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Crossed Intermolecular [2+2] Cycloaddition of Styrenes by Visible Light Photocatalysis

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Abstract

We report a method for the crossed [2+2] cycloaddition of styrenes using visible light photocatalysis. Few methods for the synthesis of unsymmetrically substituted cyclobutanes by photochemical [2+2] cycloaddition are known. We show that careful tuning of the electrochemical properties of a ruthenium photocatalyst enable the efficient crossed [2+2] cycloaddition of styrenes upon irradiation with visible light. We outline the logic that enables high crossed chemoselectivity, and we also demonstrate that this reaction is remarkably efficient; gram-scale reactions can be conducted with as little as 0.025 mol% of the photocatalyst.

Introduction

Cyclobutane-containing natural products have been isolated from a surprisingly diverse range of plant, insect, and microbial species.¹ Yet methods for the synthesis of four-membered carbocycles² are relatively undeveloped compared to those available for the construction of five- and six-membered rings, impeding the synthesis of these compounds and the exploration of a vast domain of bioactivity-rich chemical diversity space.³ Photochemical [2+2] cycloaddition reactions would be a very efficient approach to the synthesis of complex cyclobutane-containing structures,⁴ but few methods for the chemoselective heterodimerization of isolated olefins by [2+2] photocyclization have been reported.⁵ For the past several years, we have been investigating the ability of Ru(bpy)₃²⁺ and related transition metal chromophores to promote cycloaddition reactions initiated by one-electron photoredox processes,^{6,7,8} and in 2009, we reported the highly chemoselective crossed intermolecular [2+2] cycloadditions of electron-deficient enones.^{5d} In this communication, we describe a complementary approach to photochemical heterodimerization of electron-rich olefins. This process is initiated by the one-electron oxidation of styrenes, and its success relies upon the availability of ruthenium poly(pyridyl) photocatalysts with highly tunable electrochemical properties.⁹

Results and discussion

As a prerequisite for the development of a crossed [2+2] heterodimerization, we first investigated the intermolecular *homodimerization* of styrene **1**. We had previously shown that tethered bis(styrene)s undergo efficient intramolecular [2+2] cycloaddition when irradiated in the presence of Ru(bpy)₃²⁺ and the oxidative quencher methyl viologen

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Dedication

This manuscript is dedicated in memory of Prof. Howard E. Zimmerman.

(MV²⁺).^{6b,10} These conditions, however, were ineffective for intermolecular cyclodimerization of **1**. We were able to achieve modest yields of the desired cycloadduct using more strongly oxidizing conditions (Ru(bpz)₃²⁺,¹¹ air) that we found to be effective in photocatalysis of radical cation Diels–Alder cycloadditions.^{6e} However, after extensive optimization, we observed that these reactions do not proceed to complete consumption of starting material even with extended reaction times, higher loadings of catalyst, or multiple additions of catalyst.

When the cycloadduct **2** is isolated and re-subjected to the reaction conditions, the monomeric styrene **1** slowly appears in the reaction medium, suggesting that the product of the cycloaddition is prone to oxidation to and subsequent cycloreversion (Scheme 1).¹² Indeed, we measured a peak oxidation potential of +1.27 V vs SCE for cycloadduct **2**, confirming its susceptibility to oxidation by Ru*(bpz)₃²⁺, which has a reported oxidation potential of +1.45 V. Consistent with this interpretation, we find that the putative radical cation intermediate **1**^{•+} resulting from cycloreversion can be trapped with isoprene to afford Diels–Alder cycloadduct **6** in good yield. These observations indicate that the incomplete conversions in the cycloaddition process are the result of an oxidatively induced cycloreversion process that balances the rate of the desired cycloaddition at high conversions.

We reasoned that the use of a photocatalyst with a less strongly oxidizing excited state might promote the desired cycloaddition of **1** without oxidizing **2** and triggering its undesired cycloreversion. A systematic screen of ligand-modified ruthenium complexes with varied excited state oxidation potentials revealed that conversion to **2** could be increased when Ru(bpz)₃²⁺ was replaced with the less electron-deficient tris(bipyrimidine) complex Ru(bpm)₃²⁺ (Table 1, entry 5).¹³ The reported oxidation potential of Ru*(bpm)₃²⁺ is +1.20 V vs SCE,¹⁴ which should be sufficient to promote the one-electron oxidation of **1** (+1.1 V)¹⁵ but not of **2**. Interestingly, we discovered that complete consumption of **1** could be achieved by conducting the reaction at 0 °C.¹⁶ Under these conditions, the desired cycloadduct **2** could be isolated in 81% yield.¹⁷

