Pyridylidene amide Ru complex for selective oxidation in organic synthesis

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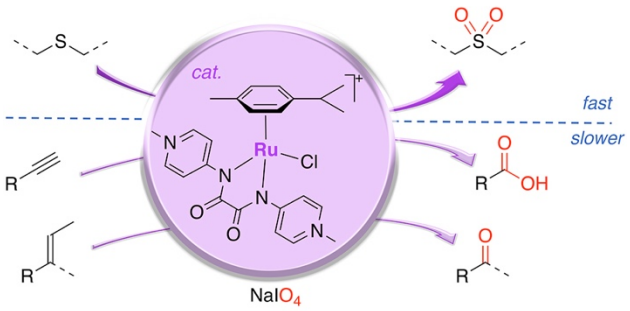

ABSTRACT: The ruthenium(II) bis(PYA) complex **1** (PYA = *para*-pyridylidene amide) is a powerful catalyst for the oxidation of sulfides to sulfones, of alkenes to carbonyl compounds, and of terminal alkynes to carboxylic acids by using $NaIO_4$ as terminal oxidant. The catalytic system shows a broad functional group tolerance and rate differences between alkyne and sulfide oxidation that are sufficiently large to effectively achieve selective sulfide oxidation with exquisite selectivity.

Sulfones are highly relevant for a wide variety of pharmaceutical active ingredients such as Sildenafil,[1] Dofetilide,[2] Torasemide,[3] and many more.[4] Likewise, they are key functional entities in herbicides, *e.g.* in Mesotrione[5] or Cafenstrole.[6] A general challenge in the preparation of sulfones from sulfides is often the incomplete oxidation.[4i,7] Full oxidation has been achieved with carbon nanotubes-Ru and $NaIO_4$.[8] and with different high-valent molybdenum systems,[9] as well as organocatalyzed with the use of ozone.[10] While ozone is inconvenient as terminal oxidant due to its hazardous properties, $NaIO_4$ constitutes a suitable alternative[11] that is also potentially applicable for large scale preparations.[12]

Considering the ultrahigh efficiency of complex **1** containing a bis-pyridylideneamide (bis-PYA) ligand in catalyzing olefin oxidation (Fig. 1),[13] we were interested to exploit its activity towards other functional groups and in particular towards sulfides to access high valuable agrochemical and pharmaceutical sulfone intermediates. Here we demonstrate that this complex is a potent catalyst for the selective oxidation of sulfides to sulfones, even in the presence of other oxidizable functional groups.

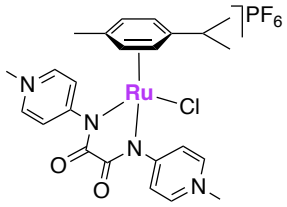

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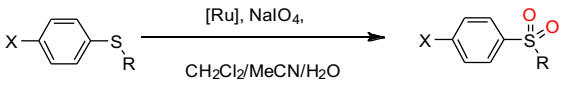
Figure 1. Ru bis-PYA complex **1**.

Complex **1** was synthesized according to previously reported procedures.[13] Its reactivity in the oxidation of sulfides was initially investigated with thioethers using 1-methoxy-4-(methylsulfinyl)benzene as model substrate (Table 1). At a 1 mol% loading of complex **1** and using $NaIO_4$

as terminal oxidant, this substrate was efficiently and essentially quantitatively oxidized to the corresponding sulfone within 20 min (entry 1). In the absence of ruthenium complex **1**, only sulfoxide was produced quantitatively in 1 h, yet no oxidation to the sulfone was observed (entry 2). When using $RuCl_3$ as a simple ruthenium salt instead of complex **1** as precatalyst, a drastic drop in yield was observed to just 16% within the time span in which complex **1** reaches quantitative yields (entry 3). These controls underpin the relevance of the bis-PYA ligand for accomplishing efficient and complete oxidation to the desired sulfone product. Both electron-donating –OH and electron-withdrawing -Br substitutents on the aryl thioethers were tolerated without any parasitic oxidation of the substituents (entries 4, 5). We note that electron-poor sulfur centres required longer reaction time to reach high yields. For example, substituting a S–CH_3 group for a S–CF_3 unit extended the reaction time from 20 min to 8 h (entries 1 *vs* 4).

