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Substrate and catalyst effects in the enantioselective copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfones

Amy E. Shiely,[a] **Leslie-Ann Clarke**,[a] **Christopher J. Flynn**,[a] **Aoife M. Buckley**,[a] **Alan Ford**,[a] **Simon E. Lawrence**[a] **and Anita R. Maguire***[b]

Abstract: Excellent enantioselectivities of up to 98% ee are achieved employing the copper-bis(oxazoline)-NaBARF catalyst system in the C–H insertion reactions of α-diazo-β-oxo sulfones. The influence of variation of the bis(oxazoline) ligand, copper salt, additive and substrate on both the efficiency and the enantioselectivities of these intramolecular C–H insertion reactions has been explored. Optimum enantioselectivities are achieved with the phenyl and diphenyl ligands across the substrate series.

Introduction

Formation of new C–C bonds through transition metal catalysed C–H insertion reactions of α-diazocarbonyl compounds is synthetically powerful resulting in the highly efficient and usually highly regioselective activation of previously unactivated C–H bonds.[1] Pioneering work in this area was carried out with rhodium catalysts, where it was found that use of the rhodium carboxylate catalysts such as $Rh_2(OAc)_4$ led to preferential five membered carbocyclic ring formation.[2] In recent years Du Bois showed that this preference could be overturned when using sulfone substrates, to favour six membered ring formation.[3] This change in preference has been rationalised by the conformational impact of the sulfonyl fragment which favours six membered ring geometry within the cyclic transition state.[3] Both Du Bois[4] and Novikov[5] have demonstrated that preferential six membered ring formation can be achieved in the C–H insertion reactions of α-diazo-β-oxo sulfones and α-diazosulfonates resulting in the formation of thiopyrans rather than sulfolanes and in δ-sultones rather than γ-sultones. Taber has also observed this preference for six membered ring formation with the rhodium mediated C–H insertion reactions of α-aryl α-diazo ketones forming cyclohexanones.[6]

Enantioselective transition metal catalysed C–H insertion reactions have been dominated by the use of rhodium, since the first report of an asymmetric C–H insertion reaction in 1990 which described the formation of cyclopentanones in up to 12% ee.[7] Following this work, insertion reactions have been further developed with high enantioselectivities achieved when sterically demanding moieties are present on the carbene carbon.[8] While very early reports in the area of C–H insertion began with copper catalysts,[9] poor reaction efficiencies meant that it has received little attention. The first copper catalysed asymmetric C–H insertion reaction was carried out by Sulikowski using bis(oxazoline) ligands in 1995 with enantioselectivities of up to 20% ee obtained.[10] In recent years within the Maguire group we have demonstrated that excellent enantiocontrol can be achieved using a copper catalyst system in the intramolecular asymmetric C–H insertion reactions of α-diazo-β-oxo sulfones, α-diazo-β-keto sulfones, and α-diazoacetamides with thiopyrans, cyclopentanones and γ-lactams generated in enantioselectivities of up to 98% ee,[11] 91% ee,[12] and 82% ee,[13] respectively. The copper catalyst system is comprised of copper-bis(oxazoline)ligand-NaBARF, with the inclusion of NaBARF essential to achieving high levels of asymmetric induction, through alteration of the catalyst geometry *via* abstraction of the chloride by the sodium cation of NaBARF as we have discussed previously.[14]

Following on from our initial report on excellent enantioselectivities in copper mediated C–H insertion in the synthesis of *cis* thiopyrans (Scheme 1),[11] herein we report a detailed investigation on the impact of variation of the ligand, copper source and substrate on the efficiency, regio- and enantioselectivity of this powerful transformation.

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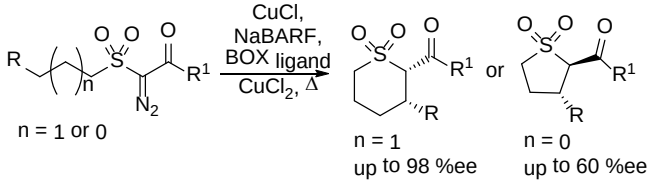
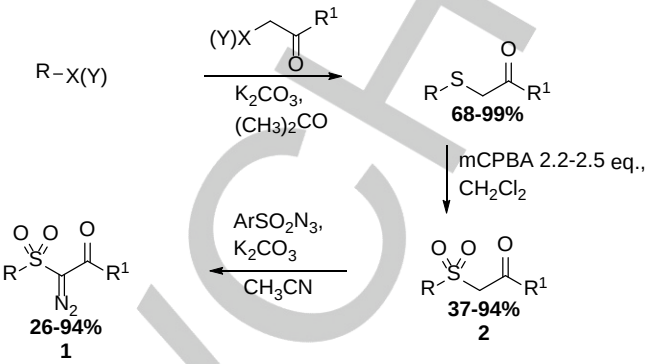


Scheme 1. Copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfones.[11]

Results and Discussion

Sixteen α-diazo-β-oxo sulfones **1** were chosen for investigation in this study, some of which were used in the preliminary investigation and others of which are novel. These compounds were selected to explore the impact of variation of the substrate structure on the ensuing enantioselective C–H insertion reactions, firstly, by focusing on substituent modification on the carbene carbon and secondly, by investigating the influence of the moiety adjacent to the C–H insertion site, and the nature of the linker chain. Exploration of the influence of the bis(oxazoline) ligand and copper source used in the catalytic system was also undertaken.

The substrates were synthesised following standard methodologies as summarised in Scheme 2, affording multi-gram quantities of these compounds which were amenable to storage for several months without noticeable degradation. The β-oxo sulfides were generated *via* two different pathways depending on the commercial availability of the precursor. One method involved the reaction of an alkyl thiol and an α-haloketone or α-haloester in the presence of potassium carbonate. The other method involved reaction of alkyl halides with α-thiocarbonyl compounds again employing potassium carbonate as the base. The crude β-oxo sulfides were used without further purification due to their malodorous nature. The β-oxo sulfides underwent oxidation using *m*-CPBA and in one instance Oxone® to form the β-oxo sulfones **2** which were purified by column chromatography and/or recrystallisation. The diazo transfer to the requisite α-diazo-β-oxo sulfones **1** was carried out under standard conditions.[15] Either *p*-tosyl azide or *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) were used as the diazo transfer reagent. In certain instances, ease of sulfonamide byproduct separation influenced choice of diazo transfer reagent. Reaction times were slower with *p*-ABSA than *p*-tosyl azide (overnight *vs* 3h), however, the yields and efficiencies were comparable therefore use of *p*-ABSA was preferable from a safety perspective.



R = $(CH_2)_2Ph$, $(CH_2)_3Ph$, $(CH_2)_4Ph$, $(CH_2)_5Ph$, $(CH_2)_4C_6H_4F$, $(CH_2)_4C_6H_4NO_2$, $(CH_2)_4C_6H_4Me$, $(CH_2)_4C_6H_4OMe$, 2-ethylphenyl, C_6H_{13}, $C_{12}H_{25}$
X = Cl, Br
Y = SH
R^1 = OMe, OEt, OBn, Me, Ph
Ar = 4-methylphenyl, 4-acetamidophenyl

See SI for more details

Scheme 2. General procedure for α-diazo-β-oxo sulfone **1** synthesis.

Focusing initially on optimisation of the ligand used in the copper catalysed system, a range of commercially available bis(oxazoline) ligands (Figure 1) were investigated with α-diazo-β-oxo sulfone **1a**. This substrate was chosen as it yielded excellent enantioselectivity of 98% ee with the (4*R*)-Ph ligand in our previous study.[11] For the enantioselective copper catalysed C–H insertion reactions a copper source (5 mol%), bis(oxazoline) ligand (6 mol%) and additive NaBARF (6 mol%) were added to the reaction flask at the same time as the α-diazo-β-oxo sulfone **1** and the resulting reaction mixture was then heated under reflux with the insertion appearing to proceed under homogenous conditions. While pre-mixing has been shown to be critical in carrying out the C–H insertion leading to the cyclopentanone, in general with the insertions to form the thiopyrans (typically slower reactions) there was very little impact on efficiency or enantioselectivity through pre-mixing the catalyst.[12, 14b] Accordingly, the experiments reported herein have been carried out without pre-mixing.

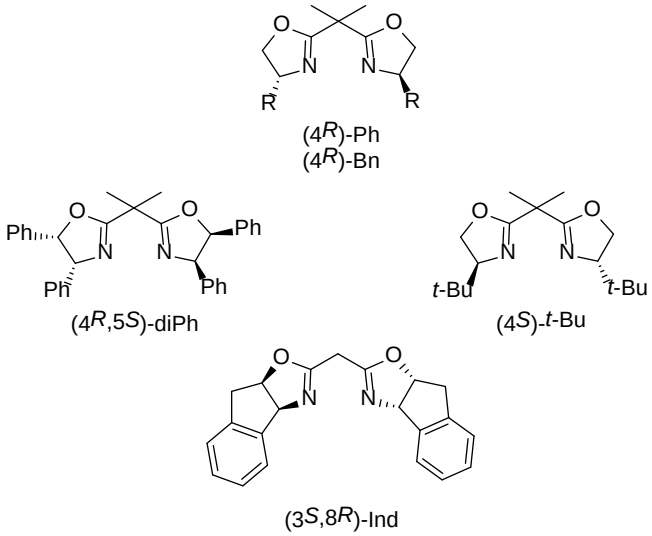
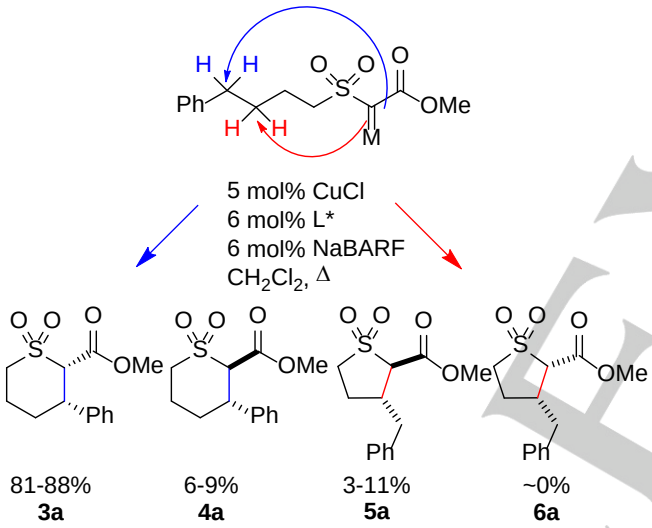


Figure 1. Commercially available bis(oxazoline) ligands.



