Science Foundation under Grant CHE-8516247 and the Welch Foundation under Grant A-1042 with a Robert A. Welch Graduate Fellowship (C.S.). We are grateful to Professor John D. Lipscomb (Department of Biochemistry, University of Minnesota) for sharing his understanding of the hydroxylase component of methane monooxygenase proteins and to Professor D. H. R. Barton (of this department) for his suggestion to use $BrCCl_3$ as an activating agent[11] and for stimulating discussions.

Cobalt-Induced Activation of Hydrogen Peroxide for the Direct Ketonization of Methylenic Carbons [c-C_6H_{12} → c-C_6H_{10}(O)], the Oxidation of Alcohols and Aldehydes, and the Dioxygenation of Aryl Olefins and Acetylenes

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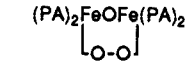
A recent study[1] has described the catalytic activation of excess hydrogen peroxide by bis(picolinato)iron(II) [$Fe^{II}(PA)_2$] for the efficient, selective ketonization of methylenic carbons and the dioxygenation of aryl olefins and acetylenes; the reactive intermediate has been postulated to be



Independent studies[2,3] report similar results, but attribute the selectivity toward methylenic carbon to an $X_3Fe^{V}{=}O$ intermediate (from $Fe^{III}X_3$ plus HOOH). The suggestion is that the hypervalent iron attacks methylenic carbon to form iron–carbon single or double bonds with subsequent reaction with a second HOOH to yield primarily ketone. Both groups agree that iron–picolinate complexes in a pyridine/acetic acid solvent matrix represent an optimal system in terms of efficiency and selectivity.

To gain further insight to the chemistry of this unique HOOH-activation system, we have investigated other transition-metal complexes. Here we report that bis(bipyridine)cobalt(II) [$Co^{II}(bpy)_2^{2+}$, **1**] activates HOOH for the selective ketonization of methylenic carbons, the oxidation of alcohols and aldehydes, and the dioxygenation of aryl olefins and acetylenes. Table I summarizes the product distributions for a series of substrates that result from the catalytic activation of HOOH or *t*-BuOOH by $Co^{II}(bpy)_2^{2+}$. The product profiles indicate that oxidase (or monooxygenase) chemistry is favored in pure MeCN solvent (c-C_6H_{12} → c-C_6H_{11}OH), but the ketonization of methylenic carbon and dioxygenase chemistry are favored in MeCN/py (4:1 molar ratio) [c-C_6H_{12} → c-C_6H_{10}(O); c-PhCH=CHPh → 2PhCH(O)]. The selective ketonization of cyclohexene in MeCN/py contrasts with its enhanced monooxygenation in pure MeCN (one/ol ratio, 16:1 vs 1:1) and is compelling evidence for two reactive intermediates. The presence of O_2 inhibits the reactivity of c-C_6H_{12} with HOOH by 10–20%. In pure MeCN, $Co^{II}(bpy)_2^{2+}$ catalyzes HOOH for the stoichiometric transformation of 1,4-cyclohexadiene to benzene.

When *t*-BuOOH is the oxygen source, the reactivity with substrates is about 10 times greater in pure MeCN than in MeCN/py (Table I). With $PhCH_3$ the dominant product is $PhCH_2OOBu$-*t*, which requires two *t*-BuOOH molecules per substrate. When c-C_6H_{12} is the substrate, c-C_6H_{10}(O) and c-C_6H_{11}OOBu-*t* are the major products (both require two *t*-BuOOH molecules per substrate) and the ketone probably results from the decomposition of c-C_6H_{11}OOBu-*t*. In contrast, with $(Me)_2CHCH_2Me$ the major product is $(Me)_2C(OH)CH_2Me$ (one *t*-BuOOH per substrate). The use of *t*-BuOOH precludes (or strongly suppresses) formation of the reactive intermediate for the direct ketonization of methylenic carbons.

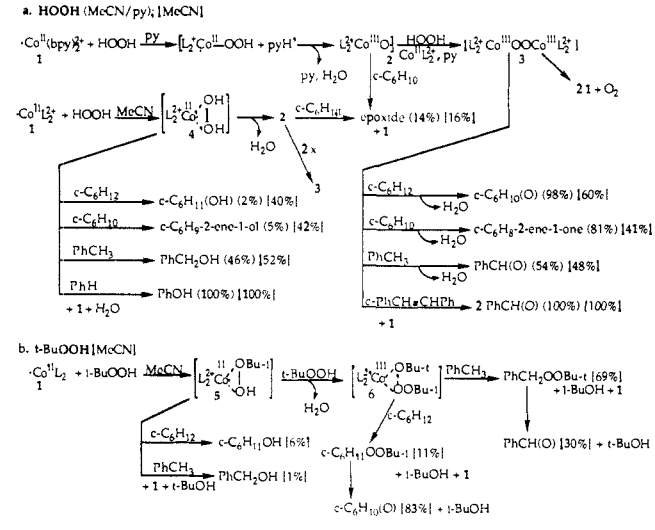
The results of Table I and the close parallels of the product profiles to those for the $Fe^{II}(PA)_2$/HOOH/(py/HOAc) system[1] prompt the conclusion that the combination of $Co^{II}(bpy)_2^{2+}$ (**1**) and HOOH results in the initial formation of an oxene intermediate [$(bpy)_2^{2+}Co^{III}O^{\bullet}$, **2**], which (in MeCN/py) rapidly reacts

