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Desymmetrization by Asymmetric Copper-Catalyzed Intramolecular C–H Insertion Reactions of α-Diazo-β-oxosulfones

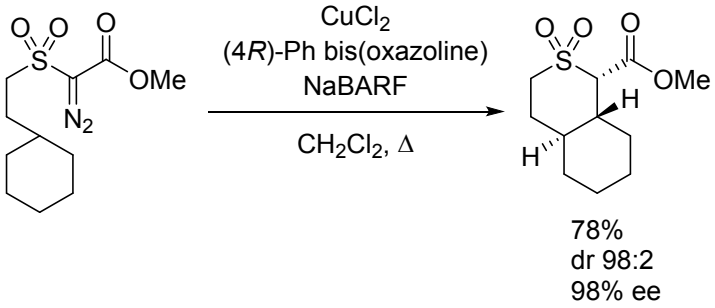
Thomas A. Brouder,[†] Catherine N. Slattery,[†] Alan Ford,[†] U. B. Rao Khandavilli,[†] Eliška Shořepová,[†] Kevin S. Eccles,[†] Matteo Lusi,[‡] Simon E. Lawrence,[†] and Anita R. Maguire*[,§]

[†]School of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Cork T12 K8AF, Ireland

[‡]Department of Chemical & Environmental Sciences, University of Limerick, Limerick V94 T9PX, Ireland

[§]School of Chemistry and School of Pharmacy, Analytical and Biological Chemistry Research Facility, Synthesis and Solid State Pharmaceutical Centre, University College Cork, Cork T12 K8AF, Ireland

Abstract



Effective desymmetrization in copper catalyzed intramolecular C–H insertion reactions of α-diazo-β-oxosulfones in the formation of fused thiopyran dioxides is described for the first time. The use of a copper–bis(oxazoline)–NaBARF catalyst complex system leads to formation of the major thiopyran dioxide stereoisomer with up to 98:2 dr and up to 98% ee. The effect of varying the bis(oxazoline) ligand, copper salt, and site of C–H insertion on both diastereo- and enantioselectivities of these intramolecular C–H insertion reactions has been investigated. Similarly, desymmetrization in the formation of a fused cyclopentanone proceeds with up to 64% ee. These results represent the highest enantioselectivity reported to date in a copper mediated desymmetrization through C–H insertion.

Introduction

Transition metal mediated C–H insertion reactions of α-diazocarbonyl compounds are versatile transformations in organic synthesis, allowing formation of a variety of heterocycles and carbocycles.[1-4] The utilization of intramolecular catalytic asymmetric C–H insertion has facilitated the formation of new C–C bonds with high diastereoselectivity and enantioselectivity.[5] While formation of five-membered rings is the most common outcome, in some instances electronic and/or conformational effects can promote the formation of other

ring sizes. Acceptor-acceptor α-diazo compounds have been the most widely explored precursors to exploit these transformations, as the highly selective electrophilic metal carbenoid generated in-situ is well-suited to intramolecular C–H insertion.

Early studies of intermolecular reactions using terminal diazocarbonyl compounds and copper(I) chloride as a catalyst showed poor efficiency for C–H insertion and a high percentage of dimerization.[6] Teyssié's pioneering work highlighted that rhodium mediated C–H insertion could be synthetically useful,[7] as evidenced by Wenkert in forming a cyclopentanone in good yield from an α-diazoketone using rhodium acetate.[8] In the subsequent decade Taber explored this methodology extensively as a general synthetic route to cyclopentanones.[9-11] Since the first rhodium catalyzed enantioselective intramolecular C–H insertion was reported by McKervey,[12] significant developments were made by Doyle[13-16] and Hashimoto[17-19] in the intramolecular asymmetric synthesis of heterocycles and carbocycles using diverse rhodium carboxylate and carboxamidate catalysts with excellent enantiocontrol in many instances, through judicious selection of catalyst/substrate pairs. Rhodium mediated C–H insertion has been used to advantage in the total synthesis of compounds such as enterolactone,[20] baclofen,[21] and imperanene.[22]

Building on the identification of effective rhodium carboxylates and carboxamidates for enantioselective C–H insertion, the groups of Doyle,[23-27] Hashimoto,[28] and Kan[29] have demonstrated desymmetrization through selective insertion processes in prochiral or meso systems; some examples are illustrated in Figure 1 (a) and (b). Doyle and co-workers showed the use of the carboxamidate Rh_2(4*S*-MACIM)$_4$ to form the cis fused bicyclic lactone (**2**) with an enantiomeric excess of 97% ee, in 99:1 ratio over the trans fused isomer (**3**) which was formed with 65% ee. Using a rhodium carboxylate catalyst, Hashimoto and co-workers synthesized a cis fused 5 membered carbocycle (**5**) in 82% yield and 99% ee, by treating the α-diazoester (**4**) with Rh_2(*S*-PTTL)$_4$ in toluene at −78 °C. One of the earliest reported examples of copper mediated intramolecular C–H insertion involved a desymmetrization, where a Cu(OTf)–bis(oxazoline) catalyst system resulted in poor diastereocontrol, but modest enantiocontrol, as reported by Sulikowski and co-workers (Figure 1 (c)).[30-31] More recently, Chiu reported up to 44% ee in a copper mediated desymmetrization in the formation of a cis fused bicyclic cyclopentanone **10** (Figure 1 (d)).[32] To date we are not aware of any reported example of highly enantioselective copper catalyzed desymmetrization through C–H insertion.

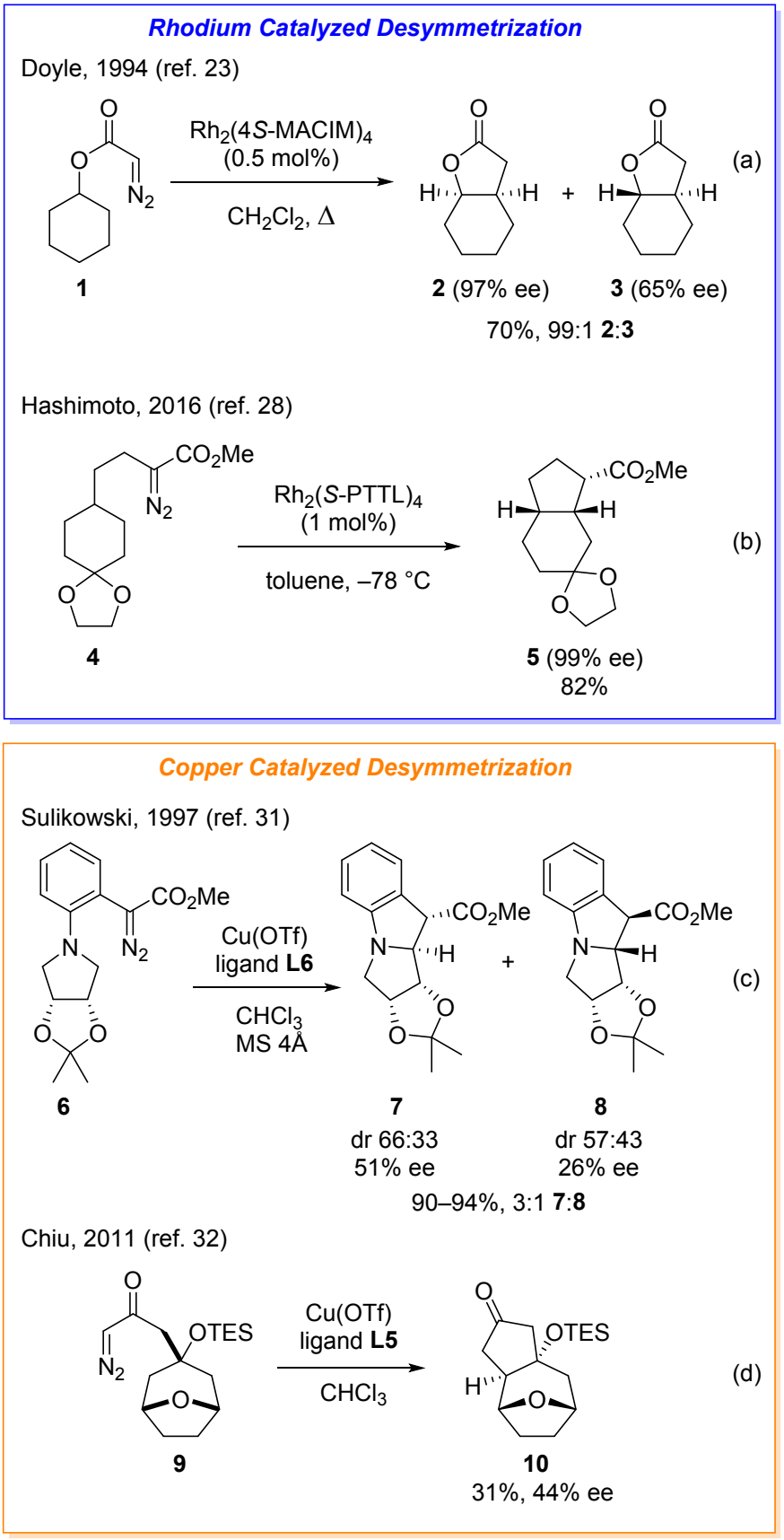


Figure 1: Rhodium and copper catalyzed desymmetrization of α-diazocarbonyl compounds

In recent years, Du Bois[33-36] and Novikov[37-39] have demonstrated that through the incorporation of a sulfone moiety into the framework, 6-membered rings including thiopyran dioxides (hereafter reported as thiopyrans for convenience), δ-sultones or oxathiazinanes are formed preferentially due to the geometry surrounding the sulfone fragment.

Within our group, excellent enantioselectivity in the intramolecular C–H insertion process has been achieved in sulfone containing substrates when utilizing the copper–bis(oxazoline)–NaBARF catalyst system (Figure 2 (a–c)). Thiopyrans (**11**), cyclopentanones (**12**) and γ-lactams (**13**) have been synthesized with enantioselectivities of up to 98% ee,[40] 91% ee,[41] and 82% ee,[42] respectively. The additive, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl)]borate, NaBARF, has been shown to be essential for inducing high levels of enantiocontrol. Investigation of the role of the additive suggest that it functions by supplying a sodium cation which sequesters the chloride anion to form the active catalyst. Fraile has conducted theoretical calculations on copper-catalyzed cyclopropanation, highlighting the influence of the coordinating chloride counter-anion on the transition state geometry and the effect of this on enantiocontrol.[43]

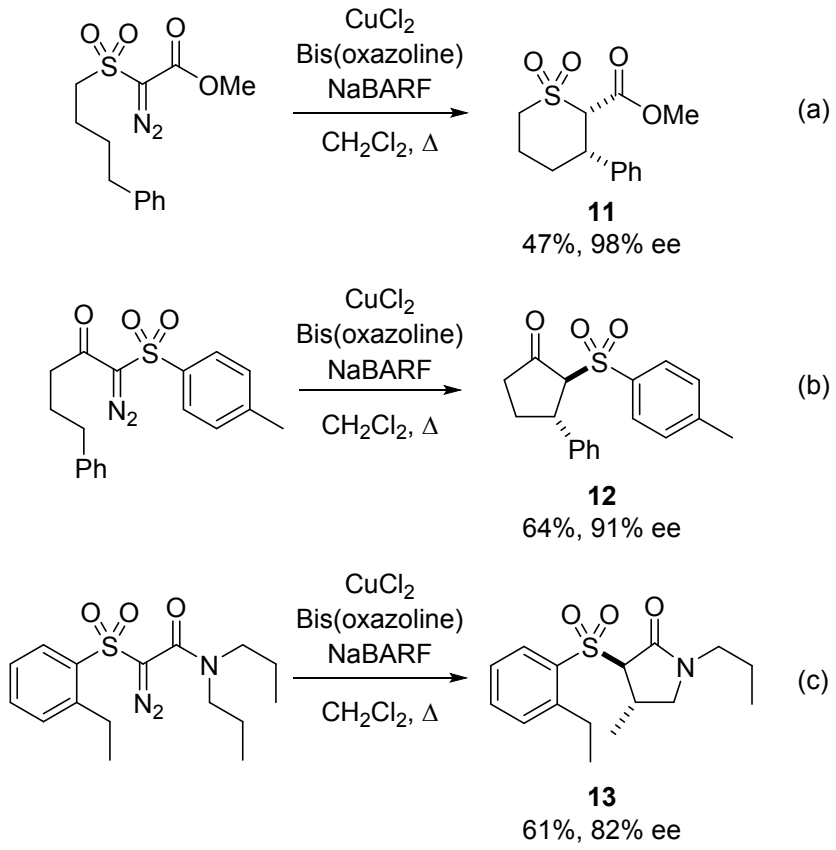


Figure 2: Highly enantioselective intramolecular C–H insertion using the copper–bis(oxazoline)–NaBARF catalyst system

Herein we report the extension of the copper–bis(oxazoline)–NaBARF catalyst system to highly enantioselective desymmetrization of prochiral α-diazo-β-oxosulfones, leading to the formation of fused thiopyrans, and cyclopentanones. Previously reported examples of successful desymmetrization through C–H insertion have focused exclusively on five membered ring formation and, to the best of our knowledge, this is the first report of desymmetrization in the formation of a six membered heterocycle.

Results and Discussion

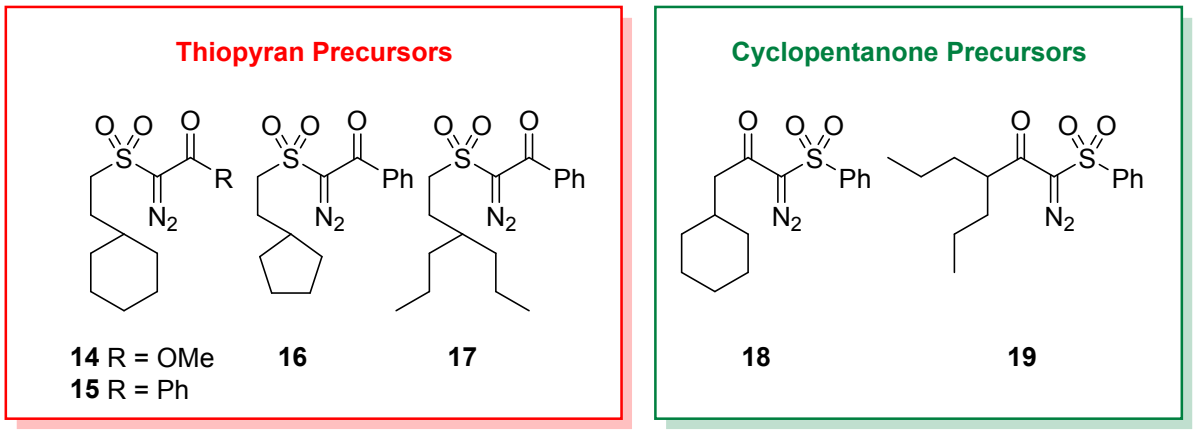


Figure 3: α-Diazo-β-oxosulfones designed for desymmetrization investigation

Six novel α-diazo-β-oxosulfones (**14–19**) (Figure 3) were designed for this investigation to enable exploration of the impact of conformational effects (insertion into a cyclohexyl, cyclopentyl or freely rotating alkyl chain), electronic effects (α-diazoester or α-diazoketone), catalyst effects through various bis(oxazoline) ligands (Figure 4), in addition to variation of the copper source. Substrates **14–17** enable investigation of desymmetrization in the formation of thiopyrans while **18** & **19** enable a similar investigation in the formation of cyclopentanones.

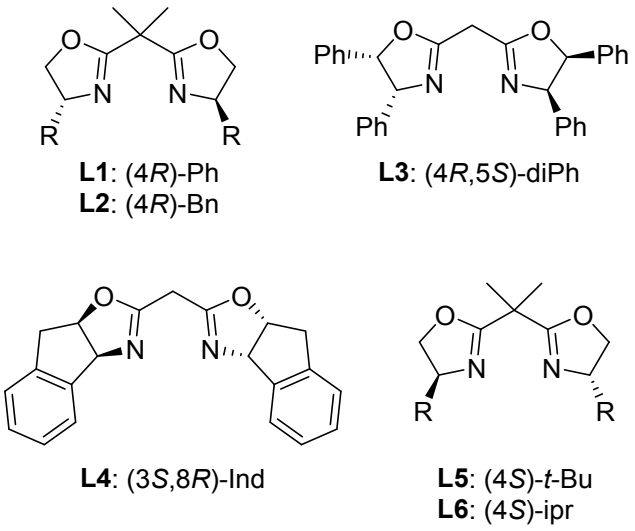
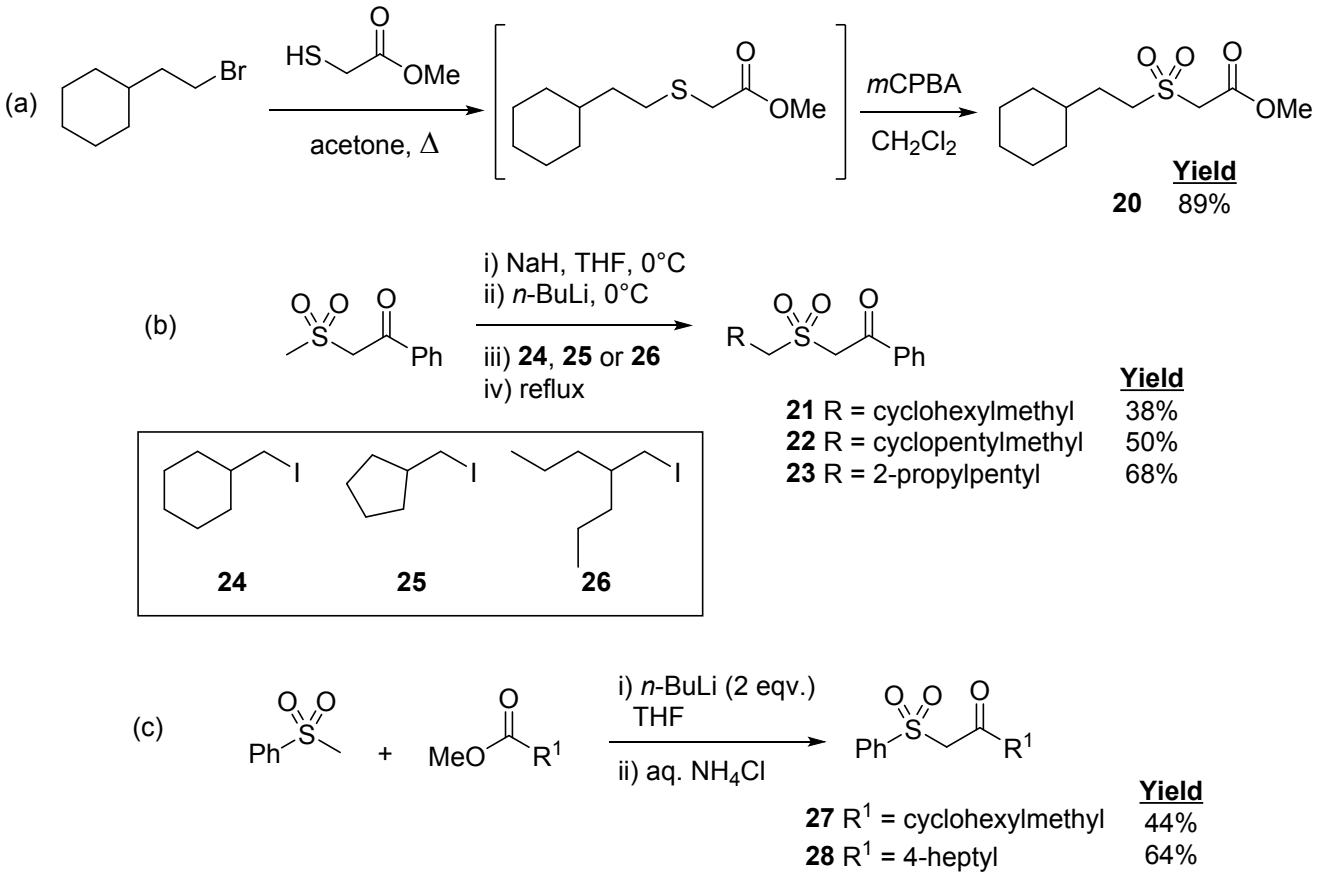


