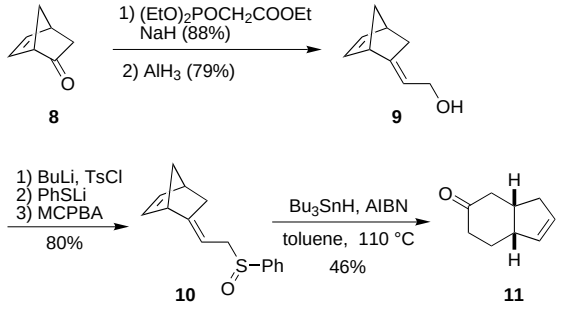
the radical oxy-Cope rearrangement.[17] For this purpose, the sulfoxide **10** was prepared from norbornenone **8** via the allylic alcohol **9** (the direct synthesis with the procedure of Evans et al. does not work in this particular case). By treating the sulfoxide **10** with Bu_3SnH and azobisisobutyronitrile (AIBN) in refluxing toluene, the desired rearranged compound **11** is obtained in an unoptimized 46% yield (Scheme 3). This reaction consists of a sequence of a [2,3]-sigmatropic rearrangement followed by generation of an allyloxyl radical, regioselective fragmentation to an allyl radical, and finally a 6-*endo* cyclization.[17]



Scheme 3. Radical oxy-Cope rearrangement.[17] MCPBA = *meta*-chloroperbenzoic acid.

In conclusion, we have demonstrated that allylsulfoxides, which are easily available from ketones, are suitable precursors for allyloxyl radicals. An unique method for the two-carbon ring expansion of cyclobutanones has been developed based on a sequential radical-chain reaction. To the best of our knowledge, this is the first cascade process in which the radical precursor is continuously generated in an equilibrium reaction as a minor component of the reaction mixture. The stability of the sulfoxide radical precursors and the mild reaction conditions of the ring expansion renders this reaction attractive for preparative purposes. The control of the regioselectivity of the process requires a proper design of the system. Extension of this reaction to other ring sizes and more complexed systems is currently under investigation.

Experimental Section

General procedure for the radical ring expansion: A solution of Bu_3SnH (0.49 mL, 1.84 mmol) and AIBN (10 mg, 0.06 mmol) in C_6H_6 (3 mL) was added over 12 h with a syringe pump to a refluxing solution of the allylic sulfoxide (1.23 mmol) in C_6H_6 (123 mL, 0.01M). (For sulfoxide **1e**, better results were obtained when irradiation with a 300-W sunlamp was performed during the reaction.) The solvent was removed under reduced pressure and the crude product was purified by flash chromatography.

2c: From **1c** (300 mg, 1.23 mmol), flash-column chromatography (EtOAc/hexane) afforded **2c** (112 mg, 67%) as a colorless oil. IR (film): $\tilde{\nu} = 3050$, 2930, 2360, 1720, 1450, 1410, 1230 cm^{-1}, ^1H NMR (360 MHz, $CDCl_3$): $\delta =$ 5.72 (m, 1H; C*H* = CH), 5.54 (m, 1H; CH = C*H*), 3.15 (m, 1H; 3a-H), 2.66–2.79 (m, 1H; 1-H), 2.49–2.65 (m, 2H; 7a-H, 4-H), 2.1–2.36 (m, 4H; 2 × 6-H, 1-H, 4-H), 1.93–2.03 (m, 1H; 7-H), 1.65–1.76 ppm (m, 1H; 7-H); ^{13}C NMR (90.5 MHz, $CDCl_3$): $\delta = 213.7$ (s), 133.3 (d), 130.2 (d), 43.2 (d), 42.4 (t), 39.6 (t), 37.5 (t), 33.6 (d), 27.1 (t). MS (EI): *m/z* (%): 136 (53) [M^+], 79 (100); HRMS (EI-MS) for $C_9H_{12}O$ ([M^+]): calcd 136.08826; found 136.08836.

