Selectivé, low-temperature hydroxylation of alkanes catalyzed by transition-metal complexes is an important area of study, given its possible applications to natural-gas conversion as well as to more efficient production of bulk chemicals and energy. Several promising electrophilic catalysts that couple C–H activation to facile oxy-functionalization of the resulting electrophilically activated M–R\(^+\) intermediates have been reported (Figure 1).\([3]\) To address practical challenges with functionalization reactions of more nucleophilic M\(\to\)electrophilic M\(\to\)Ru, and Re. However, while oxy-functionalization reactions of electrophilic metals, such as iridium, functionalization reactions of more nucleophilic M\(\to\)electrophilic M\(\to\)osmium, ruthenium, and rhenium. Yet, there are few reports of facile oxy-functionalization reactions of more nucleophilic M\(\to\)electrophilic M\(\to\)intermediates\([3]\) that would be generated by C–H activation of a negatively polarized methyl group, Re\(\to\)CH\(_3\)\(\to\)ReO\(_3\) and features the nucleophilic transfer of a negatively polarized methyl group, Re\(\to\)CH\(_3\)\(\to\)ReO\(_3\) to the electrophilic oxygen of incoming oxygen donors, YO (Figure 2, BV). To expand the range and scope of oxy-functionalization reactions of nucleophilic M\(\to\)electrophilic M\(\to\)intermediates we are exploring the range of possible mechanisms. Important goals are to identify reactions that do not involve free radicals, are compatible with CH-activation reactions with electrophilic metals, and are sufficiently fast and selective to intercept and convert nucleophilic M\(\to\)electrophilic M\(\to\)intermediates into oxygenated products.

One intriguing possibility is the use of cis-metal dioxo compounds that could react with M\(\to\)R bonds in a potentially facile addition reaction via a (3+2)-type transition state (TS, see Figure 2). Related mechanisms are well known for the cis-dihydroxylation of alkenes by OsO\(_4\)\([5]\) and the oxidation of the \(\cdot\)O\(_2\)\(\to\)bonds of hydrogen, \([6]\) silanes, \([7]\) and alkanes.\([8]\) Herein we report the quantitative and instantaneous oxy-functionalization of MTO to methanol by reaction with OsO\(_4\) in aqueous basic media at room temperature [Eq. (1)].

$$\text{CH}_3\text{ReO}_3 + \text{OsO}_4 + 3 \text{OH}^- + \text{H}_2\text{O}^{\text{\text{\(\to\)}}} \text{RT} \xrightarrow{} \text{CH}_3\text{OH} + \text{ReO}_4^{\text{\text{\(\to\)}}} + \text{OsO}_2(\text{OH})_2^{\text{\text{\(\to\)}}}$$  \hspace{1cm} (1)

Significantly, this reaction does not proceed without added base. Computational studies suggest that the large rate acceleration is the result of MTO activation by coordination of base, rather than activation of OsO\(_4\), and that the reaction...
takes place via a novel (2+3) TS that features transfer of a nucleophilic methyl group to the electrophilic oxygen of OsO₄.

Treatment of MTO at room temperature with basic, aqueous (D₂O) solutions containing excess OsO₄ resulted in the quantitative conversion (>95%) into CH₃OD upon mixing in the presence or absence of air. High yields of methanol required a 5–10-fold molar excess of both OsO₄ and OD⁻. Under these reaction conditions, no intermediates or other species were detected by in situ ¹H NMR spectroscopy, except for trace amounts of CH₂D₂ attributed to the known hydroxide-induced decomposition of MTO. The reactions are very rapid; even at temperatures as low as −40°C (using [D₆]diglyme solvent) the reaction is essentially complete on mixing. Notably, no reaction occurred between OsO₄ and MTO in D₂O in the absence of added KOD (Figure 3a).

![Figure 3. 400 MHz ¹H NMR spectra of a) MTO + OsO₄ (1:1 ratio) in D₂O and b) MTO + OsO₄ (1:1 ratio) in D₂O with 3 equivalents of added KOD.](image)

In situ ¹H NMR spectroscopic studies of the reaction of stoichiometric quantities of OsO₄, MTO and OD⁻ at room temperature showed that approximately 75% of the MTO is converted into methanol (46%, at δ = 3.30 ppm), another methyl species (29%, at δ = 4.30 ppm), and base coordinated CH₃ReO₃ (11%, at δ = 1.69 ppm, Figure 3b). It is possible that the species giving rise to the signal at δ = 4.30 ppm is an intermediate containing either a Re–OCH₃ or Os–OCH₃ fragment (that could be generated from BV or (3+2)-type mechanisms, respectively). This species is not detected at any time when excess OsO₄ and OD⁻ are used, or when the system is buffered at high pH values (see below), and could not be isolated as a discrete, well-characterized compound.

