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# **Discovery of a Photoinduced Dark Catalytic Cycle using** *in situ* LED-NMR Spectroscopy

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Supporting Information Placeholder

ABSTRACT: We report the use of LED-NMR spectroscopy to study the reaction mechanism of a newly discovered photoinduced iron-catalyzed cycloisomerization of alkyn-ols to cyclic enol ethers. By understanding on/off ligand binding to the catalyst, we were able to appropriately design reaction conditions to balance catalyst activity and stability. The utility of LED-NMR was demonstrated to be a powerful tool in elucidating reaction mechanisms of photochemical reactions. Temporal NMR spectroscopic data under visible light illumination: (1) revealed the precatalyst activation mechanism, (2) proved that photon flux provides a unique external control of the equilibrium distribution between the pre-catalyst and active catalyst, and ultimately the rate of reaction, (3) provided information about the reaction driving forces and the turnover limiting step, and (4) enabled both real-time structural and kinetic insights into elusive species (e.g. dissolved gases).

## Introduction

The feedback loop between developing new reaction methodologies and studying their mechanisms enables chemists to make critical observations which ultimately lead to a hypothesis-driven reaction optimization process. Facilitating this process, innovations in analytical tools and techniques can shed light into previously poorly understood "black box" processes. This article describes such an example of this process in which the leveraging of a newly reported tool and a related technique, namely LED-NMR<sup>1</sup> and NMR-actinometry,<sup>2</sup> was used to study in detail the mechanism of a newly discovered photochemical reaction, ultimately guiding us towards rationally improved reaction conditions and scope exploration. We believe that these analytical tools and techniques will undoubtedly be transformative for the field of photochemistry, which has secured a pillar in modern synthetic methodology for constructing organic molecules.<sup>3</sup>

As part of our efforts to develop a supply route to an active pharmaceutical ingredient (API), we became interested in developing a catalytic cycloisomerization of alkyn-ols (Scheme 1) to produce exocyclic enol ethers. While numerous cycloisomerization methodologies have been reported, including those for synthesizing enol ethers from alkyn-ol substrates, challenges remain, including controlling the mode of cyclization (i.e. 5-exo vs 6-endo cyclization) as well as preventing alkene isomerization or oligomerization processes.<sup>4,5a</sup> Additionally, many existing methodologies rely on expensive or precious metals such as Rh,<sup>5</sup> Ru,<sup>6</sup> Ir,<sup>7</sup> Au,<sup>8</sup> Ag,<sup>9</sup> Pt,<sup>10</sup> Pd,<sup>11</sup> or La,<sup>12</sup> and often provide only moderate

yields (<70%) and/or require high catalyst loadings (10 to 25 mol%).<sup>13</sup> For these reasons, we sought an inexpensive and sustainable alternative, ideally based on an Earth-abundant first row transition metal such as iron. In particular, we were drawn to several reports employing metal carbonyl complexes supported by cyclopentadienone ligands,<sup>14</sup> namely, LFe(CO)<sub>3</sub> (L = tetraphenyl-cyclopentadienone) (**cat**•**CO**). Although cycloisomerization reactivity is precedented with these complexes,<sup>15</sup> specifically with allenes to provide a net endo-cyclization, alkyn-ol cycloisomerization is unexplored, including successfully achieving the 5-exocyclization mode.

## Scheme 1. Cycloisomerization of alkyn-ols to either the 5exo or 6-endo product and related side-reactions.



A potential challenge in using these carbonyl complexes stems from the requirement for CO decomplexation to open a coordination site for substrate binding. In the aforementioned allenealcohol cycloisomerization examples,<sup>15</sup> CO dissociation was effected using an oxidant in the presence of a base and often required elevated temperatures. Classically, this elementary step has been effected by an external oxidant such as trimethylamine-Noxide, generating CO2 and trimethylamine as byproducts.15,16 However, the Lewis basic tertiary amine can potentially inhibit catalysis via coordination to the complex's resulting vacant site. Brønsted acids have also been employed to decomplex the amine from the metal via protonation,<sup>18</sup> but their presence may catalyze undesired pathways.<sup>19,20</sup> It is also unclear if Me<sub>3</sub>NO can influence the redox state of Fe(0) in the pre-catalyst, and thereby turn on undesired catalysis. Alternatively, light has been used to dissociate carbonyl ligands from metal complexes.<sup>21</sup> In the present case, we hypothesized that in addition to providing a substrate binding site, CO dissociation would generate a bifunctional catalyst containing both Lewis acidic and Lewis basic moieties (Scheme 2). We envisioned substrate binding via a metal- $\pi$ -acid interaction, and thus activating the alkyne towards nucleophilic attack. Additionally, the cyclopentadienone ligand could act as a Lewis-basic

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site to deprotonate the alcohol, thus increasing its nucleophilicity towards attack of the alkyne. This synergistic effect would result in a photogenerated Lewis pair bifunctional catalyst capable of two-point activation of alkyn-ol substrates toward cycloisomerization to generate cyclic enol ethers.

