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N-(Diazoacetyl)oxazolidin-2-thiones as Sulfur Donor Reagents: Asymmetric Synthesis of Thiiranes from Aldehydes.

*Israel Cano, Enrique Gómez-Bengoa, Aitor Landa, Miguel Maestro,[†] Antonia Mielgo, Iurre Olaizola, Mikel Oiarbide, Claudio Palomo**

((Dedication----optional))

Sulfur-containing compounds are widespread among natural products and bioactive substances, and also useful ligands in asymmetric catalysis.[1] Therefore considerable efforts have been devoted to develop stereocontrolled *C*─*S* bond forming procedures.[2] Two common approaches consist of the electrophilic sulfenylation of enolates or equivalents[3] and the conjugate addition of *S*-nucleophiles to Michael acceptors,[4] routes that afford *S*-functionalized carbonyls at either α- *or* β-position. Methods to access α,β−thioepoxy carbonyls[5] would not only provide versatile *S*-functionalized adducts at both α- *and* β-position, but also imply generation of two contiguous stereocenters (Figure 1). However, as far as we are aware there is virtually no method for achieving such a goal in a direct and stereocontrolled fashion.[6] Here we describe *N*-(diazoacetyl)oxazolidin-2-thiones as new sulfur donor reagents that in combination with aldehydes and a Rh(II) catalyst are capable of producing α,β-thioepoxy carbonyls in highly stereoselective manner.

Inspired by the dual ability demonstrated by the oxazolidin-2-thione group to act as an intramolecular sulfur-donor reagent and a stereodirecting group (Figure 2a),[7] we envisaged that *N*-(diazoacetyl)oxazolidin-2-thiones might serve as both *C*─*C* and *C*─*S* bond forming reagents while controlling reaction stereochemistry. The assumption was that thiocarbonyl ylide **I** (Figure 2b), generated from *N*-(diazoacetyl)oxazolidin-2-thione upon teatment with a metal catalyst,[8] would react with an aldehyde to afford the zwiterionic intermediate **II**, which may follow diverting paths A or B to provide either epoxide or thioepoxide product. While path A (epoxide formation) seemed to be the prefered route for both sulfide ylides[9] and carbonyl ylides,[10] and implies no sulfur-transfer, we speculated that path B might also be possible, likely through rearrangement of intermediate **III**.

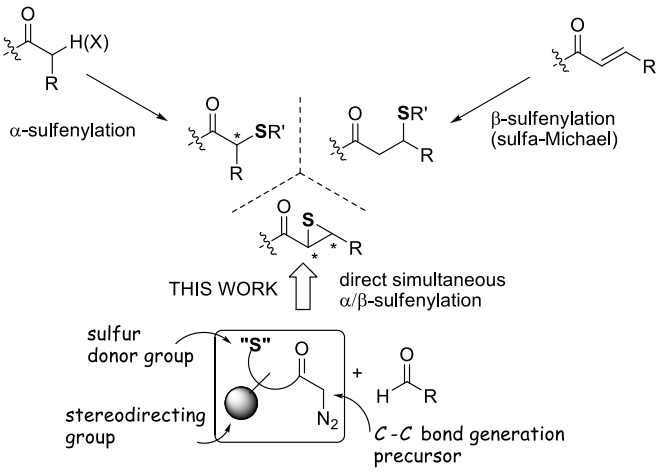

Figure 1. Common strategies for stereoselective sulfenylation of carbonyls at α or β position, and our proposal for the direct simultaneous α/β sulfenylation.

