JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Visible-Light-Activated Asymmetric β-C−H Functionalization of Acceptor-Substituted Ketones with 1,2-Dicarbonyl Compounds

Jiajia Ma,[†] Anthony R. Rosales,[‡] Xiaoqiang Huang,[†] Klaus Harms,[†] Radostan Riedel,[†] Olaf Wiest,[‡,§] and Eric Meggers*[,†]

[†]Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Strasse 4, 35043 Marburg, Germany

[‡]Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556, United States

[§]Laboratory of Computational Chemistry and Drug Design, School of Chemical Biology and Biotechnology, Peking University, Shenzhen Graduate School, Shenzhen 518055, People's Republic of China

Supporting Information

ABSTRACT: We report a visible-light-activated asymmetric β-C(sp^3)−H functionalization of 2-acyl imidazoles and 2-acylpyridines with 1,2-dicarbonyl compounds (typically α-ketoesters) catalyzed by a tailored stereogenic-at-rhodium Lewis acid catalyst. The C−C bond formation products are obtained in high yields (up to 99%) and with excellent stereoselectivities (up to >20:1 dr and up to >99% ee). Experimental and computational studies support a mechanism in which a photoactivated Rh-enolate transfers a single electron to the 1,2-dicarbonyl compound followed by proton transfer and a subsequent stereocontrolled radical−radical recombination.

The catalytic, asymmetric functionalization of C(sp^3)−H groups combines the desire to build complex structures in a sustainable fashion with the need for efficient methods to implement stereogenic carbon centers.[1] Carbonyl compounds including aldehydes, ketones, esters, and amides are ubiquitous functional groups in organic molecules. Though their α-C(sp^3)−H functionalization is well established,[2] significant efforts are currently devoted to the development of strategies for the activation of β-C(sp^3)−H groups in a catalytic and asymmetric fashion. As of today, only a limited number of such methods have been reported.[3−8] For example, Yu recently developed a catalytic enantioselective arylation and borylation of β-methylenes of aliphatic amides by palladium catalysis in the presence of a chiral bidentate ligand which proceeds through a palladacycle intermediate (**A** in Figure 1a).[4] Organocatalysis has been demonstrated to be an alternative strategy to enable the asymmetric β-functionalization (Figure 1b). Wang[5a] and Hayashi[5b] independently reported applying a chiral secondary amine to activate aldehydes in the presence of an external oxidant, thereby converting the β-methylene after two electron oxidation into an electrophilic carbon (**B**) and furnishing the concept of "oxidative enamine catalysis". A similar concept was also realized using a chiral *N*-heterocyclic carbene (NHC) catalyst (see intermediate **C**).[6] Chi extended this strategy by using a chiral NHC catalyst in the presence of stoichiometric amounts of base to convert a saturated ester or anhydride into an enol anion intermediate (**D**), in which the β-methylene group constitutes a nucleophilic carbon.[7]

The current requirement for stoichiometric amounts of base, external oxidants, high catalyst loadings, additives, and often limited stereoselectivities or low isolated yields reveal that new methodology is highly desirable. Here we introduce a different strategy for the catalytic asymmetric β-C−H functionalization of carbonyl compounds that is based on weakening of the β-C−H bond upon catalyst-induced enolate formation and visible-light induced single electron transfer. A subsequent proton transfer then sets the stage for a stereocontrolled radical−radical recombination under control of the chiral catalyst (Figure 1c).

Inspired by the reactivity of ketones in photochemical reactions,[9] we started our study by investigating the reaction of