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Low-Temperature Stopped-Flow Studies on the Reactions of Copper(II) Complexes and H_2O_2: The First Detection of a Mononuclear Copper(II)–Peroxo Intermediate**

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Mononuclear copper-active oxygen complexes are key reactive intermediates in many biological and catalytic oxidation processes.[1–4] Aliphatic hydroxylation by O_2 is accomplished at the mononuclear copper-active sites in dopamine β-hydroxylase (DβH) and peptidylglycine α-amidating monooxygenase (PAM), and the oxidative modifications of tyrosine to 2,4,5-trihydroxyphenylalanine quinone (TPQ) and lysine tyrosylquinone (LTQ) cofactors are per-

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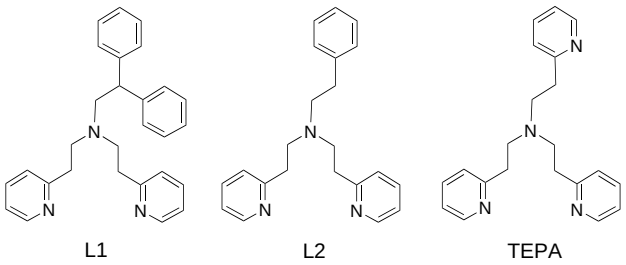
formed with the aid of cupric ions in the active sites of copper-containing amine oxidases and lysyl oxidase, respectively.[4,5] In these reactions, mononuclear Cu^{II}–hydroperoxo and/or Cu^{II}–peroxo species have been invoked as the active oxygen intermediates that participate in aliphatic and aromatic hydroxylation reactions.[4,5] To assess such intermediates, much effort has been made to develop metastable mononuclear copper model compounds. Thus, Cu^{II}–hydroperoxo complexes have been prepared by the reactions of copper(II) precursors and H_2O_2,[6–9] and mononuclear Cu^{II}–superoxo exhibiting either end-on (η^1-superoxo) or side-on (η^2-superoxo) binding mode have been prepared from the reactions of copper(I) complexes and O_2.[10–13] Although these studies have provided profound insights into the structure and spectroscopic features of the hydroperoxo and superoxo complexes, no information is presently available about mononuclear Cu^{II}–peroxo species.

Herein, low-temperature stopped-flow studies are described for the reactions of copper(II) complexes supported by tridentate ligands (L1 and L2) with H_2O_2 to demonstrate that a mononuclear Cu^{II}–peroxo complex is generated from an initially formed Cu^{II}–hydroperoxo intermediate [Eqs. (2) and (3)].[14] The results represent the first example of the direct detection of a mononuclear Cu^{II}–peroxo complex, which provides important information about the reactive intermediates involved in biological and industrial oxidation processes.



The reactions of copper(II) complexes with H_2O_2 were studied using a multi-scan double mixing stopped-flow spectrophotometer at −90 °C in methanol. Figure 1 shows a UV/Vis absorption spectral change for the first rapid process ($t = 0$–60 ms) of the reaction of $[Cu^{II}(L1)(ClO_4)_2]$ (0.2 mM), which contains the tridentate L1 ligand, and H_2O_2 (2.0 mM) in the presence of triethylamine (2.0 mM), where an absorption band at 360 nm ($\varepsilon = 2280\,M^{-1}\,cm^{-1}$) quickly appeared (spectrum (a)). The reaction obeys first-order kinetics, as shown in the inset of Figure 1, and a plot of the first-order rate constant $k_{obs(1)}$ against the concentration of H_2O_2 (2–10 mM) at a fixed concentration of triethylamine (2.0 mM) gave a Michaelis–Menten type saturation curve (as shown in Figure S1 in the Supporting Information). A similar saturation curve was obtained when the triethylamine concentration was increased from 2 to 10 mM at a fixed concentration of H_2O_2 (2.0 mM, Figure S2 in the Supporting Information). These kinetic results can be explained by the reaction sequences shown in Equations (1) and (2), where the counter anions (ClO_4^-) are omitted for simplicity.

Under the reaction conditions described above, the kinetic equation can be given as $k_{obs(1)} = (k_1 K_1[H_2O_2][Et_3N])/(K_1[H_2O_2] + 1)$ in the presence of excess H_2O_2 (for Figure S1 in the Supporting Information) and as $k_{obs(1)} = (k_1 K_1[H_2O_2][Et_3N])/(K_1[Et_3N] + 1)$ in the presence of excess Et_3N (for Figure S2 in the Supporting Information). Double reciprocal plots in both cases gave straight lines as shown in the insets of the respective figures from which the acid/base equilibrium constant K_1 and the rate constant k_1 have been determined as $7.2 \pm 0.5 \times 10^2\,M^{-1}$ and $4.1 \pm 0.3 \times 10^4\,M^{-1}\,s^{-1}$ from Figure S1, and $7.7 \pm 0.4 \times 10^2\,M^{-1}$ and $4.0 \pm 0.3 \times 10^4\,M^{-1}\,s^{-1}$ from Figure S2, respectively. The good agreement in the K_1 and k_1 values, determined independently from the rate dependence on $[H_2O_2]$ and $[Et_3N]$, strongly support the accuracy of the proposed mechanism shown in Equations (1) and (2).

