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Photoactivated artificial metalloesterases

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Abstract

A photoactivated metalloesterase has been developed. The alcohol is masked as an ester that is covalently attached to either a bi- or tridentate ligand. Yields of alcohol of up to 86% are achieved upon photolysis at $\lambda > 350$ nm. The masked alcohol undergoes *cis–trans* photoisomerization that brings the ester carboxyl into proximity with a Lewis-acidic metal ion. The metal ion catalyzes the hydrolysis of the ester bond, resulting in release of an alcohol and a coordinated carboxylate. The presence of a metal cation is sufficient to drive the *cis–trans* photostationary state completely to the *cis* (coordinating) isomer, in contrast to the 1:1 *cis*:*trans* ratio formed at the photostationary state in the absence of metal. The photorelease of the alcohol is most efficient when only one ligand is bound to the metal. The synthesis, characterization and photochemistry of the ligands are described and the implications of metal–ligand equilibria on the reaction is discussed.

Keywords: Photolabile protecting group; Photoisomerization; Metalloesterase

1. Introduction

The use of photolabile covalent bonds to "cage" molecules that can then be released photochemically is of great interest in the chemical and biological communities [1,2]. An advantage of this technology is the temporal and spatial control it allows in the behavior of the molecule. Caged molecules have been used extensively in the investigation of biochemical pathways and mechanisms, such as calcium uptake or the behavior of neurotransmitters [3]. They are also used as protecting groups in organic synthesis [4]. Many functional groups have been photoreversibly caged including alcohols [5], carboxylic acids [6], phosphates [7], amines [8] and aldehydes [9]. When used in biological applications, it is important that the excitation wavelength be at as long a wavelength as possible to avoid the many chromophores present in biological tissue and to prevent indiscriminant photodamage to such tissue. Metals are widely used in nature to cleave phosphate esters and peptide bonds either using metal-activated aquo nucleophiles or by Lewis-acid activation of carbonyl groups [10–13]. The design of artificial analogs of natural metalloproteases and nucleases is an area of intense activity in recent years [14–16].

In an ongoing search for new methods of photoreleasing molecules, we have recently investigated photoactive metal complexes with the aim of combining artificial metalloprotease/nuclease chemistry with a chromophore to allow photoactivated metal-catalyzed bond cleavages. The result is a new type of chemistry for releasing an alcohol masking group that combines Lewis-acid catalysis with photoactivation. The molecules described below meet the criteria of releasing an alcohol only when both a metal ion and light are present; neither metal nor light alone results in release of the masked alcohol. This provides two elements of control for the release of the desired compound and, therefore, greater control over that release. We envisioned masking the alcohol as an ester and separating the carboxyl group from the metal active site by a rigid *trans* alkene. Photoisomerization of the alkene would then bring the metal center and carboxyl together and accelerate hydrolysis, as shown in Fig. 1 [1]. This concept was realized in a masked alcohol covalently attached to a ligand such that the alcohol was released only when the ligand was exposed to both metal and light. The desired alcohol could be obtained in as much as 86% yield. We report the results of ligand synthesis, photochemistry and binding titrations and put forward a mechanistic hypothesis that explains the results. This work sets the foundation for

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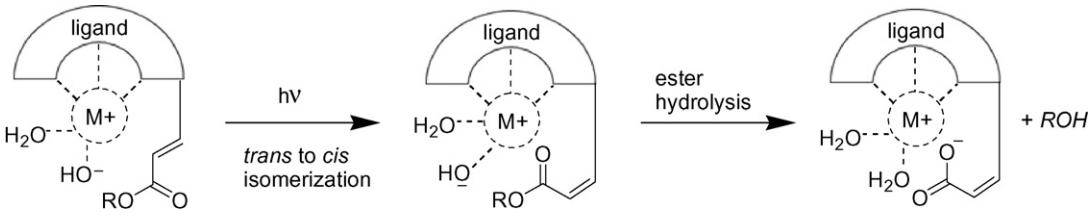


Fig. 1. Proposed plan for photoactivatable metalloesterase. The identity of the metal and ionization state of the aquo ligands are discussed below.

further development of a new strategy for release of masked alcohols.

2. Experimental

2.1. General methods

All reagents and solvents were purchased from commercial sources or prepared as described in the following pages. Melting points were determined with a Mel-Temp II instrument and are reported uncorrected. Thin layer chromatography was performed on silica gel or basic alumina (250 μm thick aluminum or plastic-backed plates doped with fluorescein). The chromatograms were visualized with UV light (254 or 365 nm). Column chromatography was carried out with silica gel (60 Å) or basic alumina (150 mesh, Brockmann I, 58 Å). ^{1}H and ^{13}C NMR spectra were performed on a Bruker Avance 300 or 500 MHz NMR spectrometer (as indicated). Photochemical reactions were conducted with either a 450 W medium pressure Hg vapor lamp with a uranium oxide doped glass filter (366 nm) or in a Rayonet reactor equipped with 16 Hg vapor lamps (350 nm). UV–vis spectra were obtained on a HP 8453 scanning spectrometer. Elemental analyses were performed by Atlantic Microlab, Norcross, GA. HRMS analysis was performed at Old Dominion University, Norfolk, VA. The samples were dissolved in 1:1:1 THF:MeOH:MeCN with NaCl and were analyzed by positive ion electrospray on a Bruker 12T Apex-Qe FTICR-MS with an Apollo II source.

2.1.1. 1,10-Phenanthroline benzyl ester (**2**)

0.50 g 1,10-phenanthroline-2-carbaldehyde [17] (**1**) (2.4 mmol), 1.08 g $Ph_3P{=}CHCO_2CH_2Ph$ (2.6 mmol), and 100 mL dry benzene were refluxed under argon for 15 h. The crude mixture was concentrated under vacuum and chromatographed on silica gel (7% acetone in $CHCl_3$), yielding 0.82 g tan solid (99.3%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (dd, 1H, J = 1.6 Hz, J = 4.3 Hz), 8.26 (m, 3H), 7.89 (d, 1H, J = 8.3 Hz), 7.79 (d, 2H, J = 1.5 Hz), 7.64 (dd, 1H, J = 4.3 Hz, J = 8.0 Hz), 7.41 (m, 5H), 7.05 (d, 1H, J = 16.1 Hz), 5.30 (s, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 153.3, 150.4, 146.0, 145.9, 145.1, 136.6, 136.0, 135.7, 128.9, 128.5, 128.4, 128.1, 127.3, 126.0, 123.3, 123.1, 121.2, 66.4 ppm. λ_{max} (MeOH) 292, 358 nm. MP = 114–116 °C. HRMS calculated for $C_{22}H_{16}N_2O_2Na^+$: 363.110399. Found: 363.110620.

