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Direct Visible-Light-Excited Asymmetric Lewis Acid Catalysis of Intermolecular [2+2] Photocycloadditions

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Supporting Information

ABSTRACT: A reaction design is reported in which a substrate-bound chiral Lewis acid complex absorbs visible light and generates an excited state that directly reacts with a cosubstrate in a highly stereocontrolled fashion. Specifically, a chiral rhodium complex catalyzes visible-light-activated intermolecular [2+2] cycloadditions, providing a wide range of cyclobutanes with up to >99% ee and up to >20:1 d.r. Noteworthy is the ability to create vicinal all-carbon-quaternary stereocenters including spiro centers in an intermolecular fashion.

Generating chiral molecules in a catalytic, asymmetric fashion induced by visible light is highly attractive both from an economical and sustainable perspective.[1,2] Most methodology reported to date involves photoinduced electron transfer,[3] often called photoredox catalysis, to generate intermediate radical ions and free radicals, but steering the reaction course of such highly reactive intermediates in a stereocontrolled and catalytic fashion is very difficult and therefore often leads to a narrow scope.[4] This renders visible-light-activated reactions that occur directly from an electronically excited state, without any charge separation, an appealing alternative.[5,6] Controlling stereoselective reactions of such excited states in a catalytic and asymmetric fashion is therefore of high interest but largely unexplored.

In pioneering work, Bach introduced strategies to control the absolute stereochemistry of photoexcited states by exploiting Lewis acid[7] and H-bond[8] activation. With respect to chiral Lewis acid catalysis, a chiral oxazaborolidine promoted an enantioselective [2+2] photocycloaddition[9] by red-shifting the UV-absorption of the substrate (Figure 1a).[7b,10] As a limitation, the method relies on less desirable UV-light, low temperatures, and high catalyst loadings. More recently, Yoon reported a visible-light-activated asymmetric [2+2] cycloaddition by using a combination of a chiral Lewis acid and an additional photosensitizer, the latter of which is responsible for absorbing the visible light and a subsequent energy transfer to the substrate-bound chiral Lewis acid, which lowers the triplet energy of the substrate (Figure 1b).[11] However, the requirement for two catalysts[12] and a limited substrate scope might restrict its applications. Here we report a previously elusive simplified catalytic system in which a chiral Lewis acid/substrate complex is directly activated by visible light toward highly stereocontrolled reactions (Figure 1c).

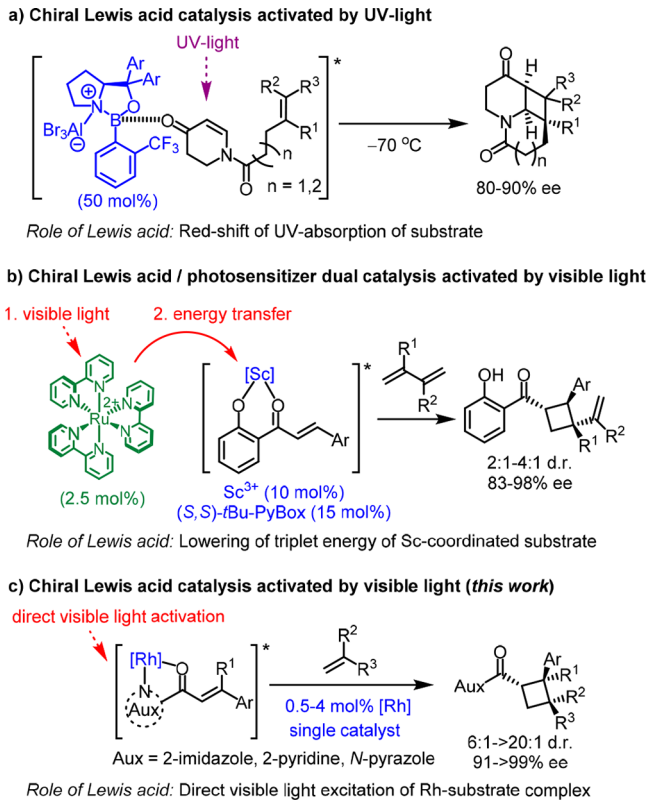

Figure 1. Asymmetric Lewis acid catalysis involving stereocontrolled reactions from an electronically excited state.

