

Photochemistry

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Asymmetric Photocatalysis by Intramolecular Hydrogen-Atom Transfer in Photoexcited Catalyst–Substrate Complex

Chenhao Zhang⁺, Shuming Chen⁺, Chen-Xi Ye, Klaus Harms, Lili Zhang, K. N. Houk,^{*} and Eric Meggers^{*}

Abstract: 3-(2-Formylphenyl)-1-pyrazol-1-yl-propenones undergo an asymmetric photorearrangement to benzo-[d]cyclopropa[b]pyranones with up to >99% ee, which is catalyzed by a bis-cyclometalated rhodium catalyst in the presence of visible light. Mechanistic experiments and DFT calculations support a mechanism in which a photoexcited catalyst/substrate complex triggers an intramolecular hydrogen-atom transfer followed by a highly stereocontrolled hetero-Diels–Alder reaction. In this reaction scheme, the rhodium catalyst fulfills multiple functions by 1) enabling visible-light $\pi \rightarrow \pi^*$ excitation of the catalyst-bound enone substrate, 2) facilitating the hydrogen-atom transfer, and 3) providing the asymmetric induction for the hetero-Diels–Alder reaction.

Photochemistry provides new synthetic and mechanistic opportunities for asymmetric catalysis.^[1] For example, visible light has been used as a convenient and mild source of energy to generate free radicals, which are then interfaced with an asymmetric catalysis cycle.^[2] In such systems, the photochemistry is not part of the catalytic cycle and often serves as an inducer of a thermal chain process. This role is distinct from mechanistic scenarios in which the photoexcited state is directly embedded within an asymmetric catalysis cycle, thereby opening untapped opportunities for exploiting the special reactivity of photoexcited states in the context of asymmetric catalysis.^[3]

Our group recently demonstrated that bis-cyclometalated iridium(III) and especially rhodium(III) complexes are exquisite catalysts for realizing visible-light-activated asymmetric catalysis.^[4,5] Upon binding to a substrate and undergoing selective visible-light activation of the formed catalyst/substrate complexes, such photoexcited assemblies are capa-

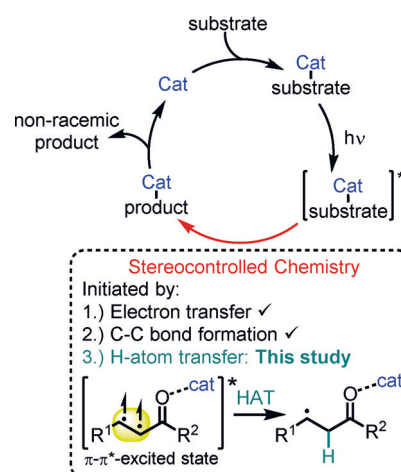


Figure 1. Photoinduced asymmetric catalysis cycle in which visible-light-photoexcited catalyst/substrate complexes are key intermediates.

ble of undergoing stereocontrolled chemical transformations, either through an initial outersphere electron transfer or by engaging in direct stereocontrolled bond-forming reactions (Figure 1).^[5] The realization of new reaction modes of photoexcited catalyst/substrate complexes is highly desirable for developing visible-light-activated asymmetric conversions that are otherwise elusive.

Here we report a unique example of a visible-light-activated catalyst/substrate complex engaging in a hydrogen-atom transfer (HAT) reaction to generate a catalyst-bound reactive intermediate, which is then primed to undergo a highly stereocontrolled intramolecular hetero-Diels–Alder reaction.

