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Oxidative Cleavage

C–C or C–O Bond Cleavage in a Phenolic Lignin Model Compound: Selectivity Depends on Vanadium Catalyst[**]

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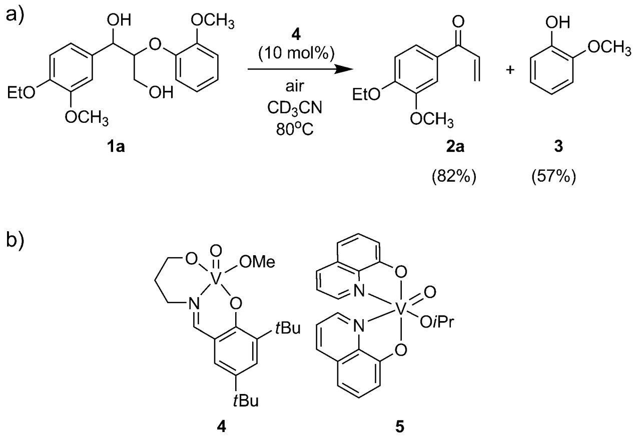
In light of diminishing fossil fuel reserves and increasing demand for energy, nonfood biomass (lignocellulose) is an attractive feedstock for the production of renewable chemicals and fuels.[1] Although it has traditionally been considered an intractable by-product of the pulp and paper industries, lignin is receiving increasing attention as a potential precursor for valuable aromatic compounds.[2–4] Lignin is a polymer composed of methoxy-substituted phenyl and phenolic subunits, and the complexity of its irregular structure poses a significant challenge to its use as a renewable feedstock.[5,6] However, a number of recent reports suggest that using a homogeneous catalyst for reduction or oxidation of lignin could be an effective way to depolymerize lignin in a selective fashion.[2,7–9] In principle, the selectivity could be tuned by the choice of the transition-metal catalyst and the ligand. For instance, Sergeev and Hartwig recently reported that a nickel carbene complex is an effective catalyst for hydrogenolysis of aryl ether bonds in several lignin model compounds,[10] and Bergman and co-workers found a ruthenium xantphos catalyst that cleaves the C–O bond in a lignin model compound by transfer hydrogenation.[11]

Catalytic aerobic oxidation is also appealing for the production of fine chemicals from lignin, as this strategy would not require added stoichiometric reagents, and would afford water as the only by-product of oxidation.[7,8] Use of an earth-abundant metal as a catalyst could provide additional benefits in terms of availability and cost. Toward this objective, Son and Toste recently reported a vanadium catalyzed C–O bond cleavage reaction in the lignin model compound **1a**, which afforded alkene **2a** and 2-methoxyphenol (**3**) as the major products (Scheme 1 a).[12] Although the overall reaction is redox-neutral, optimal activity was achieved by the use of catalyst **4** (10 mol %) under aerobic conditions.[12] As an alternative, we have investigated vanadium complexes as catalysts for oxidative C–C bond cleavage of lignin models,[13] and recently found that the 8-quinolinate complex **5** catalyzes the aerobic oxidation of benzylic and allylic alcohols when a basic additive is used.[13c]



Scheme 1. a) Non-oxidative C–O bond cleavage reported by Son and Toste.[12] b) Vanadium catalysts for the oxidation of lignin models.

Herein, we present reactivity studies of a phenolic lignin model compound **1b** with catalysts **4** and **5**. Remarkably, the two vanadium catalysts show different selectivities for the aerobic oxidation of **1b**. Vanadium catalyst **5** mediates a new type of reaction in which the C–C bond between the aryl ring and the adjacent alcohol group is broken to give 2,6-dimethoxybenzoquinone (**6**) and acrolein derivative **7**, and ketone **8b**. In contrast, catalyst **4** affords C–O bond cleavage products **2b** and **3**, and ketone **8b**. The significant difference in selectivity between the two catalysts underscores the potential of homogeneous catalysts for controlling the selectivity in the aerobic oxidation of lignin.

We were interested in investigating the reactivity of vanadium catalysts with the phenolic lignin model compound **1b**, since prior work had focused on non-phenolic lignin model compounds,[12,13] and it was envisioned that the phenolic group could influence the course of the oxidation reaction. Phenolic groups are abundant in lignin: spruce lignin is estimated to have 15–30 free phenolic groups per 100 phenylpropanoid units.[14,15] The lignin model compound [$^{13}C_2$]-**1b** was prepared as a 4:1 mixture of diastereomers (erythro:threo).

