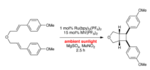
J Am Chem Soc. Author manuscript; available in PMC 2011 June 30.

Published in final edited form as:
J Am Chem Soc. 2010 June 30; 132(25): 8572–8574. doi:10.1021/ja103934y.

[2+2] Cycloadditions by Oxidative Visible Light Photocatalysis

Michael A. Ischay, **Zhan Lu**, and **Tehshik P. Yoon***
Department of Chemistry, University of Wisconsin–Madison, 1101 University Avenue, Madison, Wisconsin, 53706

Abstract



Photochemical reactions are remarkable for their ability to easily assemble cyclobutanes and other strained ring systems that are difficult to construct using other conventional synthetic methods. We have previously shown that $Ru(bpy)_3^{2+}$ is an efficient photocatalyst that promotes the [2+2] cycloadditions of electron-deficient olefins with visible light. Here, we show that $Ru(bpy)_3^{2+}$ is also an effective photocatalyst for the [2+2] cycloaddition of electron-rich olefins. This transformation is enabled by the versatile photoelectrochemical properties of $Ru(bpy)_3^{2+}$, which enables either one-electron reduction or one-electron oxidation of interesting organic substrates under appropriate conditions.

Cyclobutanes are prominent structural features of many bioactive natural products.1 Arguably the most straightforward method for the preparation of cyclobutane rings is the [2+2] photocycloaddition of olefins, and the utility of this prototypical photochemical reaction has been demonstrated in numerous synthetic applications.2 Nevertheless, the requirement for irradiation with high energy UV light is a disadvantage of this reaction in terms of the cost, scalability, and environmental impact of the methodology.3 We recently reported a new approach to [2+2] enone cycloadditions catalyzed by $Ru(bpy)_3Cl_2$ upon irradiation with low-intensity visible light.4 Several other groups5 have also recently become interested in similar strategies for utilizing the well-studied photoredox properties of metal polypyridyl complexes6 in various synthetically useful transformations.

Notably, each of the methods recently developed by us,4 MacMillan,5a,b Stephenson,5c–e and Akita5f has taken advantage of a reductive quenching photoredox cycle (Figure 1, Path A). In our method for [2+2] cycloaddition of enones, for example, the photoexcited state ($Ru^*(bpy)_3^{2+}$), generated upon visible light irradiation of the photocatalyst, abstracts an electron from a relatively electron-rich tertiary amine base (i-Pr_2NEt); the resulting $Ru(bpy)_3^+$ complex is a strong reductant that reduces an aryl enone to the key radical anion intermediate involved in the [2+2] cycloaddition. This mechanism implies that a fundamental limitation of our strategy is the requirement for an alkene that is sufficiently electron-deficient to undergo efficient one-electron reduction by $Ru(bpy)_3^+$; indeed, electron-rich olefins (e.g., styrenes) do not react under the conditions we previously reported.

We therefore became interested in designing a complementary method for photooxidative electron transfer catalysis that could engage electron-rich olefins in productive [2+2]

tyoon@chem.wisc.edu.

Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF format) are provided. This information is available free of charge via the Internet at http://pubs.acs.org.

cycloadditions. Our design plan draws upon two well-established precedents. First, electron-rich olefins are known to participate in [2+2] cycloadditions upon one-electron oxidation to afford the corresponding radical cations. This reactivity was first described by Ledwith7 in 1969 and has subsequently been shown to be accessible both by chemical oxidants and by photoinduced electron transfer with organic sensitizers.8 Second, the photochemistry of $Ru(bpy)_3^{2+}$ has been extensively investigated for solar energy applications,6a and the most well-studied among these systems rely on an oxidative quenching cycle (Figure 1, Path B) in which $Ru^*(bpy)_3^{2+}$ reacts with an electron acceptor (e.g., methyl viologen, MV^{2+}).9 The resulting oxidized $Ru(bpy)_3^{3+}$ complex is turned over by one-electron reduction using a sacrificial electron-rich organic species such as a tertiary amine base.