Figure 4: Commercially available bis(oxazoline) ligands

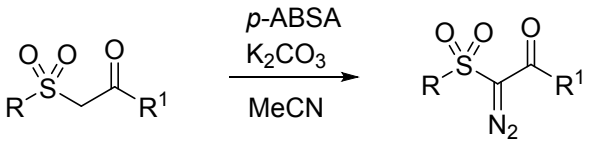
Scheme 1: Synthesis of β-oxosulfones **20**–**23**, **27** & **28**



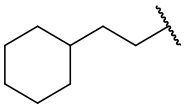
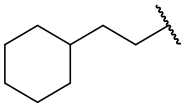
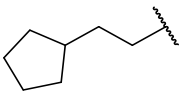
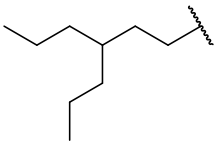
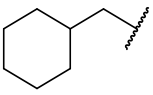
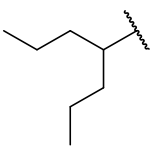
The novel sulfonyl ester **20**, outlined in Scheme 1 (a), was readily accessed through alkylation of methyl thioglycolate with (2-bromoethyl)cyclohexane followed by oxidation with *m*-CPBA (89% over two steps). The sulfonyl ketones **21**–**23** were prepared in modest yields through alkylation of the dianion of methylsulfonylacetophenone, generated using NaH and *n*-BuLi, with the appropriate alkyl iodide (**24**–**26**) in each instance, providing sufficient material for the

subsequent investigations without further optimization (Scheme 1, b). The sulfone precursors **27** & **28** were generated from dilithiated methyl phenyl sulfone by reaction with the appropriate ester in modest yields (Scheme 1, c). Following the purification and isolation of all six novel sulfone precursors, the α-diazo-β-oxosulfones **14**–**19** were readily prepared by diazo transfer to the corresponding α-sulfonyl ester or ketone using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) (or tosyl azide in the case of **19**) and K_2CO_3 in acetonitrile (Table 1). The α-diazo-β-oxosulfones **14**–**19** were isolated in good yields following column chromatography, and could be stored in the freezer without difficulty.

Table 1: Synthesis of α-diazo-β-oxosulfones (14–19)



20–**23**, **27**–**28** **14**–**19**

Entry	Sulfone	Diazo	R	R^1	Yield (%)[a]
1	**20**	**14**		OMe	79
2	**21**	**15**		Ph	75
3	**22**	**16**		Ph	71
4	**23**	**17**		Ph	84
5	**27**	**18**	Ph		80
6[b]	**28**	**19**	Ph		77

[a] Isolated yield after chromatography. [b] *p*-TsN_3 was the diazo transfer agent used in the synthesis of **19.**

Thiopyran formation

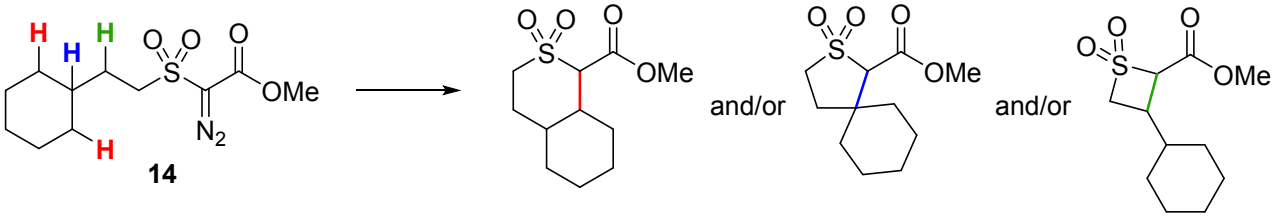
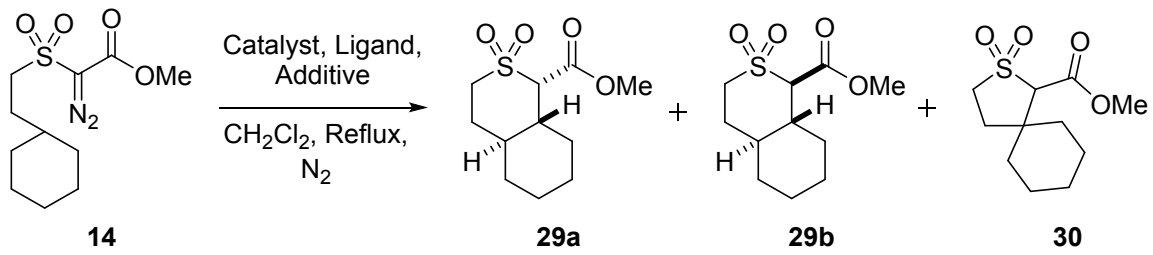


Figure 5: Possible reaction pathways with α-diazo-β-oxosulfone **14**

Initial catalyst investigations focused on the α-diazoester **14** which can undergo C–H insertion to form six-, five-, or four-membered ring products (Figure 5) along with by-products such as chlorine abstraction from the reaction solvent, diazo reduction and hydride abstraction. As a result of the two equivalent 2° positions on the cyclohexyl ring, four fused thiopyran diastereoisomers may be formed. In practise, however, only three products are observed; the ratio is determined by integration of the ^{1}H NMR spectra of the crude product. Rhodium acetate catalyzed C–H insertion of **14** proved to be very efficient, with **14** being consumed within 1 h under reflux in DCM. The trans fused, 1,8a trans substituted thiopyran **29b** was formed as the major product, while the trans fused, 1,8a cis substituted thiopyran **29a** and sulfolane **30** were observed as minor products (Table 2, entry 1). On utilizing copper triflate or copper chloride, C–H insertion proved much slower for **14** and while providing the same insertion products **29a**, **29b** and **30,** the selectivity was strongly catalyst-dependent with substantially increased formation of thiopyran **29a** using $Cu(OTf)_2$, and sulfolane **30** when $CuCl_2$ was employed (Table 2, entry 2 & 3). Addition of NaBARF to the $CuCl_2$ catalyst led to improved selectivities and an improved yield of **29a** (Table 2, entry 4).

Significantly, use of the copper chloride (5 mol%), bis(oxazoline) (6 mol%), and NaBARF (6 mol%) catalyst system, led to faster reaction times and substantially enhanced selectivities, relative to any of the achiral copper catalysts, with up to 98:2 dr and yields of up to 82% for the major thiopyran **29a** and enantioselectivities of up to 98% ee with the (4*R*)-Ph bis(oxazoline) ligand **L1** (Table 2, entry 5–9). Interestingly, while the presence of the bis(oxazoline) ligand had an enormous impact on the outcome, variation of the ligand had little impact on the product ratios, and, while the enantioselectivity was ligand sensitive (85–98% ee), this variability was notably less in these transformations than in our earlier studies of insertions into freely rotating alkyl chains.[44] There was no evidence of formation of cis-fused thiopyran products.

Table 2: Transition metal catalyzed C–H insertion of α-diazo-β-oxosulfone 14



14 **29a** **29b** **30**

Entry	Catalyst	Ligand	Additive	Time (h)	29a : 29b : 30[a]	Yield[b] 29a (%)	Yield[b] 29b (%)	Yield[b,c] 30 (%)	29a ee[d] (%)
1	$Rh_2(OAc)_4$	-	-	1	1 : 10.0 : 0.90	1	57	0	0
2	$Cu(OTf)_2$	-	-	48	1 : 0.51 : 0.74	23	6	9	0
3	$CuCl_2$	-	-	144	1 : 0.44 : 1.20	31	7	19	0
4	$CuCl_2$	-	NaBARF	120	1 : 0.12 : 0.34	62	4	13	0
5[e]	$CuCl_2$	**L1**	NaBARF	16	1 : 0.02 : 0.09	73	1	4	98[f]
6	$CuCl_2$	**L2**	NaBARF	20	1 : 0.03 : 0.12	62	<1	1	85[f]
7	$CuCl_2$	**L3**	NaBARF	32	1 : 0.07 : 0.17	60	3	4	95[f]
8	$CuCl_2$	**L4**	NaBARF	30	1 : 0.04 : 0.13	82	<1	5	88[g]
9	$CuCl_2$	**L5**	NaBARF	20	1 : 0.04 : 0.12	57	<1	3	90[g]

[a] Ratios of products were calculated from ^{1}H NMR spectra of the crude product mixture. [b]Isolated yield after chromatography. [c]Difficult to isolate **30** pure due to co-elution with **29a**, reduction product, and hydride abstraction product. [d]The enantiomeric excess was measured by chiral phase HPLC analysis (for full details see the Supporting Information). [e]When the reaction was carried out on a 1 mmol scale, the reaction was complete after 8 hours and **29a** had an isolated yield of 78% in 98:2 dr and 98% ee. [f]The major enantiomer has a 1*S*,4a*S*,8a*R* configuration. [g]The major enantiomer has a 1*R*,4a*R*,8a*S* configuration.

The desymmetrization of α-diazoester **14** is very effective, providing the trans fused, 1,8a cis substituted thiopyran **29a** in excellent diastereo- and enantiocontrol in the copper mediated transformation. The single crystal X-ray structure of **29a** (product isolated from Table 2, entry 7) confirmed the stereochemistry of the product as 1*S*,4a*S*,8a*R* when the (4*R*,5*S*)-diPh ligand **L3** is used; this aligns exactly with the stereoselectivity observed in our original study of thiopyran formation, in which **L3** leads to the formation of the 2*S*,3*S* thiopyran.[40] The enantiomeric series was confirmed by chiral phase HPLC of the single crystal used for crystallographic determination.

In addition, the optimum enantioselectivity is achieved with the (4*R*)-Ph bis(oxazoline) ligand **L1** in line with our initial report, highlighting that the key ligand-substrate interactions which determine the stereochemical outcomes of the insertion are the same in the asymmetric insertion and the desymmetrization process. Preferential formation of **29a** with the copper catalysts and **29b** using rhodium acetate is consistent with our previous observations of formation of cis thiopyrans using copper catalysts,[40, 44] and the rhodium-catalyzed trans thiopyran formation reported by Novikov.[37, 39]

In order to probe reaction parameters, various solvents and copper salts were investigated with the best performing ligand **L1** as summarized in Table 3. Increasing the reaction temperature resulted in a slight decrease in regio- and diastereoselectivity (formation of **29b** and **30** slightly enhanced) albeit with no noticeable impact on enantioselectivity in the formation of **29a** (Table 3, entry 2 & 3). Alteration of the copper salt from $CuCl_2$ to $Cu(CH_3CN)_4PF_6$ or $Cu(OTf)_2$ resulted in decreased reaction times with no impact on regio- or stereoselectivity or yields of the major thiopyran **29a** which from a practical perspective is advantageous (Table 3, entry 4 & 5).

Table 3: Solvent and copper source effects on copper catalyzed C–H insertion reaction of α-diazo-β-oxosulfone 14

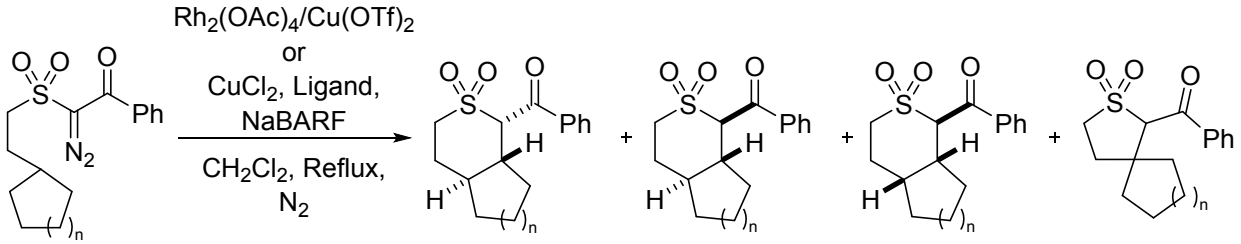
Entry	Catalyst[a]	Solvent	Time (h)	29a : 29b : 30[b]	Yield[c] 29a (%)	Yield[c] 29b (%)	Yield[c,d] 30 (%)	29a ee[e] (%)
1[f]	$CuCl_2$	DCM	16	1 : 0.02 : 0.08	73	1	4	98 [g]
2	$CuCl_2$	DCE	5	1 : 0.05 : 0.13	52	1	6	96 [g]
3	$CuCl_2$	$CHCl_3$	18	1 : 0.04 : 0.15	74	2	7	98 [g]
4	$Cu(CH_3CN)_4PF_6$	DCM	5	1 : 0.03 : 0.09	72	1	4	98 [g]
5	$Cu(OTf)_2$	DCM	4	1 : 0.04 : 0.10	73	<1	4	98 [g]

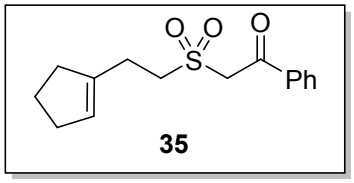
[a]All reactions were carried out using the (4*R*)-Ph ligand **L1** and NaBARF. [b]Ratios of products were calculated from ^{1}H NMR spectra of the crude product mixture. [c]Isolated yield after chromatography. [d]Difficult to isolate **30** pure due to co-elution with **29a**. [e]The enantiomeric excess was measured by chiral phase HPLC analysis (for full details see the Supporting Information). [f]Data from Table 2, Entry 5. [g]The major enantiomer is 1*S*,4a*S*,8a*R*.

Encouraged by the positive outcome in the formation of the trans fused, 1,8a cis substituted thiopyran **29a** in 73 % yield and 98% ee, the study was extended to the α-diazo-β-oxosulfones **15**–**17**. The results obtained with α-diazoketone **15** were compared to those using the α-diazoester **14**, enabling insight into electronic effects with regards to desymmetrization.

As observed with the α-diazoester **14**, when substrate **15** was cyclized with rhodium acetate in dichloromethane, preferential formation of the trans fused, 1,8a trans substituted product was observed, and **31b** was isolated with a comparable 56% yield (Table 4, entry 1). Again, when changing from the rhodium catalyst to a copper catalyst system, a switch to the trans fused, 1,8a cis substituted diastereomer was observed (Table 4). The use of $Cu(OTf)_2$ on its own as a catalyst showed poor selectivity, as observed previously with **14**, and once again the copper–bis(oxazoline)–NaBARF catalyst complex led to high efficiency and selectivity, in fact, higher isolated yields were obtained for **31a** (70–94%) compared to those seen for **29a** (57–82%). Most importantly, when comparing the selectivity of the α-diazoester **14** and the α-diazoketone **15**, the levels of regioselectivity and diastereoselectivity remain relatively unchanged for the formation of the fused thiopyran system highlighting its insensitivity towards alteration from ester to ketone functionality. A slight decrease in enantioselectivity is observed across the series when changing from the methyl ester to the phenyl ketone substrate; the best performing ligand, the (4*R*)-Ph **L1**, recorded 94% ee with the same absolute stereochemistry seen with **29a**, however the use of (4*R*)-Bn **L2** and (3*S*,8*R*)-Ind **L4** resulted in reduced enantioselectivity, affording 78% and 70% ee respectively (Table 4, entry 3–7). Notably, the (4*S*)-*t*-Bu ligand **L5** produced **31a** in 91% ee and 98:2 dr in an isolated yield of 94%. The absolute stereochemistry of **31a**, was confirmed by single crystal X-ray analysis of the isolated product from the reaction using the (4*R*)-Ph ligand **L1** (Table 4, entry 3). The minor amounts of **31b** isolated after column chromatograph showed an enantiomeric excess ranging from 64% to 75% ee, with the 3*S*,8*R*-Ind ligand **L4** producing the highest level of enantioselectivity (Table 4, entry 6).

Table 4: Transition metal catalyzed C–H insertion of α-diazo-β-oxosulfone 15 and 16





Diazo	Entry	Ligand	Time (h)	31a : 31b : 31c : 32[a]	Yield[b] 31a (%)	Yield[b] 31b (%)	Yield[b] 31c (%)	Yield[b,c] 32 (%)	31a ee[d] (%)	31b ee[d] (%)
15	1	$Rh_2(OAc)_4$	24	1 : 7.14 : 0.00 : 0.14	4	56	0	2	0	0
	2	$Cu(OTf)_2$	17	1 : 0.52 : 0.00 : 0.20	16	13	0	1	0	0
	3	**L1**	17	1 : 0.03 : 0.00 : 0.06	87	1	0	3	94 [e]	64 [f]
	4	**L2**	29	1 : 0.07 : 0.00 : 0.16	70	1	0	8	78 [e]	68 [f]
	5	**L3**	18	1 : 0.03 : 0.00 : 0.04	85	<1	0	3	93 [e]	65 [f]
	6	**L4**	30	1 : 0.06 : 0.00 : 0.14	87	<1	0	6	70 [g]	75 [h]
	7	**L5**	27	1 : 0.02 : 0.00 : 0.05	94	<1	0	2	91 [g]	71 [h]
				33a : 33b : 33c : 34[a]	**Yield[b] 33a (%)**	**Yield[b] 33b (%)**	**Yield[b] 33c (%)**	**Yield[b,i] 34 (%)**	**33a ee[d,j] (%)**	**33c ee[d] (%)**
16	8[k]	$Rh_2(OAc)_4$	3	1 : 3.57 : 2.29 : 5.71	<1	10	8	13	-	0
	9[l]	$Cu(OTf)_2$	18	1 : 0.00 : 0.75 : 2.13[m]	0	0	0	3	-	-
	10	**L1**	20	1 : 0.03 : 0.42 : 1.74	23	0	12	46	94 [n]	83 [o]
	11	**L2**	19	1 : 0.06 : 0.35 : 2.81	20	0	6	52	74 [n]	34 [o]
	12	**L3**	20	1 : 0.03 : 0.24 : 1.12	34	<1	7	35	93 [n]	79 [o]
	13[p]	**L4**	55	1 : 0.07 : 0.27 : 1.64	11	<1	5	18	51 [q]	16 [r]
	14	**L5**	21	1 : 0.01 : 0.10 : 0.27	61	0	8	19	91 [q]	49 [r]

[a] Ratios of products were calculated from signals in the crude ^{1}H NMR spectra. [b]Isolated yield after chromatography. [c]Difficult to isolate **32** pure due to co-elution with **31a**, reduction product, and hydride abstraction product. [d]The enantiomeric excess was measured by chiral phase HPLC analysis (for full details see the Supporting Information). [e]The

major enantiomer is 1*S*,4a*S*,8a*R*. [f]Major enantiomer with unassigned configuration. Specific rotation of **31b** was positive. [g]The major enantiomer is 1*R*,4a*R*,8a*S*. [h]Major enantiomer with unassigned configuration. Specific rotation of **31b** was negative. [i]Difficult to isolate **34** pure due to co-elution with **33a**, reduction product, and hydride abstraction product. [j]Chiral phase HPLC conditions for **33a** developed from 14% yield of **33a** isolated from reaction using; $CuCl_2$ (10 mol%), NaBARF (12 mol%), (4*R*)-Ph bis(oxazoline) ligand **L1** (6 mol%) and (4*S*)-Ph bis(oxazoline) ligand (6 mol%) in DCM at reflux. [k]27% of the β-hydride by-product **35** was isolated. [l]Only trace amount of the thiopyrans **33a** and **33c**, and sulfolane **34** were observed in the ^{1}H NMR of the crude product mixture. The β-hydride by-product **35** was the major product and had an isolated yield of 21%. [m]Ratio calculated from the trace quantity observed in the crude products. [n]The major enantiomer is 1*S*,4a*S*,7a*R*. [o]Major enantiomer with unassigned configuration. Specific rotation of **33c** was negative. [p]5% of the β-hydride by-product **35** was isolated. [q]The major enantiomer is 1*R*,4a*R*,7a*S*. [r]Major enantiomer with unassigned configuration. Specific rotation of **33c** was positive.