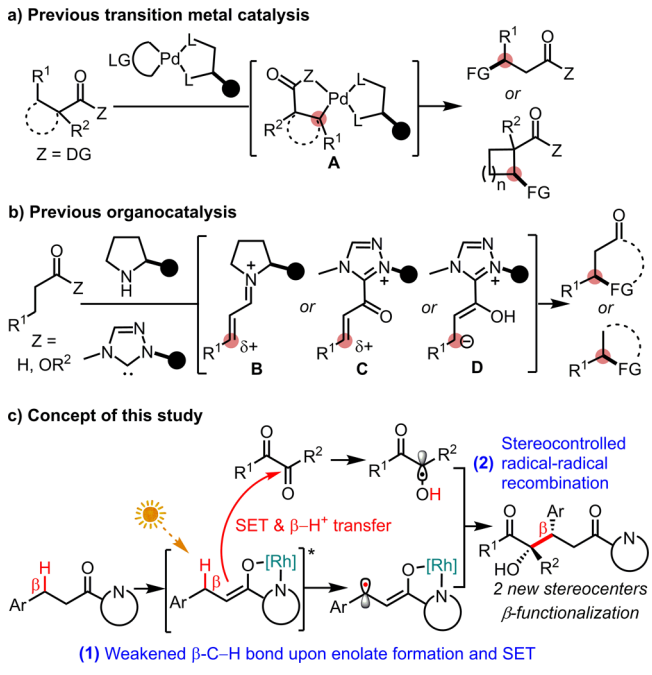


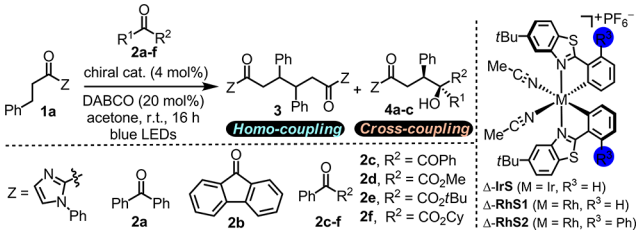
Figure 1. Previous reports and this study on the asymmetric β-C(sp^3)−H functionalization of carbonyl compounds. DG = directing group. LG = leaving group. FG = functional group.

Received: August 28, 2017
Published: November 21, 2017

DOI: 10.1021/jacs.7b09152
J. Am. Chem. Soc. 2017, 139, 17245−17248

2-acyl imidazole **1a** with a set of different carbonyl compounds **2a–f** in the presence of the stereogenic-at-rhodium catalyst Δ-**RhS1**[10] (4 mol %) and DABCO (20 mol %) under the irradiation with blue LEDs (Table 1).[11] To our surprise, the

Table 1. Reaction Development and Control Experiments[a]



			NMR yield (%)[b]			
entry	catalyst	2a–f	3	4	dr[c]	ee (%)[d]
1	Δ-**RhS1**	**2a**	0	0	n.a.	n.a.
2	Δ-**RhS1**	**2b**	40	0	n.d.	n.d.
3	Δ-**RhS1**	**2c**	73	0	>20:1	>99
4	Δ-**RhS1**	**2d**	0	95 (**4a**)	5.5:1	98
5	Δ-**RhS1**	**2e**	0	95 (**4b**)	5.9:1	98
6	Δ-**RhS1**	**2f**	0	98 (**4c**)	6.4:1	98
7	Δ-**RhS2**	**2f**	0	98 (**4c**)	10.0:1	>99
8	Δ-**IrS**	**2f**	0	0	n.a.	n.a.
9[e]	Δ-**RhS2**	**2f**	0	0	n.a.	n.a.

[a]Reaction conditions: **1a** (0.1 mmol), **2a–f** (0.3 mmol), chiral Lewis acid catalyst (0.004 mmol), and DABCO (0.02 mmol) in acetone (1 mL) stirred at r.t. for 16 h under N_2 and irradiated with blue LEDs (24 W) unless otherwise noted. [b]Determined by ^{1}H NMR of the crude products. [c]Determined by ^{1}H NMR analysis of the crude product. [d]Determined by HPLC analysis of the main product on a chiral stationary phase; ee of major diastereomer is shown. [e]Reaction conducted in the dark or under air. r.t. = room temperature. n.d. = not determined. n.a. = not applicable.

