, C(2')H, C(6')H]. $\delta_{\text{C}}\{^1\text{H}\}$ (75.5 MHz) 15.0 [CH₃, C(4')CH₃], 20.9 [CH₃, C(3')CH₃, C(5')CH₃], 28.8 [CH₃, C(3)CH₃, C(4)H₃], 36.5 [C, C(3)], 47.9 [CH₂, C(2)H₂], 124.6 [CH, C(2')H, C(6')H], 132.8 [C, C(1') or C(4')], 136.1 [C, C(3'), C(5')], 145.0 [C, C(1') or C(4')], 177.2 [C, C(1)].

*Ethyl 2-cyano-3-methylbut-2-enoate (10)*³²

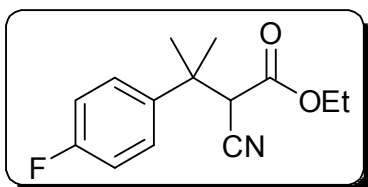


A 500 mL round bottom flask was charged with β -alanine (0.14 g, 0.15 mmol), ethyl cyanoacetate (**9**) (31.8 mL, 299 mmol), acetone (104 mL, 1.41 mol), acetic acid (6 mL) and benzene (70 mL). The contents of the flask were heated to reflux for 70 h using a

Dean–Stark trap. Purification by vacuum distillation gave the *ester 10* as a white low melting solid with about 8% percent ethyl cyanoacetate starting material present by ¹H NMR analysis. b.p 115°C at 14 mmHg; $\nu_{\max}/\text{cm}^{-1}$ (film) 2986, 2227 (CN), 1732 (CO), 1612, 1444, 1371, 1335, 1285, 1086; δ_{H} (300 MHz) 1.34 [3H, t, *J* 7.12, CH₂CH₃], 2.31, 2.41 [2 × 3H, 2 × s, C(3)CH₃, C(4)CH₃], 4.27 [2H, q, *J* 7.13, CH₂CH₃].

Ethyl cyanoacetate; δ_{H} (300 MHz) 3.50 [2H, s, C(2)H₂]. N.B. Peaks for CH₂CH₃, CH₂CH₃ were obscured by those of the product ester.

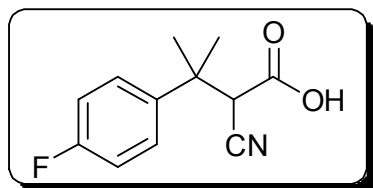
*Ethyl 2-cyano-3-methyl-3-(4-fluorophenyl)butanoate (11)*³²



Ethyl 2-cyano-3-methylbut-2-enoate **10** (7.34 g, 47.91 mmol) was added dropwise to 4-fluorophenyl magnesium bromide [freshly prepared from magnesium (3.50 g, 144.0

mmol), iodine (one crystal) in ether (60 mL), and 1-fluoro-4-iodobenzene (32.04 g, 144.0 mmol) in diethyl ether (60 mL)] at room temperature under nitrogen and the mixture was heated to reflux for 12 h. The reaction mixture was cooled to room temperature and carefully poured into aqueous hydrochloric acid (10%, 50 mL). The layers were separated and the aqueous layer was washed with diethyl ether (40 mL). The combined organic layers were washed with brine (20 mL), dried, filtered and concentrated under reduced pressure to give the crude ester as an orange oil. Purification by flash chromatography using ethyl acetate/hexane (20:80) as eluent gave the *ester 11* as a clear oil (7.80 g, 65%). $\nu_{\max}/\text{cm}^{-1}$ (film) 2982, 2248 (CN), 1741 (CO), 1604, 1513, 1236; δ_{H} (400 MHz) 1.08 (3H, t, J 7.1, CH_2CH_3), 1.62 [6H, s, $\text{C}(3)\text{CH}_3$, $\text{C}(4)\text{H}_3$], 3.72 [1H, s, $\text{C}(2)\text{H}$], 4.00-4.09 (2H, m, CH_2CH_3), 6.99-7.07, 7.34-7.40 {2 x 2H, m, [$\text{C}(2')\text{H}$, $\text{C}(6')\text{H}$ and $\text{C}(3')\text{H}$, $\text{C}(5')\text{H}$]}. $\delta_{\text{C}}\{^1\text{H}\}$ (75.5 MHz) 13.7 (CH_3 , CH_2CH_3), 25.8, 27.3 [$2 \times \text{CH}_3$, $\text{C}(3)\text{CH}_3$, $\text{C}(4)\text{H}_3$], 40.6 [C , $\text{C}(3)$], 50.3 [CH , $\text{C}(2)\text{H}$], 62.3 (CH_2 , CH_2CH_3), 115.1 [CH , d, $^2J_{\text{CF}}$ 21, $\text{C}(3')\text{H}$, $\text{C}(5')\text{H}$], 115.6 [C , CN], 127.6 [CH , d, $^3J_{\text{CF}}$ 8, $\text{C}(2')\text{H}$, $\text{C}(6')\text{H}$], 139.3 [C , d, $^4J_{\text{CF}}$ 3, $\text{C}(1')$], 161.7 [C , d, $^1J_{\text{CF}}$ 247, $\text{C}(4')$], 164.6 [C , $\text{C}(1)$]; HRMS (ESI-TOF) m/z : [$\text{M}+\text{NH}_4$] $^+$ Calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_2\text{F}$ 267.1509; Found 267.1509. m/z (ESI-) 248 [$(\text{M}-\text{H})^-$, 19%], 215 (16%), 176 [$(\text{M}-\text{CH}_3\text{CH}_2\text{OCO})^-$, 22%], 152 (51%), 139 (81%), 127 (19%), 113 (42%), 95 [$(\text{CH}_3\text{C}_6\text{H}_4)^-$, 100%].

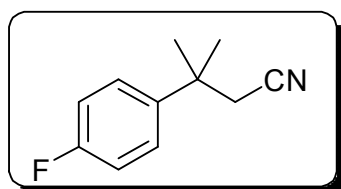
2-Cyano-3-methyl-3-(4-fluorophenyl)butanoic acid (**12**)