Given these precedents, it seems logical that the photogenerated $Ru(bpy)_3^{3+}$ complex generated upon visible light irradiation of $Ru(bpy)_3^{2+}$ in the presence of MV^{2+} should also oxidize electron-rich styrenes, affording a radical cation that would undergo subsequent [2+2] cycloaddition. Indeed, under optimized conditions, bis(styrene) **1** undergoes efficient intramolecular cycloaddition upon irradiation in the presence of 5 mol% $Ru(bpy)_3^{2+}$ and 15 mol% MV^{2+}, affording cyclobutane **2** in 89% yield with excellent diastereoselectivity. As with our previously described $Ru(bpy)_3^{2+}$-catalyzed reactions, this transformation can be conducted using a standard household light bulb and does not require specialized photochemical equipment.

Table 1 summarizes the importance of each of the experimental parameters to the efficiency of the reaction. First, we observe no cycloaddition upon irradiation of **1** with UV light under conventional photolytic conditions (entry 2). This result suggests that the reaction does not involve direct photoexcitation of the styrenic substrate. The observation that visible light, $Ru(bpy)_3^{2+}$, and MV^{2+} are each required for successful cycloaddition (entries 3–5) is instead consistent with the photoinduced one-electron oxidation mechanism that we have proposed. Other known oxidative quenchers of $Ru^*(bpy)_3^{2+}$ such as nitroarenes and quinones10 also promote cycloaddition but were not as effective as MV^{2+} (entries 6 and 7). Oxygen was an ineffective co-oxidant (entry 8).11 We observed a pronounced solvent dependency on the efficiency of the reaction (entries 9–11); reactions conducted in MeCN and acetone produced poorer yields of the cycloadduct than those using $MeNO_2$, and we observed no conversion at all in more polar solvents such as DMSO and DMF. Finally, the reaction showed a modest sensitivity to adventitious water, and we found that the addition of $MgSO_4$ provided slightly higher and more reproducible yields (entry 12).

Experiments probing the scope of [2+2] cycloadditions using the $Ru(bpy)_3^{2+}/MV^{2+}$ system are outlined in Table 2. In most cases, we found that 1 mol% of the Ru photocatalyst is sufficient for successful cycloaddition. Our mechanistic design plan is validated by the observation that at least one styrene must bear an electron-donating substituent at the *para* or *ortho* position (entries 1 and 2); *meta*-substituted and unsubstituted styrenes are presumably not electron-rich enough to undergo one-electron oxidation to afford the key radical cation intermediate (entries 3 and 4).12 However, a number of electron-donating *para* substituents are effective activators of the styrene (entries 5–6), and the presence of an electron-withdrawing substituent at the *meta* position does not seem to significantly decrease the efficiency of the cycloaddition (entry 7). Aliphatic olefins are not suitable reaction partners (entry 8). On the other hand, both electron-rich and electron-poor styrenes react smoothly with the photogenerated radical cation (entries 9–11). Substitutents at the α-position of the styrene are tolerated (entry 10), which enables access to all-carbon quaternary stereocenters on the cyclobutane framework, although β-substituents significantly retard the rate of reaction. Substituents on the tether are also tolerated, and these modifications can induce good levels of facial selectivity in the cycloaddition (entries 11 and 12, 5:1 and 7:1 d.r., respectively). The identity of the tether seems to be critical;

while both oxygen and nitrogen-containing tethers give good yields (entry 13), we have been unable to identify all-carbon tethers that promote efficient cycloaddition, and intermolecular cycloadditions are impractically slow.