course of the reaction strongly depended on the structure of the carbonyl compounds. Whereas no product was observed with benzophenone (**2a**) (entry 1), fluorenone (**2b**) provided the homocoupling product **3** in 40% yield (entry 2). Using the 1,2-diketone benzil (**2c**), the homocoupling product **3** was even formed in a yield of 73% and with excellent diastereoselectivity (>20:1 dr) and enantioselectivity (>99% ee) (entry 3). This asymmetric β-C(sp^3)–H functionalization was encouraging; however, homocouplings are typically of more limited utility and we were thus seeking to establish a more versatile heterocoupling. Revealingly, the α-ketoester **2d** in the presence of Δ-**RhS1** gave a complete switch in the reaction outcome. No homocoupling product **3** was detected but instead the heterocoupling product **4a** formed in high yield (95%) with excellent enantioselectivity (98% ee) and moderate diastereoselectivity of 5.5:1 (entry 4). Exchanging the methyl ester (**2d**) with a more bulky *tert*-butyl (**2e**) or cyclohexyl (**2f**) ester afforded slightly improved diastereoselectivities of 5.9:1 (product **4b**) and 6.4:1 (product **4c**), respectively (entries 5 and 6). We next modified the rhodium catalyst and found that introducing a phenyl group into the cyclometalating ligand, providing the catalyst Δ-**RhS2**,[12] not only improved the diastereoselectivity to 10.0:1 but afforded also a perfect enantioselectivity (>99% ee) at high yield (98%) (entry 7). It is worth noting that a related iridium complex (Δ-**IrS**), which is known to enable photoactivated enolate photoredox chemistry,[13] failed to promote this catalytic, asymmetric β-functionalization (entry 8). Control experiments verified that visible light and oxygen-free conditions are essential for this transformation (entry 9).

A proposed mechanism is outlined in Figure 2. The catalytic cycle is initiated by the bidentate coordination of substrate **1a**

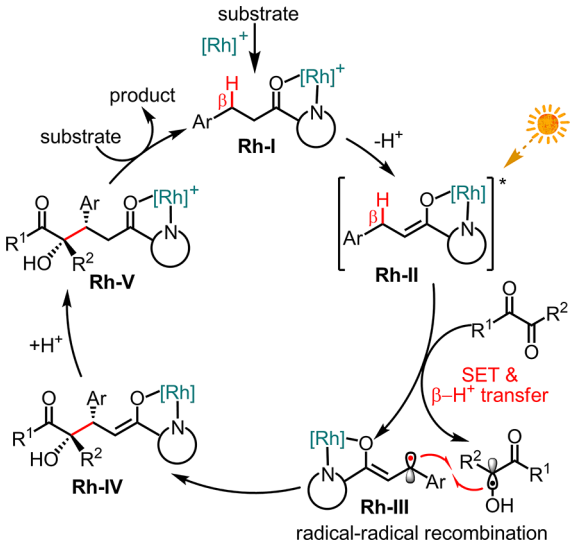


Figure 2. Proposed mechanism.

to the Rh-catalyst (**Rh-I**) followed by a base-induced deprotonation to provide the key intermediate Rh-enolate **Rh-II**. The extinction coefficient at 420 nm for the intermediate Rh-enolate is 3–4 orders of magnitude higher compared to the ketoester **2d** which disfavors a direct excitation of the 1,2-dicarbonyl compound followed by HAT[14–16] and instead supports a mechanism through photoexcited **Rh-II** (see SI). Calculated and measured redox potentials (see SI) are consistent with a reduction of the ketoester **2d** by photoexcited **Rh-II**, followed by a proton transfer, to produce the stabilized, persistent β-carbon-centered radical intermediate **Rh-III**[17] accompanied by formation of α-hydroxyl radical. In the case of using ketoesters **2d–f**, a stereocontrolled radical–radical recombination[18] occurs to provide the cross-coupling intermediate **Rh-IV**, and after protonation the Rh-coordinated product (**Rh-V**). Apparently, the radical–radical recombination efficiency depends, among other factors, on the precise nature of the involved α-hydroxyl radical which can result in a switch between homo- and heterocoupling.[19]

The outlined mechanism is conceptually related to a reported photoredox β-arylation of ketones and aldehydes through a proposed 5π-electron β-enaminyl radical intermediate. However, with respect to asymmetric catalysis, only a single example with 50% ee was provided.[20]

A number of observations support the proposed mechanism. Control experiments in the dark, under air, or in the presence of the radical scavengers TEMPO or BHT, all completely suppress the C–C bond formation (Table 1 and Figure 3a), thereby supporting a radical mechanism. A determined quantum yield of 0.08 is consistent with the absence of a chain process. Radical and enolate intermediate trapping experiments were conducted by adding phenyl vinyl ketone **5** as a trapping reagent (Figure 3b). In these experiments, the C–C bond formation product **6** was isolated in 40% yield and with 87% ee, supporting the intermediate formation of the enolate intermediate (**Rh-II**), which is then trapped by compound **5**.

