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Hydroperoxidations of Alkenes using Cobalt Picolinate Catalysts

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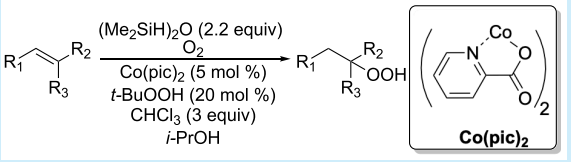
ABSTRACT: Hydroperoxides were synthesized in one step from various alkenes using $Co(pic)_2$ as the catalyst with molecular oxygen and tetramethyldisiloxane (TMDSO). The hydration product could be obtained using a modified catalyst, $Co(3\text{-mepic})_2$, with molecular oxygen and phenylsilane. Formation of hydroperoxides occurred through a rapid Co−O bond metathesis of a peroxycobalt compound with isopropanol.



Because the peroxide functional group is found in many biologically active natural products and potential drugs, efforts have been directed toward the development of methods for the synthesis of peroxides.[1−6] The cobalt-catalyzed silylperoxidation of alkenes[7−9] has emerged as a general method to introduce the peroxide functional group into unsaturated substrates. These reactions typically use metal complexes containing 1,3-diketonate ligands, such as 2,2,6,6-tetramethyl-3,5-heptanedionate (thd or dpm).[10−12] The specific 1,3-diketonate ligand employed does not dramatically influence the course of reactions, but it can influence their rates and efficiencies.[13] Cobalt porphyrin complexes have also been used to catalyze the peroxidation of alkenes, but these catalysts work best with electron-deficient dienes, converting them into γ-hydroperoxy-α,β-unsaturated carbonyl compounds.[14]

Although the available catalysts address many issues, some limitations to these reactions remain. The use of $Co(thd)_2$,[13] a particularly efficient catalyst, forms cobalt complexes that can be difficult to separate from the products,[15] which has led to the development of modified 1,3-diketonate ligands that facilitate purification.[16,17] Catalysis by Mn(III) 1,3-diketonate complexes can lead to hydroperoxides,[18] although the product is often formed along with the corresponding alcohol. Porphyrins needed to make catalysts can be costly and, although they can be prepared by the user, the yields of these syntheses are often modest.[19,20] As a result, a family of readily prepared and tunable catalysts that give control over which product is formed (hydroperoxide or alcohol) would be valuable. Furthermore, considering the biological activity of cyclic peroxides, it would be desirable to devise catalysts for peroxidations of alkenes that would enable direct access to cyclic peroxides.

In this Letter, we report a family of cobalt complexes constructed with 2-carboxypyridine (picolinate) ligands that are effective catalysts for alkene hydroperoxidation. These catalysts are simple to prepare from commercially available picolinic acids; they can be isolated, handled, and stored without demanding precautions; and they are effective at generally low catalyst loadings. These complexes share some characteristics with Co(II) porphyrin complexes, but the picolinate complexes also permit peroxidation of electron-rich dienes and alkenes. The reactivity of these catalysts can also be tuned using substituted picolinic acids.

Initial efforts focused on developing a direct hydroperoxidation of alkenes using enone **1** as a model substrate. The traditional 1,3-diketonate catalysts for these reactions, such as a cobalt atom complexed to a thd ligand, gave the expected silyl peroxide **2a** under standard reaction conditions (Table 1, entry 1).[21] Attempts to obtain the corresponding hydroperoxide using other 1,3-diketonate ligands were unsuccessful (entries 2−4). The use of methanol as a solvent or co-solvent led to formation of an alcohol, not a peroxide product (entries 5−6).[22]

The use of cobalt catalysts with picolinic acid-derived ligands led to hydroperoxidation instead of silylperoxidation under similar conditions (Table 2). The use of Ph_2SiH_2 or TMDSO were the most effective, particularly with isopropanol as the solvent (entries 4−5). Although smaller quantities of Ph_2SiH_2 could be used (entry 4), the product was contaminated with alcohol **2b**, likely because Ph_2SiH_2 is a strong reducing agent.[23,24] By contrast, use of TMDSO (entry 5) did not result in formation of alcohol **2b** and had the added benefit of facilitating the separation of the products from silicon-containing impurities.[24]