Having identified a photocatalyst with the appropriate excited state redox potential to enable high-yielding intermolecular cyclodimerizations, we next explored the feasibility of chemoselective crossed cycloadditions. We began by investigating the reaction between **1** and 4-methylstyrene **7a**. The design of this experiment took two strategic considerations into account. First, we selected a coupling partner less electron-rich than **1** in order to ensure that **1** would be selectively oxidized by Ru(bpm)₃²⁺ and that **1**^{•+} would be the only alkene radical cation generated in the reaction medium.¹⁸ Second, a variety of studies have suggested that the mechanism of the [2+2] cycloadditions of styrene radical cations is a concerted asynchronous process in which formation of the β,β' bond is significantly more advanced in the transition state than the α,α' bond.¹⁹ We hypothesized that the crossed cycloaddition of **1** with β-unsubstituted styrene **7a** might be sterically favored over homodimerization of **1**.

In the experiment, when **1** is irradiated with 2 equiv of **7a** in the presence of 0.25 mol% Ru(bpm)₃²⁺, only the crossed cycloadduct **8a** is produced (Table 2, entry 1). We observe a noticeable increase in rate and yield when the reaction is conducted at –15 °C (entry 2). However, we found that other alkenes sometimes gave poorer crossed selectivity; for example, when styrene (**7b**) is used as the reaction partner, a 4:1 mixture of crossed:homodimerization cycloadducts is obtained (entry 3). In these cases, however, the selectivity could be increased by adding **1** slowly by syringe pump over the course of the reaction to minimize the rate of homodimerization (entry 4).

Table 3 summarizes experiments exploring the range of olefins that could participate in successful crossed [2+2] cycloadditions with **1** under these conditions. A wide variety of styrene derivatives are suitable coupling partners in this reaction; substitution at all positions of the aryl ring is tolerated (entries 1–4). Substitution at the α position of the styrene is well tolerated without loss of diastereocontrol, enabling the construction of unsymmetrically substituted cyclobutanes possessing quaternary carbon stereocenters with high diastereoselectivity (entry 9). On the other hand, reactions involving β -substituted styrene acceptors exclusively gave homodimerization of **1** (entry 10), consistent with our reaction design plan. The functional group compatibility of this reaction is good; halides, esters, and unprotected alcohols are tolerated (entries 5–7), although very electron-deficient styrenes reacted sluggishly and could not fully outcompete homodimerization (entry 8). Finally, we found that other nucleophilic alkenes such as vinyl ethers and allyl silanes could also produce the crossed cycloadduct in good yield (entries 11 and 12). 1,1-Disubstituted aliphatic olefins, however, are not competent coupling partners and are a current limitation of this system (entry 13).

The range of oxidizable electron-rich styrenes that could initiate the cycloaddition was also probed (Table 4). Substitution at the allylic position is well-tolerated; substrates bearing silyloxy, acetoxy, chloride, hydroxide, and sulfonamide groups proceed smoothly (entries 1–5). Acid-labile acetal groups are also readily tolerated (entry 6). Surprisingly, substitution with electron-donating groups at the *meta* position of the arene results in a decrease in yield (entries 7 and 8), perhaps due to over-oxidation and decomposition of the more electron-rich cycloadduct. Consistent with this hypothesis, the cycloadduct in entry 8 exhibited a peak oxidation potential of +1.15 V vs SCE, which lies within the range accessible by $\text{Ru}^*(\text{bpm})_3^{2+}$. Positioning the methoxy group at the *ortho* position resulted in no reaction (entry 9). Styrenes activated with a silyloxy or alkoxy group at the *para* position undergo cycloaddition efficiently (entries 10 and 11). However, acetoxy groups are evidently insufficiently electron-donating to activate the styrene towards oxidation and subsequent cycloaddition (entry 12).

Control studies confirmed that no reaction occurs in the absence of light or the photocatalyst. In rigorously degassed solvent and under an atmosphere of argon, the reaction proceeds but to dramatically lower conversion (7% yield after 1 h). From this observation, we conclude that the cycloaddition is a chain process, consistent with Ledwith's seminal studies on radical cation [2+2] cycloadditions,²⁰ and that the role of the aerobic atmosphere is to turn over a photoreduced Ru(I) complex. We therefore propose the mechanism outlined in Scheme 2. The $\text{Ru}(\text{bpm})_3^{2+}$ chromophore is photoexcited by visible light, and the resulting photoexcited $\text{Ru}^*(\text{bpm})_3^{2+}$ complex participates in a one-electron oxidation of **1**. The resulting alkene radical cation (**1**^{•+}) undergoes [2+2] cycloaddition with **7a** to afford a cyclobutane-substituted arene radical cation (**8a**^{•+}), which undergoes one-electron reduction to afford the observed cycloadduct **8a**. The reductant in this process could either be another equivalent of unreacted **1**, in a chain propagation step, or the photoreduced $\text{Ru}(\text{bpm})_3^+$ complex. However, given the low concentration of the ruthenium catalyst and the rapid rate of its quenching by oxygen, the rate of this chain termination process is presumably quite slow.