DOI: 10.1021/jacs.7b09152
J. Am. Chem. Soc. 2017, 139, 17245–17248

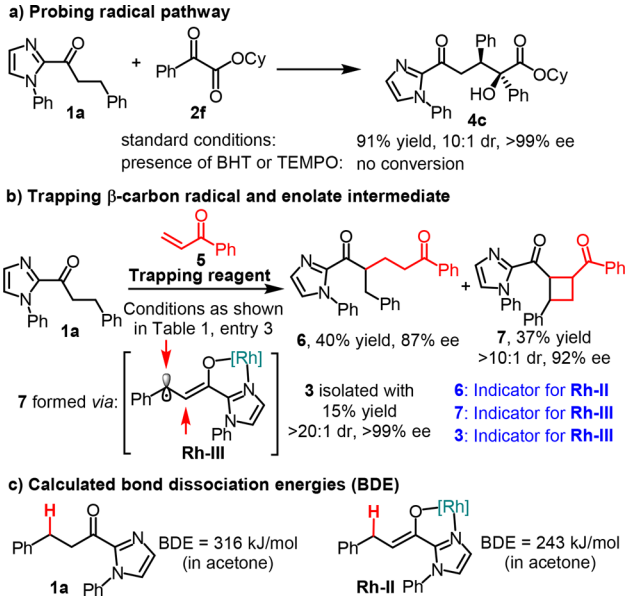


Figure 3. Mechanistic study.

Interestingly, a dual C−C formation product **7** was also obtained in 37% yield and with >10:1 dr and 92% ee, together with some amounts of the homocoupling product **3**, which is supportive of the formation of the electron-rich Rh-enolate radical intermediate **Rh-III**. Computational studies of the key Rh-enolate (**Rh-II**) intermediate at M06/6-31g*/LANL2DZ//6-311++G**/LANL2DZ+CPCM level of theory show that the bond dissociation energy (BDE) of the β-C(sp^3)−H in **Rh-II** is lowered by 73 kJ/mol (316 kJ/mol for **1a** vs 243 kJ/mol for **Rh-II**) (Figure 3c), thus facilitating the formation of the β-carbon radical. Taken together, all mechanistic studies are consistent with the role of the Rh catalyst as both a chiral Lewis acid and light-harvesting antenna which will suppress direct photoactivation of the dicarbonyl reaction partner and promote an electron- and proton-transfer (net hydrogen atom transfer) initiated by photoactivated Rh-enolate **Rh-II**.[21]

We next evaluated the substrate scope with respect to the acceptor-substituted ketones (Figure 4). 2-Acyl imidazoles (products **4c**−**p**) have good tolerance for various functional groups including alkyl groups (**4d** and **4e**), ethers (**4f**−**h**, **4n**), a thioether (**4i**), a hydroxyl (**4j**), bromines (**4k** and **4n**), an olefin (**4o**), and an indole moiety (**4p**). Strongly electron-withdrawing groups (**4l**, **4m**) lead to more sluggish reactions but provided satisfactory results upon heating to 50 °C. However, when introducing a methyl group at the β-position, no C−C formation product (**4q**) was formed and the starting material was recovered with 95% yield (analyzed by ^{1}H NMR). Apparently, the aryl moiety in β-position of the carbonyl group is required to facilitate the β-H activation. 2-Acylpyridines were also found to be tolerated well by providing the C−C formation products (**4ra**−**rc**) with excellent diastereo- and enantioselectivities (>20:1 dr and 97 to >99% ee). It is worth noting that six of these products were obtained with an enantiomeric excess of 99% or higher.