With the goal to develop a simple and robust visible-light-activated asymmetric catalysis scheme that only relies on a

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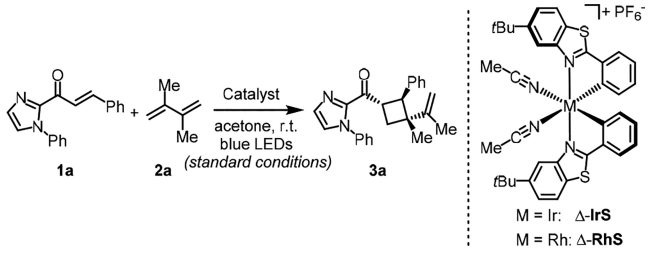
single catalyst,[13] we conceived that a substrate/chiral Lewis acid (CLA) complex is directly activated by visible light. Instead of undergoing electron transfer, which often produces undesirable, difficult to control reactive radical ion and free radical intermediates, we envisioned that this excited state directly engages in a reaction with a cosubstrate to form a CLA–product complex in a stereocontrolled fashion, and after the release of the product a new catalytic cycle is initiated upon binding of new substrate and photoactivation. This simplistic reaction design is very appealing for two reasons: First, the reactive species stay bound to the catalyst so that no free radical ion or free radical intermediates are involved, and a reaction that is more tolerant to different reaction parameters and conditions is expected. Second, only a single catalyst is required, combining a visible-light-induced electronic activation of the substrate with a chiral environment for a stereocontrolled reaction.

Recently, we introduced bis-cyclometalated chiral-at-metal complexes, synthesized through an auxiliary-mediated strategy, as catalysts for combining visible light photoredox activation with asymmetric catalysis.[14] We hypothesized that such complexes could also be used for direct photochemistry without charge separation and thus investigated the [2+2] cycloaddition of the α,β-unsaturated 2-acyl imidazole **1a** with the diene **2a** catalyzed by a single catalyst (Table 1).

Table 1. Visible-Light-Activated Asymmetric [2+2] Cycloaddition Using a Single Catalyst[a]



entry	catalyst[b]	conditions[c]	t (h)	yield (%)[d]	d.r.[e]	ee (%)[f]
1	**Δ-IrS** (2.0)	standard	16	63	5:1	0
2	**Δ-RhS** (2.0)	standard	16	99 (97)[g]	14:1	99
3	**Δ-RhS** (0.5)	standard	24	98	12:1	96
4	**Δ-RhS** (2.0)	air	16	97	14:1	99
5	**Δ-RhS** (2.0)	air, 1% H_2O	24	96	13:1	99
6	**Δ-RhS** (2.0)	DMF solvent	16	95	13:1	98
7	**Δ-RhS** (2.0)	CH_2Cl_2 solv.	16	99	14:1	99
8	**Δ-RhS** (2.0)	no light	16	0	n.a.[h]	n.a.
9	no catalyst	standard	16	19	6:1	0

[a]Standard conditions: **1a** (0.10 mmol), **2a** (0.30 mmol), and the shown amount of catalyst in acetone (0.2 M, 0.5 mL) were stirred at room temperature under nitrogen with irradiation by blue LEDs (24 W). [b]Catalyst loadings in mol % provided in brackets. [c]Deviations from standard conditions are shown. [d]NMR yields. [e]d.r. determined by ^{1}H NMR of the crude product. [f]ee determined by chiral HPLC. [g]Isolated yield provided in parentheses. [h]n.a. = not applicable.

Encouragingly, photolysis with blue LEDs in the presence of the iridium catalyst **Δ-IrS**[15] (2 mol %) provided the desired [2+2] photocycloaddition product **3a** in 63% yield after 16 h of irradiation at room temperature, albeit without any enantioselectivity (entry 1).[16] To our surprise, with the rhodium analog **Δ-RhS**,[17] the reaction proceeded smoothly spot-to-spot to provide the cycloaddition product in almost quantitative yield with high stereoselectivity (99% NMR yield, 97% isolated yield, 14:1 d.r., 99% ee) (entry 2). Even with a reduced Rh-catalyst loading of just 0.5 mol %, an excellent enantioselectivity of 96% ee was observed (entry 3). A determined quantum yield of 0.27 confirms the efficiency of this photoreaction.[7d] Interestingly, the reaction can be executed under "open-flask" conditions under air and in the presence of residual water without significantly affecting the reaction outcome (entries 4 and 5) and is insensitive to the polarity of the solvent (entries 6 and 7). Control experiments confirm that this reaction relies both on visible light (entry 8) and catalyst (entry 9). Without catalyst, asymmetric induction is obviously not feasible but small amounts of racemic product are formed.