Experiments designed to optimize the structure of the catalyst revealed that the reactivities of the cobalt picolinate complexes were sensitive to substituents on the pyridine ring (Scheme 1). Complexes possessing an NH_2 group at the 3-position or a chlorine atom at the 5-position of the pyridyl group (complexes **F** and **G**) were unreactive. A complex bearing a methyl group at the 6-position of the pyridyl group

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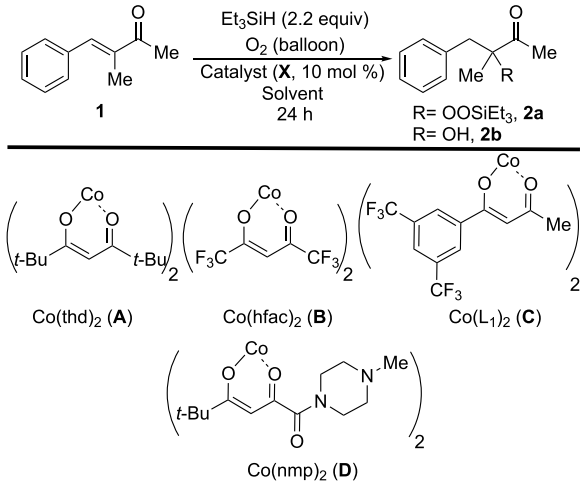
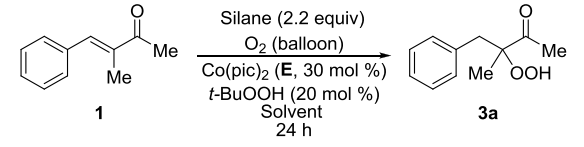
Table 1. 1,3-Diketonato Ligand and Solvent Screen



entry	catalyst	solvent	% conv	product
1	**A**	$PhCF_3$	100	**2a**
2	**B**	$PhCF_3$	0	–
3	**C**	$PhCF_3$	0	–
4	**D**	$PhCF_3$	0	–
5	**A**	$PhCF_3$:MeOH[a]	100	**2b**
6	**A**	MeOH	100	**2b**

[a]90:10 $PhCF_3$:MeOH.

Table 2. Optimization of Silane and Solvent



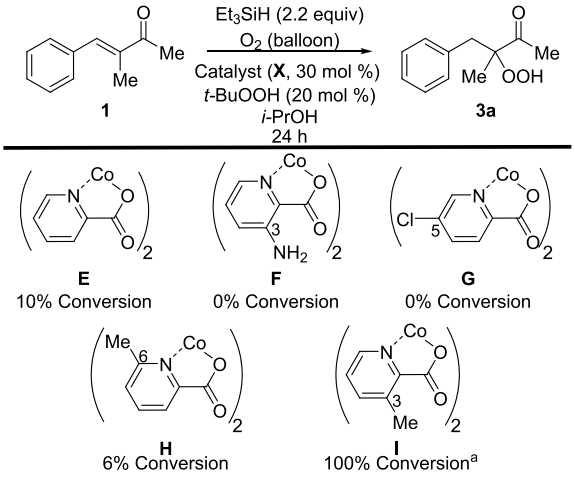
entry	silane	% conv (MeOH)	% conv (*i*-PrOH)
1	Et_3SiH	10	10
2	Ph_3SiH	9	20
3	$(i\text{-}Pr)_3SiH$	0	0
4	Ph_2SiH_2	37	100[a,b]
5	$[(CH_3)_2SiH]_2O$	–	100
6	$PhSiH_3$	9	36

[a]Use of 1.2 equiv led to full consumption of alkene. [b]Alcohol **2b** was formed when the reaction was run at 1 mmol scale.

(complex **H**) reacted much like the parent complex (complex **E**). Catalysts bearing picolinate groups with a methyl group at the 3-position of the pyridine, however, were much more reactive (complex **I**), leading to an approximately four-fold increase in the rate of reaction. The elevated reactivity of 3-substituted pyridine complexes compared to ones with substitution at other positions has been noted elsewhere.[25,26] This increase in reactivity could be attributed to interactions between the methyl and carboxylate groups, which cause the pyridyl group to twist out of the plane,[27] instead of being coplanar with the carboxylate group. Formation of the hydroperoxide product, however, was accompanied by considerable quantities of the corresponding alcohol **2b**.

