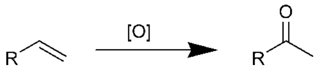
Alkene Oxidation

A Practical and Mild Method for the Highly Selective Conversion of Terminal Alkenes into Aldehydes through Epoxidation–Isomerization with Ruthenium(IV)–Porphyrin Catalysts**

*Jian Chen and Chi-Ming Che**

The Wacker-type oxidation of alkenes to carbonyl compounds is one of the most important oxidation reactions in synthetic chemistry and the pharmaceutical industry.[1] The conversion of alkenes RCH=CH$_2$ into acetaldehyde (R = H) or methyl ketones (R ≠ H) through the Wacker process [Eq. (1)] has been well documented;[1] however, the highly selective formation of aldehydes through catalytic oxidation of RCH=CH$_2$ (R ≠ H) without C=C bond cleavage [Eq. (2)] remains a challenge. Previous work by Feringa,[2a] Murahashi, and co-workers,[2b] and Wenzel[2c] showed that the oxidation of aliphatic alkenes (such as oct-1-ene and dec-1-ene), *N*-allyl amides/lactams, and allyl esters with O$_2$ or air in the presence of certain palladium or palladium/copper catalysts affords a mixture of aldehyde and methyl ketone products. Recently, Ho et al. reported the palladium/copper-catalyzed oxidation of several aliphatic 1,5-dienes with O$_2$ to form aldehydes in 60–99 % yield.[2d]



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(2)

During our efforts to develop new oxidation technology based on ruthenium–porphyrin catalysts, we found that the oxidation of a wide variety of terminal alkenes with 2,6-

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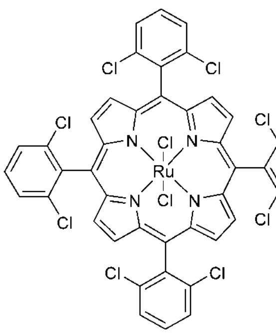
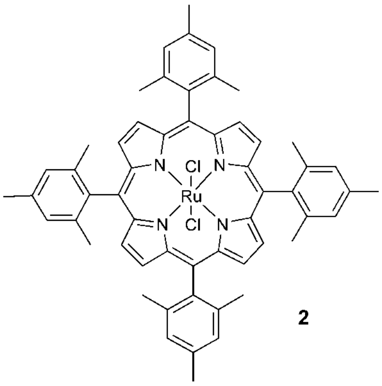
dichloropyridine *N*-oxide (Cl_2pyNO) in the presence of dichlororuthenium(IV)–porphyrin catalysts [$Ru^{IV}(por)Cl_2$] (por = tdcpp **1**, tmp **2**)[3] produced aldehydes in up to 99% yield with 100% substrate conversion without C=C bond cleavage. This unexpected ruthenium-catalyzed "Wacker-type oxidation" of terminal alkenes[4,5] reported herein apparently proceeds by a different mechanism to those proposed for the palladium- or palladium/copper-catalyzed reactions.[2] We also report herein a direct one-pot diazoacetate olefination of aldehyde substrates generated in situ by this ruthenium–porphyrin-catalyzed oxidation of alkenes.



1

[$Ru^{IV}(tdcpp)Cl_2$]



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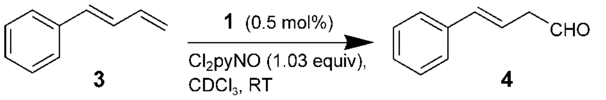
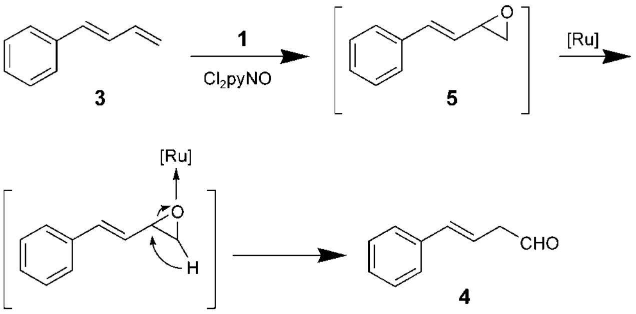
[$Ru^{IV}(tmp)Cl_2$]