Scheme 3. C–H insertion products obderved in the insertion reactions of α-diazo-β-oxo sulfone **1a.**

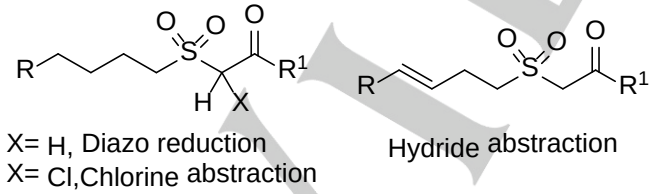
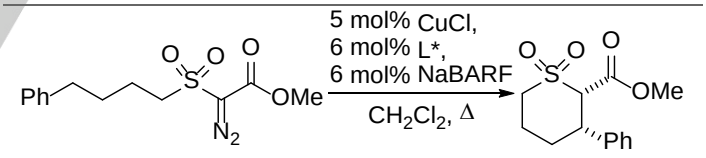


Figure 2. Potential byproducts in the copper catalysed C–H insertion reactions of 1a–p.

The C–H insertion reactions of α-diazo-β-oxo sulfone **1a** can potentially proceed *via* a number of different transition states to lead to a mixture of isomeric C–H insertion products (Scheme 3) along with other byproducts generated *via* diazo reduction, hydride abstraction and chlorine abstraction from the solvent (Figure 2). The overall efficiency for C–H insertion is calculated from the crude ^{1}H NMR spectra using signals for *cis* thiopyran **3a**; δ_H 3.99 [dd, *J* = 4.5 Hz, 2.9 Hz, 1H, C(2)*H*], *trans* thiopyran **4a**; δ_H 4.16 [d, *J* = 12.1 Hz, 1H, C(2)*H*], *trans* sulfolane **5a**; δ_H 3.74 (s, 3H, OCH_3). For the majority of insertion reactions, efficiencies of *ca.* 70–90% were observed. The major insertion product obtained differed with the use of copper or rhodium catalysts. The use of copper led to the formation of *cis* thiopyran **3** as the major insertion product (70–90%) with minor amounts of *trans* thiopyran **4** (4–19%) and *trans* sulfolane **5** (3–13%) detected in the crude ^{1}H NMR spectra as well as minor amounts of byproducts, while, use of $Rh_2(OAc)_4$ led to the formation of *trans* thiopyran **4** as the major C–H insertion product; Novikov also reported *trans* selectivity with rhodium catalysts.[16] For this reason $Cu(OTf)_2$ was used in order to obtain racemic samples of the *cis* thiopyrans **3**. By X-ray crystallography the absolute configuration of **3a** has been previously determined indicating that when the (4*R*)-Ph, (4*R*,5*S*)-diPh and (4*R*)-Bn are used the (2*S*,3*S*) *cis* thiopyran **3** is selectively formed, while using the (4*S*)-*t*-Bu and (3*S*,8*R*)-Ind ligands selectively leads to the (2*R*,3*R*) *cis* thiopyran **3**.[11] By analogy (using HPLC data and specific rotations) the absolute configuration of the remaining *cis* thiopyran derivatives **3** were similarly assigned.

Table 1. Enantioselective transition metal catalysed C–H insertion reactions of α-diazo-β-oxo sulfone **1a**



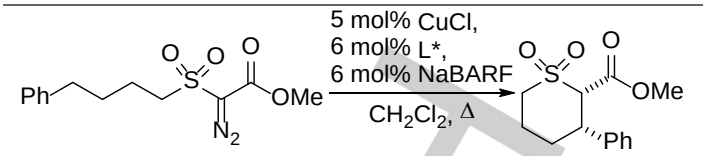
	1a			3a	
Entry	**Ligand**	**Time (h)**	**Yield[a], [b] %**	**% ee[c]**	**Configuration**
1[d],[e]	-	20	29	0	
2[e]	(4*R*)-Ph	6	47	98	(2*S*,3*S*)
3	(4*R*,5*S*)-diPh	21	45	95	(2*S*,3*S*)
4	(4*R*)-Bn	21	36	66	(2*S*,3*S*)
5	(4*S*)-*t*-Bu	21	33	71	(2*R*,3*R*)
6	(3*S*,8*R*)-Ind	21	57	62	(2*R*,3*R*)

[a] Isolated yield after chromatography. [b] Efficiency and product distribution information in SI Table S2. [c] The enantiomeric excess was measured by chiral HPLC analysis (for full details see SI). [d] $Cu(OTf)_2$ was used as the copper source. [e] Previously published result, data included for comparison.[11]

It is clear from Table 1 the (4*R*)-Ph and the (4*R*,5*S*)-diPh ligands yielded the highest enantioselectivities, with α-diazo-β-oxo sulfone **1a**, of 98% ee and 95% ee respectively, while the (4*R*)-Bn, (4*S*)-*t*-Bu and (3*S*,8*R*)-Ind ligands led to lower levels of enantiocontrol. This result is in contrast with that observed in the C–H insertion reactions of α-diazo-β-keto sulfones yielding cyclopentanones, where the (3*S*,8*R*)-Ind ligand leads to the highest levels of asymmetric induction of up to 91% ee.[12] Interestingly, a modest ligand effect on product distribution was observed. Use of the (4*R*)-Ph and (4*R*)-Bn ligand led to only *cis* thiopyran **3** signals being identified, while use of the (4*S*)-*t*-Bu, (4*R*,5*S*)-diPh and (3*S*,8*R*)-Ind led to additional signals in the crude ^{1}H NMR spectra, these signals were attributed to the *trans* thiopyran **4** and/or *trans* sulfolane **5**.

Having established the impact of variation of the ligand on the outcome of the enantioselective reactions of **1a**, the copper source was next investigated. $Cu(OTf)_2$, $CuCl_2$, CuCl and $Cu(CH_3CN)_4PF_6$ were examined (Table 2). Variation of the copper source was shown to strongly affect both efficiencies and reaction times, interestingly, the enantioselectivity displayed little or no sensitivity to the copper salt, indicating the active species is likely to be the same, irrespective of the precursor. Reactions proceeded at a quicker rate with $CuCl_2$ and $Cu(CH_3CN)_4PF_6$ when compared to CuCl and $Cu(OTf)_2$ (2–3 h versus 6h), and use of $CuCl_2$ resulted in a modest increase in yield. The presence of the additive NaBARF has been shown to be essential in achieving optimum C–H insertion outcomes, in this case the reactions carried out in the absence of NaBARF led to significantly longer reaction times, less efficient and less enantioselective reactions regardless of the copper salt used (Table 2, entries 2 and 4 cf 1 and 3).

Table 2. Influence of the copper source in C–H insertion reactions of α-diazo-β-oxo sulfone **1a**



1a **3a**

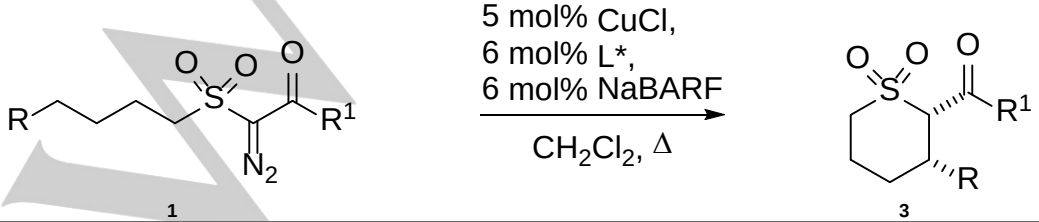
Entry	Copper Source	6 mol% NaBARF	Time (h)	Yield[a], [b] (%)	% ee[c]
1	$CuCl_2$	✓	3	61	95
2	$CuCl_2$	x	98	48	79
3	$Cu(OTf)_2$	✓	6	11	97
4	$Cu(OTf)_2$	x	1 week	17	89
5[d]	CuCl	✓	5	47	98
6[d]	$Cu(CH_3CN)_4PF_6$	x	2	19	94

[a] Isolated yield after chromatography. [b] Efficiency and product distribution information in SI Table S3. [c] The enantiomeric excess was measured by chiral HPLC analysis (for full details see SI). [d] Previously published result, data included for comparison.[11]

Once these initial studies were conducted using α-diazo-β-oxo sulfone **1a**, the ligand effect was further explored when probing the impact of substrate structure on the enantioselectivities achieved in the formation of the *cis* thiopyrans **3**.

The substrate was initially modified at the carbene substituent (ketone or ester) (Table 3). Changing from a methyl ester **1a** to a methyl ketone **1b** resulted in a decrease in enantioselectivity (Table 3, entry 1 cf entry 2). The (4*R*)-Ph and (4*R*,5*S*)-diPh ligands led to the highest levels of enantioselectivity across the substrate screen. Interestingly, with both the phenyl ketone **1c** and the benzyl ester **1d**, their sensitivity across the ligand series was less than that of the methyl ester **1a** (Table 3, entry 3 and 4 cf entry 1).

Table 3. Impact of the variation of the carbene substituent on the enantioselective C–H insertion reactions of α-diazo-β-oxo sulfones **1a–1d**



1 **3**

$CuCl_2$ + NaBARF + Ligand

Entry	Diazo	R	R[1]	(4*R*)-Ph Ligand % Yield[a],[b] (% ee)[c]	(4*R*,5*S*)-diPh Ligand % Yield[a],[b] (% ee)[c]	(4*R*)-Bn Ligand % Yield[a],[b] (% ee)[c]	(4*S*)-*t*-Bu Ligand % Yield[a],[b] (% ee)[c]	No Ligand[e] % Yield[a],[b] (% ee)[c]
					(2*S*,3*S*)		(2*R*,3*R*)	
1	**1a**	Ph	OMe	47 (98)[d]	45 (95)	36 (66)	33 (71)	29 (0)
2	**1b**	Ph	Me	30 (85)[d]	26 (73)	-	-	20 (0)
3	**1c**	Ph	Ph	19 (97)[d]	41 (93)	55 (83)	51 (78)	29 (0)
4	**1d**	Oct	OBn	73 (90)[d],[f]	12 (79)[f]	51 (80)[f]	51 (81)[g]	20 (0)

[a] Isolated yield after chromatography. [b] Efficiency and product distribution information in SI Table S4. [c] The enantiomeric excess was measured by chiral HPLC analysis (for full details see SI). [d] Previously published result, data included for comparison.[11] [e] $Cu(OTf)_2$ used as the copper source. [f] The configuration of **3** is (2*S*,3*R*). [g] The configuration of **3** is (2*R*,3*R*).

Attention next focused on variation of the substituent at the C–H insertion site (Table 4). A range of substrates was synthesised in order to probe the impact of steric and electronic properties at the site of insertion on the outcome of the insertion reactions. Investigations were conducted with the methyl esters **1a, 1e–1j** and, in one instance, the benzyl ester substituent **1d** present on the carbene carbon. As found in the previous studies the highest enantioselectivities and efficiencies were achieved with the (4*R*)-Ph and (4*R*,5*S*)-diPh ligands.

Firstly, it can be seen that the electronic nature of the phenyl ring influences both the efficiency and the enantioselectivity of the C–H insertion at the benzylic C–H. The presence of electron donating groups slightly increases the efficiency of the C–H insertion reactions, going from no substituent **1a** to a methyl **1h** and methoxy **1i** group results in an increase of yield of 47% to 64% and 56% respectively (Table 4, entries 3, 6 and 7). A modest decrease in enantioselectivity is observed in the *cis* thiopyrans **3** bearing electron donating substituents on the aryl ring 98% ee (H), 96% ee (Me) and 91% ee (OMe) (Table 4, entries 3, 6 and 7), however, the enantioselectivity is not affected by the 4-fluoro substituted substrate **1g** (Table 4, entry 4). No C–H insertion is observed when the benzylic C–H bond is adjacent to the 4-nitrophenyl substituent **1j** (Table 4, entry 8). The ligand study carried out with the 4-fluorophenyl substrate **1g** displayed the same trends and ligand sensitivities to those seen with the unsubstituted phenyl derivative **1a**.