In order to investigate conformational effects, the insertion into a cyclopentyl ring was examined, using the α-diazo-β-oxosulfone **16**. When employing the achiral catalysts, rhodium acetate and copper triflate, β-hydride abstraction product **35** was observed as the major product, in particular with $Cu(OTf)_2$ (Table 4, entry 8 & 9). After column chromatography of the crude product obtained from the $Cu(OTf)_2$ catalyzed reaction, no thiopyran **33** was isolated and only 3% sulfolane **34**. The use of the copper–bis(oxazoline)–NaBARF system led to a shift in regioselectivity, affording predominantly the sulfolane **34** due to insertion into the 3° C–H bond, and lesser amounts of the thiopyran **33**. The (4*R*)-Ph ligand **L1** which proved very selective and efficient with substrates **14** and **15** in the synthesis of the trans fused, 1,8a cis substituted thiopyran, showed greatly reduced selectivity, affording 23% yield for **33a** (Table 4, entry 10). It is worthy to note that the (4*S*)-*t*-Bu ligand **L5** showed significantly improved selectivity, with the highest isolated yield of 61% for **33a** while still retaining a 91% ee (Table 4, entry 14). The (4*S*)-*t*-Bu ligand **L5** appears as the most consistently selective bis(oxazoline) ligand across the α-diazo-β-oxosulfone substrates **14**–**16** in the formation of the trans fused, cis substituted thiopyran. The isolated product **33a** from the reaction using the (4*S*)-*t*-Bu ligand (Table 4, entry 14) was used to determine the absolute stereochemistry by single crystal X-ray analysis.

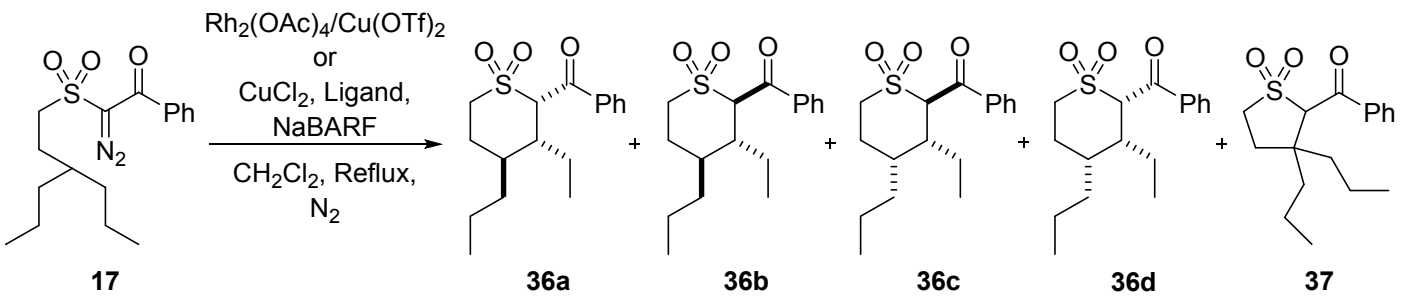
Interestingly, for the first time, the cis fused, 1,7a trans substituted thiopyran **33c** (relative stereochemistry confirmed by single crystal X-ray crystallography), was observed in the ^{1}H NMR of the crude product mixture and isolated in 12% yield, in addition to the 46% yield of the major sulfolane **34**, when using the (4*R*)-Ph ligand **L1** (Table 4, entry 10). While reduced levels of regio- and diastereoselectivity were observed, the enantiomeric excess of **33a** (94% ee) was comparable to that observed for the formation of **31a** (also 94% ee) using the (4*R*)-Ph ligand **L1**. Low diastereoselectivity was observed across the bis(oxazoline) ligand series for

16, with **33c** being isolated in all instances with varying levels of enantioselectivity ranging from 16% ee to 83% ee (Table 4, entry 10–14).

Until now, the study of copper catalyzed intramolecular desymmetrization of α-diazo-β-oxosulfones has focused on insertion into a 2° C–H bond restrained within a ring system, however in order to evaluate the importance of the ring system with regards to desymmetrization, the acyclic α-diazo-β-oxosulfones substrate **17** was designed for comparison. In contrast to insertion into a cyclic structure (**14**–**16**) which has given relatively consistent levels of desymmetrization, a greater level of variability in selectivity was observed for asymmetric intramolecular C–H insertion into the freely rotating alkyl chain of substrate **17** (Table 5). The achiral catalyst, rhodium acetate, preferentially formed the 6-membered thiopyran, **36**, after 4 hours (Table 5, entry 1). Due to increased conformational flexibility, the C–H insertion reaction of **17** leads to the formation of four diastereoisomers **36a**–**d**, and the regioisomer **37**, all observed in the crude product mixture, reflecting decreased levels of regio- and diastereocontrol in comparison to substrates **14**–**16**. The diastereoisomer **36b**, was isolated in 9% yield which indicates much lower selectivity in comparison to the major **29b** and **31b**, with the same relative stereochemistry, isolated when using rhodium acetate. Interestingly in this case, diastereoisomer **36a** was isolated in a higher yield (Table 5, entry 1).

The achiral copper triflate once more showed poor efficiency for C–H insertion with very low yields (Table 5, entry 2), however, a distinct improvement in isolated product yields was observed when the copper–bis(oxazoline)–NaBARF catalyst system was applied (Table 5, entry 3–7). Once again, the 6-membered thiopyran **36** was the predominant C–H insertion product formed, although significant amounts of the 5-membered sulfolane **37** were also evident in the crude product mixtures. Notably, the diastereocontrol in the C–H insertion of **17** to form **36a**–**d** differed from that of the earlier substrates, favoring the all cis isomer **36d** (23–29%) and affording less **36a**, in contrast to the dominance of **29a**, **31a**, **33a**.

Table 5: Transition metal catalyzed C–H insertion of α-diazo-β-oxosulfone 17



Entry	Ligand	Time (h)	36a : 36b : 36c : 36d : 37[a]	Yield[b] 36a % (ee %)[c]	Yield[b] 36b % (ee %)[c]	Yield[b] 36c % (ee %)[c]	Yield[b,d] 36d % (ee %)[c]	Yield[b,e] 37 % (ee %)[c]
1	$Rh_2(OAc)_4$	4	1 : 1.96 : 0.16 : 2.18 : 0.91	14 (0)	9 (0)	0 (-)	11 (0)	9 (0)
2	$Cu(OTf)_2$	20	1 : 0.89 : 0.29 : 1.86 : 2.17	4 (0)	3 (0)	0 (-)	0 (-)	8 (0)
3	**L1**	14	1 : 0.39 : 0.34 : 1.08 : 1.32	21 (90)[f]	7 (33)	0 (-)	29 (31)	27 (31)
4	**L2**	6	1 : 1.25 : 0.27 : 3.44 : 3.46	11 (69)[f]	11 (59)	0 (-)	29 (24)	30 (35)
5	**L3**	5	1 : 0.61 : 0.43 : 1.17 : 1.36	18 (87)[f]	9 (38)	0 (-)	26 (37)	23 (40)[g]
6	**L4**	18	1 : 0.72 : 0.23 : 2.27 : 1.13	16 (54)[h]	10 (33)	0 (-)	23 (19)	22 (31)
7	**L5**	62	1 : 0.57 : 0.60 : 2.15 : 1.94	10 (80)[h]	7 (37)	0 (-)	27 (~0)	21 (32)

[a]Ratios of products were calculated from signals in the crude ^{1}H NMR spectra. [b]Isolated yield after chromatography. [c]The enantiomeric excess was measured by chiral phase HPLC analysis (for full details see the Supporting Information). [d]Difficult to isolate **36d** pure due to co-elution with **37**, and reduction product. [e]Difficult to isolate **37** pure due to co-elution with **36d**, and reduction product. [f]The major enantiomer is 2*S*,3*R*,4*S*. [g]The sample of **37** was measured as 8% ee after storage in 2-propanol for six months at room temperature. [h]The major enantiomer is 2*R*,3*S*,4*R*.

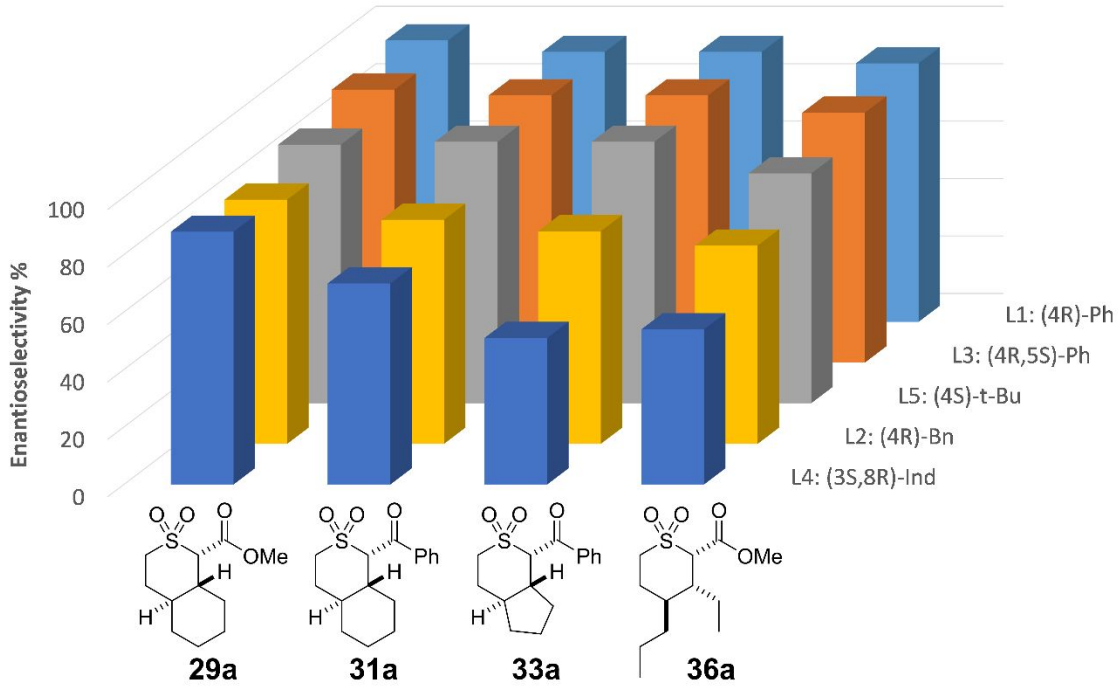
Interestingly, enantiocontrol remained high in the insertion to form **36a**, especially with the (4*R*)-Ph **L1** and (4*R*,5*S*)-diPh **L3** ligands (Table 5, entry 3 and 5, respectively), in line with the enantiocontrol observed in the formation of **29a**, **31a**, and **33a**, albeit with slightly decreased levels of enantioselectivity (up to 90% ee for **36a** cf 98% ee for **29a**). In contrast,

36b and **36d** were isolated with modest enantiomeric excess. The thiopyran diastereomer, **36b**, was isolated in yields of 7–11%, with enantiomeric excess ranging from 33–59% ee across the bis(oxazoline) series (Table 5, entry 3–7). The 5-membered sulfolane **37**, was isolated in 21–30% yield with up to 40% ee using the (4*R*,5*S*)-diPh **L3** ligand (Table 5, entry 5), reminiscent of our earlier result describing the formation of a 5-membered sulfolane bearing a methyl ketone also in 40% ee.[40]

In the proton NMR of the crude product mixtures from **17**, there was evidence for the presence of the diastereoisomer **36c** [a doublet of doublets at δ_H 4.89 ppm (*J* 4.7, 2.0 Hz) in various ratios, which markedly resembles the distinctive signal observed in **33c** (δ_H 4.89 ppm, dd, *J* 5.5, 1.6 Hz)] but this component was never isolated following chromatography and is possible that this diastereomer epimerizes on silica gel to form **36d**, and this may contribute to decreased levels of enantiopurities. Similarly, epimerization can lead to interconversion of **36a** and **36b**, and in fact evidence of this epimerization was observed during TLC. In contrast, there was no evidence of interconversion of the fused diastereomers via epimerization, presumably due to conformational effects. It is important to note, self-disproportionation of enantiomers (SDE)[45-49] was observed during the chromatographic separation of **36a** [Table 5, entry 3 (91–83% ee), entry 5 (89–83% ee), entry 6 (56–52% ee), entry 7 (84–73% ee)], while it was not observed with the other isolated thiopyrans or sulfolanes. In order to obtain an accurate measure of enantioselectivity, the values in Table 5 of **36a** are a weighted average (for full details see the Supporting Information). While the relative and absolute stereochemistry of thiopyrans **29a**, **31a** and **33a** were confirmed crystallographically, the absolute stereochemistry of **36a** is assigned by analogy on the basis of HPLC data and specific rotations.

Overall, a consistently high level of enantioselectivity was observed for the isolated cis substituted thiopyrans (**29a**, **31a**, **33a**, **36a**) (Figure 6), and excellent levels of copper catalyzed desymmetrization was observed when inserting into a 2° C–H bond of a cyclohexane ring in the formation of a 6-membered heterocycle, with 98% ee and a 98:2 dr for **29a** (Table 2, entry 5), and 94% ee and a 97:3 dr for **31a** (Table 4, entry 3). Interestingly, in the conformationally more flexible substrate, **17**, while the enantioselectivities were slightly lower, the ligand trends remained the same and up to 90% ee was obtained using the preferred (4*R*)-Ph ligand **L1** which has consistently led to the highest enantioselectivities in C–H insertion to form thiopyrans.

Figure 6: Consistently high levels of enantioselectivity observed across the bis(oxazoline) series for the isolated cis substituted thiopyrans (**29a**, **31a**, **33a**, **36a**)



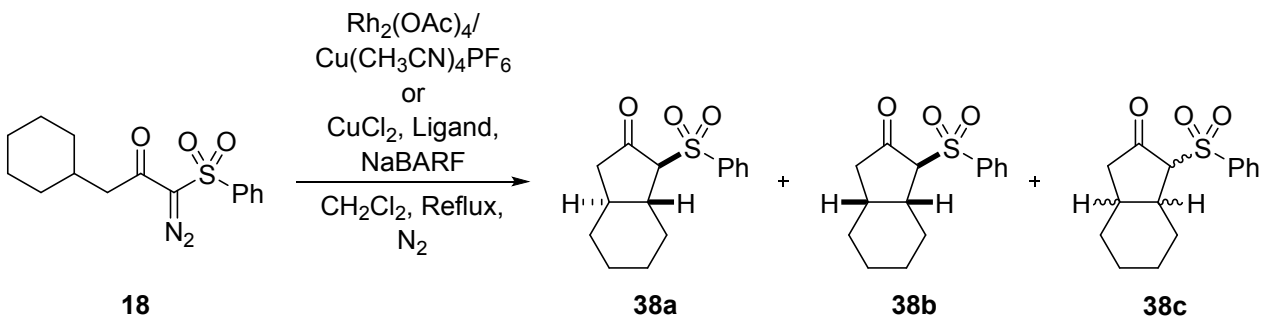
Cyclopentanone Formation

As discussed previously, desymmetrization by C–H insertion using rhodium catalysts has been explored with α-diazocarbonyl compounds containing cyclic substituents, resulting in high yields and high enantioselectivities of 5-membered rings (Figure 1 (a) and (b)). Building on our earlier work which has shown that the copper–bis(oxazoline)–NaBARF catalyst system provides high levels of enantioselectivity in the formation of cyclopentanones in freely rotating systems,[41, 50] the α-diazo-β-oxosulfone **18** was designed to enable exploration of desymmetrization in C–H insertion to form cyclopentanones (Table 6).

The rhodium acetate catalyzed C–H insertion of α-diazo-β-oxosulfone **18** was complete after 5 hours, leading to the cyclopentanone **38**. The ^{1}H NMR spectrum of the crude product mixture showed a 1 : 0.15 : 0.17 ratio of three cyclopentanone diastereoisomers (**38a**/**38b**/**38c**). The trans fused, 1,7a trans substituted cyclopentanone **38a** together with a minor amount of **38c** (1 : 0.04, **38a**/**38c** ratio) was isolated in 53% yield (Table 6, entry 1)

after chromatography, as evidenced by a characteristic doublet at δ_H 3.7 ppm (*J* 7.7 Hz) for the α-proton of **38c**. While pure **38a** was isolated by recrystallisation, it was not possible to isolate **38c** as a pure compound and accordingly its relative stereochemistry has not been confirmed.

Table 6: Transition metal catalyzed C–H insertion of α-diazo-β-oxosulfone 18



18 **38a** **38b** **38c**

Entry	Catalyst	Ligand	Additive	Time (h)	38a : 38b : 38c[a]	Yield[b,c] 38a (%)	Yield[b] 38b (%)	38a ee[d] (%)	38b ee[d] (%)
1	$Rh_2(OAc)_4$	-	-	5	1 : 0.15 : 0.17	53	2	0	0
2	$Cu(CH_3CN)_4PF_6$	-	-	27	1 : 0.21 : 0.04	43	6	0	0
3	$CuCl_2$	**L1**	NaBARF	6	1 : 0.34 : 0.03	44	14	38 [e]	7 [f]
4	$CuCl_2$	**L2**	NaBARF	5	1 : 0.17 : 0.02	53	2	64 [e]	50 [f]
5	$CuCl_2$	**L3**	NaBARF	6	1 : 0.20 : 0.04	59	11	20 [e]	22 [f]
6	$CuCl_2$	**L4**	NaBARF	28	1 : 0.21 : 0.02	51	2	59 [g]	32 [h]
7	$CuCl_2$	**L5**	NaBARF	7	1 : 0.21 : 0.04	54	9	54 [g]	7 [h]

[a]Ratios of products were calculated from signals in the crude ^{1}H NMR spectra. [b]Isolated yield after chromatography. [c]**38c** (<5%, in all cases) co-eluted with **38a**. [d]The enantiomeric excess was measured by chiral phase HPLC analysis (for full details see the Supporting Information). [e]The major enantiomer is 1*S*,3a*S*,7a*R*. [f]Major enantiomer with unassigned configuration. Specific rotation of **38b** was positive. [g]The major enantiomer is 1*R*,3a*R*,7a*S*. [h]Major enantiomer with unassigned configuration. Specific rotation of **38b** was negative.