Ethyl-2-cyano-3-methyl-3-(4-fluorophenyl)butanoate **11**

(7.36 g, 29.5 mmol) was stirred with sodium hydroxide pellets (4.72 g, 118.0 mmol) in ethanol (95%, 25 mL) for 12 h. The solution was acidified to pH 2 using aqueous hydrochloric acid (10%). The aqueous layer was extracted with diethyl ether (3×40 mL). The combined organic layers were washed with water (50 mL), brine (50 mL), dried, filtered and concentrated under reduced pressure to give the crude *acid 12* as a yellow oil (3.21 g, 75%). $\nu_{\max}/\text{cm}^{-1}$ (film) 2980 br (OH), 1728, 1604, 1513; δ_{H} (400 MHz) 1.63, 1.64 [$2 \times 3\text{H}$, $2 \times \text{s}$, $\text{C}(3)\text{CH}_3$, $\text{C}(4)\text{H}_3$], 3.73 [1H, s, $\text{C}(2)\text{H}$], 7.01-7.08, 7.34-7.40 {2 x 2H, m, [$\text{C}(2')\text{H}$, $\text{C}(6')\text{H}$ and $\text{C}(3')\text{H}$, $\text{C}(5')\text{H}$]}. δ_{C} (75.5 MHz) 13.7 (CH_3 , CH_2CH_3), 25.8, 27.3 [$2 \times \text{CH}_3$, $\text{C}(3)\text{CH}_3$, $\text{C}(4)\text{H}_3$], 40.6 [C , $\text{C}(3)$], 50.3 [CH , $\text{C}(2)\text{H}$], 62.3 (CH_2 , CH_2CH_3), 115.1 [CH , d, $^2J_{\text{CF}}$ 21, $\text{C}(3')\text{H}$, $\text{C}(5')\text{H}$], 115.6 [C , CN], 127.6 [CH , d, $^3J_{\text{CF}}$ 8, $\text{C}(2')\text{H}$, $\text{C}(6')\text{H}$], 139.3 [C , d, $^4J_{\text{CF}}$ 3, $\text{C}(1')$], 161.7 [C , d, $^1J_{\text{CF}}$ 247, $\text{C}(4')$], 164.6 [C , $\text{C}(1)$]; HRMS (ESI-TOF) m/z : [$\text{M}+\text{NH}_4$] $^+$ Calcd for $\text{C}_{14}\text{H}_{17}\text{FNO}_2$ 267.1159; Found 267.1159. m/z (ESI-) 248 [$(\text{M}-\text{H})^-$, 19%], 215 (16%), 176 [$(\text{M}-\text{CH}_3\text{CH}_2\text{OCO})^-$, 22%], 152 (51%), 139 (81%), 127 (19%), 113 (42%), 95 [$(\text{CH}_3\text{C}_6\text{H}_4)^-$, 100%].

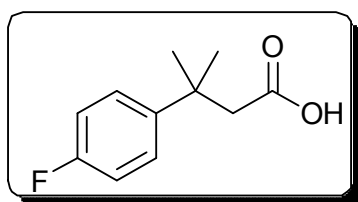
3-Methyl-3-(4-fluorophenyl)butanenitrile (**13**)



A 100 mL round bottomed flask equipped with a magnetic stirred bar was charged with 2-cyano-3-methyl-3-(4-fluorophenyl)butanoic acid **12** (4.91 g, 22.2 mmol). The flask

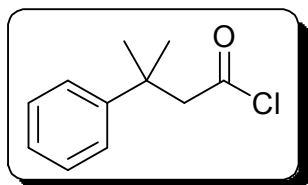
was attached to a gas bubbler and subsequently heated in an open vessel microwave reactor for 30 min at 100 W at 200°C. As 170°C was reached, degassing through the bubbler was evident. The reaction mixture was cooled to room temperature to give the crude nitrile as a viscous brown oil. Purification by vacuum distillation gave the *nitrile* **13** as a yellow oil (2.11 g, 54%). b.p. 110°C at 0.10 mmHg (Lit.⁴⁵ 138-140°C at 10 mmHg); ν_{\max} /cm⁻¹ (film) 2972, 2250 (CN), 1604, 1513; δ_{H} (300 MHz) 1.51 [6H, s, C(3)CH₃, C(4)H₃], 2.59 [2H, s, C(2)H₂], 6.99-7.08, 7.32-7.37 {2 x 2H, 2 x m, [C(3')H, C(5')H] and [C(2')H, C(6')H]}. $\delta_{\text{C}}\{^1\text{H}\}$ (75.5 MHz) 28.5 [CH₃, C(3)CH₃, C(4)H₃], 33.0 [CH₂, C(2)H₂], 36.7 [C, C(3)], 115.4 [CH, d, $^2J_{\text{CF}}$ 21.2, C(3')H, C(5')H], 118.0 [C, C(1)], 127.0 [CH, d, $^3J_{\text{CF}}$ 8.0, C(2')H, C(6')H], 141.6 [C, d, $^4J_{\text{CF}}$ 3.3, C(1')], 161.5 [C, d, $^1J_{\text{CF}}$ 246.0, C(4')].

3-Methyl-3-(4-fluorophenyl)butanoic acid (**8**)^{32,46}



A solution of potassium hydroxide (1.57 g, 27.9 mmol) in ethylene glycol (20 mL) was added to 3-methyl-3-(4-fluorophenyl)butanenitrile **13** (1.55 g, 8.70 mmol) and the resulting solution was heated under reflux for 12 h. The solution was then acidified to pH 2 using aqueous hydrochloric acid (10%). The aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with aqueous sodium hydroxide (10%, 50 mL), and then the aqueous layer was acidified to pH 1 with aqueous hydrochloric acid and extracted with diethyl ether (3 x 50 mL). The combined organic layers were then dried, filtered and concentrated under reduced pressure to give the pure *acid* **8** as a viscous, pale yellow oil (1.01 g, 59%). ν_{\max} /cm⁻¹ (film) 2918 br (OH), 1708, 1512, 1232, 833; δ_{H} (300 MHz) 1.45 [6H, s, C(3)CH₃, C(4)H₃], 2.63 [2H, s, C(2)H₂], 6.96-7.01, 7.29-7.33 {2 x 2H, m, [C(2')H, C(6')H and C(3')H, C(5')H]}. $\delta_{\text{C}}\{^1\text{H}\}$ (75.5 MHz) 29.1 [CH₃, C(3)CH₃, C(4)H₃], 36.6 [C, C(3)], 48.1 [CH₂, C(2)H₂], 114.8 [CH, d, $^2J_{\text{CF}}$ 21, C(3')H, C(5')H], 127.0 [CH, d, $^3J_{\text{CF}}$ 7, C(2')H, C(6')H], 143.6 [C, d, $^4J_{\text{CF}}$ 3, C(1')], 161.3 [C, $^1J_{\text{CF}}$ 244, C(4')], 177.4 [C, C(1)].

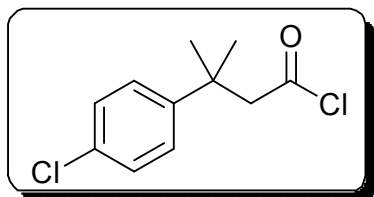
3-Methyl-3-phenylbutanoyl chloride⁴⁷



3-Methyl-3-phenylbutanoic acid (0.365 g, 2 mmol) and thionyl chloride (1.17 mL, 16 mmol) were added to a 100 mL round bottom flask. The reaction was heated to reflux under N₂ at 110°C for 3 h. The crude mixture appeared as a brown oil and was concentrated under reduced pressure. The crude product was purified by bulb-to-bulb

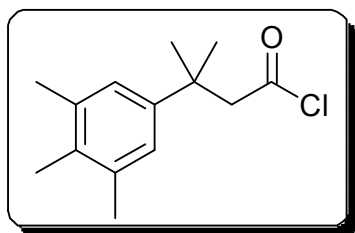
distillation (b.p. 140°C at 0.12 mmHg). The *acid chloride* was afforded as a clear oil (0.299 g, 76%). $\nu_{\max}/\text{cm}^{-1}$ (film) 2971, 1807 (CO), 1497, 1445; δ_{H} (400 MHz) 1.48 [6H, s, C(3)CH₃, C(4)H₃], 3.27 [2H, s, C(2)H₂], 7.12-7.40 (5H, m, ArH).

