Organic LETTERS
Letter
pubs.acs.org/OrgLett

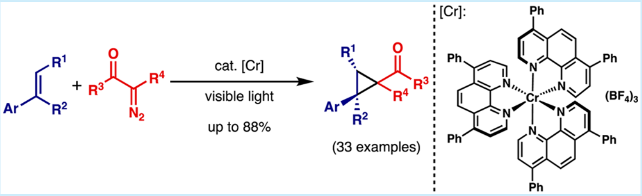
Radical Cation Cyclopropanations via Chromium Photooxidative Catalysis

Francisco J. Sarabia and Eric M. Ferreira*

Department of Chemistry, University of Georgia, Athens, Georgia 30602, United States

Supporting Information

ABSTRACT: The chromium photocatalyzed cyclopropanation of diazo reagents with electron-rich alkenes is described. The transformation occurs under mild conditions and features specific distinctions from traditional diazo-based cyclopropanations (e.g., avoiding β-hydride elimination, chemoselectivity considerations, etc.). The reaction appears to work most effectively using chromium catalysis, and a number of decorated cyclopropanes can be accessed in generally good yields.

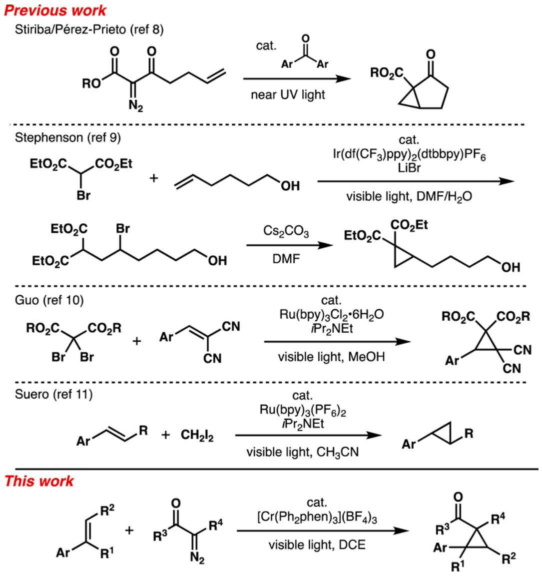


Cyclopropanes are important structures in organic chemistry.[1] Their rigid structure provides a well-defined spatiality that can be decorated with features that can impart function, and they are prevalent in natural and unnatural bioactive molecules.[2] The cyclopropane ring strain also allows them to serve as useful 3C components in the construction of larger ring systems.[3] There are several synthetic methods toward accessing cyclopropanes from alkenes,[4] including the transition-metal catalyzed reaction with diazo compounds.[5] This method, most commonly using Rh or Cu catalysis, has proven widely effective. That said, orthogonal approaches using these reactants may present strategic synthetic alternatives.

The use of photocatalysis[6] for the formation of cyclopropanes is relatively underexplored (Scheme 1). For UV-light-mediated diazo decomposition, alkene cyclopropanation can be favorable using triplet sensitization.[7] Pérez-Prieto and Stiriba have described diarylketone catalysts for sensitized cyclopropanations.[8] In terms of metal catalyst systems, Stephenson and coworkers described an atom-transfer process of bromomalonate across an alkene via iridium catalysis, which upon treatment with a base affords a cyclopropane product.[9] Guo et al. reported a $Ru(bpy)_3^{2+}$-catalyzed method that combines dibromomalonates and benzylidenemalononitriles;[10] this process occurs via the formation of the α-bromomalonate anion in situ. A Ru-catalyzed method using diiodomethane to achieve radical additions to styrene derivatives was recently described by Suero et al.[11]

Bauld had previously shown that aminium oxidants were capable of inducing radical cation-based cyclopropanations between alkenes and diazo reagents.[12] We were curious whether this transformation could be achieved using photocatalytic oxidative systems. Toward the design of sustainable synthetic methods, we have been interested in the application of photocatalysts based on first-row transition metals to supplant the traditionally employed Ru and Ir systems. We have recently reported on the use of polypyridinyl and -phenanthrolinyl ligated Cr photocatalysts for mediating (4 + 2)-cycloadditions.[13] Herein, we describe a (2 + 1)-cycloaddition between electron-rich alkenes and diazo reagents promoted by these Cr complexes. Importantly, we highlight the orthogonality of catalytic activation of this process (alkene oxidation vs diazo decomposition), which we anticipate will render this method useful in synthetic chemistry.