As a demonstration of the scalability of this process, the crossed cycloaddition between **1** and **7a** was performed on gram scale (eq 1). This reaction required only 0.025 mol% of $\text{Ru}(\text{bpm})_3^{2+}$ and produced the expected cycloadduct **8a** in good yield and without loss of chemo- or diastereoselectivity. Notably, direct UV irradiation of **1** and **7a** in a Rayonet reactor (254 nm) in the absence of a photocatalyst failed to produce any observable cycloadducts, consistent with the known inefficiency of intermolecular [2+2] cycloaddition of simple acyclic styrenes under standard photochemical conditions.²¹ Thus, visible light

photocatalysis provides a uniquely effective and scalable method for the chemoselective synthesis of a wide variety of unsymmetrical styrene dimers inaccessible using traditional photochemical techniques.

(1)

Conclusions

In summary, we have devised a highly efficient method for the chemoselective radical cation-mediated crossed [2+2] cycloaddition under photocatalytic conditions. Key to the success of this strategy was the ability to tune the electrochemical properties of the photocatalyst in order to minimize an unexpected oxidatively triggered cycloreversion of the product. Unsymmetrically substituted cyclobutanes can thus be efficiently and chemoselectively prepared on gram scale using as little as 0.025 mol% $\text{Ru}(\text{bpm})_3^{2+}$. These results, together with our previously reported method for crossed [2+2] cycloaddition of enones, suggest that the construction of a wide range of cyclobutane-containing structures are accessible via reactions of photogenerated radical ions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Notes and references

- (a) Hansen, TV.; Stenström, Y. Naturally Occurring Cyclobutanes. In: Hudlicky, T., editor. *Organic Synthesis: Theory and Applications*. Vol. 5. Elsevier; Oxford, U.K: 2001. p. 1-38.(b) Dembitsky VM. *J Nat Med*. 2008; 62:1–33. [PubMed: 18404338] (c) Sergeiko A, Proikov VV, Hanuš LO, Dembitsky VM. *Open Med Chem J*. 2008; 2:26–37. [PubMed: 19696873]
- (a) Lee-Ruff E, Mladenova G. *Chem Rev*. 2003; 103:1449–1483. [PubMed: 12683788] (b) Lee-Ruff, E. *Synthesis of Cyclobutanes*. In: Rappoport, Z.; Liebman, JF., editors. *The Chemistry of Cyclobutanes*. Wiley; 2005. p. 281-355.
- For a recently reported elegant approach to unsymmetrical cyclobutane natural products, see: Gutekunst W, Baran PS. *J Am Chem Soc*. 2011; 133:19076–19079. [PubMed: 22066860]
- (a) Crimmins MT. *Chem Rev*. 1988; 88:1453–1473.(b) Demuth M, Mikhail G. *Synthesis*. 1989:145–162.(c) Schuster DI, Lem G, Kaprinidis NA. *Chem Rev*. 1993; 93:3–22.(d) Iriondo-Alberdi J, Greaney MF. *Eur J Org Chem*. 2007:4801–4815.(e) Bach T, Hehn JP. *Angew Chem Int Ed*. 2011; 50:1000–1045.
- For selected examples, see: Caldwell RA, Mizuno K, Hansen PE, Vo LP, Frentrop M, Ho CD. *J Am Chem Soc*. 1981; 103:7263–7269.Pabon RA, Bellville DJ, Bauld NL. *J Am Chem Soc*. 1984;