2.1.2. 2-(2′-Pyridyl-6-methyl)-1,10-phenanthroline (**5**)

4.6 mL 2-bromo-6-methyl pyridine [18] (40.2 mmol) in 75 mL dry THF was chilled over dry ice and acetone to −78 °C at which point 26.0 mL *n*-BuLi (1.6 M in hexanes, 41.6 mmol) was added dropwise. After stirring 15 min, the red lithiate was cannulated into a 0 °C solution of 5.00 g 1,10-phenanthroline (27.7 mmol) in 75 mL dry THF. The dark solution was allowed to stir for 3 h at which point 400 mL bleach and 150 mL THF were added. The biphasic solution was stirred vigorously overnight [19]. The dark organic solution was washed with 2× 100 mL H_2O, 200 mL brine, dried over $MgSO_4$, and was concentrated under vacuum. The product was purified by column chromatography (basic alumina, three acetone:seven hexanes). Evaporation of solvent gave 4.04 g light yellow crystals (53.6%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (dd, 1H, J = 1.8 Hz, J = 4.4 Hz), 8.87 (d, 1H, J = 8.4 Hz), 8.79 (d, 1H, J = 7.8 Hz), 8.36 (d, 1H, J = 8.4 Hz), 8.27 (dd, 1H, J = 1.7 Hz, J = 8.1 Hz), 7.81 (m, 3H), 7.65 (dd, 1H, J = 4.4 Hz, J = 8.1 Hz), 7.23 (d, 1H, J = 7.6 Hz), 2.69 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 156.2, 155.1, 149.9, 146.0, 145.3, 136.7, 136.4, 135.7, 128.6, 128.3, 126.2, 126.1, 123.3, 122.4, 120.5, 119.4, 24.3 ppm. MP = 164–166 °C. Analysis calculated for $C_{18}H_{13}N_3$: C 79.68, H 4.83, N 15.49. Found: C 79.87, H 4.95, N 15.30.

2.1.3. 2-(2′-Pyridyl-6-carboxaldehyde)-1,10-phenanthroline (**6**)

9.44 g (34.8 mmol) of compound (**5**) was dissolved in 350 mL DMSO. 17.66 g I_2 (69.6 mmol) was then added, changing the solution from clear yellow to dark brown and the solution was allowed to stir 5 min. 8.6 mL *t*-BuI (2-iodo-2-methylpropane, 72.0 mmol) was added followed by a slow addition of 7.24 mL trifluoroacetic acid (97.44 mmol). The solution was heated to reflux for 66 h. After cooling down, a solution of 63 g sodium thiosulfate heptahydrate (0.28 mol) in 200 mL H_2O was added slowly. The black precipitate was filtered off and 400 mL saturated aqueous $NaHCO_3$ was introduced carefully bringing the pH to 9 [14]. The brown precipitate of product was filtered and re-dissolved in hot $CHCl_3$. The filtrate was extracted with $CHCl_3$. The $CHCl_3$ layers were combined, washed with 4× 200 mL H_2O, dried over $MgSO_4$, and concentrated. 7.62 g light brown solid was obtained (77%). The aldehyde moves on silica gel with 20% MeOH in acetone and 2% triethylamine. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.25 (s, 1H), 9.28 (m, 2H), 8.98 (d, 1H, J = 8.40 Hz), 8.45 (d, 1H, J = 8.41 Hz), 8.31 (dd, 1H, J = 8.08 Hz, J = 1.55 Hz), 8.09 (m, 2H), 7.89 (m, 2H), 7.69 (dd, 1H, J = 4.3 Hz) ppm [8]. ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.6, 156.6, 154.9, 152.2, 150.4, 146.2, 145.7, 138.0, 137.2, 136.3, 129.1, 127.2, 126.8, 126.5, 123.1, 121.9, 120.8 ppm. MP = 209–211 °C. HRMS calculated for $C_{18}H_{11}N_3ONa^+$: 308.079433. Found: 308.079996.

*2.1.4. General procedure for Horner–Emmons olefination of 6. Pyr-phen ethyl ester (**8a**)*

5.0 g (17.5 mmol) of aldehyde (**6**) was dissolved in 150 mL anhydrous DMF and 100 mL dry THF. 0.73 g (18.2 mmol) NaH (60% dispersion in mineral oil) was dissolved in 50 mL dry THF and was added slowly to a solution of 3.19 mL triethyl phosphonoacetate (15.9 mmol) dissolved in 50 mL dry THF. The anionic solution was added dropwise to the stirring solution of aldehyde and the reaction was allowed to stir for 3 h at room temperature. Two hundred milliliters of saturated aqueous NH_4Cl solution was added, bringing the pH to 9.5. Two hundred milliliters of H_2O and 200 mL CH_2Cl_2 were added and the solution was phase separated. The aqueous layer was extracted with 3× 200 mL CH_2Cl_2. The organics were washed with 3× 200 mL H_2O and 2× 200 mL brine. The material was then dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude material was chromatographed on silica gel (8:2 acetone:hexanes, 2% triethylamine), followed by crystallization of the product-containing fractions, yielding 3.54 g tan solid (57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (d, 1H, J = 4.23 Hz), 9.03 (d, 1H, J = 9.24 Hz), 8.93 (d, 1H, J = 8.39 Hz), 8.37 (d, 1H, J = 8.41 Hz), 8.27 (d, 1H, J = 8.02 Hz), 7.94 (t, 1H, J = 7.7 Hz), 7.81 (m, 3H), 7.66 (dd, 1H, J = 7.98 Hz, J = 4.36 Hz), 7.48 (d, 1H, J = 7.58 Hz), 7.16 (d, 1H, J = 15.6 Hz), 4.33 (q, 2H, J = 7.11 Hz), 1.38 (t, 3H, J = 7.13 Hz) ppm. MP = 163–166 °C. ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 156.0, 155.5, 151.8, 150.3, 146.1, 145.4, 143.2, 137.6, 136.8, 136.1, 128.8, 126.8, 126.4, 124.6, 123.2, 122.8, 122.2, 120.8, 60.6, 14.2 ppm. HRMS calculated for $C_{22}H_{17}N_3O_2Na^+$: 378.121298. Found: 378.122124.

*2.1.5. Pyr-phen benzyl ester (**8b**)*

Using the procedure for **8a**, 2.00 g (7.01 mmol) of aldehyde (**6**) and 1.90 g (6.64 mmol) benzyl diethylphosphonoacetate (**7**) were combined to give **8b**. The crude product was chromatographed on silica gel (8:2 acetone:hexanes + 2% TEA). The white powdery product (1.70 g, 61% yield) was obtained by recrystallization from hot CH_2Cl_2 and hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (m, 1H), 9.03 (d, 1H, J = 7.91 Hz), 8.95 (d, 1H, J = 8.41 Hz), 8.40 (d, 1H, J = 8.43 Hz), 8.29 (dd, 1H, J = 8.05 Hz, 1.45 Hz), 7.89 (m, 4H), 7.69 (dd, 1H, J = 8.08 Hz, 4.38 Hz), 7.43 (m, 6H), 7.23 (d, 1H, J = 15.5 Hz), 5.32 (s, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 156.1, 155.6, 151.7, 150.3, 146.2, 145.5, 143.9, 137.7, 136.9, 136.1, 135.9, 128.9, 128.5, 128.2, 126.8, 126.5, 124.8, 123.3, 122.9, 121.9, 120.9, 66.5 ppm. λ_{max} (MeOH) 326, 366 nm. MP = 143–144 °C. HRMS calculated for $C_{27}H_{19}N_3O_2Na^+$: 440.136948. Found: 440.137390.