We previously found that upon binding to bis-cyclometalated rhodium catalysts, α,β -unsaturated *N*-acyl pyrazoles can undergo $\pi \rightarrow \pi^*$ excitation under visible light. We further demonstrated that these ligand-centered excited states can perform stereocontrolled cycloaddition reactions.^[3d,f,6] At the onset of this study we were speculating that such photoexcited catalyst-bound enones might instead be capable of engaging in HAT reactions to generate catalyst-bound reactive intermediates followed by stereocontrolled transformations. We were inspired by a reaction reported by Xia and co-workers in which (*E*)-ethyl 3-(2-formylphenyl)acrylate (**1a**), upon photolysis with a 500 W high-pressure mercury lamp, underwent an interesting rearrangement to the cyclopropane **2a** (Table 1, entry 1), and this reaction was proposed to proceed through an intramolecular HAT from the aldehyde to the triplet excited state of the enone.^[7] As major drawbacks, the reaction required intense UV light and provided the product

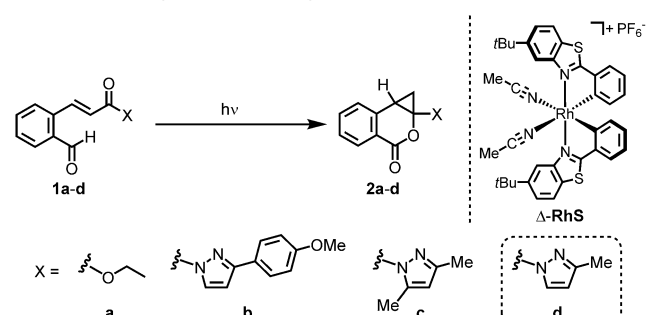
[*] C. Zhang,^[+] C.-X. Ye, Dr. K. Harms, Dr. L. Zhang, Prof. Dr. E. Meggers
Fachbereich Chemie, Philipps-Universität Marburg
Hans-Meerwein-Straße 4, 35043 Marburg (Germany)
E-mail: meggers@chemie.uni-marburg.de

Dr. S. Chen,^[+] Prof. Dr. K. N. Houk
Department of Chemistry and Biochemistry, University of California
Los Angeles, CA 90095-1569 (USA)
E-mail: houk@chem.ucla.edu

[*] These authors contributed equally to this work.

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
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Table 1: Initial experiments and optimization of reaction conditions.^[a]


Entry	Substrate	Cat (mol %)	Light ^[b]	Solvent	t [h]	Yield [%] ^[c]	ee [%] ^[d]
1 ^[e]	1a	none	UV light	benzene	5	89	—
2	1b	4	blue LEDs	CH ₂ Cl ₂	16	60	38
3	1c	4	blue LEDs	CH ₂ Cl ₂	16	74	97
4	1d	4	blue LEDs	CH ₂ Cl ₂	16	83	98
5	1d	2	blue LEDs	CH ₂ Cl ₂	24	71	95
6	1d	1	blue LEDs	CH ₂ Cl ₂	24	70	95
7	1d	0.5	blue LEDs	CH ₂ Cl ₂	48	46 ^[f]	95
8	1d	4	blue LEDs	acetone	16	72	97
9	1d	4	blue LEDs	MeCN	16	trace	—
10 ^[g]	1d	4	blue LEDs	CH ₂ Cl ₂	20	75	96
11	1d	4	CFL	CH ₂ Cl ₂	36	86	96
12	1d	none	blue LEDs	CH ₂ Cl ₂	48	0	—
13	1d	4	dark	CH ₂ Cl ₂	48	0	—

[a] Standard reaction conditions for entries 2–8: Substrates **1b–d** (0.1 mmol) in the indicated solvent (2.0 mL) with Δ -RhS (0.5–4 mol %) photolyzed for the indicated time under an atmosphere of N₂. [b] 24 W blue LEDs with emission maximum at 450 nm or 23 W CFL. [c] Yields of isolated products. [d] Enantioselectivities determined by HPLC on chiral stationary phase. [e] Taken from Ref. [7]. Irradiation with a 500 W high-pressure mercury lamp in combination with a Pyrex filter. [f] The conversion was 67%. [g] Under an atmosphere of air.

