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Catalyst, additive and counterion effects on the efficiency and enantioselectivity of copper-catalysed C–H insertion reactions of α-diazosulfones

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ABSTRACT

Asymmetric copper-catalysed intramolecular C–H insertion reactions of α-diazosulfones in the presence of various group I salts are reported leading to substantial variation in reaction efficiencies and enantioselectivities. The borate additives NaBARF and KBARF were found to be the most effective additives for permitting highly enantioselective syntheses with short reactions times and high efficiency. Significantly, direct evidence of the critical role of the additive in enantioselective carbenoid reactions has been secured.

1. Introduction

α-Diazocarbonyl compounds are synthetically versatile intermediates, capable of producing a diverse range of products upon transition metal-catalysed decomposition.[1] Carbenoid C–H insertion processes are particularly powerful transformations and while early studies were effected with copper catalysts, efficiencies and stereoselectivities were low and these reactions were of limited synthetic utility as a result. With the advent of rhodium acetate and other rhodium carboxylate catalysts in the 1970s and 1980s,[2] intramolecular C–H insertion reactions of α-diazo-β-keto esters became synthetically useful leading to very efficient synthesis of cyclopentanone derivatives with excellent regiocontrol.[3–6] The first report of asymmetric catalysis in C–H insertion chemistry in 1990 employed a chiral rhodium carboxylate catalyst and led to just 12% ee.[7] Since this time enantioselective rhodium-catalysed C–H insertion has attracted enormous attention with excellent enantiocontrol achieved in many cases using a range of carboxylate and carboxamidate catalysts.[8–10]

In contrast, while enantioselective copper catalysis has proven successful in asymmetric cyclopropanations and ylide formations, limited success has been achieved in enantioselective C–H insertion employing chiral copper catalysts. Examples of copper catalysis in C–H insertion chemistry have been reported, however, until recently the levels of asymmetric induction attained have been generally poor, with limited good results for both intramolecular[11] (up to 60% ee) and intermolecular[12] (up to 88% ee) reactions.

Recently, we reported that C–H insertion reactions of α-diazosulfones in the presence of copper–bis(oxazoline) complexes provide access to highly enantioenriched thiopyran[13] (up to 98% ee) and cyclopentanone[14] (up to 82% ee) products. Enantioselectivities obtained for these reactions represent the highest levels of asymmetric induction recorded to date for copper-catalysed C–H insertion, thereby establishing the synthetic utility of chiral copper catalysts in enabling highly enantioselective C–H insertion reactions.

The borate anion $BARF^-$ {BARF=tetrakis[3,5-bis(trifluoromethyl)phenyl] borate} was first utilised in 1981 by Kobayashi and coworkers as a negatively charged phase transfer catalyst.[15] This anionic species behaves as an extremely weakly-coordinating anion owing to distribution of the negative charge over a large area of non-nucleophilic and chemically stable functional groups.[16] Salts of $BARF^-$, including sodium, potassium, silver and thallium compounds, have been employed in several transition metal-catalysed transformations, such as hydrogenation[17,18] and hydrovinylation[19,20] reactions, where they have been shown to enhance the activity of cationic catalyst species resulting in improvements in reaction efficiencies and selectivities.

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In our previous study, the addition of NaBARF to the catalytic copper complexes was shown to be critical for achieving high enantioselectivity in the insertion reactions of α-diazo-β-keto sulfones,[14] with a dramatic decrease in enantiocontrol being observed in the absence of this borate additive. A similar effect had previously been reported by Zhou and co-workers for carbenoid insertion into O–H and N–H bonds,[21,22] however, the mechanistic role that NaBARF plays in enhancing asymmetric induction in carbenoid insertion reactions has not been discussed in these previous reports. Recently, we reported a preliminary investigation of additive effects in enantioselective copper-catalysed C–H insertion and aromatic addition reactions of α-diazocarbonyl compounds.[23] Building on the preliminary study, we report herein a more comprehensive investigation on the effect of NaBARF and a range of other group I salts on the efficiency and enantioselectivity of C–H insertion reactions of α-diazosulfones, extending our preliminary study to include a wider range of bis(oxazoline) ligands. A detailed discussion of the key role of the alkali metal cation in producing highly enantioenriched products and an examination of additive effects on chemoselectivity is included.