*2.1.6. Pyr-phen L-(−) menthyl ester (**8f**)*

Using the procedure for **8a**, 0.98 g (3.43 mmol) of aldehyde (**6**) and 1.10 g (3.29 mmol) of phosphonate (**10**) were combined to give **8f**. The crude product was chromatographed on silica gel (1:1 acetone:hexanes + 2% TEA) and recrystallized from hot acetone and water, yielding 0.68 g tan solid (44% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (dd, 1H, J = 4.37 Hz, J = 1.70 Hz), 9.02 (dd, 1H, J = 8.00 Hz, J = 0.75 Hz), 8.97 (d, 1H, J = 8.40 Hz), 8.41 (d, 1H, J = 8.43 Hz), 8.29 (dd, 1H, J = 8.05 Hz, J = 1.71 Hz), 7.91 (m, 3H), 7.79 (d, 1H, J = 15.50 Hz), 7.67 (dd, 1H, J = 8.05 Hz, J = 4.38 Hz), 7.50 (d, 1H, J = 7.63 Hz), 7.16 (d, 1H, J = 15.60 Hz), 4.89 (td, 1H, J = 10.86 Hz, J = 4.37 Hz), 2.11 (m, 1H), 2.05 (m, 1H), 1.74 (m, 2H), 1.51 (m, 2H), 1.13 (m, 2H), 0.94 (d, 7H, J = 8.04 Hz), 0.82 (d, 3H, J = 6.94 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 156.2, 155.8, 152.1, 150.5, 146.4, 145.7, 143.2, 137.8, 137.0, 136.2, 129.1, 129.0, 126.9, 126.6, 124.8, 123.3, 123.0, 122.8, 121.0, 74.5, 47.3, 41.0, 34.3, 31.5, 26.3, 23.5, 22.1, 20.8, 16.3. MP = 138–140 °C. HRMS calculated for $C_{30}H_{31}N_3O_2Na^+$: 488.230848. Found: 488.229555.

*2.1.7. Pyr-phen Li carboxylate (**9**)*

3.22 g of compound (**8a**) (9.06 mmol) and 0.38 g LiOH monohydrate (9.06 mmol) were dissolved in 50 mL THF and 30 mL H_2O and the solution was stirred at room temperature for 4 days. The solution was concentrated under vacuum, yielding 3.00 g tan solid (99%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.18 (dd, 1H, J = 4.27 Hz, J = 1.55 Hz), 8.86 (d, 1H, J = 8.39 Hz), 8.72 (d, 1H, J = 7.73 Hz), 8.64 (d, 1H, J = 8.41 Hz), 8.52 (d, 1H, J = 8.03 Hz), 8.03 (m, 3H), 7.81 (dd, 1H, J = 4.26 Hz, 3.76 Hz), 7.65 (d, 1H, J = 7.50 Hz), 7.30 (d, 1H, J = 15.69 Hz), 6.98 (d, 1H, J = 15.69 Hz) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.7, 155.3, 155.2, 150.3, 145.7, 145.2, 138.2, 137.6, 136.6, 135.2, 135.1, 129.0, 128.8, 127.3, 126.7, 123.7, 123.2, 120.5, 120.2 ppm. MP > 210 °C. HRMS calculated for $C_{20}H_{12}LiN_3O_2Na^+$: 356.098177. Found: 356.098596.

*2.1.8. General procedure for alkylation of **9**. Pyr-phen phenethyl ligand (**8c**)*

A solution of 0.50 g (1.5 mmol) of compound (**9**), 194 μL (2-bromoethyl)benzene (1.42 mmol), 0.24 g CsF (1.5 mmol), and 20 mL anhydrous DMF was heated to 60 °C for 24 h. Hundred milliliters of saturated aqueous $NaHCO_3$ and 50 mL CH_2Cl_2 were added. The aqueous layer was extracted with CH_2Cl_2 and the organics were washed with 2× 100 mL $NaHCO_3$ solution and 3× 100 mL brine. After drying over $MgSO_4$, the solution was concentrated under vacuum, yielding 0.50 g of a white solid (82% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (d, 1H, J = 4.30 Hz), 9.03 (d, 1H, J = 7.95 Hz), 8.96 (d, 1H, J = 8.36 Hz), 8.41 (d, 1H, J = 8.40 Hz), 8.29 (d, 1H, J = 8.04 Hz), 7.94 (t, 1H, J = 15.50 Hz), 7.86 (q, 2H, J = 21.44 Hz, J = 8.73 Hz), 7.79 (d, 1H, J = 15.57 Hz), 7.67 (q, 1H, J = 7.98 Hz, J = 4.40 Hz), 7.49 (d, 1H, J = 7.54 Hz), 7.30 (m, 5H), 7.16 (d, 1H, J = 15.6 Hz), 4.49 (t, 2H, J = 7.13 Hz), 3.07 (t, 2H, 7.08 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 156.2, 155.7, 151.9, 150.4, 146.3, 145.6, 143.6, 137.8, 137.7, 136.9, 136.2, 129.0, 129.0, 128.9, 128.5, 126.9, 126.6, 126.5, 124.8, 123.3, 122.9, 122.1, 120.9, 65.1, 35.2. MP = 207–209 °C. HRMS calculated for $C_{28}H_{21}N_3O_2Na^+$: 454.152598. Found: 454.152200.

*2.1.9. Pyr-phen 4-methoxy benzyl ester (**8d**)*

Using the procedure for **8c**, 1.00 g (3.0 mmol) of compound (**9**) and 386 μL 4-methoxy benzyl chloride were combined to give **8d**. An 80% yield was achieved by chromatographing the concentrated reaction solution (4:1 acetone:hexanes, silica gel + 2% TEA). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.13 (d, 1H,

J = 7.98 Hz), 9.82 (dd, 1H, J = 5.51 Hz, J = 1.31 Hz), 9.19 (d, 1H, J = 8.59 Hz), 8.94 (dd, 1H, J = 8.24 Hz, J = 1.24 Hz), 8.51 (d, 1H, J = 8.59 Hz), 8.16 (m, 3H), 8.01 (d, 1H, J = 8.92 Hz), 7.81 (d, 1H, J = 15.62 Hz), 7.54 (d, 1H, J = 7.34 Hz), 7.41 (d, 2H, J = 8.59 Hz), 7.16 (d, 1H, J = 15.60 Hz), 6.95 (d, 2H, J = 8.64 Hz), 5.25 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 159.7, 157.6, 154.0, 151.5, 144.8, 143.6, 139.0, 138.6, 137.1, 130.2, 130.0, 129.8, 129.6, 128.0, 125.8, 125.7, 124.3, 123.8, 123.6, 122.1, 114.0, 66.4, 55.3. MP = 151–154 °C. HRMS calculated for $C_{28}H_{21}N_3O_3Na^+$: 470.147513. Found: 470.147399.

2.1.10. Pyr-phen ethyl valerate (**8e**)

Using the procedure for **8c**, 1.00 g (3.0 mmol) of compound (**9**) and 0.58 g ethyl 5-bromovalerate (2.77 mmol) were combined to give **8e**. The obtained solid was dried in a vacuum oven overnight to give 1.06 g tan solid (84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (dd, 1H, J = 4.29 Hz, J = 1.51 Hz), 9.03 (d, 1H, J = 7.92 Hz), 8.96 (d, 1H, J = 8.42 Hz), 8.40 (d, 1H, J = 8.40 Hz), 8.28 (dd, 1H, J = 8.06 Hz, J = 1.54 Hz), 7.87 (m, 4H), 7.66 (dd, 1H, J = 8.07 Hz, J = 4.34 Hz), 7.49 (d, 1H, J = 7.58 Hz), 7.17 (d, 1H, J = 15.60 Hz), 4.29 (t, 2H, J = 5.74 Hz), 4.16 (q, 2H, J = 7.13 Hz), 2.41 (m, 2H), 1.81 (m, 4H), 1.27 (t, 3H). MP = 103–105 °C. ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 166.9, 156.2, 155.8, 151.9, 150.5, 146.4, 145.7, 143.6, 137.8, 137.0, 136.2, 129.1, 129.0, 126.9, 126.6, 124.8, 123.4, 123.0, 122.2, 121.0, 64.2, 60.4, 33.9, 28.2, 21.6, 14.3 ppm. HRMS calculated for $C_{27}H_{25}N_3O_4Na^+$: 478.173727. Found: 478.173429.

