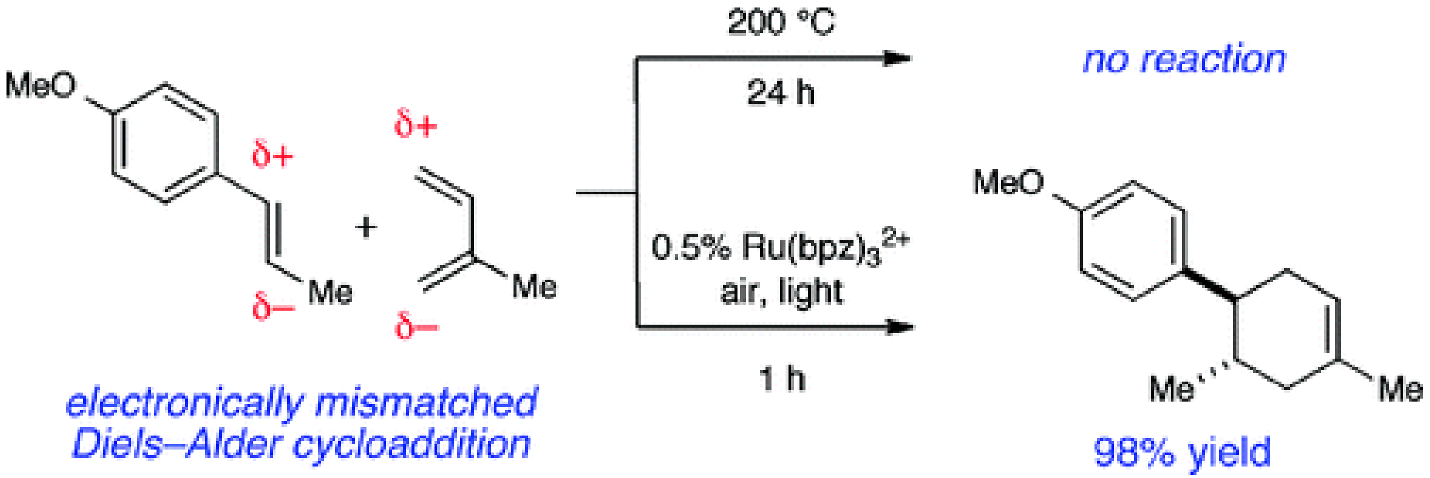
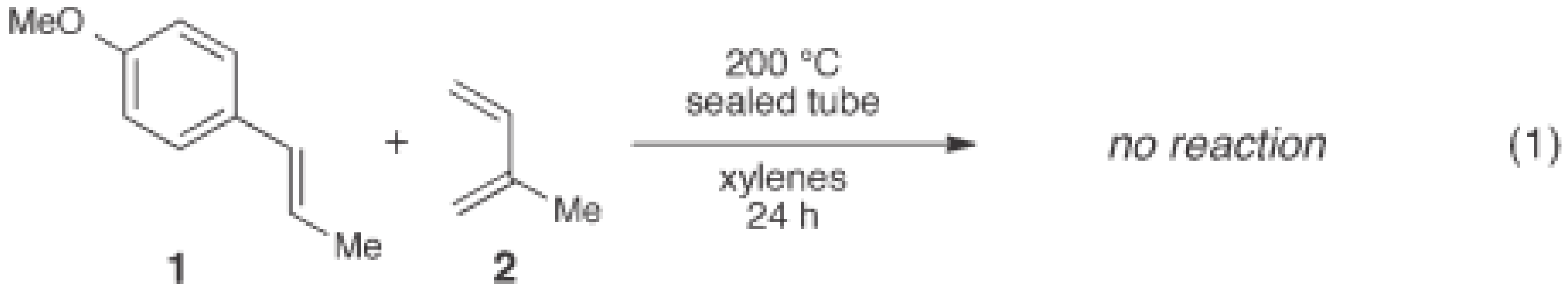
Radical Cation Diels-Alder Cycloadditions by Visible Light Photocatalysis



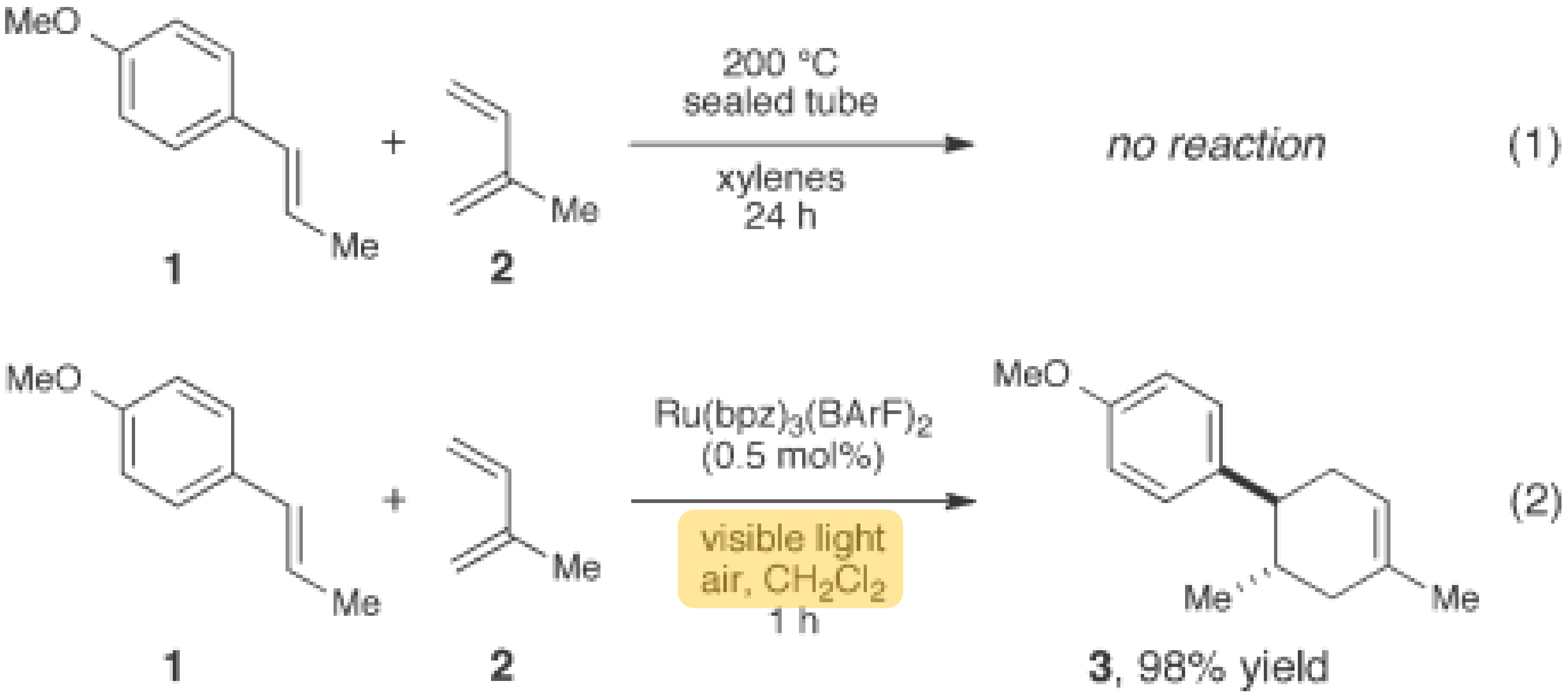
Shishi Lin, Michael A. Ischay, Charles G. Fry,
and Tehshik P. Yoon *J. Am. Chem. Soc.* **2011**, *133*, 19350-19353.