With simple and robust reaction conditions at hand, we next investigated the substrate scope using **Δ-RhS** (Figure 2 and Figure 3). A variety of α,β-unsaturated imidazoles bearing different substituents at the β-aryl moiety provided the [2+2] addition products in good to excellent yields (up to 97%), high diastereoselectivities (up to 16:1 d.r.), and essentially complete enantioselectivities (up to >99% ee) independent of the electronic nature or position of the substituents (**3a–j**) (Figure 2). Importantly, the imidazole moiety can be replaced by other coordinating groups, such as pyridine (**3k**) and the synthetically very useful pyrazoles (**3l–q**), providing the potential for further transformations. Besides dienes, a wide range of alkenes were

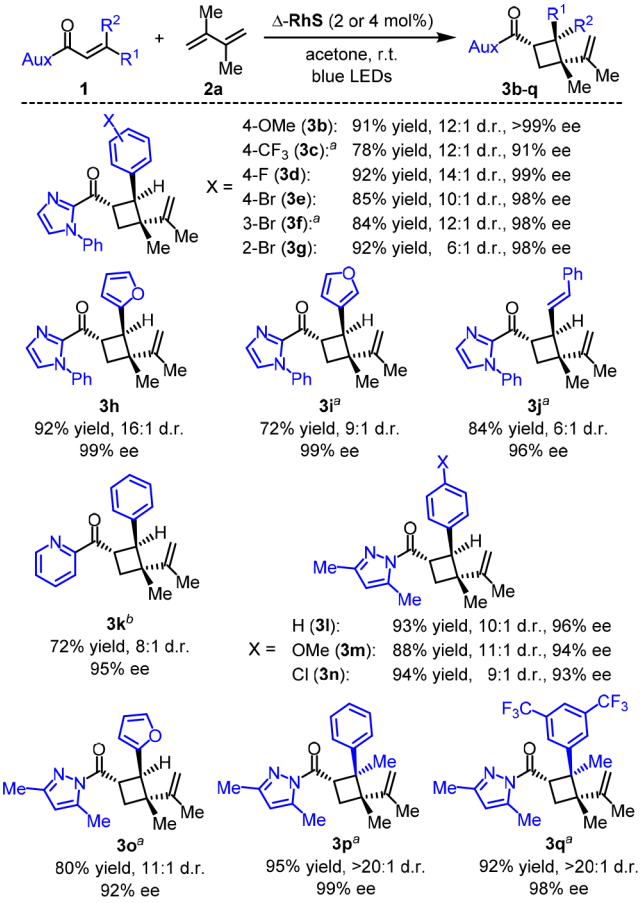


Figure 2. Scope with respect to α,β-unsaturated carbonyl compounds. Reaction conditions: see Table 1, entry 2. [a]Performed with 4.0 mol % of **Δ-RhS** and 1.0 mmol of **2a**. [b]Performed in MeCN/acetone 1:1. Configurations were assigned with crystal structures of **3e** and a derivative of **3p**.

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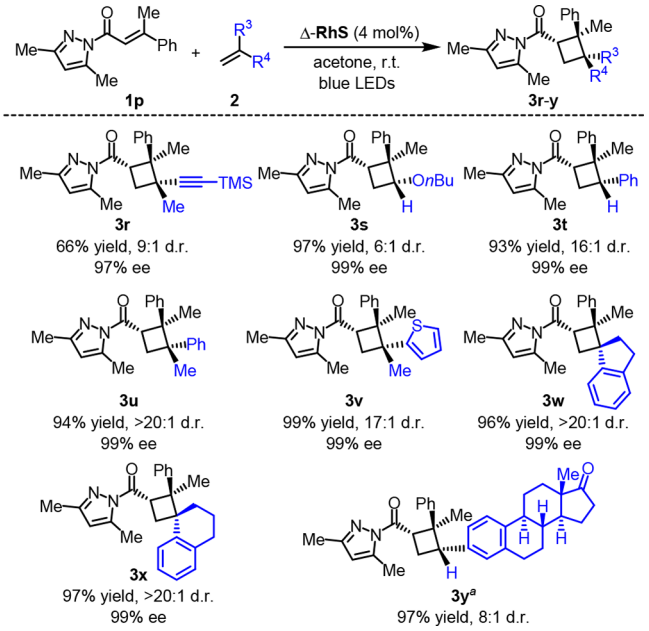