2.1.11. L-(−) menthyl diethylphosphonoacetate (**10**)

A solution of 2.00 g diethylphosphonoacetic acid (10.2 mmol), 1.27 g L-(−) menthol (8.15 mmol), 0.25 g DMAP (2.04 mmol), and 100 mL dry CH_2Cl_2 was chilled under Ar to 0 °C. 1.89 g DCC was then added and the solution was stirred overnight. The white precipitate (dicyclohexylurea) was vacuum-filtered off (twice) and the organic solution was washed with 5× 75 mL saturated sodium bicarbonate solution. The solution was dried over anhydrous $MgSO_4$ and was concentrated to an opaque oil (1.24 g, 46%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73 (td, 1H, J = 10.90 Hz, J = 4.39 Hz), 4.17 (quint, 4H, J = 7.13 Hz), 2.95 (d, 2H, J = 21.68 Hz), 1.98 (m, 2H), 1.67 (m, 2H), 1.46 (m, 1H), 1.35 (t, 6H, J = 7.07 Hz), 1.26 (m, 1H), 1.03 (m, 2H, J = 48.75 Hz), 0.90 (dd, 6H, J = 7.05 Hz, J = 2.42 Hz), 0.83 (m, 1H), 0.76 (d, 3H, J = 6.94 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 75.5, 62.4, 62.3, 46.7, 40.5, 35.0, 34.0, 33.9, 31.2, 25.6, 23.0, 21.8, 20.7, 16.2, 16.1, 16.0. HRMS calculated for $C_{16}H_{31}O_5PNa^+$: 357.180132. Found: 357.180063.

2.1.12. General procedure for yield determination by gas chromatography

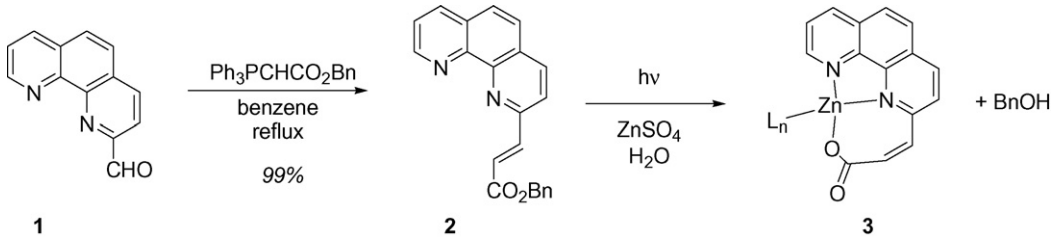
Yields of benzyl alcohol (boiling point 203–205 °C) were measured using an Agilent 6890 Series gas chromatograph with an FID detector. The column used was an Agilent HP-5 (5% phenyl-polymethylsiloxane) column (30 m length, 250 μm i.d., He carrier gas). The method parameters are as follows: 50 °C for 1 min and a ramp of 5 °C/min to 200 °C for 14 min. A calibration curve was established using 1-octanol (boiling point 196 °C) as an internal standard. The standard injections were comprised of benzyl alcohol and 1-octanol in the following ratios (1:4, 1:2, 1:1, 2:1, and 4:1). Approximately 5 μL of the ethyl acetate extraction layer was injected for analysis. The peak area ratio of the analyte and standard was obtained via electronic integration, allowing for the calculation of percent yield benzyl alcohol. Alternatively, the single point internal standard method was employed. A known amount of 1-octanol in diethyl ether was added to the aliquot. Three consecutive ether extractions were combined and concentrated under a stream of air to approximately 200 μL which was injected in the GC.

2.1.13. General procedure for preparatory scale photolysis

To a stirring aqueous solution of $CuSO_4{\cdot}5H_2O$ (69 mg, 0.275 mmol) in 180 mL H_2O was added a methanolic solution of compound (**8b**) (100 mg, 0.239 mmol in 20 mL). The solution was degassed by bubbling Ar through a needle for 1.5 h. The clear green solution was stirred and irradiated with >350 nm high intensity light for a given time. The solution was stirred in the dark for several days at which point it was extracted 5–10 times with 50 mL diethyl ether. The extracts were combined, washed with 50 mL brine, and dried over anhydrous $MgSO_4$. The ether layer was partially concentrated under vacuum at 25–30 °C at which point it was dried again, using anhydrous diethyl ether to rinse the flask. The material was concentrated under vacuum partially and was allowed to evaporate to dryness with a gentle stream of air, giving a mass of isolated benzyl alcohol. 0.22 g (2.5 equiv.) of EDTA disodium salt was added to the aqueous solution and it was stirred overnight. The pH was adjusted from 5.5 to 9 with an aqueous saturated $NaHCO_3$ solution, resulting in an opaque blue solution. The solution was extracted with 7× 50 mL CH_2Cl_2 which was then washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum, yielding a measured mass of free ligand material. The material was analyzed by ^{1}H NMR and in some cases separated by preparative TLC (silica gel, 9:1 acetone:MeOH + 2% TEA).

2.1.14. UV–vis binding titration procedure

To a solution of 24 μM $CuSO_4$ in MeOH was added a solution of 96 μM ligand in MeOH. 30 μL aliquots were added stepwise and a UV–vis spectrum was taken for each addition. Once the ligand to metal ratio had exceeded 2, the aliquot volume was increased to 60 μL. Titrations were continued out to a metal to ligand ratio greater than or equal to 3. Absorbance at 368 nm was noted for each concentration and was corrected for change in volume by using Beer's Law. Delta absorbance was calculated by adjusting the 368 nm absorbance of the various aliquots relative to the initial metal solution's value of zero. Two trend lines were created from the generated curve of wavelength versus delta absorbance. The X-axis value for the intersection of the two trend lines gave the ligand-to-metal stoichiometry.



Scheme 1.

3. Results and discussion

3.1. Ligand design and photochemistry of bidentate ligands

Our initial concept to fulfill the design shown in Fig. 1, was 1,10-phenanthroline **2** (Scheme 1). This ligand was easily prepared by Wittig olefination of the known aldehyde (**1**) [17]. The photochemistry of **2** was then examined. Fig. 2 shows the results of an initial experiment. When benzyl ester **2** was photolyzed in the presence of 1.2 equiv. of $ZnSO_4$, benzyl alcohol and **3** were slowly produced. As desired, both light and metal were required for the formation of benzyl alcohol. Notably, the *trans* to *cis* isomerization was driven completely to the *cis* isomer, despite both isomers absorbing significantly at the excitation wavelength (350 nm). The photostationary state of **2** in the absence of metal is 1:1. This is the first example of metal coordination being used to direct the photoisomerization of an alkene.