3-Methyl-3-(4-chlorophenyl)butanoyl chloride



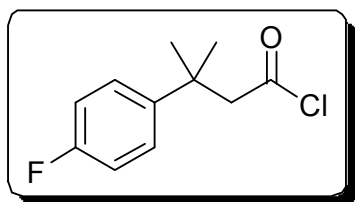
This compound was prepared using the procedure outlined for 3-methyl-3-phenylbutanoyl chloride from 3-methyl-3-(4-chlorophenyl)butanoic acid (14.98 g, 70.4 mmol), thionyl chloride (41.1 mL, 563 mmol) and *N,N*-dimethylformamide (3 drops). The pure *acid chloride* was afforded as a clear oil (11.98 g, 62%). b.p. 130°C at 0.6 mmHg; $\nu_{\max}/\text{cm}^{-1}$ (film) 2971, 1808 (CO), 1596, 1496, 1402; δ_{H} (300 MHz) 1.41 [6H, s, C(3)CH₃, C(4)H₃], 3.27 [2H, s, C(2)H₂], 7.21-7.35 (4H, m, ArH).

3-Methyl-3-(3,4,5-trimethylphenyl)butanoyl chloride



A 100 mL three neck round bottom flask was charged with 3-methyl-3-(3,4,5-methylphenyl)butanoic acid (4.012 g, 18.2 mmol) and diethyl ether (15 mL). The flask was cooled to 0°C in an ice bath and oxalyl chloride (2.0 mL, 23.3 mmol) in diethyl ether (10 mL) was slowly added to the solution through an addition funnel. The ice bath was then removed and the flask allowed to reach room temperature and the reaction mixture was stirred under N₂ for 24 h. Following concentration under reduced pressure, the crude *acid chloride* was collected as a brown oil (4.17 g, 96%), which was used immediately without purification. $\nu_{\max}/\text{cm}^{-1}$ (film) 2968, 1809 (CO), 1599, 1580, 1445, 1386; δ_{H} (300 MHz) 1.45 [6H, s, C(3)CH₃, C(4)H₃], 2.14 [3H, s, C(4')CH₃], 2.28 [6H, s, C(3')H₃, C(5')H₃], 3.26 [2H, s, C(2)H₂], 6.91 [2H, s, ArH].

3-Methyl-3-(4-fluorophenyl)butanoyl chloride



This compound was prepared using the procedure outlined for 3-methyl-3-(3,4,5-trimethylphenyl)butanoyl chloride from 3-methyl-3-(4-fluorophenyl)butanoic acid (1.40 g, 7.14 mmol) and oxalyl chloride (2.0 mL, 23.3 mmol) in diethyl ether (30 mL) giving the crude *acid chloride* as a brown oil (1.47 g, 96%), which was used immediately without purification. $\nu_{\max}/\text{cm}^{-1}$ (film) 2969, 1809 (CO),

1602, 1513, 1234, 1166, 833; δ_{H} (300 MHz) 1.44 [6H, s, C(3)CH₃, C(4)H₃], 3.26 [2H, m, C(2)H₂], 6.97-7.08, 7.26-7.37 {2 x 2H, m, [C(2)H, C(6)H and C(3)H, C(5)H]}.

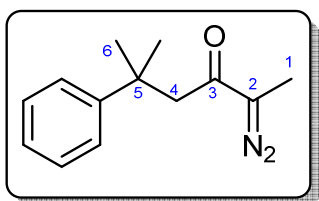
Synthesis of α -diazoketones

Caution: *N*-Ethyl-*N*-nitrosourea is a carcinogen and should be handled with appropriate care.⁴⁸

Caution: Diazoethane is both toxic and explosive. All operations should be carried out in a well ventilated fumehood with adequate shielding. The glassware used for the generation of diazoethane should have clear glass joints to minimise the risk of explosion. Any items which come in contact with diazoethane should be washed with aqueous acetic acid before being removed from the fumehood.

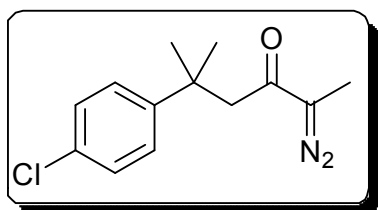
Note: Restricted rotations in the α -diazoketones leads to signal broadening in the ¹H and ¹³C NMR spectra, for example, for the signal associated with the diazocarbon [C(2)=N₂].

2-Diazo-5-methyl-5-phenylhexan-3-one (**1**)



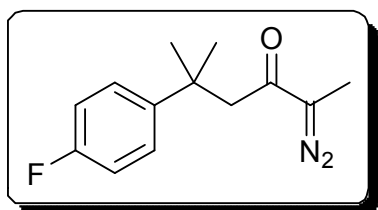
3-Methyl-3-phenylbutanoyl chloride (3.94 g, 20.0 mmol) was dissolved in diethyl ether (200 mL). This solution was added slowly, over 1 h from an addition funnel, to an ethereal diazoethane solution [freshly prepared from *N*-ethyl-*N*-nitrosourea (18.2 g, 155 mmol)]⁴⁹ in a 500 mL round bottom flask being stirred in a salt-ice bath under N₂, turning the orange solution to yellow. The resultant solution was then allowed reach room temperature over 3 h while under N₂. The solution was then concentrated under reduced affording the crude product which was purified by flash chromatography with hexane:ethyl acetate (85:15) as eluent giving *diazoketone 1* as a yellow oil (3.59 g, 83%). $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 2964, 2061, 1621, 1348, 1266, 1054; δ_{H} (300 MHz) 1.47 [6H, s, C(5)CH₃, C(6)H₃], 1.80 [3H, s, C(1)H₃], 2.69 [2H, s, C(4)H₂], 7.18-7.37 (5H, m, ArH). $\delta_{\text{C}}\{^1\text{H}\}$ (75.5 MHz) 8.2 [CH₃, C(1)H₃], 28.5 [CH₃, C(5)CH₃, C(6)H₃], 38.4 [C, C(5)], 50.7 [CH₂, C(4)H₂], 63.8 [C, C=N₂], 125.5, 126.1, 128.2 [3 x CH, Aromatic CH], 148.0 [C, Aromatic C], 193.0 [C, C=O]. HRMS (EI) *m/z*: (M-N₂)⁺ Calcd for C₁₃H₁₆O 188.1202; Found 188.1201. *m/z* (EI) 188 [(M-N₂)⁺ 12%], 173 (28%), 145 (33%), 132 (89%), 119 (100%).

2-Diazo-5-methyl-5-(4-chlorophenyl)hexan-3-one (**2**)



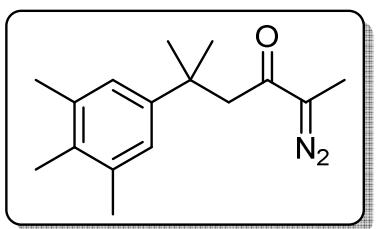
This compound was prepared, using the procedure outlined for **1**, from distilled 3-methyl-3-(4-chlorophenyl)butanoyl chloride (11.95 g, 48.50 mmol) in diethyl ether (200 mL) and an ethereal solution of diazoethane [freshly prepared from *N*-ethyl-*N*-nitrosourea (45.0 g, 385 mmol)].⁴⁹ The crude product was purified by flash chromatography with hexane:ethyl acetate (95:5) as eluent giving *diazoketone 2* a yellow oil (7.30 g, 60%). $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 2965, 2061, 1621, 1353, 1279, 1011; δ_{H} (300 MHz) 1.45 [6H, s, C(5)CH₃, C(6)H₃], 1.82 [3H, s, C(1)H₃], 2.68 [2H, s, C(4)H₂], 7.26-7.30 [4H, m, ArH]. $\delta_{\text{C}}\{^1\text{H}\}$ (75.5 MHz) 8.1 [CH₃, C(1)H₃], 29.1 [CH₃, C(5)CH₃, C(6)H₃], 38.0 [C, C(5)], 50.3 [CH₂, C(4)H₂], 63.6 [C, C=N₂], 127.0, 128.2 [CH, 2 x Aromatic CH], 131.8, 147.6 [C, 2 x Aromatic C], 192.5 [C, C=O]. HRMS (EI) *m/z*: (M-N₂)⁺. Calcd for C₁₃H₁₅O³⁵Cl 222.0779; Found 222.0811. *m/z* (EI) 222 (M⁺-N₂).