Interestingly, Taber's report of rhodium acetate catalyzed C–H insertion using a similar α-diazo-β-keto ester led to a diastereomeric ratio of 1:3.[11] The increased diastereoselectivity with the sulfone derivative **18** may be due to the impact of the sulfone moiety relative to the ester.

Achiral $Cu(CH_3CN)_4PF_6$ required a longer reaction time to catalyze C–H insertion of **18** and yielded 43% of the major cyclopentanone **38a** (containing 4% of **38c)** and 6% of the cis fused, 1,7a trans substituted cyclopentanone **38b** (Table 6, entry 2). The employment of the

copper–bis(oxazoline)–NaBARF catalyst system led to relatively efficient formation for the 5-membered cyclopentanone **38** and showed very consistent diastereoselectivity across the ligand series (Table 6, entry 3–7). The cyclopentanone, **38a**, was observed as the major product in the ^{1}H NMR spectra of the crude product mixtures and was isolated in yields of 44–59% (containing minor amounts of **38c**, <5% in all cases).

In line with our previous reported results for enantioselective C–H insertion leading to cyclopentanones,[50] the highest enantioselectivities for **38a** were obtained using the ligands (4*R*)-Bn **L2** and (3*S*,8*R*)-Ind **L4** (64% ee and 59% ee respectively, Table 6, entries 4 and 7) and the extent of enantioselectivity was very similar to the outcome in freely rotating systems. Interestingly, the enantioselectivities recorded with the other ligands were somewhat higher than those obtained in the earlier study, most notably with the (4*S*)-*t*-Bu ligand **L5** (54% ee for **38a** cf 14–28% ee previously). The α-diazoketone **18** underwent C–H insertion with enantioselectivity values ranging from 20–64% ee for **38a,** revealing some sensitivity towards the bis(oxazoline) ligands (Table 6, entry 3–7). The X-ray structure of a single crystal of **38a**, recrystallized from the reaction using the (4*R*)-Bn ligand **L2** (Table 6, entry 4), confirmed the 1*S*,3a*S*,7a*R* absolute configuration. The enantiomeric series was verified by chiral HPLC analysis of the single crystal used for crystallographic determination.

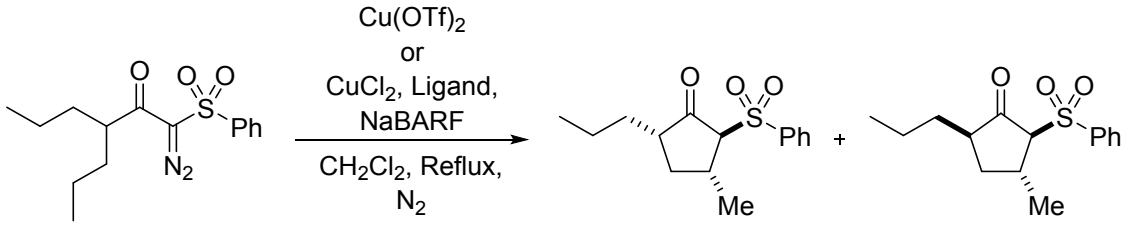
The cis fused, 1,7a trans substituted cyclopentanone **38b** was isolated as the minor product across the catalyst study (up to 14% yield) with lower enantioselectivity compared to the major cyclopentanone **38a**, but interestingly with similar ligand patterns with the highest enantioselectivity obtained with **L2** and **L4** (50% ee and 32% ee, respectively, Table 6).

Overall, a modest degree of desymmetrization was achieved for substrate **18** with the (4*R*)-Bn ligand **L2** in the formation of **38a** (Table 6, entry 4), with decreased selectivity relative to that achieved in the formation of the thiopyrans **29a**, **31a**, and **33a**. This mirrors the earlier results in the C–H insertions in freely rotating systems where higher enantioselectivities are seen for the thiopyrans relative to the cyclopentanones with the copper–bis(oxazoline)–NaBARF system.[40-41, 44, 50]

Similar to the investigation into thiopyran formation, for the cyclopentanone study the C–H insertion into the acyclic substrate **19** was compared to insertion into the cyclic structure substrate **18**. Rhodium acetate catalysed C–H insertion of α-diazo-β-oxosulfone **19** in refluxing dichloromethane provided access to cyclopentanone **39**. In the ^{1}H NMR spectrum for the crude reaction mixture, four sets of doublets were observed at δ_H 3.33, 3.40, 3.71, and

3.84, in a 1.00 : 0.61 : 1.52 : 0.31 ratio. The doublet signals at δ_H 3.33 and 3.40 were assigned to **39a** and **39b**, respectively. The doublet signals at δ_H 3.71 and 3.84 were not observed in the ^{1}H NMR spectrum of the purified material after column chromatography. These signals were ascribed to the cis diastereomer at C2 and C3, in line with the earlier reported observation of exclusive isolation of trans cyclopentanones after chromatography.[12]

Table 7: Transition metal catalyzed C–H insertion of α-diazo-β-oxosulfone 19



19 **39a** **39b**

Entry	Catalyst	Ligand	Additive	Time (h)	39a: 39b	Yield[b,c] (%)	39a ee[d] (%)	39b ee[d] (%)
1	$Cu(OTf)_2$	-	-	4	1 : 0.38	89	0	0
2	$CuCl_2$	**L1**	NaBARF	12	1 : 0.71	93	14 [e]	~0
3	$CuCl_2$	**L2**	NaBARF	4	1 : 0.48	95	63 [e]	64
4	$CuCl_2$	**L3**	NaBARF	2	1 : 0.63	89	13 [e]	~0
5	$CuCl_2$	**L4**	NaBARF	3	1 : 0.59	99	59 [f]	75
6	$CuCl_2$	**L5**	NaBARF	10	1 : 0.34	99	19 [e]	35

[a]Ratios of products were calculated from signals in the crude ^{1}H NMR spectra. [b]Isolated yield after chromatography. [c]A combined yield of **39a** and **39b**. [d]The enantiomeric excess was measured by chiral phase HPLC analysis (for full details see the Supporting Information). [e]The major enantiomer is 2*S*,3*R*,5*S*. [f]The major enantiomer is 2*R*,3*S*,5*R*.

The $Cu(OTf)_2$ catalyzed C–H insertion of α-diazo-β-keto sulfone **19** exclusively led to trans stereochemistry across the C2–C3 bond (Table 7, entry 1). A 1 : 0.38 mixture of isomers (**39a**/**39b**) was observed in a combined isolated yield of 87%. The results of the enantioselective copper–bis(oxazoline)–NaBARF catalyzed C–H insertion of **19** are shown in Table 7 (entries 2–6). For all reactions, preferential formation of **39a** over **39b** was recorded, with efficient C–H insertion observed from the ^{1}H NMR spectra of the crude product mixture, and the combined isolated yields ranged from 89–99% (Table 7, entry 2–6). Moderate levels of diastereocontrol were observed in the ^{1}H NMR spectra of the crude product mixtures across the bis(oxazoline) series with ratios ranging from 58:42 to 75:25 (**39a**/**39b**), in contrast to the dr of 73:25:2 to 84:14:2 (**38a**/**38b**/**38c**) observed with **18**.

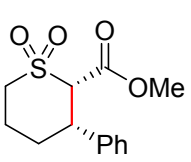
The (4*R*)-Bn **L2** and (3*S*,8*R*)-Ind **L4** ligands were found to afford the best enantiocontrol for **39a**, with up to 63% ee in the presence of **L2** (Table 7, entry 3). Interestingly, the enantioselectivity induced using the (4*R*)-Bn **L2** and (3*S*,8*R*)-Ind **L4** ligands for **19** are comparable to the values recorded for substrate **18** (64% ee for **38a** cf 63% ee for **39a** (**L2**) and 59% ee for **38a** cf 59% ee for **39a** (**L4**)). On the other hand, very poor enantioselectivity was observed with substrate **19** in the presence of (4*R*)-Ph **L1**, (4*R*,5*S*)-diPh **L3**, and (4*S*)-*t*-Bu **L5** ligands (Table 7, entry 2, 4, 6). While **39b** was not isolated in a pure state, enantioselectivities of 64% ee and 75% ee were recorded for the reactions using the (4*R*)-Bn **L2** and (3*S*,8*R*)-Ind **L4** ligands (Table 7, entry 3, 5) showing higher ee values relative to **38b**. Curiously, use of the (4*S*)-*t*-Bu ligand **L5** led to the formation of cyclopentanone **39a** with the opposite stereochemistry to that observed when using (3*S*,8*R*)-Ind **L4**, albeit at modest absolute values. Single crystal analysis of **39a**, obtained from the reaction in the presence of **L4** (Table 7, entry 5) confirmed the absolute stereochemistry of 2*R*,3*S*,5*R* as the major enantiomer isolated.

Overall, the enantioselectivities obtained for C–H insertion reactions of **19** are remarkably similar to those obtained for the analogous copper–bis(oxazoline)–NaBARF catalyzed cyclisations of **18**, although the diastereoselectivity in **39** is notably lower, presumably reflecting the formation of non-fused versus fused products, and appears to be more sensitive to alteration of the bis(oxazoline) ligands; with the (4*R*)-Ph ligand **L1** showing a 1 : 0.71 (**39a/39b**) ratio, while the (4*S*)-*t*-Bu **L5** ligand produced a more noteworthy 1 : 0.34 (**39a/39b**) ratio.

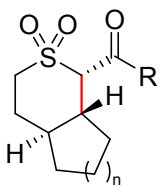
In general, asymmetric copper catalyzed C–H insertion reactions of **18** and **19** led to moderate levels of desymmetrization in the formation of cyclopentanones.

Stereochemistry

Flynn ***This work***



cis substituted
thiopyran
11



trans fused cis substituted
29a R = OMe, n = 2
31a R = Ph, n = 2
33a R = Ph, n = 1

Figure 7: The relative stereochemistry and the sense of enantioselectivity in C–H insertion to form thiopyrans using the (4*R*)-Ph bis(oxazoline) ligand **L1**.

Across the desymmetrization study using the diazo substrates **14**, **15**, **16**, and **18**, the trans fused, cis substituted diastereoisomers **29a**, **31a**, **33a** were consistently isolated as the major thiopyran products, and the trans fused, trans substituted diastereoisomer **38a** was isolated as the major cyclopentanone product, irrespective of the bis(oxazoline) ligand employed. Significantly, the sense of enantioselectivity (1*S*,4a*S*,8a*R*, for **29a** and **31a** with **L1**, **L2** and **L3**, and 1*R*,4a*R*,8a*S*, for **29a** and **31a** with **L4** and **L5**; 1*S*,4a*S*,7a*R*, for **33a** with **L1**, **L2** and **L3**, and 1*R*,4a*R*,7a*S*, for **33a** with **L4** and **L5**) and the cis relative stereochemistry on the thiopyran ring matches exactly that seen in our original study of C–H insertion to form thiopyrans (Figure 7).[40] The selective formation of the major isolated stereoisomer, 1*S*,4a*S*,8a*R*, for **29a** and **31a,** 1*S*,4a*S*,7a*R*, for **33a** can be rationalized in terms of ligand-substrate interactions in a similar fashion to that described by our earlier work in the formation of cis thiopyrans using the (4*R*)-Ph bis(oxazoline) ligand **L1**.[44]

In theoretical studies of diastereoselective rhodium mediated C–H insertions, [51] Yoshikai and Nakamura calculated that the most favorable transition state for forming fused bicyclic products involves insertion into the equatorial C–H bond of an equatorial ring substituent to give the trans fused product. In line with this analysis it is clear from our results that for thiopyran formation this is also the preferred pathway (Figure 8).

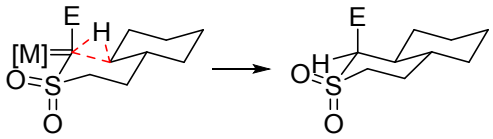


Figure 8: The favored approach of the copper–carbenoid to the equatorial C–H bond of an equatorial ring substituent.

The observed enantio- and diastereoselectivity to preferentially lead to the trans fused cis substituted **29a** through C–H insertion can be rationalized on the basis of the transition state illustrated in Figure **9A**. When inserting into the equatorial methylene C–H bond of the equatorial cyclohexane ring, the Cu-carbenoid orientates into the least sterically hindered pseudo-equatorial position with the methyl ester substituent occupying a pseudo-axial position. Effective desymmetrization results from the difference between **TS A** and **B** (Figure 9), with unfavorable substrate-ligand interactions due to approach from the opposite face of the copper carbenoid leading to steric interaction between the cyclohexyl ring and the phenyl

substituent on the ligand in the upper quadrant in **TS B**. High diastereoselectivity arises from the difference between transition states **A** and **C**, where rotation of the cyclohexyl ring leads to unfavorable ligand interactions with the axial hydrogen at the ring junction. The least favorable transition state **D** suffers from the combined disadvantages of **TS B** and **C**. This results in the overall diastereoselectivity observed in the copper mediated insertions which proceed predominantly via **TS A**.

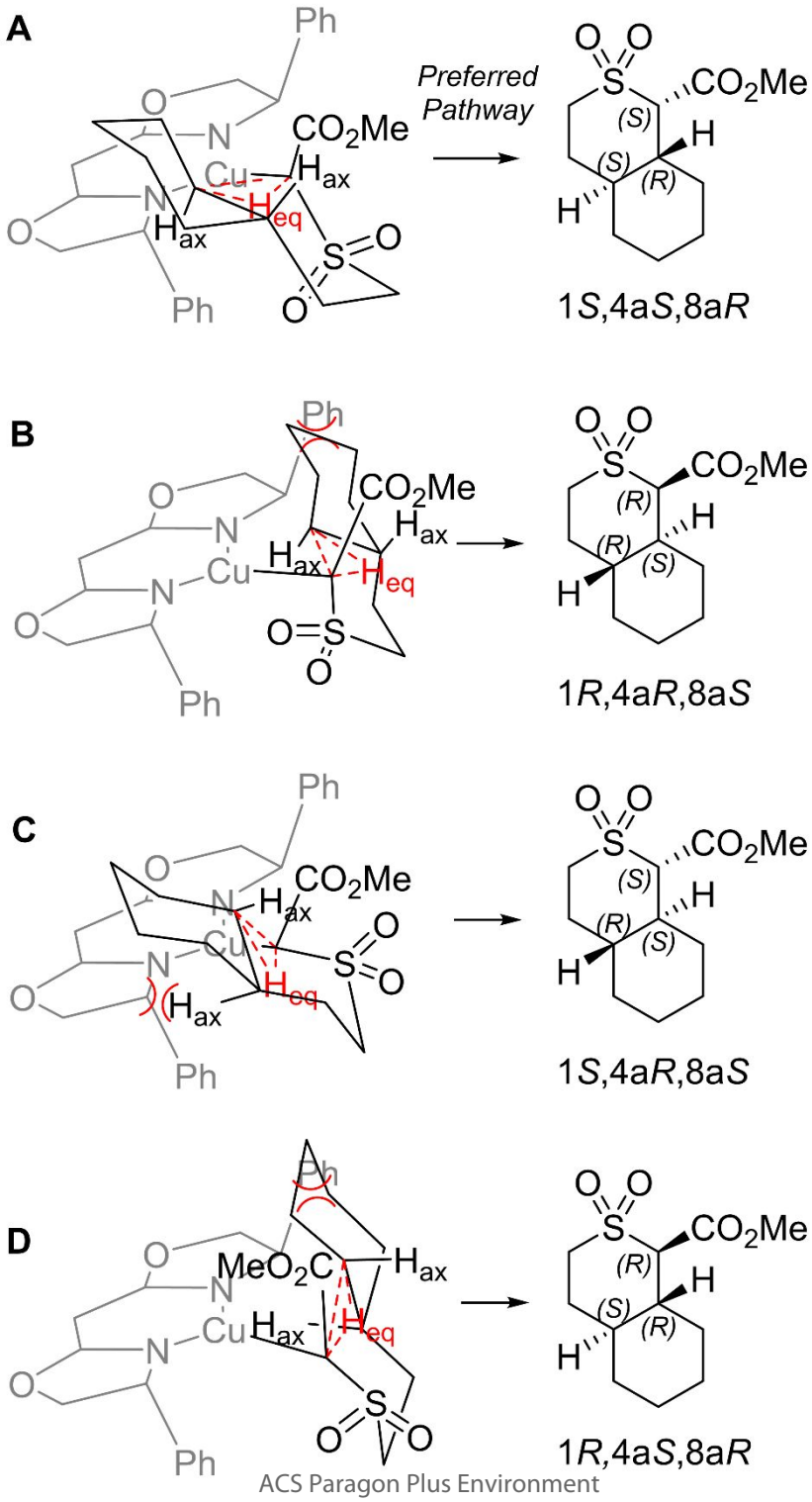


Figure 9: Proposed transition states leading to thiopyran formation using the (4*R*)-Ph bis(oxazoline) ligand **L1**.

The outcome of the copper mediated insertions with α-diazo-β-oxosulfones **15** and **16** are similarly rationalized leading selectively to the analogous trans fused cis substituted stereochemistry in **31a** and **33a**. The selective formation of cyclopentanone **38a** can be similarly rationalized; notably the diastereoselectivity is in agreement with Nakamura's analysis.[51]

Conclusion

In conclusion, we have shown that the copper–bis(oxazoline)–NaBARF catalyst system is effective in achieving high levels of desymmetrization in the C–H insertion reactions of cyclic α-diazo-β-oxosulfones **14**, **15**, **16**, **18** to form fused thiopyrans **29a**, **31a**, **33a** or a fused cyclopentanone **38a**.

For each of the thiopyrans **29a**, **31a**, **33a**, the trans fused, cis substituted thiopyran diastereoisomers are the major products with up to 98:2 dr and up to 98% ee mirroring both the sense and extent of enantioselection seen in our earlier work on formation of thiopyrans by insertion into an unconstrained alkyl chain. Significantly, the optimum ligand for the enantioselective C–H insertion, (4*R*)-Ph bis(oxazoline) ligand **L1**, also leads to the best outcome in the desymmetrization C–H insertions. Furthermore, the outcome of the desymmetrization displayed little alterations between α-diazoester **14** and α-diazoketone **15** precursors. The C–H insertion at the 3° bond to form the spiro sulfolane **34** competed more effectively with the thiopyran formation for the precursor containing the more conformationally constrained cyclopentane ring in certain cases, however the enantioselectivity of the major trans fused cis substituted thiopyran diastereoisomer isolated was comparable across the bis(oxazoline) ligand series. While not providing the highest enantioselectivies across the series, the use of the (4*S*)-*t*-butyl bis(oxazoline) ligand **L5** provided the most consistent C–H insertion results, with regards to the isolated yields, diastereo- and enantioselectivity in the reactions of **14**, **15** and **16**. The outcome of the desymmetrization with the α-diazoester **14** was somewhat insensitive to variation of the

copper source or solvent. Interestingly, in the more conformationally mobile precursor **17** while the enantiopurity of the resulting thiopyran **36a** was consistent with enantiopurities of the fused thiopyrans, there was a significant change in the diastereoselectivity of the C–H insertion process.