## Scheme 2. Photogeneration of Lewis Pair Catalyst for Bifunctional Catalysis.



## 2. Results and Discussion

#### 2.1 Reaction Optimization

We initially selected substrate **1a** and **cat-CO** for evaluation. As discussed above, metal carbonyls can be activated in one of three methods: (1) heat, (2) oxidant (e.g.  $Me_3NO$ ), or (3) light. We explored known methods<sup>15</sup> of activating these types of catalysts, specifically using combinations of temperatures and oxidants in the absence or presence of a base (Table 1). Varying ratios of kinetic product **2a**, thermodynamic product **3a**, and dimer **4a** were observed. While room temperature conditions did afford cycloisomerization-derived products, the conversion was poor. Increasing the reaction temperature to 70 °C provided improved levels of conversion, although the selectivity for **2a** was diminished, as alkene isomerization (**3a**) and oligomerization (**4a**) became predominant.

Table 1. Exploration of thermal conditions for the cycloisomerization of alkyn-ol 1a with cat•CO (1 mol%) in CD<sub>2</sub>Cl<sub>2</sub>.

Me Me 1a	$LF$ $\frac{oxio}{C}$ $L = te$ cyclo	e(CO) <sub>3</sub> dant/base CD <sub>2</sub> Cl <sub>2</sub> etraphenyl- pentadienone	Me Me CH <sub>2</sub> 2a	Me + Me Me 3a	Me Me Me Me 4a
entry	temp.	oxidant	base	2a : 3a : 4a	conversion
1	RT	Me₃NO	-	96 : 1.4 : 2.8	25%
2	RT	-	K <sub>2</sub> CO <sub>3</sub>	90:1.7:8.0	7%
3	RT	Me₃NO	K <sub>2</sub> CO <sub>3</sub>	99 : 0.05 : 0.8	24%
4	RT	-	-	0:0:100	5%
5	70 °C	Me₃NO	-	3.5 : 32 : 65	100%
6	70 °C	-	K <sub>2</sub> CO <sub>3</sub>	91:3.9:4.7	31%
7	70 °C	Me₃NO	$K_2CO_3$	96:4.0:0.15	14%
8	70 °C	-	-	0:0:100	8%

We next turned our attention to photochemical methods of CO dissociation (Table 2). We initially sparged the solution with  $N_2$  for the first hour to purge CO and thus render the catalyst activation process irreversible. Although this resulted in highly selective formation of **2a**, it resulted in incomplete conversion (45%, entry 1). Interestingly, full conversion to the desired product **2a** was achieved when using a closed system (entry 2), with negligible isomerization of the alkene to **3a**. To ensure this was not a solvent dependent effect, we repeated the reaction in CD<sub>2</sub>Cl<sub>2</sub> and observed comparable results (entry 3).

Table 2. Exploration of photochemical conditions for the cycloisomerization of alkyn-ol 1a with cat•CO (1 mol%).

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entry	λ [nm]	modification	solvent	2a : 3a : 4a	conversion
1	450	N <sub>2</sub> sparge (1 <sup>st</sup> 1 h)	d <sub>8</sub> -toluene	100 : NA : NA	45%
2	450	closed vial	d <sub>8</sub> -toluene	100 : NA : NA	100%
3	450	closed vial	$CD_2Cl_2$	99:0.05:0.8	100%

Intrigued by the detrimental effect caused by the removal of the seemingly-inhibitory CO ligand, we decided to carry out a detailed mechanistic study of this reaction with an eye towards developing improved reaction conditions and scope exploration. Three main challenges were encountered when attempting to study this reaction by standard analytical tools such as HPLC, ReactIR, etc.: (1) decomposition of product 2a when exposed to chromatography precluded ex situ methods such as HPLC analysis. (2) the absence of a pristine standard of product 2a rendered it challenging to obtain an accurate response factor for ReactIR, (3) quantitative detection of volatile CO by ex situ methods was challenging. In light of these challenges, we recognized that LEDbased NMR illumination devices introduced by Gschwind and coworkers<sup>1</sup> could serve us as simple and powerful tools to obtain data-rich kinetic and structural insights into this reaction. In contrast to other established analytical tools, in situ NMR monitoring has a multitude of advantages:<sup>22</sup> (1) it provides quantitative data that does not require standards or calibration curves, (2) being a non-destructive method, it provides structural information of both stable and unstable compounds, (3) it enables in situ time course measurements from a single sample, minimizing sample manipulation errors, (4) it typically requires modest sample amounts due to the high sensitivity of modern NMR spectrometers, and (5) it provides the ability to observe multiple nuclei independently (<sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F, <sup>31</sup>P, etc.) to provide complementary structural information. In addition, the coupling of NMR with in situ LED illumination provides capabilities that are essential for determining kinetics and gaining insight into the mechanisms of photochemical transformations. Specifically, this combination affords the ability to observe intermediates or transient species, as well as the aggregation state or molecular size of the components in the reaction mixture potentially only present under illumination conditions. In this work we demonstrate the utility of LED-NMR as a powerful tool in elucidating reaction mechanisms of photochemical reactions.