2-Diazo-5-methyl-5-(4-fluorophenyl)hexan-3-one (**3**)



This compound was prepared, using the procedure outlined for **1**, from crude 3-methyl-3-(4-fluorophenyl)butanoyl chloride (1.47 g, 7.14 mmol) in diethyl ether (50 mL) and an ethereal solution of diazoethane [freshly prepared from *N*-ethyl-*N*-nitrosourea (6.70 g, 57.2 mmol)].⁴⁹ The crude product was purified by flash chromatography with hexane:ethyl acetate (95:5) as eluent giving *diazoketone 3* as a yellow oil (0.639 g, 38%). $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 2967, 2066, 1625; δ_{H} (300 MHz) 1.46 [6H, s, C(5)CH₃, C(6)H₃], 1.81 [3H, s, C(1)H₃], 2.68 [2H, s, C(4)H₂], 6.96-7.02, 7.28-7.33 {2 x 2H, m, [C(2')H, C(6')H and C(3')H, C(5')H]}. $\delta_{\text{C}}\{^1\text{H}\}$ (75.5 MHz) 8.1 [CH₃, C(1)H₃], 28.8 [CH₃, C(5)CH₃, C(6)H₃], 38.0 [C, C(5)], 50.7 [CH₂, C(4)H₂], 63.7 [C, C=N₂], 114.8 [CH, d, ²J_{CF} 20.9, C(3')H, C(5')H], 127.1 [CH, d, ³J_{CF} 7.8, C(2')H, C(6')H], 143.6 [C, C(1')], 161.2 [C, d, ¹J_{CF} 244.2, C(4')], 192.8 [C, C(3)]; HRMS (ESI-TOF) *m/z*: [(M+H)]⁺ Calcd for C₁₃H₁₆FN₂O 235.1247; Found 235.1240. *m/z* (ESI+) 235 [(M+H)⁺, 75%], 207 (54%), 189 (100%), 137 (14%), 123 (48%).

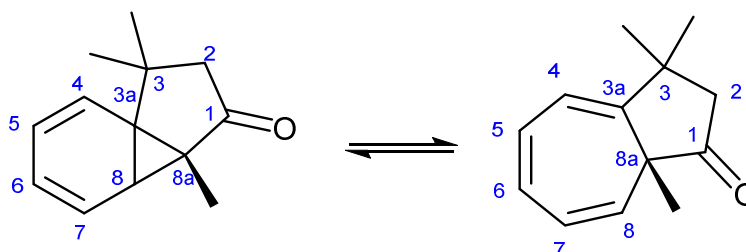
2-Diazo-5-methyl-5-(3,4,5-trimethylphenyl)hexan-3-one (**4**)



This compound was prepared, using the procedure outlined for **1**, from crude 3-methyl-3-(3,4,5-phenyl)butanoyl chloride (4.17 g, 17.5 mmol) in diethyl ether (50 mL) and

an ethereal diazoethane solution [freshly prepared from *N*-ethyl-*N*-nitrosourea (16.50 g, 140.9 mmol)].⁴⁹ The crude product was purified by flash chromatography with hexane:ethyl acetate (95:5) as eluent giving *diazoketone* **4** as a yellow oil (3.13 g, 67%). $\nu_{\max}/\text{cm}^{-1}$ (film) 2963, 2061, 1712, 1624, 1445, 1346; δ_{H} (300 MHz) 1.43 [6H, s, C(5)CH₃, C(6)H₃], 1.83 [3H, s, C(1)H₃], 2.14 [3H, s, C(4')CH₃], 2.28 [6H, s, C(3')CH₃, C(5')CH₃], 2.68 [2H, s, C(4)CH₂], 6.98 [2H, s, C(2')H, C(6')H]. $\delta_{\text{C}}\{^1\text{H}\}$ (75.5 MHz) 8.3 [CH₃, C(1)H₃], 15.1 [CH₃, C(4')CH₃], 20.9 [CH₃, C(3')CH₃, C(5')CH₃], 28.5 [CH₃, C(5)CH₃, C(6)H₃], 37.9 [C, C(5)], 50.7 [CH₂, C(4)H₂], 63.8 [C, C=N₂], 124.7 [CH, C(2')H, C(6')H], 132.7 [C, C(4')], 136.1 [C, C(3'), C(5')], 145.0 [C, C(1')], 193.4 [C, C(1)]; HRMS (ESI-TOF) m/z : [(M+H)]⁺ Calcd for C₁₆H₂₃N₂O 259.1810; Found 259.1803. m/z (ESI+) 259 [(M+H)⁺, 46%], 231 (100%), 213 (61%), 147 (27%), 111 (28%), 93 (11%). This α -diazoketone can be stored in a freezer but is labile at room temperature – decomposition has been seen during chromatography and even during spectroscopic analysis.

Synthesis of azulenones

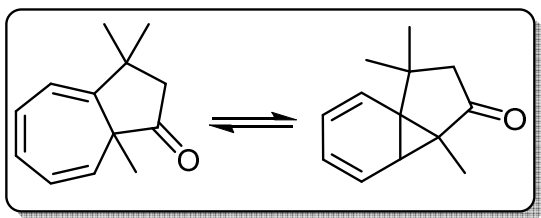


General procedure for heterogeneously catalyzed reaction in batch

Doubly distilled dichloromethane and catalyst **20** (10 mol%) were added to a flame-dried three neck round bottom flask which was brought to reflux at 40°C under N₂. A solution of α -*diazoketone* (1 eq) in dichloromethane was added over 20 min to the stirred solution. The reaction was monitored by IR until the diazo peak was no longer visible. The crude product was purified by flash chromatography, with hexane:ethyl acetate as eluent, giving *azulenone* as a yellow oil. The spectral details were consistent with those described below.

3,8a-Dihydro-3,3,8a-trimethylazulen-1(2H)-one (23)^{12,30}

(a) Batch conditions



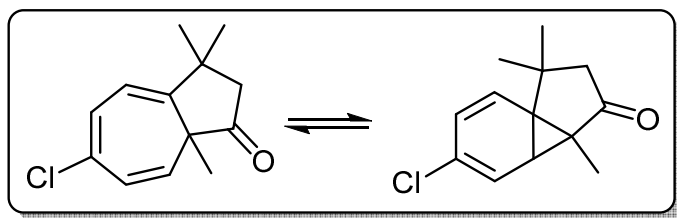
Doubly distilled dichloromethane (50 mL) and $\text{Rh}_2(\text{OAc})_4$ (0.5 mg, 1 mol%) were added to a flame-dried 250 mL three neck round bottom flask which was brought to reflux at 40°C under N_2 . A solution of **1** (0.110 g, 0.510 mmol) in dichloromethane (50 mL) was added over 20 min to the stirred solution. The reaction was monitored by IR until the diazo peak was no longer visible. The crude product was purified by flash chromatography, with hexane:ethyl acetate (85:15) as eluent, giving *azulenone* **23** as a yellow oil (0.065 g, 67%). The spectral details were consistent with those described below.