When a solution of 1-phenyl-1,3-butadiene (**3**), Cl_2pyNO (1.03 equiv), and catalyst **1** (0.5 mol%) in $CDCl_3$ was stirred for 30 min at room temperature, the β,γ-unsaturated aldehyde 4-phenylbut-3-enal (**4**, styrylacetaldehyde) was formed in 99% yield [Eq. (3)]. No ketone products were detected in the reaction mixture. Similar results were obtained with $CHCl_3$ or CH_2Cl_2 as the solvent. Other solvents, such as benzene, toluene, acetone, ether, and methanol, were inferior to $CHCl_3$ and CH_2Cl_2 for this catalytic process.



(3)

We propose that the 1,3-diene **3** is first oxidized by Cl_2pyNO to form epoxide **5** in the presence of catalyst **1** (Scheme 1). The same catalyst, or a derivative thereof, induces subsequent isomerization of the epoxide to the β,γ-unsaturated aldehyde.[6] We abbreviate the epoxidation of terminal alkenes followed by isomerization of the epoxide products as E–I reactions.



Scheme 1. Proposed mechanism for the formation of aldehyde **4** by the Cl_2pyNO oxidation of **3** catalyzed by **1**.

To provide support for the above mechanism, we examined the effect of Cl_2pyNO on the catalysis (Table 1). With excess Cl_2pyNO, the yield of aldehyde **4** decreased significantly from 99 to 51%, and epoxide **5** was obtained in 49% yield. This result could be rationalized by considering coordination of the epoxide to active ruthenium–porphyrin species for the isomerization reactions. Excess Cl_2pyNO would compete with the epoxide for coordination to ruthenium, thus decreasing the yield of the aldehyde. We found that the use of 1.01–1.03 equivalents of Cl_2pyNO gave the best results in terms of reaction time (30 min) and aldehyde yield (99%). Changing the temperature from room temperature to 10 °C or 40 °C did not affect the reaction appreciably.

Table 1: Oxidation of **3** catalyzed by **1** with varying amounts of Cl_2pyNO.[a]

Entry	Cl_2pyNO [equiv]	Conversion of **3** [%]	Yield [%][b]	
			5	**4**
1	2.0	100	49	51
2	1.03	100	0	99
3	0.9	90	0	>99

[a] Reaction conditions: **3**: 0.1 mmol, **1**: 0.5 mol%, $CDCl_3$: 0.5 mL; 25 °C, open to air. [b] Determined by ^1H NMR spectroscopy (based on consumed substrate).

We also examined the effect of catalyst loading on the E–I reaction. When a lower loading of **1** (0.3 mol%) was used, with a molar ratio **3**/Cl_2pyNO/**1** of 1:1.03:0.003, a mixture of **5**, **4**, and **3** was detected after the reaction. Figure 1 shows the

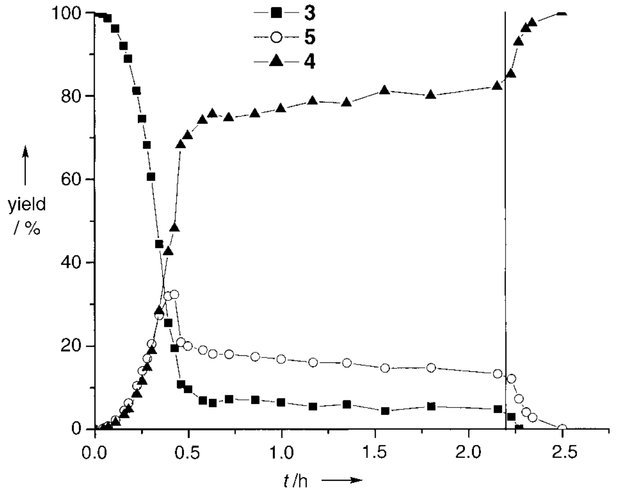


Figure 1. Time-course plot for the Cl_2pyNO oxidation of **3** catalyzed by **1**. Reaction conditions: **3**: 0.1 mmol, Cl_2pyNO: 1.03 equiv, **1**: 0.3 mol%, $CDCl_3$: 0.5 mL; 17 °C, open to air. The product yields were determined by ^1H NMR spectroscopy. More **1** (0.3 mol%) was added when the reaction had proceeded for about 2.2 h.