#### 2.2 Kinetics and Actinometry

A proposed catalytic cycle is shown in Scheme 3. Pre-catalyst **cat**•**CO** absorbs a photon, resulting in the photomediated loss of CO to generate active catalyst LFe(CO)<sub>2</sub> (**cat**) which complexes to substrate **1a**. This catalyst-substrate complex (**cat**•**1a**) may facilitate the cyclization step *via* ligand-enabled deprotonation of the alcohol and concomitant attack onto the pendant alkyne to generate **5-exo-int**. This vinyl-iron intermediate then undergoes proto-demetallation to release product **2a** and regenerate the active catalyst LFe(CO)<sub>2</sub> (**cat**).

To validate our proposed catalytic cycle, we initiated a mechanistic investigation using LED-NMR spectroscopy, including our recently developed NMR actinometry method.<sup>2</sup> Monitoring by *in situ* LED-NMR, photo-irradiation of substrate **1a** in the presence of catalyst **cat**•**CO** in CD<sub>2</sub>Cl<sub>2</sub> afforded quantitative conversion to **2a** (Figure 1). Notably, the use of *in situ* NMR was crucial for obtaining both structural and quantitative data, as offline methods such as HPLC were not suitable due to the instability of **2a** toward isomerization to **3a**. The observation that all NMR signals, including those associated with the catalyst, remained sharp throughout the reaction time course is consistent with the catalyst and all associated species remaining diamagnetic (e.g. Fe(0)), likely pre-

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cluding the existence of paramagnetic iron species (e.g.  $Fe^{3+}$ ). This is in contrast to other metal carbonyls which can generate paramagnetic species upon photoirradiation (e.g.  $Mn_2(CO)_{10}$  and  $Re_2(CO)_{10}$  can generate 'Mn(CO)<sub>5</sub> and 'Re(CO)<sub>5</sub>).<sup>23,24,25</sup>

Scheme 3. Proposed reaction mechanism.



The reaction progress kinetics  $(\text{RPK})^{26}$  obtained by LED-NMR in Figure 1 revealed an induction period that is postulated to be associated with the photomediated loss of a CO from the 18electron pre-catalyst **cat**•**CO**, LFe(CO)<sub>3</sub>, to generate the active 16electron catalyst (**cat**), LFe(CO)<sub>2</sub>. The photomediated activation of **cat**•**CO** leaves a vacant coordination site on the active catalyst, enabling **cat** to bind substrate **1a** to both reach an 18-electron complex as well as activate the substrate for catalysis. UV-vis absorption of dichloromethane solutions of **cat**•**CO** before and after irradiation at 450 nm using a PennOC m1 photoreactor<sup>27,28</sup> illustrated an overall red-shift in a low energy absorption band concomitant with increased molar absorptivity in the 440 nm region (Figure 2), providing further evidence of catalyst activation via photomediated loss of a CO.<sup>29</sup>



**Figure 1.** Temporal concentration profiles of **1a** and **2a** monitored by <sup>1</sup>H NMR spectroscopy recorded under 440 nm illumination using  $[1a]_0 = 0.60$  M and  $[cat \cdot CO]_T = 0.018$  M in CD<sub>2</sub>Cl<sub>2</sub> (pretreated with solid K<sub>2</sub>CO<sub>3</sub>).



**Figure 2.** UV-vis absorption spectra of catalyst **cat**•**CO** in  $CH_2Cl_2$  before and after 450 nm irradiation. Vertical dashed lines indicate wavelengths associate with isosbestic points.

In order to perform relevant kinetic measurements, we next needed to locate the linear absorption regime. By avoiding the photon-limited regime, the catalyst concentration was low enough relative to the photon flux to ensure the reaction rate was not limited by a lack of photons reaching the photocatalyst. By measuring the initial rate of product formation as a function of catalyst loading (Figure 3), we determined the linear absorption regime ( $0 < [cat+CO]_T < 4.50 \text{ mM}$ ). In order to ensure we were characterizing the intrinsic kinetics, reaction mixtures containing 2.25 mM of pre-catalyst cat+CO were used for further kinetic studies.



Figure 3. Dependence of initial rate of product formation (measured after the induction period) as a function of catalyst loading. Kinetic data collected using  $[1a]_0 = 0.6$  M in CH<sub>2</sub>Cl<sub>2</sub> with varying amounts of pre-catalyst [cat•CO]<sub>T</sub> (0.375, 0.75, 1.5, 3.0 and 6.0 mol%) under 440 nm irradiation using LED-NMR.