Desymmetrization in the formation of the fused cyclopentanone **38a** resulted in similar efficiencies and enantioselectivies to those seen in cyclopentanone formation using conformationally unconstrained precursors, with lower levels of enantiopurity seen in comparison to the thiopyrans with the copper–bis(oxazoline)–NaBARF catalyst system. The isolated trans fused trans substituted cyclopentanone **38a** is synthesized with consistent diastereoselectivity across the bis(oxazoline) series and with moderate levels of enantioselectivity in comparison to the freely rotating alkyl chain system **19** where the diastereoselectivity observed is ligand sensitive. However across the cyclopentanone series, the sense of enantioselectivity remains the same.

Overall, the copper–bis(oxazoline)–NaBARF catalyst system which has led successfully to thiopyran and cyclopentanone formation via C–H insertions, is equally effective as a desymmetrization catalyst system leading to fused derivatives extending the synthetic utility of this methodology. Clearly, the catalyst-ligand-substrate interactions which result in enantiocontrol persist in the desymmetrization process.

Experimental Section

General Procedures:

Solvents were distilled prior to use as follows: tetrahydrofuran (THF) was distilled from sodium benzephenone ketyl; dichloromethane (DCM) was distilled from phosphorus pentoxide and, when used for C–H insertion reactions, was further distilled from calcium hydride; ethyl acetate was distilled from potassium carbonate; and hexane was distilled prior to use. All commercial reagents were used without further purification unless otherwise stated.

^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a 300 MHz NMR spectrometer. ^{1}H (400 MHz) NMR spectra were recorded on a 400 MHz NMR spectrometer. All spectra were recorded at 300 K in deuterated chloroform ($CDCl_3$) unless otherwise stated, using tetramethylsilane (TMS) as an 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 ^{1}H NMR spectra are designated as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), dq (doublet of quartets), ddd (doublet of doublet of doublets), dddd (doublet of doublet of doublet of doublets), dt (doublet of triplets), ddt (doublet of doublet of triplets), td (triplet of doublets), tt (triplet of triplets), qd (quartet of doublets), and m (multiplet). ^{13}C NMR spectra were calibrated using the solvent signal, *i.e.* $CDCl_3$: δ_C 77.0 ppm, and multiplicities were assigned with the aid of DEPT experiments.

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

Flash column chromatography was carried out using Kieselgel silica gel 60, 0.035–0.075 mm (Merck). Thin layer chromatography (TLC) was carried out on pre-coated silica gel plates (Merck 60 PF254). Visualization was achieved by UV (254 nm) light absorption, and potassium permanganate staining.

The enantiopurity of chiral compounds was measured using chiral stationary phase high performance liquid chromatography (HPLC), carried out on a Lux® 3μm Amylose-1 purchased from Phenomenexon, or a Chiralpak® OJ-H purchased from Daciel Chemical Industries Limited. Details of the column conditions and mobile phase employed are included in the supporting information. HPLC analysis was performed on a Waters alliance 2695 separations module with a Waters alliance 2996 Photodiode Array detector. Optical rotations were measured on an Autopol V Plus Automatic 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 a Perkin-Elmer 240 and Exeter Analytical CE440 elemental analyzer. Low resolution mass spectra (LRMS) was 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) was 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. High resolution (precise) mass spectra (HRMS) were also recorded on an Agilent 6530B Accurate Mass Q-TOF LC/MS instrument in electrosprayionization mode using 50% acetonitrile–water containing 0.1%

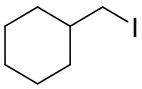
formic acid as eluent. Samples prepared for either LRMS or HRMS by employing acetonitrile as solvent.

Melting points were obtained using a unimelt Thomas–Hoover capillary melting point apparatus and are uncorrected.

Single crystal X-ray analysis was performed on a Bruker APEX II DUO diffractometer at room temperature using either graphite monochromatic Mo Kα (λ = 0.7107 Å) or Cu Kα (λ = 1.5418 Å) radiation from a microfocus source fitted with an Incoatec Montel Multilayer Mirror. All calculations and refinement were made using the APEX software,[52] except for the use of PLATON for a disordered solvent in **33a**.[53] Analysis was undertaken with the SHELX suite of programs and diagrams prepared with Mercury 3.8.[54-55] All non-hydrogen atoms were located and refined with anisotropic thermal parameters, except for the minor disordered component in **39a**. Hydrogen atoms were included in calculated positions or were located and refined with isotropic thermal parameters.

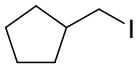
Synthesis of alkyl iodides

*(Iodomethyl)cyclohexane (**24**)*



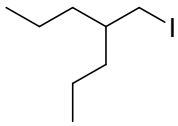
Bromomethylcyclohexane (5.00 g, 3.94 mL, 28.2 mmol) was added neat to a mixture of sodium iodide (12.69 g, 84.7 mmol) in acetone (100 mL). The reaction mixture was stirred while heating under reflux for 40 h. The reaction mixture was cooled before being diluted with aqueous sodium thiosulfate (15%, 100 mL) and extracted with diethyl ether (2 × 75 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product as a pale pink/red oil. The crude oil was redissolved in diethyl ether (25 mL) and washed with aqueous sodium thiosulfate (15%, 3 × 25 mL) for a second time, dried ($MgSO_4$) and concentrated under reduced pressure to give (iodomethyl)cyclohexane **24** as a colorless oil (5.44 g, 86%); ν_{max} (ATR)/cm^{-1} (neat) 2920, 2850, 1447, 1170, 597; δ_H ($CDCl_3$, 300 MHz) 0.86–1.04 (2H, m), 1.04–1.35 (3H, m), 1.35–1.51 (1H, m), 1.56–1.66 (1H, m), 1.66–1.79 (2H, m), 1.79–1.93 (2H, m), 3.09 (2H, d, *J* 6.4 Hz); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 16.2 (CH_2), 25.9 (CH_2), 26.1 (CH_2), 33.5 (CH_2), 40.0 (CH). Spectroscopic characteristics were consistent with previously reported data.[56]

*(Iodomethyl)cyclopentane (**25**)*



The title compound was prepared using the procedure described for (iodomethyl)cyclohexane **24** using bromomethylcyclopentane (2.54 g, 15.6 mmol) and sodium iodide (7.01 g, 46.8 mmol) in acetone (100 mL) which was stirred under reflux for 40 h. Following the work up described previously, (iodomethyl)cyclopentane **25** was obtained as a transparent yellow oil (2.71 g, 83%); ν_{max} (ATR)/cm^{-1} (neat) 2948, 2863, 1178, 583; δ_H ($CDCl_3$, 300 MHz) 1.14–1.33 (2H, m), 1.51–1.76 (4H, m), 1.76–1.93 (2H, m), 2.08–2.27 (1H, apparent septet, *J* 7.5 Hz), 3.20 (2H, d, *J* 6.9 Hz); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 14.3 (CH_2), 25.6 (CH_2), 33.5 (CH_2), 42.8 (CH). Spectroscopic characteristics were consistent with previously reported data.[57]

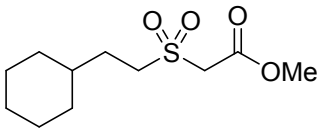
*4-(Iodomethyl)heptane (**26**)*



A mixture of triphenylphosphine (15.11 g, 57.6 mmol) and iodine (14.62 g, 57.6 mmol) in dry dichloromethane (300 mL) was stirred at room temperature for 10 min, followed by the addition of imidazole (6.54 g, 96.0 mmol). The mixture was stirred for an additional 10 min before 2-propyl-1-pentanol (5.0 g, 38.4 mmol, 6.02 mL) was added neat, and the resulting mixture was stirred at room temperature for 4 h before being heated to 40 °C overnight. The reaction mixture was cooled to room temperature and quenched using saturated sodium metabisulfite (100 mL). The separated organic layer was washed further with saturated sodium metabisulfite (2 × 40 mL) and the combined aqueous layers were extracted with diethyl ether (2 × 30 mL). The combined organic layers were washed with brine (80 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a crude colorless oil. Following purification by column chromatography on silica gel, using hexane (100%) as eluent, 4-(iodomethyl)heptane **26** was isolated as a colorless oil (7.84 g, 85%); Anal. Calcd for $C_8H_{17}I$: C, 40.02; H, 7.14. Found: C, 40.23; H, 6.99; ν_{max} (ATR)/cm^{-1} (neat) 2956, 2926, 1464, 1186, 585; δ_H ($CDCl_3$, 300 MHz) 0.82–1.01 (6H, m), 1.08–1.43 (9H, m), 3.26 (2H, d, *J* 4.39 Hz); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 14.2 (CH_3), 16.6 (CH_2), 19.7 (CH_2), 36.7 (CH_2), 38.2 (CH).

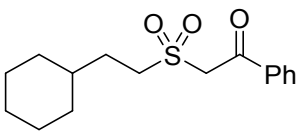
Synthesis of β-oxosulfones

*Methyl 2-((2-cyclohexylethyl)sulfonyl)acetate (**20**)*



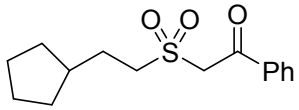
Potassium carbonate (1.94 g, 14.0 mmol) was added as a solid to a solution of methyl thioglycolate (1.36 g, 1.14 mL, 12.8 mmol) in acetone (50 mL). The reaction mixture was stirred at room temperature for 15 minutes. 1-Bromo-2-cyclohexylethane (2.44 g, 2.0 mL, 12.8 mmol) was added dropwise over 2 minutes, neat, to the reaction mixture. The reaction mixture was stirred while heating under reflux for 22 h. The mixture was cooled, filtered to remove insoluble salts, and concentrated under reduced pressure to give the crude sulfide, methyl 2-((2-cyclohexylethyl)thio)acetate as a colorless oil (3.10 g, >100% yield), which was used without further purification (due to its malodourous nature). A suspension of *m*-CPBA (~77% w/w, 7.71 g, 44.6 mmol) in dichloromethane (50 mL) was added dropwise to a solution of methyl 2-((2-cyclohexylethyl)thio)acetate (3.10 g, 14.3 mmol) in dichloromethane (100 mL) over approximately 30 min while stirring at 0 °C. The resulting mixture was stirred for 23 h, while warming to room temperature. The crude mixture was washed with saturated aqueous sodium metabisulfite solution (2 × 50 mL), saturated aqueous sodium bicarbonate (3 × 150 mL), and the separated organic layers were washed with brine (200 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude sulfone. Following purification by column chromatography on silica gel, using ethyl acetate/hexane (50:50) as eluent, methyl 2-((2-cyclohexylethyl)sulfonyl)acetate **20** was isolated as a colorless oil (3.17 g, 89%); Anal. Calcd for $C_{11}H_{20}O_4S$: C, 53.20; H, 8.12. Found: C, 52.95; H, 8.06; ν_{max} (ATR)/cm^{-1} (neat) 1740 (CO), 1312, 1104 (SO_2); δ_H ($CDCl_3$, 300 MHz) 0.86–1.06 (2H, m), 1.06–1.47 (4H, m), 1.59–1.82 (7H, m), 3.20–3.31 (2H, symmetrical m), 3.82 (3H, s), 3.97 (2H, s); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 25.9 (CH_2), 26.1 (CH_2), 28.8 (CH_2), 32.6 (CH_2), 36.5 (CH), 51.5 (CH_2), 53.2 (CH_3), 56.9 (CH_2), 163.5 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{11}H_{21}O_4S$, 249.1161; found 249.1161.

*2-((2-Cyclohexylethyl)sulfonyl)-1-acetophenone (**21**)*



A solution of 2-(methylsulfonyl)acetophenone (1.20 g, 6.05 mmol) in dry THF (30 mL) was added dropwise over 20 min to a suspension of sodium hydride [0.27 g, 0.16 g calculated, 60% w/w (suspension in mineral oil), 6.65 mmol] in THF (5 mL) at 0 °C under an atmosphere of nitrogen. The mixture was stirred at 0 °C for 30 min at which point *n*-butyllithium (2.03 M in hexanes, 3.28 mL, 6.65 mmol) was added dropwise over 30 min. After an additional 90 min of stirring at 0 °C, a solution of (iodomethyl)cyclohexane **24** (1.36 g, 6.05 mmol) in dry THF (5 mL) was added dropwise over 30 min, and the resulting mixture was stirred overnight, while returning to room temperature. The reaction mixture was heated to 40 °C while stirring for 6 h, cooled to room temperature, acidified with aqueous hydrochloric acid (2 M, 5 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (60 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Following purification by column chromatography on silica gel, using ethyl acetate/hexane (10:90) as eluent, 2-((2-cyclohexylethyl)sulfonyl)-1-acetophenone **21** was isolated as white solid (0.69 g, 39%); mp 82–83 °C; Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.28; H, 7.53. Found: C, 65.25; H, 7.40; ν_{max} (ATR)/cm^{-1} (neat) 1678 (CO), 1294, 1122 (SO); δ_H ($CDCl_3$, 300 MHz) 0.86–1.06 (2H, m), 1.06–1.48 (4H, m), 1.57–1.84 (7H, m), 3.19–3.32 (2H, symmetrical m), 4.56 (2H, s), 7.46–7.57 (2H, m), 7.60–7.70 (1H, m), 7.97–8.05 (2H, m); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 26.0 (CH_2), 26.3 (CH_2), 28.9 (CH_2), 32.8 (CH_2), 36.7 (CH), 51.8 (CH_2), 59.4 (CH_2), 129.0 (CH), 129.3 (CH), 134.6 (CH), 135.8 (C), 189.3 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{23}O_3S$ 295.1368; found 295.1356.

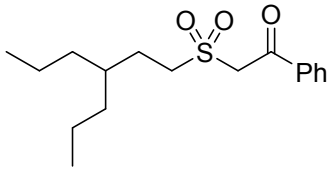
*2-((2-Cyclopentylethyl)sulfonyl)-1-acetophenone (**22**)*



A solution of 2-(methylsulfonyl)acetophenone (2.0 g, 10.0 mmol) in dry THF (30 mL) was added dropwise over 20 min to a suspension of sodium hydride [0.44 g, 0.27 g calculated, 60% w/w (suspension in mineral oil), 11.1 mmol] at 0 °C under an atmosphere of nitrogen. The mixture was stirred at 0 °C for 30 min at which point *n*-butyllithium (2.23 M in hexanes, 4.97 mL, 11.1 mmol) was added dropwise over 30 minutes. After an additional 90 min of stirring at 0 °C, a solution of (iodomethyl)cyclopentane **25** (2.12 g, 10 mmol) in dry THF (5 mL) was added dropwise over 30 min. The resulting mixture was stirred at room temperature for 3 h, before being heated to 60 °C overnight. The reaction was heated to 70 °C while stirring for a further 24 h. The reaction mixture was cooled to room temperature, acidified

with aqueous hydrochloric acid (2 M, 8 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (60 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography on silica gel, using ethyl acetate/hexane (15:75) as eluent, gave the pure 2-((2-cyclopentylethyl)sulfonyl)-1-acetophenone **22** as a white solid (1.42 g, 50%); mp 118–119 °C; Anal. Calcd for $C_{15}H_{20}O_3S$: C, 64.26; H, 7.19. Found: C, 64.19; H, 7.14; ν_{max} (ATR)/cm^{-1} (neat) 1670 (CO), 1278, 1131 (SO); δ_H ($CDCl_3$, 300 MHz) 1.05–1.27 (2H, m), 1.46–1.72 (4H, m), 1.72–1.98 (5H, m), 3.18–3.35 (2H, symmetrical m), 4.57 (2H, s), 7.47–7.58 (2H, m), 7.60–7.71 (1H, m), 7.96–8.07 (2H, m); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 25.0 (CH_2), 27.8 (CH_2), 32.2 (CH_2), 38.8 (CH), 53.1 (CH_2), 59.2 (CH_2), 128.9 (CH), 129.3 (CH), 134.6 (CH), 135.7 (C), 189.3 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{21}O_3S$ 281.1211; found 281.1210.

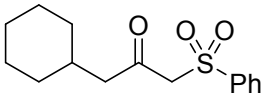
*2-((3-Propylhexyl)sulfonyl)-1-acetophenone (**23**)*



A solution of 2-(methylsulfonyl)acetophenone (2.5 g, 12.6 mmol) in dry THF (30 mL) was added dropwise over 20 min to a suspension of sodium hydride [0.56 g, 0.33 g calculated, 60% w/w (suspension in mineral oil), 13.9 mmol] at 0 °C under an atmosphere of nitrogen. The mixture was stirred at 0 °C for 30 min at which point *n*-butyllithium (2.36 M in hexanes, 5.88 mL, 13.9 mmol) was added dropwise over 30 min to ensure the temperature was maintained at 0 °C. After an additional 90 min of stirring at 0 °C, a solution of 4-(iodomethyl)heptane **26** (3.03 g, 12.6 mmol) in dry THF (5 mL) was added dropwise over 30 min. The resulting mixture was stirred at room temperature for 3 h, before being heated under reflux overnight. The reaction mixture was cooled to room temperature and additional 4-(iodomethyl)heptane **26** (1.0 g, 4.2 mmol) was added in dropwise over 1 h. The reaction was stirred under reflux for 24 h, cooled to room temperature, acidified with aqueous hydrochloric acid (2 M, 11 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (60 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Following purification by column chromatography on silica gel, using ethyl acetate/hexane (10:80) as eluent, gave the pure 2-((3-propylhexyl)sulfonyl)-1-acetophenone **23** as a white solid (2.67 g, 68 %); mp 45–46 °C; Anal. Calcd for $C_{17}H_{26}O_3S$: C, 65.77; H, 8.44. Found: C, 65.96; H, 8.43; ν_{max} (ATR)/cm^{-1} (neat) 1669 (CO), 1287, 1156, 1120 (SO);

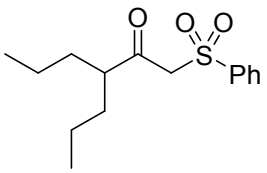
δ_H ($CDCl_3$, 300 MHz) 0.81–1.00 (6H, m), 1.15–1.40 (8H, m), 1.42–1.59 (1H, m), 1.77–1.92 (2H, m), 3.16–3.30 (2H, symmetrical m), 4.56 (2H, s), 7.46–7.58 (2H, m), 7.60–7.70 (1H, m), 7.96–8.06 (2H, m); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 14.3 (CH_3), 19.5 (CH_2), 25.3 (CH_2), 35.4 (CH_2), 36.1 (CH), 51.6 (CH_2), 59.3 (CH_2), 128.9 (CH), 129.3 (CH), 134.5 (CH), 135.8 (C), 189.3 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{27}O_3S$ 311.1681; found 311.1676.