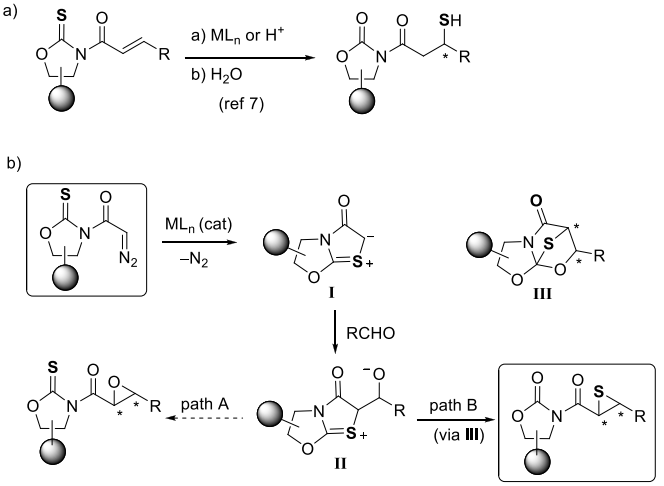

Figure 2. Working hypothesis for stereoselective thiirane synthesis via sulfur transfer with concomitant *C*─*C* bond formation.

Starting thione-diazo compounds were readily prepared by reaction of oxazolidin-2-thiones with 2-(2-tosylhydrazono)acetyl chloride in yields of 47-67%. Initial screening of catalysts and conditions revealed that both Rh(II) and Cu(II) salts catalyzed the reaction of **1** with benzaldehyde in CH_2Cl_2 at 0 ºC to afford thiirane **5a** in isolated yields from 53% to 62% and *cis*/*trans* ratios from 85:15 to 88:12 (entries 1, 2, and 7). Remarkably, in both cases no oxirane formation was detected from the corresponding reaction crudes.[10] This process is thus particularly significant in that the new *C*─*S* σ-bond

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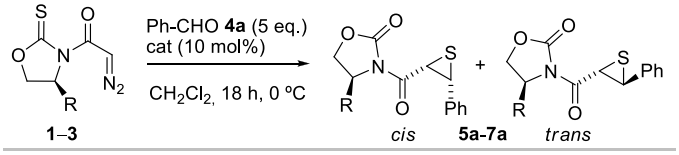
formation occurs in detriment of the *C─O* σ-bond and with concomitant generation of two contiguous stereocenters. The nature of the counterion of the transition metal salt used has an influence on the catalytic activity: while both $Rh_2(OAc)_4•2H_2O$ and $Cu(acac)_2$ demonstrated to be active and induced good reaction yields, no reaction at all was observed with either $Rh_2(OCOCF_3)_4$ or $Cu(OTf)_2$ salts (entries 1/2/7 vs. 5/8). Other divalent metal salts such as $CoCl_2$, $FeCl_2•H_2O$, or $Pd(OAc)_2$, potentially capable of inducing ylide formation, resulted inactive and led to sluggish or no reaction at all (entries 6, 10, 13).

Table 1. Screening of catalysts for the reaction of *N*-(diazoacetyl) 2-oxazolidinethiones **1**−**3** and benzaldehyde.[a]

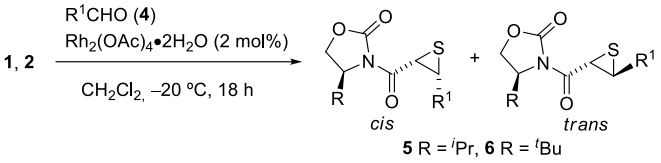


Entry	R	Substrate	Catalyst	T (ºC)	Prod.	*cis*:*trans*[b]	Yield (%)[c]
1	^{i}Pr	**1**	$Rh_2(OAc)_4$	0	**5a**	86:14	50
2		**1**	$Rh_2(OAc)_4•2H_2O$	0	**5a**	88:12	62
3		**1**		−10	**5a**	94:6	64[d]
4		**1**		−20	**5a**	97:3	62[d]
5		**1**	$Rh_2(OCOCF_3)_4$	0	**5a**	--	0[e]
6		**1**	$CoCl_2$	0	**5a**	--	0
7		**1**	$Cu(acac)_2$	0	**5a**	85:15	53
8		**1**	$Cu(OTf)_2$	0	**5a**	--	0[e]
9		**1**	CuCl	0	**5a**	91:9	40
10		**1**	$FeCl_2.4H_2O$	0	**5a**	--	0[e]
11		**1**	AuCl	0	**5a**	99:1	18
12		**1**	AgOTf	0	**5a**	--	0[e]
13		**1**	$Pd(OAc)_2$	0	**5a**	--	17
14	^{t}Bu	**2**	$Rh_2(OAc)_4•2H_2O$	−20	**6a**	94:6	60[d]
15	Ph	**3**	$Rh_2(OAc)_4•2H_2O$	−20	**7a**	92:8	45[d]