(b) *Continuous flow method*

A solution (0.039 M) of diazoketone **1** (0.210 g, 0.971 mmol) in doubly distilled dichloromethane (25 mL) was prepared. An Omnifit[®] glass column (150 mm, 6.6 mm internal diameter) was packed with immobilized catalyst **20** (0.338 g, 10 mol%) along with glass wool. The solution of **1** (14 mL) was pumped at 1.0 mL/min through the polymer contained within the column while the column was heated at 45°C . The reaction stream then passed through a tube (32 cm) and back pressure regulator (8 bar), after which the crude *azulenone* was collected as a yellow solution. Tetrahydrofuran was pumped through the column after the reaction stream in order to recover the polymer, removing the brown discolouration and returning its original green colour. The crude product was purified by flash chromatography, with hexane:ethyl acetate (95:05) as eluent, giving *azulenone* **23** as a yellow oil (0.072 g, 70%). $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 3042, 2926, 1747 (CO), 1715 (CO); δ_{H} (400 MHz) 0.76 [3H, s, C(8a)CH₃], 1.14, 1.31 [2 × 3H, 2 × s, C(3)(CH₃)₂], 2.20 [1H, A of AB, J_{AB} 17.3, one of C(2)H₂], 2.28 [1H, B of AB, J_{AB} 17.3, one of C(2)H₂], 4.18 [1H, d, J 8.0, C(8)H], 6.07-6.14 [1H, m, C(7)H], 6.23-6.43 [3H, m, C(4)H, C(5)H, C(6)H]. $\delta_{\text{C}}\{^1\text{H}\}$ (75.5 MHz) 11.43 [CH₃, C(8a)CH₃], 28.6, 28.8 [2 × CH₃, 2 × C(3)CH₃], 38.6 [C, C(8a)], 40.7 [C, C(3)], 50.1 [CH₂, C(2)H₂], 84.9 [CH, C(8)H], 109.6 [C, C(3a)], 119.7, 125.3, 126.8, 127.1 [4 × CH, C(4)H – C(7)H], 218.5 [C, C=O]. Found HRMS (EI) m/z : [M]⁺ Calcd for C₁₃H₁₆O 188.1187; Found 188.1201. m/z (EI) 188 [(M)⁺, 22%], 173 (42%), 145 (40%), 132 (100%), 104 (57%).

*3,8a-Dihydro-6-chloro-3,3,8a-trimethylazulen-1(2H)-one (24)*³⁰

(a) Batch conditions



This compound was prepared, using the procedure outlined for **23**, from diazoketone **2** (0.160 g, 0.64 mmol) in doubly distilled dichloromethane (50 mL) and

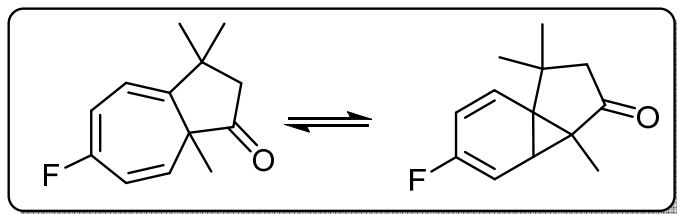
$\text{Rh}_2(\text{OAc})_4$ (0.5 mg, 1 mol%). The crude product was purified by flash chromatography, with hexane:ethyl acetate (97:3) as eluent, giving azulenone **24** (0.105 g, 70%) as a yellow oil. The spectral details were consistent with those described below.

(b) Continuous flow method

This compound was prepared, using the procedure outlined for **23**, from a solution (8 mL, 0.071 M) of diazoketone **2** (0.445 g, 1.770 mmol) in doubly distilled dichloromethane (25 mL) and immobilized catalyst **20** (0.500 g, 10 mol%). The crude product was purified by flash chromatography, with hexane:ethyl acetate (97:3) as eluent, giving azulenone **24** as a yellow oil (0.083 g, 65%). $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 2963, 2928, 1748 (CO), 1718 (CO); δ_{H} (300 MHz) 0.86 [3H, s, C(8a)CH₃], 1.14, 1.33 [2 × 3H, 2 × s, C(3)(CH₃)₂], 2.22 [1H, A of AB, J_{AB} 17.3, one of C(2)H₂], 2.39 [1H, B of AB, J_{AB} 17.3, one of C(2)H₂], 4.54 [1H, d, J 9.0, C(8)H], 6.14 [1H, dd, J 8.9, 0.7, C(7)H], 6.23 [1H, d, J 8.0, C(4)H], 6.52 [1H, dd, J 8.0, 1.1, C(5)H]. $\delta_{\text{C}}\{^1\text{H}\}$ (75.5 MHz) 13.6 [CH₃, C(8a)CH₃], 28.9 [CH₃, one of C(3)CH₃], 29.6 [CH₃, one of C(3)CH₃], 38.8 [C, C(8a)], 44.6 [C, C(3)], 50.4 [CH₂, C(2)], 100.3 [CH, C(8)H], 119.1 [CH], 125.6 [C, C(3)], 127.1, 127.4 [2 × CH], 131.6 [C, C(6)], 217.2 [C, C=O]. HRMS (EI) m/z : [M]⁺ Calcd for C₁₃H₁₅O³⁵Cl 222.0809; Found 222.0811. m/z (EI) 222, 224 [(M)⁺, 13%, 4%], 207, 209 (28%, 9%), 179, 181 (19%, 6%), 166, 168 (100%, 33%), 138, 140 (62%, 31%).

3,8a-Dihydro-6-fluoro-3,3,8a-trimethylazulen-1(2H)-one (**25**)³⁰

(a) Batch conditions



This compound was prepared, using the procedure outlined for

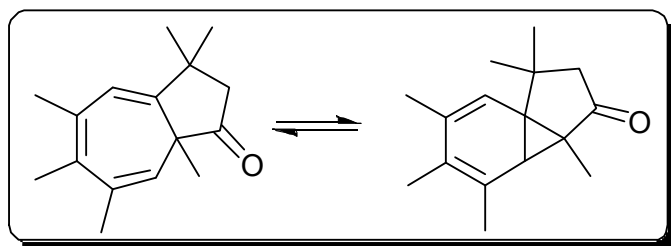
23, from diazoketone **3** (0.093 g, 0.400 mmol) in doubly distilled dichloromethane (50 mL) and $\text{Rh}_2(\text{OAc})_4$ (0.5 mg, 1 mol%). The crude product was purified by flash chromatography, with hexane:ethyl acetate (97:3) as eluent, giving *azulenone* **25** as a yellow oil (0.060 g, 71%). The spectral details were consistent with those described below.