The dependence of initial rates on catalyst concentration shown in Figure 3 can be fit to equation  $1.^{2,30,31}$  The term  $\varepsilon_{app}$  (apparent molar absorptivity) arises due to dissociation of **cat**•**CO** into **cat** and **CO**, with both **cat**•**CO** and **cat** contributing to the absorption at 440 nm. The apparent molar absorptivity of 505 M<sup>-1</sup>•cm<sup>-1</sup> was obtained from the fit, and then compared to the value of 345 M<sup>-1</sup>•cm<sup>-1</sup> measured for **cat**•**CO** alone. The larger  $\varepsilon_{app}$  value is consistent with higher molar absorptivity of the active catalyst (**cat**) compared to the pre-catalyst **cat**•**CO**.

$$\frac{d[2\mathbf{a}]}{dt} = I_0 \phi \left( 1 - 10^{-\varepsilon_{app} b[\mathsf{cat} \cdot \mathbf{C0}]} \right) \tag{1}$$

Utilizing our recently developed chemical actinometer, 2,4dinitrobenzaldehyde, the light intensity of our 440 nm LED source was determined to be  $5.72 \times 10^{-5}$  einstein•L<sup>-1</sup>•s<sup>-1</sup> (see Supporting Information for details). Having determined both the light intensity and the zeroth order kinetic constant ( $k_0 = 1.75 \times 10^{-4}$ M•s<sup>-1</sup>) calculated from the fitting of the data in Figure 3 (see Supporting Information for details), the quantum yield was calculated to be  $3.06 \pm 0.09$  based on equation 2, indicating that three molecules of product were formed for every photon absorbed by the catalyst (*vide infra*). (2)

$$k_0 = I_0 \phi$$

From the kinetics in the photon-saturated regime ([**cat**•**CO**]<sub>T</sub> = 0 - 4.50 mM) in Figure 3, a clear positive order in catalyst was revealed. RPK analysis of reaction mixtures with 0.30 M and 0.60 M of substrate **1a** are shown in Figure 4. The overlay of the rate of product formation indicates that the reaction is zeroth order in substrate **1a**. To gain insight into the catalyst stability, an x-adjusted plot<sup>26</sup> (Figure 5) from reactions carried out in the presence of 2.25 mM of **cat**•**CO** with either 0.30 M or 0.60 M of **1a** show deviation eventually arises at later time points. This suggests either weak product inhibition or mild catalyst deactivation upon extended periods of photoirradiation.



**Figure 4.** Graphical RPK data for reaction carried out in the LED-NMR setup using either  $[1a]_0 = 0.30$  or 0.60 M with  $[cat \cdot CO]_T = 2.25$  mM in CD<sub>2</sub>Cl<sub>2</sub> irradiated at 440 nm. RPK illustrating zeroth order in substrate when overlaying product formation.



**Figure 5.** Graphical RPK data for reaction carried out in the LED-NMR setup using either  $[1a]_0 = 0.30$  or 0.60 M with  $[cat•CO]_T = 2.25$  mM in CD<sub>2</sub>Cl<sub>2</sub> irradiated at 440 nm. X-adjusted RPK data for consumption of starting material 1a illustrating partial catalyst deactivation.

In order to discern between cyclization and proto-demetalation as the turnover limiting step, a Hammett plot<sup>32</sup> was constructed by measuring the initial rate of 5-exo-cyclization for a series of electronically varied 2-ethynylbenzylalcohols (**1b–1g**) (Figure 6). A clear correlation between the initial rate of product formation and the  $\sigma_{para}$  parameter ( $\mathbb{R}^2 = 0.96$ ) was observed. The positive slope ( $\rho = +0.76$ ) indicates that there is a build-up of negative charge on the alkynyl carbon, which is consistent with the turnover limiting step being the concomitant deprotonation and nucleophilic attack by oxygen on the alkyne. This is in clear contrast to a scenario where protodemetalation would have provided a negative slope due to decreasing negative charge on the vinyl carbon.

In order to determine the role of light in catalysis, we exposed two identical reaction mixtures to two different temporal illumination conditions in the LED-NMR setup. In the first experiment, the reaction mixture was illuminated for the full time course (blue data points in Figure 7, top), whereas in the second (data points in red), the mixture was illuminated for the first 30 min, kept dark for nearly 4 h, and then illuminated once again until the reaction reached full conversion at T = 7 h. Clearly, the data show high reproducibility under identical conditions in the first 30 min, but as soon as irradiation was ceased (data set shown in red), the rate of product formation significantly decreased relative to that observed for the reaction under constant irradiation at 440 nm (data in blue). However, product formation did not stop immediately in the absence of irradiation, suggesting the existence of a lightindependent ('dark') pathway. Importantly, when irradiation was resumed at 4.17 h (data in red), the reaction went through a 2<sup>nd</sup> induction period (see Supporting Information for details) and proceeded at an accelerated rate relative to dark conditions, effectively reacting at rates comparable to those under illumination conditions (consistent with negligible catalyst deactivation), and eventually reached full conversion.