Since hydroxide is consumed in the reaction, we examined the reaction at room temperature with buffers at various pH values. Importantly, in situ ¹H NMR spectroscopic analysis of the stoichiometric reaction in a NaH₂PO₄/Na₂HPO₄ buffer at pH 7.8 showed that free MTO is completely consumed after 2 h and that a dark, unidentified precipitate is generated, along with a 15% yield of methanol. In contrast, reaction in a pH 11.1 buffer (Na₂HPO₄/Na₃PO₄) resulted in 70% yield of methanol (relative to added MTO) after the same length of time, with no other detectable methyl products. As noted above, with excess NaOD and OsO₄ the reaction is essentially quantitative on mixing. We are currently investigating the pH dependence of this reaction as well as the identity and reactivity of the intermediates and precipitate. Significantly, reactions of ¹⁸O-MTO with ¹⁸O-enriched OsO₄ unequivocally show that the methanol oxygen is derived either from OsO₄ or H₂O but not from MTO. As oxygen exchange between H₂O and OsO₄ is fast (but slower with MTO) in aqueous basic solution on the time scale of the reaction we could not unambiguously determine if the methanol oxygen is derived from OsO₄ or H₂O.

Several plausible mechanisms can account for this functionalization reaction and its acceleration by hydroxide. One possibility is a BV-type reaction with base-coordinated OsO₄ playing the role of oxygen donor. Another is a (3+2)-type reaction between the various possible hydroxide adducts of MTO and OsO₄. Given the experimental challenges in distinguishing between these different mechanisms, we used B3LYP density functional theory (DFT) to investigate pathways for the reaction of OsO₄ and MTO under basic conditions.

Consistent with the detected reaction spontaneity, B3LYP predicts the transformation of [OsO₄(OH)]⁻ and [CH₃ReO₄]⁻ (the predicted ground state base adducts of OsO₄ and MTO in aqueous basic media) to methanol, [OsO₄(OH)]⁻ and [ReO₄]⁻ to be highly exothermic (ΔH = −82.6 kcal mol⁻¹, Figure 4). As the various methylrhenium and osmium oxoanions are likely to equilibrate, we explored plausible TSs from the various combinations of these reactants.

Consistent with the rapid reaction that occurs at room temperature, a low energy pathway with an activation enthalpy of only 11.7 kcal mol⁻¹ was calculated for the reaction of [CH₃ReO₄]⁻ with uncoordinated OsO₄ (Figure 4, Path A, (2+3)). In this pathway, one of the oxygen atoms on the [CH₃ReO₄]⁻ coordinates to the metal center of OsO₄, as the methyl group is transferred to a cis-oxygen on OsO₄. Interestingly, by the pericyclic nomenclature, the Os=O bond is the two-atom fragment and [CH₃ReO₄]⁻ is the three-atom fragment, although no formal adduct is formed. In the Sharpless dihydroxylation reaction between ligated OsO₄ and olefins, a cis-Os=O motif is the three-atom fragment and the alkene is the two-atom fragment. Similarly, in the recently reported reactions of H₂ with base-coordinated OsO₄, that is, [OsO₄(OH)]⁺, the H–H bond is the two-atom fragment and the cis-Os=O the three-atom fragment. Similar to these TSs, a (3+2) pathway where [OsO₄(OH)]⁻ reacts as the three-atom fragment with the two-atom fragment of MTO was also located (Figure 4, Path B, (3+2)). However, the activation enthalpy (27.8 kcal mol⁻¹) is nearly twice as large as that for the (2+3)-type pathway. Other reaction pathways involving reactions of hydroxide-coordinated MTO with uncoordinated and base-coordinated OsO₄ as well as base-coordinated OsO₄ with uncoordinated MTO were also examined. Several BV-type TSs exist, but they are substantially higher in energy than the (2+3) TS (see Supporting Information). We have also located a new intramolecular decomposition TS for [CH₃ReO₄(OH)]⁻ that may explain the trace amount of decomposition to methane (see Supporting Information).
In spite of the high formal oxidation state of the Re\textsuperscript{VII} center, that would be expected to favor electrophilic reactions at the methyl group, the (2 + 3) TS features a nucleophilic methyl group transfer to an electrophilic oxygen, which is consistent with the acceleration of the reaction, detected in the presence of base, as coordination of O\textsuperscript{2-} to MTO would be expected to substantially increase the nucleophilicity of the methyl group. The facile loss of OH\textsuperscript{-} from ground state [OsO\textsubscript{4}(OH)]\textsuperscript{-} would generate the most electrophilic oxygen in uncoordinated OsO\textsubscript{4}.