- 106:2730–2731. Bauld NL, Harirchian B, Reynolds DW, White JC. *J Am Chem Soc.* 1988; 110:8111–8117. Du J, Yoon TP. *J Am Chem Soc.* 2009; 131:14604–14605. [PubMed: 19473018]
6. (a) Ischay MA, Anzovino ME, Du J. *J Am Chem Soc.* 2008; 130:12886–12887. [PubMed: 18767798] (b) Ischay MA, Lu Z, Yoon TP. *J Am Chem Soc.* 2010; 132:8572–8574. [PubMed: 20527886] (c) Lu Z, Shen M, Yoon TP. *J Am Chem Soc.* 2011; 133:1162–1164. [PubMed: 21214249] (d) Hurlley AE, Cismesia MA, Ischay MA, Yoon TP. *Tetrahedron.* 2011; 67:4442–4448. [PubMed: 21666769] (e) Lin S, Ischay MA, Fry CG, Yoon TP. *J Am Chem Soc.* 2011; 133:19350–19353. [PubMed: 22032252]
7. For reviews of recent advances in visible light photocatalysis, see: Zeitler K. *Angew Chem Int Ed.* 2009; 48:9785–9789. Yoon TP, Ischay MA, Du J. *Nat Chem.* 2010; 2:527–532. [PubMed: 20571569] Narayanam JMR, Stephenson CRJ. *Chem Soc Rev.* 2011; 40:102–113. [PubMed: 20532341] Tepley F. *Collect Czech Chem Commun.* 2011; 76:859–917. Tucker JW, Stephenson CRJ. *J Org Chem.* 2012; 77:1617–1622. [PubMed: 22283525] Ravelli D, Fagnoni M. *ChemCatChem.* 2012; 4:169–171.
8. For recent reports of visible light photocatalysis of cycloaddition reactions by other groups, see: Zou YQ, Lu LQ, Fu L, Chang NJ, Rong J, Chen JR, Xiao WJ. *Angew Chem Int Ed.* 2011; 50:7171–7175. Maity S, Zhu M, Shinabery RS, Zheng N. *Angew Chem Int Ed.* 2012; 51:222–226.
9. Juris A, Balzani V, Barigelletti F, Campagna S, Belser P, von Zelewsky A. *Coord Chem Rev.* 1988; 84:85–277.
10. For seminal reviews of radical cation mediated [2+2] cycloadditions, see: Ledwith A. *Acc Chem Rev.* 1972; 5:133–139. Bauld NL. *Tetrahedron.* 1989; 45:5307–5363.
11. Crutchley RJ, Lever ABP. *J Am Chem Soc.* 1980; 102:7128–7129.
12. For examples of radical cation initiated fragmentations of aryl cyclobutanes, see: Mukai T, Sato K, Yamashita Y. *J Am Chem Soc.* 1981; 103:670–672. Pac C, Ohtsuki T, Fukunaga T, Yanagida S, Sakurai H. *Chem Lett.* 1985:1855–1858. Yamashita Y, Yaegashi H, Mukai T. *Tetrahedron Lett.* 1985; 26:3579–3582.
13. Hunziker M, Ludi A. *J Am Chem Soc.* 1977; 99:7370–7371.
14. Kawanishi Y, Kitamura N, Kim Y, Tazuke S. *Sci Pap Inst Phys Chem Res (Jpn).* 1984; 78:212–219.
15. Value from: Yueh W, Bauld NL. *J Phys Org Chem.* 1996; 9:529–538.
16. Bauld has suggested that the rate of radical cation induced cyclobutane fragmentation is influenced by temperature. See: Bauld NL, Pabon R. *J Am Chem Soc.* 1983; 105:633–634.
17. Consistent with the hypothesis that high-yielding cycloaddition relies upon inhibition of photooxidatively triggered cycloreversion, when 2 is irradiated in the presence of $\text{Ru}(\text{bpm})_3^{2+}$ at 0 °C for 2 h, only a trace of 1 is observed by ^1H NMR analysis of the unpurified reaction mixture (<2%).
18. Electrochemical measurements confirm that neither 7a (+1.74 V) nor 8a (+1.31 V) possess peak oxidation potentials within a range accessible by $\text{Ru}^*(\text{bpm})_3^{2+}$.
19. (a) Bauld NL, Bellville DJ, Pabon R, Chelsky R, Green G. *J Am Chem Soc.* 1983; 105:2378–2382. (b) Pabon RA, Bauld NL. *J Am Chem Soc.* 1984; 106:1145–1146. (c) Schepp NP, Johnston LJ. *J Am Chem Soc.* 1994; 116:6895–6903. (d) Wiest O. *J Phys Chem A.* 1999; 103:7907–7911.
20. Crellin RA, Lambert MC, Ledwith A. *J Chem Soc D, Chem Commun.* 1970:682–683.
21. (a) Mayo FR. *J Am Chem Soc.* 1968; 90:1289–1295. (b) Brown WG. *J Am Chem Soc.* 1968; 90:1916–1917.

Scheme 1.
Reversibility of the [2+2] cycloaddition.