(b) Continuous flow method

This compound was prepared, using the procedure outlined for **23**, from a solution (14 mL, 0.056 M) of diazoketone **3** (0.330 g, 1.40 mmol) in doubly distilled dichloromethane (25 mL) and immobilized catalyst **19** (0.350 g, 10 mol%). The crude product was purified by flash chromatography, with hexane:ethyl acetate (97:3) as eluent, giving *azulenone* **25** as a yellow oil (0.089 g, 55%). $\nu_{\text{max}}/\text{cm}^{-1}$ (film) 2964, 2869, 1750 (CO), 1716 (CO), 1646, 1626; δ_{H} (300 MHz) 0.91 [3H, s, C(8a)CH₃], 1.15, 1.37 [$2 \times 3\text{H}$, $2 \times \text{s}$, C(3)(CH₃)₂], 2.25 [1H, A of AB, J_{AB} 17.3, one of C(2)H₂], 2.51 [1H, B of AB, J_{AB} 17.3, one of C(2)H₂], 5.12 [1H, dd, J_{HH} 10.0, J_{HF} 5.1, C(8)H], 6.03-6.10 [1H, m, C(7)H], 6.16-6.25 [2H, m, C(4)H, C(5)H]. $\delta_{\text{C}}\{^1\text{H}\}$ (75.5 MHz) 15.5 [CH₃, C(8a)CH₃], 29.3, 30.9 [$2 \times \text{CH}_3$, C(3)(CH₃)₂], 38.9 [C, C(3a)], 48.7 [C, C(8a)], 51.2 [CH₂, C(2)H₂], 111.0 [CH, d, $^2J_{\text{CF}}$ 28, C(5)H or C(7)H], 115.5-116.0 (weak) [CH, m, C(8)H], 116.1 [CH, $^3J_{\text{CF}}$ 11, C(4)H], 117.6 [CH, d, $^2J_{\text{CF}}$ 34, C(5)H or C(7)H], 135.3 (weak) [C, C(3a)], 159.7 [C, d, $^1J_{\text{CF}}$ 242, C(6)], 217.7 [C, C(1)]; HRMS (ESI-TOF) m/z : [(M+H)]⁺ Calcd for C₁₃H₁₆FO 207.1185; Found 207.1182. m/z (ESI+) 207 [(M+H)⁺, 100%], 203 (12%), 109 (4%).

*3,8a-Dihydro-3,3,5,6,7,8a-hexamethylazulen-1(2H)-one (26)*³⁰

(a) Batch conditions

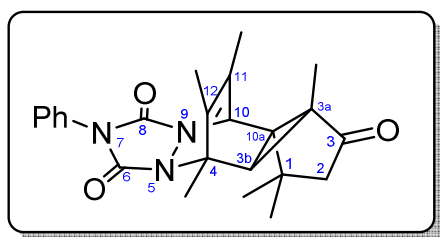


Doubly distilled dichloromethane (50 mL) and $\text{Rh}_2(\text{OAc})_4$ (0.5 mg, 1 mol%) were added to a flame-dried 250 mL three neck round bottom flask. A solution of diazoketone **4** (0.202 g, 0.770 mmol) in doubly distilled dichloromethane (50 mL) was added over 20 min to this solution at room temperature under N₂. The reaction was monitored by IR until the diazo peak was no longer visible. The reaction was concentrated under reduced pressure affording the crude *azulenone*. The spectral details were consistent with those described below.

(b) Continuous flow method

A solution (0.056 M) of diazoketone **4** (0.360 g, 1.40 mmol) in doubly distilled dichloromethane (25 mL) was prepared. An Omnifit[®] glass column (150 mm, 6.6 mm internal diameter) was packed with immobilized catalyst **20** (0.493 g, 10 mol%) along with glass wool. The solution of **10** (12 mL) was pumped at 0.75 mL/min through the polymer contained within the column, which was maintained at room temperature. The reaction stream passed through a tube (32 cm) and back pressure regulator (8 bar) before it was collected. The solvent was removed using the rotary evaporator giving the crude *azulenone* **26** as a yellow solution. Tetrahydrofuran was pumped through the column after the reaction stream in order to recover the polymer, removing the brown discolouration and returning its original green colour. ¹H NMR signals and IR bands corresponding to the literature values were observed for the crude *azulenone*. $\nu_{\max}/\text{cm}^{-1}$ (film) 2958-2866, 1710 s (CO), 1571; δ_{H} (300 MHz) 0.56 [3H, s, C(8a)CH₃], 1.02, 1.19 [2 × 3H, 2 × s, C(3)(CH₃)₂], 1.85 [1H, A of ABq, J_{AB} 17.2, one of C(2)H₂], 1.86, 1.89 {2 × 3H, 2 × s, C(6)CH₃ and one of [C(5)CH₃, C(7)CH₃]}, 1.96 {3H, d, J 1.0, one of [C(5)CH₃, C(7)CH₃]}, 2.08 [1H, B of ABq, J_{AB} 17.3, one of C(2)H₂], 2.47 [1H, s, C(8)H], 5.81 [1H, br s, C(4)H].

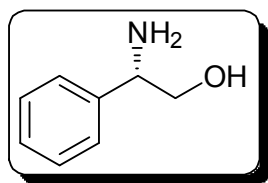
1,2,3b,4-Tetrahydro-1,1,3a,4,11,12-hexamethyl-7-phenyl-4,10-etheno-6H,10H-cyclopenta[1,3]cyclopropa[1,2-d][1,2,4]triazolo[1,2-a]pyridazine-3,6,8(3aH,7H)-trione (27)



Doubly distilled dichloromethane (50 mL) and Rh₂(OAc)₄ (0.5 mg, 1 mol%) were added to a flame dried 250 mL three neck round bottom flask under N₂. A solution of diazoketone **4** (0.202 g, 0.770 mmol) in doubly distilled dichloromethane (50 mL) was added over 20 min to the solution at room temperature. The progress of the reaction was monitored by IR until the diazo peak was no longer visible. The reaction mixture was then cooled to 0 °C and sublimed 4-phenyl-1,2,4-triazoline-3,5-dione (0.130 g, 0.740 mmol) [freshly prepared from *t*-butyl hypochlorite (0.080 g, 0.727 mmol), 4-phenyl urazole (0.130 g, 0.733 mmol) in acetone (10 mL)]⁵⁰ was added as a solid in one portion. The reaction mixture was stirred at 0 °C for 10 min after which the ice bath was removed and the reaction mixture was warmed to room temperature. The reaction mixture turned from the brick-red colour of the dienophile to a clear solution within minutes of the addition, indicating completion of the reaction. It was stirred for a further 30 min before concentration of the reaction mixture under reduced pressure gave the crude *adduct* as an off-white solid. Purification by flash chromatography with hexane:ethyl acetate (97:3) as eluent afforded the *adduct* **27** as a white solid. m.p. 176-