as a racemic mixture. We speculated that by replacing the ester with an *N*-acyl pyrazole moiety to generate a binding site for the rhodium catalyst, the rearrangement could be rendered visible-light-activated and asymmetric. Accordingly, when we submitted *N*-acyl 3-(4-methoxyphenyl)pyrazole (**1b**) to photolysis with blue LEDs ($\lambda_{\text{max}} = 450$ nm) in the presence of catalytic amounts of the chiral-at-metal rhodium catalysts Δ -RhS (4 mol %), **2b** was obtained in an encouraging 60% yield but with a disappointing 38% *ee* (entry 2). However, it turned out that this rearrangement is very sensitive to the nature of the pyrazole substituent. Using instead the *N*-acyl 3,5-dimethylpyrazole **1c** provided the cyclopropane in 74% yield and 97% *ee* as a single diastereomer (entry 3). The best results were achieved with the *N*-acyl 3-methylpyrazole **1d**, which provided the rearrangement product in 83% yield with 98% *ee* upon photolysis in CH₂Cl₂ at room temperature for 16 hours (entry 4). Reducing the catalyst loading fourfold to 1.0 mol % only gradually affected the yield and enantioselectivity (entries 5 and 6). Even at a catalyst loading of merely 0.5 mol %, 46% of the pyranone **4d** with 95% *ee* was isolated after a longer irradiation time of 48 hours, thus demonstrating the efficiency of this asymmetric photorearrangement (entry 7). The reaction can be performed in other solvents, such as acetone, with

similar results (entry 8), but MeCN only provided traces of the product (entry 9). Interestingly, the presence of air only slightly affects yield and enantioselectivity, indicating that free-radical chemistry is not operational in this photoreaction (entry 10). Finally, CFL as a light source provided similar results (entry 11). Control experiments furthermore confirmed that the reaction requires the rhodium catalyst and light for product formation (entries 12 and 13).

With the optimized reaction conditions in hand, we screened substrates for this reaction. Figure 2 reveals that this asymmetric visible-light-activated photorearrangement tolerates methyl substituents at any position of the phenyl moiety (**2e–h**), bulky substituents (**2i, 2j**), electron-withdrawing substituents (**2k–q**), electron-donating substituents (**2r–u**), and a thioether (**2v**). For all these reactions, yields of 50–93% and enantioselectivities of 87–>99% *ee* were observed. Lower yield and lower enantioselectivity were obtained with a thiophene derivative (cyclopropane **2w**), but a methyl group in the β -position of the α,β -unsaturated *N*-acyl pyrazole provided the corresponding rearrangement product