Figure 6. Hammett plot illustrating the relationship between relative rates of product formation as a function of  $\sigma_{\text{para}}$  values (slope  $(\rho) = +0.76$ ,  $R^2 = 0.96$ ).

Toward gaining insight into the dynamics of the CO ligand as a result of switching between light and dark regimes, we repeated the latter experiment described above but using pre-catalyst cat•13CO which contained 13C enriched CO ligands. We recorded <sup>13</sup>C NMR spectra to monitor the temporal evolution of the reaction mixture, particularly related to the kinetics of the decomplexation of the CO ligand.<sup>33</sup> We were able to observe both the Febound<sup>34</sup> ( $\delta_C = 208.8$  ppm) and unbound ( $\delta_C = 184.2$  ppm) <sup>13</sup>CO in solution upon irradiation (Figure 7, middle). This experiment enabled us to probe the reversibility of the complexation of CO to the iron complexes in solution. When the light was turned off, the concentration of the free <sup>13</sup>CO in solution decreased, with concomitant re-complexation to the LFe(CO)<sub>2</sub> to generate the precatalyst LFe(CO)<sub>3</sub>. In contrast, if the reaction mixture is illuminated until full conversion, a steady state is reached between both Fe-bound and free CO after ca. 30-40 minutes (Figure 7, bottom). While direct observation of CO being released and re-ligated depending on illumination state supported our mechanistic hypothesis for the pre-catalyst losing a CO ligand to generate the active catalyst (cat), it also illustrated that once the active catalyst was formed, the catalytic cycle could proceed in the absence of light until catalyst deactivation via CO reassociation occurred. The latter scenario is in good agreement with the obtained quantum yield of  $3.06 \pm 0.09$ , suggesting that one photon converts  $LFe(CO)_3$  to  $LFe(CO)_2$  to undergo three catalytic turnovers on

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average before being deactivated by a molecule of CO in solution and returning to the inactive pre-catalyst. An alternative mechanistic scenario was initially considered, namely, photoexcitation of the catalyst-substrate complex (**cat-1a**) to facilitate the proton transfer and cyclization (see Supporting Information for details). The fact that the reaction proceeds in the absence of light rules out this scenario from being the exclusive pathway. Additionally, since energy transfer cannot proceed via a chain process,<sup>35</sup> it is also ruled out as the dominant pathway under photoirradiation conditions based on the quantum yield.



**Figure 7.** Experiment carried out under 440 nm illumination using  $[\mathbf{1a}]_{o} = 0.30$  M and  $[\mathbf{cat} \cdot \mathbf{CO}]_{T} = 2.25$  mM in CD<sub>2</sub>Cl<sub>2</sub>. (Top) Temporal concentration profiles of **1a** and **2a** monitored by <sup>1</sup>H NMR spectroscopy. Data in blue is irradiated at 440 nm for the entire duration of the reaction; data in red is irradiated from T = 0 h to T = 0.5 h, followed by darkness (grey region on plot) until T = 4.17 h at which point 440 nm irradiation is resumed. (Middle and bottom) Temporal equivalents of Fe-bound and dissolved (free) <sup>13</sup>CO as determined by <sup>13</sup>C NMR under conditions for either light/dark (middle) or constant light illumination (bottom).

Interestingly, if one graphs the sum of the Fe-bound <sup>13</sup>CO and free <sup>13</sup>CO in solution in Figure 7 (bottom) as a function of reaction time, the total only slowly decreases, demonstrating that there is minimal CO loss from the solution. In part, this is due to loss of CO to the headspace and ultimately slow leakage from the reaction vessel (i.e. our NMR tube). We hypothesized this CO loss could account for the mild catalyst deactivation observed in Figure 5 if the active catalyst (**cat**) is prone to losing a second CO ligand to form an inactive catalyst. The incomplete conversion of

**1a** observed in Table 2 when CO is removed from the reaction mixture by sparging with  $N_2$  is consistent with the catalytic deactivation hypothesis presented above. This observation clearly demonstrates the need for CO to be present to stabilize the catalyst which can be achieved either by (a) minimizing the headspace volume relative to the solution volume, or (b) performing the reaction under a partial pressure of CO if headspace is present in the reaction vessel. At first glance, the requirement for CO seems counterintuitive since it appears in the denominator of the rate law shown in equation 3 (see Supporting Information for details). However, a constant supply of photons provides for a constant regeneration of the active catalyst from the **cat-CO** via photomediated CO loss.

$$\frac{d[product]}{dt} = \frac{k_{rds}K_1K_2[\mathbf{1a}][cat]_T}{K_1K_2[\mathbf{1a}] + [C0] + K_1}$$
(3)

The bifunctional nature of the catalyst with its Lewis basic (ketone) and Lewis acidic (coordinatively unsaturated Fe) sites potentially renders it prone to dimerization, analogous to sterically unencumbered frustrated Lewis pair (FLP) catalysts.<sup>36</sup> We wondered if such a dimerization process could occur under the reaction conditions (Scheme 4), resulting in an inactive, off-cycle species (**cat-cat**).<sup>37</sup> Once again, LED-NMR afforded a unique ability to answer this question via *in situ* photo-DOSY experiments. While high concentration samples of **cat-CO** (22.5 mM) in CD<sub>2</sub>Cl<sub>2</sub> and a headspace present (ca. 20% v/v headspace to solution) did indeed result in the observation of a species with a slower diffusion coefficient, consistent with a dimer such as **cat-cat**, these signals were not observed under typical reaction conditions, precluding the relevance of this postulated dimer to the overall mechanism (see Supporting Information for details).