2. Results and discussion

The role of the additive in the cyclisation of two α-diazosulfones was explored to determine the impact of the variation of both the additive metal ion and counteranion. The intramolecular insertion reactions of 1-diazo-1-phenylsulfonyl-5-phenylpentan-2-one **4** and methyl 2-diazo-2-(4-phenylbutylsulfonyl)acetate **6** were performed in refluxing dichloromethane with a copper catalyst generated in situ from 5 mol % $CuCl_2$, 6 mol % bis(oxazoline) ligand and 6 mol % group I salt. Three chiral bis(oxazoline) ligands **1**–**3** (Fig. 1) were employed in this study. In general, *trans*-cyclopentanone **5** and *cis*-thiopyran **7** were the major products for the insertion reactions of **4** and **6**, respectively.

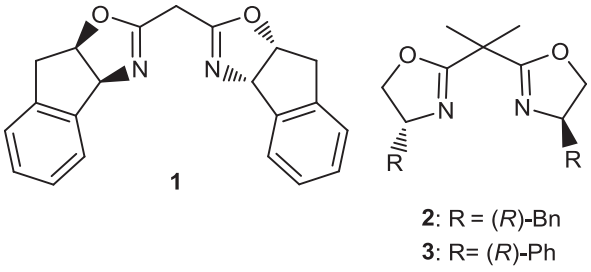
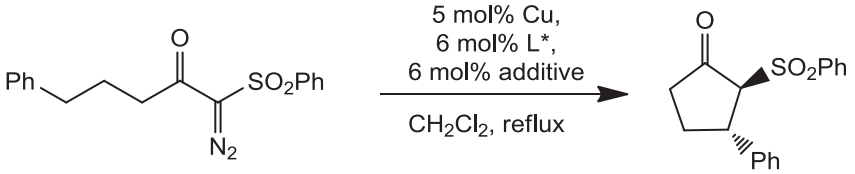


Fig. 1. Bis(oxazoline) ligands.

While our previous study examining asymmetric copper-catalysed intramolecular C–H insertion reactions of α-diazo-β-keto sulfones employed CuCl,[14] $CuCl_2$ was the chosen copper source in this study. Such a change was found to have little effect on the levels of enantioselectivity achieved in the insertion reactions, however, significantly shorter reaction times were recorded in the presence of $CuCl_2$ and NaBARF. As was previously observed for reactions in the presence of CuCl,[14] C–H insertion of α-diazo-β-keto sulfone **4** in the presence of $CuCl_2$ and bis(oxazoline) ligand resulted in very low levels of enantioselectivity (Table 1, entry 1). A large improvement in enantiocontrol was recorded for reactions employing the weakly-coordinating counterion $BARF^-$ (Table 1, entry 2), with up to 89% ee observed for cyclisation with the indane-derived bis(oxazoline) **1**. In addition to enhanced enantiocontrol, the addition of NaBARF also results in a dramatic decrease in the time taken to achieve reaction completion.

The addition of a variety of other sodium salts (displaying varying solubilities in dichloromethane) was explored to determine their effects on enantioselectivity in the cyclisations of α-diazosulfone **4**. Enantioselectivities obtained in the presence of sodium hexafluorophosphate were found to largely parallel those achieved with NaBARF, although increased reaction times were recorded (Table 1, entry 3). Reactions with the remaining sodium salts, sodium tetraphenylborate and sodium tetrafluoroborate, displayed significantly decreased enantiocontrol and considerably longer reaction times were required (Table 1, entries 4 and 5). From the results obtained for the C–H insertion reactions of α-diazosulfone **4** the following order of effect on enantioselectivity may be defined: $NaBF_4$<$NaB(C_6H_5)_4$<<$NaPF_6$<NaBARF. This pattern is in line with results reported by Pfaltz and co-workers for studies of anion effects in asymmetric hydrogenation reactions employing iridium-phosphinooxazoline catalysts, in which increased reaction rates and catalyst stability were observed in the

Table 1
Copper-catalysed C–H insertion reactions of 1-diazo-1-phenylsulfonyl-5-phenylpentan-2-one **4**