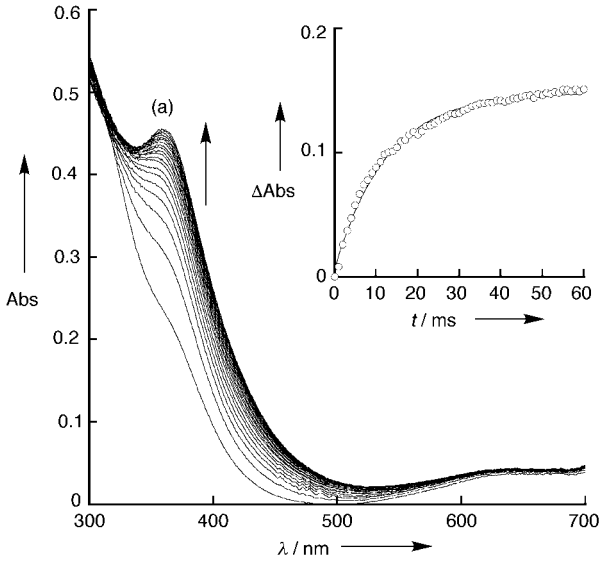


Figure 1. UV/Vis absorption spectra illustrating the first 60 ms of the reaction of $[Cu^{II}(L1)(ClO_4)_2]$ (0.2 mM) with H_2O_2 (2.0 mM) in the presence of triethylamine (2.0 mM) in CH_3OH at −90 °C. Inset: The change in absorption at 360 nm from $t = 0$–60 ms and its fit to a first-order model.

$$H_2O_2 + Et_3N \underset{}{\overset{K_1}{\rightleftharpoons}} HO_2^- Et_3NH^+ \quad (1)$$

$$[LCu^{II}]^{2+} + HO_2^- Et_3NH^+ \xrightarrow{k_1} [LCu^{II}\text{–}OOH]^+ + Et_3NH^+ \quad (2)$$

(A)

The reaction of $[Cu^{II}(TEPA)(ClO_4)](ClO_4)$, which contains the tetradentate tris[2-(2-pyridyl)ethyl]amine (TEPA) ligand, and H_2O_2 under the same experimental conditions also gave an intermediate that exhibited a similar absorption spectrum ($\lambda_{max} = 332$ nm, $\varepsilon = 4240\,M^{-1}\,cm^{-1}$, Figure S3 in the Supporting Information), and also similar kinetic behavior ($K_1 = 7.6 \pm 0.4 \times 10^2\,M^{-1}$ and $k_1 = 8.2 \pm 0.4 \times 10^2\,M^{-1}\,s^{-1}$, and $K_1 = 8.3 \pm 0.4 \times 10^2\,M^{-1}$ and $k_1 = 7.9 \pm 0.4 \times 10^2\,M^{-1}\,s^{-1}$ from Figures S4 and S5, respectively, in the Supporting Information) as the reactions described above for the complex with the L1 ligand. Moreover, the λ_{max} and ε values in the UV/Vis spectra, as well as the resonance Raman band at 851 cm^{-1} (Figure S6 in the Supporting Information)[15] of the intermediate are fairly close to those for the reported mononuclear Cu^{II}–hydroperoxo complexes supported by other tetradentate pyridine ligands.[7–9] All of the spectroscopic features, as well as the

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good agreement in the K_1 values between the TEPA and L1 ligand systems ($K_1 = 7.2–7.9 \times 10^2\,M^{-1}$) indicate that the initially formed intermediates for both the tridentate and tetradentate ligand systems involve an η^1-OOH group, as shown in Equation (2).