*1-Cyclohexyl-3-(phenylsulfonyl)propane-2-one (**27**)*



n-Butyllithium (2.0 M solution in cyclohexane, 32 mL, 0.064 mol) was added dropwise to a solution of (methylsulfonyl)benzene (5.0 g, 0.032 mol) in THF (100 mL) while stirring at 0 °C. The resulting cloudy yellow mixture was stirred for 1.5 h at 0 °C before a solution of methyl cyclohexylacetate (5.0 g, 5.26 mL, 0.032 mol) in THF (50 mL) was added dropwise over 15 min producing a light yellow mixture. The reaction mixture was stirred overnight and quenched with saturated ammonium chloride solution (100 mL). The organic layer was separated and the aqueous layer extracted with diethyl ether (3 × 50 mL). The organic layers were combined and washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the crude β-keto sulfone as an orange oil. Purification by column chromatography on silica gel, using ethyl acetate/hexane (5:95 to 20:80) as eluent, followed by recrystallization from hot ethanol, gave the pure 1-cyclohexy-3-(phenylsulfonyl)propane-2-one **27** as a white solid (3.97 g, 44%); mp 81–83 °C; Anal. Calcd for $C_{15}H_{20}O_3S$: C, 64.26; H, 7.19. Found: C, 64.39; H, 7.15; ν_{max} (ATR)/cm^{-1} (neat) 1716 (CO), 1300, 1149 (SO); δ_H ($CDCl_3$, 300 MHz) 0.83–1.02 (2H, m), 1.03–1.35 (3H, m), 1.55–1.90 (6H, m), 2.57 (2H, d, *J* 6.6 Hz), 4.12 (2H, s), 7.53–7.63 (2H, m), 7.64–7.73 (1H, m), 7.85–7.93 (2H, m); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 26.0 (CH_2), 26.1 (CH_2), 32.9 (CH_2), 33.2 (CH), 51.9 (CH_2), 67.1 (CH_2), 128.3 (CH), 129.3 (CH), 134.2 (CH), 138.8 (C), 197.7 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{21}O_3S$ 281.1211; found 281.1201.

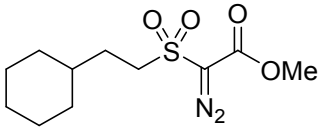
*1-(Phenylsulfonyl)-3-propylhexan-2-one (**28**)*



n-Butyllithium (2.2 M solution in hexanes; 22.4 mL, 0.049 mol), methyl 2-propylpentanoate (3.90 g, 0.0246 mol), (methylsulfonyl)benzene (3.85 g, 0.0246 mol) and THF (200 mL) were used following the procedure described for **27** to the give the crude β-keto sulfone as an orange oil. Purification by column chromatography on silica gel, using ethyl acetate/hexane (20:80) as eluent, gave the pure 1-phenylsulfonyl-3-propylhexane-2-one **28** as a white solid (4.48 g, 64%); mp 32–35 °C; Anal. Calcd for $C_{15}H_{22}O_3S$: C, 63.80; H, 7.85. Found: C, 63.88; H, 7.99; ν_{max} (KBr)/cm^{-1} (disc) 1715 (CO), 1311, 1156 (SO_2); δ_H ($CDCl_3$, 400 MHz) 0.88 (6H, t, *J* 7.2), 1.17–1.28 (4H, m), 1.30–1.40 (2H, m), 1.51–1.62 (2H, m), 2.69–2.77 (1H, m), 4.20 (2H, s), 7.55–7.60 (2H, m), 7.65–7.70 (1H, m), 7.90–7.94 (2H, m); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 14.1 (CH_3), 20.3 (CH_2), 32.5 (CH_2), 52.9 (CH), 65.2 (CH_2), 128.5 (CH), 129.2 (CH), 134.1 (CH), 139.1 (C), 201.5 (C); *m/z* (ES+): 283.2 [$(M+H)^+$, 22%], 300.2 [$(M+H_2O)^+$, 100%].

Synthesis of α-diazo-β-oxosulfones

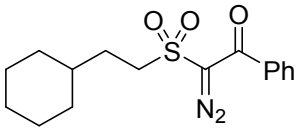
*Methyl 2-((2-cyclohexylethyl)sulfonyl)-2-diazoacetate (**14**)*



Potassium carbonate (1.85 g, 13.4 mmol) was added to a stirring solution of methyl 2-((2-cyclohexylethyl)sulfonyl) acetate **20** (3.03 g, 12.2 mmol) in acetonitrile (30 mL) at room temperature. The reaction mixture was stirred for 10 min before being cooled to 0 °C while a solution of 4-acetamidobenzenesulfonyl azide (ABSA) (2.93 g, 12.2 mmol) in acetonitrile (30 mL) was added. The reaction mixture was stirred at 0 °C for 30 min and returned to room temperature while stirring overnight before the addition of a non-polar co-solvent, hexane (20 mL) and diethyl ether (10 mL), to precipitate amide salts. The reaction mixture was stirred for a further 15 minutes, concentrated under reduced pressure and dichloromethane was added in order to decant from the bulk amide salts. Purification by column chromatography on silica gel, using ethyl acetate/hexane (20:80) as eluent, gave pure methyl 2-((2-cyclohexylethyl)sulfonyl)-2-diazoacetate **14** as a yellow oil (2.65 g, 79%); Anal. Calcd for $C_{11}H_{18}N_2O_4S$: C, 48.16; H, 6.61; N, 10.21. Found: C, 47.97; H, 6.60; N, 9.97; ν_{max} (ATR)/cm^{-1} (neat) 2124 (CN) 1713 (CO), 1331, 1294, 1144 (SO_2); δ_H ($CDCl_3$, 300 MHz) 0.84–1.05 (2H, m), 1.06–1.46 (4H, m), 1.58–1.81 (7H, m), 3.34–3.46 (2H, symmetrical m), 3.88 (3H, s); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 25.9 (CH_2), 26.1 (CH_2), 29.5 (CH_2), 32.7 (CH_2),

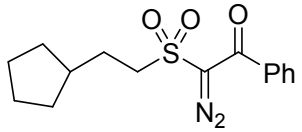
36.4 (CH), 52.9 (CH_3), 54.6 (CH_2), 72.8 (C), 160.4 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{11}H_{19}N_2O_4S$ 275.1066; found 275.1064.

*2-((2-Cyclohexylethyl)sulfonyl)-2-diazo-1-acetophenone (**15**)*



The title compound was prepared using the procedure described for methyl 2-((2-cyclohexylethyl)sulfonyl)-2-diazoacetate **14**, using potassium carbonate (0.20 g, 1.58 mmol), 2-((2-cyclohexylethyl)sulfonyl)-1-acetophenone **21** (0.42 g, 1.43 mmol) in acetonitrile (30 mL) and ABSA (0.38 g, 1.58 mmol) in acetonitrile (20 mL). The mixture was stirred at 0 °C for 30 min and returned to room temperature while stirring overnight. Purification by column chromatography on silica gel, using ethyl acetate/hexane (7:93 to 10:90) as eluent, gave the pure product 2-((2-cyclohexylethyl)sulfonyl)-2-diazo-1-acetophenone **15** as a yellow solid (0.34 g, 75%); mp 93–95°C; Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N, 8.74. Found: C, 59.99; H, 6.25; N, 8.52; ν_{max}(ATR)/cm^{-1} (neat) 2132 (CN), 1637 (CO) 1330, 1226, 1144 (SO); δ_H ($CDCl_3$, 300 MHz) 0.81–1.05 (2H, m), 1.05–1.48 (4H, m), 1.55–1.84 (7H, m), 3.48–3.62 (2H, symmetrical m), 7.45–7.56 (2H, m), 7.56–7.74 (3H, m); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 25.9 (CH_2), 26.2 (CH_2), 29.7 (CH_2), 32.8 (CH_2), 36.4 (CH), 54.9 (CH_2), 80.2 (C), 127.4 (CH), 129.1 (CH), 133.3 (CH), 135.7 (C), 183.4 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{21}N_2O_3S$ 321.1273; found 321.1280.

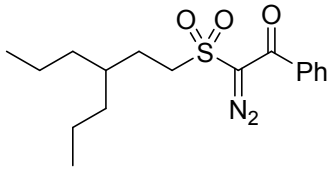
*2-((2-Cyclopentylethyl)sulfonyl)-2-diazo-1-acetophenone (**16**)*



The title compound was prepared using the procedure described for methyl 2-((2-cyclohexylethyl)sulfonyl)-2-diazoacetate **14**, using potassium carbonate (0.61 g, 4.39 mmol), 2-((2-cyclopentylethyl)sulfonyl)-1-phenylethan-1-one **22** (1.12 g, 3.99 mmol) in acetonitrile (30 mL) and ABSA (1.06 g, 4.39 mmol) in acetonitrile (20 mL). The mixture was stirred at 0 °C for 30 min and returned to room temperature while stirring overnight. Purification by column chromatography on silica gel, using ethyl acetate/hexane (10:90) as eluent, gave the pure product 2-((2-cyclopentylethyl)sulfonyl)-2-diazo-1-acetophenone **16** as a yellow solid (0.87 g, 71%); mp 84–86 °C; Anal. Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14.

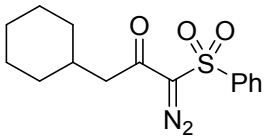
Found: C, 58.80; H, 5.98; N, 8.93; ν_{max}(ATR)/cm^{-1} (neat) 2131 (CN), 1641 (CO) 1330, 1142 (SO); δ_H ($CDCl_3$, 300 MHz) 1.04–1.23 (2H, m), 1.46–1.72 (4H, m), 1.73–1.97 (5H, m), 3.48–3.62 (2H, symmetrical m), 7.46–7.57 (2H, m), 7.57–7.73 (3H, m); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 25.0 (CH_2), 28.5 (CH_2), 32.3 (CH_2), 38.5 (CH), 56.1 (CH_2), 80.1 (C), 127.4 (CH), 129.1 (CH), 133.3 (CH), 135.6 (C), 183.4 (C); HRMS (ESI−TOF) (*m*/*z*): [M+H]$^+$ calcd for $C_{15}H_{19}N_2O_3S$ 307.1116; found 307.1112.

*2-Diazo-1-phenyl-2-((3-propylhexyl)sulfonylethan-1-one (**17**)*



The title compound was prepared using the procedure described for methyl 2-((2-cyclohexylethyl)sulfonyl)-2-diazoacetate **14**, using potassium carbonate (1.24 g, 8.99 mmol), 1-phenyl-2-((3-propylhexyl)sulfonyl)ethan-1-one **23** (2.33 g, 7.48 mmol) in acetonitrile (30 mL) and ABSA (2.34 g, 9.74 mmol) in acetonitrile (20 mL). The mixture was stirred at 0 °C for 30 min and returned to room temperature while stirring overnight. Purification by column chromatography, employing ethyl acetate/hexane (10:90) as eluent, gave the pure product 2-diazo-1-phenyl-2-((3-propylhexyl)sulfonylethan-1-one **17** as a yellow oil (2.13 g, 84%); Anal. Calcd for $C_{17}H_{24}N_2O_3S$: C, 60.69; H, 7.19; N, 8.33. Found: C, 60.32; H, 7.20; N, 8.00; ν_{max}(ATR)/cm^{-1} (neat) 2107 (CN), 1640 (CO) 1330, 1282, 1139 (SO); δ_H ($CDCl_3$, 300 MHz) 0.82–0.96 (6H, m), 1.15–1.38 (8H, m), 1.44–1.58 (1H, m), 1.74–1.86 (2H, m), 3.45–3.57 (2H, symmetrical m), 7.46–7.56 (2H, m), 7.57–7.72 (3H, m); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 14.2 (CH_3), 19.5 (CH_2), 26.0 (CH_2), 35.4 (CH_2), 35.8 (CH), 54.5 (CH_2), 80.2 (C), 127.3 (CH), 129.0 (CH), 133.3 (CH), 135.7 (C), 183.3 (C); HRMS (ESI−TOF) (*m*/*z*): [M+H]$^+$ calcd for $C_{17}H_{25}N_2O_3S$ 337.1586; found 337.1586.

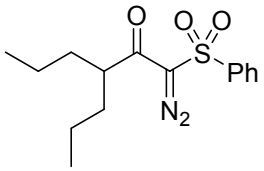
*3-Cyclohexyl-1-diazo-1-(phenylsulfonyl)propan-2-one (**18**)*



The title compound was prepared using the procedure described for methyl 2-((2-cyclohexylethyl)sulfonyl)-2-diazoacetate **14**, using potassium carbonate (1.36 g, 9.81 mmol), 1-cyclohexyl-3-(phenylsulfonyl)propane-2-one **27** (2.50 g, 8.92 mmol) in acetonitrile (50

mL) and ABSA (2.14 g, 8.92 mmol) in acetonitrile (20 mL). The reaction mixture was stirred at 0 °C for 30 min and returned to room temperature while stirring overnight. Purification by column chromatography, employing hexane/DCM (55:45) as eluent, gave the pure product 3-cyclohexyl-1-diazo-1-(phenylsulfonyl)propan-2-one **18** as a yellow oil (2.18 g, 80%); Anal. Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14. Found: C, 59.02; H, 5.98; N, 8.86; ν_{max}(ATR)/cm^{-1} (neat) 2104 (CN), 1659 (CO) 1328, 1149 (SO); δ_H ($CDCl_3$, 300 MHz) 0.76–0.98 (2H, m), 0.99–1.31 (3H, m), 1.51–1.69 (5H, m), 1.69–1.90 (1H, m), 2.40 (2H, d, *J* 6.8 Hz), 7.52–7.63 (2H, m), 7.63–7.72 (1H, m), 7.94–8.03 (2H, m); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 25.9 (CH_2), 26.0 (CH_2), 32.9 (CH_2), 34.2 (CH), 46.5 (CH_2), 85.4 (C), 127.4 (CH), 129.4 (CH), 134.1 (CH), 142.1 (C), 188.0 (C); HRMS (ESI−TOF) (*m*/*z*): [M+H]$^+$ calcd for $C_{15}H_{19}N_2O_3S$ 307.1116; found 307.1108.

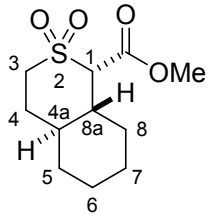
*1-Diazo-1-(phenylsulfonyl)-3-propylhexan-2-one (**19**)*



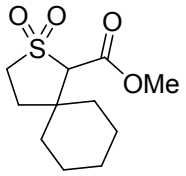
The title compound was prepared using the procedure described for methyl 2-((2-cyclohexylethyl)sulfonyl)-2-diazoacetate **14**, using potassium carbonate (2.68 g, 19.4 mmol), 1-(phenylsulfonyl)-3-propylhexan-2-one **28** (4.20 g, 14.9 mmol) in acetonitrile (100 mL) and *p*-tosyl azide (2.93 g, 14.9 mmol). The reaction mixture was stirred for 4 h before the addition of hexane (40 mL) and diethyl ether (20 mL) and was concentrated under reduced pressure. Purification by column chromatography, employing ethyl acetate/hexane (10:90) as eluent, gave the pure product 1-diazo-1-(phenylsulfonyl)-3-propylhexan-2-one **19** as a yellow solid (3.54 g, 77%); mp 64–66 °C; Anal. Calcd for $C_{15}H_{20}N_2O_3S$: C, 58.42; H, 6.54; N, 9.08. Found: C, 58.53; H, 6.38; N, 9.06; ν_{max} (KBr)/cm^{-1} (neat) 2120 (CN), 1662 (CO) 1338, 1158 (SO); δ_H ($CDCl_3$, 400 MHz) 0.77 (6H, t, *J* 7.2 Hz), 1.05–1.15 (4H, symmetrical m), 1.26–1.35 (2H, m), 1.46–1.55 (2H, m), 2.71–2.80 (1H, m), 7.54–7.60 (2H, m), 7.64–7.69 (1H, m), 7.70–8.01 (2H, m); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 14.0 (CH_3), 20.3 (CH_2), 34.1 (CH_2), 48.0 (CH), 127.5 (CH), 129.3 (CH), 134.1 (CH), 142.1 (C), 192.6 (C), CN signal not observed; *m*/*z* (ES+): 309.1 [(M+H)$^+$, 100%].

Synthesis of C–H insertion products

Methyl (1S,4aS*,8aR*)-octahydro-1H-isothiochromene-1-carboxylate 2,2-dioxide (**29a**)*



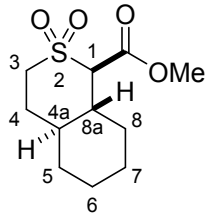
A suspension of $CuCl_2$ (3.67 mg, 27.38 μmol), sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBARF) (29.07 mg, 32.81 μmol) and (4*R*)-Ph bis(oxazoline) ligand **L1** (10.97 mg, 32.81 μmol) in dichloromethane (20 mL) were heated under reflux for 1.5 h under an inert atmosphere. A solution of methyl 2-((2-cyclohexylethyl)sulfonyl)-2-diazoacetate **14** (150 mg, 0.55 mmol) in dichloromethane (20 mL) was added to the pre-generated catalyst over ~90 min. The mixture was heated under reflux while stirring until the reaction was deemed complete upon the disappearance of the diazo stretch at 2124 cm^{-1} by IR spectroscopy. The reaction mixture was cooled to room temperature, filtered through a short pad of Celite® and activated charcoal, and concentrated under reduced pressure to give the crude product, which was then analyzed by ^1H NMR spectroscopy. The crude product mixture, which was loaded using Celite®, was purified using column chromatography on silica gel, employing ethyl acetate/hexane (10:90 to 40:60) as eluent and gave methyl (1*S**,4a*S**,8a*R**)-octahydro-1*H*-isothiochromene-1-carboxylate 2,2-dioxide **29a** (98.4 mg, 73%), methyl 2-thiaspiro[4.5]decane-1-carboxylate 2,2-dioxide **30** (5.6 mg, 4%), and methyl (1*R**,4a*S**,8a*R**)-octahydro-1*H*-isothiochromene-1-carboxylate 2,2-dioxide **29b** (2 mg, 1%). **29a**, least polar fraction, white solid; mp 123–125 °C; $[\alpha]_D^{20}$ +26.6 (*c* 1.0, CH_2Cl_2); 98% ee (determined by chiral phase HPLC); Anal. Calcd for $C_{11}H_{18}O_4S$: C, 53.64; H, 7.37. Found: C, 53.46; H, 7.37; ν_{max} (ATR)/cm^{-1} (neat) 1731 (CO) 1315, 1288, 1229, 1167, 1109 (SO); δ_H ($CDCl_3$, 300 MHz) 0.92–1.11 (2H, m), 1.14–1.36 (2H, m), 1.62–2.14 (8H, m), 2.96 (1H, dq, *J* 14.0, 3.2 Hz), 3.58–3.77 (2H, m), 3.80 (3H, s); δ_c {^1H} ($CDCl_3$, 75.5 MHz) 25.4 (CH_2), 25.5 (CH_2), 30.9 (CH_2), 31.1 (CH_2), 32.9 (CH_2), 33.6 (CH), 43.0 (CH), 48.5 (CH_2), 52.8 (CH_3), 68.9 (CH) 166.9 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{11}H_{19}O_4S$ 247.1004; found 247.1008.