The scope of asymmetric functionalization of β-methylene with respect to 1,2-dicarbonyl compounds is shown in Figure 5. The C−C coupling products **4s**−**w** were obtained in yields of 87−97% with 8:1 to 19:1 dr and excellent 98−99% ee. 1,2-Dicarbonyl compounds as simple as 3,4-hexanedione could also enable this transformation by affording product **4x** in 85% yield

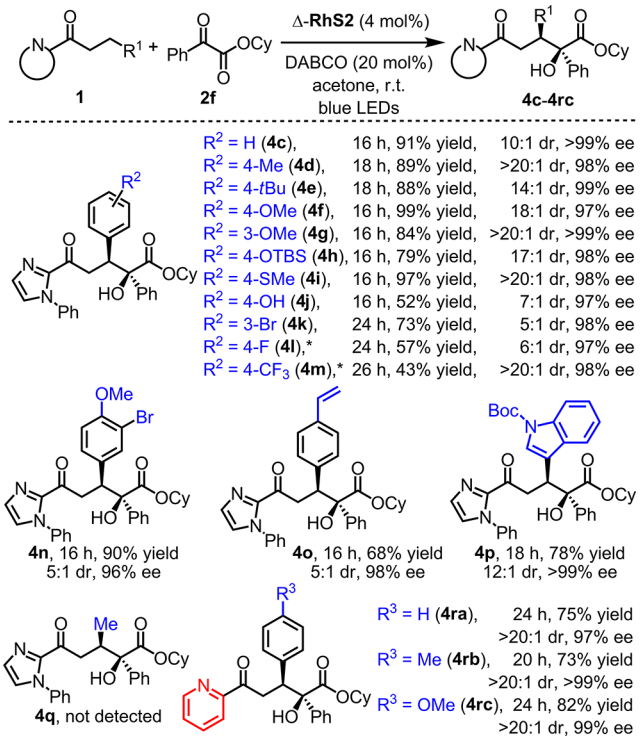


Figure 4. Substrate scope with respect to 2-acyl imidazoles and 2-acylpyridines. Structure of **4i** was determined by X-ray crystallography, and all other compounds were assigned accordingly. *Reaction was performed at 50 °C.

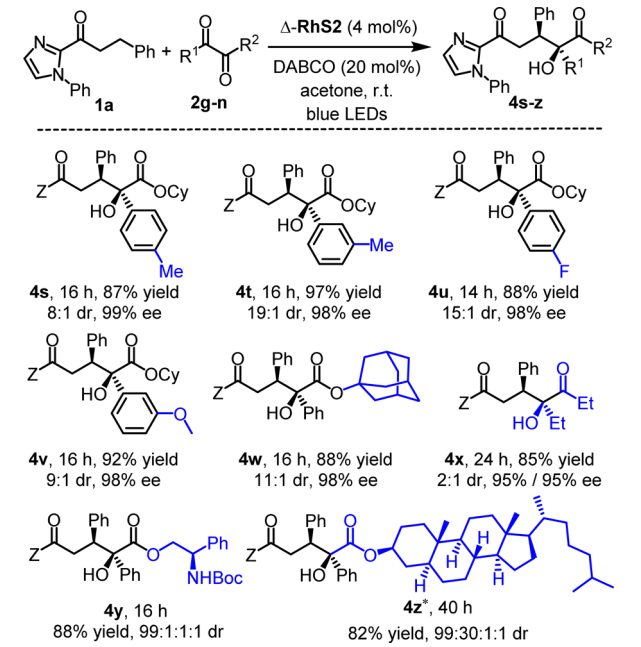


Figure 5. Substrate scope with respect to 1,2-dicarbonyl compounds. *Acetone/CH_2Cl_2 (1:1, vol/vol) was used as solvent. Z = 2-(*N*-phenyl imidazolyl).

with 2:1 dr and 95% ee for both diastereomers. Furthermore, two chiral α-ketoesters provide the expected products **4y** and **4z** in good yields of 88% and 82% and with excellent diastereoselectivities of 99:1:1:1 and 99:30:1:1, respectively. This demonstrates the versatility of this catalytic approach in the context of complex molecules.