Figure 3. Scope with respect to alkenes. Reaction conditions: (*E*)-**1p** (0.10 mmol), alkene **2** (1.0 mmol), and **Δ-RhS** (4.0 mol %) in acetone (0.2 M, 0.5 mL) were stirred at room temperature under irradiation with blue LEDs (24 W). [a]Performed with 0.3 mmol of alkene in CH_2Cl_2 (0.2 M, 0.5 mL).

well accommodated in this transformation, including an enyne (**3r**), a vinyl ether (**3s**), and styrenes (**3t**–**y**) (Figure 3). However, simple aliphatic alkenes and internal alkenes did not provide any desired products (see Supporting Information). It is worth noting that cyclobutanes with three contiguous stereogenic centers and vicinal all-carbon quaternary stereocenters can be constructed in a single step using this new methodology in high yields, with excellent d.r. and ee (**3p**–**r**, **3u**–**x**), highlighting the versatility of this protocol in generating molecular complexity in a catalytic, asymmetric fashion.[18] Furthermore, this transformation can be applied to the late-stage modification of complex biomolecules (**3y**). In summary, this novel methodology provides a very simple protocol to access structurally complex cyclobutanes in a catalytic and highly stereoselective fashion and therefore constitutes a valuable complement to existing protocols.[9] Very useful catalytic asymmetric photoinduced[9] and thermal[9b] [2+2] cycloadditions have been reported. However, the here introduced methodology is unique in its ability to install two adjacent all-carbon quaternary stereocenters (**3p**–**r**, and **3u**–**x**) including spiro centers (**3w** and **3x**), in an intermolecular fashion.

The proposed mechanism is shown in Figure 4.[19] Substrate **1** coordinates to the rhodium catalyst via an established *N*,*O*-chelate (intermediate **I**)[14] and is excited by visible light to its lowest singlet state (S_1, intermediate **II**). After intersystem crossing (ISC), the excited triplet state (T_1, intermediate **III**) reacts with alkene **2** under control of the stereochemistry by the chiral catalyst, generating the rhodium-bound 1,4-diradical intermediate **IV**. After ISC and cyclization, the Rh-coordinated [2+2] cycloaddition product (intermediate **V**) is formed.[20] A subsequent release of product **3** and recoordination of unreacted substrate then closes the catalytic cycle.

The excited state redox potentials of the rhodium/substrate complex **RhS**-**1a**, estimated from the redox potentials of ground

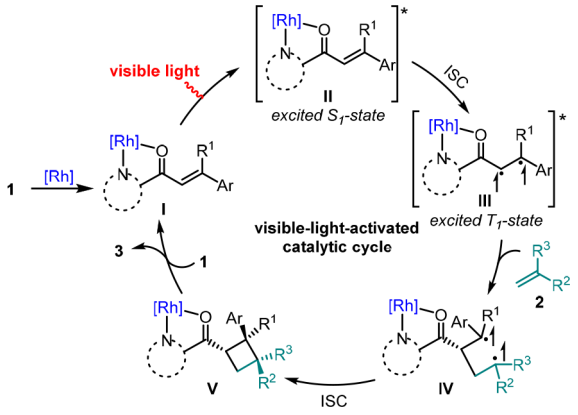

Figure 4. Proposed mechanism. ISC = intersystem crossing.

state and the calculated S_0–T_1 gap ($E^{[Rh]+/[Rh]*}$ = −0.78 V, $E^{[Rh]*/[Rh]^-}$ = +0.88 V vs Fc/Fc^+), are insufficient for an effective reduction or oxidation of substrate **2** (for styrene, E_p^{red} = −2.91 V vs Ag/Ag^+; $E_{1/2}^{ox}$ = +2.05 V vs SCE)[21] and render a photoredox process unlikely. Instead, the direct, stereocontrolled reaction of the intermediate rhodium/substrate complex in its T_1 state (intermediate **III**) with the alkene cosubstrate is supported by a number of experiments.[22] First, related [2+2] cycloadditions have been reported to proceed through the triplet state of one of the involved alkenes.[9,19] Indeed, the racemic [2+2] cycloaddition **1a** + **2a** → **3a** can be catalyzed by the triplet sensitizer benzil (Figure 5a).[23] Second,