Compound **30**, more polar fraction, colorless oil; ν_{max} (ATR)/cm^{-1} (neat) 1738 (CO) 1316, 1161, 1111 (SO); δ_H ($CDCl_3$, 300 MHz) 1.28–1.68 (8H, m), 1.74–1.88 (1H, m), 1.90–2.11

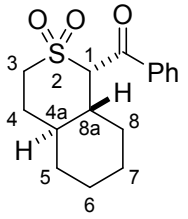
(2H, m), 2.52 (1H, dt, *J* 13.5, 9.4 Hz), 3.19–3.43 (2H, m), 3.81 (3H, s), 3.85 (1H, s); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 22.0 (CH_2), 22.5 (CH_2), 25.4 (CH_2), 32.6 (CH_2), 34.2 (CH_2), 36.0 (CH_2), 44.5 (C), 51.1 (CH_2), 52.8 (CH_3), 72.8 (CH), 165.6 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{11}H_{19}O_4S$ 247.1004; found 247.1000. Compound **29b**, most polar fraction; the spectroscopic and analytical data exactly matches with that of **29b** obtained from the rhodium catalyzed cyclization (see below).

Methyl (1R,4aS*,8aR*)-octahydro-1H-isothiochromene-1-carboxylate 2,2-dioxide (**29b**)*

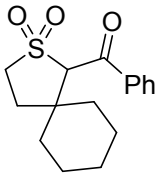


A suspension of $Rh_2(OAc)_4$ (2.42 mg, 5.45 μmol) in dichloromethane (20 mL) was heated to reflux under an atmosphere of nitrogen. After approximately 10 minutes, a solution of methyl 2-((2-cyclohexylethyl)sulfonyl)-2-diazoacetate **14** (149 mg, 0.54 mmol) in dichloromethane (20 mL) was added to this over ~90 min. The mixture was heated under reflux while stirring until the reaction was deemed complete upon the disappearance of the diazo stretch at 2124 cm^{-1} by IR spectroscopy. The reaction mixture was cooled to room temperature, filtered through a short pad of Celite® and activated charcoal, and concentrated under reduced pressure to give the crude product, which was then analyzed by ^{1}H NMR spectroscopy. The crude product mixture, which was loaded using Celite®, was purified using column chromatography on silica gel, employing ethyl acetate/hexane (10:90 to 40:60) as eluent, and gave methyl (1*R**,4a*S**,8a*R**)-octahydro-1*H*-isothiochromene-1-carboxylate 2,2-dioxide **29b** (76 mg, 57%), and methyl (1*S**,4a*S**,8a*R**)-octahydro-1*H*-isothiochromene-1-carboxylate 2,2-dioxide **29a** (1.9 mg, 1%). **29b**, most polar fraction, white solid; mp 163–164 °C; Anal. Calcd for $C_{11}H_{18}O_4S$: C, 53.64; H, 7.37. Found: C, 53.55; H, 7.25; ν_{max} (ATR)/cm^{-1} (neat) 1733 (CO) 1291, 1127 (SO); δ_H ($CDCl_3$, 300 MHz) 0.96–1.39 (5H, m), 1.58–1.86 (4H, m), 1.90–2.03 (2H, m), 2.13 (1H, qd, *J* 11.7, 3.2 Hz), 2.93–3.22 (2H, m), 3.63 (1H, d, *J* 11.7 Hz), 3.85 (3H, s); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 24.9 (CH_2), 25.6 (CH_2), 30.75 (CH_2), 30.83 (CH_2), 32.7 (CH_2), 40.5 (CH), 42.9 (CH), 52.4 (CH_2), 53.2 (CH_3), 71.2 (CH), 164.0 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{11}H_{19}O_4S$ 247.0993; found 247.0995. Compound **29a**, least polar fraction; the spectroscopic and analytical data exactly matches with that of **29a** obtained from the copper catalyzed cyclization (see above).

((1S,4aS*,8aR*)-2,2-Dioxidooctahydro-1H-isothiochromen-1-yl)(phenyl)methanone (**31a**)*

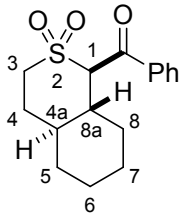


The title compound was prepared using the procedure described for methyl (1*S**,4a*S**,8a*R**)-octahydro-1*H*-isothiochromene-1-carboxylate 2,2-dioxide **29a**, using $CuCl_2$ (1.34 mg, 9.99 μmol), 2-((2-cyclohexylethyl)sulfonyl)-2-diazo-1-acetophenone **15** (64 mg, 0.20 mmol), sodium tetrakis[3,5-bis(trifluoromethyl) phenyl]borate (NaBARF) (10.6 mg, 11.9 μmol) and (4*R*)-Ph bis(oxazoline) ligand **L1** (4.0 mg, 11.9 μmol) in dichloromethane (40 mL). The mixture was heated under reflux while stirring until the reaction was deemed complete upon the disappearance of the diazo stretch at 2132 cm^{-1} by IR spectroscopy. The reaction mixture was cooled to room temperature, filtered through a short pad of Celite® and activated charcoal, and concentrated under reduced pressure to give the crude product, which was then analyzed by ^1H NMR spectroscopy. The crude product mixture, which was loaded using Celite®, was purified using column chromatography on silica gel, employing ethyl acetate/hexane (10:90 to 40:60) as eluent and gave ((1*S**,4a*S**,8a*R**)-2,2-dioxidooctahydro-1*H*-isothiochromen-1-yl)(phenyl)methanone **31a** (51 mg, 87%), (2,2-dioxodo-2-thiaspiro[4.5]decan-1-yl)(phenyl)methanone **32** (2 mg, 3%), and ((1*R**,4a*S**,8a*R**)-2,2-dioxidooctahydro-1*H*-isothiochromen-1-yl)(phenyl)methanone **31b** (0.6 mg, 1%). **31a**, least polar fraction, white solid; mp 125–127 °C; $[\alpha]_D^{20}$ +6.4 (*c* 1.0, CH_2Cl_2); 94% ee (determined by chiral phase HPLC); Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.73; H, 6.89. Found: C, 65.77; H, 6.96; ν_{max} (ATR)/cm^{-1} (neat) 1666 (CO) 1320, 1293, 1227, 1130, 1116 (SO); δ_H ($CDCl_3$, 300 MHz) 0.90–1.10 (2H, m), 1.10–1.35 (2H, m), 1.51–1.62 (1H, m), 1.62–1.84 (3H, m), 1.85–1.99 (1H, m), 1.99–2.17 (2H, m), 2.18–2.32 (1H, m), 2.99 (1H, dq, *J* 13.9, 3.3 Hz), 3.78 (1H, td, *J* 13.7, 3.9 Hz), 4.89 (1H, dd, *J* 4.5, 3.0 Hz), 7.45–7.56 (2H, m), 7.58–7.67 (1H, m), 7.92–8.00 (2H, m); δ_c {^1H} ($CDCl_3$, 75.5 MHz) 25.5 (CH_2), 25.6 (CH_2), 31.2 (CH_2), 31.3 (CH_2), 33.1 (CH_2), 33.4 (CH), 44.6 (CH), 48.8 (CH_2), 67.3 (CH), 128.8 (CH), 128.9 (CH), 134.2 (CH), 138.0 (C), 194.6 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{21}O_3S$ 293.1211; found 293.1206.



Compound **32**, more polar fraction, white solid; mp 84–87 °C; ν_{max} (ATR)/cm^{-1} (neat) 1661 (CO) 1304, 1108 (SO); δ_H ($CDCl_3$, 400 MHz) 1.02–1.14 (1H, m), 1.36–1.52 (4H, m), 1.52–1.61 (1H, m), 1.62–1.77 (2H, m), 1.77–1.86 (1H, m), 2.00–2.19 (2H, m), 2.66 (1H, dt, J 13.4, 9.5 Hz), 3.28–3.39 (1H, m), 3.42–3.52 (1H, m), 4.91 (1H, s), 7.48–7.57 (2H, m), 7.59–7.67 (1H, m), 7.94–8.01 (2H, m); δ_c {^{1}H} ($CDCl_3$, 100.6 MHz) 22.4 (CH_2), 22.9 (CH_2), 25.5 (CH_2), 33.1 (CH_2), 34.5 (CH_2), 36.9 (CH_2), 46.5 (C), 51.7 (CH_2), 71.7 (CH), 128.5 (CH), 129.1 (CH), 134.0 (CH), 138.0 (C), 192.5 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{21}O_3S$ 293.1211; found 293.1206. Compound **31b**, most polar fraction; the spectroscopic and analytical data exactly matches with that of **31b** obtained from the rhodium catalyzed cyclization (see below).

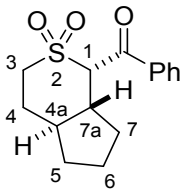
((1R,4aS*,8aR*)-2,2-Dioxidooctahydro-1H-isothiochromen-1-yl)(phenyl)methanone (**31b**)*



The title compound was prepared using the procedure described for methyl (1*R**,4a*S**,8a*R**)-octahydro-1*H*-isothiochromene-1-carboxylate 2,2-dioxide **29b**, using $Rh_2(OAc)_4$ (0.81 mg, 1.84 μmol) and 2-((2-cyclohexylethyl)sulfonyl)-2-diazo-1-acetophenone **15** (59 mg, 184 μmol) in dichloromethane (40 mL). The mixture was heated under reflux while stirring until the reaction was deemed complete upon the disappearance of the diazo stretch at 2132 cm^{-1} by IR spectroscopy. The reaction mixture was cooled to room temperature, filtered through a short pad of Celite® and activated charcoal, and concentrated under reduced pressure to give the crude product, which was then analyzed by ^{1}H NMR spectroscopy. The crude product mixture, which was loaded using Celite®, was purified using column chromatography on silica gel, employing ethyl acetate/hexane (10:90 to 40:60) as eluent, and gave ((1*R**,4a*S**,8a*R**)-2,2-dioxidooctahydro-1H-isothiochromen-1-yl)(phenyl)methanone **31b** (51.0 mg, 87%), ((1*S**,4a*S**,8a*R**)-2,2-dioxidooctahydro-1H-isothiochromen-1-yl)(phenyl)methanone **31a** (2 mg, 4%), and (2,2-dioxodo-2-thiaspiro[4.5]decan-1-

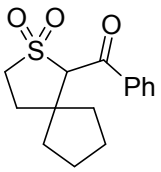
yl)(phenyl)methanone **32** (1 mg, 2%). **31b**, most polar fraction, white solid; mp 191–193°C; ν_{max} (ATR)/cm^{-1} (neat) 1671 (CO) 1287, 1258, 1127 (SO); δ_H ($CDCl_3$, 300 MHz) 0.80–1.01 (1H, m), 1.11–1.45 (4H, m), 1.51–1.87 (4H, m), 1.92–2.15 (2H, m), 2.45 (1H, qd, *J* 11.3, 2.9 Hz), 3.05–3.28 (2H, m), 4.74 (1H, d, *J* 11.5 Hz), 7.43–7.56 (2H, m), 7.56–7.67 (1H, m), 7.97–8.09 (2H, m); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 25.0 (CH_2), 25.8 (CH_2), 30.8 (CH_2), 31.0 (CH_2), 32.9 (CH_2), 40.7 (CH), 43.7 (CH), 53.1 (CH_2), 70.6 (CH), 128.8 (CH), 129.1 (CH), 134.0 (CH), 138.0 (C), 190.5 (C); HRMS (ESI−TOF) (*m*/*z*): [M+H]$^+$ calcd for $C_{16}H_{21}O_3S$ 293.1211; found 293.1205. Compound **31a**, least polar fraction; the spectroscopic and analytical data exactly matches with that of **31a** obtained from the copper catalyzed cyclization. Compound **32**, more polar fraction; the spectroscopic and analytical data exactly matches with that of **32** obtained from the copper catalyzed cyclization (see above).

((1S,4aS*,7aR*)-2,2-Dioxidooctahydrocyclopenta[c]thiopyran-1-yl)(phenyl)methanone* ***(33a)***

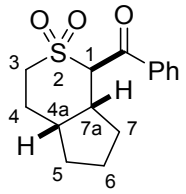


The title compound was prepared using the procedure described for methyl (1*S**,4a*S**,8a*R**)-octahydro-1*H*-isothiochromene-1-carboxylate 2,2-dioxide **29a**, using $CuCl_2$ (2.19 mg, 13.3 μmol), 2-((2-cyclopentylethyl)sulfonyl)-2-diazo-1-acetophenone **16** (100 mg, 0.33 mmol), sodium tetrakis[3,5-bis (trifluoromethyl)phenyl] borate (NaBARF) (17.4 mg, 19.6 μmol) and (4*S*)-*t*-Bu bis(oxazoline) ligand **L5** (5.77 mg, 19.6 μmol) in dichloromethane (40 mL). The mixture was heated under reflux while stirring until the reaction was deemed complete upon the disappearance of the diazo stretch at 2131 cm^{-1} by IR spectroscopy. The reaction mixture was cooled to room temperature, filtered through a short pad of Celite® and activated charcoal, and concentrated under reduced pressure to give the crude product, which was then analyzed by ^{1}H NMR spectroscopy. The crude product mixture, which was loaded using Celite®, was purified using column chromatography on silica gel, employing ethyl acetate/hexane (10:90 to 40:60) as eluent and gave ((1*S**,4a*S**,7a*R**)-2,2-dioxidooctahydrocyclopenta[*c*]thiopyran-1-yl)(phenyl)methanone **33a** (56 mg, 61%), (2,2-dioxido-2-thiaspiro[4.4]nonan-1-yl)(phenyl)methanone **34** (17.5 mg, 19%), and ((1*R**,4a*R**,7a*R**)-2,2-dioxidooctahydrocyclopenta[*c*]thiopyran-1-yl)(phenyl)methanone **33c**

(7 mg, 8%). **33a**, least polar fraction, white solid; mp 103–106 °C; $[\alpha]_D^{20}$ −7.6 (*c* 0.7, CH_2Cl_2); 91% ee (determined by chiral phase HPLC); Anal. Calcd for $C_{15}H_{18}O_3S$: C, 64.72; H, 6.52. Found: C, 64.33; H, 6.69; ν_{max} (ATR)/cm^{-1} (neat) 1677 (CO) 1316, 1280, 1118 (SO); δ_H ($CDCl_3$, 300 MHz) 1.03–1.30 (2H, m), 1.54–2.00 (5H, m), 2.11–2.34 (2H, m), 2.35–2.52 (1H, m), 3.02 (1H, dq, *J* 13.9, 3.2 Hz), 3.79 (1H, td, *J* 13.6, 3.9 Hz), 5.12 (1H, dd, *J* 4.9, 2.5 Hz), 7.45–7.56 (2H, m), 7.58–7.68 (1H, m), 7.90–7.99 (2H, m); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 22.1 (CH_2), 27.8 (CH_2), 28.8 (CH_2), 29.3 (CH_2), 36.7 (CH), 46.4 (CH), 49.6 (CH_2), 68.0 (CH), 128.6 (CH), 129.0 (CH), 134.3 (CH), 137.6 (C), 193.8 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{19}O_3S$ 279.1055; found 279.1065.

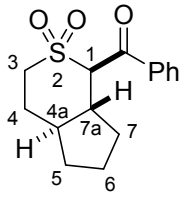


Compound **34**, more polar fraction, white solid and was recrystallized from ethanol; mp 121–124 °C; ν_{max} (ATR)/cm^{-1} (neat) 1673 (CO) 1294, 1117 (SO); δ_H ($CDCl_3$, 300 MHz) 1.51–1.93 (7H, m), 1.96–2.18 (2H, m), 2.80 (1H, dt, *J* 13.1, 9.7 Hz), 3.25–3.51 (2H, m), 4.76 (1H, s), 7.47–7.56 (2H, m), 7.58–7.67 (1H, m), 7.90–8.00 (2H, m); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 23.8 (CH_2), 24.0 (CH_2), 34.0 (CH_2), 36.2 (CH_2), 39.7 (CH_2), 52.8 (C), 53.1 (CH_2), 73.1 (CH), 128.6 (CH), 129.0 (CH), 134.0 (CH), 137.8 (C), 192.6 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{19}O_3S$ 279.1055; found 279.1049.

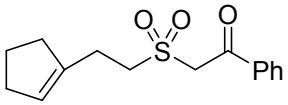


Compound **33c**, more polar fraction, white solid; mp 148–151 °C; ν_{max} (ATR)/cm^{-1} (neat) 1667 (CO) 1270, 1124 (SO); δ_H ($CDCl_3$, 300 MHz) 1.50–1.99 (6H, m), 2.11–2.25 (2H, m), 2.40–2.55 (1H, m), 2.70–2.82 (1H, m), 2.98–3.11 (1H, m), 3.36–3.50 (1H, m), 4.89 (1H, dd, *J* 5.6, 1.6 Hz), 7.46–7.57 (2H, m), 7.59–7.68 (1H, m), 7.96–8.05 (2H, m); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 21.5 (CH_2), 25.7 (CH_2), 28.5 (CH_2), 29.6 (CH_2), 35.3 (CH), 43.2 (CH), 48.4 (CH_2), 64.8 (CH), 128.9 (CH), 129.1 (CH), 134.2 (CH), 136.7 (C), 192.6 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{19}O_3S$ 279.1049; found 279.1045.

((1R,4aS*,7aR*)-2,2-Dioxidooctahydrocyclopenta[c]thiopyran-1-yl)(phenyl)methanone* ***(33b)***



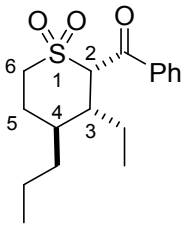
The title compound was prepared using the procedure described for methyl (1*R**,4a*S**,8a*R**)-octahydro-1*H*-isothiochromene-1-carboxylate 2,2-dioxide **29b**, using $Rh_2(OAc)_4$ (1.4 mg, 3.17 μmol) and 2-((2-cyclopentylethyl)sulfonyl)-2-diazo-1-acetophenone **16** (97 mg, 0.32 mmol) in dichloromethane (40 mL). The mixture was heated under reflux while stirring until the reaction was deemed complete upon the disappearance of the diazo stretch at 2131 cm^{-1} by IR spectroscopy. The reaction mixture was cooled to room temperature, filtered through a short pad of Celite® and activated charcoal, and concentrated under reduced pressure to give the crude product, which was then analyzed by ^1H NMR spectroscopy. The crude product mixture, which was loaded using Celite®, was purified using column chromatography on silica gel, employing ethyl acetate/hexane (10:90 to 40:60) as eluent, and gave ((1*R**,4a*S**,7a*R**)-2,2-dioxidooctahydrocyclopenta[*c*]thiopyran-1-yl)(phenyl)methanone **33b** (9 mg, 10%), 2-((2-(cyclopent-1-en-1-yl)ethylsulfonyl)-1-phenylethan-1-one **35** (24 mg, 27%), (2,2-dioxido-2-thiaspiro[4.4]nonan-1-yl)(phenyl)methanone **34** (11.5 mg, 13%), and ((1*R**,4a*R**,7a*R**)-2,2-dioxidooctahydrocyclopenta[*c*]thiopyran-1-yl)(phenyl)methanone **33c** (7 mg, 8%). **33b**, most polar fraction, white solid; mp 149–152 °C; ν_{max} (ATR)/cm^{-1} (neat) 1672 (CO) 1283, 1128 (SO); δ_H ($CDCl_3$, 300 MHz) 1.01–1.20 (1H, m), 1.21–1.48 (1H, m), 1.53–2.10 (6H, m), 2.23 (1H, dq, *J* 14.0, 3.5 Hz), 2.63 (1H, dddd, *J* 11.5, 6.7 Hz), 3.09–3.32 (2H, m), 4.82 (1H, d, *J* 11.6 Hz), 7.45–7.57 (2H, m), 7.57–7.68 (1H, m), 8.03–8.13 (2H, m); δ_c {^1H} ($CDCl_3$, 75.5 MHz) 22.2 (CH_2), 27.3 (CH_2), 29.5 (CH_2), 30.1 (CH_2), 43.9 (CH), 45.8 (CH), 53.7 (CH_2), 71.9 (CH), 128.8 (CH), 129.5 (CH), 134.2 (CH), 137.1 (C), 189.0 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{19}O_3S$ 279.1049; found 279.1047.