Photolysis of **2** showed that benzyl alcohol was only produced in the presence of Zn(II). Photolysis of a mixture of **2** and $ZnSO_4$ in DMSO-d_6:D_2O (10:1) gave a 20% yield (as determined using an internal standard) after 24 h. In the absence of metal no benzyl alcohol was produced and prolonged irradiation eventually led to decomposition of the substrate. Mixing **2** with Zn(II) in the dark had a dramatic effect on the ^{1}H NMR, but again no benzyl alcohol was formed. The ^{1}H NMR signals of **2** in the presence of Zn(II) were dramatically broadened, which indicated fast exchange of ligands on the metal. The coordination of two, or even three, ligands (**2**) per zinc ion would possibly make it more difficult for the ester carbonyl or water to coordinate to the metal. Because at least one of these coordinations (water or carboxyl) is necessary for metal activated ester hydrolysis, we surmised that this was the cause of the slow hydrolysis of the ester following irradiation. Therefore, we decided to prepare a tridentate ligand that would bind the metal more tightly, with the belief that this would produce a more hydrolytically active complex. This ligand was prepared as shown in Scheme 2.

Addition of 2-lithio-6-methylpyridine, **4**, to 1,10-phenanthroline followed by oxidative workup to re-aromatize the ring, gave **5** in good yield [17,18]. The methyl group was oxidized using the method of Angeloff to give aldehyde **6** [19]. The target ester could then be obtained in two ways. The first involved Horner–Emmons olefination with **7**; for example the synthesis of ethyl ester **8a** (Scheme 2). Horner–Emmons olefination also gave benzyl ester **8b** and menthyl ester **8f**. Alternatively, hydrolysis of **8a** gave carboxylate **9**, which could be alkylated to give the desired esters **8c–e** (Scheme 3).

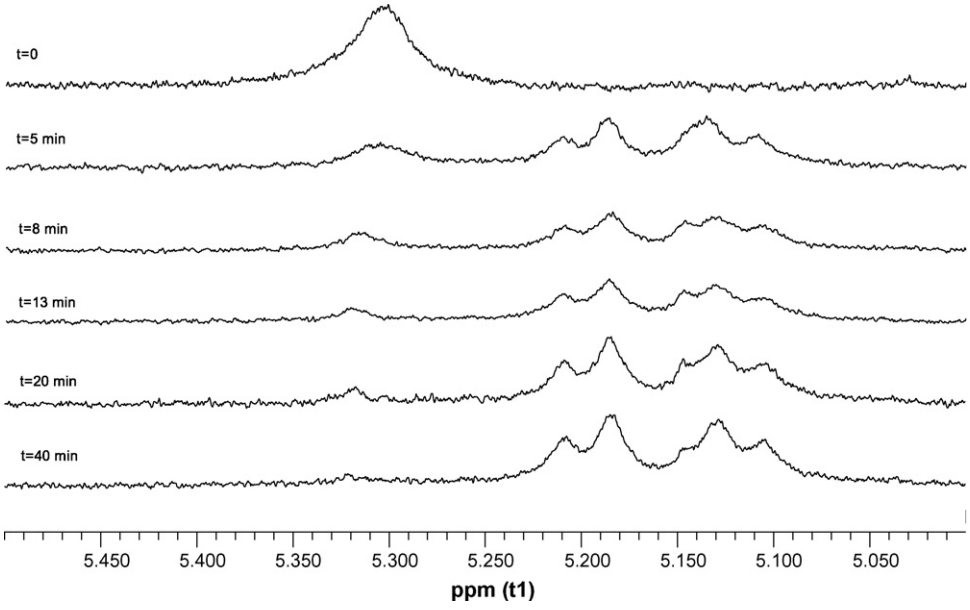
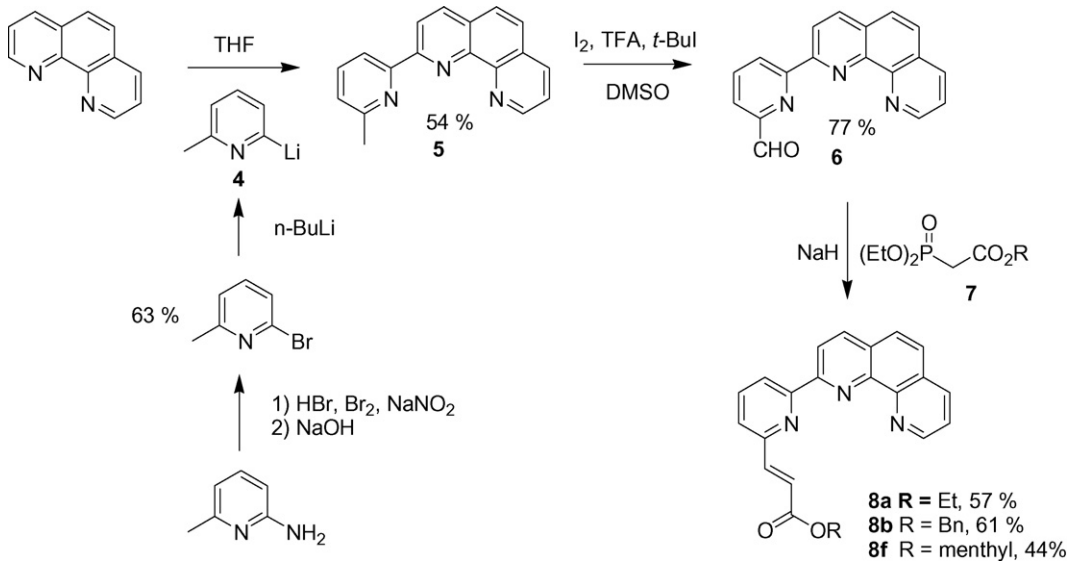


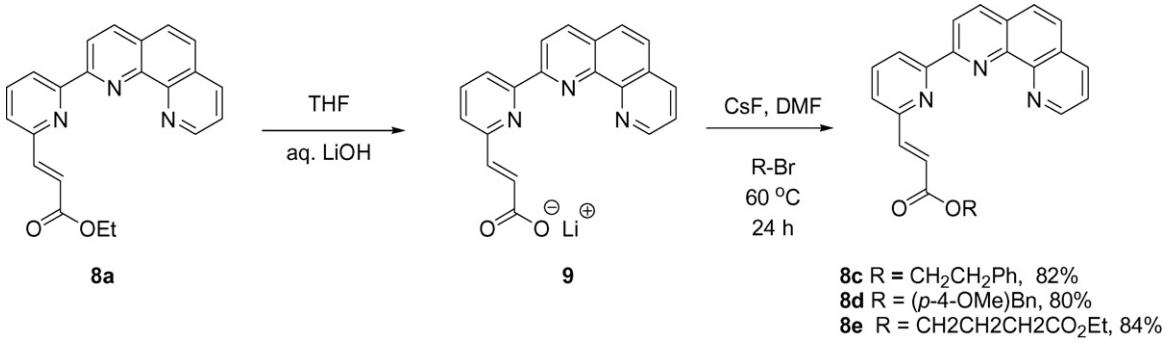
Fig. 2. ^{1}H NMR of **8b**-Zn(II) during photolysis. This spectrum was obtained at a concentration of 10 mM in 9:1 DMSO-d_6:D_2O.



Scheme 2.