[a] The reactions were performed on a 0.30 mmol scale. [b] Determined by ^{1}H NMR. [c] Yield of isolated major isomer after chromatography. [d] Using 2 mol% catalyst. [e] Extensive decomposition was observed.

On the other hand, some metals in the oxidation state +1 were also effective. For instance, while no reaction was observed with AgOTf, both CuCl and AuCl promoted the reaction to give rise product **5a** with *cis/trans* ratios of 91:9 and 99:1, respectively, although yields were in these cases low or very low (40%, 18%). Further optimization of the reaction conditions using as catalyst $Rh_2(OAc)_4•2H_2O$ indicated that lower (2 mol%) catalyst loading suffices and the *cis/trans* ratio could be improved by lowering the temperature (up to 97:3 *cis/trans* ratio, entries 3 and 4). Finally, diazo-oxazolidinethiones **2** and **3**, bearing respectively a ^{t}Bu and a Ph substituent group, were also tolerated, although in the case of the Ph analog **3** slight erosion of both yield and selectivity was observed (entries 14 and 15).

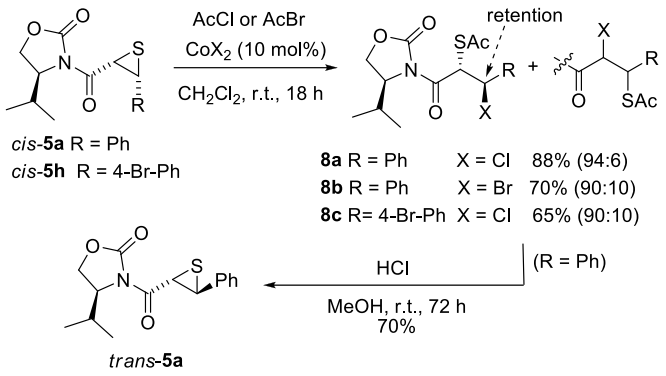
Table 2. Scope of the reaction.[a]



Entry	Substrate	R^1	Product	*cis*:*trans*[b]	Yield (%)
1	**1**	Ph	**5a**	93:7	65[c]
2	**1**	4-Me-C_6H_4	**5b**	82:18	60
3	**1**	3,5-diMe-	**5c**	83:17	61
4	**1**	4-MeO-C_6H_4	**5d**	1:99	61
5	**1**	4-TBSO-C_6H_4	**5e**	1:99	31[d]
6[e]	**1**	4-Cl-C_6H_4	**5f**	88:12	63
7	**1**	3-Cl-C_6H_4	**5g**	86:14	57
8	**1**	4-Br-C_6H_4	**5h**	91:9	56
9	**1**	4-NO_2-C_6H_4	**5i**	92:8	61
10	**1**	4-CN-C_6H_4	**5j**	91:9	56
11	**1**	PhC≡C	**5k**	72:28	65
12[f]	**2**	PhC≡C	**6k**	83:17	75
13[g]	**2**	PhC≡C	**6k**	86:14	69
14[f]	**2**	3-Cl-PhC≡C	**6l**	85:15	60
15	**1**	3-furyl	**5m**	62:38	ND[h]
16[g]	**2**	3-furyl	**6m**	83:17	70
17	**1**	3-Pyridyl	**5n**	--	0[i]