4 **5**

Entry	Cu	Additive	Time (h)			Yield[a] (%)			ee[b,c] (%)		
		L*	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
1	$CuCl_2$	—	21	21	30	62	57	48	14 (2*R*, 3*R*)	9 (2*S*, 3*S*)	0
2	$CuCl_2$	NaBARF	2	2	2	87	65	69	89 (2*R*, 3*R*)	79 (2*S*, 3*S*)	57 (2*S*, 3*S*)
3	$CuCl_2$	$NaPF_6$	4	8	5	66	75	43	83 (2*R*, 3*R*)	76 (2*S*, 3*S*)	55 (2*S*, 3*S*)
4	$CuCl_2$	$NaB(C_6H_5)_4$	5	36	20	77	77	71	25 (2*R*, 3*R*)	46 (2*S*, 3*S*)	15 (2*S*, 3*S*)
5	$CuCl_2$	$NaBF_4$	20	35	20	63	56	53	11 (2*R*, 3*R*)	22 (2*S*, 3*S*)	7 (2*S*, 3*S*)
6	$CuCl_2$	KBARF	2	2	2	59	67	80	91 (2*R*, 3*R*)	78 (2*S*, 3*S*)	49 (2*S*, 3*S*)
7	$CuCl_2$	KPF_6	20	25	29	43	36	42	35 (2*R*, 3*R*)	56 (2*S*, 3*S*)	37 (2*S*, 3*S*)
8	$CuCl_2$	$LiPF_6$	5	5	5	78	83	59	71 (2*R*, 3*R*)	78 (2*S*, 3*S*)	51 (2*S*, 3*S*)
9	$Cu(MeCN)_4PF_6$	—	4	2	3	56	83	90	60 (2*R*, 3*R*)	71 (2*S*, 3*S*)	52 (2*S*, 3*S*)
10	$Cu(OTf)_2$	—	4	2	5	66	79	90	57 (2*R*, 3*R*)	76 (2*S*, 3*S*)	46 (2*S*, 3*S*)

[a] Isolated after flash chromatography.
[b] Determined by chiral HPLC (see Supplementary data for details).
[c] Stereochemical assignments are in agreement with previously reported data.[31]

presence of $BARF^-$ compared to other anionic species, such as PF_6^- and BF_4^-.[17,18] Indeed a similar effect was also observed by Zhou and co-workers for asymmetric hydrovinylation reactions employing catalytic palladium complexes of chiral phosphoramidite and phosphate ligands.[19] In this previous work, improving reactivity and enantioselectivity were recorded for various counteranions in the order: $OTf^- < BF_4^- << SbF_6^- < BARF^-$.

Reactions employing KBARF as an additive (Table 1, entry 6), were found to result in similar levels of enantioselectivity in comparison to C–H insertions in the presence of NaBARF (Table 1, entry 2), with reaction times and yields also seen to be generally in agreement. A slight increase in the level of enantioinduction achieved (91% ee) was recorded for the KBARF reaction with ligand **1**. Notably, this result represents the highest level of asymmetric induction recorded to date for cyclopentanone synthesis via C–H insertion, proving superior to previous rhodium-catalysed enantioselective cyclisations employing α-diazo-β-keto esters in which up to 80% ee was achieved.[24,25]

In contrast to reactions employing NaBARF and $NaPF_6$ as additives in which similar levels of enantioselectivity were recorded, a significant falloff in enantioselectivity was recorded for cyclisations in the presence of KPF_6 relative to the corresponding KBARF reactions (Table 1, entries 7 vs 6). This decrease in asymmetric induction, as well as the considerable increase in reaction times, is believed to be a related to poor solubility of KPF_6 in the reaction solvent, which may limit its effect in the C–H insertion process.

Despite a slight increase in reaction times, high levels of asymmetric induction were again observed for C–H insertions in the presence of $LiPF_6$ (Table 1, entry 8). Enantioselectivities obtained for these cyclisations were largely in line with those previously observed for reactions employing NaBARF, however, a decrease in enantioselectivity was recorded for insertion with the indane-derived ligand **1** (Table 1, entries 2 vs 8).

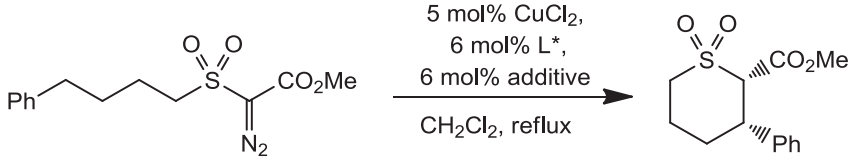
In studies examining the role of the counterion in copper/bis(oxazoline)-catalysed enantioselective cyclopropanation reactions, the presence of the chloride counteranion was shown to dramatically decrease enantioselectivity compared to reactions with the more weakly-coordinating triflate anion.[26] Theoretical calculations conducted in this previous study revealed that the presence of the strongly-coordinating chloride ion results in significant geometric changes in the catalyst structure, with the result that the diastereomeric transition structures for the carbenoid insertion do not possess any clear steric interaction that allows for discrimination between the two prochiral faces of the carbene–carbon. It has been suggested in earlier reports that the primary function of NaBARF is the abstraction of chloride from the catalytic structure.[27–29] It is therefore envisaged that complete or partial abstraction of chloride by the naked sodium ion of NaBARF occurs in the C–H insertion reactions of **4**, thereby altering the geometry of the catalytic complex resulting in higher levels of enantiocontrol. The observation of small amounts of an insoluble white solid in the reaction flask following reaction completion, found to be sodium chloride by PXRD analysis, supports this theory.

