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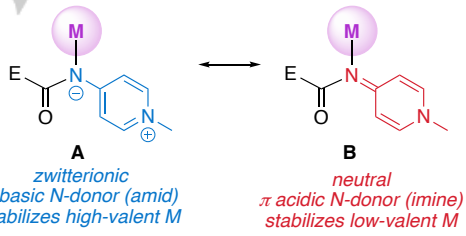
Donor-flexible bis-pyridine amide ligands for highly efficient ruthenium-catalyzed olefin oxidation

Kevin Salzmann,† Candela Segarra,† and Martin Albrecht*

Abstract. An exceptionally efficient ruthenium-based catalyst for olefin oxidation has been designed by exploiting *N,N'*-bis(pyridylidene)oxalamide (bisPYA) as donor-flexible ligand. The dynamic donor ability of the bisPYA ligand, imparted by variable zwitterionic and neutral resonance structure contributions, paired with the redox-activity of ruthenium provided catalytic activity for Lemieux-Johnson-type oxidative cleavage of olefins to efficiently prepare ketones and aldehydes. The ruthenium bisPYA complex largely outperforms state-of-the-art systems and displays extraordinary catalytic activity in this oxidation, reaching turnover frequencies of 1,000,000 h^{-1} and turnover numbers of several millions.

The carbonyl group is arguably the most versatile synthetic functionality for organic transformations.[1] It is most conveniently accessible by oxidation of alcohols,[2] or by the oxidative cleavage of olefins, for example through ozonolysis.[3] Catalytic versions of olefin oxidation are remarkably scarce. The most established catalytic system is the osmium-based Lemieux-Johnson catalyst,[4] as well as variations thereof based on osmium as well as ruthenium,[5] which generally require high catalyst loading and tend to suffer from rapid overoxidation to produce the acid predominantly.[6] Recently, Bera and coworkers pioneered a more efficient system based on an abnormal carbene for the oxidation of C=C bonds into C=O functional groups which operates at ambient temperature and with high selectivity.[7] Preliminary mechanistic insights suggest a catalytic cycle involving toggling between a low-valent Ru^{II} intermediate and a high-valent $Ru^{IV}(=O)_2$ species.

We hypothesized that switching between these two critical intermediates is greatly facilitated when modifying the spectator ligands from a static donor system to a donor-flexible scaffold which has the potential to adapt its donor properties during a catalytic cycle. Pyridylidene amides (PYAs; Scheme 1) are a particularly attractive class of ligands[8] as they are characterized by two limiting resonance structures that are comprised of either a zwitterionic structure with a π-basic N-donor site (**A**), or a neutral representation with a π-acidic N-donor coordinated to the metal center (**B**). We recently demonstrated that the contribution of the two limiting resonance structures is flexible and dependent on several factors such as the polarity of the solvent, the nature of the spectator ligands, and the metal oxidation state.[9] This behaviour provides unique opportunities for redox-catalysis, as this ligand system has potential for promoting *both* reductive elimination in its π-acidic form as well as oxidative additions in its zwitterionic π-basic form on a putative catalytic cycle. As a first proof of concept, a cyclometalated PYA iridium complex was observed to outperform the corresponding cyclometalated analogue containing a static pyridyl ligand in water oxidation,[10] which requires the accessibility of iridium in several oxidation states. Here we have exploited the synthetic flexibility of PYA ligands[11] as easily accessible systems to generate ruthenium-based olefin oxidation catalysts with ultra-high efficiency.



Scheme 1. Limiting resonance structures of the PYA ligand.

The bisPYA ligand precursor **1** was prepared starting from cheap and readily available 4-aminopyridine by thermally induced condensation with diethyl oxalate,[12] followed by pyridine N-methylation with MeI and anion metathesis using KPF_6 (Scheme 2). This procedure afforded the bis-pyridinium salt **1** in 81% overall yield and at a cost of less than 3€ per gram (Table S1). Subsequent reaction of this salt with $[RuCl_2(p\text{-cym})]_2$, in the presence of K_2CO_3 at 90 °C afforded the cationic ruthenium complex **2** containing a N,N-bidentate chelating bisPYA ligand, as an air- and moisture-stable orange solid.

