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A Highly Regioselective Palladium Catalyzed *O,S* Rearrangement of Cyclic Thiocarbonates

William Mahy,[a] Sinéad Cabezas-Hayes,[a] Gabriele Kociok-Köhn,[b] and Christopher G. Frost*[a]

Abstract: This work describes an operationally simple catalytic synthesis of cyclic *S*-thiocarbonates with predictable regioselectivity in good yields. A crystal structure is presented that clearly confirms the regioselectivity of the reaction.

Introduction

Sulfur containing chemicals are prevalent starting materials for the synthesis of highly functionalized, high value molecules. Sulfur is renowned for its importance in the pharmaceutical industry, where roughly 20% of the Top 200 US pharmaceuticals in 2011 contained sulfur.[1] *O*-thiocarbamates have demonstrated synthetic utility in *N*- to *C*- aryl migrations allowing for the synthesis of highly functionalized thiols.[2] They have also proven useful intermediates for the Barton-McCombie reaction,[3] and their use in thermal Newman-Kwart rearrangements,[4] as well as catalytic variants,[5] has allowed for the efficient synthesis of aryl sulfides *via* an *O*- to *S*- aryl migration. Our group recently developed the synthetic utility of *O*-thiocarbamates, accessing the previously unreported *O*- to *S*- alkyl migration by employing a ruthenium catalyst to generate thiooxazolidinones.[6] These reactions, however, are constrained to thiocarbamates, thus limiting the generality of the reactions.

We envisioned that by tuning the catalytic system, we could exploit the reactivity of thiocarbonyls towards rearrangement of an *O*-thiocarbonate system, thus allowing access to 1,3-oxathiolane-2-ones. The ring-opening of these structures could in turn provide access to β-hydroxythiols,[7] a sub-class of organosulfur compounds which have been used in the synthesis of high value starting materials.[8] Generally, the synthesis towards β-hydroxythiols involves oxidative addition of sulfur across an alkene, however the regioselectivity tends to yield the anti-Markovnikov product, and therefore the less-substituted thiol.[9] There are scant literature examples of *O*- to *S*- rearrangements 1,3-dioxolane-2-thiones, and the products have largely been reported as byproducts in low yields.[10] As such, attempts to direct the exclusive formation of 1,3-oxathiolane-2-ones using catalysis remains, to the best of our knowledge, underexplored.

Results and Discussion

Based on our previous findings, we investigated the rearrangement of cyclic thiocarbonates towards the generation of masked β-hydroxythiols. The rearrangement of thiocarbonates has an additional level of complexity due to the possibility of the formation of two regioisomers. The following study was focused not only on the efficiency of rearrangement, but also the generation of a highly predictive and regioselective catalytic system.

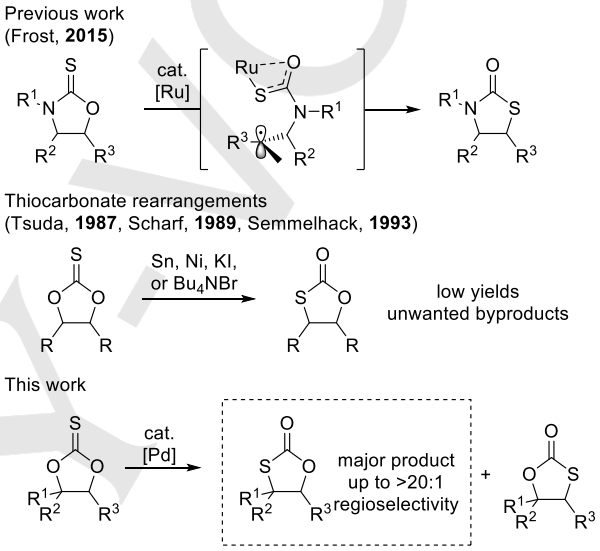

Figure 1. *O* to *S* alkyl migrations.

For this purpose, 4-phenyl-1,3-dioxolane-2-thione (**1**) was readily synthesized as a model substrate for the investigation of a metal-catalyzed rearrangement. $[RuCl_2(p\text{-cymene})]_2$ was initially employed to probe the efficacy of the transformation due to the excellent reactivity observed in previous studies. In the presence of 5 mol% catalyst (10 mol% [Ru]) (table 1, entry 1) we achieved products (**2a** and **2ab**) and a small (6%) amount of the desulfurized carbonate **2ac**.