3.2. Photochemistry of tridentate ligands

Having obtained a set of five esters (**8b–f**) we began to examine the photochemistry of the tridentate ligand system using the benzyl ester **8b** as the prototype. Once again, photolysis of a mixture of **8b** and 1.15 equiv. of $ZnSO_4$ led to complete conversion of the *trans* alkene to *cis*, despite a 1:1 photostationary state when **8b** was photolyzed in the absence of metal. Fig. 2 shows the ^{1}H NMR of the benzyl methylene over the course of this conversion. As with ligand **2**, mixing **8b** and Zn(II) dramatically broadened the signals in the ^{1}H NMR spectrum of the molecule, indicating fast exchange of ligands on the metal. This indicates that our structural modification in going from **2** to **8b** was not successful in producing a well defined complex. Also note that in the *cis* isomer, the benzyl methylene appears as an AB quartet, indicating it exists in a chiral environment. When DMSO-d_6 was excluded, the signals became considerably sharper (Fig. 3). At 1.2 mM in 90% D_2O–CD_3OD, the benzyl methylene in the *trans*



Scheme 3.

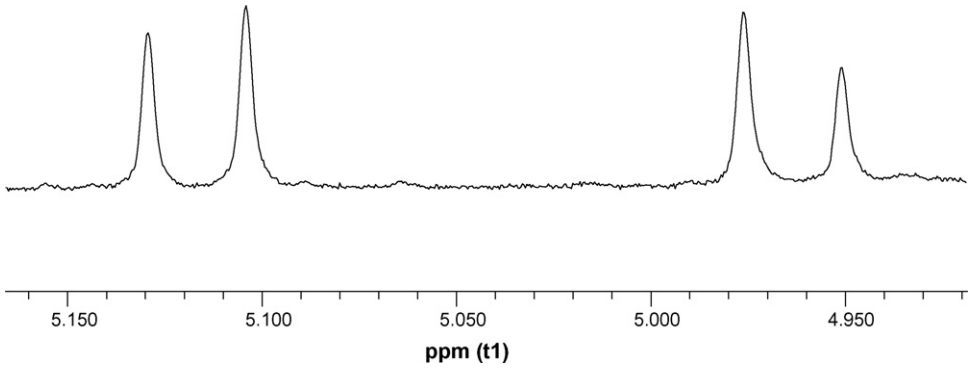


Fig. 3. ^{1}H NMR of **8b** (1.2 mM in 90% D_2O–CD_3OD). This set of signals is due to the benzyl methylene protons.

Table 1
Effect of metal on hydrolysis analyzed by GC

Metal	% yield BnOH	Rel. hydrolysis
Zn(II)	12	1.0
Co(II)	19	1.6
Ni(II)	20	1.7
Cu(II)	32	2.7
No metal	–	0

Solutions of metal and **8b** were irradiated for 30 min, then followed by GC over 3 days. Yields are calculated by GC against an internal standard after 3 days.

complex was also an AB quartet, suggesting that the initially formed complex is also chiral.

An experiment was devised to evaluate the performance of an array of metals as their sulfate salts, using **8b**. The ligand was mixed with metal sulfates at 1.2 mM in 5 mL 9:1 H_2O:MeOH. The resulting solutions were irradiated for 30 min at 350 nm using a rotary platform. The solutions were then stored in the dark at ambient temperature for 3 days, at which point each was extracted with diethyl ether containing 1-octanol as an internal standard. The extracts were analyzed by GC and yields of alcohol calculated relative to the standard (Table 1). This analysis showed that Cu(II) outperformed the other metals, while Zn(II), surprisingly, performed the worst.

Because the Cu(II) complex of **8b** showed the most promising results, further experiments were carried out using $CuSO_4$. A 1.2 mM solution of **8b** with 1.15 equiv. of $CuSO_4$ was irradiated for 30 min and monitored daily by GC for 6 days. The formation of benzyl alcohol leveled off after 2 days in the dark, giving an approximate yield of 50%. A degassed sample gave a 70% yield of benzyl alcohol under the same conditions. In both aerobic and anaerobic photolyses, there appeared to be a "burst" in the yield of the alcohol. Immediately after the irradiation period (30 min), the yield of benzyl alcohol was approximately 10%. Following this, 48 h were required for the yield of alcohol to climb to 50%, indicating a much faster rate of hydrolysis in the first half-hour than was observed after photolysis was discontinued. However, continued irradiation did not lead to an increase in yield and, in fact, dramatically lowered yields. In neither case was more than a trace of benzyl alcohol observed in the absence of photolysis. In the absence of metal, no hydrolysis was observed.

The alcohols could be recovered on either a preparatory or analytical scale by extraction of the aqueous solutions of metal complexes with diethyl ether. The phenanthroline-containing by-products could be isolated by stirring the extracted aqueous solutions with excess EDTA overnight to displace the ligand from the metal, raising the pH (to approximately 9) by addition of saturated $NaHCO_3$ and extraction with CH_2Cl_2. The material obtained from this extract was analyzed by ^1H NMR to determine the fate of the phenanthroline ligand.

Table 2 shows results for the preparatory scale experiments, where the metal complexes of **8b–f** (1.2 mM in 39:1 H_2O:MeOH) were degassed, irradiated for 7 h [20], and stirred in the dark for 6 days. The Zn(II) complex of **8b** yielded 31% benzyl alcohol. Analysis of the ligand material indicated much photodegradation, while some *trans* and *cis*-**8b** were detected. Benzaldehyde (3%) was detected in both the ether and CH_2Cl_2 extracts and formed the only unexpected and identifiable by-product.

The same conditions with the Cu(II) complex of **8b** gave 52 % benzyl alcohol. Analysis of the remaining ligand material indicated that all but a trace of the material had been photoisomerized and all but 2% of *cis*-**8b** had been hydrolyzed. The photoisomerization appears to occur more rapidly with the Zn(II) complex, while the hydrolysis is more rapid in the case of the Cu(II) complex. The *cis*-acid (*cis*-**9**, by-product of hydrolysis) was observed in the case of Cu(II), but was not recovered from the Zn(II) experiment. Recoveries of *cis*-**9** were generally poor, as this is a tetradentate ligand that should form a tight complex with the metal ion and remain in the aqueous layer during extraction. Thus, de-metalation of the *cis* complex was expected to be poor.

In the reaction run with $CuSO_4$ a small yield (<5%) of methyl ester **8g** (R = CH_3) was obtained. Presumably, this arises from a transesterification where methanol, the co-solvent, acts as the nucleophile in attacking the benzyl ester. Interestingly, the methyl ester was only observed with Cu(II) while benzaldehyde, presumably the result of photo-oxidation of benzyl alcohol, was only detected when Zn(II) was used. Yields of alcohol did increase slightly when oxygen was excluded but degassed reac-

Table 2
Preparatory scale photolyses of **8** with 1.15 equiv. of metal ($CuSO_4$, unless otherwise indicated)

Entry	Substrate	Yield of alcohol[a]	*Cis*-**9**[a]	*Cis*-**8**[a]	*Trans*-**8**[a]	Total recovery
1	**8b**	52%	19%	2%[b]	<1%	55%
2	**8b**-Zn(II)	31%	–	–	–	31%
3	**8b**-3 equiv. pyridine	77%	nd	nd	nd	nd
4	**8b**-dark	Trace	–	–	–	–
5	**8c**	36%	9%	14%	4%	54%
6	**8d**	68%	15%	<1%	<1%	70%
7	**8d**-5 equiv. Cu(II)	86%	Trace	0	Trace	86%
8	**8e**	42% (5% EtOH)	7%	26%	4%	72%
9	**8e**-5 equiv. Cu(II)	44% (10% EtOH)	7%	12%	3%	59%
10	**8f**	5%	1%	51%	17%	73%
11	**8f**-5 equiv. Cu(II)	1%	4%	25%	20%	49%

nd: not determined.
[a] Isolated yields.
[b] Less than 5% of the corresponding methyl ester was isolated.