Insertion adjacent to an ethyl or benzyl group displayed remarkably similar enantioselectivities when compared to insertion adjacent to the phenyl ring (97% ee, 96% ee and 98% ee respectively) (Table 4, entries 1–3) showing once again that the enantiocontrol is not very sensitive to electronic effects. However, insertion adjacent to an alkyl or benzyl substituent does lead to a change in product distribution compared to insertion at a benzylic site (Figure 3). When no longer inserting into a benzylic C–H the efficiency for *cis* thiopyran **3** formation is reduced from 70–90% to 60–70%. This decrease in *cis* thiopyran **3** formation is accompanied by an increase in *trans* sulfolane **5** formation (3–13% to 17–28%), while the extent of *trans* thiopyran **4** formation is not impacted (4–19%). Trace amounts of the *cis* sulfolane **6** were observed in the reaction of the benzyl ester with the (4*R*,5*S*)-diPh and (4*S*)-*t*-Bu ligands but none was isolated after purification. Overall the data indicates that the enantioselective C–H insertion to form thiopyrans is remarkably insensitive to changes to the substituent at the site of insertion or on the carbene carbon. Furthermore, ligand trends persist across the series with optimum results obtained with the (4*R*)-Ph and (4*R*,5*S*)-diPh ligands (Figure 4).

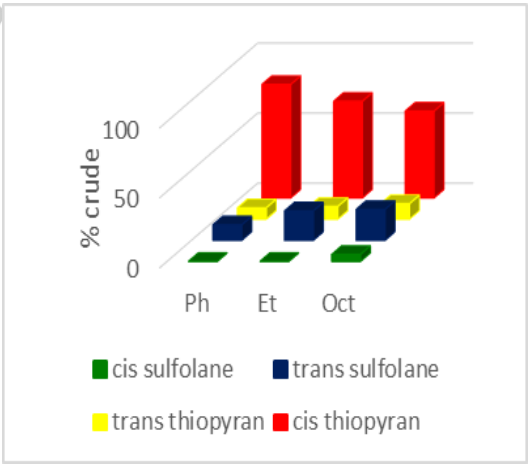
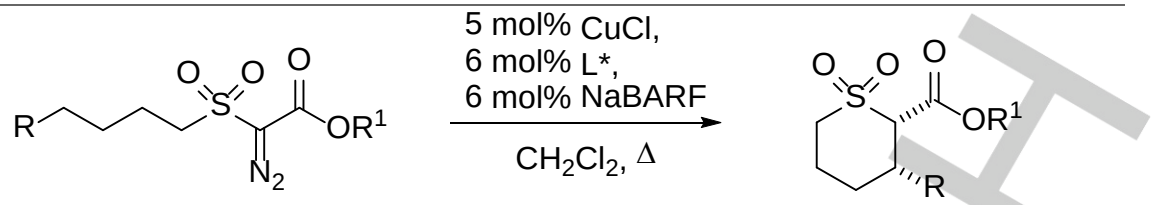
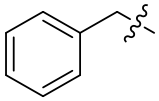
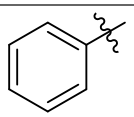
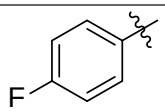
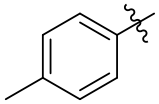
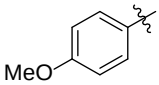
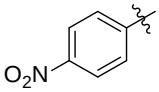


Figure 3. Impact of variation of the substituent adjacent to the C–H insertion site on product distribution with the (4*R*,5*S*)-diPh ligand.

Table 4. Enantioselective C–H insertion reactions of α-diazo-β-oxo sulfones **1a, 1e**–**1j**, variation of the moiety adjacent to the insertion site



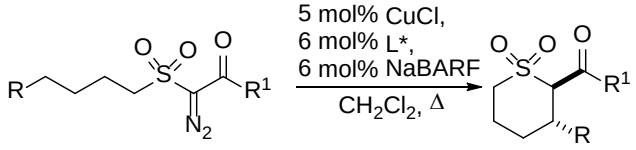
1 **3**

				$CuCl_2$ + NaBARF + Ligand				
				(4*R*)-Ph Ligand % Yield[a],[b] (% ee) [c]	(4*R*,5*S*)-diPh Ligand % Yield[a],[b] (% ee)[c]	(4*R*)-Bn Ligand % Yield[a],[b] (% ee)[c]	(4*S*)-*t*-Bu Ligand % Yield[a],[b] (% ee)[c]	No Ligand[e] % Yield[a],[b] (% ee)[c]
Entry	**Diazo**	**R**	**R^1**	**(2*S*,3*S*)**			**(2*R*,3*R*)**	
1	**1e**		Me	68 (97)[d],[f]	30 (99)[f]	56 (87)[f]	49 (92)[g]	11 (0)
2	**1f**		Me	42 (96)[d]	37[h] (94)	21[h] (80)	2[h] (90)	8 (0)
3	**1a**		Me	47 (98)[d]	45 (95)	36 (66)	33 (71)	29 (0)
4	**1g**		Me	49 (98)	55 (98)	25 (55)	52(80)	24 (0)
5	**1d**	C_8H_{17}	Bn	73 (90)[d],[f]	12 (79)[f]	51 (80)[f]	51 (81)[g]	20 (0)
6	**1h**		Me	64 (96)[d]	-	-	-	-
7	**1i**		Me	56 (91)[d]	-	-	-	-
8	**1j**		Me	Not formed[d]	-	-	-	-

[a] Isolated yield after chromatography. [b] Efficiency and product distribution information in SI Table S5. [c] The enantiomeric excess was measured by chiral HPLC analysis (for full details see SI). [d] Previously published result, data included for comparison.[11] [e] $Cu(OTf)_2$ used as the copper source. [f] The configuration of **3** is (2*S*,3*R*). [g] The configuration of **3** is (2*R*,3*S*). [h] An overall yield is calculated from amounts of each compound in various fractions.

There was no evidence seen for interconversion between *cis* and *trans* thiopyran. Minor amounts of *trans* thiopyrans **4d** and **4e** were isolated after column chromatography (Table 5); interestingly the enantiopurities were considerably lower for both the octyl *trans* thiopyran **4d** and the ethyl *trans* thiopyran **4e**. The best results were obtained using the (4*S*)-*t*-Bu ligand with values of 59% ee and 57% ee being obtained for the octyl and ethyl *trans* thiopyran respectively (Table 5, entries 3 and 5).

Table 5. Enantioselectivites of **4d** and **4e** *trans* thiopyrans isolated from the C–H insertion reactions of α-diazo-β-oxo sulfone **1d** and **1e.**



	1a				**3a**	
Entry	**Diazo**	**R**	**R^1**	**Ligand**	**%Yield [a],[b]**	**% ee[c]**
1	**1d**	Oct	OBn	(4*R*)-Ph	9	45

2	**1d**	Oct	OBn	(4*R*)-Bn	4	10
3	**1d**	Oct	OBn	(4*S*)-*t*-Bu	10	59
4	**1e**	Et	OMe	(4*R*)-Bn	5	6
5	**1e**	Et	OMe	(4*S*)-*t*-Bu	6	57

[a] Isolated yield after chromatography. [b] Efficiency and product distribution information in SI Table S5. [c] The enantiomeric excess was measured by chiral HPLC analysis (for full details see SI).

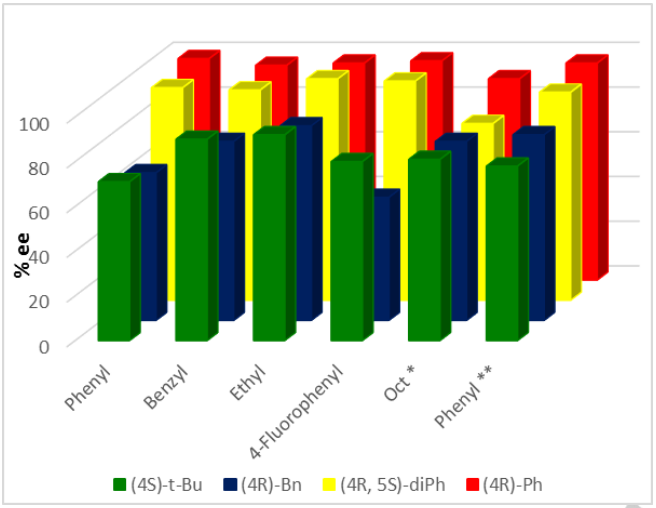
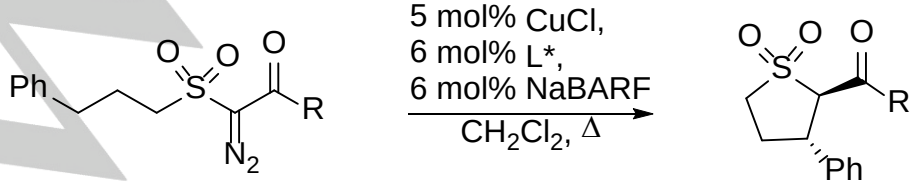


Figure 4. Impact of variation of the substituent adjacent to the C–H insertion site on enantioselectivities with the bis(oxazoline) ligands (* carried out with benzyl ester on the carbene carbon **1f**) (** carried out with the phenyl ketone on the carbene carbon **1c**)

Having investigated the enantioselective C–H insertion reactions of α-diazo-β-oxo sulfones **1a–1j** in which either 6 membered thiopyran or 5 membered sulfolane formation was possible, attention next focused on a range of α-diazo-β-oxo sulfones **1k** and **1l** in which only insertion to form sulfolanes **5** or **6** was possible due to decreased chain length. The efficiencies in terms of product yield were similar to those obtained thus far in the study (Table 1–4), however, the enantioselectivities were, in general, significantly lower for the *trans* sulfolanes **5** than for the *cis* thiopyrans **3**, with the highest level of enantiocontrol (65% ee) achieved with the (4*R*,5*S*)-diPh ligand. Interestingly, the C–H insertion reactions to form sulfolanes **5k** and **5l** were more sensitive to ligand variation in comparison to the thiopyran series (Table 6). Reactions conducted with the ethyl ester **1l** and the (4*R*)-Ph and (4*R*,5*S*)-diPh ligands afforded the highest levels of enantiocontrol (60% ee and 65% ee respectively), while use of the (4*S*)-*t*-Bu and (4*R*)-Bn led to essentially racemic samples of sulfolane **5** (0% ee and 5% ee). With the methyl ketone **1k** a switch in ligand preference was observed, the best enantioselectivity was obtained with the (4*R*)-Bn (59% ee) and (4*S*)-*t*-Bu (51% ee) ligands with a decrease in enantioselectivity obtained with the (4*R*)-Ph and (4*R*,5*S*)-diPh ligands (Table 6, entry 1). While the absolute difference in terms of enantioselectivity is relatively small (Figure 5), the switch in preference is interesting from a mechanistic perspective.