Encouraged by this result, a number of different transition metals were investigated (table 1, entries 2-5). Cu, Ni, and Fe catalysts (see supporting information) gave consistently poor conversions and selectivities, however late transition group metals proved promising. $RuCl_2(phen)3{\bullet}H_2O$ gave improved overall conversion but reduced regioselectivity, and a large proportion of 2-phenylthiirane formation was also observed (table 1, entry 2). It was believed the phenanthroline ligand was responsible for nucleophilic attack of **2a**, resulting in a decarboxylative ring contraction. Palladium catalysts showed the highest propensity for the formation of the desired regioisomer, exhibiting superior selectivity, however, significant levels of desulfurization were observed. Importantly, no rearrangement or desulfurization products were observed in the absence of catalyst (table 1, entry 6). Rigorous exclusion of moisture and oxygen when employing palladium catalysts proved effective in eliminating the formation of the desulfurized byproduct (table 1,

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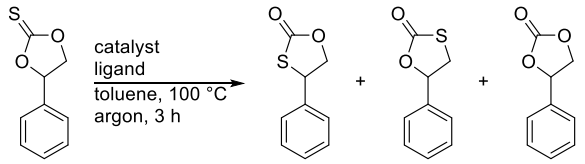
entry 7), leading to high conversion (99%) and selectivity for **2a** over **2ab** (>20:1).

Table 1. Selected screening results[a]



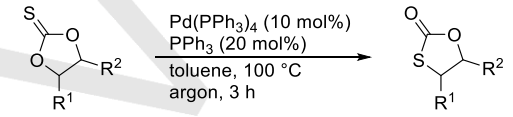
1a **2a** **2ab** **2ac**

Entry	Catalyst	Ligand	Conversion[b]		
			2a	**2ab**	**2ac**
1[c]	$[RuCl_2(p\text{-cymene})]_2$	-	50	10	6
2[c]	$RuCl_2(phen)_3.H_2O$	-	31 (42)[d]	21	0
3[c]	$Ni(PPh_3)Cl_2$	-	6	5	7
4[c]	$[Rh(OAc)]_2$	-	0	0	0
5[c]	$Pd(PPh_3)_4$	-	36	1	31
6[c]	-	-	0	0	0
7	$Pd(PPh_3)_4$	-	95	1	3
8[e]	$Pd(PPh_3)_4$	-	33	1	0
9[e],[f]	$Pd(PPh_3)_4$	DMAP	18 (12)[d]	5	7
10[e], [g]	$Pd(PPh_3)_4$	DPPF	32	4	0
11[e],[g]	$Pd(PPh_3)_4$	BINOL	24	0	0
12[e], [f]	$Pd(PPh_3)_4$	SPhos	45	0	0
13[e], [f]	$Pd(PPh_3)_4$	PPh_3	44	0	1
14[h]	$Pd(PPh_3)_4$	PPh_3	99	0	1

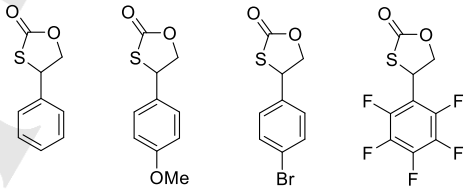
[a]Standard reaction conditions: substrate (0.25 mmol), catalyst (10 mol%), toluene (0.1 M), 100 °C, 3 h [b] Conversion calculated by crude ^{1}H NMR [c] Under air [d] Conversion to 2-phenylthiirane [e] $Pd(PPh_3)_4$ (2 mol%), 1 h [f] Ligand (4 mol%) [g] (2 mol%) [h] PPh_3 20 mol%), toluene (0.2 M)

The addition of ligands was investigated in the presence of $Pd(PPh_3)_4$ to ascertain if properties of the catalytic system could be enhanced by prevention of catalyst deactivation and poisoning. Due to the already excellent conversion at 10 mol% catalyst, the catalyst loading was reduced to 2 mol% for 1 h for these studies (table 1, entry 8). DMAP (table 1, entry 9) exhibited increased total conversion over the control reaction, however, the use of pyridine based ligands (see supporting information) resulted in reduced regioselectivity and 2-phenylthiirane formation, consistent with the observed reactivity with the use of $RuCl_2(phen)3{\bullet}H_2O$. Bi-dentate ligands (table 1, entries 10, 11) gave no enhancement of reactivity, or proved detrimental to both conversion and regioselectivity, whereas mono-dentate ligands (table 1, entries 12,13) resulted in improved conversion whilst maintaining high regioselectivity. The comparable results of PPh_3 to the more expensive Buchwald-type ligand SPhos led us to select PPh_3 as our additive ligand. An excess of phosphine was believed to improve product liberation and hence catalyst turnover. Despite being able to achieve quantitative conversion of **1a** in only 3 hours in the absence of ligands, addition of PPh_3 at higher catalyst loadings was retained to form general conditions that would perform well for both facile and more challenging substrates. Varying reaction concentration had negligible effect on conversion, and as such a higher working concentration was employed for the optimized conditions (table 1, entry 14).