Scheme 1. Approaches to Cyclopropane Synthesis Using Photocatalysis



We began our studies by investigating the proposed cycloaddition between *trans*-stilbene and ethyl diazoacetate using the catalysts in Figure 1. We first utilized the reaction conditions developed in the original Cr-catalyzed report (1 mol % $[Cr(Ph_2phen)_3](BF_4)_3$, NUV irradiation, CH_3NO_2) with 5 equiv of the diazoacetate (Table 1, entry 1). To our delight, the

Received: April 12, 2017

DOI: 10.1021/acs.orglett.7b01095
Org. Lett. XXXX, XXX, XXX−XXX

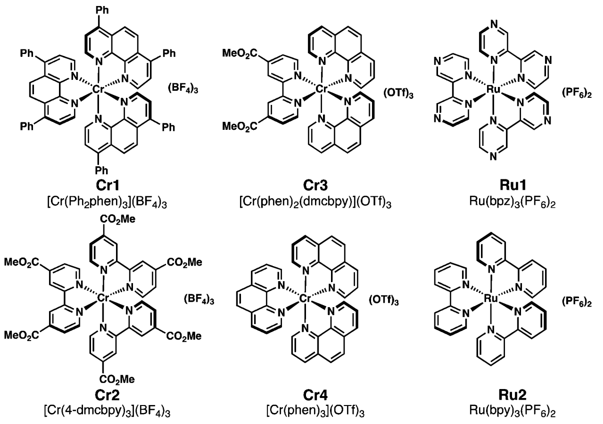
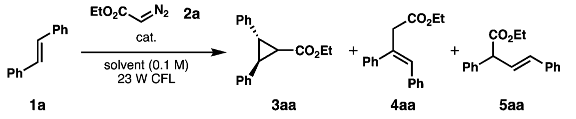


Figure 1. Photocatalysts evaluated.

Table 1. Optimization of Cr-Catalyzed Cyclopropanation



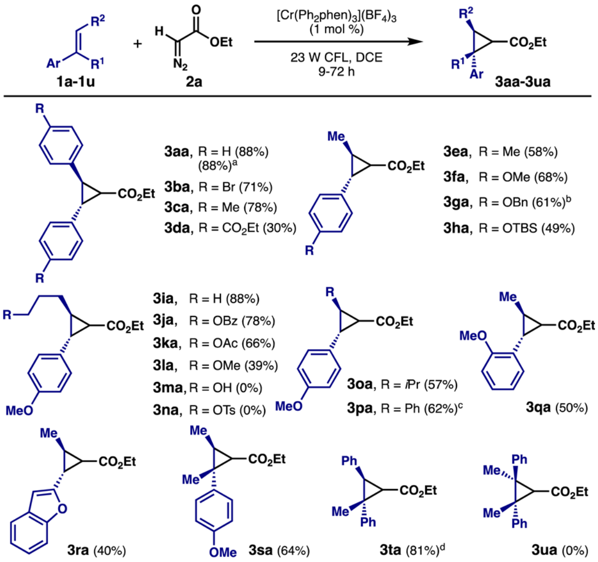
entry	cat. (mol %)	solvent	2a (equiv)	time (h)	NMR yield (%)[a] 3aa	4aa	5aa
1[b]	**Cr1** (1)	CH_3NO_2	5	24	60	8	7
2	**Cr1** (1)	CH_3NO_2	5	24	61	10	8
3	**Cr1** (1)	CH_3NO_2	1.1	40	60	8	11
4	**Cr2** (1)	CH_3NO_2	1.1	40	5	1	1
5	**Cr3** (1)	CH_3NO_2	1.1	40	40	8	7
6	**Cr4** (1)	CH_3NO_2	1.1	40	50	9	8
7	**Ru1** (1)	CH_3NO_2	1.1	24	3	0	0
8	**Ru1** (1)	CH_3NO_2	5	14	9	4	5
9	**Ru2** (5) + **MV** (15)[c]	CH_3NO_2	5	21	12	2	2
10	**Ru2** (5)	CH_3NO_2	5	21	0	0	0
11	**Cr1** (1)	$CHCl_3$	1.1	24	18	1	2
12	**Cr1** (1)	acetone	1.1	24	57	5	8
13	**Cr1** (1)	CH_2Cl_2	1.1	24	73	2	7
14	**Cr1** (1)	CH_3CN	1.1	24	67	8	10
15	**Cr1** (1)	DCE	1.1	24	73	0	5
16	none	DCE	1.1	14	0	0	0
17	$CrCl_3$ (10)	DCE	1.1	49	0	0	0
18[d]	**Cr1** (1)	DCE	1.1	49	0	0	0