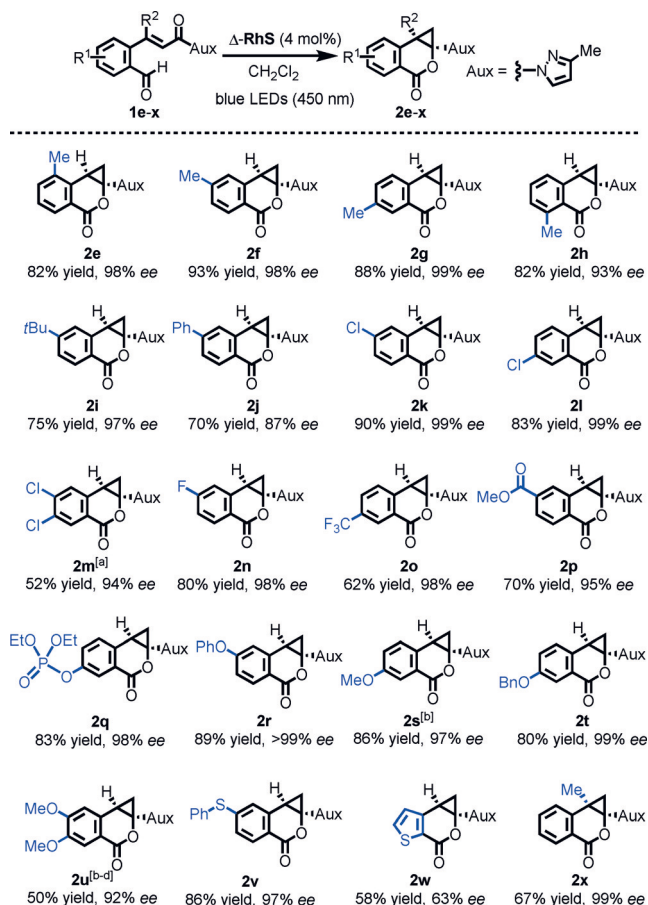


Figure 2. Substrate scope. Standard conditions (entry 4 of Table 1) were applied if not indicated otherwise. Modified reaction conditions were used for obtaining products **2m**, **2s**, and **2u**. [a] Catalyst loading of 8 mol % was used to increase the *ee* value. [b] Reduced substrate concentration of 0.005 M was used to improve the yield. [c] Photolysis with weaker blue LEDs (3 W, 420 nm) for 10 h afforded an improved yield. [d] 1,2-Dichloroethane was used as the solvent which provided a higher *ee* value.

2x, containing an all-carbon quaternary center, in 67% yield and excellent 99% *ee*. For practical reasons, it is worth noting that this new asymmetric photoreaction can be scaled up. On a scale of 4.5 mmol (1.08 g), the reaction **1d**→**2d** afforded an improved yield of 90% with a slightly increased enantiomeric excess of 99% and the rhodium catalyst was reisolated in 86% yield by capture with an auxiliary ligand in a procedure reported recently.^[8]

The proposed mechanism is shown in Figure 3. The catalytic cycle starts with the rhodium catalyst binding to the *N*-acyl pyrazole substrate in a bidentate fashion (int. **I**). This catalyst/substrate complex constitutes the photoactive species. Upon absorption of visible light, the photoexcited

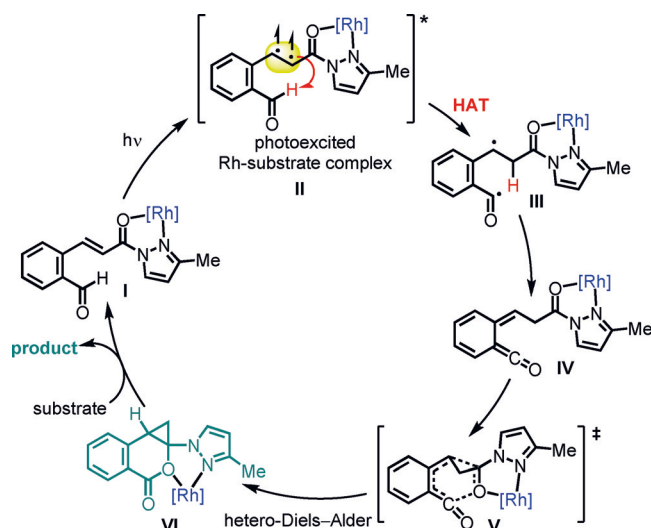
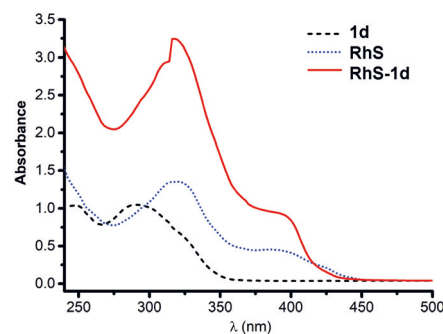


Figure 3. Proposed mechanism.

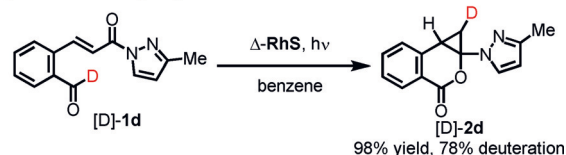
catalyst/substrate complex **II** is formed. In previous work we demonstrated that such rhodium-bound α,β -unsaturated *N*-acyl pyrazoles populate a ligand-centered $\pi \rightarrow \pi^*$ photoexcited state with the spin density localized mainly at the olefinic double bond.^[3d,f] The close vicinity of the aldehyde moiety now permits HAT to the α -position to generate the diradical intermediate **III**.^[9,10] An intersystem crossing to the singlet-state ketene **IV** sets the stage for an intramolecular asymmetric hetero-Diels-Alder reaction^[11] to form the rhodium bound cyclopropane product **VI**. Product release and recoordination of new substrate then initiates a new catalytic cycle.