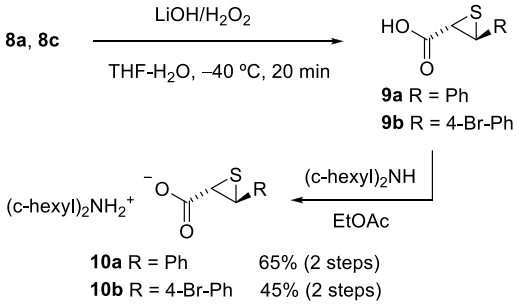
[a] Reaction conditions: **1** (0.5 mmol), **4** (3 equiv, 1.5 mmol), $Rh_2(OAc)_4•2H_2O$ (2 mol%), −20 ºC, 18 h in CH_2Cl_2 (1 mL). [b] Determined by ^{1}H NMR. [c] Yields of isolated compounds **5**/**6** after column chromatography. [d] Reaction carried out at 2 mmol scale. [e] Yield not optimized; partial desilylation occurred during chromatography (SiO_2). [e] 91:9 diastereoselectivity in the presence of 2,2'-bipyridyl as additive. [f] Reaction run at −60 ºC. [g] Reaction run at −78 ºC. [h] ND: Not determined [i] Unchanged SM recovered.

We next investigated the scope of the reaction with respect to the aldehyde component. As the results in Table 2 show, a range of aromatic aldehydes bearing either electron-releasing, neutral, or electron-withdrawing substituents all produced the corresponding thiirane product smoothly within 18 hours at −20 ºC. In each case a mixture of *cis/trans* isomers was formed from which the major isomer was obtained in 57%−75% isolated yield. Interestingly, while in most cases *cis*-thiirane was obtained as the major isomer (*cis/trans* ratio from 97:3 to 82:18, entries 1−3, 6−10), in case of *p*-anisidine, and *p-tert*-butyldimethylsilyloxybenzaldehyde (products **5d-e**), the *trans*-configured thiirane was the exclusive reaction product (entries 4−5). This unusual reversal of the reaction stereochemistry observed for benzaldehydes bearing electron releasing substituents could be explained on the basis of the proposed reaction mechanism (*vide infra*). The catalytic generation of thiiranes **5**/**6** did also work with other non enolizable aldehydes explored, such as alkynyl and heteroaryl aldehydes (entries 11-16). Pyridylcarbaldehyde was an exception (entry 17). Assignment of the *cis*/*trans* relative configuration of the formed thiirane ring was primarily made by correlation of the coupling constants between the two *vec* H nucleus in NMR: from 7.4 Hz to 7.7 Hz for the *cis*-thiirane systems; from 4.80 Hz to 4.90 Hz for the *trans* isomer. In addition, an X-ray single-crystal structure analysis of compound *cis*-**5a** served to confirm the proposed structure.[11]



Scheme 1. *Thiirane ring opening on adducts 5.*

Next conditions for the selective opening of the thiirane ring and the release of the oxazolidinone auxiliary were explored. For example, Scheme 1, treatment of thiiranes *cis*-**5a** and *cis*-**5h** with acetyl chloride in CH_2Cl_2 at room temperature in the presence of $CoCl_2$ (10 mol%), according to the procedure of Iranpoor and Firouzabadi,[12] gave rise to the β-chloro-α-thio imide derivatives **8a** and **8c** in 88% and 65% isolated yields, respectively, after chromatography. Similarly, treatment of *cis*-**5a** with acetyl bromide in the presence of $CoBr_2$ as a catalyst afforded the corresponding bromo-derivative **8b** in 70% isolated yield. In all these three cases a minor amount (6%–10%) of the corresponding regioisomeric ring opening product was also observed in the respective reaction crude. It is important to note that substitution at β carbon during ring opening leading to products **8** occurred with retention of configuration, perhaps via a double inversion pathway involving a transient *C*-*O* adduct. Interestingly, acid-promoted cyclisization of compounds **8** to restore the thiirane ring took place very efficiently, with inversion of the configuration of β-carbon. For instance, the treatment of **8a** with methanolic HCl afforded *trans*-**5a** in 70% yield. Accordingly, a two-step thiirane ring isomerization from *cis* to the more stable *trans* isomer is feasible.