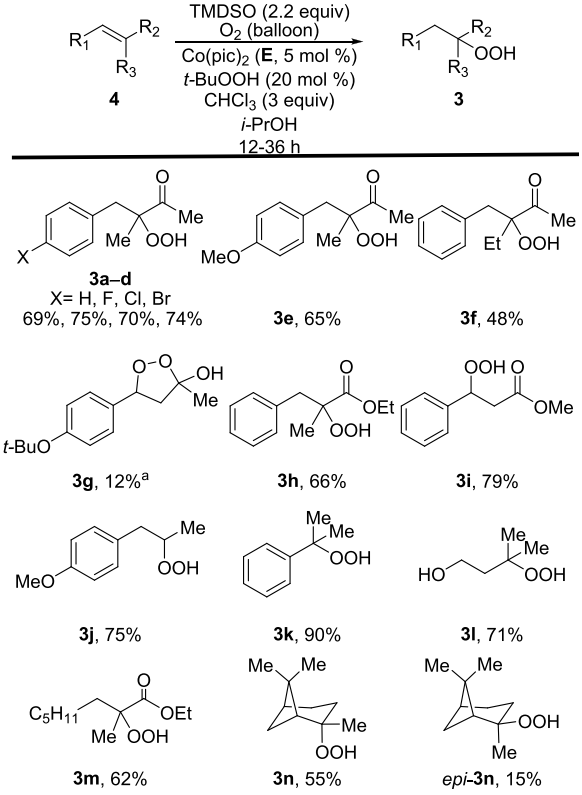
The cobalt picolinate-catalyzed hydroperoxidation of alkenes was general for a number of electron-rich and electron-deficient alkenes (Scheme 2).[28] Both α,β-unsaturated ketones and esters were effective substrates, although the latter alkenes, which should be less electron-deficient than enones,[29] required

Scheme 1. Catalyst Screen using Substituted 2-Carboxypyridine Catalysts



[a]50:50 mixture of alcohol **2b** and hydroperoxide **3a**.

Scheme 2. Substrate Scope



[a]% conversion reported

longer reaction times. Addition of *t*-BuOOH shortened the induction period of the reactions,[30,31] but no compounds containing OO*t*-Bu groups were isolated from the reaction mixture.[32,33] Addition of chloroform in some, but not all, cases increased yields between 5 and 10%.

Reactions involving conjugated dienes showed different reactivity when using $Co(pic)_2$ compared to reactions using complexes with 1,3-diketonate ligands (Scheme 3). Subjecting diene **5a** to standard peroxidation conditions[21] using $Co(thd)_2$ resulted in a mixture of products. Six C–O–O groups were identified in the $^{13}C\{^1H\}$ NMR spectrum of the unpurified

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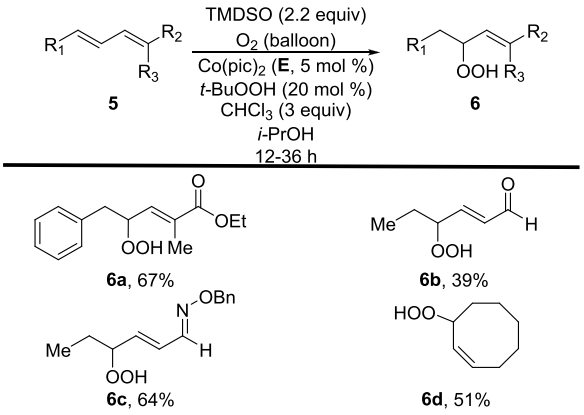
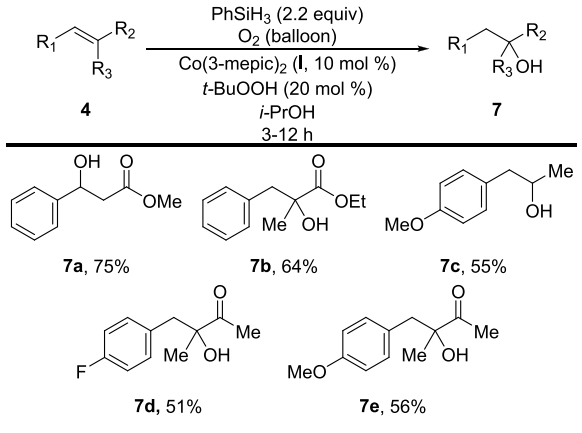
Scheme 3. Diene Substrate Scope