Challenge



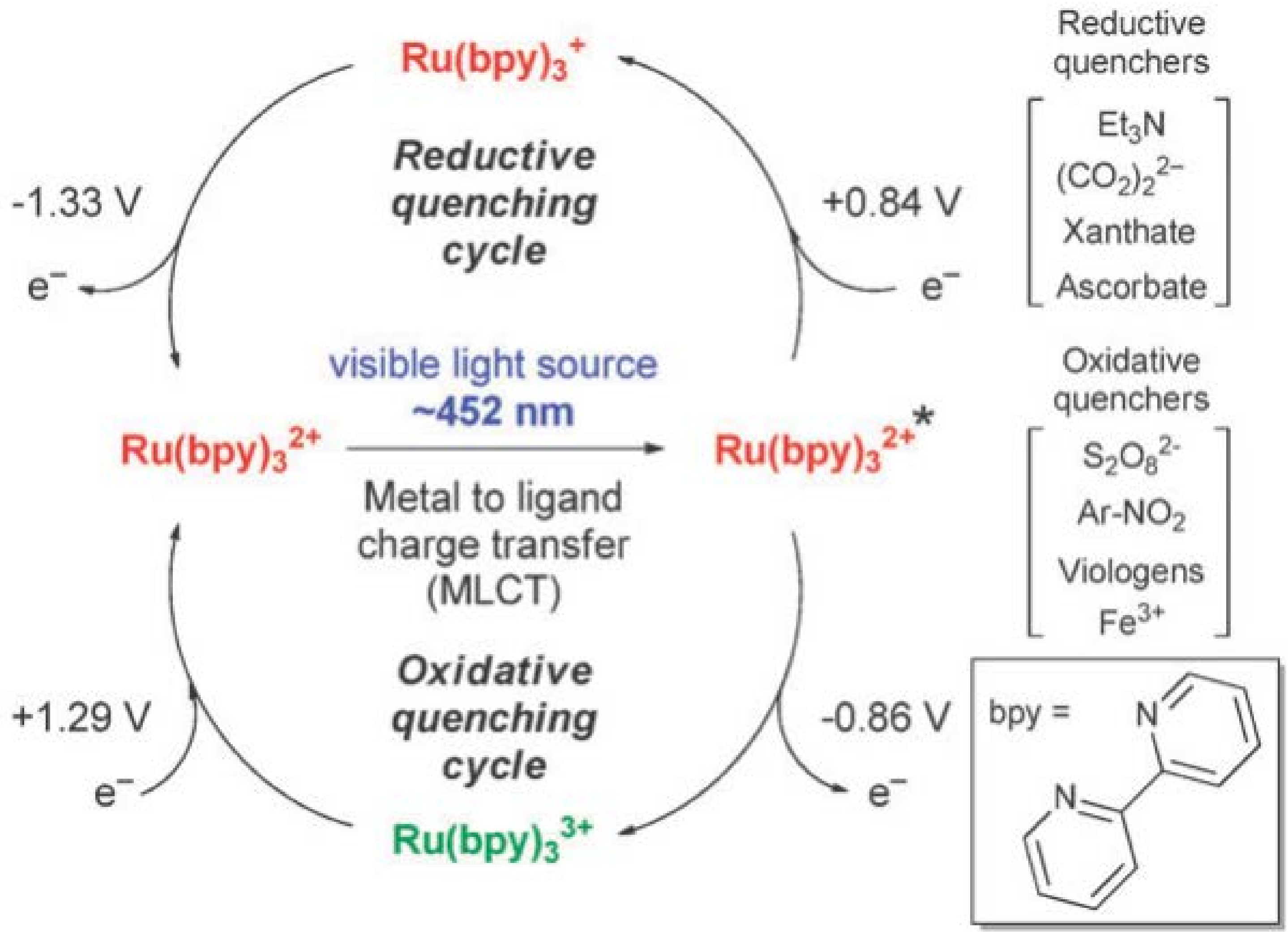
Reviews on Diels-Alder reaction:
ACIE **2001** *40*, 820; *ACIE* **2002**, *41*, 1668; *ACIE* **2003**, *42*, 3078.

Success



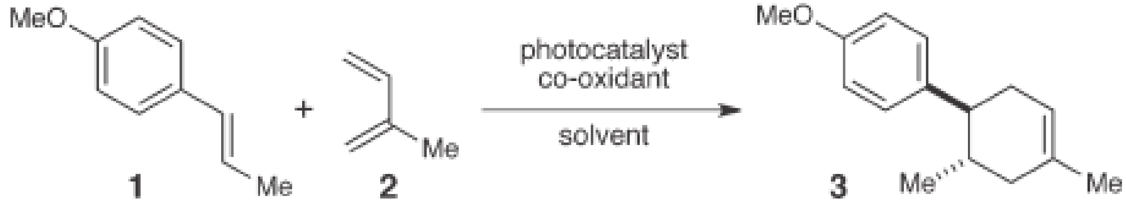
MeO
Me
1
+
Me
2
200 °C
sealed tube
xylenes
24 h
no reaction
(1)
MeO
Me
1
+
Me
2
Ru(bpz)3(BArF)2
(0.5 mol%)
visible light
air, CH2Cl2
1 h
MeO
Me
Me
3, 98% yield
(2)

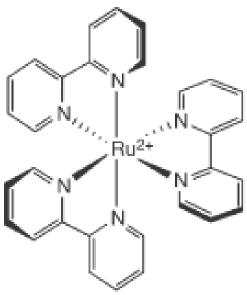
Visible Light Photocatalysis



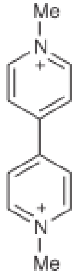
Reviews on recent developments in transition metal photoredox catalysis:
ACIE **2009** *48*, 9785; *CSR* **2011**, *40*, 102; *Nat. Chem.* **2010**, *2*, 527.