Substrates **3** and **4**, the (*E*,*Z*) bis(styrenes) isomeric to the model (*E*,*E*) substrate **1** were also prepared and irradiated with visible light in the presence of $Ru(bpy)_3^{2+}$ and MV^{2+} (Scheme 2). In both cases, the major product observed is the same *cis* diasteromer obtained from cycloaddition of **1**, indicating that the stereochemical integrity of the olefins is lost over the course of the reaction. To better understand the origins of the stereoconvergency, we monitored the cycloaddition of **4** by GC (see Supporting Information). During the course of this reaction, **4** undergoes isomerization to **1** at a rate competitive with cycloaddition. As the reaction proceeds, the ratio of *cis*-**4** to the isomeric *trans* cycloadduct increases from 1:1 at 1 h to 5:1 upon completion of the reaction. We conclude from these studies that the [2+2] cycloaddition step is itself stereospecific, as predicted from previous theoretical and experimental studies of radical cation cyclobutanations,13 but that the rate of cycloaddition is relatively slow compared to the rate of olefin isomerization. This conclusion is consistent with Bauld's studies of intermolecular [2+2] cycloadditions chemically initiated by an aminium radical cation.13a It is also consistent with the observation that the minor *trans* isomers produced from cycloaddition of **3** and of **4** are different and are consistent the stereoretentive suprafacial cycloadditions of each of these (*E*,*Z*) substrates.

Thus, the experimental evidence suggests that cycloaddition using the $Ru(bpy)_3^{2+}/MV^{2+}$ catalyst system indeed involves a radical cationic intermediate whose reactivity is identical to those generated using other methods. Photoinduced electron transfer has previously been used to initiate similar radical cation [2+2] cycloadditions of electron-rich olefins,14 but these reactions have generally required mercury arc lamps and relatively high loadings of an aromatic nitrile photosensitizer. Consistent with these reports, we find that when the cycloaddition of **1** is conducted using 5 mol% of 9,10-dicyanoanthracene (DCA)14b,c in place of $Ru(bpy)_3^{2+}$, the reaction is considerably slower and produces cyclobutane **2** in only 19% yield after 3.5 h under otherwise identical conditions. The faster reaction rates using $Ru(bpy)_3^{2+}$ may be attributable to its longer excited state lifetime (600 ns vs 15 ns), its larger extinction coefficients (13000 vs 11500 M^{-1} cm^{-1}), and its broader absorption in the visible range compared to DCA.6,15

As in the photoreductive enone cycloaddition we previously reported,4 this method for photooxidative cycloaddition does not require the use of any specialized photochemical equipment, and our reactions are typically conducted using a standard household light bulb. To highlight the efficiency of the $Ru(bpy)_3^{2+}/MV^{2+}$ system in promoting the radical cation mediated cycloaddition, we conducted the cycloaddition of **5** on gram scale in a laboratory window using ambient sunlight as the only source of irradiation. The cycloaddition still proceeded to completion in 2.5 h and provided a nearly identical yield of the cyclobutane product as smaller-scale experiments under more controlled conditions. In addition, the larger-scale reaction was conducted in undistilled nitromethane and without rigorous degassing of the solvent. Thus, these conditions provide a powerful and operationally facile method to perform photochemical cycloadditions using convenient sources of visible light including ambient sunlight.

Thus, we have shown that $Ru(bpy)_3^{2+}$ is a powerful photocatalyst for the [2+2] cycloaddition of both electron-rich and electron-deficient olefins. The versatility of this catalyst arises from the ability to access either photooxidative or photoreductive reactivity by choosing the appropriate oxidative or reductive quencher, respectively. In both regimes, the photophysical properties of $Ru(bpy)_3^{2+}$ enable a variety of inexpensive, readily available sources of visible light to be utilized, including sunlight. In addition, there exists a vast wealth of electrochemical literature that describes synthetically useful organic transformations initiated by one-electron redox processes. We expect that photocatalytic systems exploiting the reactivity of $Ru(bpy)_3^{2+}$ should also be able to efficiently promote similar reactivity. The exploration of this reactivity will continue to be a focus of research in our lab.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Chris Shaffer and Prof. Robert McMahon for their assistance performing the direct photolysis experiment (Table 1, entry 2). We thank the Sloan Foundation, Beckman Foundation, and Research Corporation for financial support. The NMR facilities at UW-Madison are funded by the NSF (CHE-9208463, CHE-9629688) and NIH (RR08389-01).