Notably, the product resulting from the Cu^{II}–hydroperoxo intermediate of L1 was totally different from that resulting from the TEPA complex. The hydroperoxo intermediate (**A**) supported by TEPA was converted into the corresponding copper(I) complex, $[Cu^{I}(TEPA)]^+$ ($k_{obs(2)} = 0.19 \pm 0.1\ s^{-1}$),[16] whereas the hydroperoxo species supported by L1 readily gave a mononuclear Cu^{II}–peroxo intermediate (**B**) as demonstrated below.

The Cu^{II}–OOH intermediate **A** further reacted in the next timeframe ($t = 100$ ms–1.5 s) to give the spectral change shown in Figure 2, where the absorption band of intermediate **A** (spectrum (a)) further increased to give spectrum (b) with $\lambda_{max} = 366$ nm ($\varepsilon = 3110\,M^{-1}cm^{-1}$). The observed first-order rate constant ($k_{obs(2)} = 1.6 \pm 0.1\ s^{-1}$) of this process was independent of both $[H_2O_2]$ and $[Et_3N]$ (Figures S7 and S8), which indicates that an intramolecular reaction of the mononuclear hydroperoxo intermediate **A** is involved. The position of the peak maximum in spectrum (b) of Figure 2 is consistent with that of the reported (μ-η^2:η^2-peroxo)dicopper(II) complexes, but the absorption intensity (ε) is significantly smaller than that of the reported dinuclear copper(II) peroxo complexes.[17,18] Furthermore, an ESR spectrum of a copper(II) complex with a $d_{x^2-y^2}$ ground state (spectrum (b) in Figure S9 in the Supporting Information) was recorded in the early stage of the reaction. This spectrum differed from that of the starting material (spectrum (a) in Figure S9). In addition, a similar absorption spectrum was obtained in the reaction of $[Cu^{II}(L2)(ClO_4)_2]$ with H_2O_2 under the same experimental conditions ($\lambda_{max} = 362$ nm, $\varepsilon = 4880\,M^{-1}cm^{-1}$), although the Cu^{II}–OOH intermediate of L2 was too reactive to be detected. Based on these results, together with the totally different reaction patterns of intermediate **A** in the tridentate and tetradentate ligand systems, we tentatively assigned the second intermediate observed in Figure 2 as a mononuclear Cu^{II}–peroxo complex (**B**), presumably having a side-on binding mode, as indicated in Equation (3).

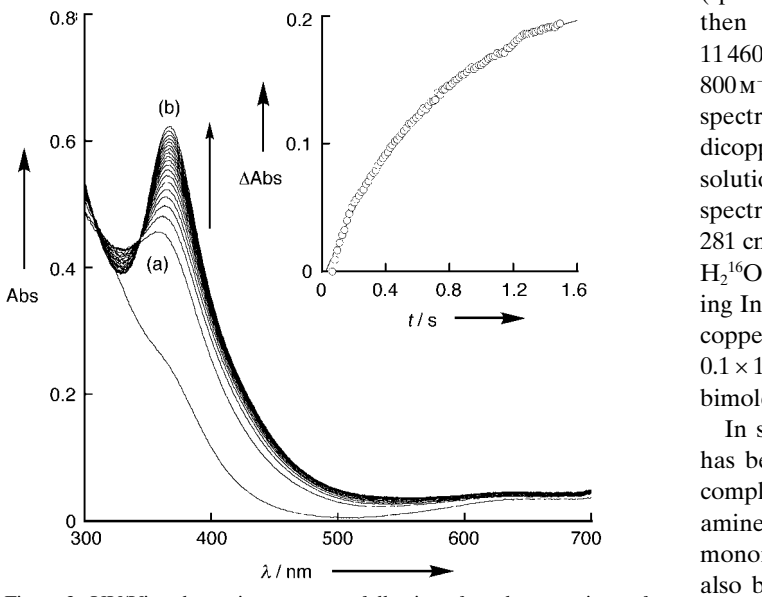

Figure 2. UV/Vis absorption spectra following for the reaction of $[Cu^{II}(L1)(ClO_4)_2]$ (0.2 mM) with H_2O_2 (2.0 mM) in the presence of triethylamine (2.0 mM) in CH_3OH at −90 °C from $t = 0.1$–1.5 s. Inset: The change in absorption at 366 nm from $t = 0.1$–1.5 s and its fit to a first-order model.

$$\underset{\textbf{(A)}}{LCu^{II}\text{-}OOH} \xrightarrow{k_2} \underset{\textbf{(B)}}{LCu^{II}(O_2)} \xrightarrow{k_3[Cu^{II}(L)]} \underset{\textbf{(C)}}{LCu^{II}(O_2)Cu^{II}L} \qquad (3)$$