Successful complexation was indicated by NMR spectroscopy through the loss of the amide protons and an upfield shift of the pyridyl α proton resonance from δ_H = 8.85 in the ligand precursor to 8.52 ppm in complex **2**. In contrast, the resonance of the β protons shifts slightly downfield from δ_H = 8.38 to 8.42 ppm

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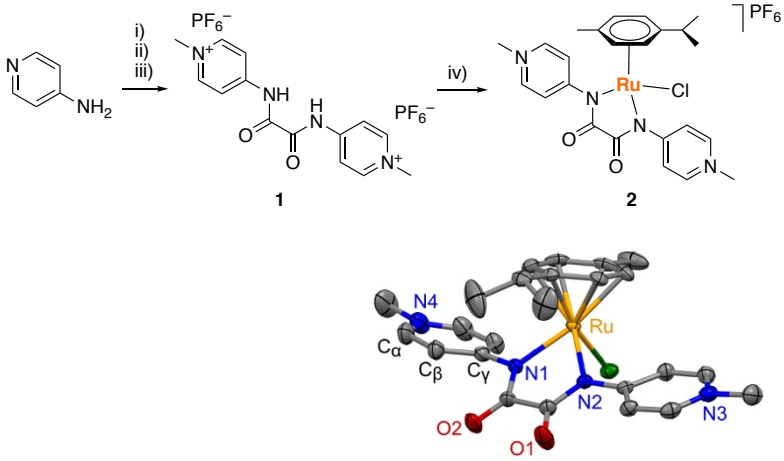

Scheme 2. Synthesis and ORTEP representation (50% probability elipsoids) of the bisPYA ruthenium complex **2**. Reagents and conditions: i) diethyl oxalate ii) MeI, MeCN; iii) KPF_6, H_2O; iv) $[RuCl_2(cym)]_2.K_2CO_3$, MeCN. Selected bond lengths and angles: Ru–N1 2.097(3) Å, Ru–N2 2.119(2) Å, N1–Ru–N2 76.94(10)°.

upon ruthenation. The single set of resonances for the pyridyl and cymene resonances suggests Cs-symmetry in solution, in agreement with N,N-bidentate chelation. Complexation also induces an indicative 6 ppm downfield shift of the amide carbon and was unambiguously confirmed by single-crystal X-ray diffraction analysis (Table S3).

The donor flexibility of the bisPYA ligand in complex **2** was established by NMR spectroscopic and electrochemical analysis. Specifically, the NMR chemical shift difference of the doublet resonances due to the pyridylidene *α* and *β* protons serves as a diagnostic probe for the prevalence of the zwitterionic or neutral resonance forms **A** and **B**.[13] NMR experiments in solvents of different polarity revealed a gradual downfield shift of H_α from δ_H 7.98 to 8.18, and 8.52 when measured in DMSO-d_6 (ε = 46.45), CD_3CN (ε = 35.94), and CD_2Cl_2 (ε = 8.93)[14] while the H_β resonance drifts to higher field (from δ_H 8.72 to 8.53 and 8.42; Fig. S3, Table S5). This behaviour is in agreement with a more pronounced zwitterionic resonance structure contribution in polar solvents.[13]

Likewise, electrochemical analysis of the Ru^{II}/Ru^{III} oxidation potential reveals a gradual shift to lower oxidation potential as the solvent polarity is increased, with the anodic peak potential E_{pa} of complex **2** lowered from 1.00 V in CH_2Cl_2 to 0.89 V ($MeNO_2$), 0.85 V (acetone), 0.71 V (MeCN), and to 0.55 V (DMSO; all potentials *vs* ferrocene; Fig. S4, Table S6). This behavior is in good agreement with a higher contribution of the neutral PYA resonance structure with a π-acidic nitrogen in apolar solvents (stabilization of the low-valent Ru^{II}), and a larger impact of the zwitterionic PYA resonance structure with an anionic and π-basic nitrogen donor in polar solvents and hence better stabilization of the Ru^{III} center. Of note, the analogous complex **3** containing a bipyridine instead of a bisPYA ligand does not show similar solvent-dependent redox shifts, indicating much less donor flexibility than the bisPYA ligand. This solvent-induced change of resonance structure of the bisPYA ligand corroborates the electronic flexibility of the ligand as observed by NMR spectroscopy.