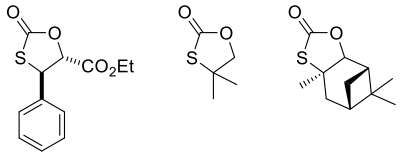
Table 2. Synthesis of secondary 1,3-oxothiolane-2-ones



1 **2**



2a, 62% >20:1 **2b**, 62% 10:1 **2c**, 51% 2:1 **2d**, 26% >20:1



(±)2e, 54% >20:1 **2f**, 0% **2g**, 0%

Reaction conditions: **1** (1 mmol), $Pd(PPh_3)_4$ (0.1 mmol), PPh_3 (0.2 mmol) in toluene (5 mL) under argon at 100 °C for 3 h. Isolated yields.

After the optimal conditions were established, we focused our attention on investigating the scope and limitations of the catalytic rearrangement. A number of cyclic thiocarbonates were prepared from commercially available 1,2-diols (or readily accessible through commercially available alkenes *via* a dihydroxylation strategy or Grignard addition to hydroxyacetone), and by treatment of the 1,2-diols with thiophosgene (see supporting information). Electron-rich and electron-deficient aryl secondary 1,3-dioxolane-2-thiones (table 2) were subjected to the reaction conditions, and the system proved tolerant of a number of functionalities resulting in good conversions and high regioselectivity.

Although substrates demonstrated high conversion in all cases, isolated yields were significantly lower due to the poor UV visibility and staining with TLC indicators. Despite the inclusion of an aryl bromide in the reaction, no proto-dehalogenation was observed in the case of the *para*-bromo substituted substrate (**2c**),

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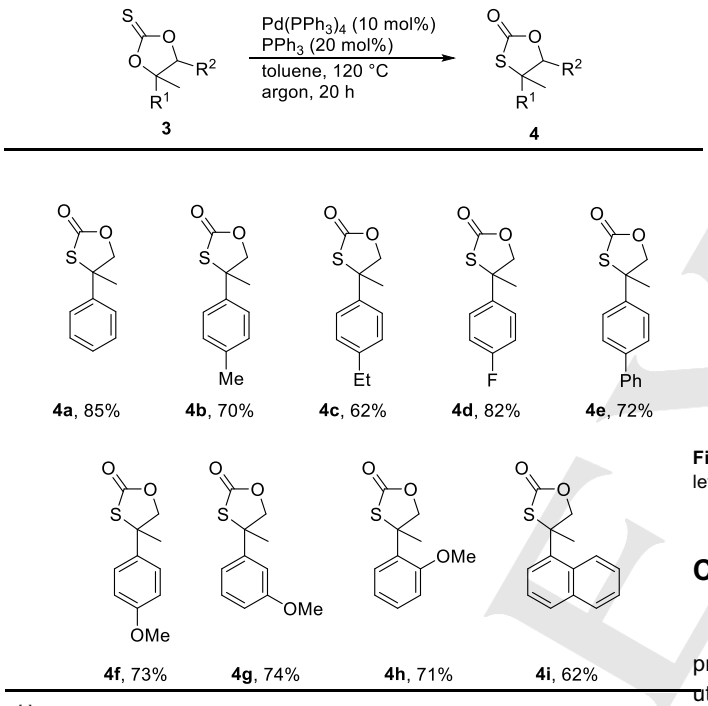
however erosion of regioselectivity was observed. The reaction was also tolerant of cinnamyl ester derivative, giving the single regioisomer **2e**. Interestingly, this is the opposite selectivity than the rearrangement reported by Ko with the use of catalytic bromide.[11] Additionally, only a single pair of diastereomers was isolated, with no evidence of racemization of the benzylic position in crude ^{1}H NMR spectroscopy.

Upon the introduction of any non-benzylic substituents (**2f, 2g**), the reaction proved unviable, where high levels of desulfurization were witnessed, but no conversion to desired product.

