Pseudoreversible Reactions

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Ruthenium-Catalyzed *O*- to *S*-Alkyl Migration: A Pseudoreversible Barton–McCombie Pathway

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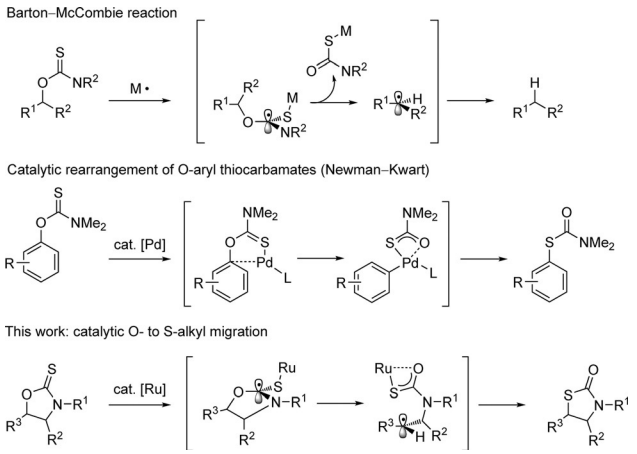
Abstract: *A practical ruthenium-catalyzed O- to S-alkyl migration affords structurally diverse thiooxazolidinones in excellent yields. Our studies suggest this catalytic transformation proceeds through a pseudoreversible radical pathway drawing mechanistic parallels to the classic Barton–McCombie reaction.*

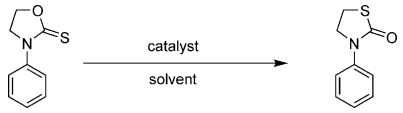
The prevalence of sulfur-containing functionality in chemical biology, pharmaceutical drugs, agrochemicals, and material science is of fundamental importance and dictates the development and application of new synthetic methods in organosulfur chemistry. Historically, *O*-thiocarbamates have proved valuable as directing groups for the chemoselective reduction of alcohol functional groups to the corresponding alkane (Barton–McCombie reaction)[1] and also in the generation of Ar–S compounds from phenols through an O_{Ar} to S_{Ar} migration (Newman–Kwart rearrangement).[2] The emergence of efficient metal-mediated techniques for the construction and transformation of carbon–sulfur bonds provides valuable tools for contemporary organic synthesis.[3] In this context, Lloyd-Jones et al. have reported an elegant palladium-catalyzed variant of the Newman–Kwart rearrangement facilitating rearrangements at lower temperatures through an oxidative addition/tautomerization/reductive elimination sequence.[4] Herein, we report a selective ruthenium-catalyzed O_{alkyl} to S_{alkyl} migration that occurs when the *O*-thiocarbamate functionality is constrained in a readily available ring structure (Scheme 1).[5] Our studies suggest this catalytic transformation proceeds through a pseudoreversible radical pathway drawing mechanistic parallels to the classic Barton–McCombie reaction.[6]

At the onset of our investigation, we explored the *O*- to *S*-alkyl migration of *N*-phenyloxazolidine-2-thione (**1a**) under traditional Barton–McCombie deoxygenation conditions using a variety of organic-based radical initiators (Table 1).[7] The use of a number of transition-metal catalysts (10 mol% equivalence of metal) known for their catalytic activity in single electron transfer processes were also investigated.[8] $[RuCl_2(p\text{-cymene})]_2$ showed exceptional reactivity and selectivity toward *O*- to *S*-alkyl migration, giving rise to 82% **2a** after 1 hour, during which no observable desulfonated *N*-phenyl oxazolidinone from the competitive radical pathway was observed. Given that ligation of ruthenium species is well known to improve both physical and chemical properties in ruthenium-mediated transformations



Scheme 1. Conceptual rationale for a catalytic *O*- to *S*-alkyl migration.

Table 1: Selected screening results.