Optimization

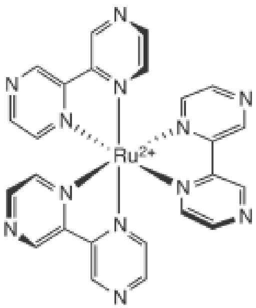




$Ru(bpy)_3^{2+}$ (**4**)



MV^{2+} (**5**)



$Ru(bpz)_3^{2+}$ (**6**)

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4[b]	$Ru(bpz)_3(PF_6)_2$ (1)	air (1 atm)	10	$MeNO_2$	1 h	78
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6[b]	$Ru(bpz)_3(BArF)_2$ (1)	air (1 atm)	3	$MeNO_2$	30 min	83
7[b]	$Ru(bpz)_3(BArF)_2$ (1)	air (1 atm)	3	CH_2Cl_2	30 min	85
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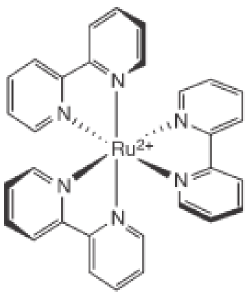
Optimization



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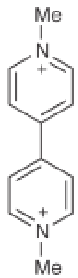

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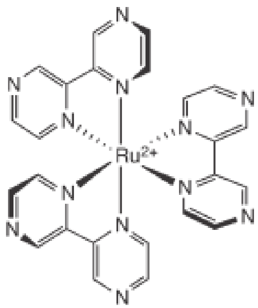

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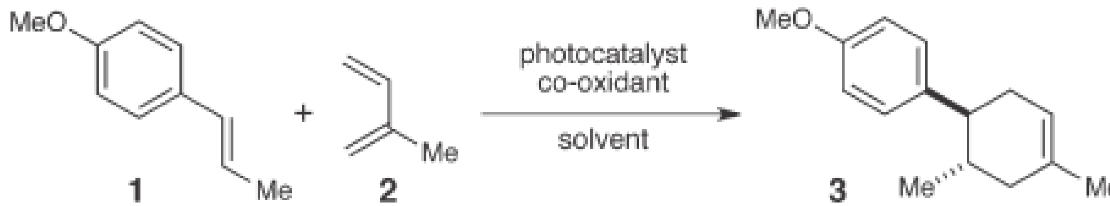

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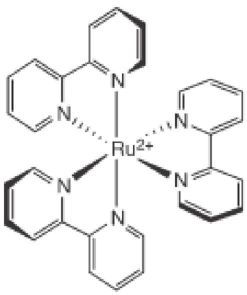
Optimization



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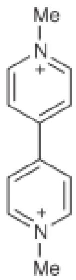

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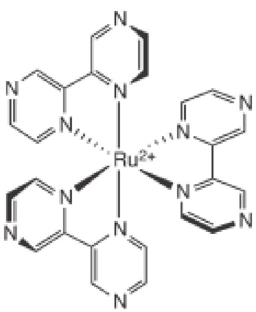

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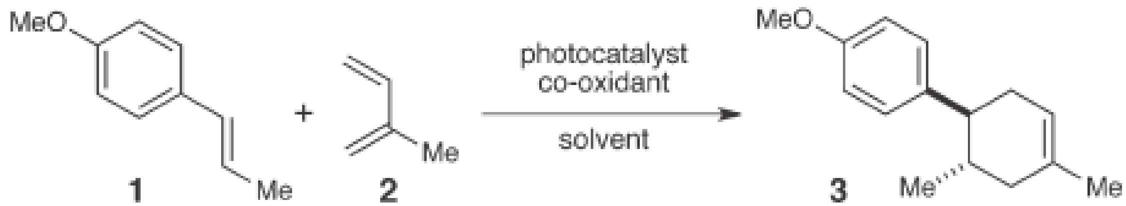

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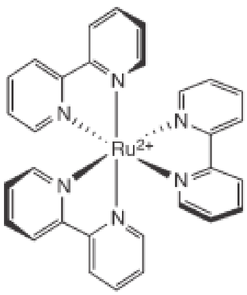

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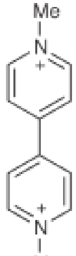

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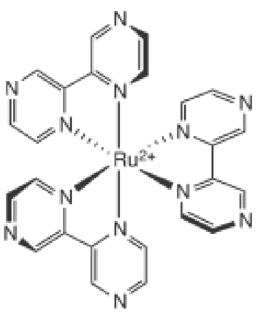

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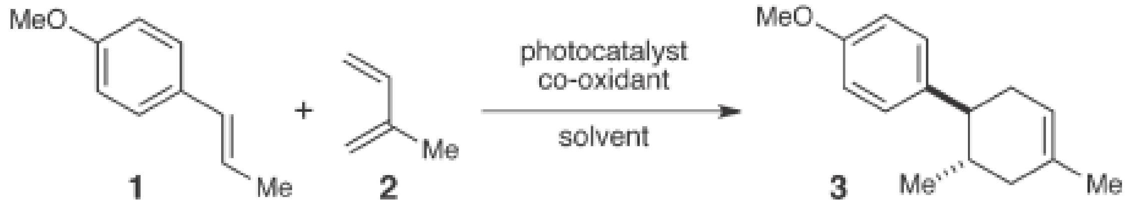

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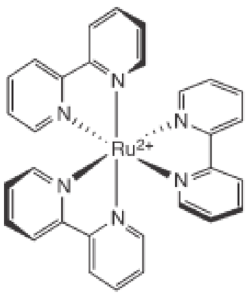

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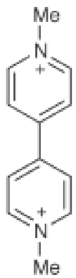

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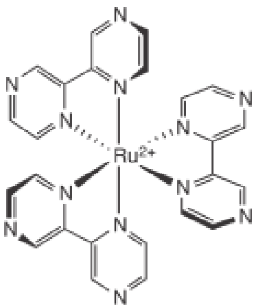

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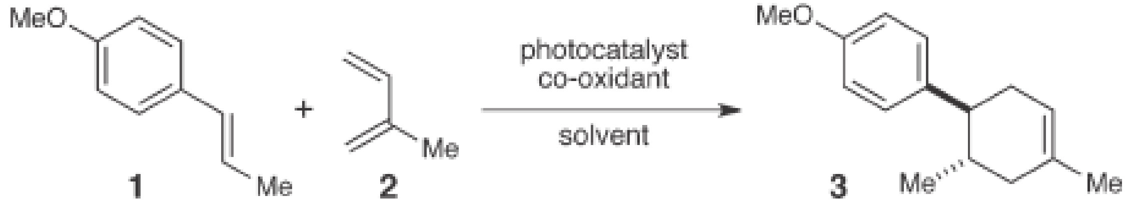

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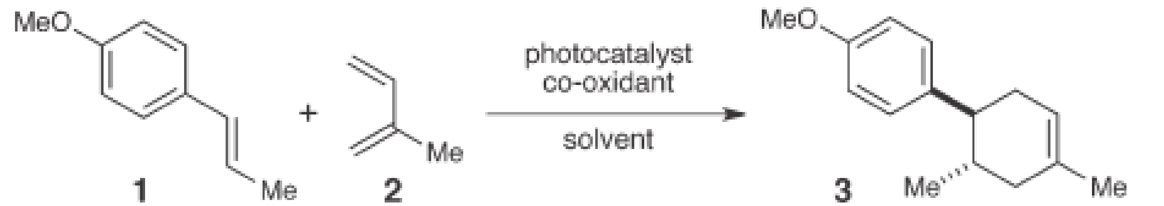

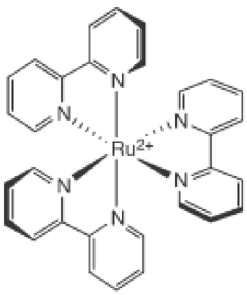

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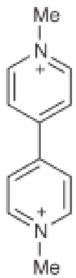
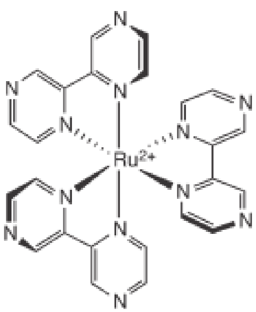