The absolute configuration of *trans* sulfolane **5l** was previously established by X-ray crystallography indicating that when the (4*R*)-Ph, (4*R*,5*S*)-diPh and (4*R*)-Bn are used the (2*R*,3*S*) *trans* sulfolane **5** is preferentially formed, while using the (4*S*)-*t*-Bu ligand selectively leads to the (2*S*,3*R*) *trans* sulfolane **5**.[11] By analogy (using HPLC data and specific rotations) the absolute configuration of the remaining *trans* sulfolane derivatives **5** were similarly assigned.

Table 6. Enantioselective transition metal catalysed C–H insertion reactions of α-diazo-β-oxo sulfone **1k** and **1l**



			1			5	
			$CuCl_2$ + NaBARF + Ligand				
Entry	Diazo	R	(4*R*)-Ph Ligand % Yield[a],[b] (% ee)[c]	(4*R*,5*S*)-diPh Ligand % Yield[a],[b] (% ee)[c]	(4*R*)-Bn Ligand % Yield[a],[b] (% ee)[c]	(4*S*)-*t*-Bu Ligand % Yield[a],[b] (% ee)[c]	No Ligand[e] % Yield[a],[b] (% ee)[c]
			(2*R*,3*S*)			(2*S*,3*R*)	
1	1k	Me	40 (40)[d]	19 (36)	33 (59)	53 (51)	0 (0)
2	1l	OEt	57 (60)[d]	69 (65)	53 (5)	61 (0)	29 (0)

[a] Total yield of cyclised products after chromatography. [b] Efficiency and product distribution information in SI Table S6. [c] The enantiomeric excess was measured by chiral HPLC analysis (for full details see SI). [d] Previously published result, data included for comparison.[11] [e] $Cu(OTf)_2$ used as the copper source.

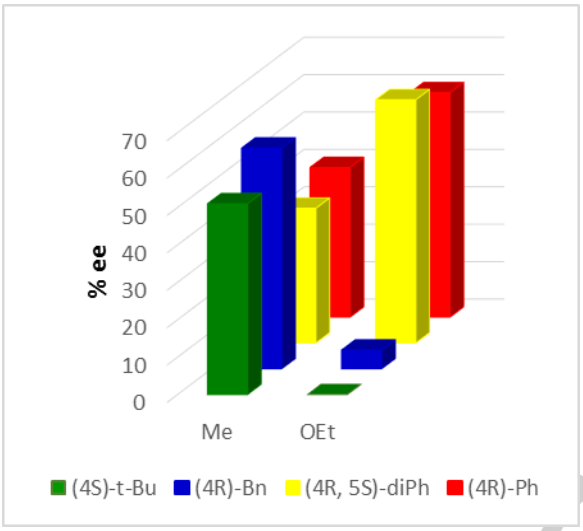


Figure 5. Impact of bis(oxazoline) ligand variation on enantiopurity of *trans* sulfolanes **5k** and **5l**.

The stereochemical outcome of the C–H insertion to selectively produce (2*S*,3*S*) *cis* thiopyran can be rationalised on the basis of the transition states illustrated in Figure 6. Thus, in transition state A leading to the (2*S*,3*S*) *cis* thiopyran the phenyl substituent at the site of the insertion occupies the less sterically hindered quadrant above the plane in the copper complex. Clearly the transition state leading to the *trans* thiopyran would result in significant steric interaction as shown in Figure 6 (transition state B). Furthermore, in transition state A the phenyl substituent occupies a pseudo equatorial position, while in transition state B a pseudo axial orientation is necessary. Transition state C leading to the (2*R*,3*R*) *cis* thiopyran would involve steric interaction between the phenyl substituent on the ligand and the substrate, and is therefore disfavoured relative to A.

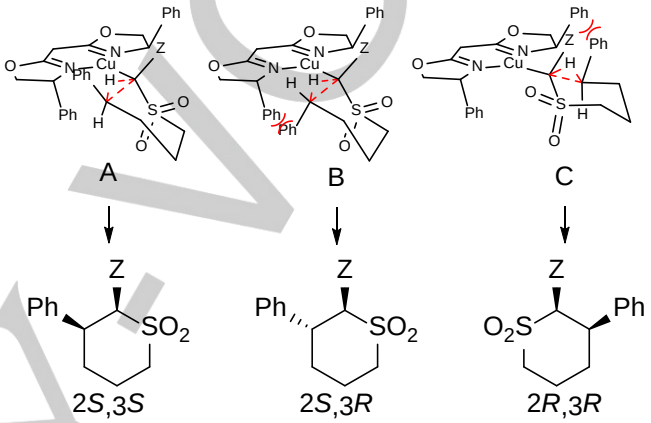


Figure 6. Proposed transition states leading to thiopyran formation.

In contrast, with the sulfolanes the C–H insertion proceeds selectively from the opposite face of the copper carbene/carbenoid such that the phenyl substituent of the substrate occupies the vacant quadrant below the plane of the copper bis(oxazoline) complex, leading to the (2*R*,3*S*) sulfolane. 1,3 Diaxial interactions in transition state B disfavour formation of the *cis* sulfolane, while significantly increased steric interaction in transition state C disfavour formation of the (2*S*,3*R*) enantiomer (Figure 7).

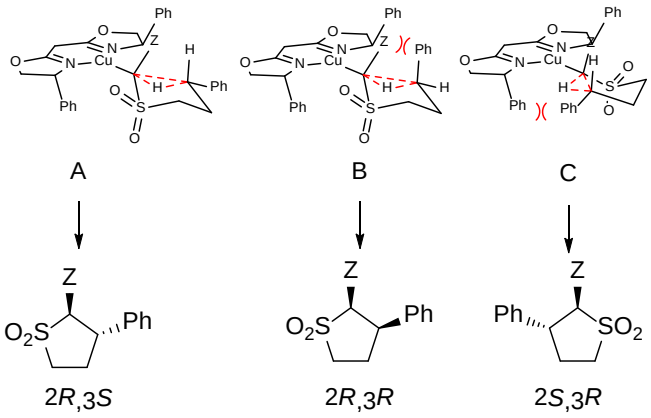
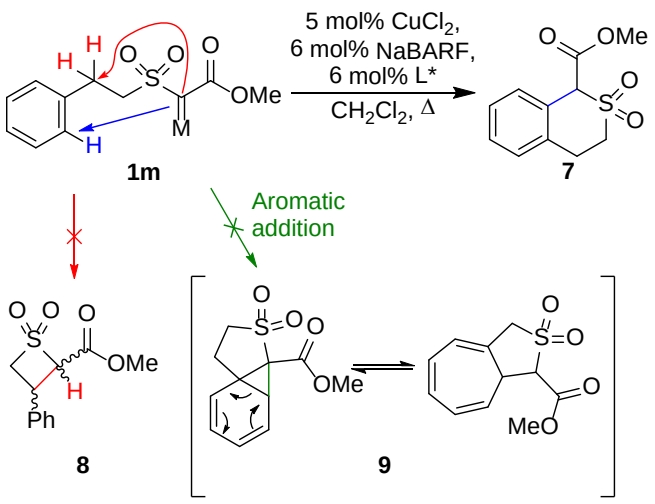


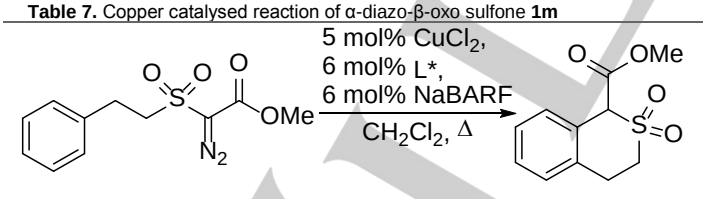
Figure 7. Proposed transition states leading to sulfolane formation.



Scheme 4. Possible reaction pathways of α-diazo-β-oxo sulfone **1m**

The cyclisation of α-diazo-β-oxo sulfone **1m** was explored to establish if C–H insertion to form the highly strained dioxothietane **8** could compete with alternative reaction pathways, for example aromatic addition to form the aromatic addition product **9**, or aromatic substitution to form fused thiopyran **7** (Scheme 4). In the event, when α-diazo-β-oxo sulfone **1m** was subjected to the copper-bis(oxazoline)-NaBARF catalyst the main reaction pathway was found to be aromatic substitution resulting in the production of fused thiopyran **7** with no evidence for C–H insertion or aromatic addition products. As the stereogenic centre in the fused thiopyran **7** is very labile, the product **7** was obtained in racemic form (Table 7).

Table 7. Copper catalysed reaction of α-diazo-β-oxo sulfone **1m**

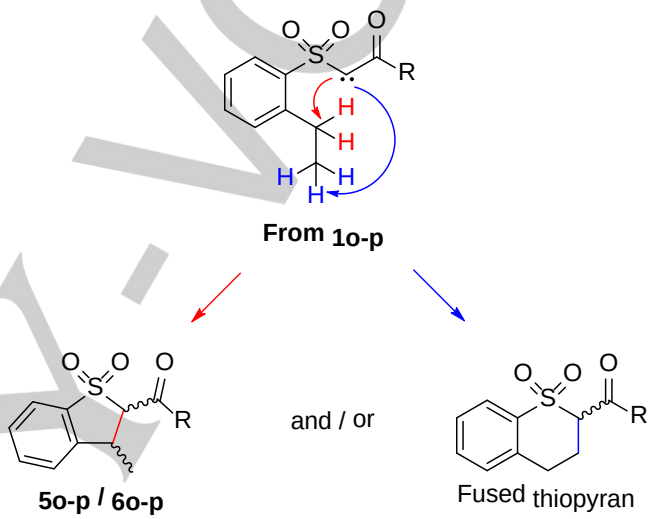


1m **7**

Entry	Ligand	Time (h)	Yield (%)[a],[b]	% ee[c]
1	(4*R*)-Ph	2	70	0
2	(4*R*,5*S*)-diPh	2	68	0
3	(4*R*)-Bn	3	69	0
4	(4*S*)-*t*-Bu	2	66	0

[a] Total yield of cyclised products after chromatography. [b] Efficiency and product distribution information in SI Table S7. [c] The enantiomeric excess was measured by chiral HPLC analysis (for full details see SI).

Up to this point in our investigation excellent enantioselectivities had been achieved in the C–H insertion reactions of substrates possessing a freely rotating alkyl chain (up to 98% ee). Extension of the study to α-diazo-β-oxo sulfones **1n**–**1p** enabled investigation of the influence of a more conformationally constrained linker chain. The substrates were designed to enable exploration of competition between insertion into a benzylic C–H bond to lead to sulfolanes **5**/**6** or a primary C–H bond to lead to thiopyrans **3**/**4** (Scheme 5).