Entry	Catalyst (mol%)	Solvent	*t* [h]	Conv. [%][b]
1	–	PhMe	1	–
2[c]	DTBP (10)	PhMe	3	6 (8)[d]
3	$Pd(OAc)_2$ (10)	PhMe	1	7 (11)[d]
4	$NiBr_2(PPh_3)_2$ (10)	PhMe	1	5 (–)[d]
5	$[RuCl_2(p\text{-cymene})]_2$ (5)	PhMe	1	82 (–)[d]
6[e]	$[RuCl_2(p\text{-cymene})]_2$ (1)	THF	3	12
7[e]	$[RuCl_2(p\text{-cymene})]_2$ (1)	MeCN	3	6
8[e]	$[RuCl_2(p\text{-cymene})]_2$ (1)	PhMe	3	17
9[f]	$[RuCl_2(p\text{-cymene})]_2$ (1)	PhMe	3	79
10[f,g]	$[RuCl_2(p\text{-cymene})]_2$ (1)	PhMe	3	100

[a] Reaction conditions: **1a** (0.25 mmol), catalyst, toluene (2.5 mL), 100°C, air. Yields of isolated products are given. [b] Conversion of **1b** was determined by ^{1}H NMR spectroscopy. [c] Additional 1.0 equiv Bu_3SnH used. [d] Conversion to *N*-phenyl oxazolidinone. [e] Reactions performed at 70°C. [f] 2 mol% SPhos. [g] Toluene (1.25 mL). Full screening results reported in the SI.

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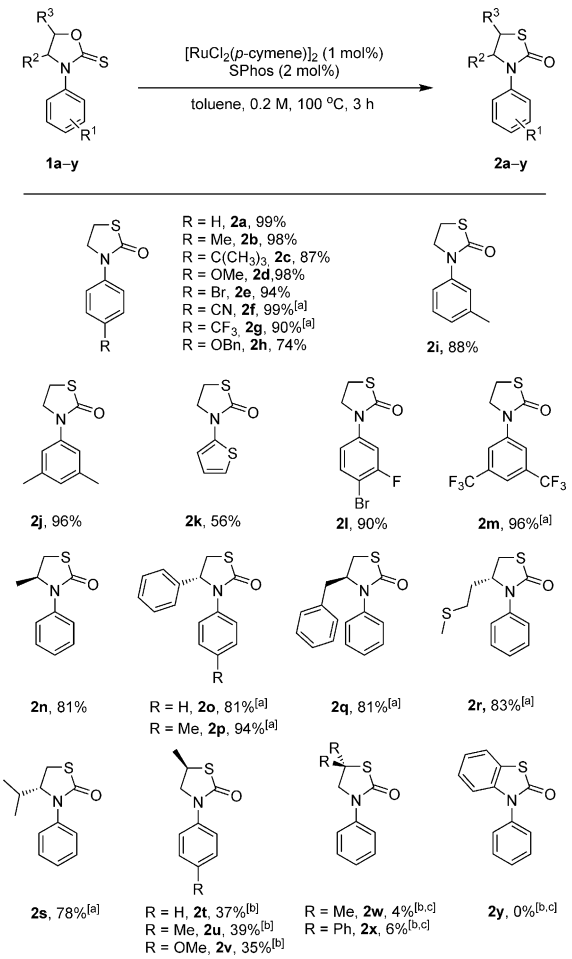
we tested a range of mono- and bidentate ligands in combination with 1 mol% $[RuCl_2(p\text{-cymene})]_2$ (2 mol% Ru) in toluene at 100 °C.[9] Monodentate biaryl phosphines proved most effective, and SPhos gave the highest improved reactivity after 3 h, giving 81% conversion of **1a**. The effect of concentration was then explored and higher concentrations were found to be by far the most effective, allowing quantitative conversion of **1a** at 100 °C in 3 h with just 1 mol% of the Ru dimer. In the absence of catalyst there was no detectable rearrangement.

With the optimized reaction conditions in hand we turned our attention to the scope and limitations of this ruthenium-promoted rearrangement. To our delight a wide range of *N*-aryl oxazolidine-2-thiones[10] were tolerated under the reaction conditions, affording the corresponding *N*-aryl thiazolidin-2-ones in excellent yields (Scheme 2).