Table 1. Catalytic oxidation of thioethers.[a]



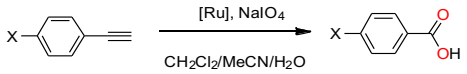
Entry	[Ru]	X	R	time	Isolated yield
1	**1**	$-OCH_3$	$-CH_3$	20 min	96%
2	--	$-OCH_3$	$-CH_3$	60 min	n.d.[b]
3	$RuCl_3$	$-OCH_3$	$-CH_3$	20 min	16%
4	**1**	–OH	$-CF_3$	8 h	72%
5	**1**	–Br	$-CH_3$	8 h	88%

[a] General conditions: substrate (0.5 mmol), Ru complex **1** (1 mol%), $NaIO_4$ (1.5 mmol), in 1:1:3 solvent mixture of MeCN /CH_2Cl_2/H_2O (5.0 mL) at 25 ºC; [b] quantitative formation of sulfoxide, no sulfone formed.

Attempts to oxidize thioethers directly into the corresponding sulfonimines as another relevant compound class for agrochemicals, we performed (aryl)(methyl)sulfide oxidation catalysis in the presence of $NH_4(CH_3CO_2)$ and $NH_4(H_2NCO_2)$, respectively, as potential N donors (Table S1). However, neither of the two systems produced any sulfonimine and only the corresponding sulfones were obtained, independent of the reaction conditions and irrespective of the electronic nature of the aryl substituents.[14] This outcome indicates that under catalytic conditions, complex **1** is either inert towards the sulfonimination reaction or that the oxidation of the S-group to sulfone occurs faster than the formation of the sulfonimine.

Oxidation of other functional groups revealed distinct selectivities. For example, pyridine is inert and does not form any pyridine-N-oxide. This inertness is remarkable[15] and persists also when incorporating electron-withdrawing $-CF_3$ or -donating –OMe substituents in *para* position of the pyridine, even when gently warming the reaction to 40 ºC over 2 days (Table S2). In contrast, complex **1** oxidizes terminal alkynes selectively to the corresponding acids (Table 2). Within 8 h, isolated yields are gradually increasing when modulating the para substituent of phenylacetylene from electron-withdrawing $-CF_3$ (62%) to neutral –H (70%), and to electron-donating –OMe (80%; entries 1–3), suggesting that acetylene coordination to the catalytically active ruthenium center may be a critical step for determining conversion. Running the reaction under N_2 atmosphere did not modify the product selectivity, though yields of the acid are consistently slightly lower.

Table 2. Catalytic oxidation of ethynyl-substituted aryl substrates.[a]



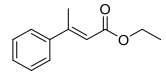
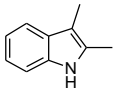
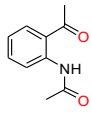
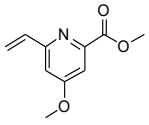
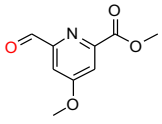
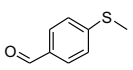
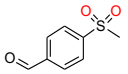
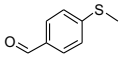
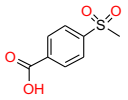
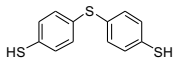
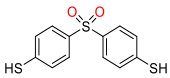
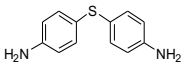
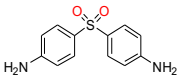
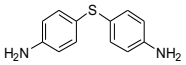
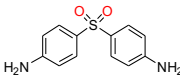
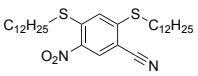
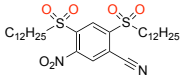
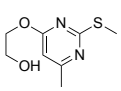
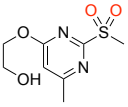
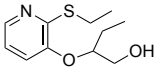
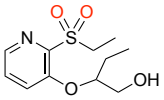
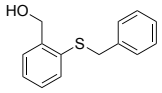
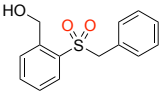
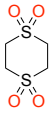
Entry	X	Isolated yield
1	$-CF_3$	62%
2	–H	70%
3	$-OCH_3$	80%
4[b]	$-CF_3$	58%
5[b]	–H	67%
6[b]	$-OCH_3$	75%

[a] General conditions: substrate (0.5 mmol), Ru complex **1** (1 mol%), NaIO4 (1.5 mmol), in 1:1:3 solvent mixture of MeCN/ CH_2Cl_2/H_2O (5.0 mL) at 25 ºC for 8 h; [b] Reaction run under N_2 atmosphere, under otherwise identical conditions.