DOI: 10.1021/jacs.7b09152
J. Am. Chem. Soc. 2017, 139, 17245−17248

In summary, we developed a new strategy for the catalytic, asymmetric β-C(sp^3)–H functionalization of the carbonyl substrates 2-acyl imidazoles and 2-acylpyridines. Visible light excitation of a rhodium enolate intermediate initiates a single electron transfer to a 1,2-dicarbonyl compound, followed by proton transfer, and subsequent stereocontrolled radical–radical recombination. This method should be of practical value for the asymmetric functionalization of β-C(sp^3)–H bonds.[22]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b09152.

Experimental and computational details (PDF)
Data for $C_{49}H_{41}Br_2FN_3O_2RhS_2$ (CIF)
Data for $C_{33}H_{34}N_2O_4S$ (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*meggers@chemie.uni-marburg.de

ORCID

Xiaoqiang Huang: 0000-0002-0927-4812
Olaf Wiest: 0000-0001-9316-7720
Eric Meggers: 0000-0002-8851-7623

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Funding from the Deutsche Forschungsgemeinschaft (ME 1805/13-1) and the U.S. National Science Foundation (NSF CHE1565669) is gratefully acknowledged. A.R.R. is a recipient of a CBBI Fellowship (NIH T32 GM075762).

■ REFERENCES

(1) For catalytic asymmetric functionalizations of C(sp^3)–H, see: (a) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (b) Zheng, C.; You, S.-L. *RSC Adv.* **2014**, *4*, 6173. (c) Zhao, Y.-L.; Wang, Y.; Luo, Y.-C.; Fu, X.-Z.; Xu, P.-F. *Tetrahedron Lett.* **2015**, *56*, 3703. (d) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. *Chem. Rev.* **2017**, *117*, 8908. (e) Qin, Y.; Zhu, L.; Luo, S. *Chem. Rev.* **2017**, *117*, 9433. (f) Lu, Q.; Glorius, F. *Angew. Chem., Int. Ed.* **2017**, *56*, 49.

(2) Smith, A. M. R.; Hii, K. K. *Chem. Rev.* **2011**, *111*, 1637.

(3) Selected reviews on β-C(sp^3)–H functionalization of carbonyl compounds: (a) Huang, Z.; Dong, G. *Tetrahedron Lett.* **2014**, *55*, 5869. (b) Qiu, G.; Wu, J. *Org. Chem. Front.* **2015**, *2*, 169. (c) Xiao, J. *ChemCatChem* **2012**, *4*, 612.

(4) (a) Chen, G.; Gong, W.; Zhuang, Z.; Andrä, M. S.; Chen, Y.-Q.; Hong, X.; Yang, Y.-F.; Liu, T.; Houk, K. N.; Yu, J.-Q. *Science* **2016**, *353*, 1023. (b) He, J.; Shao, Q.; Wu, Q.; Yu, J.-Q. *J. Am. Chem. Soc.* **2017**, *139*, 3344.

(5) (a) Zhang, S.-L.; Xie, H.-X.; Zhu, J.; Li, H.; Zhang, X.-S.; Li, J.; Wang, W. *Nat. Commun.* **2011**, *2*, 211. (b) Hayashi, Y.; Itoh, T.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 3920. See also: (c) Zeng, X.; Ni, Q.; Raabe, G.; Enders, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 2977. (d) Zhao, Y.-L.; Wang, Y.; Hu, X.-Q.; Xu, P.-F. *Chem. Commun.* **2013**, *49*, 7555. (e) Zhou, X.-L.; Wang, P.-S.; Zhang, D.-W.; Liu, P.; Wang, C.-M.; Gong, L.-Z. *Org. Lett.* **2015**, *17*, 5120.

(6) Mo, J.; Shen, L.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2013**, *52*, 8588.

(7) (a) Fu, Z.; Xu, J.; Zhu, T.; Leong, W. W. Y.; Chi, Y. R. *Nat. Chem.* **2013**, *5*, 835. (b) Fu, Z.; Jiang, K.; Zhu, T.; Torres, J.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 6506. (c) Jin, Z.; Chen, S.; Wang, Y.; Zheng, P.; Yang, S.; Chi, Y. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 13506.