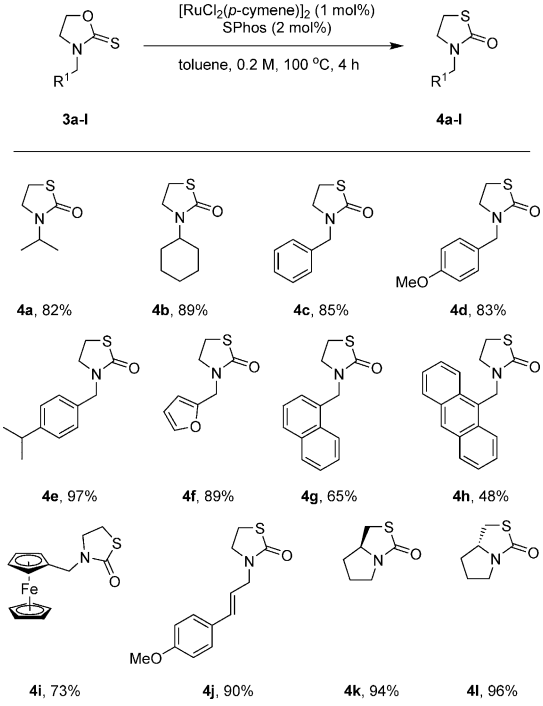
Notably, the reaction conditions are tolerant of a number of valuable and reactive functional groups, including Br, CN, CF_3, OBn, and F (products **2e–h**, **2l**), in the case of **2e** and **2l** no dehalogenation was observed. A trend in the electronic nature of the aryl substituents was observed, where strongly electron-rich and strongly electron-poor aromatics showed lower rates with respect to the unsubstituted aromatic; this effect was most pronounced with electron-poor systems, for which an increase in catalytic loading to 2 mol% of $[RuCl_2(p\text{-cymene})]_2$ (4 mol% Ru) was required to afford improved yields (products **2f**, **2g**, and **2m**). Enantiomerically pure 4-substituted oxazolidine-2-thiones also showed excellent reactivity under the reaction conditions, affording the corresponding enantiopure 4-substituted thiazolidin-2-ones with complete enantiomeric retention (**2n–s**).

The 5-substituted oxazolidine-2-thiones were significantly less reactive. Monosubstitution at this position required elevated temperatures (130 °C), increased catalyst loading (5 mol%), and extended reaction times (24 h) to afford modest conversion (**2t–v**), a slight erosion of the enantiopurity (91% *ee*) was also observed. Geminal substituents showed an even more pronounced reduction in reactivity (**2w–x**). Phenol derivatives (**2y**), more closely mimicking substrates used in Newman–Kwart rearrangements showed no conversion even at more forcing conditions.[2]

Subsequently we turned our attention to the rearrangement of *N*-alkyl-substituted oxazolidine-2-thiones (Scheme 3). In all cases the corresponding *N*-alkyl thiazolidin-2-ones were formed in good to excellent yields. However, the reaction using an anthracene derivative gave only moderate conversion, which could be ascribed to the poor solubility of the substrate in toluene.

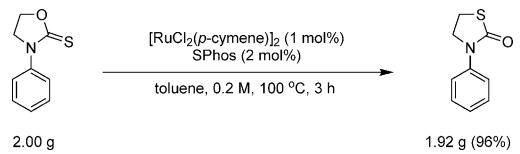


Scheme 2. Synthesis of *N*-aryl thiazolidin-2-ones from a variety of *N*-aryl oxazolidine-2-thiones. Reaction conditions: *N*-aryl oxazolidine-2-thiones (0.25 mmol), $[RuCl_2(p\text{-cymene})]_2$ (1 mol%), SPhos (2 mol%), toluene (1.25 mL), 100 °C, 3 h, air. Yields of isolated products are given. [a] $[RuCl_2(p\text{-cymene})]_2$ (2 mol%), SPhos (4 mol%) used. [b] $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), SPhos (10 mol%), 130 °C, 24 h used. [c] Conversion calculated from ^{1}H NMR spectra.



Scheme 3. Synthesis of *N*-alkyl thiazolidin-2-ones from a variety of *N*-alkyl oxazolidine-2-thiones. Reaction conditions: *N*-aryl oxazolidine-2-thiones (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (1 mol%), SPhos (2 mol%), toluene (2.5 mL), 100 °C, 4 h, air. Yields of isolated products are given.