References

1. (a) Hansen, TV.; Stenstrøm, Y. "Naturally Occurring Cyclobutanes.". In: Hudlicky, T., editor. Organic Synthesis: Theory and Applications. Vol. Vol 5. Oxford, U.K: Elsevier; 2001. p. 1-38. (b) Dembitsky VM. J. Nat. Med. 2008; 62:1–33. [PubMed: 18404338]
2. For recent reviews, see: (a) Crimmins MT. Chem. Rev. 1988; 88:1453–1473. (b) Bach T. Synthesis. 1998:683–708. (c) Lee-Ruff E, Mladenova G. Chem. Rev. 2003; 103:1449–1483. [PubMed: 12683788] (d) Hoffman N. Chem. Rev. 2008; 108:1052–1103. [PubMed: 18302419]
3. Esser P, Pohlmann B, Scharf H-D. Angew. Chem. Int. Ed. Engl. 1994; 33:2009–2023.
4. (a) Ischay MA, Anzovino ME, Du J, Yoon TP. J. Am. Chem. Soc. 2008; 130:12886–12887. [PubMed: 18767798] (b) Du J, Yoon TP. J. Am. Chem. Soc. 2009; 131:14604–14605. [PubMed: 19473018]
5. (a) Nicewicz D, MacMillan DWC. Science. 2008; 322:70–80. (b) Nagib DA, Scott ME, MacMillan DWC. J. Am. Chem. Soc. 2009; 131:10875–10877. [PubMed: 19722670] (c) Narayanam JMR, Tucker JW, Stephenson CRJ. J. Am. Chem. Soc. 2009; 131:8756–8757. [PubMed: 19552447] (d) Tucker JW, Narayanam JMR, Krabbe SW, Stephenson CRJ. Org. Lett. 2010; 12:368–371. [PubMed: 20014770] (e) Condie AG, González-Gómez JC, Stephenson CRJ. J. Am. Chem. Soc. 2010; 132:1464–1465. [PubMed: 20070079] (f) Koike T, Akita M. Chem. Lett. 2009; 38:166–167.
6. For reviews, see: (a) Kalyanasundaram K. Coord. Chem. Rev. 1982; 46:159–244. (b) Juris A, Balzani V, Barigelletti F, Campagna S, Belser P, von Zelewsky A. Coord. Chem. Rev. 1988; 84:85–277. (c) Flamigni L, Barbieri A, Sabatini C, Ventura B, Barigelletti F. Top. Curr. Chem. 2007; 281:143–203.
7. (a) Bell FA, Crellin RA, Fugii N, Ledwith A. J. Chem. Soc. Chem. Commun. 1969:251–252. (b) Carruthers RA, Crellin RA, Ledwith A. J. Chem. Soc. Chem. Commun. 1969:252–253.
8. For reviews, see: (a) Ledwith A. Acc. Chem. Res. 1972; 5:133–139. (b) Bauld NL, Bellville DJ, Harirchian B, Lorenz KT, Pabon RA Jr, Reynolds DW, Wirth DD, Chiou HS, Marsh BJ. Acc. Chem. Res. 1987; 20:371–378. (c) Bauld NL. Tetrahedron. 1989; 45:5307–5363.
9. For example: (a) Kalyanasundaram K, Kiwi J, Grätzel M. Helv. Chim. Acta. 1978; 61:2720–2730. (b) Kirch M, Lehn J-M, Sauvage J-P. Helv. Chim. Acta. 1979; 62:1345–1383.
10. (a) Bock CR, Meyer TJ, Whitten DG. J. Am. Chem. Soc. 1975; 97:2909–2911. (b) Darwent JR, Kalyanasundaram K. J. Chem. Soc., Faraday Trans. 2. 1981; 77:373–373.
11. Oxygen is generally believed to quench $Ru^*(bpy)_3^{2+}$ by energy transfer in organic solvents. See: (a) Mulazzani QG, Sun H, Hoffman MZ, Ford WE, Rodgers MAJ. J. Phys. Chem. 1994; 98:1145–1150. (b) Tanielian C, Wolff C, Esch M. J. Phys. Chem. 1996; 100:6555–6560.
12. The oxidation potential of $Ru(bpy)_3^{3+}$ is +1.3 V (Ref. 6a). This should be sufficient to oxidize 4-methoxy-β-methylstyrene (+1.2 V) but not β-methylstyrene itself (+1.7 V). Values from: Yueh W, Bauld NL. J. Phys. Org. Chem. 1996; 9:529–538.