[a] Determined using veratraldehyde as a standard. [b] Near-UV light (bulbs at 300, 350, and 419 nm) used instead of 23 W CFL. [c] MV: methyl viologen$^{2+}\cdot(PF_6)_2$. [d] Reaction performed in dark (foil wrapped).

cycloaddition occurred, and cyclopropane **3aa** was formed in good yield, validating the hypothesis that these oxidizing catalysts could induce this process. Byproducts **4aa** and **5aa** were also detected in small quantities. We found that lowering the equivalents of the diazoacetate to 1.1 equiv and using visible light were comparably effective to the original conditions. Other photooxidizing chromium catalysts we have explored were able to promote the transformation, albeit in lower yields (entries 4–6). Additionally, when oxidizing systems based on Ru(II) photocatalysts were employed, the yields were poor (entries 7–10). A range of solvents were evaluated, and we ultimately found that dichloroethane was optimal for the transformation, affording the highest yield of cyclopropane **3aa** with minimal formation of byproducts **4aa** and **5aa** (entry 15).[14] Control experiments (entries 16–18) confirmed the importance of both the light and the photocatalyst to reactivity.

With optimized conditions for cyclopropanation in hand, we established the alkene scope (Scheme 2). A range of stilbenes were competent reactants, and the products were accessed in generally high yields. Aryl alkyl alkenes were also participatory in this cycloaddition. Although the yields were overall good, there was in general little diastereoselectivity, as the cyclopropanes were observed as approximately 1:1 mixtures with a couple of exceptions. For compounds **3ia**–**3ma**, the reactivity pattern somewhat mirrors that of the (4 + 2)-cycloaddition; the pendant oxygenated group if electron-rich (i.e., alcohol or ether) will hamper reactivity due to donation into the presumed radical cation intermediate.[15] Curiously, an alkyl tosylate also rendered the reaction unproductive (**3na**).[16] Gratifyingly, trisubstituted alkenes were reactive in this chemistry (e.g., **3sa**, **3ta**), which had not been the case for the (4 + 2) process. Tetrasubstituted olefins unfortunately proved unreactive.

Scheme 2. Cyclopropanation: Alkene Scope



[a] Gram scale experiment. [b] Reaction performed with needle outlet open to air. [c] Product observed in 3.0:1 dr. [d] Product observed in 4.1:1 dr.

The alkene reactivity observed appears to correlate well with respective reduction potentials. As seen in Figure 2, a window of competent reactivity was observed for alkenes with reduction potentials in the range $E_{1/2} = +1.11 - 1.80$ V (vs SCE).[17,18] Stilbene derivatives **1v** ($E_{1/2} = +0.99$ V) and **1w** ($E_{1/2} = +1.94$ V) were both unproductive in the cycloaddition. This spectrum of reactivity is reflective of the presumed radical cation mechanism

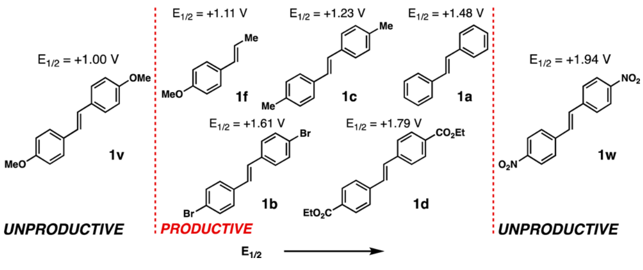
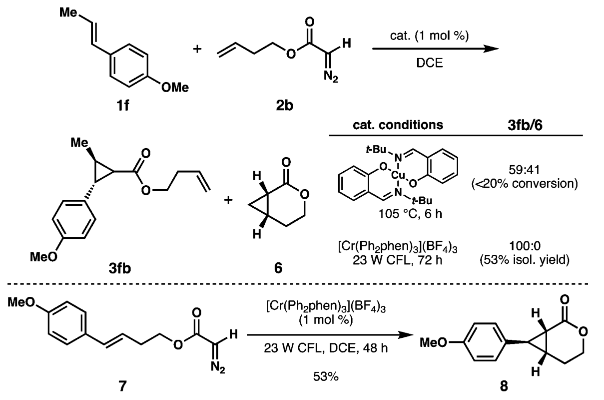


Figure 2. Alkene reactivity range based on reduction potential.

pathway, necessitating an appropriate oxidation capacity in order to achieve proper activity.