178°C; Anal. Calcd for C₂₄H₂₇N₃O₃: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.63; H, 7.17; N, 9.85. $\nu_{\max}/\text{cm}^{-1}$ (ATR) 2966, 2927, 1757, 1727, 1699, 1504, 1396; δ_{H} (300 MHz) 1.12 [3H, s, C(3a)CH₃] 1.24, 1.30 [2 x 3H, 2 x s, C(1)(CH₃)₂], 1.69 [1H, s, C(3b)H], 1.75 [3H, d, *J* 1.1, C(4)CH₃], 1.84 [3H, d, *J* 1.1, C(11)CH₃], 1.95 [1H, A of AB, *J* 17.8, one of C(2)H₂], 2.02 [3H, s, C(12)CH₃], 2.13 [1H, B of AB, *J* 17.9, one of C(2)H₂], 5.13 [1H, s, C(10)H], 7.31-7.47 [5H, m, ArH]. $\delta_{\text{C}}\{^1\text{H}\}$ (100.6 MHz) 7.6 [CH₃, C(3a)CH₃], 13.3, 16.8 [2 x CH₃, C(4)CH₃, C(11)CH₃], 21.1 [CH₃, C(12)CH₃], 23.9, 27.1 [2 x CH₃, C(1)(CH₃)₂], 34.5 [CH, C(3b)H], 36.4, 41.0, 43.5 [3 x C, C(1), C(3a), C(10a)], 48.5 [CH₂, C(2)H₂], 57.3 [CH, C(10)H], 66.2 [C, C(4)], 125.4, 128.1, 129.0 [3 x CH, Aromatic CH], 129.6 [C, Aromatic C], 130.7, 131.5 [2 x C, C(11), C(12)], 155.4, 156.1 [2 x C, C(6), C(9)], 211.7 [C, C(3)]; HRMS (ESI-TOF) *m/z*: [(M+H)]⁺ Calcd for C₂₄H₂₈N₃O₃ 406.2131; Found 406.2147. *m/z* (ESI+) 406 [(M+H)+, 100%], 229 (30%), 105 (30%).

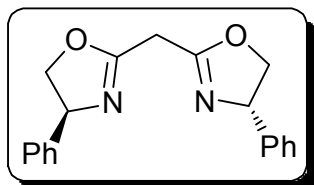
(*S*)-Phenylglycinol (**15**)³³



Lithium aluminium hydride (7.00 g, 184 mmol) was added to a flame-dried 250 mL three neck round bottom flask which was charged with anhydrous tetrahydrofuran (THF) (120 mL) while under N₂. The round bottom flask was then placed in an ice bath and (*S*)-phenylglycine (6.20 g, 41.0 mmol) was added while stirring, along with further anhydrous tetrahydrofuran (60 mL). The mixture was heated to reflux for 48 h. The reaction was allowed to cool to room temperature and before cooling to 0°C in an ice bath. Water (12 mL) was added to the reaction *very* slowly through an addition funnel while stirring vigorously. Aqueous NaOH (10%, 12 mL) was then added to the reaction mixture dropwise through the addition funnel followed by a further portion of water (15 mL). The reaction mixture was stirred at room temperature until a yellow suspension formed. The reaction solution was collected from the suspension by suction filtration, concentrated under reduced pressure to remove THF and extracted with dichloromethane (3 x 50 mL). The organic layers were collected and washed with brine and concentrated under reduced pressure to afford the *amino alcohol* **15** as a yellow crystalline solid (5.01 g, 89%). $\nu_{\max}/\text{cm}^{-1}$ (ATR) 3349-2400 (OH), 1954, 1882, 1813, 1602, 1494, 1453; δ_{H} (400 MHz) 2.30 [3H, br s, NH₂, OH], 3.55 [1H, dd, A of ABX, *J*_{AB} 10.8, *J*_{AX} 8.4, one of C(1)H₂], 3.73 [1H, dd, B of ABX, *J*_{AB} 10.8, *J*_{BX} 4.3, one of C(1)H₂], 4.04 [1H, dd, X of ABX, *J*_{AX} 8.3, *J*_{BX} 4.3, C(2)H], 7.24-7.38 (5H, m, ArH).

$\delta_{\text{C}}\{^1\text{H}\}$ (100.6 MHz) 57.4 [CH, CHNH₂], 68.0 [CH₂, CH₂OH], 126.5, 127.5, 128.6 [C, 3 x Aromatic CH], 142.6 [C, Aromatic C].

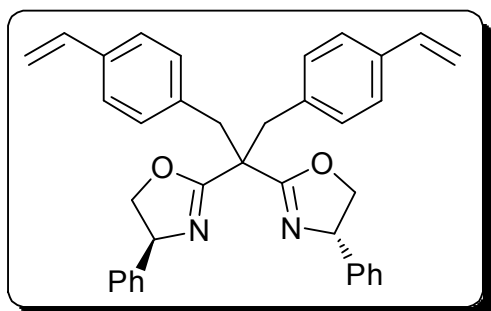
2,2'-Methylenebis[(4S)-4-phenyl-2-oxazoline] (**16**)³⁵



(*S*)-Phenylglycinol **15** (2.50 g, 18.0 mmol) was added to a flame dried two neck round bottom flask with dichloromethane (50 mL). Diethyl malonoimide dihydrochloride (2.11 g, 9.00 mmol) was added to the flask and the solution was stirred at

room temperature under N₂ for 72 h. Water (15 mL) was added to the solution which was washed with dichloromethane (3 x 50 mL). The organic layers were collected and were concentrated under reduced pressure affording a crude product. The crude product was purified by flash chromatography on neutral alumina, which was freshly deactivated prior to use with ammonium hydroxide, with 50:50 hexane:ethyl acetate as eluent. The *bis*(oxazoline) **16** was collected as a brown oil (1.40 g, 50%) and used without further purification. δ_{H} (400 MHz) 3.58 [2H, s, CH₂(C=N)₂], 4.17-4.21 [2H, overlapping dd, apparent t, A of ABX, *J* 8.2, 2 x one of OCH₂], 4.68-4.72 [2H, dd, B of ABX, *J*_{BX} 10.2, *J*_{AB} 8.4, 2 x one of OCH₂], 5.24-5.29 [2H, overlapping dd, apparent t, X of ABX, *J* 9.0, 2 x C=NCH], 7.25-7.35 [10H, m, Ar *H*]. $\delta_{\text{C}}\{^1\text{H}\}$ (100.6 MHz) 28.4 [CH₂, CH₂(C=N)₂], 69.7 [CH, 2 x C=NCH], 75.4 [CH₂, 2 x OCH₂CH], 126.7, 127.6, 128.7 [CH, 6 x Aromatic CH] 142.1 [C, 2 x Aromatic C], 163.1 [C, 2 x C=N].

2,2'-[2-(4-Vinylphenyl)-1-(4-vinylbenzyl)ethylidene]bis[(4S)-4-phenyl-4,5-dihydro-2-oxazole] (**17**)^{36,37}

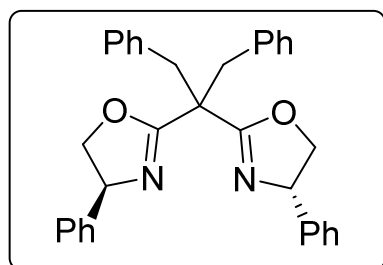


A solution of 2,2'-methylenebis[(*4S*)-4-phenyl-2-oxazoline] **16** (2.21 g, 7.20 mmol) in tetrahydrofuran (10 mL) was added slowly to stirring sodium hydride (60% dispersion) (2.02 g, 50.4 mmol) in tetrahydrofuran (10 mL). This mixture was stirred for 1 h under N₂. A solution of 4-chloromethylstyrene (4.08 mL, 28.9 mmol) in

tetrahydrofuran (5 mL) was transferred to an addition funnel and added slowly to the stirring solution. This mixture was stirred under N₂ at room temperature for 24 h, then the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (50 mL). The