Compound **35**, least polar fraction, white solid; mp 65–68 °C; ν_{max} (ATR)/cm^{-1} (neat) 1677 (CO) 1307, 1276, 1118 (SO); δ_H ($CDCl_3$, 300 MHz) 1.81–1.95 (2H, m), 2.24–2.36 (4H, m), 2.61–2.73 (2H, m), 3.37–3.47 (2H, symmetrical m), 4.59 (2H, s), 5.48 (1H, br s), 7.49–7.58 (2H, m), 7.62–7.71 (1H, m), 7.97–8.05 (2H, m); δ_c {^1H} ($CDCl_3$, 75.5 MHz) 23.3 (CH_2), 23.7 (CH_2), 32.5 (CH_2), 34.9 (CH_2), 52.2 (CH_2), 59.7 (CH_2), 126.4 (CH), 129.0 (CH), 129.3 (CH), 134.6 (CH), 135.8 (C), 139.8 (C), 189.2 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for

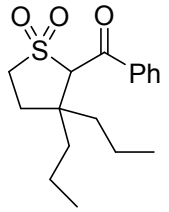
$C_{15}H_{19}O_3S$ 279.1049; found 279.1038. Compound **34**, more polar fraction; the spectroscopic and analytical data exactly matches with that of **34** obtained from the copper catalyzed cyclization. Compound **33c**, more polar fraction; the spectroscopic and analytical data exactly matches with that of **33c** obtained from the copper catalyzed cyclization (see above).

((2S,3R*,4S*)3-Ethyl-1,1-dioxido-4-propyltetrahydro-2H-thiopyran-2-yl)(phenyl)methanone (**36a**)*

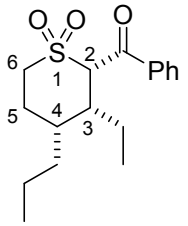


The title compound was prepared using the procedure described for methyl (1*S**,4a*S**,8a*R**)-octahydro-1*H*-isothiochromene-1-carboxylate 2,2-dioxide **29a**, using $CuCl_2$ (3.11 mg, 23.1 μmol), 2-diazo-1-phenyl-2-((3-propylhexyl)sulfonylethan-1-one **17** (156 mg, 0.46 mmol), sodium tetrakis[3,5-bis (trifluoromethyl) phenyl] borate (NaBARF) (24.6 mg, 27.8 μmol) and (4*R*)-Ph bis(oxazoline) ligand **L1** (9.29 mg, 27.8 μmol) in dichloromethane (40 mL). The mixture was heated under reflux while stirring until the reaction was deemed complete upon the disappearance of the diazo stretch at 2107 cm^{-1} by IR spectroscopy. The reaction mixture was cooled to room temperature, filtered through a short pad of Celite® and activated charcoal, and concentrated under reduced pressure to give the crude product, which was then analyzed by ^1H NMR spectroscopy. The crude product mixture, which was loaded using Celite®, was purified using column chromatography on silica gel, employing ethyl acetate/hexane (5:95 to 40:60) as eluent and gave ((2*S**,3*R**,4*S**)3-ethyl-1,1-dioxido-4-propyltetrahydro-2*H*-thiopyran-2-yl)(phenyl)methanone **36a** (24 mg, 21%), (1,1-dioxido-3,3-dipropyltetrahydrothiophen-2-yl)(phenyl)methanone **37** (31 mg, 27%), ((2*S**,3*R**,4*R**)3-ethyl-1,1-dioxido-4-propyltetrahydro-2*H*-thiopyran-2-yl)(phenyl)methanone **36d** (34 mg, 29%), and ((2*R**,3*R**,4*S**)3-ethyl-1,1-dioxido-4-propyltetrahydro-2*H*-thiopyran-2-yl)(phenyl)methanone **36b** (8 mg, 7%). **36a**, least polar fraction, white solid; mp 141–144 °C; $[\alpha]_D^{20}$ +43.3 (*c* 0.9, CH_2Cl_2); 90% ee (determined by chiral phase HPLC); ν_{max} (ATR)/cm^{-1} (neat) 1667 (CO) 1294, 1119 (SO); δ_H ($CDCl_3$, 300 MHz) 0.74 (3H, t, *J* 7.5 Hz), 0.93 (3H, t, *J* 7.1 Hz), 0.98–1.60 (5H, m), 1.69–1.84 (1H, m), 1.84–2.00 (1H, m), 2.12–2.29 (2H, m), 2.30–2.45 (1H, m), 2.96 (1H, dq, *J* 14.1, 3.5), 3.57 (1H, td, *J* 13.9, 3.7 Hz), 5.05 (1H, dd, *J* 4.2, 3.3 Hz), 7.46–7.56 (2H, m), 7.58–7.67 (1H, m), 7.95–8.04 (2H, m); δ_c {^1H} ($CDCl_3$, 75.5

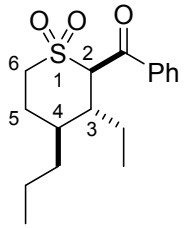
MHz) 11.7 (CH_3), 14.4 (CH_3), 18.8 (CH_2), 23.0 (CH_2), 29.0 (CH_2), 33.4 (CH), 34.7 (CH_2), 46.2 (CH), 47.7 (CH_2), 64.9 (CH), 128.7 (CH), 128.9 (CH), 134.0 (CH), 138.1 (C), 194.7 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{24}O_3S$ 309.1519; found 309.1525.



Compound **37**, more polar fraction, colorless oil; $[\alpha]_D^{20}$ +12.1 (*c* 0.8, CH_2Cl_2); 31% ee (determined by chiral phase HPLC); ν_{max} (ATR)/cm^{-1} (neat) 1682 (CO) 1305, 1224, 1139 (SO); δ_H ($CDCl_3$, 300 MHz) 0.78 (3H, t, *J* 7.0 Hz), 0.81–1.03 (4H, m overlaying a t, *J* 7.2 Hz), 1.19–1.41 (3H, m), 1.46–1.60 (1H, m), 1.62–1.86 (3H, m), 2.08–2.21 (1H, m), 2.59 (1H, dt, *J* 13.5, 9.5 Hz), 3.22–3.49 (2H, m), 4.76 (1H, s), 7.45–7.56 (2H, m), 7.57–7.67 (1H, m), 7.90–7.99 (2H, m); δ_c $\{^1H\}$ ($CDCl_3$, 75.5 MHz) 14.4 (CH_3), 16.9 (CH_2), 17.6 (CH_2), 32.1 (CH_2), 35.8 (CH_2), 38.1 (CH_2), 49.3 (C), 52.2 (CH_2), 72.8 (CH), 128.4 (CH), 129.0 (CH), 133.9 (CH), 138.1 (C), 192.4 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{25}O_3S$ 309.1519; found 309.1514.

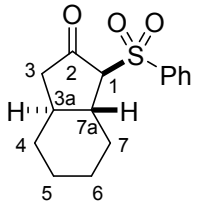


Compound **36d**, more polar fraction, white solid; 102–105 °C; Anal. Calcd for $C_{17}H_{24}O_3S$: C, 66.20; H, 7.84. Found: C, 66.29; H, 7.81; ν_{max} (ATR)/cm^{-1} (neat) 1672 (CO) 1287, 1130 (SO); δ_H ($CDCl_3$, 300 MHz) 0.82–0.93 (3H, m), 1.11 (3H, t, *J* 7.3 Hz), 1.17–1.36 (4H, m), 1.41–1.57 (1H, m), 1.83–2.29 (5H, m), 3.02–3.14 (1H, m), 3.52–3.68 (1H, m), 4.99 (1H, dd, *J* 4.0, 2.3 Hz), 7.46–7.55 (2H, m), 7.59–7.67 (1H, m), 7.93–8.00 (2H, m); δ_c $\{^1H\}$ ($CDCl_3$, 75.5 MHz) 12.5 (CH_3), 14.0 (CH_3), 18.7 (CH_2), 20.3 (CH_2), 25.3 (CH_2), 32.6 (CH), 32.7 (CH_2), 43.9 (CH), 50.3 (CH_2), 65.2 (CH), 128.8 (CH), 129.0 (CH), 134.2 (CH), 136.2 (C), 192.9 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{25}O_3S$ 309.1519; found 309.1522.



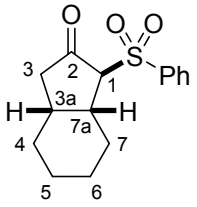
Compound **36b**, most polar fraction, white solid; mp 165–168 °C; $[\alpha]_D^{20}$ +15.5 (*c* 0.2, CH_2Cl_2); 33% ee (determined by chiral phase HPLC); Anal. Calcd for $C_{17}H_{24}O_3S$: C, 66.20; H, 7.84. Found: C, 66.05; H, 7.87; ν_{max} (ATR)/cm^{-1} (neat) 1668 (CO) 1279, 1131 (SO); δ_H ($CDCl_3$, 300 MHz) 0.72 (3H, t, *J* 7.6 Hz), 0.89–0.99 (3H, m), 1.17–1.71 (7H, m), 1.95–2.12 (1H, m), 2.19 (1H, dq, *J* 14.6, 3.9), 2.66 (1H, tt, *J* 11.1, 3.7 Hz), 3.08 (1H, td, *J* 13.5, 3.7 Hz), 3.24 (1H, dt, *J* 14.1, 3.9 Hz), 4.96 (1H, d, *J* 11.2 Hz), 7.46–7.55 (2H, m), 7.57–7.67 (1H, m), 8.02–8.10 (2H, m); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 8.3 (CH_3), 14.3 (CH_3), 18.9 (CH_2), 21.8 (CH_2), 28.0 (CH_2), 33.9 (CH_2), 36.6 (CH), 42.6 (CH), 52.5 (CH_2), 68.4 (CH), 128.9 (CH), 129.1 (CH), 134.0 (CH), 137.7 (C), 190.5 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{17}H_{25}O_3S$ 309.1519; found 309.1524.

(1S,3aS*,7aR*)1-(Phenylsulfonyl)octahydro-2H-inden-2-one (**38a**)*



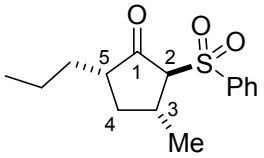
The title compound was prepared using the procedure described for methyl (1*S**,4a*S**,8a*R**)-octahydro-1*H*-isothiochromene-1-carboxylate 2,2-dioxide **29a**, using $CuCl_2$ (2.4 mg, 17.6 μmol), 3-cyclohexyl-1-diazo-1-(phenylsulfonyl)propan-2-one **18** (108 mg, 0.35 mmol), sodium tetrakis[3,5-bis (trifluoromethyl)phenyl] borate (NaBARF) (18.74 mg, 21.2 μmol) and (4*R*)-Bn bis(oxazoline) ligand **L2** (7.66 mg, 21.2 μmol) in dichloromethane (40 mL). The mixture was heated under reflux while stirring until the reaction was deemed complete upon the disappearance of the diazo stretch at 2104 cm^{-1} by IR spectroscopy. The reaction mixture was cooled to room temperature, filtered through a short pad of Celite® and activated charcoal, and concentrated under reduced pressure to give the crude product, which was then analyzed by ^{1}H NMR spectroscopy. The crude product mixture, which was loaded using Celite®, was purified using column chromatography on silica gel, employing ethyl acetate/hexane (10:90 to 20:80) as eluent and gave (1*S**,3a*S**,7a*R**)1-

(phenylsulfonyl)octahydro-2*H*-inden-2-one **38a** (52 mg, 53%, containing <5% of **38c**, δ_H 3.7 ppm, d, *J* 7.7 Hz), and (1*S**,3a*R**,7a*R**)1-(phenylsulfonyl)octahydro-2*H*-inden-2-one **38b** (2 mg, 2%). **38a**, most polar fraction, white solid; $[\alpha]_D^{20}$ +119.0 (*c* 1.0, CH_2Cl_2); 64% ee (determined by chiral phase HPLC). An analytically pure sample of **38a** was recrystallized from ethanol; mp 115–117 °C; Anal. Calcd for $C_{15}H_{18}O_3S$: C, 64.72; H, 6.52. Found: C, 64.86; H, 6.47; ν_{max} (ATR)/cm^{-1} (neat) 1753 (CO) 1302, 1151 (SO); δ_H ($CDCl_3$, 300 MHz) 1.16–1.60 (5H, m), 1.77–1.92 (2H, m), 1.92–2.08 (2H, m), 2.16–2.41 (3H, m), 3.48 (1H, d, *J* 11.4 Hz), 7.51–7.62 (2H, m), 7.62–7.72 (1H, m), 7.85–7.94 (2H, m); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 25.86 (CH_2), 25.91 (CH_2), 31.2 (CH_2), 40.8 (CH), 45.1 (CH), 45.6 (CH_2), 74.4 (CH), 129.0 (CH), 129.2 (CH), 134.0 (CH), 138.7 (C), 204.8 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{19}O_3S$ 279.1055; found 279.1052.



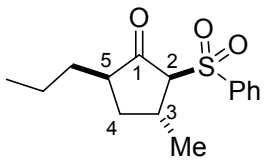
Compound **38b**, least polar fraction, white solid; mp 102–104 °C; $[\alpha]_D^{20}$ +31.6 (*c* 0.16, CH_2Cl_2); 50% ee (determined by chiral phase HPLC); Anal. Calcd for $C_{15}H_{18}O_3S$: C, 64.72; H, 6.52. Found: C, 64.52; H, 6.54; ν_{max} (ATR)/cm^{-1} (neat) 1749 (CO) 1294, 1142 (SO); δ_H ($CDCl_3$, 300 MHz) 0.94–1.12 (1H, m), 1.22–1.46 (2H, m), 1.46–1.86 (5H, m), 2.08–2.24 (1H, m), 2.38–2.57 (2H, m), 3.02–3.14 (1H, m), 3.56 (1H, d, *J* 7.8 Hz), 7.52–7.63 (2H, m), 7.63–7.73 (1H, m), 7.83–7.91 (2H, m); δ_c {^{1}H} ($CDCl_3$, 75.5 MHz) 21.7 (CH_2), 22.8 (CH_2), 27.2 (CH_2), 28.1 (CH_2), 33.4 (CH), 37.5 (CH), 45.1 (CH_2), 72.0 (CH), 129.09 (CH), 129.11 (CH), 134.1 (CH), 138.4 (C), 207.1 (C); HRMS (ESI−TOF) (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{19}O_3S$ 279.1055; found 279.1049.

(2S,3R*,5S*)3-Methyl-2-(phenylsulfonyl)-5-propylcyclopentan-1-one (**39a**)*



The title compound was prepared using the procedure described for methyl (1*S**,4a*S**,8a*R**)-octahydro-1*H*-isothiochromene-1-carboxylate 2,2-dioxide **29a**, using copper(II) triflate (11.7 mg, 32.4 μmol) and 1-diazo-1-(phenylsulfonyl)-3-propylhexan-2-one **19** (200 mg, 0.65 mmol) in double distilled dichloromethane (40 mL). The mixture was heated under reflux

while stirring until the reaction was deemed complete upon the disappearance of the diazo stretch at 2120 cm^{-1} by IR spectroscopy. The reaction mixture was cooled to room temperature, filtered through a short pad of Celite® and activated charcoal, and concentrated under reduced pressure to give the crude product, which was then analyzed by ^1H NMR spectroscopy. The crude product mixture, which was loaded using Celite®, was purified using column chromatography on silica gel, employing ethyl acetate/hexane (0:100 to 10:90) as eluent and three product fractions were isolated containing; (2*S**,3*R**,5*S**)3-methyl-2-(phenylsulfonyl)-5-propylcyclopentan-1-one **39a** (84 mg, 46%), a mixture of **39a** and **39b** (65 mg, 36%) and (2*S**,3*R**,5*R**)3-methyl-2-(phenylsulfonyl)-5-propylcyclopentan-1-one **39b** (13 mg, 7%, containing ~10% of **39a**). **39a**, most polar, white solid; mp 45–48 °C; Anal. Calcd for $C_{15}H_{20}O_3S$: C, 64.26; H, 7.19. Found: C, 64.39; H, 7.03; ν_{max} (KBr)/cm^{-1} 1744 (CO) 1308, 1149 (SO); δ_H ($CDCl_3$, 400 MHz) 0.88 (3H, t, *J* 7.4 Hz), 1.02–1.22 (2H, m), 1.25–1.38 (2H, m), 1.31 (3H, d, *J* 6.4 Hz), 1.66–1.76 (1H, m), 2.30–2.44 (2H, m), 2.79–2.93 (1H, m), 3.33 (1H, d, *J* 9.6 Hz), 7.54–7.60 (2H, m), 7.65–7.70 (1H, m), 7.85–7.90 (2H, m); δ_c {^1H} ($CDCl_3$, 75.5 MHz) 14.0 (CH_3), 20.4 (CH_2), 20.8 (CH_3), 30.4 (CH_2), 31.2 (CH), 35.6 (CH_2), 50.7 (CH), 76.0 (CH), 129.0 (CH), 129.1 (CH), 134.1 (CH), 138.2 (C), 207.6 (C); *m*/*z* (ES+) 281.2 [$(M+H)^+$, 38%], 298.2 [$(M+H_2O)^+$, 48%], 449.6 (100 %).



Compound **39b**, least polar fraction, white solid. δ_H ($CDCl_3$, 400 MHz) 0.88 (3H, t, *J* 7.2 Hz), 1.20–1.38 (3H, m), 1.25 (3H, d, *J* 6.8 Hz), 1.54–1.66 (1H, m), 1.71–1.80 (1H, m), 2.01–2.11 (1H, m), 2.27–2.38 (1H, m), 3.02–3.13 (1H, m), 3.40 (1H, d, *J* 6.0 Hz), 7.54–7.60 (2H, m), 7.65–7.70 (1H, m), 7.85–7.90 (2H, m); δ_c {^1H} ($CDCl_3$, 75.5 MHz) 13.8 (CH_3), 20.5 (CH_2), 21.1 (CH_3), 31.1 (CH), 32.1 (CH_2), 34.9 (CH_2), 47.9 (CH), 76.6 (CH), 129.1 (CH), 129.2 (CH), 134.1 (CH), 138.3 (C), 209.4 (C).

Supporting Information Statement

X-ray crystallographic data for compounds **29a**, **29b**, **31a**, **33a**, **33c**, **38a**, **38b**, **39a**; chiral phase HPLC conditions; copies of chiral phase HPLC chromatographs; and copies of ^1H and ^{13}C NMR spectra.

Author Information

Corresponding Author

*E-mail: a.maguire@ucc.ie

ORCID

Anita R. Maguire: 0000-0001-8306-1893

Simon E. Lawrence: 0000-0001-9430-7983

Notes

The authors declare no competing financial interest.

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