In order to evaluate the selectivity of the catalyst, a set of multifunctional substrates was screened in oxidation catalysis, including substrates with several oxidizable entities (Table 3). Trisubstituted electron-deficient olefins in α,β,-unsaturated esters such as **2a** are oxidized to the ketone product **3a** without any oxidation of the ester unit (entry 1), thus complementing previous work that showed that highly substituted olefins are converted.[13] Moreover, 2,3-dimethyl-1*H*-indole **2b** is selectively oxidized in a ring-opening reaction to N-(2-acetylphenyl)acetamide **3b** in 74% yield (entry 2). This reaction is of interest as it typically requires ozone, proceeds only in moderate yield, and affords mixtures of up to 3 different oxidized products.[16] Selective oxidation of a terminal C=C bond on the multisubstituted pyridine **2c** containing ester and methoxy functional groups afforded the corresponding aldehyde **3c** at room temperature in 2 h (entry 3). This process is relevant since it converts a side product from a Stille cross coupling into a useful intermediate for further functionalization of the carbonyl by nucleophilic addition.[17] This direct transformation has no precedent in literature.[18] No overoxidation of the aldehyde was observed, and this reactivity was also confirmed in the oxidation of 4-(methylthio)benzaldehyde **2d** (entry 4). This substrate is selectively oxidized in excellent yields to the corresponding sulfone **3d** without affecting the aldehyde functionality. Notably, the use of $RuCl_3$ instead of complex **1** as catalyst precursor resulted in aldehyde oxidation to the carboxylic acid **4** in addition to thioether oxidation (entry 5). Transformation of the thiol-functionalized thioether **2e** to the sulfone **3e** in essentially quantitative yield indicates selective oxidation of thioethers but not thiols (entry 6). The tolerance to amine functional groups has been demonstrated by an expedient one-step synthesis of dapsone **3f**, a

potent antibacterial agent (entry 7). While the typical synthesis of Dapsone from the di(aniline)thioether **2f** requires two steps and proceeds with low yields,[4g,19] oxidation of **2f** with complex **1** proceeds smoothly in just 3 h and in high 82% isolated yield. The benefit of the bis-PYA ligand in the catalyst is revealed when comparing the outcome of oxidation reactions using just $RuCl_3$ as catalyst precursor. With the latter catalyst precursor, activity to sulfone formation is drastically lower and only traces of **3f** were formed within the same reaction time (entry 8). The amphiphilic substrate **2g** containing a polar nitro group and two aliphatic dodecyl thioether units is completely oxidized to the corresponding di(sulfone) **3g** in excellent yields without affecting the nitro group (entry 9). Due to the peculiar solubility of this substrate, the reaction was performed under more dilute conditions to accomplish high yields. Neither primary alcohols (entries 10, 11), nor heterocyclic amines such as pyrimidines in **2h** or pyridines in **2i** are affected upon sulfone formation. Of note, also benzylic alcohols are compatible with the sulfide oxidation protocol and oxidation of **2j** under standard conditions afforded the sulfone **3j** in high 74% yield with only traces (3%) oxidation of the benzylic alcohol to the aldehyde (entry 12). Likewise, dithiane **2k** is readily oxidized on both sites to afford the disulfone **3k** in appreciable yields (entry 13). In summary, these substrate conversions indicate an exquisite functional group tolerance of complex **1** in sulfide oxidation, including primary and benzylic alcohols, esters, aldehydes, amines, imines, nitriles, nitro and halide functionalities, as well as heterocycles. Of note, neither heterocycle nor amine, thiol, or benzylic alcohol functional group tolerance has been demonstrated with other catalytic systems such as high valent molybdenum complexes.[9] Tolerance to these functional groups—ubiquitous in compounds for agricultural and pharmaceutical application—is particularly attractive for late-stage oxidation of complex molecular structures as demonstrated here with the one-step synthesis of Dapsone.

Table 3. Catalytic oxidation of substrates containing multiple functional groups.[a]

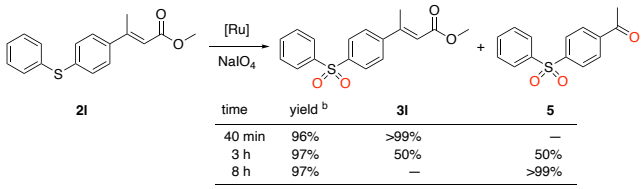
Entry	Substrate	Product	time	isolated yield
1	 **2a**	 **3a**	8 h	88%
2	 **2b**	 **3b**	8 h	74%
3	 **2c**	 **3c**	2 h	65%
4	 **2d**	 **3d**	3 h	92%
5[b]	 **2d**	 **4**	3 h	68%
6	 **2e**	 **3e**	1 h	96%
7[c]	 **2f**	 **3f**	3 h	82%
8[b,c]	 **2f**	 **3f**	3 h	8%
9[d]	 **2g**	 **3g**	3 h	92%
10	 **2h**	 **3h**	1.5 h	53%[e]
11	 **2i**	 **3i**	1.5 h	61%[e]
12	 **2j**	 **3j**	18 h	74%[f]
13[g]	 **2k**	 **3k**	1 h	68%