13. (a) Bauld NL, Pabon R. J. Am. Chem. Soc. 1983; 105:633–634. (b) Bauld NL, Bellville DJ, Pabon R, Chelsky R, Green G. J. Am. Chem. Soc. 1983; 105:2378-232. (c) Bauld NL, Yang J. Org. Lett. 1999; 1:773–774. [PubMed: 16118883] (d) Wiest O. J. Phys. Chem. A. 1999; 13:7907–7911.

14. For a recent review, see: (a) Fagnoni M, Dondi D, Ravelli D, Albini A. Chem. Rev. 2007; 107:2725–2756. [PubMed: 17530909] For examples using a 9,10-dicyanoanthracene photosensitizer, see: (b) Mizuno K, Kagano H, Otsuji Y. Tetrahedron Lett. 1983; 24:3849–3850. (c) Lewis FD, Kojima M. J. Am. Chem. Soc. 1988; 110:8664–8670.

15. Gould IR, Ege D, Moser JE, Farid S. J. Am. Chem. Soc. 1990; 112:4290–4301.

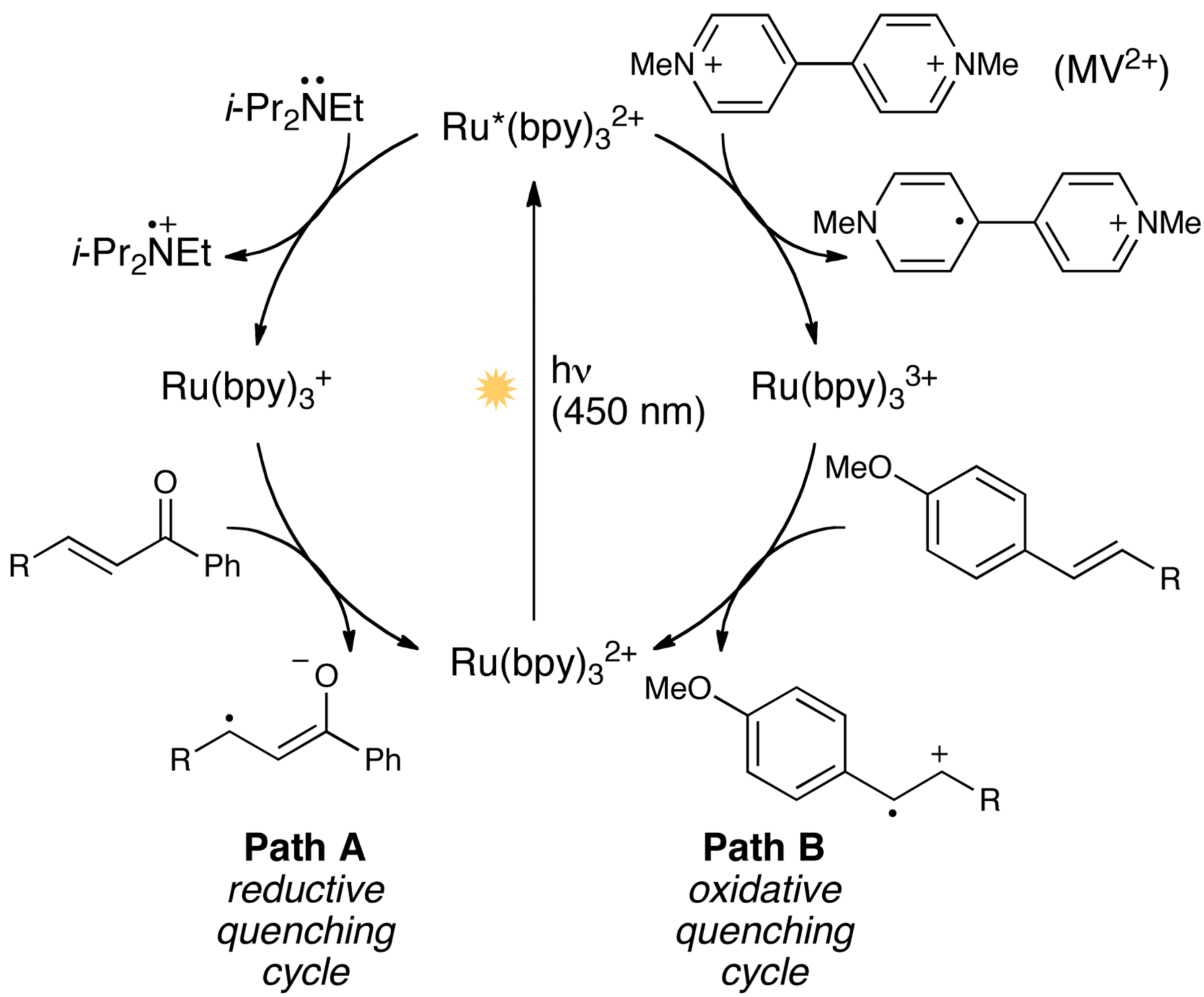
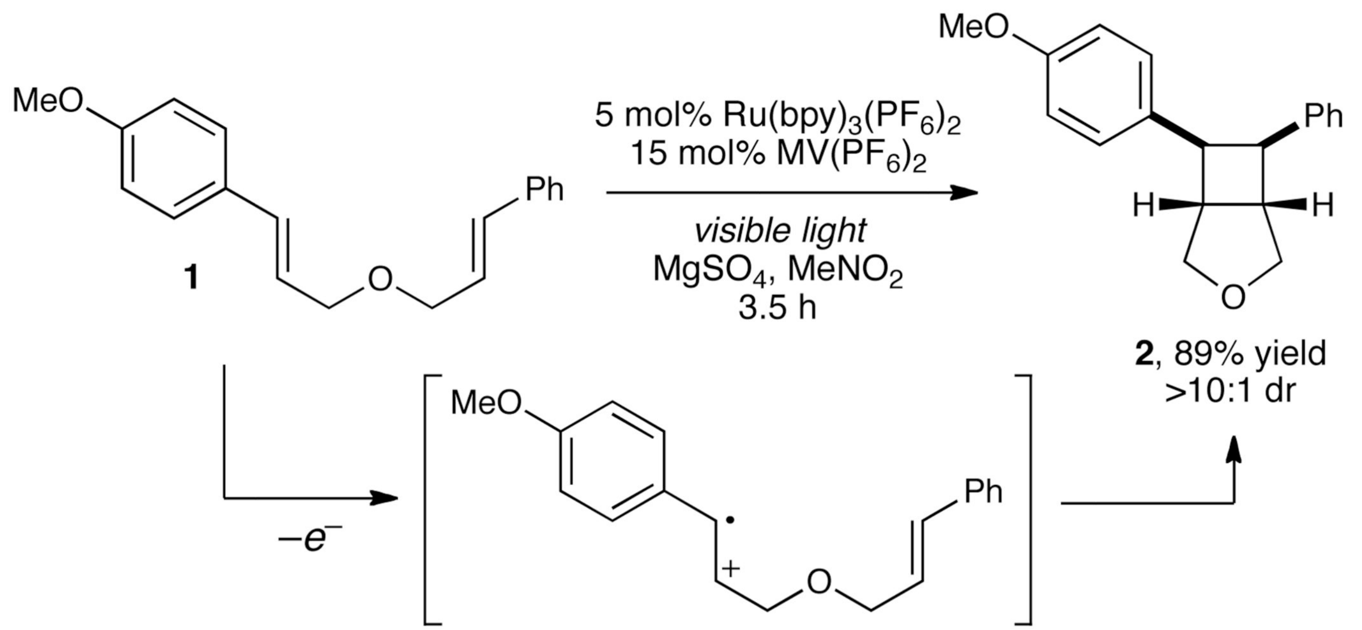
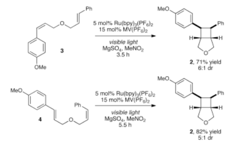