The reactivity of [$^{13}C_2$]-**1b** was then tested with the 8-quinolinate vanadium complex **5**. Unexpectedly, the reaction of [$^{13}C_2$]-**1b** with **5** (1 equiv) in [D$_5$]-pyridine under air at 80 °C afforded coproducts derived from cleavage of the C(alkyl)–C(phenyl) bond, 2,6-dimethoxybenzoquinone (**6**, 40 %) and acrolein derivative [$^{13}C_2$]-**7** (38 %), as well as ketone [$^{13}C_2$]-**8b** (20 %; Scheme 2).[16] The ^{1}H NMR spectrum (CDCl$_3$) of acrolein derivative [$^{13}C_2$]-**7** shows a characteristic resonance for the aldehyde proton at 9.46 ppm (d, $^2J_{C-H} = 32$ Hz), and

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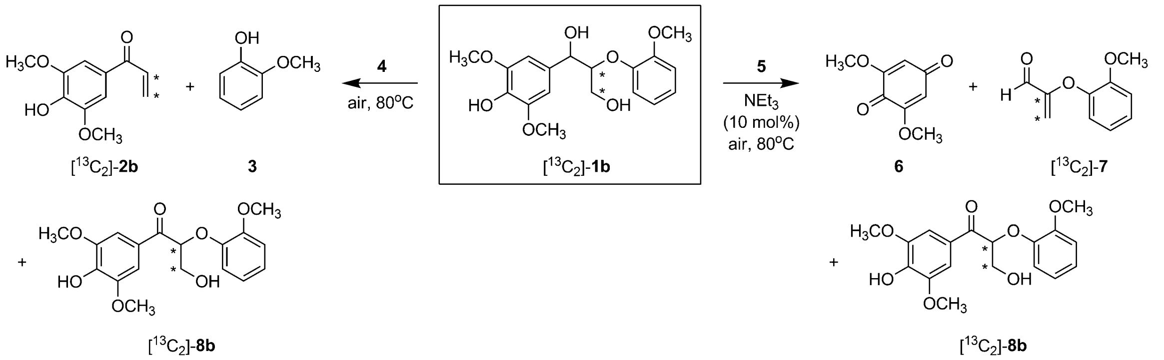


Scheme 2. Oxidation of phenolic lignin model compound [^{13}C$_2$]-**1b** with vanadium catalysts **4** (C–O bond cleavage) and **5** (C–C bond cleavage).

the ^{13}C NMR spectrum of [^{13}C$_2$]-**7** shows resonances at 158.4 and 107.4 ppm ($^1J_{C-C}$ = 80 Hz), which are consistent with the chemical shifts of an enol ether.

The formation of acrolein derivative **7** was surprising, as the cleavage of the C(alkyl)–C(phenyl) bond is a rather unusual reaction. Vanadium complexes have been reported to oxidatively break the C–C bonds between vicinal diols,[17] α-hydroxyketones,[18] and α-hydroxyethers,[13a] as well as mediate the decarboxylation of 1,2- and 1,3-hydroxycarboxylic acids,[19] but vanadium-mediated cleavage of a benzylic C–C bond has not been reported. In a closely related reaction, cobalt–salen complexes have been shown to break C–C bonds in several phenolic compounds, including isoeugenol, 3-methoxy-4-hydroxyacetophenone, and **1b**.[20–22] For cobalt, the C–C bond cleavage is proposed to proceed through a superoxocobalt intermediate, which likely abstracts a hydrogen atom from the substrate to generate a cobalt-bound oxygen-centered radical.[23,23]

Encouraged by the observation of this new reaction mode, we tested the catalytic aerobic oxidation of [^{13}C$_2$]-**1b** by using catalyst **5**. Phenolic lignin model [^{13}C$_2$]-**1b** was heated under air with **5** (10 mol%) in [D$_5$]-pyridine at 80 °C. Complete consumption of [^{13}C$_2$]-**1b** was observed after 48 hours at 80 °C; the reaction afforded **6** (30%), [^{13}C$_2$]-**7** (34%), and [^{13}C$_2$]-**8b** (27%), thus demonstrating that the C(alkyl)–C(phenyl) bond could be broken catalytically. The C–C bond cleavage reaction also occurred in ethyl acetate, [D$_8$]-THF, or 2-methyltetrahydrofuran (2-MeTHF) by using a combination of catalyst **5** (10 mol%) and NEt$_3$ (10 mol%). When the reaction was carried out in ethyl acetate (48 h, 80 °C), formation of **6** (44%), [^{13}C$_2$]-**7** (45%), and [^{13}C$_2$]-**8b** (14%) was observed. Comparable yields of **6** (26%), [^{13}C$_2$]-**7** (45%), and [^{13}C$_2$]-**8b** (11%) were obtained in 2-MeTHF.