[a] General conditions: substrate (0.5 mmol), Ru complex **1** (1 mol%), $NaIO_4$ (1.5 mmol), in 1:1:3 solvent mixture of $MeCN/CH_2Cl_2/H_2O$ (5.0 mL) at 25 ºC; [b] $RuCl_3$ used as precatalyst; [c] Total volume of the solvent mixture increased to 25mL and temperature increased to 40 ºC; [d] substrate (0.1 mmol), Ru catalyst (1 mol%), $NaIO_4$ (0.3 mmol), in 1:1:3 solvent mixture of $MeCN/CH_2Cl_2/H_2O$ (5.0 mL) at 25 ºC; [e] >99% yield by LC-MS, isolated yield lower because of unoptimized purification; [f] in addition sulfoxide (5%) and sulfone aldehyde (3%) detected; [e] substrate (0.5 mmol), Ru complex **1** (2 mol%), $NaIO_4$ (3 mmol).

Since complex **1** is known to also oxidize olefins to aldehydes, an intramolecular competition experiment was performed to assess the chemoselectivity of this catalyst. To

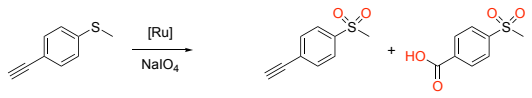
this end, substrate **2i** containing both oxidizable C=C and sulfide functionalities was subjected to oxidation conditions (Scheme 1). Monitoring the reaction revealed initial oxidation of the sulfide selectively, affording **3i** exclusively after 40 min. Extension of the reaction time to 3 h produced the two sulfone products **3i** and **5**, suggesting that the C-S oxidation occurs faster than oxidation of the C=C bond. After even longer reaction times (8 h) full oxidation of both functional groups was achieved to yield **5** as the exclusive product.

Scheme 1. Competitive oxidation of thioethers *vs* C-C multiple bonds. [a]



2l

time	yield [b]	**3l**	**5**
40 min	96%	>99%	–
3 h	97%	50%	50%
8 h	97%	–	>99%



2m

time	yield [b]	**3m**	**4**
15 min	96%	>99%	–
3 h	70%	70%	30%
16 h	74%	–	>99%

[a] General conditions: substrate (0.5 mmol), Ru complex **1** (1 mol%), $NaIO_4$ (1.5 mmol), in 1:1:3 solvent mixture of CH_3CN/CH_2Cl_2/H_2O (5.0 mL) at 25 ºC; [b] overall yield determined by ^{1}H-NMR spectroscopy using DMSO as internal standard.

Similar competition experiments using 4-ethynylthioanisole **2j** as substrate reveal much faster oxidation of the thioether to the sulfone as compared the alkyne oxidation to the carboxylic acid. Thus, after 15 min reaction, the sulfone **3j** is obtained selectively, while long reaction times provide access to the carboxylic acid **4**. These competition experiments demonstrate that even in the presence of oxidizable C=C and C≡C bonds, thioether oxidation to the corresponding sulfone can be accomplished with exquisite selectivity.

In conclusion, the bis(PYA) ruthenium complex **1** shows excellent catalytic activity in the direct oxidation of sulfides to sulfones with unprecedented selectivity as formation of (often undesired) sulfoxide side products is completely suppressed. The functional group tolerance is outstanding and offers ample flexibility for the oxidation of complex molecules at late stages. Olefins and alkynes are also oxidized, albeit considerably slower. Notably, terminal alkynes are oxidized to carboxylic acids, thus providing an interesting protecting group strategy for carboxylic acids that is complementary to the more commonly employed esters, amides, and nitriles.

ASSOCIATED CONTENT

Supporting Information

Detailed catalytic procedures, extended catalytic oxidation data, and NMR spectra of new compounds, The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

We thank Dr. Nicolas Lentz (University of Bern) for technical assistance and the Swiss National Science Foundation (200020_182663 and 200020_172507), the Marie Sklodowska Curie ITN NoNoMeCat (grant 675020-MSCA-ITN-2015-ETN), and the European Research Council (CoG 615653) for generous financial support of this work.

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