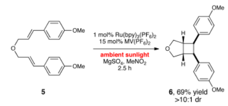
Figure 1.
Reductive and oxidative photocatalytic cycles.



Scheme 1.
Photooxidative [2+2] cycloaddition.



Scheme 2.
Stereoconvergent [2+2] cycloadditions.



Scheme 3.

Gram-scale cycloaddition with ambient sunlight

NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1

Modification of experimental parameters.

entry	variation from optimized conditions	yield[a]
1	No change	89%[b]
2[c]	Conventional photolysis (Xe arc lamp, no Ru)	0%
3	No light	0%
4	No $Ru(bpy)_3^{2+}$	0%
5	No MV^{2+}	0%
6	1,4-Dinitrobenzene instead of MV^{2+}	13%
7	1,4-Benzoquinone instead of MV^{2+}	14%
8	1 atm O_2 instead of MV^{2+}	0%
9	MeCN instead of $MeNO_2$	36%
10	Acetone instead of $MeNO_2$	11%
11	DMSO or DMF instead of $MeNO_2$	0%
12	No $MgSO_4$	73%

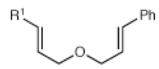
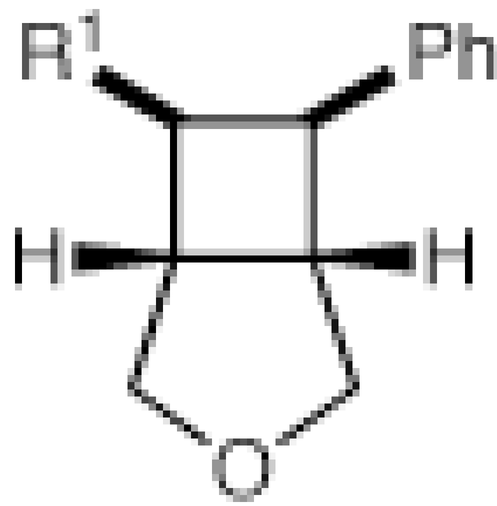
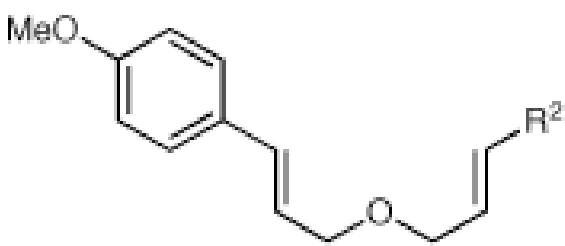
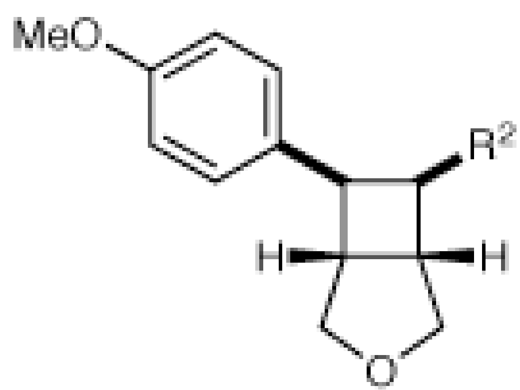
[a]Yields determined by ^{1}H NMR spectroscopy using an internal standard, unless noted.