(8) For asymmetric functionalizations of carboxamides through β-lithiation with (−)-sparteine, see: (a) Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *115*, 2516. (b) Lutz, G. P.; Du, H.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 4542.

(9) (a) Ravelli, D.; Fagnoni, M.; Albini, A. *Chem. Soc. Rev.* **2013**, *42*, 97. (b) Romero, N. A.; Nicewicz, D. A. *Chem. Rev.* **2016**, *116*, 10075. (c) Chen, C. *Org. Biomol. Chem.* **2016**, *14*, 8641.

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

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

(12) For related modifications, see for example: Li, S.-W.; Gong, J.; Kang, Q. *Org. Lett.* **2017**, *19*, 1350.

(13) 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.

(14) For diarylketones as visible-light-activated HAT mediators, see: Xia, J.-B.; Zhu, C.; Chen, C. *J. Am. Chem. Soc.* **2013**, *135*, 17494.

(15) For 1,2-dicarbonyls as HAT mediators, see: (a) Papadopoulos, G. N.; Limnios, D.; Kokotos, C. G. *Chem. - Eur. J.* **2014**, *20*, 13811. (b) Papadopoulos, G. N.; Kokotos, C. G. *J. Org. Chem.* **2016**, *81*, 7023. (c) Papadopoulos, G. N.; Kokotos, C. G. *Chem. - Eur. J.* **2016**, *22*, 6964. (d) Limnios, D.; Kokotos, C. G. *Adv. Synth. Catal.* **2017**, *359*, 323.

(16) For Norrish–Yang photocyclizations of 1,2-diketones, see: (a) Urry, W. H.; Trecker, D. J. *J. Am. Chem. Soc.* **1962**, *84*, 118. (b) Turro, N. J.; Lee, T.-J. *J. Am. Chem. Soc.* **1969**, *91*, 5651. (c) Hamer, N. K. *J. Chem. Soc., Perkin Trans. 1* **1983**, 61. (d) Obayashi, M.; Mizuta, E.; Noguchi, S. *Chem. Pharm. Bull.* **1979**, *27*, 1679. (e) Herrera, A. J.; Rondón, M.; Suárez, E. *Synlett* **2007**, 1851.

(17) For Lewis acid stabilized enolate radicals as reactive intermediates applied into asymmetric catalysis, see: (a) Du, J.; Skubi, K. L.; Schultz, D. M.; Yoon, T. P. *Science* **2014**, *344*, 392. (b) Zhou, Z.; Li, Y.; Han, B.; Gong, L.; Meggers, E. *Chem. Sci.* **2017**, *8*, 5757. See also: (c) Suárez-Pantiga, S.; Colas, K.; Johansson, M. J.; Mendoza, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 14094.

(18) For selected examples of asymmetric radical–radical recombination, see: (a) Uraguchi, D.; Kinoshita, N.; Kizu, T.; Ooi, T. *J. Am. Chem. Soc.* **2015**, *137*, 13768. (b) Kizu, T.; Uraguchi, D.; Ooi, T. *J. Org. Chem.* **2016**, *81*, 6953. (c) Wang, C.; Qin, J.; Shen, X.; Riedel, R.; Harms, K.; Meggers, E. *Angew. Chem., Int. Ed.* **2016**, *55*, 685. (d) Silvi, M.; Verrier, C.; Rey, Y. P.; Buzzetti, L.; Melchiorre, P. *Nat. Chem.* **2017**, *9*, 868.

(19) For fluorenone we found a solvent dependence of homo versus hetero coupling. See SI for more details.

(20) Pirnot, M. T.; Rankic, D. A.; Martin, D. B. C.; MacMillan, D. W. C. *Science* **2013**, *339*, 1593.

(21) An energy transfer mechanism is unlikely because the emission of photoexcited ketoester **2d** is completely supressed in the presence of a Rh-enolate.

(22) The imidazole moiety can be easily removed by methyl triflate induced conversion to the corresponding lactone (see SI).

DOI: 10.1021/jacs.7b09152
J. Am. Chem. Soc. 2017, 139, 17245–17248