MV^{2+} (**5**)



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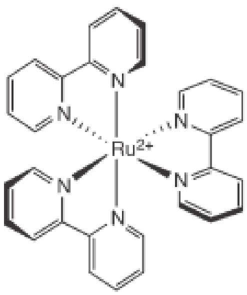

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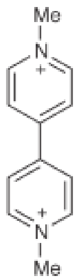

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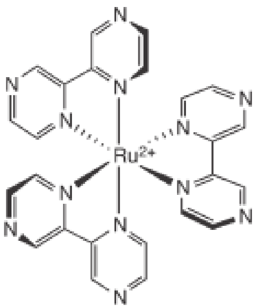

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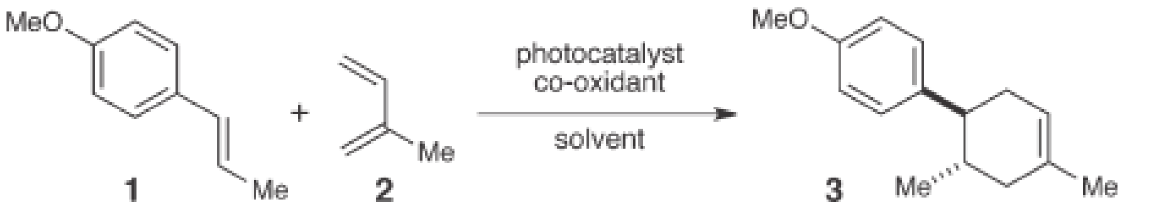

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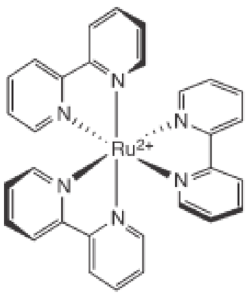

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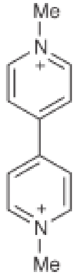

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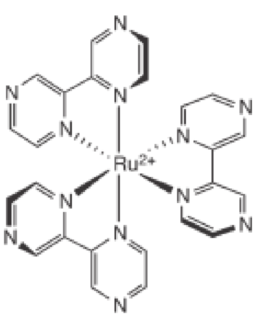

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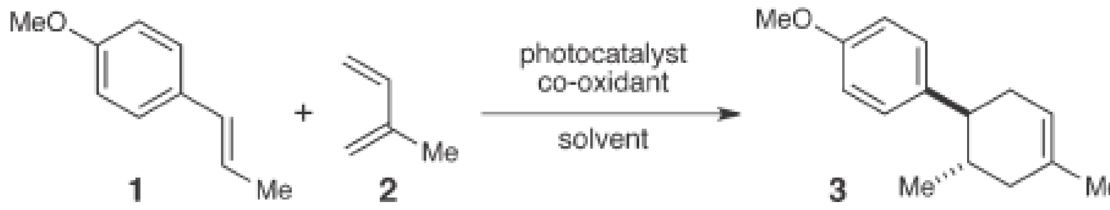

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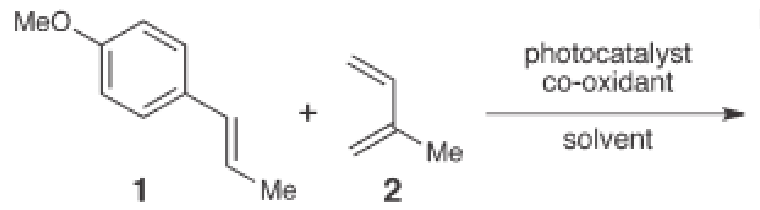
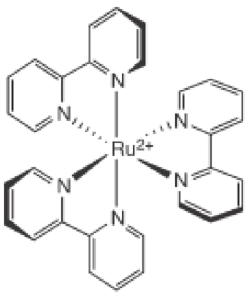
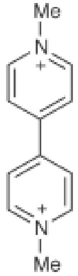
no desiccant (entries 8–9)

Optimization

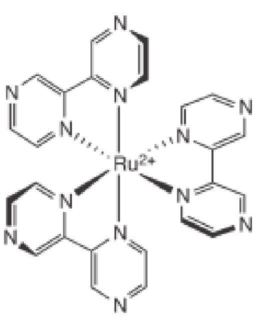




Ru(bpy)$_3^{2+}$ (**4**)



MV^{2+} (**5**)

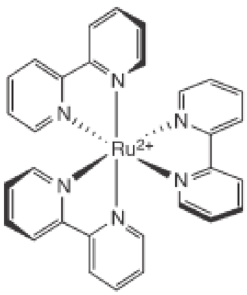


Ru(bpz)$_3^{2+}$ (**6**)

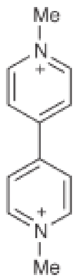
entry	catalyst (mol %)	co-oxidant (amount)	diene (equiv)	solvent	time	yield (%)[a]
1[b]	Ru(bpy)$_3$(PF$_6$)$_2$ (5)	MV(PF$_6$) (15 mol %)	10	MeNO$_2$	1 h	98
2[b]	Ru(bpy)$_3$(PF$_6$)$_2$ (1)	MV(PF$_6$) (3 mol %)	10	MeNO$_2$	1 h	25
3[b]	Ru(bpy)$_3$(PF$_6$)$_2$ (1)	air (1 atm)	10	MeNO$_2$	1 h	0
4[b]	Ru(bpz)$_3$(PF$_6$)$_2$ (1)	air (1 atm)	10	MeNO$_2$	1 h	78
5[b]	Ru(bpz)$_3$(PF$_6$)$_2$ (1)	air (1 atm)	3	MeNO$_2$	1 h	76
6[b]	Ru(bpz)$_3$(BArF)$_2$ (1)	air (1 atm)	3	MeNO$_2$	30 min	83
7[b]	Ru(bpz)$_3$(BArF)$_2$ (1)	air (1 atm)	3	CH$_2$Cl$_2$	30 min	85
8	Ru(bpz)$_3$(BArF)$_2$ (1)	air (1 atm)	3	CH$_2$Cl$_2$	30 min	92
9	Ru(bpz)$_3$(BArF)$_2$ (0.5)	air (1 atm)	3	CH$_2$Cl$_2$	1 h	98[c]

no desiccant (entries 8–9)

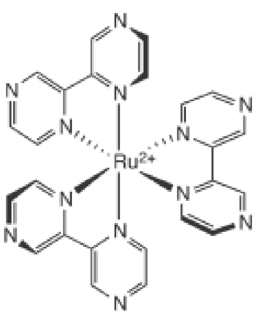
Control and Comparison Studies



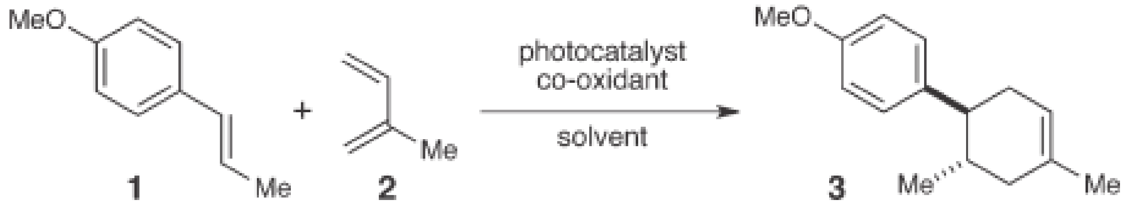
$Ru(bpy)_3^{2+}$ (**4**)