Complex **2** is an excellent catalyst for oxidative cleavage of olefins using $NaIO_4$ as sacrificial oxidant. Initial catalytic runs were performed with styrene as model substrate and with 2 equiv. $NaIO_4$ in the solvent mixture $CH_3CN/AcOEt/H_2O$ (2:2:1 v/v) as described by Bera and coworkers.[7] Under these conditions, complex **2** afforded a moderate 53% conversion to benzaldehyde along with small quantities of benzoic acid. Optimization of the amount of oxidant to 3 equiv. (Table S7) and the solvent mixture to $MeCN/CH_2Cl_2/H_2O$ (1:1:3 v/v) (Table S8) resulted in quantitative conversion of benzaldehyde in just 5 min when using 1 mol% complex **2** as catalyst. Larger quantities of sacrificial oxidant led to considerably higher fractions of over-oxidized product and can in fact drive the reaction completely towards the selective formation of the carboxylic acid (> 5 equiv $NaIO_4$), while deoxygenation of the solvent and headspace suppressed over-oxidation markedly (Table S9). It is interesting to note that complex **2** performs significantly better under more polar conditions, *viz.* larger quantities of H_2O, which suggests a higher relevance of the polar resonance structure **A**.

The catalytic system is ultra-active. At high catalyst loading (1 mol%), the olefin oxidation is completed in 5 min. Gradual lowering of the catalyst loading requires longer reaction times, though activity is preserved (Table 1; Fig. S5). Even catalyst loadings as low as 0.1 ppm afford full conversion within an acceptable time range (24 h), leading to turnover numbers of 9,700,000. Under these dilute conditions, maximum turnover frequencies of the catalyst TOF_{max} = 1,000,000 h^{-1} were noted. Repetitive blank reactions in the absence of complex **2** indicate less than 2% conversion in the same 24 h time frame, revealing the high impact of complex **2** in this oxidation. The prolonged reaction times led, however to a larger portion of overoxidation (up to 24% acid). Nonetheless, these high activities at ambient temperature provide excellent opportunities for large scale transformations with catalyst loadings at sub-ppm level.

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Table 1. Effect of low catalyst loading.[a]

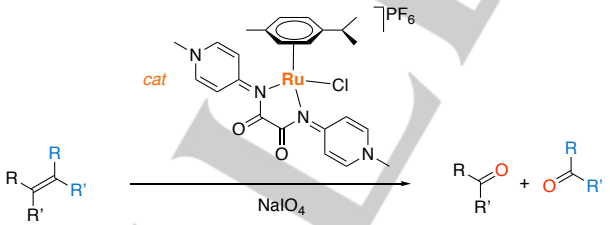
Entry	**2** [mol%]	Time [h]	Conversion [%] [b]	Selectivity [%] [b, c]	TON	TOF_{max} [h^{-1}] [d]
1	1	0.08	>99	92	>99	900
2	0.1	2	>99	91	>990	1,800
3	0.01	6	>99	92	>9,900	11,000
4	0.001	8	>99	93	>99,000	31,000
5	0.0001	10	>99	81	>990,000	160,000
6	0.00001	24	>99	76	>9,900,000	650,000

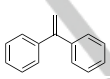
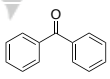
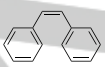
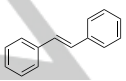
[a] Conditions: styrene (0.5 mmol), complex **2**, $NaIO_4$ (1.5 mmol), in $MeCN/CH_2Cl_2/H_2O$ (1:1:3; 5.0 mL) at 25 °C. [b] Conversion/selectivity determined by ^1H NMR spectroscopy relative to external standard (anisole). [c] Selectivity towards benzaldehyde (in %) *vs.* overoxidation to benzoic acid. [d] maximum turnover frequency TOF_{max} extracted from time-conversion profiles (Fig. S5).