The results in Table 1 indicate that the nature of the counterion in the alkali metal (Na, K, Li) salts only plays a role in terms of enantioselectivity in so far as it enables solubility of the group I cations. Thus, the key role of the additives is in generating a poorly-solvated naked alkali metal cation in the dichloromethane solution.

Taking the above findings into account, the replacement of $CuCl_2$ with a copper source possessing a more weakly-coordinating anion was envisioned to lead to increased levels of enantioselectivity for our C–H insertion reactions. Such an effect has been previously observed by Zhou and co-workers for copper-catalysed carbenoid insertions into Si–H bonds in which enantioselectivites in excess of 90% ee were recorded for reactions in the presence of $Cu(MeCN)_4PF_6$ and $Cu(OTf)_2$ without addition of NaBARF.[30] In this study, insertion reactions of diazosulfone **4** with the weakly-coordinating $Cu(MeCN)_4PF_6$ and $Cu(OTf)_2$ salts (Table 1, entries 9 and 10) were found to result in significantly higher levels of enantiocontrol compared to $CuCl_2$/bis(oxazoline)-catalysed reactions (Table 1, entry 1), although failing to reach the levels recorded for $CuCl_2$/NaBARF cyclisations. This outcome is consistent with $BARF^-$ being much less coordinating than both PF_6^- and OTf^-.[16]

C–H insertion reactions with methyl 2-diazo-2-(4-phenylbutylsulfonyl)acetate **6** were also conducted (Table 2). As was previously observed for cyclisation of α-diazosulfone **4**, achievement of high levels of enantioselectivity was possible for reactions employing NaBARF, KBARF, $NaPF_6$ and $LiPF_6$ (Table 2, entries 2, 3, 6 and 8). In this instance, maintenance of enantiocontrol was observed for insertions in the presence of KPF_6 (Table 2, entry 7) despite long reaction times being required. This observation is in contrast with results recorded for insertion with α-diazo-β-keto sulfone **4** in which a decrease in ee was noted for insertion in the presence of KPF_6 (Table 1, entry 7). Bis(oxazoline) **3**, which

Table 2
Copper-catalysed C–H insertion reactions of methyl 2-diazo-2-(4-phenylbutylsulfonyl)acetate **6**



6 **7**

Entry	Additive	Time (h)		Yield[a] (%)		ee[b,c] (%)	
	L*	**2**	**3**	**2**	**3**	**2**	**3**
1	—	—	98	—	48	—	—[d]
2	NaBARF	2.5	1.5	67	61	60 (2*S*, 3*S*)	95 (2*S*, 3*S*)
3	$NaPF_6$	6	6	48	68	73 (2*S*, 3*S*)	96 (2*S*, 3*S*)
4	$NaB(C_6H_5)_4$	56	56	0	4	—[d]	—[d]
5	$NaBF_4$	48	24	22	43	—[d]	—[d]
6	KBARF	2	3	51	46	62 (2*S*, 3*S*)	95 (2*S*, 3*S*)
7	KPF_6	48	30	48	45	70 (2*S*, 3*S*)	93 (2*S*, 3*S*)
8	$LiPF_6$	21	21	35	47	69 (2*S*, 3*S*)	85 (2*S*, 3*S*)

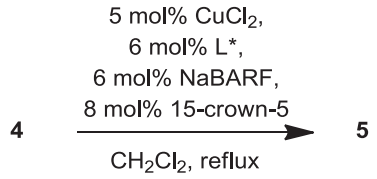
[a] Isolated after flash chromatography.
[b] Determined by chiral HPLC (see Supplementary data for details).
[c] Stereochemical assignments are in agreement with previously reported data.[13]
[d] No analytically pure sample isolated.

displayed only moderate asymmetric induction for reactions with **4**, was found to be the best performing ligand for reactions with diazosulfone **6**, providing in excess of 90% ee for cyclisations in the presence of NaBARF, KBARF, $NaPF_6$ and KPF_6. Notably, high levels of enantioselectivity (94% ee) have also previously been observed for C–H insertion reactions of **6** in the presence of $Cu(MeCN)_4PF_6$ and ligand **3**.[13] Cyclisation of **4** in the presence of CuCl, ligand **1** and NaBARF provided thiopyran **7** in 57% yield and 54% ee.