time course for this catalytic process. Evidently, after the reaction had proceeded for 2 h, **3** and **5** had not been completely converted into **4**. Analysis of the ruthenium–porphyrin species in the reaction mixture revealed that catalyst **1** had been converted into [Ru^{II}(tdcpp)(CO)].[7] Upon subsequent addition of a new batch of **1**, both **3** and **5** were completely converted into **4** in excellent yields within 15 min.

The E–I reaction of **3** with Cl_2pyNO was catalyzed equally efficiently by **2**, but less efficiently by [Ru^{VI}(tdcpp)O_2]. The oxidation of **3** with Cl_2pyNO catalyzed by [Ru^{VI}(tdcpp)O_2] under similar conditions to those used with catalyst **1** (Cl_2pyNO: 1.03 equiv, catalyst loading: 1.7 mol %) afforded **4** in 41 % yield within 5 h. However, the complex [Ru^{II}(tdcpp)(CO)] was a relatively inactive catalyst in the E–I reaction.

A series of other 1,3-dienes were treated with Cl_2pyNO (1.01–1.03 equiv) and **1** (0.5–1.0 mol %) at room temperature [Eq. (4), Table 2]. With dienes **6–10**, the corresponding β,γ-unsaturated aldehydes **13–17** were obtained in 81–99 % yield and were stable enough to be purified by flash chromatography on silica gel. However, the aldehyde product **18a**, formed in 90 % yield from the oxidation of diene **11**, was converted into **18b** upon flash chromatography on silica gel. The nonterminal diene **12** was oxidized more slowly to afford the β,γ-unsaturated ketone **19** in 99 % yield after a reaction time of 6 h at 60 °C (Table 2, entry 7).

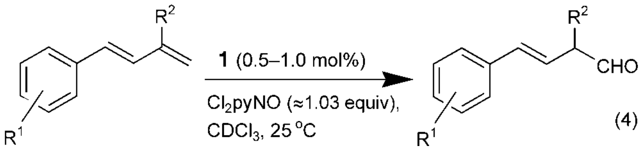


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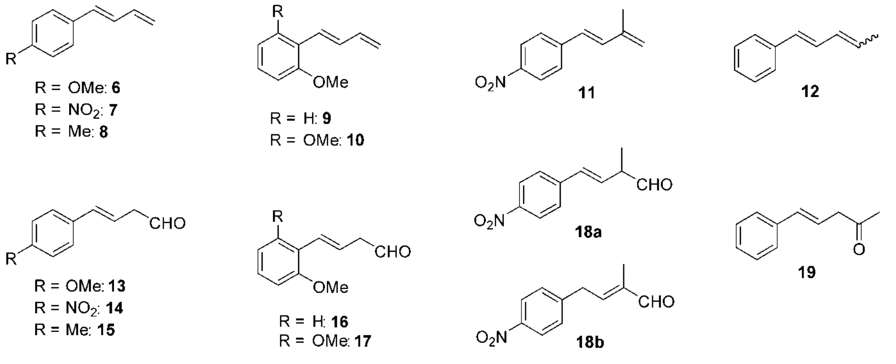
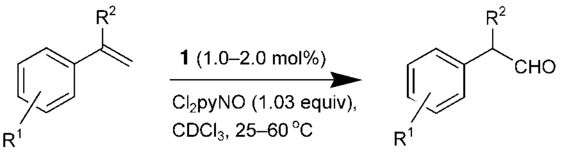
Table 2: Oxidation of 1,3-dienes **6–12** with Cl_2pyNO catalyzed by **1**.[a]