Scheme 2. *Recovery of the auxiliary.*

On the other hand, the removal of the oxazolidinone moiety from thiirane adducts **5** through imide hydrolysis or alcoholysis under usual conditions led to extensive desulfurilation. This problem could be circumvent by performing imide hydrolysis on the open adducts **8** instead (Scheme 2). Thus, saponification with $LiOH/H_2O_2$ of adducts **8a** and **8c** proceeded with restoration of the thiirane ring, affording the corresponding acids **9**, which were isolated as crystalline bench stable dicyclohexylamine salts **10**. In this transformation oxazolidinone was also formed which could be recovered and transformed into the thione auxiliary and recycled.[7] Unambiguous determination of the structure of salt **10b** and compound **8a** by X-ray analysis[11] served for further confirmation of the products identity as well as the stereochemical outcome of the reactions involved.

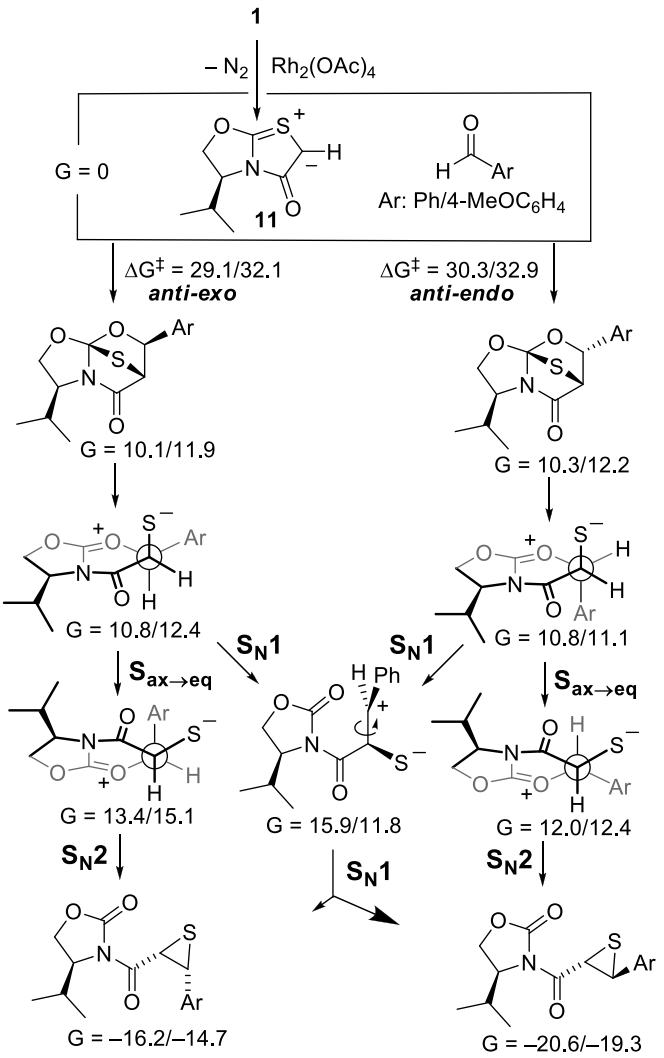


Figure 3. Principal pathways found (DFT-B3LYP) for the Rh-catalyzed reaction between diazocompound **1** and either benzaldehyde or *p*-anisaldehyde. Values of Gibbs energy in kcal/mol.

A DFT investigation was carried out at the B3LYP level of theory, which provided a plausible pathway for this intriguing thiirane forming reaction. Calculations predict that the corresponding Rh-carbenoid species[11] formed upon treatment of diazo-thione compound **1** with $Rh_2(OAc)_4$, evolves into bicyclic ylide **11** (Figure 3)[13] with no activation barrier, probably because of the high charge delocalization exhibited by this particular ylide.[14] According to calculations subsequent reaction of **11** with either benzaldehyde or *p*-anisaldehyde would generate a unique tricyclic adduct,[15] and among the four possible relative orientations of the ylide and aldehyde component during the cycloaddition, those leading to *anti-exo* and *anti-endo* isomers are preferred. The complementary *syn* transition states lie considerably higher in energy because unfavorable interactions between the ylide isopropyl substituent and the incoming aldehyde. The energy differences between *anti-exo* and *anti-endo* approaches for benzaldehyde and *p*-anisaldehyde, (1.2 and 0.8 kcal/mol, respectively) would justify preferential formation of *anti-exo* adduct with expected diastereoselectivities near 90:10. Transformation of these tricyclic high energy intermediates into the final thiirane products would follow a more or less downhill energy