We next examined the rearrangement methodology on a multigram scale to probe the scalability of the process. *N*-phenyl oxazolidine-2-thione was subjected to the ruthenium-catalyzed *O*- to *S*-alkyl migration with 1 mol% $[RuCl_2(p\text{-cymene})]_2$ under air using the standard conditions (Scheme 4). Isolation of the target thiazolidin-2-one was

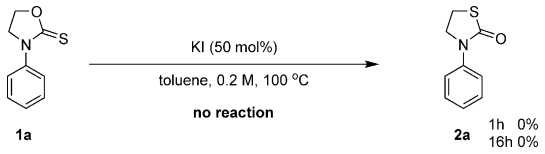


Scheme 4. Multigram synthesis of **2a**. Reaction conditions: *N*-aryl oxazolidine-2-thiones (11.16 mmol), $[RuCl_2(p\text{-cymene})]_2$ (1 mol%), SPhos (2 mol%), toluene (55.8 mL), 100°C, 3 h, air. Yields of isolated products are given

achieved in a similarly high yield of 96% following column chromatography.

To determine the mechanism of the reaction catalyzed by $[RuCl_2(p\text{-cymene})]_2$, a number of kinetic and control experiments were performed. Cross-over experiments showed no formation of cross-over products when reacted under the optimized conditions. Reaction rates displayed a first-order dependency in both [**1a**] and [Ru] which eliminates a possible polymerization/depolymerization process reported previously in the thermally mediated rearrangement of *N*-phenyl-oxazolidine-2-thione.[11]

The isomerization of cyclic thiocarbonate esters in the presence of potassium iodide is known to selectively generate primary monothiolcarbonates through an ionic pathway.[12] To investigate the reactivity of *N*-phenyl oxazolidine-2-thiones under ionic rearrangement conditions, **1a** was heated in the presence of catalytic potassium iodide (50 mol%) and the reaction was monitored over time (Scheme 5). Analysis of the

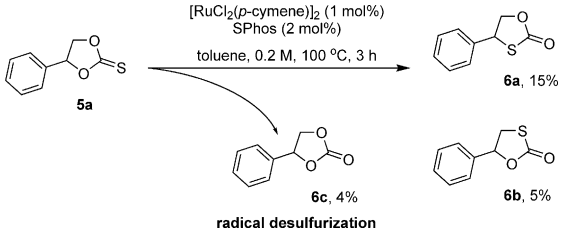


Scheme 5. Treatment of *N*-phenyl oxazolidine-2-thione under ionic conditions. Reaction conditions: *N*-phenyl oxazolidine-2-thione (0.25 mmol), KI (0.125 mmol), toluene (1.25 mL), 100°C, air. Reaction was monitored by ^{1}H NMR spectroscopy.

crude reaction mixtures by ^{1}H NMR spectroscopy showed that even after extended reaction times no rearrangement of the oxazolidine-2-thione occurred. Therefore it was concluded that it is unlikely that the reaction proceeds through a nucleophilic ring opening/recombination process.

It has been reported that the treatment of cyclic thiocarbonates under Barton–McCombie-promoted conditions results in the formation of the *O*- to *S*-rearrangement product when catalytic amounts of the radical promoter is used.[13] Tsuda et al. found that cyclic thiocarbonates derived from glycosides gave a distribution of rearrangement, deoxy, and oxo products when reacted under catalytic radically promoted conditions. Whilst only organic-based radical initiators were investigated, the choice of radical initiator and promoter were shown to have a significant effect on reactivity as well as selectivity. In contrast to ionic-based mechanisms, both secondary and primary rearrangement products were observed in addition to the oxo derivative produced by the reaction of atmospheric oxygen and an intermediate radical.

To probe consistencies with the ruthenium-catalyzed *O*- to *S*-alkyl migration of oxazolidine-2-thiones and this reported radical mechanism, $[RuCl_2(p\text{-cymene})]_2$ and cyclic thiocarbonate **5a** were reacted using the standard conditions (Scheme 6). As with previous reported works, a distribution



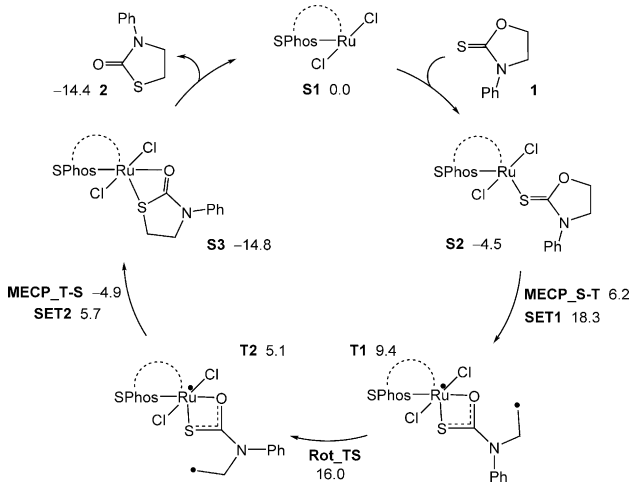
Scheme 6. Reaction of cyclic thiocarbonate **5a**. Reaction conditions: thiocarbonate (0.25 mmol), $RuCl_2(p\text{-cymene})]_2$ (1 mol%), SPhos (2 mol%), toluene (1.25 mL), 100°C, 3 h, air. Ratio of products was determined by ^{1}H NMR spectroscopy.