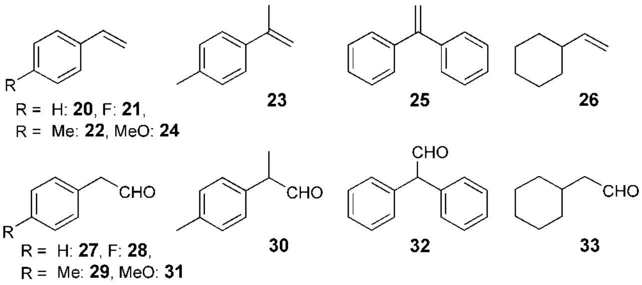
Entry	Substrate	T [°C]	t [h]	Product	Yield [%][b]
1	**6**	25	0.5	**13**	83
2	**7**	25	1	**14**	99
3	**8**	25	0.5	**15**	88
4	**9**	25	0.5	**16**	81
5[c]	**10**	25	0.5	**17**	91[d]
6	**11**	25	0.5	**18a**	90
7	**12**	60	6	**19**	99

[a] Reaction conditions: diene: 0.1 mmol, Cl_2pyNO: 1.03 equiv, **1**: 0.5–1.0 mol %, $CDCl_3$: 0.5–1.0 mL; open to air. [b] Determined by GC or ^{1}H NMR spectroscopy. [c] Reaction conditions: diene: 0.65 mmol, Cl_2pyNO: 1.03 equivalents, **1**: 1.0 mol %, $CHCl_3$: 10 mL; open to air. [d] Yield of isolated product.



(5)

Table 3: Oxidation of terminal alkenes **20–26** with Cl_2pyNO catalyzed by **1**.[a]

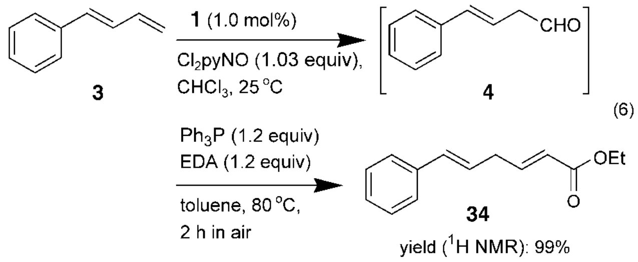


Entry	Substrate	T [°C]	t [h]	Product	Yield [%][b]
1	**20**	60	12	**27**	99
2	**21**	60	12	**28**	99
3	**22**	60	2	**29**	96
4	**22**	25	60	**29**	99
5	**23**	25	0.5	**30**	91
6	**24**	25	0.5	**31**	99
7	**25**	25	0.5	**32**	92
8	**26**	60	24	**33**	0[c]

[a] Reaction conditions: alkene: 0.1 mmol, Cl_2pyNO: 1.03 equiv, **1**: 1.0–2.0 mol %, $CDCl_3$: 0.5–2.0 mL; open to air. [b] Determined by GC or ^{1}H NMR spectroscopy. [c] The corresponding epoxide was produced in 99 % yield (determined by ^{1}H NMR spectroscopy).

When styrene (**20**) was treated with Cl_2pyNO (1.03 equiv) and **1** (1.0 mol %) in CH_2Cl_2 at reflux for 5 h, styrene oxide and phenylacetaldehyde (**27**) were obtained as a mixture in 90 and 10 % yield, respectively.[8] To our surprise, when more of catalyst **1** was added, and the reaction time was increased, the styrene oxide was completely converted into aldehyde **27**. For example, the reaction of styrene with Cl_2pyNO (1.03 equiv) in the presence of 2.0 mol % of **1** in $CHCl_3$ at 60 °C for 12 h afforded **27** in 99 % yield; no benzaldehyde was observed.[5] Other styrene derivatives **21–25** could also be converted into the corresponding aryl acetaldehydes **28–32** in excellent yields [Eq. (5) and Table 3]. However, with the nonaromatic alkene **26**, only the epoxide product was obtained.