The lack of rate-dependence on $[Et_3N]$ in the $k_{obs(2)}$ process (Figure S8) may suggest that internal rearrangement of the ligand framework from the η^1-hydroperoxo motif (**A**) to an η^2-hydroperoxo form (**A′**, a side-on hydroperoxo binding mode, not shown in Equation (3)) is rate-determining, while the following deprotonation from **A′** to give **B** is much faster. The higher reactivity of intermediate **A** for ligand L2, as compared to that of L1, can be attributed to the relative steric bulk of the *N*-alkyl substituents (-CH_2CHPh_2 in L1 versus -CH_2CH_2Ph in L2). The larger *N*-alkyl group in L1 may retard the rearrangement of the monodentate η^1-hydroperoxo ligand in **A** to the bidentate η^2-hydroperoxo ligand in **A′**, which stabilizes intermediate **A** in the L1 complex more strongly than in the L2 system. Furthermore, this process is completely prohibited in the case of the tetradentate TEPA ligand system, since there is no extra coordination site available for formation of side-on (hydro)peroxo intermediate(s). Thus the kinetic results, as well as the ligand effects of L2 and TEPA, are all consistent with formation of the proposed side-on peroxo intermediate **B**.

Intermediate **B** was further converted into a (μ-η^2:η^2-peroxo)dicopper(II) complex (**C**) at higher concentrations of the copper complex. Thus, the reaction of $[Cu^{II}(L1)(ClO_4)_2]$ (2.0 mM) with H_2O_2 (2.0 mM) in the presence of triethylamine (2.0 mM) in methanol at −90 °C gave absorption spectra where the peak for intermediate **B** immediately appeared (spectrum b in Figure S10 in the Supporting Information), and then the characteristic absorption band at 366 nm ($\varepsilon = 11\,460\,M^{-1}cm^{-1}$) together with a small band at 540 nm ($\varepsilon = 800\,M^{-1}cm^{-1}$) gradually developed (spectrum (c)). The final spectrum is nearly the same as that of the (μ-η^2:η^2-peroxo)-dicopper(II) complex supported by L2,[18] and the resulting solution was ESR-silent. Furthermore, the resonance Raman spectrum of the product exhibits Raman bands at 741 and 281 cm^{-1}, the former of which is shifted to 700 cm^{-1} when $H_2{}^{16}O_2$ is substituted with $H_2{}^{18}O_2$ (Figure S11 in the Supporting Information).[19] The formation of the (μ-η^2:η^2-peroxo)dicopper(II) complex obeys second-order kinetics ($k_3 = 2.6 \pm 0.1 \times 10^2\,M^{-1}s^{-1}$), which demonstrates that this reaction is a bimolecular process, with respect to the copper(II) complex.

In summary, the low-temperature stopped-flow technique has been applied to study the reactions between copper(II) complexes of the tridentate and tetradentate pyridylethylamine ligands and H_2O_2, which has enabled us to detect a mononuclear Cu^{II}–peroxo complex for the first time. It has also been found that the ligand denticity (tridentate versus tetradentate) and the steric effects of the *N*-alkyl substituents in the pyridylethylamine derivatives drastically alter the reactivity of the initially formed Cu^{II}–hydroperoxo intermedi-

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ates. These results provide significantly important information about the dioxygen-activation mechanism in biological and industrial systems.

Experimental Section

Synthetic procedures of ligands L2 and TEPA, as well as the copper(II) complex of L2 have been reported elsewhere.[18,20]