profile, involving *S*-ring opening, $S_{ax \rightarrow eq}$ conformational switch, and internal S_N2 displacement. Accordingly, from tricyclic *anti-exo* intermediate the *cis*-configured thiirane would be formed; reversely, from the less favorable *anti-endo* precursor, the *trans*-thiirane would be formed, a prediction that agrees with the experimentally observed trend for most of the aldehydes tested. Interestingly, calculations also offer a plausible explanation of the reversal of the reaction stereochemistry observed experimentally for *p*-anisaldehyde and other related electron-rich aromatic aldehydes. Indeed, thiirane generation could occur through an alternatively S_N1-type pathway, which is about 2.5 kcal/mol less favorable than the S_N2 pathway for benzaldehyde, but conversely about 3.3 kcal/mol more favorable than the S_N2 pathway for *p*-anisaldehyde. As expected, S_N1-type cyclisation would preferentially lead to the most stable *trans*-thiirane product.

In conclusion, we have reported the first Rh-catalyzed reaction of a diazoacetyl compound with aldehydes that affords thiiranes, instead of oxiranes as known before. This unusual reactivity relies on the development of *N*-(diazoacetyl)oxazolidin-2-thiones as new chiral sulfur donor reagents and enables the direct production of optically active thiiranes with very high stereoselectivity. Work towards expanding the scope of this sulfur transfer technology is currently underway in our laboratory.

Experimental Section

General catalytic procedure for the synthesis of Thiiranes 5-7
To a solution of the corresponding diazocompound **1**-**3** (0.50 mmol) and aldehyde **4a**-**p** (3 eq, 1.5 mmol) in dry CH_2Cl_2 (1.5 mL) at a given temperature, was added rhodium (II) acetate dihydrate (4.8 mg, 0.01 mmol, 2 mol %) under argon atmosphere. The reaction mixture was stirred overnight at the same temperature and afterwards quenched with saturated $NaHCO_3$, the organic layer was separated, dried with $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (eluent: AcOEt/Hexane 1:4) to afford the desired product.

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Keywords: asymmetric synthesis · thiiranes · sulfur donor reagents · sulfur ylides · diazocompounds

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[15] An alternative pathway to this tricyclic adduct would involve attack of the thione group into the epoxide initially generated from the reaction between the aldehyde and the diazocarbonyl moiety (see ref 11). However, the fact that no even traces of epoxide product was detected in the reaction mixtures and a 14.4 kcal/mol energy barrier is calculated for such epoxide formation, work against the epoxide pathway and favors the sulfur ylide mediated pathway.

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Layout 2:

Asymmetric Synthesis

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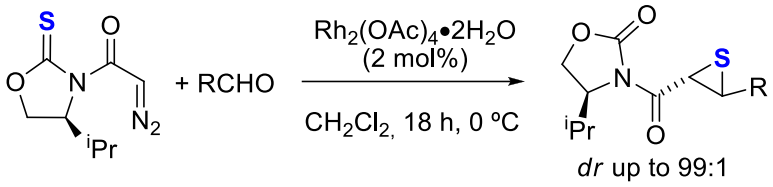
N-(Diazoacetyl)oxazolidin-2-thiones as Sulfur Donor Reagents: Asymmetric Synthesis of Thiiranes from Aldehydes



Sulphur tyranny: thiiranes, instead of oxiranes, can be obtained in highly stereoselective manner through cycloaddition reaction of *N*-acyl oxazolidine tethered diazo-thione compounds with aldehydes catalyzed by Rh(II).