aqueous layer was washed with dichloromethane (2 x 20 mL) and the combined organic layers were dried, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography, with hexane:ethyl acetate (80:20) as eluent, giving the desired product **17** as a yellow oil (2.64 g, 68%). $[\alpha]_D^{20}$ -106.54 [*c* 0.764, CHCl₃]; δ_H (400 MHz) 3.51 [4H, ABq, J_{AB} 14.1, H_A δ = 3.53, H_B δ = 3.49, 2 x CH₂C(C=N)₂], 4.01 [2H, overlapping dd, apparent t, A of ABX, J 8.6, 2 x one of OCH₂], 4.64 [2H, dd, B of ABX, J_{BX} 8.5, J_{AB} 10.2, 2 x one of OCH₂], 5.12 [2H, overlapping dd, apparent t, X of ABX, J 9.6, 2 x C=NCH], 5.25 [2H, d, J_{cis} 11.1, 2 x one of C=CH₂], 5.75 [2H, d, J_{trans} 17.5, 2 x one of C=CH₂], 6.70 [2H, dd, J_{cis} 10.9, J_{trans} 17.6, 2 x CH=CH₂], 6.90-6.96 [4H, m, Ar *H*], 7.18-7.27 [6H, m, Ar *H*], 7.31-7.37 [8H, m, Ar *H*]. $\delta_C\{^1H\}$ (100.6 MHz) 39.0 [CH₂, 2 x CH₂C(C=N)₂], 48.0 [C, C(CH₂)₂], 69.7 [CH, 2 x C=NCH], 75.1 [CH₂, 2 x OCH₂CH], 113.7 [CH₂, 2 x C=CH₂], 126.2, 126.9, 127.5, 128.6, 130.9 [CH, 18 x Aromatic CH], 136.3, 136.5 [C, 4 x Aromatic C], 136.6 [CH, 2 x CH=CH₂], 141.8 [C, 2 x Aromatic C], 167.7 [C, 2 x C=N].

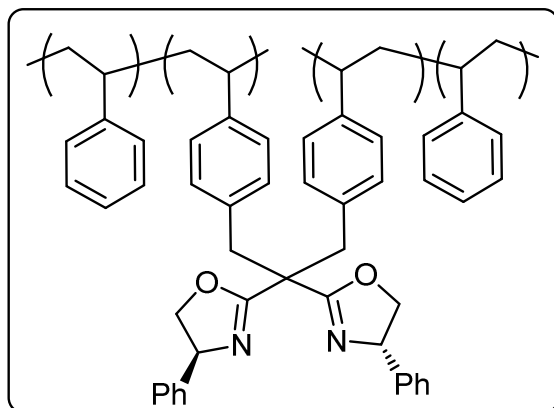
2,2'-(1-Benzyl-2-phenylethylidene)bis[(4*S*)-4-phenyl-4,5-dihydro-2-oxazole] (**21**)^{36,37}



This compound was prepared, using the procedure outlined for **17**, from 2,2'-methylenebis[(4*S*)-4-phenyl-2-oxazoline] **16** (1.01 g, 3.26 mmol), sodium hydride (60% dispersion) (0.91 g, 22.9 mmol) and benzyl chloride (1.65, 13.4 mmol). The crude product was purified by flash chromatography, with hexane:ethyl acetate (80:20) as eluent, giving **21** as a

yellow oil (2.64 g, 68%). $[\alpha]_D^{20}$ -102.87 [*c* 0.748, CHCl₃]; δ_H (400 MHz) 3.51 [4H, ABq, J_{AB} 14.1, H_A δ = 3.53, H_B δ = 3.49, 2 x CH₂C(C=N)₂], 4.02 [2H, overlapping dd, apparent t, A of ABX, J 8.6, 2 x one of OCH₂], 4.62 [2H, dd, B of ABX, J_{BX} 8.5, J_{AB} 10.2, 2 x one of OCH₂], 5.12 [2H, overlapping dd, apparent t, X of ABX, J 9.5, 2 x C=NCH], 6.98-7.13 [4H, m, Ar *H*], 7.13-7.40 [16H, m, Ar *H*]. $\delta_C\{^1H\}$ (100.6 MHz) 39.3 [CH₂, CH₂C(C=N)₂], 48.8 [C, C(CH₂)₂], 69.7 [CH, 2 x C=NCH], 75.0 [CH₂, 2 x OCH₂CH], 126.9, 127.5, 128.3, 128.6, 130.7 [CH, 20 x Aromatic CH, 5 signals seen for 6 carbons], 136.8, 141.9 [C, 4 x Aromatic C], 167.9 [C, 2 x C=NCH].

2,2'-[2-(4-Vinylphenyl)-1-(4-vinylbenzyl)ethylidene]bis[(4*S*)-4-phenyl-4,5-dihydro-2-oxazole] polymer (**18**)³⁷



2,2'-[2-(4-Vinylphenyl)-1-(4-vinylbenzyl)-ethylidene]bis[(4*S*)-4-phenyl-4,5-dihydro-2-oxazole] **17** (1.80 g, 3.34 mmol), styrene (3.45 mL, 30.0 mmol), 1-dodecanol (6.16 g, 33.1 mmol), toluene (1.24 g) and azobisisobutyronitrile (AIBN) (0.123 g, 0.750 mmol) were added to a microwave vial. The vial was placed in an oil bath and stirred under N₂

for 48 h at 100°C. A white solid product was removed from the vial with tetrahydrofuran and crushed with a mortar and pestle. The crushed solid was then washed with a further quantity of tetrahydrofuran (20 mL) and collected by suction filtration. Anal. Calcd for (C₁₀₉H₁₀₄N₂O₂)_n: C, 86.68; H, 7.25; N, 1.9. Found: C, 86.70; H, 8.51; N, 0.45. Empirical formula calculated on the basis of the relative ratios of the ligand and the styrene precursor.

Preparation of insoluble polymer bound copper–bis(oxazoline) catalyst **19**

Copper(II) triflate (0.300 g, 0.83 mmol, 1.2 equivalent) was added to a suspension of 2,2'-[2-(4-vinylphenyl)-1-(4-vinylbenzyl)ethylidene]bis[(4*S*)-4-phenyl-4,5-dihydro-2-oxazole polymer **18** (3.994 g, 1.4 mmol of nitrogen determined by elemental analysis) stirring in methanol. The mixture was stirred at room temperature for 24 h. The green solid was collected by suction filtration and dried *in vacuo*. The copper content of **19** (0.09 mmol/g) was determined by atomic absorption spectroscopy.

Preparation of insoluble polymer bound copper bis(oxazoline) catalyst **20**

[Cu(MeCN)₄]PF₆ (0.160 g, 0.43 mmol, 1 equivalent) was added to a suspension of 2,2'-[2-(4-vinylphenyl)-1-(4-vinylbenzyl)ethylidene]bis[(4*S*)-4-phenyl-4,5-dihydro-2-oxazole polymer **18** (2.405 g, 0.86 mmol of nitrogen determined by elemental analysis) stirring in methanol. The mixture was stirred at room temperature for 24 h. The green solid was collected by suction filtration and dried *in vacuo*. The copper content of **20** (0.24 mmol/g) was determined by atomic absorption spectroscopy.

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Notes

The authors declare no competing financial interest.

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Supporting Information Available

Experimental details for the flow platform; copies of chiral stationary phase HPLC chromatograms; details for ^1H NMR determination of enantiopurity of azulenones **23**, **24** and **25**; copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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