In addition to the observed benefits in terms of enantiocontrol, the use of the additive species in this study was also found to lead to increased chemoselectivity towards C–H insertion. In particular, reactions conducted in the presence of NaBARF or KBARF provided **5** and **7** with very high levels of efficiency relative to reactions without additives present, where increased evidence of side reactions, for example, with adventitious water or oxygen, is observed.

In order to confirm the key role that the metal ion (Na^+, K^+, Li^+) plays in enhancing the efficiency and enantioselectivity of the C–H insertion reactions of α-diazosulfones **4** and **6**, a number of experiments were conducted with NaBARF in the presence of 15-crown-5 (Table 3). Crown ethers are widely recognised as strong binding agents for metal ions, with 15-crown-5 known to have a particular high affinity for sodium cations.[32] Addition of 15-crown-5 to our catalytic system comprising $CuCl_2$, bis(oxazoline) ligand and NaBARF was found to have a significant detrimental effect on both the time required to achieve reaction completion and the level of enantioselectivity obtained (Table 3, entries 1–3 vs Table 1, entry 2). Through crown ether-mediated complexation of the sodium cation, chloride abstraction is prevented with the result that the copper–bis(oxazoline) complex can no longer adopt a geometry leading to efficient asymmetric induction. Thus, the presence of the crown ether negates the enhancement of enantioselectivity previously observed for insertions employing NaBARF, thereby confirming the key role of the sodium cation in this effect.

Table 3
C–H insertion in the presence of 15-crown-5



Entry	L*	Time (h)	Yield[a] (%)	ee[b] (%)
1	**1**	20	63	25 (2*R*, 3*R*)
2	**2**	48	50	28 (2*S*, 3*S*)
3	**3**	20	62	20 (2*S*, 3*S*)

[a] Isolated after flash chromatography.
[b] Determined by chiral HPLC (see Supplementary data for details).

3. Conclusion

In conclusion, copper bis(oxazoline)-catalysed C–H insertion reactions of two α-diazosulfones in the presence of various group I salts have been carried out. We have demonstrated that variation of the group I additive can have a significant effect on reaction time, yield and enantioselectivity. The borate additives NaBARF and KBARF were found to be the most effective for permitting highly enantioselective cyclopentanone and thiopyran syntheses with short reaction times and minimal side product formation. Significantly, direct experimental evidence providing insight into the role of NaBARF as an additive in carbenoid chemistry has been established. It is clear that the key factor is generation of a highly reactive naked alkali metal cation, which alters the nature of the copper catalyst through partial or complete chloride abstraction.

4. Experimental

4.1. General

DCM was distilled from phosphorous pentoxide and was further distilled from calcium hydride. All C–H insertion reactions were performed in oven-dried or flame-dried glassware under an atmosphere of dry N_2. Thin layer chromatography (TLC) was carried out on precoated silica gel plates. Visualisation was achieved by UV light detection (254 nm) and vanillin staining. Infra red spectra were recorded as thin films on sodium chloride plates for oils or as potassium bromide (KBr) discs for solids on a 1000 FT-IR spectrometer. ^1H (300/400 MHz), ^{13}C (75.5 MHz) and ^1H COSY NMR spectra were recorded on a 300/400 NMR spectrometer. All spectra were recorded at 20 °C in deuterated chloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal standard unless otherwise stated. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to TMS and coupling constants are expressed in Hertz (Hz). Splitting patterns in ^1H spectra are designated as s (singlet), d (doublet), t (triplet), q (quartet), qu (quintet), dd (doublet of doublets), m (multiplet) and sym m (symmetrical multiplet). ^{13}C NMR spectra were calibrated using the solvent signals, i.e., $CDCl_3$: δ_C 77.0 ppm. Low resolution mass spectra were recorded in electrospray ionisation (ESI) mode using 50% acetonitrile/water containing 0.1% formic acid as eluent; samples were made up in acetonitrile. High resolution precise mass spectra (HRMS) were recorded in electrospray ionisation (ESI) mode using 50% acetonitrile/water containing 0.1% formic acid as eluent; samples were made up in acetonitrile. Melting points were measured on a capillary melting point apparatus. Enantiopurity of the chiral compounds were determined by chiral HPLC performed on a Chiralpak AS-H, Chiralpak OJ-H or Chiralcel OD-H column.