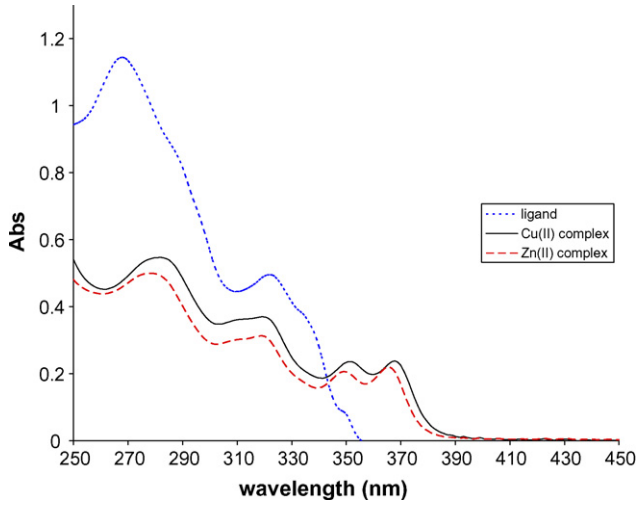


Fig. 4. UV–vis absorption spectra of ligand **8b** and the corresponding Cu(II) and Zn(II) complexes. The concentration of each was 2.25×10^{-5} M. The spectrum of **8b** was taken in CH_3OH and that of the two complexes in H_2O.

tions involving Zn(II) continued to exhibit lower yields and more ligand degradation than the corresponding Cu(II) reactions.

Phenethyl ester **8c** gave mediocre performance, as phenethyl alcohol was only obtained in 36% yield. The hydrolysis was slow as evidenced by the amount of recovered *cis* ligand. Ester **8d** gave by far the best results; photolysis in the presence of 1.15 equiv. of $CuSO_4$ gave a 68% yield of *p*-methoxybenzyl alcohol (PMB-OH), which was in good accord with our GC results. Very little unisomerized and unhydrolyzed ligand were recovered from the photolysis of **8d**. Using 5 equiv. of Cu(II) with **8d** increased the yield of PMB-OH to 86%. The ethyl valerate analogue **8e** gave a lower yield of alcohol, but did demonstrate that the ester proximal to the metal center could be hydrolyzed selectively in the presence of another ester (>8:1 in favor of the proximal ester relative to the ethyl ester). A significant amount of *cis*-**8e** was recovered in the valerate ligand, again indicating a slow hydrolysis. In the case of the menthyl ester **8f**, only 5% L-(−) menthol was isolated. This hydrolysis was very slow as was the photoisomerization. A significant amount of *cis*-**8f** was recovered (51% yield) along with a 17% yield of the *trans*-**8f**.

Table 3
UV–vis binding titration results (ligand/metal mole ratio)

Entry	Compound	Ligand:metal
1	**8b**-Cu(II)	1.8
2	**8b**-Zn(II)	2.2
3	**8c**	1.7
4	**8d**	2.2
5	**8e**	1.5
6	**8f**	1.8
7	5	1.6

See text and Section 2 for details.

3.3. Binding stoichiometry

In the case of the preparatory scale experiments using 1.15 equiv. of Cu(II), no more than 73% of the material was ever accounted for. Furthermore, increasing the amount of metal increased the yield of alcohol. This suggested the possibility that more than one ligand (**8**) coordinated a single metal ion (throughout we refer to a 1:1 metal:**8** complex as "ML" and a 1:2 metal:**8** complex as "ML_2" with the stereochemistry of the alkene given afterward). We speculated that the ML_2 complex would reluctantly give up metal to EDTA and, thus, be difficult to extract from the aqueous layer. To investigate the stoichiometry of coordination of ligands 8 and Cu(II) (and Zn(II) in some cases), binding titrations were performed. These experiments exploited the absorption band around 368 nm that is unique to the Cu(II)–ligand complex (Fig. 4).

From a plot of the ligand/metal mole ratio against the change in absorbance at 368 nm, a value for the ligand/metal mole ratio could be determined. This was achieved by finding the intersection of the two trend lines. Fig. 5 below shows the results for the benzyl ester **8b**. Table 3 shows the data for the analogues. A tri-

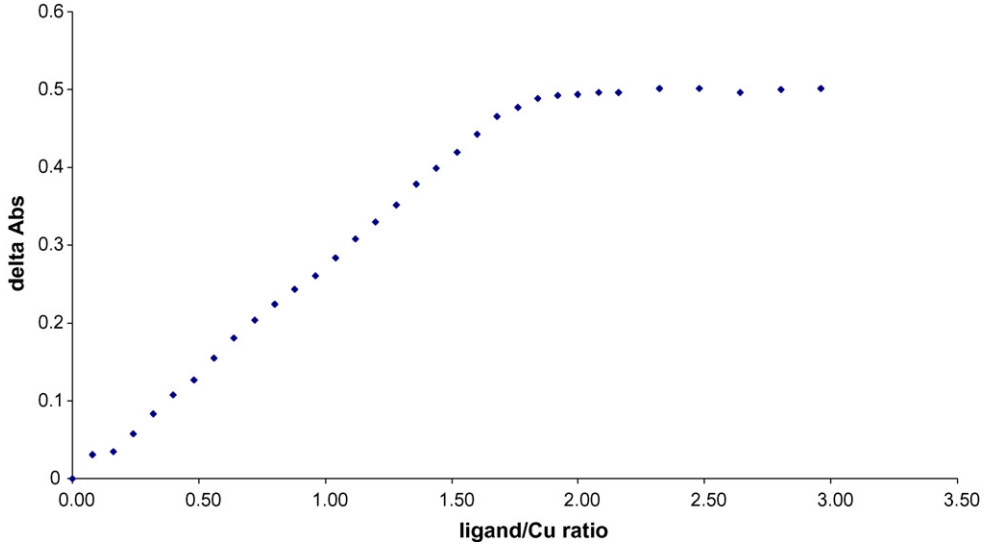


Fig. 5. UV–vis binding titration curve for the **8b**-Cu(II) complex. See text and Section 2 for details.