Several control experiments back up this mechanism. Absorption spectra shown in Figure 4a reveal that the catalyst/substrate complex absorbs visible light significantly more efficiently compared to the catalyst (**RhS**), whereas the free substrate does not absorb significantly in the visible-light region. Thus, under the reaction conditions, the catalyst/substrate complex is the main light absorbing species. The HAT reaction from the photoexcited catalyst/substrate complex **II** was verified by a deuterium isotope-labelling experiment. The reaction of **[D]-1d**, with a deuterated aldehydic position, yielded **[D]-2d**, in which the deuterium ended up in the expected position of the cyclopropane moiety (78% deuteration; Figure 4b).^[12]

a) UV/Vis-absorption



b) Verification of hydrogen atom transfer



c) Background sensitization

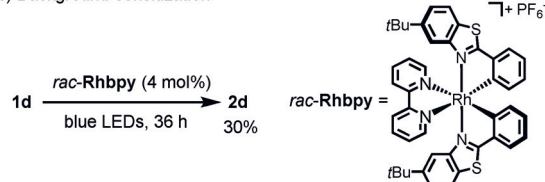


Figure 4. Mechanistic experiments. UV/Vis-absorption spectra measured in CH_2Cl_2 (0.05 mm).

Density-functional theory (DFT) calculations were performed to evaluate the energetic feasibility of the proposed mechanistic pathway (Figure 5a). The intramolecular HAT reaction of the Rh-bound substrate was found to have a free-energy barrier of 8.0 kcal mol⁻¹, compared to 9.7 kcal mol⁻¹ for the free substrate (see Figure S2 in the Supporting Information). After intersystem crossing back to the singlet state to furnish the ketene **IV**, the intramolecular hetero-Diels-Alder reaction leading to the major enantiomer proceeds through **hDA-TS-1** with a barrier of 5.4 kcal mol⁻¹ (Figure 5b). In contrast, **hDA-TS-2**, the hetero-Diels-Alder transition state leading to the minor enantiomer, has a much higher barrier of 16.6 kcal mol⁻¹. The 11.2 kcal mol⁻¹ difference in free energy between **hDA-TS-1** and **hDA-TS-2** can be attributed to 1) stabilization from a π - π stacking interaction between the aryl group on the substrate and the ligand framework in **hDA-TS-1**, and 2) severe steric clashes between the substrate and the *tert*-butyl group on the ligand in **hDA-TS-2**.

Even though the direction of enantioselectivity predicted by our calculations is in good agreement with the experimentally observed asymmetric induction, the calculated $\Delta\Delta G^\ddagger$ value of 11.2 kcal mol⁻¹ far exceeds the experimental value of 2.2–2.4 kcal mol⁻¹ (corresponding to 98% *ee*). Further calculations revealed that two possible triplet excited-state structures exist for **II**, one with the substrate alkene carbon centers possessing most of the spin density (**II-1** in Figure 5c), and the other with the majority of its spin density localized on Rh (**II-2** in Figure 5c). Though the two triplet excited species lie