MV^{2+} (**5**)



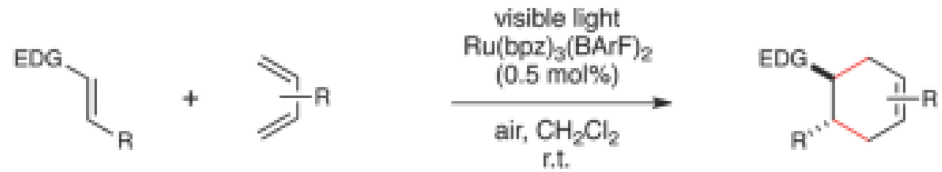
$Ru(bpz)_3^{2+}$ (**6**)

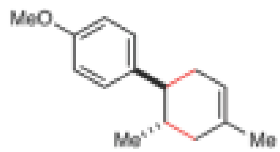


9 $Ru(bpz)_3(BArF)_2$ (0.5) air (1 atm) 3 CH_2Cl_2 1 h 98[c]

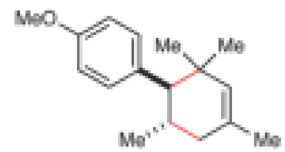
entry	conditions	time	yield (%)
1	standard conditions	1 h	98
2	no $Ru(bpz)_3(PF_6)_2$	1 h	0
3	no light	1 h	0
4	ambient sunlight instead of fluorescent lamp	1 h	98
5	no air (under N_2)	1 h	46
6	Rose Bengal instead of $Ru(bpz)_3^{2+}$	1 h	0
7	9,10-dicyanoanthracene instead of $Ru(bpz)_3^{2+}$	1 h	0
8	triphenylpyrilium · BF_4 instead of $Ru(bpz)_3^{2+}$	1 h	28

Scope

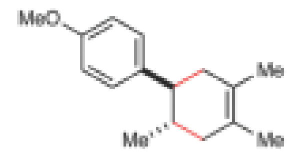




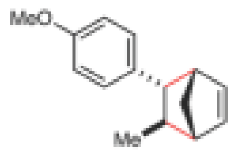
3, 98%, 1 h
[25%][b]



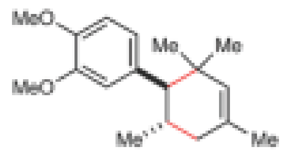
7, 91%, 2 h
[10%][b]



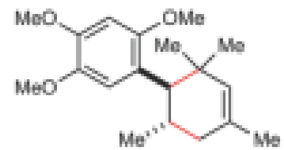
8, 98%, 1 h
[57%][b]