Although the ^{1}H NMR spectrum ([D$_5$]-pyridine) of the catalytic reaction mixture did not show distinct signals that could be attributed to unidentified products, the ^{13}C NMR spectrum showed two additional broad signals at 85.8 and 62.0 ppm, and examination of the mass balance for the overall reaction indicated that not all material was accounted for. We postulated that the low mass balance observed in the reaction of **1b** could be due to instability of the products, which could polymerize or further react under the experimental conditions. Consistent with this idea, 40% of the material was consumed and an intractable mixture of products was obtained when an independently synthesized sample of ketone **8b** was heated with vanadium catalyst **5** (1 equiv) under air in [D$_5$]-pyridine (48 h, 80 °C). Likewise, attempts to isolate acrolein product **7** showed that it was not stable when stored as a solid at room temperature for several weeks. MS analysis of the catalytic reaction mixture showed the presence of several higher molecular weight species, which potentially originated from oligomerization of reaction intermediates or unstable products. Competing polymerization has previously been reported in the electrochemical oxidation of several phenolic lignin model compounds.[24]

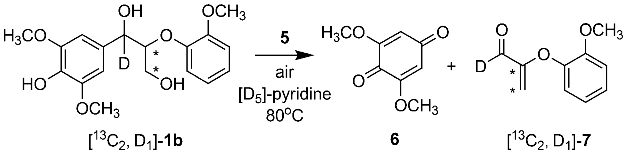
The unusual cleavage reaction of the C(alkyl)–C(phenyl) bond observed in phenolic lignin model [^{13}C$_2$]-**1b** with vanadium complex **5** differed significantly from the non-oxidative C–O bond cleavage in non-phenolic lignin model **1a** reported for Toste's catalyst **4**.[12] Consequently, we wondered if the incorporation of the phenolic functional group into the lignin model was responsible for the difference in reactivity. To gain more insight into the influence of the phenolic group, we tested the reaction of phenolic lignin model [^{13}C$_2$]-**1b** with Toste's catalyst **4**. Surprisingly, when [^{13}C$_2$]-**1b** was heated with **4** (1 equiv) under air (80 °C, 48 h) in CD$_3$CN, complete conversion of [^{13}C$_2$]-**1b** was observed and a mixture of C–O bond cleavage coproducts [^{13}C$_2$]-**2b** (28%) and **3**, and ketone [^{13}C$_2$]-**8b** (43%) was obtained. Formation of acrolein product [^{13}C$_2$]-**7** was not observed, thus indicating that the reaction selectivity was dependent on the specific vanadium catalyst, and not merely changing because of the incorporation of the phenolic group into the substrate. A similar product distribution ([^{13}C$_2$]-**2b**, 30%; [^{13}C$_2$]-**8b**, 41%) was obtained when the reaction of [^{13}C$_2$]-**1b** with **4** was carried out in [D$_5$]-pyridine (80 °C, 48 h), thus suggesting that the observed selectivity was not significantly affected by the presence of the basic pyridine. The catalytic oxidation of [^{13}C$_2$]-**1b** by Toste's complex **4** (10 mol%) in [D$_5$]-pyridine also afforded C–O bond cleavage products [^{13}C$_2$]-**2b** (32%) and **3**, and [^{13}C$_2$]-**8b** (44%).[25] The ^{13}C NMR spectrum (CDCl$_3$) of compound [^{13}C$_2$]-**2b** showed characteristic resonances at 132.2 and 129.7 ppm ($^1J_{C-C}$ = 69 Hz).

In an effort to increase the yields of monomeric products, a mixture of catalysts **4** (5 mol%) and **5** (5 mol%), and NEt$_3$ (10 mol%) was evaluated for the oxidation of [^{13}C$_2$]-**1b** in ethyl acetate. Complete consumption of [^{13}C$_2$]-**1b** was observed after heating the mixture at 80 °C for 48 hours, and a mixture of C–O (**2b** (24 %), **3**) and C–C bond cleavage products (**5** (36 %), **6** (30 %)), and ketone **8b** (14 %) was obtained. [$^{13}C_1$]-formic acid (4 %) was also detected by ^1H and ^{13}C NMR spectroscopy. Although the yields of monomeric products were slightly increased by using a combination of both catalysts, the mass balance (ca. 74 % for the ^{13}C-labeled portion of the molecule) and the presence of a brown precipitate suggested that some undesired side reactions still occurred.

Intrigued by the selectivity difference between the two vanadium catalysts, we aimed to gain insight into the reaction mechanisms that might underlie the observed selectivities. Previously, a one-electron pathway was proposed for the C–O bond cleavage reaction reported by Toste, in which the benzylic hydrogen is abstracted to generate a vanadium-bound ketyl radical intermediate.[12] To further examine the role of the benzylic C–H bond in the C–O and C–C bond cleavage reactions, the lignin model compound [$^{13}C_2$, D_1]-**1b** was prepared with a deuterium incorporated into the benzylic position.