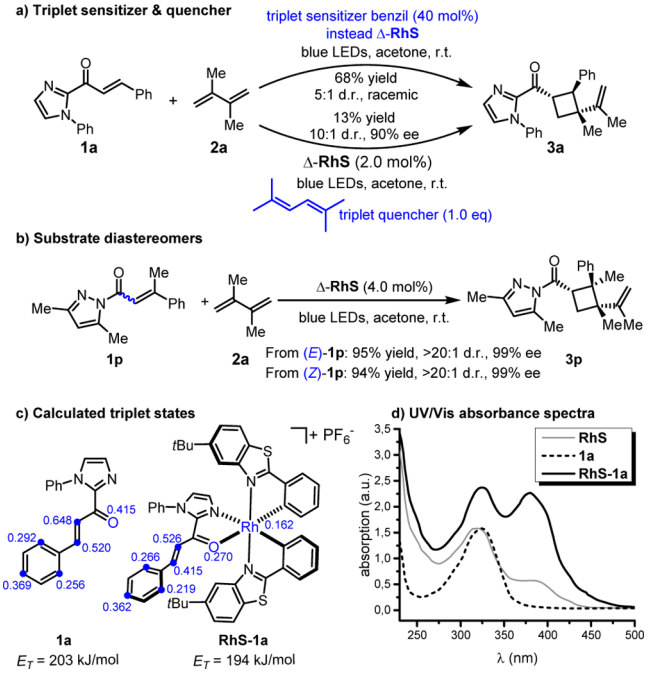

Figure 5. Mechanistic experiments. For panel c, only spin densities >0.1 are shown.

the reaction **1a** + **2a** → **3a** is significantly inhibited by the triplet quencher 2,5-dimethylhexa-2,4-diene (Figure 5a).[24] Third, computational studies reveal that in the T_1 state of the rhodium/substrate complex **RhS**-**1a**, the spin density is localized at the alkene carbons (Figure 5c), consistent with the observed reactivity toward [2+2] cycloadditions. This should lead to a configurational lability of the alkene. Indeed,

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the stereochemical outcome of the reaction is found to be independent of the configuration of the double bond in substrate **1p** (Figure 5b). Forth, when executed in the presence of oxygen, the efficient formation of singlet oxygen was detected, which is furthermore indicative of the formation of the **RhS-1a** complex in its excited T_1 state (see Supporting Information).

Finally, the question remains how almost complete enantioselectivities of >99% ee can be observed given the visible-light-activated, racemic background reaction in the absence of the catalyst (Table 1, entry 9). UV/vis spectra reveal that complex **RhS-1a** (intermediate **I**) (ε_{400} = 34 950 M^{-1} cm^{-1}) has a molar extinction coefficient that is 169 times higher than the free substrate (ε_{400} = 207 $M^{-1}cm^{-1}$) at 400 nm (Figure 5d). Thus, the rhodium/substrate complex serves as a light harvesting antenna and suppresses most of the background reaction.[7]

In conclusion, we here introduced a previously elusive reaction scheme where a chiral Lewis acid is directly activated by visible light to catalyze a highly stereoselective [2+2] cycloaddition reaction, thus acting both as the visible light harvesting antenna and as the chiral entity to achieve excellent asymmetric induction. Based on a simple setup with a single catalyst, complex cyclobutanes can be accessed with high diastereo- and enantioselectivities. We anticipate that this design will spur further investigations into asymmetric photochemistry via stereocontrolled reactions of photoexcited substrate/catalyst complexes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b04363.

Experimental details and chiral HPLC traces (PDF)
Data for $C_{24}H_{23}BrN_2O$ (CIF)
Data for $C_{25}H_{28}N_2O_2S$ (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Brimioulle, R.; Lenhart, D.; Maturi, M. M.; Bach, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 3872.

(2) (a) Uraguchi, D.; Kinoshita, N.; Kizu, T.; Ooi, T. *J. Am. Chem. Soc.* **2015**, *137*, 13768. (b) Murphy, J. J.; Bastida, D.; Paria, S.; Fagnoni, M.; Melchiorre, P. *Nature* **2016**, *532*, 218. (c) Zuo, Z.; Cong, H.; Li, W.; Choi, J.; Fu, G. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2016**, *138*, 1832. (d) Stache, E. E.; Rovis, T.; Doyle, A. G. *Angew. Chem., Int. Ed.* **2017**, *56*, 3679. (e) Yang, Q.; Zhang, L.; Ye, C.; Luo, S.; Wu, L.-Z.; Tung, C.-H. *Angew. Chem., Int. Ed.* **2017**, *56*, 3694. (f) Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. *Nat. Chem.* **2017**, DOI: 10.1038/nchem.2748.