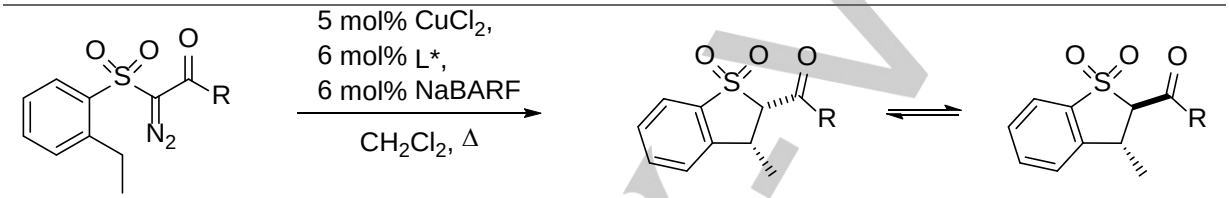
Scheme 5. Possible C–H insertion pathways with the α-diazo-β-oxo sulfones **1n–1p**

When exposed to copper-bis(oxazoline)-NaBARF catalyst, only the sulfolane products **5** and **6** were observed. Interestingly, the preference for insertion at a benzylic position overcomes the six membered ring preference. This observation was in keeping with similar work carried out by Katsuki with iridium catalysed nitrene insertion employing analogous sulfonyl azides to generate sultams.[17] Efficiencies were highest with the ethyl ester **1n** (61–91%) with a slight decrease observed with the phenyl and methyl ketones **1o** (38–55%) and **1p** (38–65%). In the ^{1}H NMR spectra of the crude product of the insertion reactions both the *cis* **6** and *trans* **5** isomers were identified, however, upon chromatographic purification, the *trans* sulfolanes **5** predominated (Table 8). While the diastereomeric ratio in the crude products was sensitive to the ligand employed, this is principally influenced by the rate of epimerisation due to the relative acidity of the α proton.

Once again use of the (4*R*)-Ph and (4*R*,5*S*)-diPh ligands resulted in the highest enantioselectivities across the series with the optimum enantiocontrol achieved with the ethyl ester derivative **1n** and the (4*R*)-Ph ligand (82% ee *cis* **6n** and 80% ee *trans* **5n**). While use of the (4*R*)-Bn and (3*R*,8*S*)-Ind resulted in a significant drop in asymmetric induction the (4*S*)-*t*-Bu yielded intermediate results (Figure 8). This is significant as the trend holds up across the ethyl ester **5n**, methyl **5p** and phenyl ketone **5o** series in contrast to patterns seen with the simple sulfolanes **5k** and **5l**.

The term self-disproportionation of enantiomers (SDE),[18] refers to the phenomenon whereby enantiomeric products are separated into enantioenriched and enantiodepleted fractions by means of a physical process such as achiral column chromatography.[19] A degree of SDE was encountered during the chromatographic separation of sulfolanes **5o** and **5p** [Table 8, entry 6 (70–80% ee), entry 7 (68–75% ee) and entry 12 (66–80% ee)], while it was not observed with the thiopyrans or other sulfolanes. The values in the table are weighted averages to provide an accurate measure of enantioselectivity.

Table 8. Enantioselective transition metal catalysed C–H insertion reactions of α-diazo-β-oxo sulfone **1n**–**1p**



1 **6** **5**

Entry	Ligand	Diazo	R	Combined Yield %[a]	Crude Ratio[b] (Purified Ratio)[b] 6:5	Cis % ee[c] 6	Trans % ee[c] 5
1	(4*R*)-Ph	**1n**	OEt	91	89:11 (6:94)	82 (2*S*,3*R*)	80 (2*R*,3*R*)
2	(4*R*,5*S*)-diPh	**1n**	OEt	67	83:17 (14:86)	83 (2*S*,3*R*)	75 (2*R*,3*R*)
3	(4*R*)-Bn	**1n**	OEt	75	32:68 (7:93)	18 (2*S*,3*R*)	15 (2*R*,3*R*)
4	(4*S*)-*t*-Bu	**1n**	OEt	61	52:48 (11:89)	54 (2*R*,3*S*)	49 (2*S*,3*S*)
5	(3*S*,8*R*)-Ind	**1n**	OEt	84	63:37 (7:93)	3 (2*R*,3*S*)	2 (2*S*,3*S*)
6	(4*R*)-Ph	**1o**	Ph	38	9:91 (1:99)	-	71 (2*R*,3*R*)
7	(4*R*,5*S*)-diPh	**1o**	Ph	50	54:46 (1:99)	-	70 (2*R*,3*R*)
8	(4*R*)-Bn	**1o**	Ph	48	1:99 (1:99)	-	12 (2*R*,3*R*)
9	(4*S*)-*t*-Bu	**1o**	Ph	55	42:58 (1:99)	-	39 (2*S*,3*S*)
10	(3*S*,8*R*)-Ind	**1o**	Ph	42	7:93 (1:99)	-	13 (2*S*,3*S*)
11	(4*R*)-Ph	**1p**	Me	65	2:98 (2:98)	-	64 (2*R*,3*R*)
12	(4*R*,5*S*)-diPh	**1p**	Me	42	2:98 (1:99)	-	76 (2*R*,3*R*)
13	(4*R*)-Bn	**1p**	Me	60	4:96 (1:99)	-	13 (2*R*,3*R*)
14	(4*S*)-*t*-Bu	**1p**	Me	38	2:98 (2:98)	-	12 (2*S*,3*S*)
15	(3*S*,8*R*)-Ind	**1p**	Me	45	5:95 (2:98)	-	16 (2*R*,3*R*)

[a] Total yield of cyclised products after chromatography, contains both the *cis* **6** and *trans* **5** isomers. .[b] Efficiency and product distribution information in SI Table S8. [c] The enantiomeric excess was measured by chiral HPLC analysis (for full details see SI).

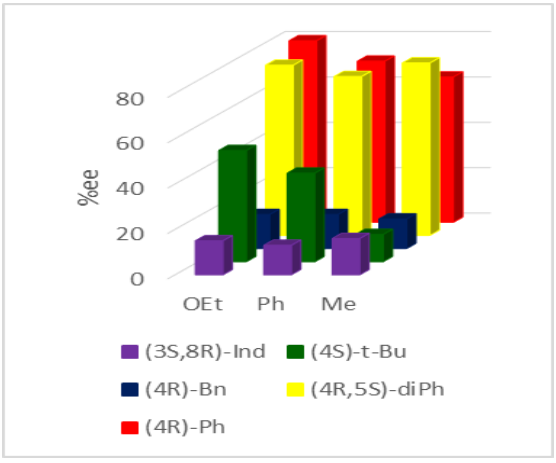
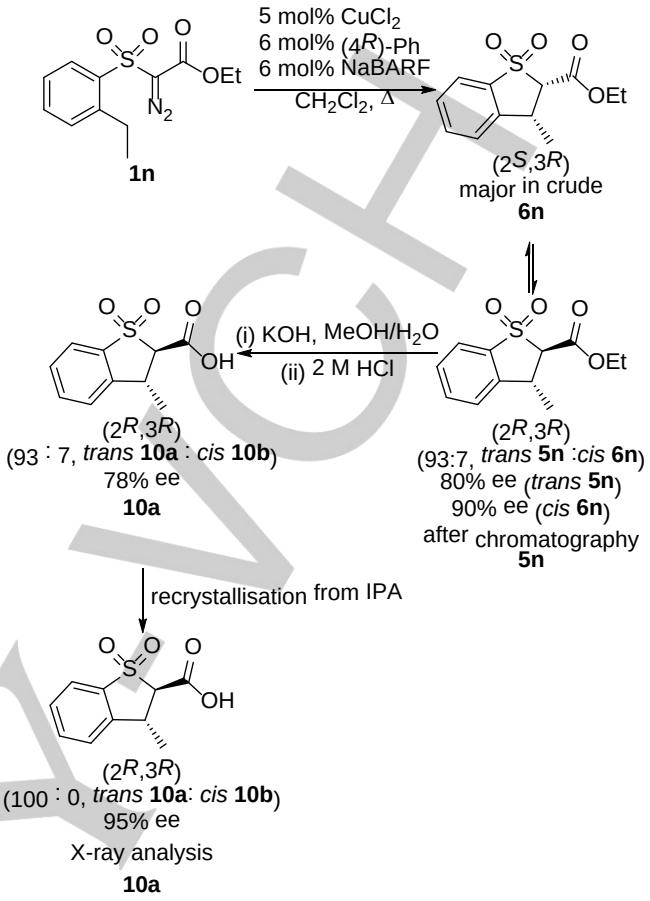


Figure 8. Impact of bis(oxazoline) ligand variation on enantiopurity of *trans* sulfolanes **5n-5p**

The absolute configuration of *trans* sulfolane **5n** was established from the X-ray crystal structure of the acid **10a** obtained by saponification of **5n** (Scheme 6). It was determined that when the (4*R*)-Ph ligand is used the (2*R*,3*R*) *trans* sulfolane **5** is formed. By analogy (using HPLC data) the absolute configuration of the remaining *trans* sulfolane derivatives **5** is similarly assigned (see SI for more details). Therefore when the (4*R*)-Ph, (4*R*,5*S*)-diPh and (4*R*)-Bn ligands are used the (2*R*,3*R*) *trans* sulfolane **5** is selectively formed and use of the (4*S*)-*t*-Bu and the (3*S*,8*R*)-Ind ligands results in selective formation of the (2*S*,3*S*) *trans* sulfolane **5**. Interestingly there was one exception where the (3*S*,8*R*)-Ind when used with the methyl ketone **1p** led to the opposite sense of enantioselectivity to what was expected (Table 8, entry 15); as the absolute enantioselectivites are small, this is not believed to be significant.



Scheme 6. Conversion of ethyl ester 1n to carboxylic acid **10a**

Conclusions

We have established that the copper-bis(oxazoline)-NaBARF system is extremely efficient at achieving high levels of asymmetric induction in the C–H insertion reactions of a broad range of α-diazo-β-oxo sulfones **1**. In freely rotating systems the major product formed in the majority of these C–H insertion reactions is the *cis* thiopyran **3** with enantioselectivities of up to 98% ee. In systems where thiopyran formation is not possible insertion to form the *trans* sulfolane **5** in up to 65% ee becomes the dominant pathway. With fused systems *trans* sulfolane **5** formation dominates with enantioselectivities of up to 83% ee. The phenyl and diphenyl bis(oxazoline) ligands consistently lead to high levels of enantioselectivity across a diverse range of substrates. The copper source and presence of NaBARF have been shown to have a dramatic effect on the rate, efficiency and enantioselectivities achieved in the synthesis of *cis* thiopyrans,

with $CuCl_2$ giving similar levels of enantiocontrol but faster reactions than CuCl. In terms of substrate structure, to date, in the formation of thiopyrans we have found that the level of enantiocontrol achieved in the insertion reactions is remarkably insensitive to the nature of the substituent present on the carbene carbon or at the site of insertion. Achieving good enantioselectivities across a range of substrates using the same catalyst ligand system is advantageous.