Figure 5 shows the changes in the B3LYP CH\textsubscript{3}-Re bonding orbitals, relative to MTO, as hydroxide and then O\textsubscript{2}/CO are coordinated to the Re center. Coordination of the strong base, O\textsuperscript{2-}, localizes the highest occupied molecular orbital (HOMO) on the methyl group and increases the negative polarization while significantly stretching the Re–C bond. This bond lengthens from 2.086 Å (for MTO) to 2.218 Å (on coordination of hydroxide) to 2.368 Å (on coordination of O\textsuperscript{2-}), while the Mulliken charge on the carbon atom becomes more negative and the energy of the HOMO increases. Combined, these factors serve to facilitate the interaction of the nucleophilic methyl group with the electrophilic oxygen of uncoordinated OsO\textsubscript{4}, ultimately providing a low barrier for oxy-functionalization and a basis for the enormous acceleration of the reaction by the addition of base.

In the (2 + 3) TS, the Re–C bond is almost completely broken (2.920 Å), and the incipient O–C bond length is 2.540 Å, which indicates possible radical character.\cite{4b} However, exploration of both the singlet and triplet surfaces along the intrinsic reaction coordinate show that this TS does not decompose to discrete free radicals. Furthermore, there is no change in reaction yield or methanol selectivity upon carrying out the reactions under approximately 200 psig of pure oxygen, precluding a free-radical mechanism.

We also considered that activation of MTO might be possible using other bases by similar mechanisms. Common Lewis bases, such as pyridine and amines, are known to activate OsO\textsubscript{4} in alkene cis-dihydroxylation\cite{14} reactions and to bind well to MTO. Hydroxide was thus replaced with the water-soluble substituted pyridine, isonicotinic acid (pyridine-4-carboxylic acid). The reaction of MTO with OsO\textsubscript{4} and 3 equivalents of isonicotinic acid, buffered at pH 7.8, resulted in 65% yield of methanol. The significantly higher yield upon addition of a pyridine base (relative to 15% without pyridine base, see above) is evidence for the possibility of general base activation of the MTO, and could potentially lead to methods for the stereoselective oxy-functionalization of M–R intermediates by the use of chiral bases as activating agents.

The work herein establishes the viability of using cis-dioxo metal compounds, such as OsO\textsubscript{4}, as reagents for the facile, selective functionalization of nucleophilic metal alkyl species via a low energy (2 + 3) transition state.

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\[\text{[1]}\] We define C–H activation as a coordination reaction with a reactive species “M”, that proceeds without the involvement of free radicals, carbocations, or carbanions to generate discrete M–R intermediates. Functionalization is the conversion of the M–R intermediate into an R-heteroatom product; a) A.E. Shilov, G.B. Shul’pin, \textit{Chem. Rev.} 1997, 97, 2879; b) R.A. Periana, O. Mironov, D. Taube, G. Bhalla, C. Jones, \textit{Science} 2003,


[10] From theory we suspect the formation of [CH3ReO4]2– as reported in the text (Figure 4). Espenson (Ref. [9]) suggests formation of [CH3ReO3(OH)]– under less basic conditions and reports a chemical shift in D2O of δ = 1.9 ppm. Our shift of δ = 1.69 ppm would be consistent with a more nucleophilic methyl species formed from subsequent deprotonation of the bound hydroxide.


[13] As a result of aqueous solvation of the dianion, [CH3ReO4]2– is the ground state in water, not [CH3ReO3(OH)]– as was found in our previous investigation in THF containing OH–. Gas phase calculations predict [CH3ReO3(OH)]– as the ground state. See Supporting Information for Re– and Os–oxo equilibrium calculations.