(3) (a) Pandey, G. *Top. Curr. Chem.* **1993**, *168*, 175. (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.

(4) (a) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263. (b) Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 58.

(5) Albini, A. *Synthesis* **1981**, 249.

(6) (a) Heitz, D. R.; Tellis, J. C.; Molander, G. A. *J. Am. Chem. Soc.* **2016**, *138*, 12715. (b) Shields, B. J.; Doyle, A. G. *J. Am. Chem. Soc.* **2016**, *138*, 12719. (c) Welin, E. R.; Le, C.; Arias-Rotondo, D. M.; McCusker, J. K.; MacMillan, D. W. C. *Science* **2017**, *355*, 380.

(7) (a) Guo, H.; Herdtweck, E.; Bach, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7782. (b) Brimioulle, R.; Bach, T. *Science* **2013**, *342*, 840. (c) Brimioulle, R.; Bach, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 12921. (d) Brimioulle, R.; Bauer, A.; Bach, T. *J. Am. Chem. Soc.* **2015**, *137*, 5170.

(8) (a) Maturi, M. M.; Bach, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 7661. (b) Tröster, A.; Alonso, R.; Bauer, A.; Bach, T. *J. Am. Chem. Soc.* **2016**, *138*, 7808.

(9) (a) Poplata, S.; Tröster, A.; Zou, Y.-Q.; Bach, T. *Chem. Rev.* **2016**, *116*, 9748. (b) Xu, Y.; Conner, M. L.; Brown, M. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 11918.

(10) For pioneering work on Lewis acid catalysis for photochemical [2+2] cycloadditions, see: (a) Lewis, F. D.; Howard, D. K.; Oxman, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 3344. (b) Lewis, F. D.; Quillen, S. L.; Hale, P. D.; Oxman, J. D. *J. Am. Chem. Soc.* **1988**, *110*, 1261. (c) Lewis, F. D.; Barancyk, S. V. *J. Am. Chem. Soc.* **1989**, *111*, 8653.

(11) Blum, T. R.; Miller, Z. D.; Bates, D. M.; Guzei, I. A.; Yoon, T. P. *Science* **2016**, *354*, 1391.

(12) (a) Hopkinson, M. N.; Sahoo, B.; Li, J.-L.; Glorius, F. *Chem. - Eur. J.* **2014**, *20*, 3874. (b) Skubi, K. L.; Blum, T. R.; Yoon, T. P. *Chem. Rev.* **2016**, *116*, 10035.

(13) For recent examples, see: (a) Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. *Science* **2016**, *351*, 681. (b) Ding, W.; Lu, L.-Q.; Zhou, Q.-Q.; Wei, Y.; Chen, J.-R.; Xiao, W.-J. *J. Am. Chem. Soc.* **2017**, *139*, 63.

(14) Zhang, L.; Meggers, E. *Acc. Chem. Res.* **2017**, *50*, 320.

(15) Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L.-A.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. *Nature* **2014**, *515*, 100.

(16) Photoexcited **IrS** might transfer energy to the free substrate **1a**, followed by a racemic cycloaddition. See Supporting Information for a comparison with other iridium photocatalysts.

(17) Ma, J.; Shen, X.; Harms, K.; Meggers, E. *Dalton Trans.* **2016**, *45*, 8320.

(18) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181.

(19) Schuster, D. I.; Lem, G.; Kaprinidis, N. A. *Chem. Rev.* **1993**, *93*, 3.

(20) Wilsey, S.; González, L.; Robb, M. A.; Houk, K. N. *J. Am. Chem. Soc.* **2000**, *122*, 5866.

(21) (a) Senboku, H.; Komatsu, H.; Fujimura, Y.; Tokuda, M. *Synlett* **2001**, 418. (b) Schepp, N. P.; Johnston, L. J. *J. Am. Chem. Soc.* **1996**, *118*, 2872.

(22) The insensitivity of this reaction to the presence of air is not contradictory to a triplet mechanism. See the Supporting Information for further experiments and a discussion.

(23) Herkstroeter, W. G.; Lamola, A. A.; Hammond, G. S. *J. Am. Chem. Soc.* **1964**, *86*, 4537.

(24) *Handbook of Photochemistry*, 3rd ed.; Montalti, M.; Credi, A.; Prodi, L.; Gandolfi, M. T., Ed.; CRC, Taylor & Francis Group: Boca Raton, FL, 2006.

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