L1: 2,2-Diphenylethylamine (1.97 g, 10 mmol) and 2-vinylpyridine (5.25 g, 50 mmol) were heated to reflux in CH_3OH (20 mL) containing acetic acid (3.01 g, 50 mmol) for 10 days. The solvent was removed by evaporation, and the resulting viscous material was dissolved in H_2O (200 mL) and extracted with $CHCl_3$ (3×200 mL). After drying over anhydrous K_2CO_3, evaporation of the organic solvent gave yellow oily material, from which L1 was isolated by SiO_2 column chromatography ($CHCl_3$/AcOEt as eluent) in 54% yield (2.21 g); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.76$–2.96 (m, 8H; -CH_2-CH_2-Py), 3.16 (d, $J = 7.5$ Hz, 2H; -CH_2-CH-Ph_2), 4.09 (t, $J = 7.5$ Hz, 1H; -CH-Ph_2), 6.76 (d, $J = 7.8$ Hz, 2H; $H_{py\text{-}5}$), 7.03–7.26 (m, 12H; C_6H_4 and $H_{py\text{-}3}$), 7.43 (td, $J = 1.8$ and 7.8 Hz, 2H; $H_{py\text{-}4}$), 8.50 ppm (ddd, $J = 0.9$, 1.8, and 4.8 Hz, 2H; $H_{py\text{-}6}$); FAB-HRMS (positive ion): calcd for $C_{28}H_{29}N_3$: m/z 406.2283; found: m/z 406.2289 [M^+].

$[Cu^{II}(L1)(ClO_4)_2]\cdot H_2O$: Ligand L1 (122.3 mg, 0.3 mmol) was treated with $Cu^{II}(ClO_4)_2\cdot 6H_2O$ (111.2 mg, 0.3 mmol) in CH_3OH (10 mL) for 30 min at room temperature. Addition of Et_2O (200 mL) to the mixture gave blue solids that were isolated by decantation, washed three times with Et_2O, and dried (83% yield). Single crystals were obtained by vapor diffusion of Et_2O into a solution of the complex in CH_3OH. FTIR (KBr): $\tilde{\nu} = 1130$, 1043, 621 cm^{-1} (ClO_4^-); FAB-MS (positive ion): m/z 569.2 [M^+]; elemental analysis for $[Cu^{II}(L1)(ClO_4)_2]\cdot H_2O$, calcd (%) for $C_{28}H_{31}O_9N_3CuCl_2$: C 48.88, H 4.54, N 6.11; found: C 48.72, H 4.48, N 6.06.

$[Cu^{II}(TEPA)(ClO_4)]ClO_4$: The TEPA ligand (332.5 mg, 1.0 mmol) was treated with $Cu^{II}(ClO_4)_2\cdot 6H_2O$ (370.5 mg, 1.0 mmol) in CH_3CN (10 mL) for 30 min at room temperature. Addition of Et_2O (200 mL) to the mixture gave a blue oily material that was isolated by decantation and redissolved into CH_3OH (10 mL). Addition of the CH_3OH solution into Et_2O (200 mL) gave blue solids that were isolated by decantation, washed with Et_2O three times, and dried (95% yield). Single crystals were obtained by vapor diffusion of Et_2O into a solution of the complex in CH_3OH. FTIR (KBr): $\tilde{\nu} = 1143$, 1081, 625 cm^{-1} (ClO_4^-); FAB-MS (positive ion): m/z 494.07 [M^+]; elemental analysis for $[Cu^{II}(TEPA)(ClO_4)](ClO_4)$, calcd (%) for $C_{21}H_{28}O_8N_4CuCl_2$: C 39.98, H 4.47, N 8.88; found: C 40.18, H 4.16, N 8.87.

Caution! The perchlorate salts in this study are all potentially explosive and should be handled with care.

Kinetic measurements for the reaction of copper(II) complexes (0.2 mM) and H_2O_2 were performed by using a multi-scan double mixing stopped-flow spectrophotometer designed for low-temperature measurements (RSP-1000, Unisoku Co., Ltd.) in CH_3OH at $-90\,^\circ$C. The reaction of $[Cu^{II}(L1)(ClO_4)_2]$ and H_2O_2 at the higher concentration (Figure S10 in the Supporting Information) was followed using the previously reported[18] Hewlett Packard HP8453 diode array spectrophotometer with a Unisoku thermostated cell holder designed for low-temperature measurements.

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Indenol Ether Formation from Aryl Alkynes Bearing *ortho*-Acetals: An Unprecedented Rearrangement in Palladium-Catalyzed Carboalkoxylation

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The catalytic addition reaction to a C–C multiple bond is one of the most important processes for organic synthesis, because this process can construct new chemical bonds in an efficient and atom-economic manner. A wide variety of transition-metal-catalyzed (TM-catalyzed) addition reactions of pronucleophiles (H–CR_3,[1] H–NR_2,[2] H–OR,[3] H–OC(O)R,[4] H–SR,[5] H–PR_2,[6] etc.) and hydrides (H–B,[7]

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