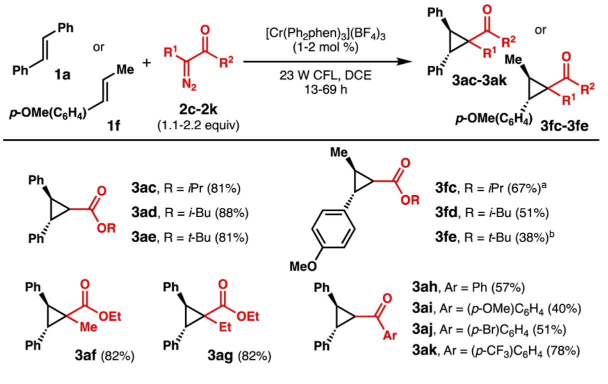
The chemoselectivity of the cycloaddition, dictated by electronics, is a unique and important attribute of this transformation. The more commonly employed cyclopropanations of diazo compounds using metal catalysis (i.e., Rh or Cu catalysts) may be governed by other factors, such as favorable intramolecularity. Scheme 3 is illustrative. *trans*-Anethole (**1f**) and diazoacetate **2b** were combined under both Cu-catalyzed cyclopropanation conditions and our standard Cr photocatalytic conditions. The Cu-catalyzed reaction[19] afforded a mixture of both possible cyclopropane products (**3fb** and **6**) in low conversion.[20] Alternatively, with Cr catalysis the intermolecular addition product (**3fb**) was observed exclusively. Additionally, the cyclopropanation of compound **7** was successful, establishing that intramolecular processes can occur on the condition that it is electronically feasible. We anticipate this type of chemoselectivity can be strategically employed in complex synthetic settings, a distinguishing feature of this Cr-catalyzed cyclopropanation.

Scheme 3. Alkene Chemoselectivity



Different diazo esters and arylketones were also generally effective (Scheme 4). Notably, α-alkyl diazo esters were competent partners, with no observation of β-hydride elimination, typically a common phenomenon in diazo decomposition cyclopropanations.[21] The mechanistic pathway differentiation of this process enables cyclopropanation to predominate. Additionally, the mechanism ensures that diazo dimerization is avoided, and thus no slow addition protocols were necessary.[22]

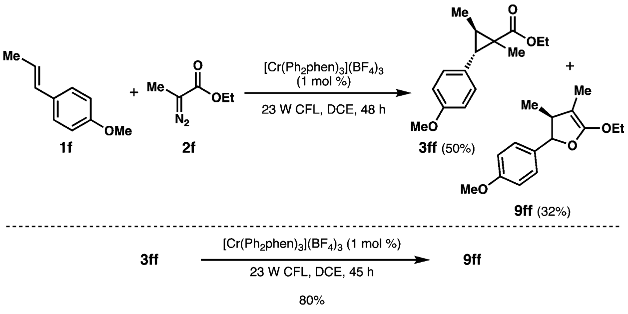
Scheme 4. Cyclopropanation: Diazo Scope



^{a}Product observed in 1.4:1 dr. ^{b}Product observed in 1.5:1 dr.

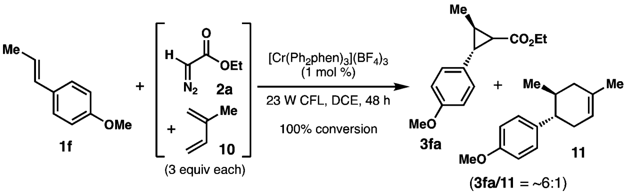
A different outcome was observed in the reaction between *trans*-anethole and diazopropionate **2f**. Expected cyclopropane **3ff** was indeed the main product, but byproduct dihydrofuran **9ff** was also observed in measurable yield (Scheme 5). Resubjecting the cyclopropane product to the photocatalyst conditions also generated the dihydrofuran in high yield.[23] Control experiments indicated that the chromium catalyst and light were both required for this rearrangement to occur.[24]

Scheme 5. Cyclopropanation and Rearrangement



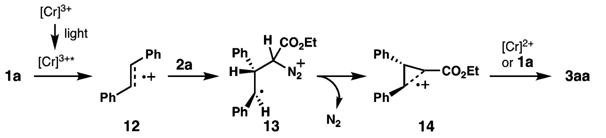
Additionally, when a competition experiment was performed with both diazoacetate **2a** and diene **10**, the cyclopropane product was the predominant observed species, highlighting the increased nucleophilicity of **2a** in intercepting the radical cation (Scheme 6).