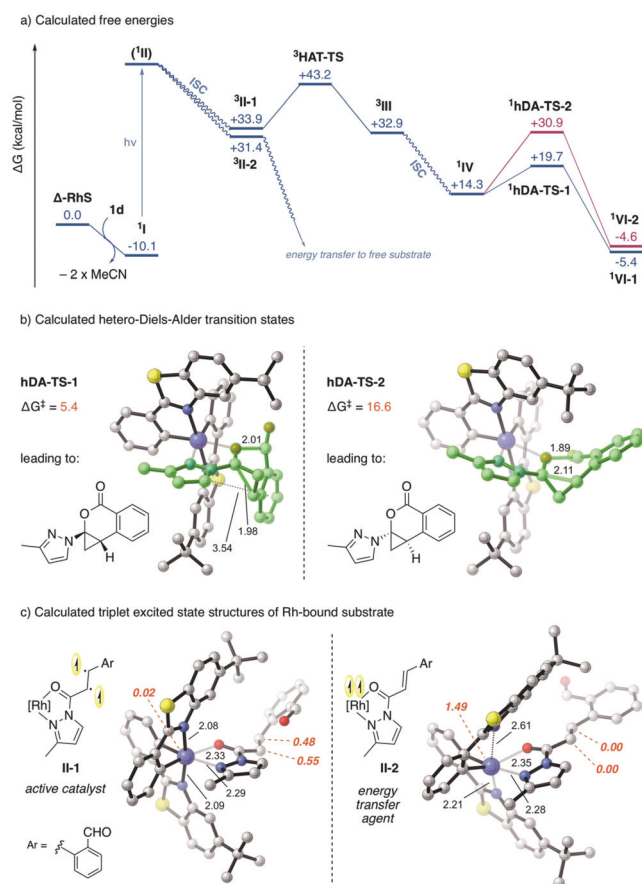


Figure 5. Computational study. a) Computed free-energy diagram of the photoinduced HAT/hetero-Diels-Alder cascade reaction catalyzed by Δ -RhS. b) Calculated transition states for the intramolecular hetero-Diels-Alder reaction leading to major and minor product enantiomers. Energies are in kcal mol⁻¹, and interatomic distances are in Ångströms. Hydrogen atoms are omitted for clarity. c) Two different calculated triplet excited states, **II-1** and **II-2**, for the Rh-bound substrate. Interatomic distances denoted in Ångströms. Hydrogen atoms are omitted for clarity. Spin densities on atoms are shown with red italic numbers.

close in energy, **II-2** is incapable of undergoing the intramolecular HAT reaction, and instead serves as a triplet sensitizer^[13] transferring its energy to the free substrate **1d**. The resultant background reaction might account for the lower than computationally predicted experimental *ee* value. To experimentally confirm that background sensitization is eroding enantioselectivity, *rac*-**Rhbp**, a Rh complex incapable of coordinating to the substrate was synthesized and subjected to standard experimental conditions with **1d** (Figure 4c). And indeed, as a result **2d** was obtained in 30% yield after photolysis for 36 hours. Despite this undesirable background sensitization, high enantioselectivities are obtained because of extremely high levels of asymmetric induction in the Rh-mediated hetero-Diels-Alder reaction.

In conclusion, we report herein a unique example of a catalytic asymmetric photoreaction which closely combines a HAT from a photoexcited catalyst/substrate complex followed by a highly stereocontrolled intramolecular oxo-Diels-Alder reaction. Rhodium catalyst binding to the

substrate does not only facilitate a visible-light-induced substrate-centered $\pi \rightarrow \pi^*$ excitation, which permits the intramolecular HAT, but also enables a highly stereocontrolled intramolecular oxo-Diels-Alder reaction through a very congested transition state. Despite its mechanistic appeal, the photochemistry introduced here provides access to non-racemic, complex tricyclic architectures which are attractive building blocks for further derivatizations.^[14] Further catalytic schemes which exploit the unique reactivities of photoexcited catalyst/substrate complexes in the context of asymmetric catalysis are ongoing in our laboratory.

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Conflict of interest

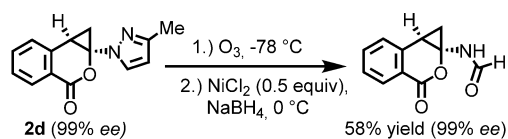
The authors declare no conflict of interest.

Keywords: asymmetric catalysis · Diels-Alder · hydrogen atom transfer · photochemistry · rhodium

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