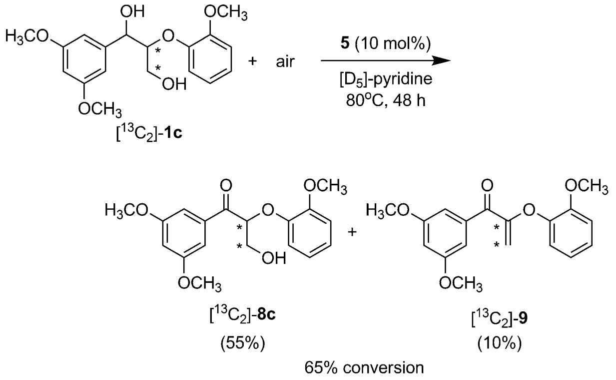
Compared to the reaction of [$^{13}C_2$]-**1b**, the reaction of [$^{13}C_2$, D_1]-**1b** with Toste's catalyst **4** (1 equiv) in CD_3CN (80 °C, 48 h) was found to be qualitatively slower. When the reactions of complex **4** with [$^{13}C_2$]-**1b** and [$^{13}C_2$, D_1]-**1b** were monitored side-by-side, only 56 % of [$^{13}C_2$, D_1]-**1b** had reacted after 18 hours, as compared to 83 % of [$^{13}C_2$]-**1b**. A conversion of 87 % was observed for [$^{13}C_2$, D_1]-**1b** after 72 hours at 80 °C, and **2b** (14 %), **3**, and **8b** (35 %) were obtained. Dimethoxybenzoquinone (**6**) was also a minor product of the reaction (8 %). The slower reaction rate observed for [$^{13}C_2$, D_1]-**1b** and the increase in the yield of **8b** relative to **2b** implicate cleavage of the benzylic C–H bond duringthe formation of both **2b** and **8b**.

A change in product distribution was also observed upon oxidation of [$^{13}C_2$, D_1]-**1b** with quinolinate catalyst **5** (1 equiv). When the reaction of [$^{13}C_2$, D_1]-**1b** with **5** was carried out under air in [D_5]-pyridine (80 °C, 48 h; Scheme 3), the products consisted of acrolein derivative [$^{13}C_2$, D_1]-**7** (57 %) and 2,6-dimethoxybenzoquinone **6** (54 %), with less than 3 % formation of [$^{13}C_2$]-**8b**. Both the retention of the deuterium label in the product [$^{13}C_2$, D_1]-**7** and the increased yield of **7** relative to **8b** suggest that cleavage of the benzylic C–H bond is not involved in the formation of **7**.



Scheme 3. Oxidation of [$^{13}C_2$, D_1]-**1b** with vanadium catalyst **5**.

With subsequent experiments, we aimed to establish whether the phenolic group is necessary for the oxidative C–C bond cleavage reaction. When non-phenolic lignin model [$^{13}C_2$]-**1c** was heated under air with **5** (10 mol %) in [D_5]-pyridine (80 °C, 48 h; Scheme 4), 65 % conversion was observed and ketone [$^{13}C_2$]-**8c** (55 %) and dehydrated ketone [$^{13}C_2$]-**9** (10 %) were obtained. No C–C bond cleavage products were observed, thus indicating that the phenolic group plays an important role in the C(alkyl)–C(phenyl) bond cleavage pathway. C–O bond cleavage product [$^{13}C_2$]-**2c** was also not detected in the reaction mixture, thus suggesting that the formation of **2** and **8** proceeds by distinct reaction pathways.



Scheme 4. Oxidation of non-phenolic lignin model compound [$^{13}C_2$]-**1c** with vanadium catalyst **5**.

Key differences emerge in the selectivity of vanadium catalysts **4** and **5**. While Toste's catalyst **4** breaks the C–O bond in lignin model **1b** through a pathway that involves cleavage of the benzylic C–H bond, quinolinate complex **5** breaks the C(alkyl)–C(phenyl) bond through a pathway that does not involve the benzylic C–H bond. A phenoxy group is required for the C–C bond cleavage reaction, which may proceed through a phenoxy radical intermediate, as has been proposed for related cobalt-mediated C–C bond cleavage reactions.[21–24]

Overall, the remarkably different selectivities observed for the two vanadium catalysts show the complexity of vanadium-mediated oxidations and support the viability of homogeneous catalysts for controlling selectivity in the aerobic oxidation of lignin. Efforts to explore vanadium-mediated oxidation of other types of lignin substructures are currently under way.

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