Table I. Activation of HOOH and *t*-BuOOH by $Co^{II}(bpy)_2^{2+}$ for the Oxygenation of Hydrocarbons, the Oxidation of Alcohols and Aldehydes, and the Dioxygenation of Aryl Olefins and Acetylenes in 4:1 MeCN/py[a]

substrate (1 M)	oxidant (200 mM)	products (concn, mM)[b]
c-C_6H_{12}	HOOH	c-C_6H_{10}(O) (61), c-C_6H_{11}OH (1)
c-C_6H_{12} (MeCN)	HOOH	c-C_6H_{10}(O) (14), c-C_6H_{11}OH (9)
c-C_6H_{12}	*t*-BuOOH	c-C_6H_{11}OOBu-*t* (1.5)
c-C_6H_{12} (MeCN)	*t*-BuOOH	c-C_6H_{10}(O) (15), c-C_6H_{11}OOBu-*t* (2), c-C_6H_{11}OH(1)
Me_2CHCH_2Me	HOOH	$Me_2CHC(O)Me$ (12), $Me_2C(OH)CH_2Me$ (5)
Me_2CHCH_2Me (MeCN)	*t*-BuOOH	$Me_2C(OH)CH_2Me$ (9), $Me_2CHC(O)Me$ (1)
$PhCH_2CH_3$	HOOH	PhC(O)Me (30), $PhCH_2CH_2OH$ (11)
$PhCH_3$	HOOH	PhCH(O) (20), $PhCH_2OH$ (17)
$PhCH_3$ (MeCN)	*t*-BuOOH	$PhCH_2OOBu$-*t* (28), PhCH(O) (12)
c-C_6H_{10}	HOOH	R-one (50),[c] epoxide (8), ROH (3)[d]
c-C_6H_{10} (MeCN)	HOOH	ROH (31), R-one (30), epoxide (12), RR (1)
c-C_6H_{10} (MeCN)	*t*-BuOOH	ROOBu-*t* (41), R-one (6), ROH (3), RR (1)
PhH (MeCN)	HOOH	PhOH (34)
c-C_6H_{11}OH (MeCN)	HOOH	c-C_6H_{10}(O) (28)
$PhCH_2OH$ (MeCN)	HOOH	PhCH(O) (40)
PhCH(O) (MeCN)	HOOH	PhC(O)OH (108)
c-PhCH=CHPh (0.65 M)	HOOH	PhCH(O) (87), epoxide (4)
PhC≡CPh	HOOH	PhC(O)C(O)Ph (24)
2,6-$(Me)_2$PhOH	HOOH	2,6-$(Me)_2$Ph(O)$_2$ (5),[e] ROOR (3)
2,6-$(Me)_2$PhOH (MeCN)	*t*-BuOOH	ROOR (9)

[a] Substrates and catalyst [20 mM $Co(bpy)_2^{2+}$] were combined in 7 mL of MeCN/py (4:1 molar ratio) (or MeCN), followed by the slow addition (1–2 min) of either 100 μL of 17.6 M HOOH (50% in H_2O), to give 200 mM HOOH, or 600 μL of 3.0 M *t*-BuOOH (in 2,2,4-trimethylpentane), to give 200 mM *t*-BuOOH. Reaction time and temperature: 6 h at 22 ± 2 °C. [b] The product solutions were analyzed by capillary gas chromatography and GC–MS (either by direct injection of the product solution or by quenching with H_2O and extracting with diethyl ether). [c] Cyclohex-2-ene-1-one. [d] Cyclohex-2-ene-1-ol. [e] 2,6-Dimethyl-*p*-benzoquinone.

Scheme I. Activation of HOOH and *t*-BuOOH by $Co^{II}(bpy)_2^{2+}$



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with a second HOOH to give a dioxygenase reactive intermediate [$(bpy)_2^{2+}Co^{III}OOCo^{III}(bpy)_2^{2+}$, **3**] (Scheme I).

In pure MeCN, species **1** appears to activate HOOH and *t*-BuOOH via formation of 1:1 adducts [$(bpy)_2^{2+}Co^{II}$(HOOH) (**4**) and $(bpy)_2^{2+}Co^{II}$(*t*-BuOOH) (**5**)], which, when formed in the presence of substrates, act as monooxygenases (c-C_6H_{12} → c-C_6H_{11}OH). As such, they are closely similar to the reactive intermediate from the combination of $[Fe^{II}(MeCN)_4](ClO_4)_2$ and HOOH in MeCN.[4,5] The formation of two reactive intermediates [**4**, favored in MeCN, and **3**, favored in MeCN/py] in combination with the product profiles of Table I is the basis for the proposed reaction pathways of Scheme I. Species **3** transforms methylenic carbons (>CH_2) to ketones (>C=O) and dioxygenates aryl olefins and acetylenes, and its precursor (species **2**) epoxidizes aliphatic olefins. Combination of *t*-BuOOH and $Co^{II}(bpy)_2^{2+}$ appears to form intermediates **5** and **6**; species **5** has reactivity similar to that of species **4**, but species **6** is unique and necessary to account for the observed ROOBu-*t* products (Table I).