Table 3. Synthesis of tertiary 1,3-oxothiolane-2-ones[a]



4a, 85% **4b**, 70% **4c**, 62% **4d**, 82% **4e**, 72%

4f, 73% **4g**, 74% **4h**, 71% **4i**, 62%

[a] Reaction conditions: **1** (1 mmol), $Pd(PPh_3)_4$ (0.1 mmol), PPh_3 (0.2 mmol) in toluene (5 mL) under argon at 120 °C for 20 h. Isolated yields.

Tertiary 4-methyl-4-aryl-1,3-dioxolane-2-thiones (Table 3) were also investigated. The observed reactivity was significantly slower under the standard reaction conditions, however elevating the temperature and extending the reaction time (120 °C, 20 h) proved sufficient in improving conversion. The use of tertiary substrates also resulted in the formation of the more highly substituted regioisomer in all cases, and their identity was confirmed absolutely through the crystal structure of **4e** (Figure 2). High conversions were observed, however the prolonged reaction times, and hence exposure to sub-stoichiometric quantities of phosphine, led to competitive Corey-Winters olefination, as indicated by the presence of styrene derivatives by crude ^{1}H NMR spectroscopy. Two particularly interesting examples were *ortho*-methoxy (**4h**) and naphthyl (**4i**) derivatives, as the congestion around the quaternary center gives no apparent reduction in reactivity and allows highly substituted sulfur compounds to be synthesized.

In this more highly substituted system (table 3), neither yield nor regioselectivity significantly fluctuated with electronics, as both electron-donating and electron-withdrawing substituents were well tolerated. In the case of the secondary substrates (table 2), increasing electron-withdrawing character resulted in lower isolated yields. We believe mechanistic parallels can be drawn between this and our previous work,[5] with the transformation occurring through a possible radical pathway, however the possibility of an ionic intermediate has not been ruled out. As we did not observe any erosion of stereochemical information in **2e**, it is likely that the reaction does not proceed *via* a planar intermediate, or that any planar intermediate formed is short-lived.

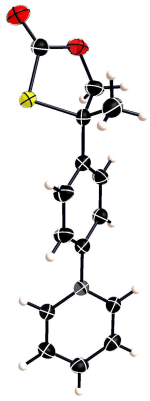


Figure 2. Crystal structure of **4e CCDC 1557205** (ellipsoids drawn at the 50% level)

Conclusions

We have developed a novel catalytic rearrangement procedure towards the installation of benzylic thiols. The reaction utilizes substrates derived from ubiquitous 1,2-diols in an atom economical intramolecular rearrangement, catalysed by an inexpensive and simple catalyst-ligand system. This process exhibits highly predictable regioselectivity, with excellent retention of stereochemical information to form secondary and tertiary masked thiol building blocks, 1,3-oxathiolane-2-ones, which could prove to be versatile intermediates in the synthesis of a number of sulfur containing molecules.

Experimental Section

General Procedure: $Pd(PPh_3)_4$ (0.1 mmol) and PPh_3 (0.2 mmol) was charged into an oven-dried carousel tube, sealed and the contents of the reaction vessel were purged with argon, before a solution of 1,3-dioxolane-2-thione (1.0 mmol) in dry, degassed toluene (5 mL) was added via septum. The solution was heated to 100 °C for 3 h (or 120 °C for 20 h). After this time the reaction was cooled to room temperature and concentrated under reduced pressure. The crude material was purified *via* flash silica gel chromatography.

Acknowledgements

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Keywords: alkyl migrations • thiocarbonates • homogeneous catalysis • Newman-Kwart

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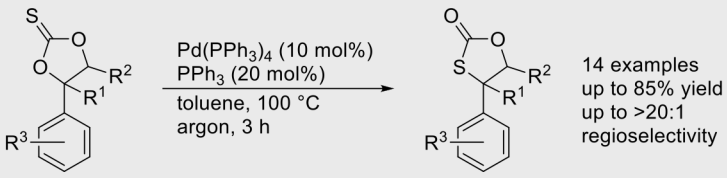

Catalytic O,S rearrangements

*William Mahy, Sinead Cabezas-Hayes, Gabriele Kociok-Köhn, Christopher G. Frost**

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Title

This work describes an operationally simple synthesis of cyclic *S*-thiocarbonates with predictable regioselectivity in good yields. A crystal structure has clearly confirmed the regioselectivity of the reaction.