Experimental Section

General Procedures.
Solvents were distilled prior to use as follows: dichloromethane was distilled from phosphorus pentoxide and was further distilled from calcium hydride for use in the cyclisation reactions, ethyl acetate was distilled from potassium carbonate. All commercial reagents were used as received unless otherwise stated. ^{1}H NMR spectra were run at either 600, 500, 400 or 300 MHz and ^{13}C NMR spectra were recorded at either 150.9, 125.8, 100 or 75.5 MHz. All spectra were recorded at room temperature (300 K) in deuterated chloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal standard. Chemical shifts were expressed in parts per million (ppm) and coupling constants (*J*) in hertz (Hz). Assignments were made with the aid of DEPT experiments and 2D NMR experiments including COSY, HSQC, HMBC. Elemental analyses was carried out by the Microanalysis Laboratory, National University of Ireland, Cork. Melting points were carried out on a capillary melting point apparatus and are uncorrected. Mass spectra were recorded on a double-focusing high-resolution mass spectrometer (EI), a time-of-flight spectrometer (ESI), and a triple quadrupole spectrometer (ESI). Infrared (IR) spectra were recorded as potassium bromide (KBr) discs for solids, as thin films on sodium chloride plates for oils using a FT-IR spectrometer or on the neat compound using an instrument with a UATR single reflection diamond, and only characteristic peaks are reported. Thin-layer chromatography (TLC) was carried out on precoated silica gel plates. Visualization was achieved by UV (254 nm) light detection, iodine staining, vanillin staining, and/or ceric sulfate staining. Column chromatography was performed using silica gel 60, 0.040–0.063 mm. Chiral HPLC was performed using Chiralpak OJ-H and AS-H columns and Lux™ Cellulose-2, eluting with *n*-hexane and 2-propanol. Specific rotations were recorded at 20 °C in the solvents indicated. The Sodium D line (589 nm) was used. Samples were analyzed in a 1 mL dual-walled thermostatted glass cell of path length 10 cm. Sample temperature control was maintained using an immersion circulator. Procedures and experimental details for compounds **1a**–**1f**, **1h**–**1l**, **1p**, **2a**–**2p**, **3a**–**3f**, **3h**–**3j**, **4d**–**4e**, **5k**–**5l** and **11**–**23** can be found in supporting information.

General Procedure for preparation of α-diazo-β-oxo sulfones
Procedure A: Potassium carbonate (ACS reagent, >99.0%) was added to a stirring solution of sulfone in acetonitrile at room temperature. Stirring was continued for 10 min and then the reaction mixture was cooled to 0°C. A solution of 4-toluenesulfonic azide in acetonitrile was added dropwise over 10 min under an atmosphere of nitrogen. Stirring was continued for a further 30 min at 0°C, then the mixture was removed from the ice bath and stirring was continued for 2–17 h at room temperature. Diethyl ether was then added to the crude reaction mixture. The volume of diethyl ether added was approximately half the total volume of acetonitrile used. Following filtration and concentration under reduced pressure the crude product was isolated. The crude α-diazo-β-oxo sulfone was further purified using column chromatography on silica gel, with hexane : ethyl acetate as the solvent system.

Procedure B: Potassium carbonate (ACS reagent, >99.0%) was added to a stirring solution of sulfone in acetonitrile at room temperature. Stirring was continued for 10 min and then the reaction mixture was cooled to 0°C. A solution of 4-toluenesulfonic azide in acetonitrile was added dropwise over 10 min under an atmosphere of nitrogen. Stirring was continued for a further 30 min at 0°C, then the mixture was removed from the ice bath and stirring was continued for 2–17 h at room temperature. On reaction completion (as indicated by TLC analysis), the contents of the flask were poured (adsorbed) onto silica gel and the solvent was removed by evaporation. The residual solid was loaded on top of a column of silica gel and was purified using column chromatography with hexane : ethyl acetate as the solvent system.

Methyl 2-diazo-2-[4-(4-fluorophenyl)butyl]sulfonylacetate 1g The title compound was prepared using general procedure **A**, using potassium carbonate (1.18 g, 8.6 mmol), methyl 2-(4-fluorophenylbutyl)sulfonylacetate **2g** (2.25 g, 7.8 mmol) in acetonitrile (40 mL) and 4-toluenesulfonyl azide (1.54 g, 7.8 mmol) in acetonitrile (10 mL). The mixture was stirred at 0 °C for 0.5 h followed by 3 h at room temperature. Following work up and purification of the crude product by chromatography, on silica gel using ethyl acetate-hexane (20:80) as eluent, methyl 2-diazo-2-[4-(4-fluorophenyl)butyl]sulfonylacetate **1g** (1.04 g, 42%) was isolated as a yellow oil. In addition another fraction was recovered (0.52 g, 21%) that contained *approx*. 7% of an aromatic impurity. Therefore the overall yield is estimated to be 62%, by ^{1}H NMR analysis; ν_{max}/cm^{-1} (film): 2132 (C=N_2), 1718 (CO), 1510, 1336, 1299, 1222 (SO_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 1.67–1.94 [m, 4H, C(2')H_2, C(3')H_2], 2.63 [t, *J* = 7.3 Hz, 2H, C(4')H_2], 3.35–3.43 [m, 2H, C(1')H_2], 3.86 (s, 3H, OCH_3), 6.92–7.03 (m, 2H, Ar*H*), 7.06–7.16 (m, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm) = 22.0, 29.8 [2 × CH_2, *C*(2')H_2, *C*(3')H_2], 34.4 [CH_2, *C*(4')H_2], 53.2 (CH_3, O*C*H_3), 56.4 [CH_2, *C*(1')H_2], 72.9 (C, *C*=N_2), 115.2 [2 × ArCH, d, $^2J_{CF}$ 21.1, *C*(3)H, *C*(5)H], 129.7 [2 × ArCH, d, $^3J_{CF}$ 7.7, *C*(2)H, *C*(6)H], 136.7 [C, d, $^4J_{CF}$ 3.2, *C*(1)], 160.5 (C, *C*O), 161.4 [C, $^1J_{CF}$ 243.8, *C*(4)]; HRMS (ESI+): Exact mass calculated for $C_{13}H_{16}FN_2O_4S$ $[M+H]^+$, 315.0815. Found 315.0828. m/z (ESI+): 315.1 $[M+H]^+$.

Methyl 2-diazo-2-(phenethylsulfonyl)acetate 1m The title compound was prepared using general procedure **B**, using DBU (0.69 g, 0.67 mL, 4.5 mmol), methyl 2-(phenethylsulfonyl)acetate **2m** (1.0 g, 4.1 mmol) and 4-acetamidobenzenesulfonyl azide (0.99 g, 4.1 mmol) in acetonitrile (30 mL) stirred at 0 °C for 1 h and then for 5 h while warming slowly to room temperature. The reaction mixture was subsequently quenched with silica gel and purified by chromatography, on silica gel using ethyl acetate-hexane (40:80) as eluent to afford methyl 2-diazo-2-(phenylsulfonyl)acetate **1m** (0.62 g, 53%) as a yellow oily solid; (Found: C, 49.40; H, 4.64; N, 10.30; S, 12.30; $C_{11}H_{12}N_2O_4S$ requires ; C, 49.24; H, 4.51; N, 10.44; S, 11.95 %); ν_{max}/cm^{-1} (KBr): 2960, 2925 (CH), 2136 (C=N_2), 1718 (CO), 1401, 1325, 1302, 1128, 1192 (SO_2), 751, 738, 713, 701 (CS); ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) = 3.08–3.24 [2H, m, C(1')*H*$_2$ or C(2')*H*$_2$], 3.65–3.74 [2H, m, C(1')*H*$_2$ or C(2')*H*$_2$], 3.78 (3H, s, COOC*H*$_3$), 7.15–7.20 (2H, m, Ar*H*), 7.21–7.27 (1H, m, Ar*H*), 7.29–7.34 (2H, m, Ar*H*); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ (ppm) = 29.1 [CH_2, *C*(1')H_2 or *C*(2')H_2], 53.0 (CH_3, COO*C*H_3), 57.1 [CH_2, *C*(1')H_2 or *C*(2')H_2], 73.5 (C, *C*N_2), 127.2 (CH, aromatic *C*H), 128.2 (CH, aromatic *C*H), 128.9 (CH, aromatic *C*H), 136.7 (C, aromatic *C*), 160.3 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{11}H_{13}N_2O_4S$ $[M+H]^+$, 269.0596; Found 269.0588. m/z (ESI+):269.26 $[M+H]^+$.

Ethyl 2-diazo-2-(2-ethylphenyl)sulfonylacetate 1n The title compound was prepared using general procedure **B**, using potassium carbonate (0.57 g, 4.13 mmol), ethyl 2-(2-ethylphenylsulfonyl)acetate **2n** (1.07 g, 3.8 mmol) in acetonitrile (40 mL) and 4-acetamidobenzenesulfonyl azide (0.90 g, 3.8 mmol) in acetonitrile (10 mL) stirred at 0 °C for 1 h and then removed from the ice bath and stirred at room temperature for 3 h. The reaction mixture was subsequently adsorbed onto silica gel and purified by chromatography, on silica gel using ethyl acetate-hexane (20:80) as eluent to afford ethyl 2-diazo-2-(2-ethylphenyl)sulfonylacetate **1n** (0.73 g, 69%) as a yellow oil. (Found: C, 51.05; H, 5.15; N 9.64, $C_{12}H_{14}N_2O_4S$ requires C, 51.05; H, 5.00; N 9.92%); ν_{max}/cm^{-1} (film): 2982 (CH), 2126 (C=N_2), 1719 (CO), 1337, 1292, 1159 (SO_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 1.17 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.31 (t, *J* = 7.5 Hz, 3H, ArCH$_2$C*H*$_3$), 3.00 (quartet, *J* = 7.5 Hz, 2H, ArC*H*$_2$CH$_3$), 4.16 (quartet, *J* = 7.1 Hz, 2H, OC*H*$_2$CH$_3$), 7.32–7.48 (overlapping dd and ddd, appears as m, 2H, 2 × Ar*H*), 7.57 (ddd, *J* = 7.6 Hz, 5.9 Hz, 1.4 Hz, 1H, Ar*H*), 8.10 (dd, *J* = 8.0 Hz, 1.3 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm) = 14.0 (CH_3, OCH$_2$*C*H$_3$), 15.2 (CH_3, ArCH$_2$*C*H$_3$), 25.8 (CH_2, ArC*H*$_2$CH$_3$), 62.3 (CH_2, OC*H*$_2$CH$_3$), 126.2 (CH, aromatic *C*H), 130.8 (CH, aromatic *C*H), 131.4 (CH, aromatic *C*H), 134.1 (CH, aromatic *C*H), 138.9 (C, aromatic *C*), 143.6 (C, aromatic *C*), 159.7 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{12}H_{14}N_2O_4S$ $[M+H]^+$, 283.0761. Found 283.0753. m/z (ESI+): 283.1 $[M+H]^+$.