4.2. General procedure for C–H insertion reactions of 1-diazo-1-phenylsulfonyl-5-phenylpentan-2-one 4

The $CuCl_2$-L*-(NaBARF) catalyst was generated in situ from a mixture of $CuCl_2$ (5 mol %) and bis(oxazoline) ligand (6 mol %) in CH_2Cl_2 (15 mL), with or without NaBARF (6 mol %). This catalytic mixture was stirred under nitrogen at 40 °C for 1.5 h. α-Diazo-β-keto sulfone **4** (150 mg, 1 equiv) was then added dropwise in CH_2Cl_2 (15 mL) over 0.5 h to the refluxing solution. The progress of the reaction was monitored by TLC and IR spectroscopy, where reaction completion was indicated by the disappearance of the characteristic diazo peak at 2122 cm^{-1}. Upon reaction completion, evaporation of the reaction solvent at reduced pressure gave the crude product. Purification by flash chromatography on silica gel, employing ethyl acetate/hexane as eluent, gave the pure cyclopentanone product as a white solid.

*4.2.1. trans-2-Phenylsulfonyl-3-phenylcyclopentanone (**5**).*[31] White solid, (found C, 67.59; H, 5.43. $C_{17}H_{16}O_3S$ requires C, 67.98; H, 5.37%); mp 96–99 °C; ν_{max} (KBr)/cm^{-1} 1743 (C=O), 1306, 1150 (SO_2), δ_H (400 MHz, $CDCl_3$) 1.92–2.07 [1H, m, one of C(4)H_2], 2.49–2.70 [3H, m, C(5)H_2, one of C(4)H_2], 3.91 [1H, d, *J* 7.5, C(2)*H*SO_2], 4.05–4.17 [1H, m, C(3)*H*Ph], 7.12–7.16 (2H, m, aromatic *H*), 7.20–7.32 (3H, m, aromatic *H*), 7.47–7.53 (2H, m, aromatic *H*), 7.59–7.65 (1H, m, aromatic *H*), 7.77–7.83 (2H, m, aromatic *H*).

4.3. General procedure for C–H insertion reactions of methyl 2-diazo-2-(4-phenylbutylsulfonyl)acetate 6

$CuCl_2$ (5 mol %), L* (6 mol %), and NaBARF (6 mol %) were weighed out and added to CH_2Cl_2 (8 mL). The required diazo material (200 mg) was added as a CH_2Cl_2 solution (2 mL) and the mixture was brought to reflux conditions. The reaction was

monitored by IR spectroscopy and kept at reflux until the diazo absorbance in the IR spectrum had disappeared. The solvent was removed under reduced pressure and the crude product was purified by column chromatography.

*4.3.1. cis-Methyl 2-(3-phenyl-1,1-dioxo-hexahydrothiopyran-2-yl)carboxylate (**7**).*[13] White solid, mp 116–118 °C; (found C, 58.11; H, 6.19; S, 11.94, $C_{13}H_{16}O_4S$ requires C, 58.19; H, 6.02; S, 11.93%); ν_{max}/cm^{-1} (KBr) 1727 (CO), 1323, 1118 (SO_2); δ_H (300 MHz, $CDCl_3$) 1.86 [1H, dddd, appears as dq, *J* 13.8, 3.3, H_A of C(4)H_2], 2.11–2.36 [2H, m, C(5)H_2], 2.61 [1H, dddd, appears as qd, 13.3, 4.0, H_B of C(4)H_2], 3.05 [1H, dddd, appears as dq, *J* 14.0, 3.2, H_A of C(6)H_2], 3.54 (3H, s, OCH_3), 3.62–3.75 [2H, m, H_B of C(6)H_2 and C(3)*H*], 3.99 [1H, dd, *J* 4.5, 3.0, C(2)*H*], 7.15–7.21 (2H, m, aromatic *H*), 7.24–7.37 (3H, m, aromatic *H*).

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Supplementary data

Supplementary data (chiral HPLC analysis and PXRD analysis). Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.12.003.

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