reaction mixture.[31] When the same diene was oxidized with $Co(pic)_2$, however, only one hydroperoxide product was observed after 16 h. This observation suggests that the cobalt picolinate complexes may share characteristics with the cobalt porphyrin complexes but with the ability to catalyze the hydroperoxidation of electron-rich and electron-poor alkenes.[34]

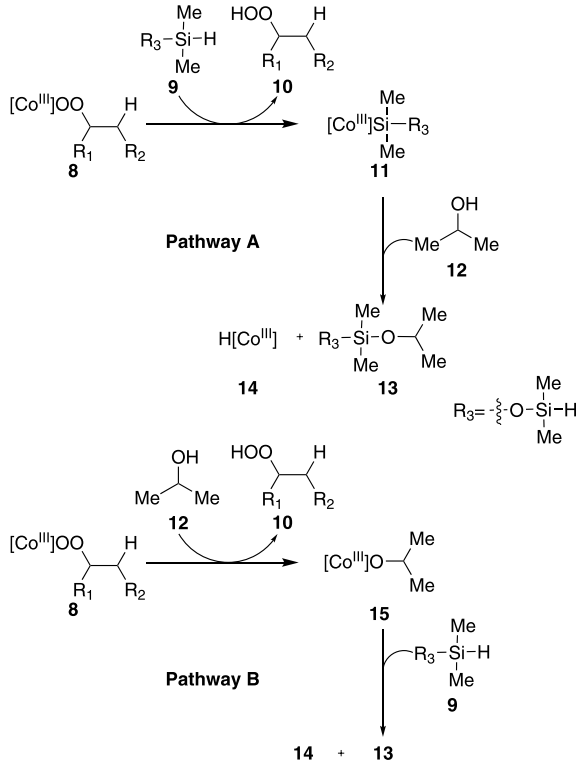
The major product of the reaction can be controlled by the choice of the picolinic acid employed to make the cobalt complex. Using the methyl-substituted version of the catalyst, **I**, and $PhSiH_3$,[23] alkenes could be converted to their corresponding alcohols regioselectively (Scheme 4). This reaction complements other methods that can be employed to achieve metal-catalyzed alkene hydration using O_2.[7]

Scheme 4. Alcohol Substrate Scope

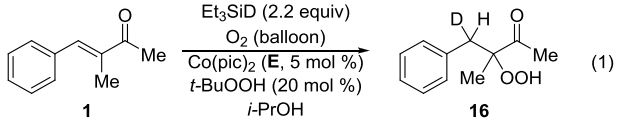


Several mechanistic pathways can be considered for the formation of hydroperoxides instead of the silyl peroxides usually obtained with cobalt catalysts. The pathways diverge after formation of the cobalt-hydroperoxo complex **8**, which would be formed by cobalt-catalyzed hydrometallation in the presence of O_2.[31] Complex **8** could lead to silyl-protected peroxide **2a**, which could then be deprotected. This possibility was discounted by the observation that resubjecting silyl-peroxide **2a** to the reaction conditions led to recovery of starting material.[35] Alternatively, transmetallation of **8** could occur to form O−H and Si−Co bonds (Scheme 5, pathway A).[36] The resulting silylcobalt complex, **11**, could then undergo reaction with isopropanol to form the product and regenerate the cobalt hydride.[36−38] Another pathway, pathway

Scheme 5. Suggested Mechanism for Hydroperoxidation



B, would involve exchange of a peroxide ligand on cobalt with isopropanol to give the hydroperoxide and an isopropoxycobalt complex, **15**, which could react with the silane to regenerate the cobalt hydride species.[39−41] Both of these pathways would generate an isopropoxysilane, which was observed in the unpurified reaction mixtures.[35]