2-Diazo-2-(2-ethylphenyl)sulfonyl-1-phenylethanone 1o The title compound was prepared using the general procedure **B**, using potassium carbonate (1.38 g, 10 mmol), 2-(2-ethylphenylsulfonlyl)-1-phenylethanone **2o** (3.0 g, 9.1 mmol) in acetonitrile (50 mL) and 4-acetamidobenzenesulfonyl azide (2.2 g, 9.1 mmol) in acetonitrile (25 mL) stirred at 0 °C for 1 h and then removed from the ice bath and stirred at room temperature for 4 h. The reaction mixture was subsequently adsorbed onto silica gel and purified by chromatography, on silica gel using ethyl acetate-hexane (20:80–30:70) as eluent to afford 2-diazo-2-(2-ethylphenyl)sulfonyl-1-phenylethanone **1o** (2.32 g, 81%) as a yellow crystalline solid: An analytical sample was obtained by recrystallisation from isopropyl alcohol; mp 104–105 °C (Found: C, 61.05; H, 4.55; N 8.92, $C_{16}H_{14}N_2O_3S$ requires C, 61.13; H, 4.49; N, 8.91%); ν_{max}/cm^{-1} (KBr): 2967 (CH), 2117 (C=N_2), 1659 (CO), 1332, 1279, 1153 (SO_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 1.32 (t, *J* = 7.5 Hz, 3H, ArCH$_2$C*H*$_3$), 3.02 (q, *J* = 7.5 Hz, 2H, ArC*H*$_2$CH$_3$), 7.28–7.46 (m, 4H, Ar*H*), 7.47–7.61 (m, 4H, Ar*H*), 8.08 (dd, *J* = 8.0 Hz, 1.3 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ (ppm) = 15.2 (CH_3, ArCH$_2$*C*H$_3$), 25.8 (CH_2, *C*H$_2$CH$_3$), 126.3 (CH, aromatic *C*H), 127.4 (CH, aromatic *C*H), 128.8 (CH, aromatic *C*H), 130.7 (CH, aromatic *C*H), 131.6 (CH, aromatic *C*H), 132.9 (CH, aromatic *C*H), 134.2 (CH, aromatic *C*H), 135.9 (C, aromatic *C*), 138.8 (C, aromatic *C*), 143.5 (C, aromatic *C*), 182.8 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{15}N_2O_3S$ $[M+H]^+$, 315.0803. Found 315.0799. m/z (ESI+): 315.1 $[M+H]^+$.

General Procedure C for asymmetric copper catalysed intramolecular C–H insertion reactions:

The copper source (5 mol%), NaBARF (6 mol%) and the bis(oxazoline) ligand (6 mol%) were suspended/dissolved in distilled dichloromethane. A solution of the α-diazocarbonyl compound **1** in distilled dichloromethane was added to this. The contents of the reaction flask were then heated to reflux under an atmosphere of nitrogen. The progress of the reaction was monitored by IR spectroscopy; the reaction was deemed complete upon the disappearance of the diazo stretch at ~2100 cm^{-1}. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure to give the crude product, which was then analysed by ^{1}H NMR spectroscopy. The crude product mixture was then adsorbed onto silica. This was achieved by dissolving the mixture in dichloromethane, followed by the addition of silica gel (~ 2.5 g) and subsequent evaporation of the solvent. The crude product mixture was then purified using flash chromatography on silica gel.

(2*S*,3*S*)-Methyl 3-(4-fluorophenyl)tetrahydro-2H-thiopyran-2-carboxylate 1,1-dioxide *cis* 3g The title compounds were prepared according to general procedure **C**, using methyl 2-diazo-2-{[4-(4-fluorophenyl)butyl]sulfonylacetate **1g** (100 mg, 31.8 mmol), CuCl (1.57 mg, 16 μmol), NaBARF (16.92 mg, 19 μmol) and bis(oxazoline) ligand (4*R*)-Ph (6.35 mg, 19 μmol) in dichloromethane (15 mL), stirred while heating under reflux for 21 h. Following purification, by flash chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, (2*S*,3*S*)-methyl 3-(4-fluorophenyl)tetrahydro-2H-thiopyran-2-carboxylate 1,1-dioxide *cis* **3g** (45 mg, 49%) was isolated as a white solid; mp 155–156 °C; $[\alpha]_D^{20}$ +92.0 (*c*, 1.0 CH_2Cl_2) 98% ee (determined by chiral-HPLC); (Found C, 54.57; H 5.31; S, 11.44, $C_{13}H_{15}O_4FS$ requires C,

54.53; H, 5.28; S, 11.20%); ν_{max}/cm^{-1} (KBr): 2956, 2939 (CH) 1735 (CO), 1512 (C=C, Ar), 1317, 1114 (SO_2) 840; ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 1.84 [dq, *J* = 13.6 Hz, 3.2 Hz, 1H, one of C(4)H_2], 2.10–2.36 [m, 2H, C(5)H_2], 2.58 [qd, *J* = 13.2 Hz, 3.9 Hz, 1H, one of C(4)H_2], 3.05 [dq, *J* = 14.1 Hz, 3.4 Hz, 1H, one of C(6)H_2], 3.56 (s, 3H, OCH_3), 3.61–3.73 [m, 2H, one of C(6)H_2 and C(3)*H*], 3.96 [dd, *J* = 4.5 Hz, 2.9 Hz, 1H, C(2)*H*], 6.95–7.07 (m, 2H, Ar*H*), 7.12–7.23 (m, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm) = 22.9, 23.8 [2 × CH_2, *C*(4)H_2, *C*(5)H_2], 43.8 [CH, *C*(3)H], 47.8 [CH_2, *C*(6)H_2], 52.7 (CH_3, OCH_3), 70.4 [CH, *C*(2)H], 115.8 [2 × ArCH, d, $^2J_{CF}$ 21.4, *C*(3')H, *C*(5')H], 128.6 [2 × ArCH, d, $^3J_{CF}$ 8.1, *C*(2')H, *C*(6')H], 135.3 [C, d, $^4J_{CF}$ 3.3, *C*(1')], 162.1 [C, $^1J_{CF}$ 246.9, *C*(4')], 166.4 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{13}H_{16}O_4FS$ $[M+H]^+$, 287.0753. Found 287.0767. m/z (ESI+): 287.1 $[M+H]^+$.

Methyl isothiochroman-1-carboxylate 2,2-dioxide 7 The title compound was prepared according to general procedure **C**, using methyl 2-diazo-2-(phenethylsulfinyl)acetate **1m** (80 mg, 0.30 mmol), $CuCl_2$ (2.0 mg, 15 µmol), NaBARF (15.7 mg, 18 µmol) and bis(oxazoline) ligand (4*R*,5*S*)-diPh (8.2 mg, 18 µmol) in dichloromethane (20 mL), stirred while heating under reflux for 2 h. Following purification by column chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, methyl isothiochroman-1-carboxylate 2,2-dioxide **7** (49 mg, 68%) was isolated as a white solid; mp 118–119 °C; 0% ee (determined by chiral HPLC); ν_{max}/cm^{-1} (KBr): 2936 (CH), 1736 (CO), 1429 (C=C, ArH), 1321, 1312, 1298, 1121 (SO_2), 740 (CS); ^1H NMR ($CDCl_3$, 600 MHz) δ (ppm) = 3.22 (dddd, *J* = 14.1 Hz, 5.1 Hz, 3.8 Hz, 2.6 Hz, 1H, one of SO_2CH_2), 3.43–3.59 (m, 2H, $SO_2CH_2CH_2$), 3.84 (s, 3H, OCH_3), 3.93–4.01 (ddd, *J* = 14.1 Hz, 11.4 Hz, 5.7 Hz, 1H, one of SO_2CH_2), 4.99 (d, *J* = 2.5, 1H, SO_2CH), 7.11–7.14 (m, 1H, Ar*H*), 7.24–7.29 (m, 2H, Ar*H*), 7.31–7.36 (m, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ (ppm) = 29.0 (CH_2, $SO_2CH_2CH_2$), 45.9 (CH_2, SO_2CH_2), 53.8 (CH_3, OCH_3), 67.8 (CH, SO_2CH), 127.4 (CH, aromatic *C*H), 128.1 (C, aromatic *C*), 129.3 (CH, aromatic *C*H), 130.0 (CH, aromatic *C*H), 130.1 (CH, aromatic *C*H), 132.0 (C, aromatic, *C*), 166.5 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{11}H_{13}O_4S$ $[M+H]^+$, 241.0535. Found 241.0527. m/z (ESI+): 241.1 $[M+H]^+$.

(2*R*,3*R*) Ethyl 3-methyl-2, 3-dihydrobenzo[b]thiophene-2-carboxylate 1, 1-dioxide 5n The title compound was prepared according to general procedure **C**, using ethyl 2-diazo-2-(2-ethylphenyl)sulfonylacetate **1n** (150 mg, 0.53 mmol), $CuCl_2$ (3.53 mg, 26.6 µmol), NaBARF (28mg, 31.9 µmol) and bis(oxazoline) ligand (4*R*)-Ph (10.6 mg, 31.9 µmol) in dichloromethane (20 mL), stirred while heating under reflux for 2 h. ^1H NMR spectroscopy of the crude product showed that the reaction was *approx* 90% efficient (89% *cis* **6n**: 11% *trans* **5n**). Following purification by column chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, (2*R*,3*R*) ethyl 3-methyl-2, 3-dihydrobenzo[b]thiophene-2-carboxylate 1,1-dioxide (6% *cis* **6n**, 94% *trans* **5n**) (130 mg, 91%) was isolated as a colourless oil (*cis* **6n** -82% ee, *trans* **5n** -80% ee); (determined by chiral-HPLC); The following spectral characteristics are reported for *trans* **5n**. ν_{max}/cm^{-1} (film): 1741 (CO), 1317, 1282, 1251, 1213, 1180 (SO_2), 761 (CS); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) = 1.37 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.55 [d, *J* = 6.70 Hz, 3H, C(1')H_3], 3.93–4.08 [m, 2H, C(2)*H* and C(3)*H*], 4.17–4.47 (sym m, 2H, OCH_2CH_3), 7.39–7.57 (overlapping dd and ddd, appears as m, 2H, Ar*H* × 2), 7.64 (ddd, *J* = 7.6 Hz, 7.6 Hz, 1.1 Hz, 1H, Ar*H*), 7.71 (d, *J* = 7.9 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm) = 14.1 (CH_3, OCH_2CH_3), 18.7 [CH_3, *C*(1')H_3], 35.7 [CH, *C*(3)H], 62.9 (CH_2, OCH_2CH_3), 72.3 [CH, *C*(2)H], 121.6 (CH, aromatic *C*H), 125.4 (CH, aromatic *C*H), 129.0 (CH, aromatic *C*H), 134.1 (CH, aromatic *C*H), 137.4 (C, aromatic *C*), 140.3 (C, aromatic *C*), 164.0 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{12}H_{15}O_4S$ $[M+H]^+$, 255.0691. Found 255.0688. m/z (ESI+): 255.2 $[M+H]^+$.