Recently, the research groups of Woo,[9a] Aggarwal,[9b] and Zhang[9c] reported that the iron and ruthenium *meso*-tetraaryl porphyrins [Fe^{II}(ttp)] (H_2ttp = *meso*-tetrakis(*p*-tolyl)porphyrin), [Fe^{III}(tpp)Cl], and [Ru^{II}(tpp)(CO)] catalyze the olefination of certain classes of aldehydes with ethyl diazoacetate (EDA) in the presence of triphenylphosphane. We observed that both **1** and



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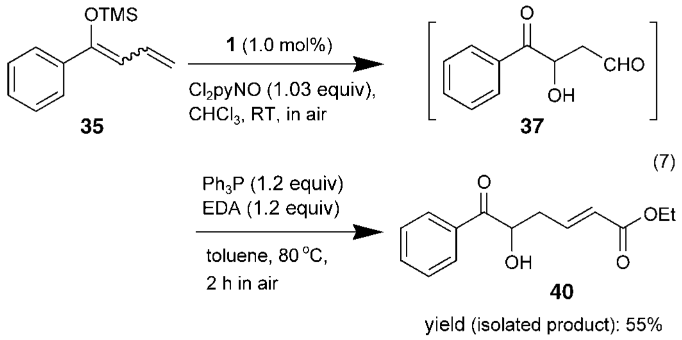
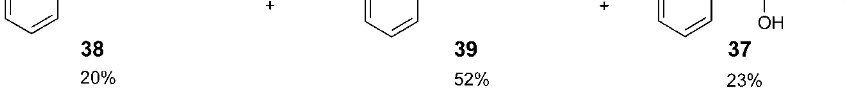


(7)

[Ru^{II}(tdcpp)(CO)] also catalyze such olefination reactions. We recognized that the aldehyde products of the **1**-catalyzed E–I reactions could be used in situ as the substrates for olefination reactions and wanted to develop a practical one-pot E–I–olefination reaction, that is, a one-pot diazoacetate olefination starting directly from alkenes rather than from aldehydes.

By using the "**1**+Cl$_2$pyNO" protocol, **3** (0.1 mmol) was converted into aldehyde **4** in CHCl$_3$ within 30 min. Remarkably, upon removal of the solvent, followed by the addition of Ph$_3$P (1.2 equiv), toluene (1 mL), and EDA (1.2 equiv) and heating the reaction mixture at 80 °C for 2 h, the olefination product **34** was obtained in 99 % yield [Eq. (6)].

4-Oxo-4-aryl butanal derivatives are useful compounds in organic synthesis. For example, the preparation and application of 4-oxo-4-phenylbutanal (**39**) have been studied extensively.[10] In this work, we found that **39** could be prepared in 52 % yield (by ^{1}H NMR spectroscopy; isolated yield: 41 %) through the E–I reaction of silyl enol ether **35** (Scheme 2).



Scheme 2. Oxidation of silyl enol ether **35** with Cl$_2$pyNO catalyzed by **1**. (The yields of **37**–**39** were determined by ^{1}H NMR spectroscopy).

The same reaction also afforded hydroxyketoaldehyde **37** in 23 % yield. When 2.06 equivalents of Cl$_2$pyNO were used, **37** could be obtained in 88 % yield (determined by ^{1}H NMR spectroscopy). From a one-pot E–I–olefination reaction of **35** similar to that of **3**, we isolated the olefination product **40** in 55 % yield [Eq. (7)].

In summary, we have developed a mild and practical method with [Ru^{IV}(tdcpp)Cl$_2$] as a catalyst for the highly regioselective formation of aldehydes from terminal alkenes without C=C bond cleavage. This protocol supplements the Wacker process for the oxidation of terminal alkenes to ketones or aldehydes. The catalytic reactions reported herein can be conducted in air at room temperature to afford a series of isolable β,γ-unsaturated aldehydes in good to excellent yields. The present work provides a new, practical, and convenient method for preparing multifunctionalized compounds. The application of this method to the synthesis of natural products is in progress.

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