Control experiments provided support that the cobalt picolinate-catalyzed reaction proceeds via pathway B. If the reaction proceeded through pathway A, the use of isopropanol-d_8 as solvent would result in a cobalt deuteride, so deuterium atoms would be incorporated into the product. Peroxidation in isopropanol-d_8, however, gave no deuterated hydroperoxide products after filtration through silica gel, as determined by ^1H and $^{13}C\{^1H\}$ NMR spectroscopy. This experiment indicates that the silane is the source of the hydrogen atom on the cobalt atom. This conclusion was supported by an experiment using the deuterated silane, Et_3SiD (eq 1). Although this silane is not optimal for the preparative process, deuterated hydroperoxide **16** could be observed in the reaction mixture. Taken together, these labeling experiments suggest that pathway B is the most likely pathway.

The direct hydroperoxidation of α,β-unsaturated ketones allowed for the one-step formation of endoperoxides. Hydroperoxidation of enone **17** resulted in the formation of the corresponding endoperoxide **18** (Scheme 6). When the same enone substrates were subjected to peroxidation using catalysts derived from a 1,3-diketone, the uncyclized silyl-protected peroxides were isolated instead (Scheme 6).

The hydroperoxidation/cyclization sequence can be applied to $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl compounds (Scheme 7).

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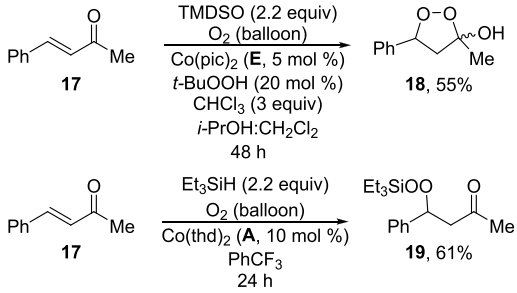
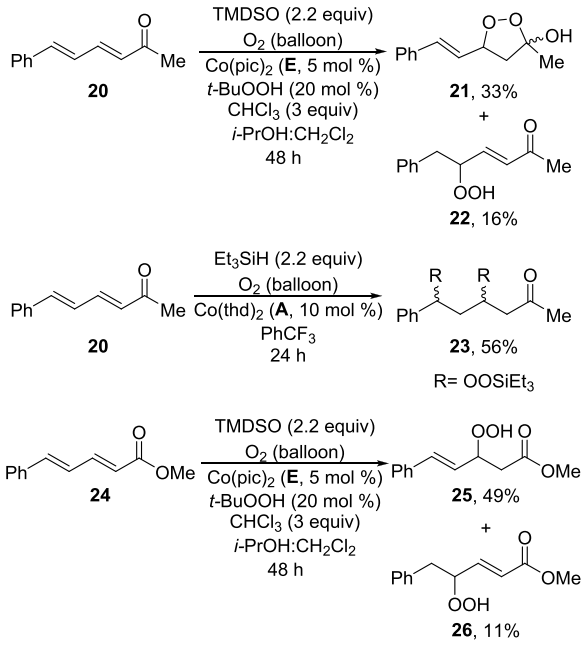
Scheme 6. One-Step Formation of Endoperoxides



Scheme 7. One-Step Formation of Endoperoxides Using Dienes



Treatment of dienone **20** to the reaction conditions gave the dioxolane **21** as the major product. The hydroperoxide **22** was also formed, which indicated that the two carbon−carbon double bonds were not electronically different enough to permit the catalyst to distinguish between them.[42] By contrast, peroxidation using $Co(thd)_2$ led to a mixture of peroxides with a different regioselectivity. The formation of the peroxide products **18** and **21** likely proceed by initial hydroperoxidation, as evidenced by hydroperoxidation of the dienoate **24**.

In conclusion, cobalt picolinate complexes are useful catalysts for both the hydroperoxidation and hydration of alkenes. These complexes are easily prepared from commercially available starting materials, and after the reactions are complete, cobalt-containing impurities can be readily removed from reaction mixtures. The hydroperoxide products proved to be useful for one-step cyclization reactions to form 1,2-dioxolanes, which are the core structure of a number of biologically active compounds.[43−45]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01489.

Experimental procedures, characterization, determination of regioselectivity, and NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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