of products was observed, including the radical desulfurization product (**6c**, 4%). Interestingly, both secondary and primary rearrangement products (**6a** and **6b**) were observed in a 3:1 ratio, well within the ratios observed for classical radical-promoted rearrangements. The observed consistencies would strongly suggest that the presented ruthenium-catalyzed system is capable of proceeding through a similar radical-promoted reaction pathway.[14]

Analysis of the ruthenium-catalyzed *O*- to *S*-alkyl migration by DFT (see the Supporting Information (SI) for details) supports the proposed reaction proceeding through radical adducts (Scheme 7).

Thus, the formation of the starting $[RuCl_2(p\text{-cymene})$-(SPhos)] complex (**S0**) is followed by a thermoneutral loss of the *p*-cymene ligand, generating the catalytic species **S1**. The reaction proceeds with the coordination of the *N*-aryl oxazolidine-2-thione (**1**) through the sulfur atom to give rise to complex **S2**. The reaction interchanges then from the singlet to the triplet energy surface through the minimum energy crossing point **MECP_S-T**, this transformation requires approximately 10 kcal mol^{-1}. Subsequently, one electron is transferred from the metal to the substrate (**SET1**), automatically provoking the cleavage of the C–O bond and generating the Ru^{III} diradical species **T1**. The single-electron transfer process requires 12 kcal mol^{-1} but still remains at a quite reasonable height.

Once **T1** is obtained, the pendant radical rotates through the corresponding transition state (**Rot_TS**), which is less than 7 kcal mol^{-1} higher than the previous intermediate, to form the diradical complex **T2**. The second electron transfer process (**SET2**) generates the C–S bond, the reaction then



Scheme 7. Proposed model for ruthenium-catalyzed *O*- to *S*-alkyl migration. Numbers are DFT-derived free energies (in kcal mol^{-1}) at 100 °C.

returns to the singlet energy surface through the corresponding minimum energy crossing point (**MECP_T-S**), giving rise to the Ru^{II} intermediate **S3**. Finally, the product is liberated into the reaction mixture and the starting catalytic species is regenerated. The computed Gibbs free energy of the catalytic cycle is −14.4 kcal mol^{-1}, indicating that the whole process is thermodynamically favored. The computed overall barrier for the reaction, obtained as the free-energy difference between **S2** and **SET1**, is approximately 23 kcal mol^{-1}, which is highly plausible for a reaction occurring at 100 °C.

In addition, a classical, non-radical, oxidative addition/reductive elimination catalytic cycle through ruthenium C–O insertion has been also computed (see SI for details). DFT calculations showed that the energy requirements for this pathway are much higher than those obtained for the radical mechanism; in this case, the massive barrier obtained for the concerted oxidative addition step (+52.2 kcal mol^{-1}) would completely shut down the reaction. In addition, the rotational transition-state barrier is also very high (+42.7 kcal mol^{-1} from the lowest species), likely due to the charge separation produced in the ligand replacement process on ruthenium.

In summary, we have developed a robust and efficient ruthenium-catalyzed *O*- to *S*-alkyl migration process for the practical preparation of N-substituted thiazolidine-2-thiones from readily accessible N-substituted oxazolidine-2-thiones. The products from the reaction are useful as sulfur-implanted heterocycles or as precursors to aminothiols which are significantly more challenging to access than amino alcohols. Further studies are underway to explore new applications of catalytic *O*- to *S*-alkyl migrations in organic synthesis. Initial experimental and computational investigations into the mechanism of this transformation suggest a pseudoreversible Barton–McCombie-type pathway is plausible.

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Keywords: alkyl migration · Barton–McCombie reaction · catalysis · *O*-thiocarbamates · pseudoreversible reaction

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