In summary, the $Co^{II}(bpy)_2^{2+}$/HOOH/(4:1 MeCN/py) system forms a reactive intermediate (**3**) that selectively ketonizes methylenic carbon and, as such, is closely similar to the intermediate of the $Fe^{II}(PA)_2$/HOOH/(2:1 py/HOAc) system[1] and of related systems.[2,3] We believe that the common feature is a stabilized-dioxygen intermediate rather than a hypervalent metal-centered carbon oxidant.[2] The ability of $Fe^{II}(DPAH)_2$ to active O_2 to an intermediate that has the same unique selectivity for hydrocarbon ketonization[6] is further support for a common stabilized-dioxygen reactive complex. Several cobalt-dioxygen complexes exhibit oxygenase reactivity with organic substrates,[7,8] which is consistent with the dioxygen formulation for species **3**.

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New Procedure for the Direct Generation of Titanium Enolates. Diastereoselective Bond Constructions with Representative Electrophiles

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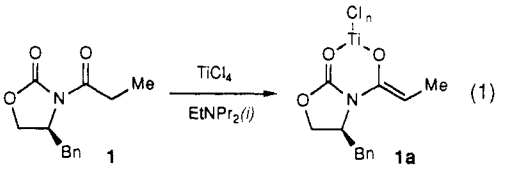
Metal enolates are one of the most valuable families of nucleophiles employed in organic synthesis, and those advances that provide more practical and more selective methods for the enolization of carbonyl compounds continue to be of considerable value to the field. The purpose of this communication is to describe a straightforward procedure for the formation of titanium enolates from the corresponding carbonyl precursors with titanium tetrachloride and a tertiary amine base under mild conditions (CH_2Cl_2, −78 → 0 °C). This method for titanium enolate formation complements related procedures based on transmetalation from alkali-metal enolates[1] or silyl enol ethers[2] while offering the advantage of operational simplicity.

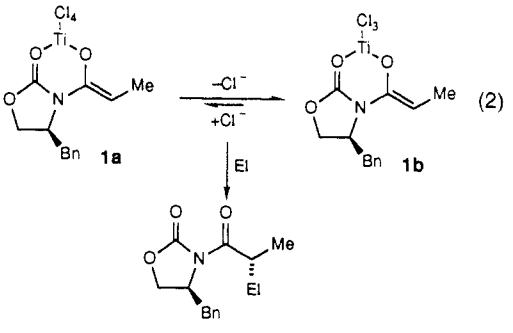
This enolization procedure, which was initially studied in detail for the *N*-propionyloxazolidone **1**,[3] has subsequently been generalized to other substrates. The following discussion reflects this order of development. Successive treatment of a 0.2–0.5 M solution of **1** in CH_2Cl_2 with 1.0 equiv of $TiCl_4$ and then 1.0 equiv of diisopropylethylamine (DIPEA) for 1 h at 0 °C results in the quantitative formation of the characteristic dark-red titanium enolate, as determined by a DCl/D_2O quench (eq 1). It is critical



(1)

that this order of reagent addition is followed so that substrate–$TiCl_4$ complexation (ca. 5 min) precedes the introduction of base. The reaction of uncomplexed $TiCl_4$ with DIPEA leads to irreversible complexation and, as a consequence, no enolization. Other titanium reagents may also effect substrate enolization. Quantitative enolate formation under the above conditions using isopropoxytitanium trichloride (*i*-PrO$TiCl_3$) in place of $TiCl_4$ may also be achieved. Increasing the number of alkoxy substituents on the titanium reagent decreases its enolization potential. For example, $(i\text{-PrO})_2TiCl_2$ and $(i\text{-PrO})_3TiCl$ afforded 70 and 10% enolization of **1**, respectively, with DIPEA under otherwise identical conditions. *A valuable attribute of these alkoxytitanium halides is that both DIPEA and triethylamine (TEA) complex reversibly with all three oxygenated titanium species; as a consequence, the order of reagent addition no longer has to be strictly followed.* For most of the substrates evaluated during the course of this study, DIPEA or TEA may be used interchangeably as the enolization base.

We have not yet unequivocally established the number of halogens associated with the metal center (eq 2); however, we have circumstantial evidence in this and related systems for the ate-complexed enolate **1a** rather than the expected trichlorotitanium enolate **1b**. Nonetheless, in reactions with most electrophiles, the stereochemical outcome is consistent with the presence of a chelated (*Z*) enolate and is the same as that observed with the analogous alkali-metal enolates previously described by us.[4]



(2)

Representative reactions of the titanium enolates derived from five carbonyl substrates and a selection of electrophiles are provided in Table I. The enolate derived from *N*-propionyloxazolidone **1** undergoes reaction with alkyl halides with a predisposition toward S_N1 reactivity (entry A).[5] Orthoesters and acetals (entries B and C) are also exceptionally good substrates. These enolates

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