Scheme 2.
Proposed mechanism of crossed cycloaddition

Table 1

Photocatalytic homodimerization of **1**^a

entry ^b	Ru complex	co-oxidant	time	yield ^c
1 ^d	Ru(bpy) ₃ (PF ₆) ₂	MV(PF ₆) ₂	24 h	9%
2	Ru(bpy) ₃ (BArF) ₂	air	8 h	1%
3	Ru(bpz) ₃ (BArF) ₂	air	2 h	57%
4	Ru(bpz) ₃ (BArF) ₂	air	16 h	65%
5	Ru(bpm) ₃ (BArF) ₂	air	2 h	72%
6 ^e	Ru(bpm) ₃ (BArF) ₂	air	2 h	83% (81%) ^f

^aExcited state oxidation potentials reported in MeCN vs. SCE. Values from Ref. 9.^bReactions conducted using 0.5 mol% of the photocatalyst (with respect to product) in CH₂Cl₂ using a 20 W compact fluorescent lightbulb unless otherwise noted.^cYields determined by ¹H NMR analysis against an internal standard unless otherwise noted.^dConducted under the conditions of Ref 6b: 5 mol% Ru(bpy)₃(PF₆)₂, 15 mol% methyl viologen hexafluorophosphate (MV(PF₆)₂), in MeNO₂.^eReaction conducted at 0 °C.^fIsolated yield in parentheses.

Table 2

Optimization of crossed [2+2] cycloaddition

entry ^a	R	T	time	8:2 ^b	yield 8b ^c
1	Me (7a)	23 °C	2 h	>10:1	77%
2	Me (7a)	-15 °C	1 h	>10:1	86%
3	H (7b)	-15 °C	1 h	4:1	55% ^d
4 ^e	H (7b)	-15 °C	1 h	>10:1	79%

^aReaction conducted using 0.25 mol% Ru(bpm)₃(BArF)₂ in CH₂Cl₂ and a 20 W compact fluorescent lightbulb.^bRatio determined by ¹H NMR analysis of the unpurified reaction mixture.^cIsolated yield unless otherwise noted.^dYield determined by ¹H NMR analysis against an internal standard.^e**1** was added by syringe pump over 1 h.

Table 3

Scope studies in [2+2] cycloadditions involving **1**.

entry ^a	alkene	cycloadduct	time	yield ^b
1	Ar = 4-MePh		1 h	86%
2	Ar = 3-MePh		2.5 h	86%
3	Ar = 2-MePh		1 h	81%
4 ^c	Ar = Ph		1.5 h	79%
5 ^d	Ar = 4-FPh		2.5 h	78%
6	Ar = 4-AcOPh		3 h	78%
7 ^d	Ar = 4-(HOCH ₂)Ph		2.5 h	56%
8 ^e	Ar = 4-(MeO ₂ C)Ph		4.5 h	31%
9			2 h	87% ^f
10 ^d			3.5 h	0%
11			3.5 h	67%
12 ^d			2.5 h	48% ^g

entry ^a	alkene	cycloadduct	time	yield ^b
13			4.5 h	0%

^aReactions were irradiated with a 20 W compact fluorescent lightbulb at -15°C using 0.25 mol% $\text{Ru}(\text{bpm})_3(\text{BArF})_2$, 1 equiv of **1**, and 2 equiv of coupling partner.

^bValues reflect the average isolated yields from two reproducible experiments. Products isolated in >10:1 d.r. unless otherwise noted.

^cAlkene **1** added over 1 h.

^dAlkene **1** added over 2 h.

^eAlkene **1** added over 4 h.

^f9:1 d.r.

^g3:1 d.r.

Table 4

Scope studies of crossed cycloadditions involving **7a**.

entry ^a	substrate	cycloadduct	time	yield ^b
1	R ¹ = OTBS		2.5 h	63%
2	R ¹ = OAc		4 h	91%
3	R ¹ = Cl		3 h	37%
4	R ¹ = OH		3 h	74%
5	R ¹ = NHTs		24 h	74%
6			1.5 h	79%
7			1.5 h	59%
8			24 h	28%

entry ^a	substrate	cycloadduct	time	yield ^b
9			24 h	0%
10	R ² = TBSO		2.5 h	88%
11	R ² = BnO		1.5 h	79%
12	R ² = AcO		24 h	0%

^aReactions were irradiated with a 20 W compact fluorescent lightbulb at -15 °C using 0.25 mol% Ru(bpm)₃(BARF)₂, 1 equiv of **1**, and 2 equiv of coupling partner.

^bValues reflect the average isolated yields from two reproducible experiments.