#### Scheme 4. Potential dimerization of active catalyst.



22.5 mM, with headspace (ca. 20% v/v): dimerization observed 2.25 mM, without headspace (reaction conditions): negligible dimerization

## **2.3 DFT Calculations**

Next, DFT calculations were performed to gain further insight into aspects of the reaction and solidify our mechanistic hypothesis. Single point energies presented in Figure 8 were obtained using B3LYP-D3(BJ)/6-311+G(2d,2p) based on geometries optimized using the B3LYP-D3(BJ) functional and a mixed basis set approach in which 6-31G(d,p) was utilized for C,H,O and the effective core potential LANL2DZ was used for Fe. The loss of CO from the pre-catalyst  $LFe(CO)_3$  to the active catalyst  $LFe(CO)_2$  was computed to be +28.0 kcal/mol in Gibbs free energy at 298.15 K. This energy cost is easily paid through the excitation of the pre-catalyst to enable the photomediated loss of CO. The binding of substrate can occur in two ways: (1) hydroxyl bound (cat-1a<sub>(C-bound)</sub>) or (2) alkyne bound (cat-1a<sub>(C-bound)</sub>), the latter disfavored but required for product formation. Consistent with our experimental data, the DFT results also indicate that the cyclization step is turnover limiting, as it displays a higher barrier than the protodemetalation step (20.3 vs 14.9 kcal/mol, respectively).

DFT calculations also enable insight into the structural changes of the tetraphenylcyclopentadienone ligand throughout the catalytic cycle. While DFT calculated structures of **cat**•**CO**, **cat**, and (**cat**•**1a**<sub>(C-bound)</sub>) clearly support the presence of ketone character in

the tetraphenylcyclopentadienone (C=O distance of 1.22, 1.25, and 1.23 Å, respectively), lengthening of the ketone begins to occur in the turnover limiting transition state TS1 (C=O distance = 1.26 Å) resulting in loss of double bound character (1.34 Å) with the formation of 5-exo-intermediate (5-exo-int) as a result of complete protonation and generation of a C-OH moiety on the ligand. This analysis highlights the importance of the bifunctional nature of the catalyst, as the ligand-embedded ketone and Fe center serve as Lewis basic and Lewis acidic sites respectively to enable cycloisomerization. The binding between Fe and the tetraphenylcyclopentadienone ligand also changes throughout the catalytic cycle.  $\eta_4$ -Binding to the tetraphenylcyclopentadienone ligand by Fe is calculated for all 18-electron structures,<sup>38</sup> with ligand non-planarity resulting from the carbonyl pointing away from the Fe relative to the plane generated by the diene moiety. On the other hand, the formal 16-electron cat structure is predicted to result in planarization of the ligand to enable the Fe to bind  $\eta_5$  to the cyclopentadienone moiety (see Supporting Information for details). Collectively, both the DFT and the experimental data support the mechanism proposed in Scheme 3.<sup>3</sup>