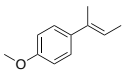
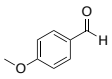
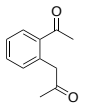
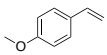
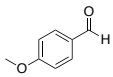
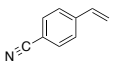
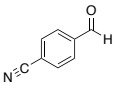
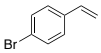
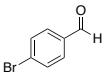
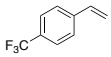
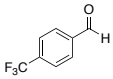
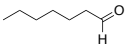
In addition to styrene, also polysubstituted olefins are successfully oxidized with complex **2** (Table 2). Geminally substituted olefins are converted slower than *trans* disubstituted olefins, while *cis* olefins are converted at the same rate as monosubstituted olefins (entries 1–6). Of note, geminal olefin oxidation leads to the formation of ketones that are not amenable to overoxidation, while *cis* and *trans* olefins produced traces of acid. Trisubstituted olefins are efficiently oxidized to the corresponding ketone in short reaction time (entry 7), and even tetrasubstituted olefins are fully converted, albeit only after substantially longer reaction time (2 h *vs* 5 min; entry 8). These different conversion rates suggest that complex **2** has potential to discriminate tri- from tetrasubstituted olefins for conversion.[15]

Introduction of substituents on the aromatic portion of styrene had a moderate effect on catalytic efficiency and require up to 30 min for full conversion (entries 9–13), though activity is not correlated with the electronic effects of the substituents (Hammett σ_p parameters varying between –0.27 for OMe to 0.66 for CN).[16] Halides and cyano groups are tolerated as functional groups and are not affected. Allylic substrates are converted slightly slower (entry 14), while the transformation of aliphatic substrates requires considerably longer reaction times to reach completion (entries 15 and 16). Significant steric shielding hampers catalytic turnover markedly and conversion stalls at less than 30% (entry 17, *cf* full conversion if the *t*Bu group is replaced by a methyl group, entry 5).

Table 2. Scope of olefin oxidation with complex **2**.[a]

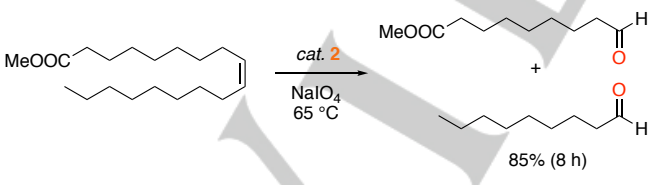


Entry	Substrate	Product	Time [min]	Temp. [°C]	Conversion [%][b]	Selectivity [%][b, c]
1			5	25	100	92
2			120	50	100	100
3			5	25	100	81
4			30	25	100	87
5			5	35	100	100

6			5	25	100	96
7			5	35	100	100
8			120	35	100	100
9			5	25	100	80
10			30	25	100	85
11			5	35	100	76
12			15	35	100	73
13			15	35	100	75
14			15	25	100	64
15			180	50	100	67
16			240	50	100	100
17			18 h	35	25	25

[a] Conditions: substrate (0.5 mmol), Complex **2** (1 mol%), $NaIO_4$ (1.5 mmol) in MeCN/CH_2Cl_2/H_2O (1:1:3, 5 mL). [b] Conversion/selectivity determined by ^1H NMR spectroscopy or GC analysis relative to external standard (anisole or hexamethylbenzene). [c] Selectivity towards carbonyl product (in %) *vs.* overoxidation to the corresponding acid.

Methyl oleate as abundant biomass feedstock[17] has been a particularly challenging substrate for oxidative functionalization.[18] The bisPYA Ru(II) complex converts this substrate with considerable activity, reaching up to 85% of nonanal due to oxidative C=C cleavage.[19]



Scheme 3. Oxidative cleavage of methyl oleate.

The impact of the bisPYA ligand is revealed when considering ruthenium complexes with similar bidentate formally neutral ligands (Fig. 1). Complex **3** containing a related N,N-bidentate bipyridine ligand with less strong donor properties and no donor flexibility is inactive in this oxidative reaction. Similarly, the mixed PYA-carbene ligand in complex **4**[9a] displays essentially no activity in the first 30 min and then slowly induces conversion with rates that are orders of magnitude lower than those of complex **2** under identical reaction conditions. Bera's complex featuring a heteroaryl-stabilized mesoionic carbene is slightly less active (30 min to reach full conversion), though suppresses overoxidation more efficiently.[7] These data suggest a highly beneficial effect of the donor flexibility of PYA and mesoionic ligands for promoting catalytic oxidation activity, presumably through imposing an electron relay mechanism of the ligand similar to that observed in other electron transfer processes.[20]