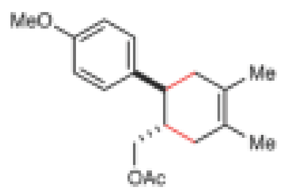
12, 91%, 1.5 h
6:1 *endo:exo*



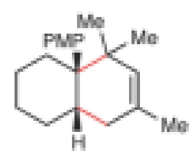
13, 78%, 1 h



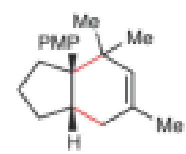
14, 72%, 8h



18, 88%, 4 h

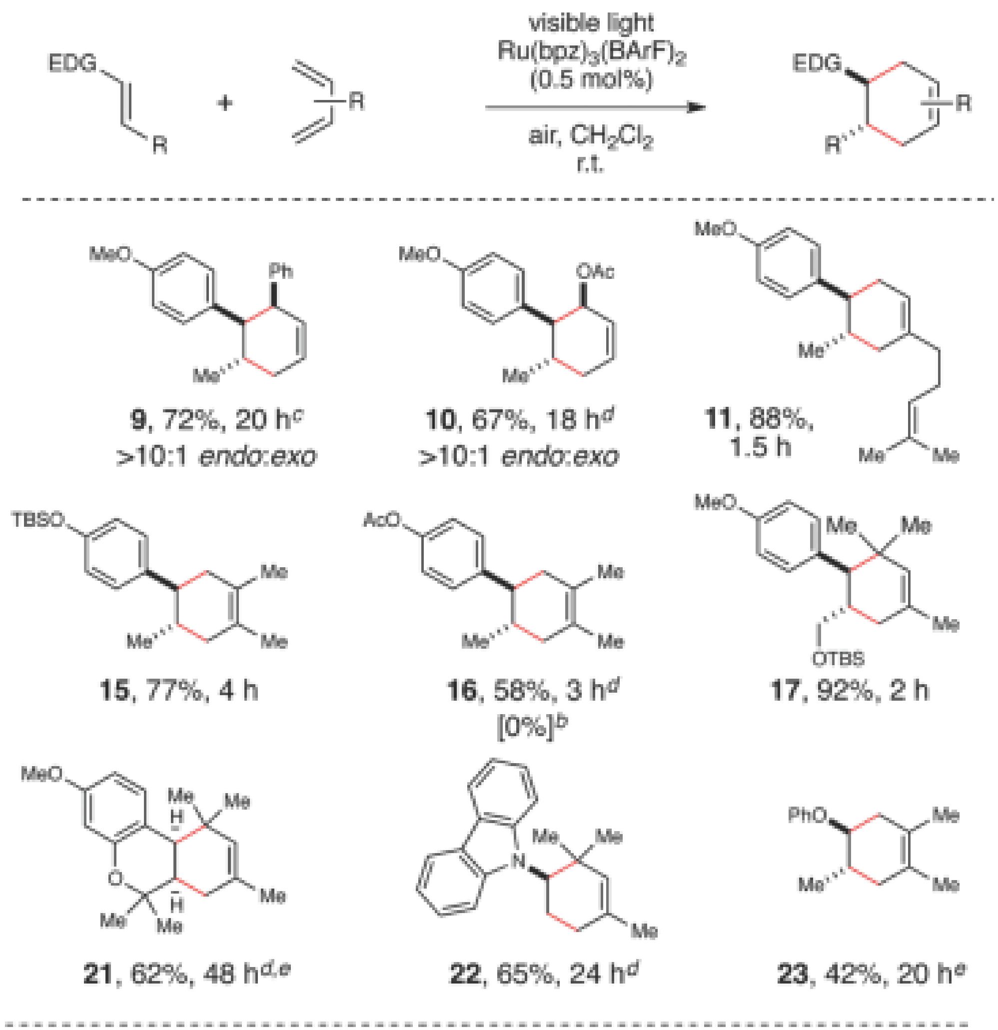


19, 92%, 20 h



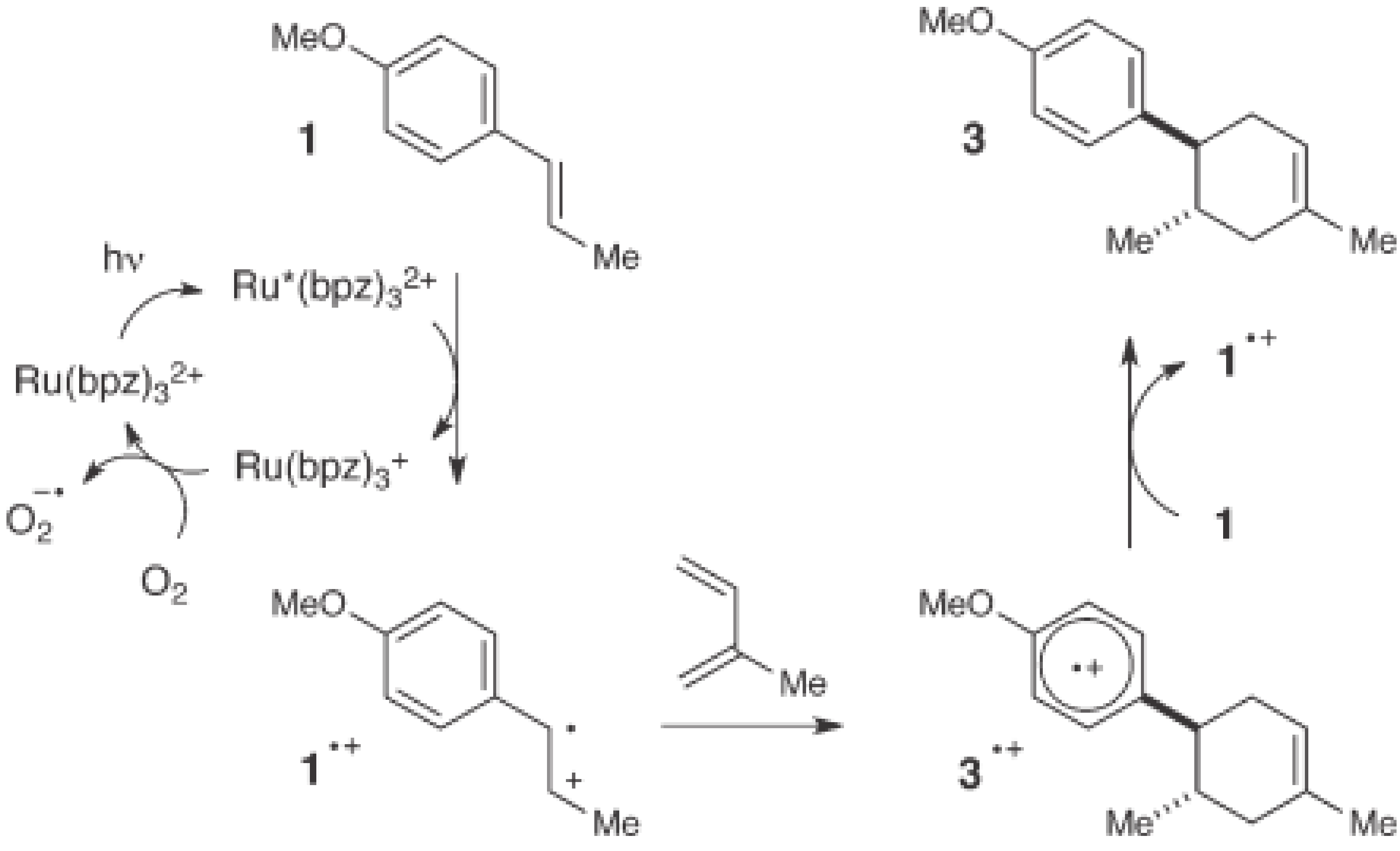
20, 85%, 1.5 h

Scope



visible light
Ru(bpz)3(BArF)2
(0.5 mol%)
air, CH2Cl2
r.t.
EDG
R
9, 72%, 20 h[c]
>10:1 endo:exo
10, 67%, 18 h[d]
>10:1 endo:exo
11, 88%,
1.5 h
15, 77%, 4 h
16, 58%, 3 h[d]
[0%][b]
17, 92%, 2 h
21, 62%, 48 h[d,e]
22, 65%, 24 h[d]
23, 42%, 20 h[e]

Proposed Mechanism



Outlook

- ***Development of a robust protocol for radical cation Diels-Alder cycloadditions using visible-light photocatalysis***

❶ ***Low catalyst loading*** *(up to 0.5 mol%).*
❷ ***Short reaction times*** *(up to 1 h)*
❸ ***Conducted under open atmosphere*** *(no need of artificial co-oxidant).*

- ***Large scale solar cycloaddition!***

- ***Application to the Total Synthesis of Heitzamide A.***

- ***Access to electronically mismatched Diels-Alder cycloadditions between electron-rich coupling partners*** *(otherwise difficult!).*

Thank you for your attention

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Radical Cation Diels−Alder Cycloadditions by Visible Light Photocatalysis

Shishi Lin, Michael A. Ischay, Charles G. Fry, and Tehshik P. Yoon*

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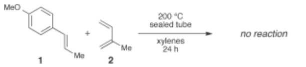
Supporting Information

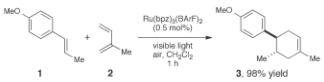
ABSTRACT: Ruthenium(II) polypyridyl complexes promote the efficient radical cation Diels−Alder cycloaddition of electron-rich dienophiles upon irradiation with visible light. These reactions enable facile [4 + 2] cycloadditions that would be electronically mismatched under thermal conditions. Key to the success of this methodology is the availability of ligand-modified ruthenium complexes that enable rational tuning of the electrochemical properties of the catalyst without significantly perturbing the overall photophysical properties of the system.

The Diels−Alder reaction ranks among the most important carbon−carbon bond-forming reactions in the repertoire of synthetic organic chemistry.[1] Factors governing the rate, stereoselectivity, and catalysis of this powerful transformation have been extensively studied and are well-understood. In particular, the reaction rate is generally synthetically useful only when an electron-rich component (typically the diene) engages an electron-deficient reaction partner (typically the dienophile). Electronically mismatched Diels−Alder reactions between two electron-rich components require more forcing conditions and significantly longer reaction times.

On the other hand, the radical cations of electron-rich olefins undergo exceptionally facile [4 + 2] cycloadditions with electron-rich dienes. These radical cation Diels−Alder reactions can occur with high regio-, stereo-, and chemoselectivity and often occur at rates several orders of magnitude greater than thermal cycloaddition of the corresponding neutral species.[2] The requisite radical cations are most commonly generated using either one-electron chemical oxidants such as aminium salts[2a−c,3] or photoinitiated electron transfer (PET) with an organic photosensitizer.[4] Both approaches require somewhat high loadings of the oxidant or photosensitizer, and the photochemical methods generally call for the use of high-intensity xenon lamps. In this communication, we report a highly efficient and operationally facile protocol for radical cation Diels−Alder cycloaddition that utilizes low loadings of a ruthenium photosensitizer and visible light irradiation (eq 2).