The following signals appear in ^1H NMR spectra of the crude product and are tentatively assigned to *cis* **6n**; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) = 1.26 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.55 [d, *J* = 7.1 Hz, 3H, C(1')H_3], 3.92 [quint, *J* = 6.8 Hz, 1H, C(3)*H*], 4.16–4.32 (m, 2H, OCH_2CH_3), 4.38 [d, *J* = 6.6 Hz, 1H, C(2)*H*] 7.40–7.54 (m, 2H, Ar*H*), 7.59–7.66 (m, 1H, Ar*H*), 7.71 (d, *J* = 7.1 Hz, 1H, Ar*H*).

[(2*R*,3*R*)-3-Methyl-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-2-yl](phenyl)methanone 5o The title compound was prepared according general procedure **C**, using 2-diazo-2-(2-ethylphenyl)sulfonyl-1-phenylethanone **1o** (100 mg, 0.32 mmol), $CuCl_2$ (2.2 mg, 16 µmol), NaBARF (16.9 mg, 19 µmol) and bis(oxazoline) ligand (4*R*)-Ph (6.4 mg,19 µmol) in dichloromethane (25 mL), stirred while heating under reflux for 5 h. ^1H NMR spectroscopy of the crude product showed that the reaction was *approx* 65% efficient (9% *cis* **6o**: 91% *trans* **5o**). Following purification by column chromatography on silica gel, using ethyl acetate-hexane (10:90) as eluent, [(2*R*,3*R*)-3-methyl-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-2-yl](phenyl)methanone (1% *cis* **6o**, 99% *trans* **5o**) (34 mg, 38%) was isolated as a colourless oil; 71% ee (*trans* **5o**) (determined by chiral HPLC); ν_{max}/cm^{-1} (film): 2922, 2851 (CH), 1684 (CO), 1597 (C=C, Ar), 1309, 1156 (SO_2), 751 (CS); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) = 1.54 [d, *J* = 7.0 Hz, 3H, C(1')H_3], 4.41 [quint, *J* = 6.9 Hz, 1H, C(3)*H*], 5.02 [d, *J* = 6.9 Hz, 1H, C(2)*H*], 7.46–7.60 (m, 4H, Ar*H*), 7.63–7.72 (m, 3H, Ar*H*), 8.19–8.22 (m, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm) = 18.8 [CH_3, *C*(1')H_3], 35.7 [CH, *C*(3)H], 73.8 [CH, *C*(2)H], 121.6 (CH, aromatic *C*H), 125.4, 129.1, 129.5, 134.2, 134.6 (CH, aromatic *C*H), 136.3 (C, aromatic *C*), 137.3 (C, aromatic *C*), 141.2 (C, aromatic *C*), 188.2 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{16}H_{15}O_3S$ $[M+H]^+$, 287.0742. Found 287.0732. m/z (ESI+): 287.1 $[M+H]^+$.

The following signals appear in ^1H NMR spectra of the crude product and are tentatively assigned to *cis* **6o:** ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm) = 1.81 [d, *J* = 6.3 Hz, 3H, C(1')H_3], 4.09 [quint, *J* = 6.4 Hz, 1H, C(3)*H*], 5.45 [d, *J* = 5.4 Hz, 1H, C(2)*H*].

1-(3-Methyl-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-2-yl)ethanone *cis* 5p The title compound was prepared according to general procedure **C**, using 1-diazo-1-(2-ethylphenyl)sulfonylpropan-2-one **1p** (80 mg, 0.32 mmol), $CuCl_2$ (2.1 mg, 16 µmol), NaBARF (16.8 mg, 19 µmol) and

bis(oxazoline) ligand (4*R*)-Bn (6.9 mg, 19 μmol) in dichloromethane (20 mL), stirred while heating under reflux for 21 h. ^{1}H NMR spectroscopy of the crude product showed that the reaction was *approx* 70% efficient (4% *cis* **6p**: 96% *trans* **5p**). Following purification by column chromatography on silica gel, using gradient ethyl acetate-hexane (5:95–10:90–20:80) as eluent, 1-[(2*R*,3*R*)-3-methyl-1,1-dioxido-2,3-dihydrobenzo[b]thiophen-2-yl]ethanone (1% *cis* **6p**, 99% *trans* **5p**) (42 mg, 60%) was isolated as a colourless oil; 10% ee (*trans* **5p**) (determined by chiral HPLC). The following spectral characteristics are reported for *trans* **5p**. ν_{max}/cm^{-1} (film): 2912 (CH), 1726 (CO), 1647, 1595 (C=C, Ar), 1299, 1209, 1173, 1126 (SO_2), 768 (CS); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) = 1.49 [d, *J* = 7.0 Hz, 3H, C(1')*H*$_3$], 2.55 (s, 3H, COC*H*$_3$), 4.04 [quint, *J* = 7.0 Hz, 1H, C(3)*H*], 4.17 [d, *J* = 7.0 Hz, 1H, C(2)*H*], 7.44–7.52 (overlapping dd and ddd, appears as m, 2H, Ar*H* × 2), 7.64 (ddd, *J* = 7.6 Hz, 7.6 Hz, 1.1 Hz, 1H, Ar*H*), 7.70 (d, *J* = 7.8 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ (ppm) = 18.7 [CH_3, *C*(1')H_3], 31.1 [CH_3, CO*C*H_3], 34.3 [CH, *C*(3)H], 78.5 [CH, *C*(2)H], 121.5 (CH, aromatic *C*H), 125.5 (CH, aromatic *C*H), 129.0 (CH, aromatic *C*H), 134.2 (CH, aromatic *C*H), 137.0 (C, aromatic *C*), 140.8 (C, aromatic *C*), 195.8 (C, *C*O); HRMS (ESI+): Exact mass calculated for $C_{11}H_{13}O_3S$ [M+H]$^+$, 225.0585. Found 225.0584. m/z (ESI+): 225.1 [M+H]$^+$.

The following signals appear in ^{1}H NMR spectra of the crude product and are tentatively assigned to *cis* **6p**; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) = 2.42 (s, 3H, COC*H*$_3$), 3.89 [quint *J* = 6.5 Hz, 1H, C(3)*H*], 4.44 [d, *J* = 6.5 Hz, 1H, C(2)*H*].

(2*R*,3*R*)-3-Methyl-2,3-dihydrobenzo[b]thiophene-2-carboxylic acid 1,1-dioxide 10a Potassium hydroxide (1.47 g, 26.3 mmol) in water (15 mL) was added to ethyl 3-methyl-2, 3-dihydrobenzo[b]thiophene-2-carboxylate 1,1-dioxide {*cis* **6n** [90% ee (2*S*,3*R*)] : *trans* **5n** [80% ee (2*R*,3*R*)], 7 : 93}c (0.67 g, 2.6 mmol) in methanol (30 mL) and the resulting solution was stirred for 2 h at room temperature, after which TLC analysis indicated that the reaction was complete. Methanol was removed from the crude reaction mixture by evaporation under reduced pressure, then ethyl acetate (30 mL) and aqueous HCl (15 mL, 2 M, aqueous solution) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (40 mL), dried with $MgSO_4$ and concentrated under reduced pressure to yield (2*R*,3*R*) 3-methyl-2,3-dihydrobenzo[b]thiophene-2-carboxylic acid 1,1-dioxide (5% *cis* **10b**, 95% *trans* **10a**) (0.46 g, 78%) as a white crystalline solid; mp 75–76 °C; $[\alpha]_D^{20}$ -35.5 (*c* 1.1, CH_2Cl_2); 78% ee (*trans* **10a**) (determined by chiral-HPLC); (Found: C, 51.50; H, 4.53; $C_{10}H_{10}O_4S.0.5H_2O$ requires C, 51.05; H, 4.71 %); ν_{max}/cm^{-1} (neat): 3176 (OH), 2926 (CH), 1725 (CO), 1281, 1151, 1123 (SO_2), 764 (CS); The following spectral characteristics are reported for *trans* **10a**. ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) =1.57 [d, *J* 7.0, 3H, C(1')*H*$_3$], 3.99 [quint, *J* = 6.9 Hz, 1H, C(3)*H*], 4.13 [d, *J* = 7.3 Hz, 1H, C(2)*H*], 7.08 (br s, 1H, COO*H*), 7.45–7.54 (overlapping d and t, appears as m, 2H, Ar*H* × 2), 7.66 (td, *J* = 7.6 Hz, 1.0 Hz, 1H, Ar*H*), 7.73 (d, *J* = 7.8 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm) = 18.5 [CH_3, *C*(1')H_3], 35.8 [CH, *C*(3)H], 72.2 [CH, br, *C*(2)H], 121.7 (CH, aromatic *C*H), 125.1 (CH, aromatic *C*H), 129.1 (CH, aromatic *C*H), 134.3 (CH, aromatic *C*H), 137.0 (C, aromatic *C*), 140.3 (C, aromatic *C*), 167.4 (C, *C*O).

The relative stereochemistry was determined by single crystal X-ray diffraction of a crystalline sample of **10a** recrystallised from IPA. Crystals of **10a** are triclinic, space group *P*1, formula $C_{20}H_{22}O_9S_2$, M_R = 470.49, *a* = 8.1731(8) Å, *b* = 8.5779(9) Å, *c* = 9.0489(9) Å, α = 74.180(2)°, β = 76.474(2)°, γ = 63.539(2)°, *U* = 541.75(10) Å3, *F(000)* = 246, μ(Mo Kα) = 0.295 mm^{-1}, *R*(Fo) = 0.024, for 3965 observed reflections with I > 2σ(I), *wR*$_2$(F^2) = 0.056 for all 4147 unique reflections. Data in the θ range 2.36 – 26.35° were collected on a Bruker APEX DUO diffractometer using Mo Kα radiation, λ = 0.71073 Å, and corrected for Lorentz and polarisation effects. The structure was solved by direct methods and refined by full-matrix least-squares using all F^2 data. The hydrogen atoms were placed in calculated positions and allowed to ride on the parent atom.

CCDC 1815488 **10a** contains crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The following signals appear in ^{1}H NMR spectra of purified product; and are tentatively assigned to *cis*, **10b** ^{1}H NMR ($CDCl_3$, 600 MHz) δ (ppm) = 1.59 [d, *J* = 7.1 Hz, 3H, C(1')*H*$_3$], 4.46 [d, *J* = 6.8 Hz, 1H, C(2)*H*].

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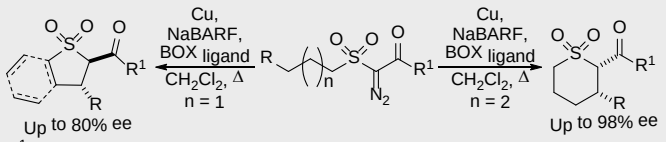

Excellent enantioselectivities of up to 98% ee are achieved employing the copper-bis(oxazoline)-NaBARF catalyst system in the C–H insertion reactions of α-diazo-β-oxo sulfones. The influence of variation of the bis(oxazoline) ligand, copper salt, additive and substrate on both the efficiency and the enantioselectivities of these intramolecular C–H insertion reactions has been explored.

*Copper catalysed C–H insertion up to 98% ee

Copper catalysed enantioselective C–H insertion reactions

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Substrate and catalyst effects in the enantioselective copper catalysed C–H insertion reactions of α-diazo-β-oxo sulfones