## 2.4 Reaction Scope

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The scope of the reaction<sup>40</sup> was briefly explored using a greener solvent (toluene),<sup>41</sup> at high substrate concentration (1 M) using 1 mol% of pre-catalyst cat•CO under illumination at 450 nm in the PennOC m1 photoreactor. Based on our mechanistic understanding, all the reactions were performed in closed vials to minimize the loss of CO. Model substrate 1a could be converted to 2a in 98% yield with no observable formation of thermodynamically preferred regioisomeric product 3a or dimer 4a.20 Arylacetylene derivatives 1b-1f were suitable substrates (entries 2-6), providing clean formation of the 5-exo-cylization product in nearly quantitative yield, with methoxy analogue 1g slightly lower (71 %, entry 7). Generation of spirocyclic analogues of 2e (2h and 2i, entries 8-9) occurred smoothly in 90% and 88% yield, respectively. Interestingly, inclusion of only a single benzylic methyl group (1i, entry 10) resulted in considerably diminished reactivity (45% yield after 8 h), with starting material accounting for the mass balance. Full conversion of 1i could be achieved by increasing the catalyst loading to 3 mol% (91% yield of 2j in 8 h). However. 1k, which lacks substitution  $\alpha$  to the nucleophilic hydroxyl group, was completely unreactive. We postulate that this result is due to unproductive off-cycle binding of the alcohol to the catalyst as a result of steric accessibility proximal to the hydroxyl group (Figure 8). This result led us to wonder if the Thorp-Ingold effect was critical for the success of the cycloisomerization and turned our attention to 11 which is devoid of one of the two methyl groups found in model substrate 1a. Cycloisomerization of 11 with 1 mol% indeed provided product 21 in 55% yield, with the starting material constituting the remainder of the mass balance. While increasing the catalyst loading to 3 mol% can effect full conversion and 94% yield of 2l, we wondered if reducing the reaction headspace volume relative to total reaction vessel volume could enhance catalytic activity. Indeed, when the headspace volume was reduced from ca. 80% v/v to <5% v/v, an increased yield was observed (55% yield vs 98% yield at 1 mol% catalyst loading). We postulate this enhanced catalytic activity is due to the minimization of catalyst deactivation via reversible dimer cat•cat formation (Scheme 4) and/or irreversible over-decarbonylation of cat (i.e. cat•CO losing more than one CO). Towards probing this effect further, we carried out the cycloisomerization of 1j using 1 mol% of cat•CO with different percent fill volume (Figure 9). A clear increase in yield is observed by reducing the headspace volume relative to the reaction fill volume, consistent with decreased irreversible catalyst deactivation when headspace is minimized. Having proved that catalyst deactivation is a viable pathway, it is

unlikely that product inhibition is also operating to cause the deviation observed between the same experiments shown in Figure 5. Returning to the remainder of the substrate scope, substrates bearing sterically hindered hydroxyl groups such as 1m showed excellent performance, generating bicyclic product 2m in 97% yield. Due to poor solubility of substrate 1n in toluene, the reactivity of this acyclic substrate was explored in dichloromethane and provided 91% of the Boc-amino functionalized product using 3 mol% of pre-catalyst cat•CO. Secondary benzylic alcohol 10 provided 20 in 68% yield with 3 mol% of catalyst owing to incomplete conversion. Substrate 1p, containing a ketal protecting group, smoothly underwent cycloisomerization without unmasking the ketone functionality, highlighting the mild reaction conditions. Benzylic alcohols featuring tethered alkene substitution of varying tether length in entries 17-18 (1q and 1r) highlight not only the alkyne over alkene selectivity, but also the tolerance of alkene functionality in the cycloisomerization. The ability to carry out the cycloisomerization with low catalyst loadings<sup>42</sup> coupled with the ubiquitous use of enol ethers in organic synthesis renders this method attractive for the direct use of the products in subsequent derivatizations without purification due to the presence of minimal impurities in the enol ether products.<sup>43,44</sup> Others heteroatoms such as nitrogen can be utilized to obtain the net hydroamination product as exemplified by conversion of 1s into 2s in 93% yield. More traditional methods to these products rely on Au<sup>45</sup> or Pd<sup>46</sup> catalytic systems in combination with elevated reactions temperatures, in contrast to the mild catalytic conditions presented herein.



Figure 9. Illustration of how the percent fill volume affects the cycloisomerization yield of 1a in  $d_8$ -toluene using 1 mol% of cat•CO. Note: percent fill volume = 100%•(volume of solution)/(volume of solution + volume of headspace).

#### 3. Conclusions

In conclusion, we report the use of LED-NMR to gain mechanistic insights into a newly-discovered photoinduced Fe-catalyzed 5-exo-cyclization of alkyn-ols. In the present work, LED-NMR has been applied: (1) to understand the pre-catalyst activation and to prove that the equilibrium between pre-catalyst and active catalyst is controlled by the externally adjustable photon flux, a concept that has remained under-explored, despite its potentially broad reaching impact,<sup>47</sup> (2) to obtain real time reaction kinetics to reveal the reaction driving forces and the turnover limiting step, (3) to capture transient intermediates or phenomena such as molecular aggregation that occurs exclusively under illumination conditions, (4) to easily discern the existence of a dark reaction pathway after an initial photoactivation of the catalyst, (5) to measure the quantum yield of the reaction and the apparent catalyst absorptivity by using our recently developed NMR actinometry methodology,<sup>2</sup> and most importantly, (6) to understand that catalyst stability could be achieved through its re-association to free CO in solution. Based on this final insight, we recognized



**Figure 8.** DFT calculated Gibbs Free energies (B3LYP-D3(BJ)/6-311+G(2d,2p) // B3LYP-D3(BJ)/6-31G(d,p) for C,H,O and LANL2DZ for Fe) for the proposed reaction mechanism.

Chart 1. Substrate Scope for Cycloisomerization of Alkyn-ols.