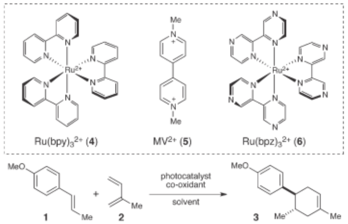


(1)



(2)

Table 1. Optimization of the Conditions for the Radical Cation Diels−Alder Cycloaddition



entry	catalyst (mol %)	co-oxidant (amount)	diene (equiv)	solvent	time	yield (%)[a]
1[b]	$Ru(bpy)_3(PF_6)_2$ (5)	$MV(PF_6)$ (15 mol %)	10	$MeNO_2$	1 h	98
2[b]	$Ru(bpy)_3(PF_6)_2$ (1)	$MV(PF_6)$ (3 mol %)	10	$MeNO_2$	1 h	25
3[b]	$Ru(bpy)_3(PF_6)_2$ (1)	air (1 atm)	10	$MeNO_2$	1 h	0
4[b]	$Ru(bpz)_3(PF_6)_2$ (1)	air (1 atm)	10	$MeNO_2$	1 h	78
5[b]	$Ru(bpz)_3(PF_6)_2$ (1)	air (1 atm)	3	$MeNO_2$	1 h	76
6[b]	$Ru(bpz)_3(BArF)_2$ (1)	air (1 atm)	3	$MeNO_2$	30 min	83
7[b]	$Ru(bpz)_3(BArF)_2$ (1)	air (1 atm)	3	CH_2Cl_2	30 min	85
8	$Ru(bpz)_3(BArF)_2$ (1)	air (1 atm)	3	CH_2Cl_2	30 min	92
9	$Ru(bpz)_3(BArF)_2$ (0.5)	air (1 atm)	3	CH_2Cl_2	1 h	98[c]

[a] Yields were determined by ^{1}H NMR analysis using CH_2Br_2 as an internal standard, unless otherwise noted. [b] Conducted in the presence of 200 wt % $MgSO_4$. [c] Isolated yield.

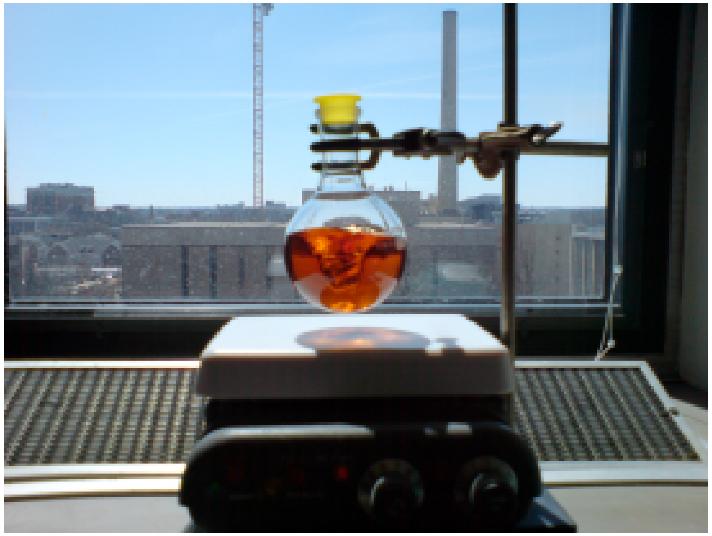
We recently reported that the [2 + 2] photocycloadditions of electron-rich olefins can be conducted upon visible light irradiation in the presence of catalytic $Ru(bpy)_3^{2+}$ and methyl viologen (MV^{2+}).[5−7] This reaction involves oxidative quenching of the $Ru^*(bpy)_3^{2+}$ photoexcited state with MV^{2+} to afford an oxidized $Ru(bpy)_3^{3+}$ complex that is sufficiently oxidizing (+1.3 V vs SCE) to convert a variety of electron-rich styrenes to the corresponding radical cations. Given the facility of this approach, we speculated that other reactions known to involve radical cation intermediates, including the Diels−Alder cycloaddition, might also be amenable to visible light photocatalysis under similar conditions.

Received: October 4, 2011
Published: October 27, 2011

dx.doi.org/10.1021/ja2093579 | J. Am. Chem. Soc. 2011, 133, 19350−19353

Unsuccessful Substrates

Large-scale solar cycloaddition (Table 2, entry 4). A 250 mL round-bottom flask was charged with 2.01 g (13.6 mmol) *trans*-anethole, 31 mg (0.013 mmol) Ru(bpz)$_3$(BArF)$_2$, 4.1 mL (41.0 mmol) isoprene, and 250 mL CH_2Cl_2. The reaction was stirred in a laboratory window for 2 h. The reaction mixture was concentrated and passed through a short pad of silica with EtOAc. The solvent was removed by rotary evaporation to afford 2.79 g (12.9 mmol, 95% yield, dr >10:1) of analytically pure cycloadduct.

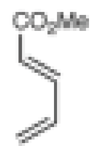


Catalysts Synthesis

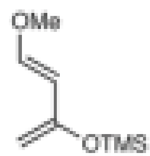
2,2'-Bipyrazine (bpz). Chloropyrazine (5.0 g, 43.7 mmol), $Pd(PPh_3)_4$ (1.5 g, 1.3 mmol), tetrabutylammonium bromide (14.0 g, 43.4 mmol), K_2CO_3 (20.5 g, 148.3 mmol) and DMF (42 mL) were placed together in a 250 mL round-bottomed flask. The reaction was heated to 140 °C, open to the atmosphere. After 16 h, the reaction was cooled to ambient temperature and filtered through celite. The filter pad was rinsed with CH_2Cl_2, and the filtrate was washed with water (400 mL). The aqueous phase was extracted 3 times with CH_2Cl_2. The combined organic layers were washed 3 times with water, dried over $MgSO_4$ and concentrated by rotary evaporation. Flash column chromatography (1:1 hexanes/ethyl acetate) gave the crude product, which was triturated with MeOH to afford 1.46 g (9.23 mmol, 42 % yield) of a pale yellow solid. All spectroscopic data were consistent with previously reported values.[13]

$Ru(bpz)_3(BArF)_2$. A solution of tris(bipyrizyl)ruthenium(II) dichloride[14] (450 mg, 0.70 mmol) in 30 mL water was placed in a 100 mL round-bottomed flask. Sodium (tetrakis[(3,5-trifluoromethyl)phenyl]borate)[15] (1.36 g, 1.53 mmol) dissolved in methanol (10 mL) was added to the reaction mixture followed by water (10 mL). The resulting heterogeneous suspension was filtered through a fritted glass funnel. The collected solids were dissolved in 1:1 acetone:CH_2Cl_2 and purified by alumina flash column chromatography using CH_2Cl_2 as the eluent. Upon concentration by rotary evaporation, the crude product was recrystallized from CH_2Cl_2:benzene to afford 820 mg (0.356 mmol, 51 % yield) of an orange solid. IR (neat) 3000, 2090, 1653, 1265 cm^{-1}. ^1H NMR: (500 MHz, CD_3CN) δ 9.8 (d, J = 1.3 Hz, 6H), 8.6 (d, J = 3.2 Hz, 6H), 7.8 (dd, J = 3.2, 1.3 Hz, 6H), 7.7 (m, 16H), 7.7 (s, 8H). ^{13}C NMR: (125 MHz, CD_3CN) δ 162.7 (q, J = 50.5 Hz), 151.3, 149.8, 148.1, 146.5, 135.7, 130.0 (q, J = 31.6 Hz), 125.5 (q, J = 124.44 Hz), 118.7.