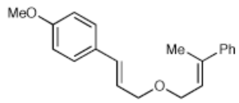
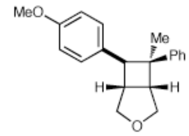
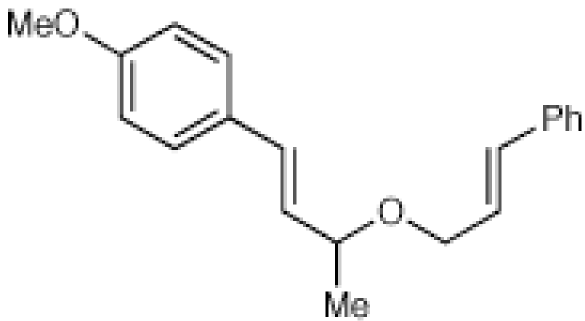
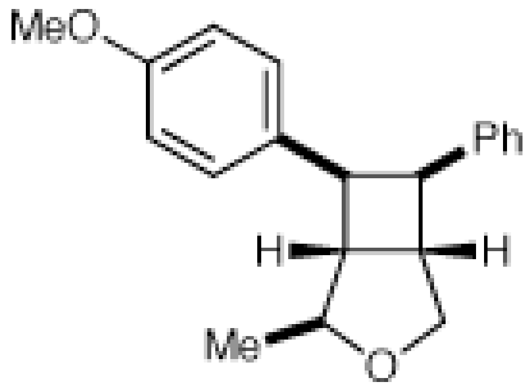
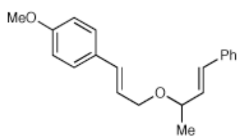
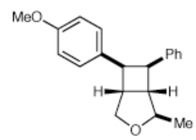
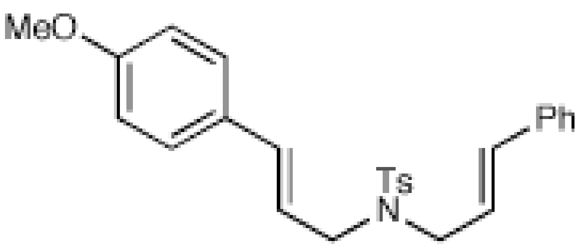
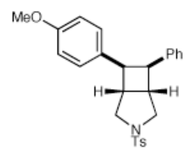
[b]Isolated yield.

[c]A solution of **1** in $MeNO_2$ was irradiated with a mercury arc lamp for 3.5 h.

Table 2

Representative [2+2] cycloadditions.[a]

entry	bis(styrene)	cycloadduct	time	yield[b]
				
1[c]		R^1 = 4-MeOPh	3.5 h	88%
2		R^1 = 2-MeOPh	11 h	73%
3		R^1 = 3-MeOPh	22 h	0%
4		R^1 = Ph	22 h	0%
5		R^1 = 4-TIPSOPh	2.5 h	69%
6[c]		R^1 = 4-HOPh	13 h	64%
7		R = 3-Br-4-MeOPh	8 h	71%
				
8		R^2 = Me	22 h	0%
9		R^2 = 4-MeOPh	2 h	67%
10		R^2 = 4-ClPh	5 h	92%
11		R = 3-FPh	5 h	78%

entry	bis(styrene)	cycloadduct	time	yield[b]
12[c]			6 h	54%
13[d]			7 h	69%
14[e]			6 h	69%
15[c]			6 h	67%

[a]Unless otherwise noted, reactions conducted using 1 mol% $Ru(bpy)_3(PF_6)_2$ and 15 mol% $MV(PF_6)_2$.

[b]Yields represent the averaged results of two reproducible experiments.

[c]Conducted using 5 mol% $Ru(bpy)_3(PF_6)_2$ and 15 mol% $MV(PF_6)_2$.

[d]5:1 d.r.

[e]7:1 d.r.