[a] Reactions were run at 1 M in substrate in  $d_8$ -toluene using 1 mol% of catalyst **3a**, unless noted otherwise, under 450 nm irradiation for 8 h using the PennOC m1 photoreactor; yields determined by <sup>1</sup>H NMR using 1,2-dichlorethane as an internal standard. [b] Reaction run in abensence of headspace. [c] Alternate solvent was used due to poor solubility of the substrate in  $d_8$ -toluene, entry 14 was run in CD<sub>2</sub>Cl<sub>2</sub>; entry 16 was performed in 1:1 CD<sub>2</sub>Cl<sub>2</sub>/ $d_8$ -toluene (0.5 M in substrate). [d] Run at 0.2 M in substrate.

that a closed system with minimal headspaces should be employed for optimal results.

The use of the LED-NMR tool to study photochemical reactions provides several advantages over alternative, ex situ methods (e.g. aliquot analysis with HPLC or GC) in which the nature of reaction intermediates or products may be altered during the analysis. Furthermore, offline analysis renders characterization of induction periods or chain processes challenging, particularly when temporal differences between sampling and analysis may lead to significant errors in the determination of reaction rate. The observance of photo-generated transient intermediates and the measurement of the kinetics of simultaneous light and dark cycles further highlight the information-rich nature of the technique. We demonstrated the utility of LED-NMR to provide full structural characterization and quantification of unknown intermediates, products and byproducts without isolation, and to determine quantum yield in order to obtain detailed mechanistic understanding of photocatalytic reactions. We expect that the approach presented herein will result in widespread adoption by the photocatalysis community, facilitating increased mechanistic understanding and thereby advancing the field.

## ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

All experimental procedures, complete characterization (NMR, MS, UV-vis absorption, kinetic data) for all new compounds and xyz coordinates of DFT computed structurers (PDF) Crystallographic information file for **3a** (CIF)

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#### Notes

The authors declare no competing financial interests.

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(20) Compound **3a** is thermodynamically preferred by 1.9 kcal/mol Gibbs Free energy relative to **2a** as calculated by DFT using B3LYP-D3(BJ)/6-311+G(2d,2p) // B3LYP-D3(BJ)/6-31G(d,p) in the gas phase.

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(32) A primary KIE was not measured. Due to the high acidity of the terminal alkyne, selective deuteration of the primary alcohol in **1a** using MeOD was unsuccessful.

(33) Independent measurements of  $T_1$  relaxation of <sup>13</sup>CO gas dissolved in CD<sub>2</sub>Cl<sub>2</sub> and of **cat•CO** pre-catalyst revealed corresponding  $T_1$  times of 2.6 s and 1.5 s, respectively. Quantitative <sup>13</sup>C NMR experiments were designed using this information; see Supporting Information for details.

(34) The Fe-bound CO signal corresponds to a time-averaged signal for **cat**•CO and **cat** due to a fast exchange on the NMR timescale.

(35) For examples of characterizing chain processes in photochemical reactions, see: Cismesia, M. A.; Yoon, T. P. Characterizing chain processes in visible light photoredox catalysis. *Chem. Sci.* **2015**, *6*, 5426–5434.

(36) For examples from the FLP literature, see: (a) Stephan, D. W.; Erker, G. Frustrated Lewis Pair Chemistry: Development and Perspectives. *Angew. Chem. Int. Ed.* **2015**, *54*, 6400–6441. For examples with organocatalysts, see: (b) Ford, D. D.; Lehnherr, D.; C. R. Kennedy, Jacobsen, E. N. On- and Off-Cycle Catalyst Cooperativity in Anion-Binding Catalysis. *J. Am. Chem. Soc.* **2016**, *138*, 7860–7863. (c) C. R. Kennedy, Lehnherr, D.; Rajapaksa, N. S.; Ford, D. D.; Park, Y.; Jacobsen, E. N. Mechanism-Guided Development of a Highly Active Bis-thiourea Catalyst for Anion-Abstraction Catalysis. *J. Am. Chem. Soc.* **2016**, *138*, 13525–13528.

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(38) X-ray crystallographic data of the pre-catalyst as a CH<sub>2</sub>Cl<sub>2</sub> solvate (cat•CO•CH<sub>2</sub>Cl<sub>2</sub>, CCDC 1852119) also displays non-planar cyclopentadienone ligand geometry (see Supporting Information for details).

(39) Although related iron complexes (see Ref.14) have been shown to catalyze reactions via iron hydride intermediates, the following pieces of circumstantial evidence argue against the existence of such an intermediate in the present case: 1) the reaction was observed to be zero order in substrate. In a scenario in which an iron hydride were generated, it would be expected to be the resting state of the catalytic cycle, however, we were unable to observe such a species by <sup>1</sup>H NMR (see Supporting Information for details), and 2) tertiary alcohols, which are unable to undergo  $\beta$ -hydride elimination, are competent substrates in this system.

(40) Due to product instability on silica gel, all yields were determined by quantitative <sup>1</sup>H NMR.

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(42) The quantitative conversion of **1a** to **2a** can be carried out with catalyst loadings as low as 0.375 mol% of **cat**•CO in the absence of head-space.

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