Mechanistic insights obtained from experiments using lower quantities of oxidant indicate a reaction pathway that is reminiscent to the osmium-catalyzed Lemieux-oxidation, involving the metal catalyzed dihydroxylation followed by gradual oxidation of the diol to the carbonyl product with C–C bond cleavage. Specifically, phenyl-1,2-diol as well as α-hydroxy acetophenone were identified by ^1H and ^{13}C NMR spectroscopy when styrene oxidation was performed with lower quantities of $NaIO_4$ (2 equiv.) and intercepted at partial conversion (Fig. S6–8). Since diols are known to react with $NaIO_4$ spontaneously with C–C bond cleavage, these experiments suggest that the

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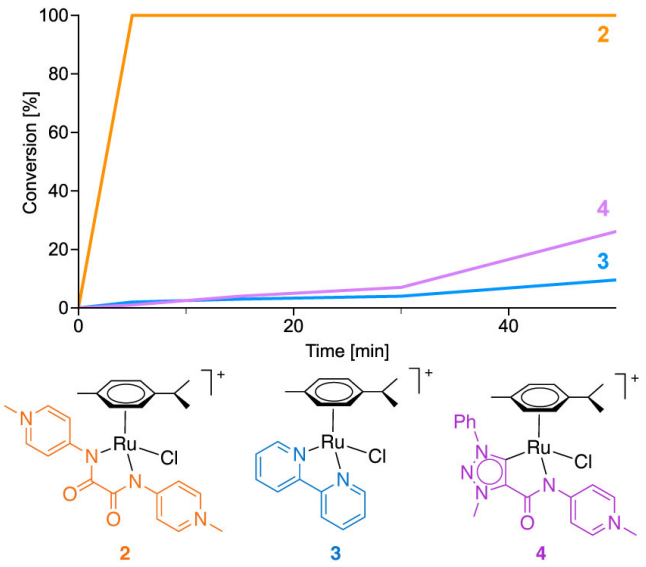

Figure 1. Comparison of time-conversion profiles for the olefin oxidation of styrene using complexes **2–4** reveals the benefit of the bisPYA ligand in complex **2** for oxidation catalysis.

ruthenium complex is predominantly catalyzing the diol formation. Moreover, $NaIO_3$ was identified as the product of the sacrificial oxidant at the end of the reaction using X-ray diffraction analysis, which suggests that $NaIO_4$ serves as a formal $2e^-$ oxidant that releases one equivalent of oxygen. These observations are consistent with a catalytic cycle involving the formation of a bisPYA stabilized high-valent ruthenium dioxo species such as [(bisPYA)$Ru^{IV}(=O)_2$] for the activation and oxidation of the olefin to produce the diol.[3c, 7] The exceptionally fast catalytic rates are therefore attributed to a high stabilization of both, the $Ru^{IV}(=O)_2$ intermediate through the zwitterionic resonance structure **A** of the PYA ligands, as well as a high stabilization of the $Ru^{II}(-OH)_2$ precursor via the neutral PYA resonance structure **B** (*cf* Scheme 1). This donor flexibility of the PYA units provides a rationale for a flat energy surface of the catalytic cycle and hence efficient turnover without catalyst deactivation.

In conclusion, we present a readily accessible, cheap, and ultra-efficient ruthenium bisPYA catalyst for olefin oxidation with exceptionally high activity and life time, reaching TOFs and TONs in the millions. The carbonyl products are obtained with high selectivity, even when using challenging biomass-derived substrates. Future work will focus on elucidating the mechanistic role of the donor-flexible bisPYA ligand in order to use even milder oxidants, as well as the evaluation of selectivity in the oxidation of industrially relevant heteroatom-functionalized substrates.

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Keywords: olefin oxidation • ruthenium • donor flexibility • N-donor ligands

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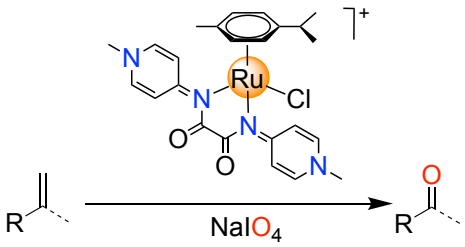

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Unstoppable: A ruthenium complex catalyzes Lemieux-type olefin oxidation at ppm level catalyst loading and with turnover frequencies of up to a million per hour when coordinated to a donor-flexible bis-pyridylidene amide (PYA) ligand that can switch donor properties and hence facilitates redox changes of the metal center.

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