Unsuccessful Substrates

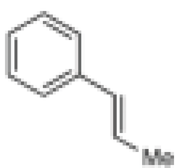


24



25

unsuccessful dienes



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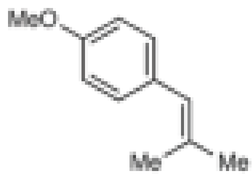

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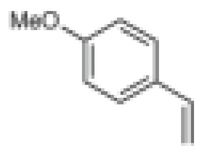

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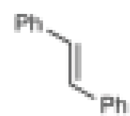

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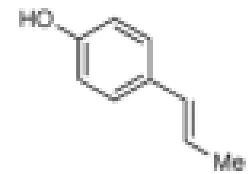
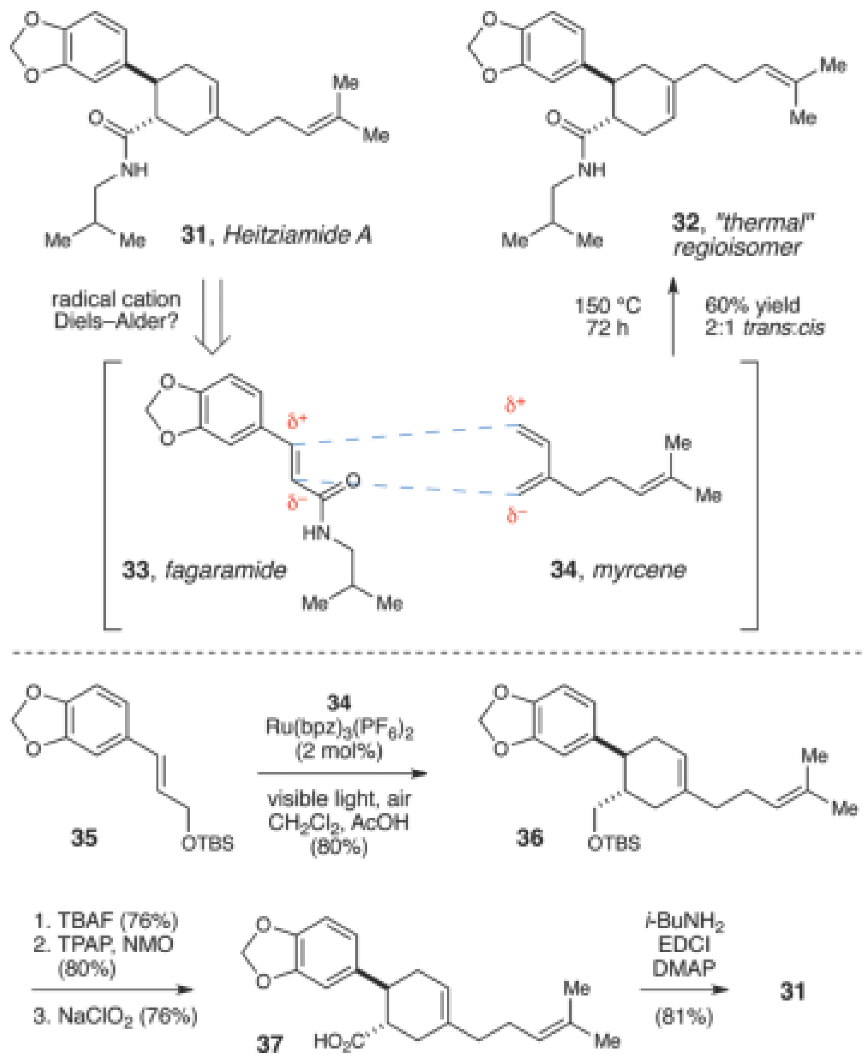


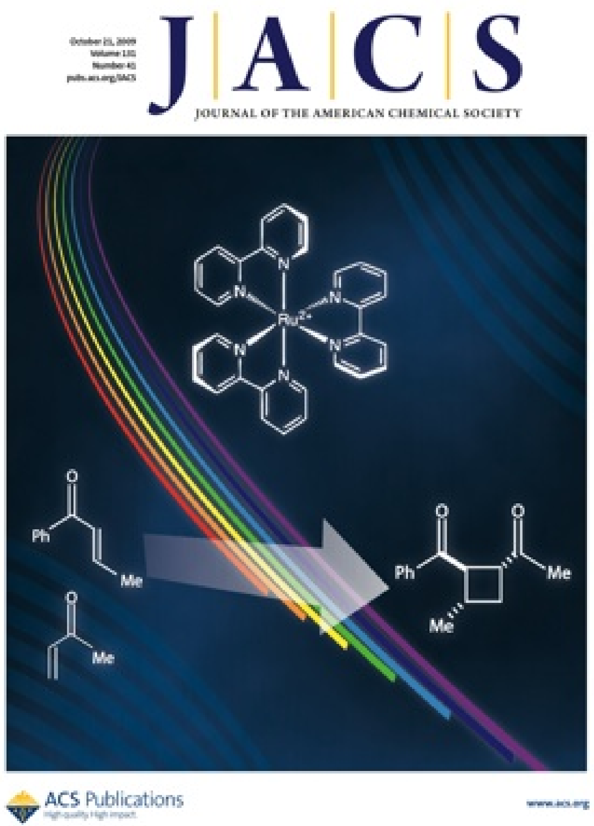
30

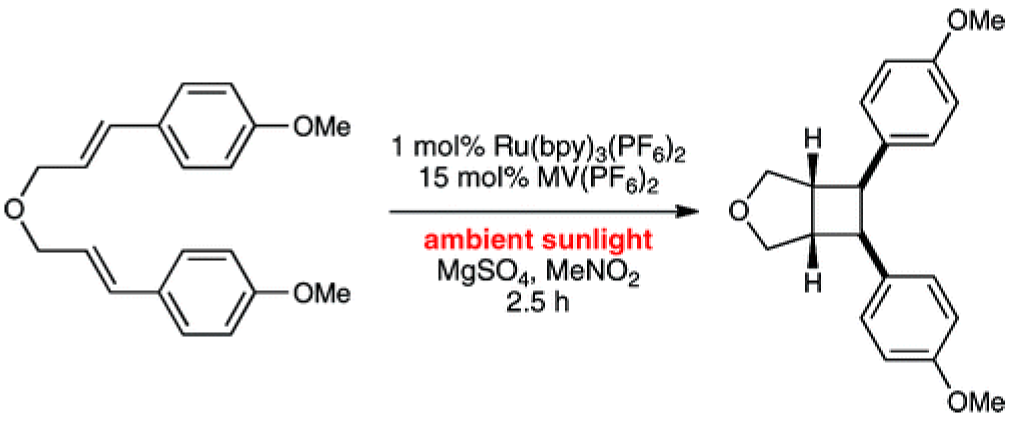
unsuccessful dienophiles

Synthetic Studies on Heitziamide A



Previous work: [2+2]





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