Scheme 6. Competition Experiment between Diazo and Diene



Our proposed mechanism for the cycloaddition is consistent with the previous processes described by Bauld (Scheme 7, shown for formation of cyclopropane **3aa**).[12b] The excited state Cr(III) catalyst induces alkene single electron oxidation.[25] The resulting radical cation undergoes nucleophilic attack by the diazo compound. Loss of N_2 affords a "long-bonded" radical cation intermediate **14**.[12b] At this stage, electron transfer from either the reduced-state Cr complex or another equivalent of alkene yields the cyclopropane product. Turnover occurs either via reentry of the Cr complex into the photocatalytic cycle, or through radical propagation by the electron transfer from the alkene component.[26] Byproducts **4aa** and **5aa** would arise from intermediate **13** when N_2 is lost via phenyl or hydrogen migration, respectively.[27] The observation of differential reactivities between this process and our reported (4 + 2)-cycloadditions (alkene competencies, O_2 dependencies) indicate that a more thorough analysis of the mechanism will be necessary for full elucidation.

Scheme 7. Proposed Mechanism



In summary, a radical cation cycloaddition between alkenes and diazo species using Cr catalysis and visible light is described. The formation of polysubstituted cyclopropanes via this process may offer an attractive alternative to the more commonly employed Rh or Cu complexes. The chemoselectivity aspects are a distinguishing characteristic of this transformation, and by virtue of this no syringe pump mode of addition is necessary. Current efforts are dedicated toward enriching our mechanistic understanding and expanding the suite of cycloadditions mediated by these Cr photocatalysts; these endeavors will be later disclosed.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01095.

Experimental procedures, compound characterization data, and spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: emferr@uga.edu.

ORCID

Eric M. Ferreira: 0000-0001-9412-0713

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was carried out by the Catalysis Collaboratory for Light-activated Earth Abundant Reagents (C-CLEAR), which is supported by the NSF and EPA through the Network for Sustainable Molecular Design and Synthesis program (NSF-CHE-1339674). F.J.S. is supported by the NSF Graduate Research Fellowship Program under Grant No. 038550-02. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the NSF. We acknowledge collaborators Niels Damrauer (Univ. Colorado), Anthony Rappé (Colorado St. Univ.), and Matthew Shores (Colorado St. Univ.) and their groups for enriching discussions.

■ REFERENCES

(1) (a) *The Chemistry of the Cyclopropyl Group*; Patai, S., Rappoport, Z., Eds.; Wiley & Sons: New York, 1987. (b) *Small Ring Compounds in Organic Synthesis VI*; de Meijere, A., Ed.; Springer: Berlin, Germany, 2000; Vol. 207.

(2) (a) Faust, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2251. (b) Wessjohann, L. A.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625. (c) Brackmann, F.; de Meijere, A. *Chem. Rev.* **2007**, *107*, 4493.

(3) For select reviews, see: (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (b) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (c) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.

(4) For reviews, see: (a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (b) Kamimura, A. In *Methods and Applications of Cycloaddition Reactions in Organic Syntheses*; Nishiwaki, N., Ed.; John Wiley & Sons: Hoboken, NJ, 2014; Pt. I-1.

(5) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998. (b) Davies, H. M. L.; Antoulinakis, E. G. *Org. React.* **2001**, *57*, 1.

(6) For select reviews on photocatalysis, see: (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (b) Xuan, J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828. (c) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (d) Angnes, R. A.; Li, Z.; Correia, C. R. D.; Hammond, G. B. *Org. Biomol. Chem.* **2015**, *13*, 9152. (e) Yoon, T. P. *ACS Catal.* **2013**, *3*, 895.

(7) (a) Ando, W.; Imai, I.; Migita, T. *J. Org. Chem.* **1972**, *37*, 3596. (b) Moss, R. A.; Joyce, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 1262. (c) Fien, J.; Kirmse, W. *Angew. Chem., Int. Ed.* **1998**, *37*, 2232.

(8) (a) Pastor-Pérez, L.; Wiebe, C.; Pérez-Prieto, J.; Stiriba, S.-E. *J. Org. Chem.* **2007**, *72*, 1541. (b) Pastor-Pérez, L.; Barriau, E.; Frey, H.; Pérez-Prieto, J.; Stiriba, S.-E. *J. Org. Chem.* **2008**, *73*, 4680.

(9) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160.

(10) Zhang, Y.; Qian, R.; Zheng, X.; Zeng, Y.; Sun, J.; Chen, Y.; Ding, A.; Guo, H. *Chem. Commun.* **2015**, *51*, 54.