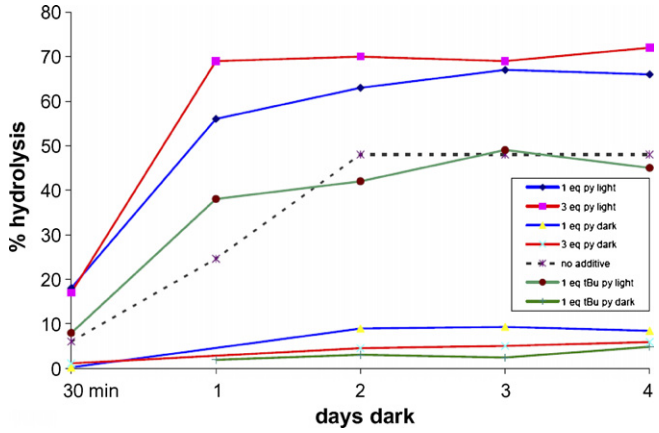


Fig. 6. Photolysis yields of **8b**. All solutions were 1.2 mM **8b** in 9:1 H_2O:CH_3OH with 1.15 equiv. of $CuSO_4$. Samples were irradiated ($\lambda = 350$ nm) for 30 min and aliquots extracted at the indicated time. Yields were measured by GC against an internal standard. See Section 2 for details.

dentate analogue that lacked the α,β-unsaturated ester group (**5**) was included to investigate the effect of the ester moiety. All of the data are consistent with the major component of the mixtures of ligand and metal being ML_2, pictured in Fig. 6. The chirality of the proposed complex explained the AB quartet observed for the methylene signals in **8b**-Zn(II) (Fig. 3).

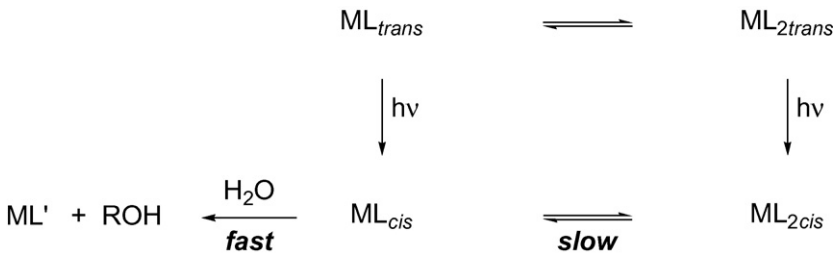
3.4. Mechanistic proposal

The possibility that release of alcohol is a direct result of photolysis was ruled out by testing the effect of extended irradiation of the complex on yield of alcohol. It was found that irradiation past the point of complete photoisomerization did not increase either the total yield or rate of formation of alcohol. In some cases, yields declined significantly. This was presumably due to photodegradation of either the *cis* complexes or the alcohols themselves.

The equilibrium between ML and ML_2 also explained the "burst" of hydrolysis that was observed immediately after photolysis in the GC experiments. In our early GC experiments, we noted that a significant amount of hydrolysis had occurred immediately after irradiation. The rate of hydrolysis then slowed. This is understandable if we assume that the solution irradiated is actually an equilibrium mixture of ML*trans* and ML_2*trans*. Photoisomerization of these two complexes immediately gives ML*cis* and ML_2*cis*. If an aquo ligand or availability of a coordinating site for the ester carbonyl on the metal is necessary for hydrolysis, ML*cis* would undergo rapid hydrolysis, which provides the observed "burst." The rate determining step in the hydrolysis of ML_2*cis* is disassociation of one ligand (Scheme 4). Thus, immediately after the burst, only ML_2*cis* is present. This species slowly loses one ligand to form ML*cis*, which quickly hydrolyzes.

The model shown in Scheme 4 predicts that any change that shifts the equilibrium toward ML*trans* should increase the rate of hydrolysis. We tested this prediction by conducting GC-scale photolyses of **8b**-Cu(II) in the presence of 1 and 3 equiv. of pyridine, which should serve as an alternative ligand for Cu(II) and allow the formation of ML-Py or ML-Py_3 complexes. The ester carbonyl or water should be able to displace a pyridine ligand easier than a bidentate phenanthroline ligand. The addition of pyridine significantly increased the rate of benzyl alcohol formation (Fig. 6). With 3 equiv. of pyridine, a 70% yield of benzyl alcohol was obtained from **8b** in only 1 day (as compared with 2 days in the absence of pyridine). The experiment with 1 equiv. of pyridine gave a 55% yield of benzyl alcohol in 1 day. Once again, these experiments provided an initial burst. In each case with added pyridine, a 20% yield of benzyl alcohol was observed immediately following 30 min of photolysis, in contrast to the same reaction without pyridine, where less than a 10% yield of benzyl alcohol is observed immediately after irradiation. A preparatory scale photolysis (7 h irradiation, 14 h in the dark) of **8b** with 1.15 equiv. of $CuSO_4$ and 3 equiv. of pyridine gave a 77% isolated yield of benzyl alcohol. Thus, the presence of pyridine increased both the final yield and the observed burst following photolysis.

We proposed that the role of pyridine was to act as a stabilizing ligand for the ML complex. However, the basicity of pyridine raised the question of whether or not the increased rate of hydrolysis was simply due to an increase in the pH of the solution. The pyridine containing solutions had a higher pH than solutions that did not contain pyridine. The pH of a solution with 1 and 3 equiv. of pyridine was 5.66 and 5.87, respectively. In the absence of pyridine, the pH of an otherwise identical solution was 5.40. In an attempt to separate the buffering effect of the pyridine from its coordination effect, we conducted another GC experiment exactly as above but substituting the non-coordinating 2,6-di-*tert*-butylpyridine (**11**) for pyridine. When 1 equiv. of **11** was added, the pH was very similar to when pyridine was used (5.68 with **11**, 5.66 with pyridine). However, the production of benzyl alcohol in the presence of **11** was essentially the same as when no base is added, indicating that the role of pyridine is to alter the equilibrium between ML



Scheme 4.

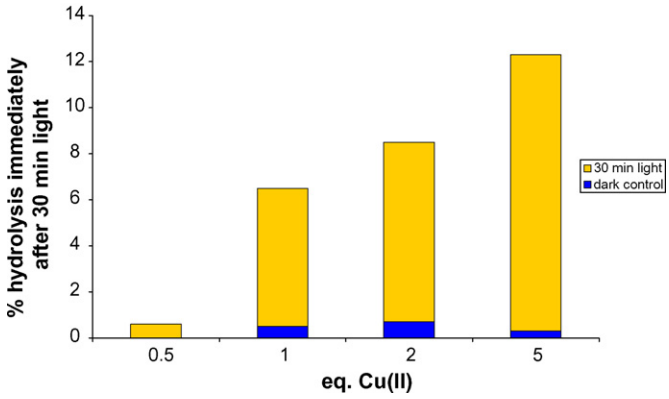


Fig. 7. Initial burst of benzyl alcohol following photolysis of **8b** for 30 min.

and ML_2, rather than to increase the concentration of hydroxide.

If the mechanism shown in Scheme 4 is operating, the initial burst should also be dependent on the concentration of metal ion. Fig. 7 shows how the initial burst varies with the number of equivalents of Cu(II). The magnitude of the initial burst increases with increasing amounts of Cu(II) present. With more Cu(II), there should be more of the 1:1 complex present, which hydrolyzes quickly following photolysis. Of special note is that when only half an equivalent of Cu(II) is used, conditions that should lead primarily to 1:2 (metal:ligand) complex, a very small burst is observed, consistent with the 1:2 complex not hydrolyzing rapidly.

4. Conclusion

The above data demonstrates that photoisomerization of α,β-unsaturated esters can be driven entirely to the *cis* isomer when β-substituents capable of coordinating metals are included. The *cis*-complexes so obtained are hydrolytically active, with good yields of alcohols being produced. The rate of hydrolysis is dependent on the stoichiometry of the complex and increases with increasing 1:1 complex concentration. We are continuing to optimize the ligand design and plan to continue exploring hydrolysis reactions as well as the optimal ligand design. Further developments will be reported in due course.

Acknowledgements

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