(11) del Hoyo, A. M.; Herraiz, A. G.; Suero, M. G. *Angew. Chem., Int. Ed.* **2017**, *56*, 1610.

(12) (a) Stufflebeme, G.; Lorenz, K. T.; Bauld, N. L. *J. Am. Chem. Soc.* **1986**, *108*, 4234. (b) Bauld, N. L.; Stufflebeme, G. W.; Lorenz, K. T. *J. Phys. Org. Chem.* **1989**, *2*, 585. (c) Yueh, W.; Bauld, N. L. *J. Am. Chem. Soc.* **1995**, *117*, 5671.

(13) (a) Stevenson, S. M.; Shores, M. P.; Ferreira, E. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 6506. (b) Higgins, R. F.; Fatur, S. M.; Shepard, S. G.; Stevenson, S. M.; Boston, D. J.; Ferreira, E. M.; Damrauer, N. H.; Rappé, A. K.; Shores, M. P. *J. Am. Chem. Soc.* **2016**, *138*, 5451. (c) Stevenson, S. M.; Higgins, R. F.; Shores, M. P.; Ferreira, E. M. *Chem. Sci.* **2017**, *8*, 654.

(14) The alkene byproducts were only observed in the diaryl alkene-based cyclopropanations in <10% yield and were readily removed by column chromatography.

(15) (a) Gassman, P. G.; Bottorff, K. J. *Tetrahedron Lett.* **1987**, *28*, 5449. (b) Gassman, P. G.; Bottorff, K. J. *J. Am. Chem. Soc.* **1987**, *109*, 7547. (c) Mizuno, K.; Tamai, T.; Nishiyama, T.; Tani, K.; Sawasaki, M.; Otsuji, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2113. (d) Asaoka, S.; Kitazawa, T.; Wada, T.; Inoue, Y. *J. Am. Chem. Soc.* **1999**, *121*, 8486. (e) Hamilton, D. S.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 18577.

(16) For this specific reaction, sulfonyloxy transfer to the diazoacetate was observed instead.

(17) (a) Kubota, T.; Uno, B.; Matsuhisa, Y.; Miyazaki, H.; Kano, K. *Chem. Pharm. Bull.* **1983**, *31*, 373. (b) Reference 12b.

(18) The reduction potential of $[\mathrm{Cr(Ph_2phen)_3}]^{3+}$ ($E^*_{1/2}$ = + 1.33 V vs SCE in CH_3NO_2) is within a viable range for alkene oxidation competency. We note that these values should only be used as a general guide, as they are sensitive to the conditions of measurement (solvent, etc.).

(19) (a) Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559. (b) Sacconi, L.; Ciampolini, M. *J. Chem. Soc.* **1964**, 276.

(20) Attempts at Rh catalysis were less effective than those with Cu.

(21) For an elegant solution using Rh catalysis, see: Panne, P.; DeAngelis, A.; Fox, J. M. *Org. Lett.* **2008**, *10*, 2987.

(22) Other potential carbene precursors, such as tosylhydrazones, triazoles, sulfur and iodonium ylides, as well as donor–donor and acceptor–acceptor diazo species, were ineffective.

(23) Although this ring expansion (acylcyclopropane → dihydrofuran) is more commonly observed with ketones and aldehydes, there are isolated reports of this process with donor–acceptor based cyclopropylesters promoted by a Lewis acid and/or heat. See: (a) Abdallah, H.; Grée, R.; Carrié, R. *Tetrahedron* **1985**, *41*, 4339. (b) Granger, K.; Snapper, M. L. *Eur. J. Org. Chem.* **2012**, *2012*, 2308. (c) Yadav, V. K.; Balamurugan, R. *Org. Lett.* **2001**, *3*, 2717. (d) Saalfrank, R. W.; Gündel, J.; Roßmann, G.; Hanek, M.; Rost, W.; Peters, K.; Von Schnering, H. G. *Chem. Ber.* **1990**, *123*, 1175.

(24) Dihydrofuran formation was not observed for the stilbene-based cyclopropanes.

(25) Ethyl diazoacetate ($E_{1/2}$ = + 2.10 V)[12b] is outside of the range of oxidation capability.

(26) In our (4 + 2) studies, we noted an important O_2 dependency that was consistent with a photocatalyst turnover pathway. We do not observe a similar dependency for this cycloaddition.

(27) In a singular example, Bauld reported a similar methyl migration. See ref 12b.