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COMMUNICATION

Visible light-induced difunctionalization of electron-enriched styrenes: synthesis of tetrahydrofurans and tetrahydropyrans

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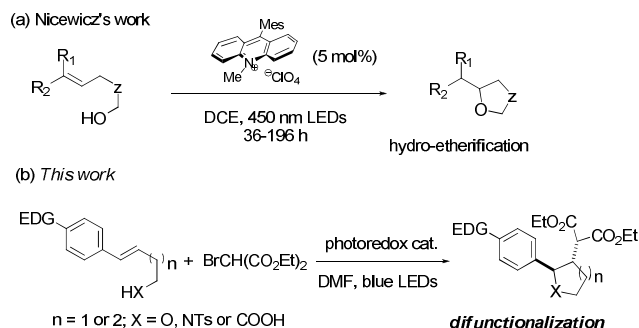
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The difunctionalization of electron-enriched styrenes for synthesis of substituted tetrahydrofurans and tetrahydropyrans through photoredox catalyst is described. The procedure is highlighted by its operational simplicity, low catalyst loading (1 mol%), excellent stereoselectivity and mild reaction conditions.

Tetrahydrofurans and tetrahydropyrans are common structural cores of a broad range of bioactive natural products.^[1] Numerous research efforts therefore have been focused on the construction of these moieties through Lewis acid or Metal catalyzed reactions^[2], and among which the catalytic protocols of direct cycloetherification of alkenes provide the efficient and valuable synthetic transformations.^[3] However, to our knowledge, the application of the visible light catalyst system^[4] to achieve this regard is quite rare. Recently, one example from Nicewicz's group reported a visible light-induced intramolecular anti-Markovnikov hydro-etherification of alkenols (Scheme 1, a).^[5] The detailed mechanism reveals that the reaction proceeds upon one-electron oxidation of electron-enriched olefins to afford corresponding radical cation, which is subsequently trapped by hydroxyl group to construct the tetrahydrofuran rings.^[6]



With our continuous investigations on the photoredox catalytic reactions,^[7] we envisioned that difunctionalization of alkenes through radical addition followed by intramolecular etherification might realize the synthesis of substituted tetrahydrofurans (as shown in Scheme 1, b).

Table 1 Optimization of cycloetherification of styrenes (**1a**).

Entry	Conditions	Time (h)	Yield (%) ^b
1	Standard conditions ^a	3	89
2	MeCN as solvent	16	0
3	Acetone as solvent	16	38
4	THF as solvent	16	42
5	DCM as solvent	5	45
6	DMSO as solvent	3	62
7	Ru(bpy) ₃ Cl ₂ as catalyst	48	0
8	Ir(ppy) ₂ (dtb-bpy)PF ₆ as catalyst	14	28
9	No K ₂ HPO ₄	13	83
10	No light	48	0
11	No catalyst	48	0

^aStandard conditions: styrenes **1a** (0.2 mmol), diethyl 2-bromomalonate (1.2 equiv.), K₂HPO₄ (2 equiv.) and [*fac*-Ir(ppy)₃] (1 mol%) in DMF (1M) irradiated with blue LEDs (1W); ^bIsolated yield.

Our initial studies was carried out on styrene **1a** with diethyl 2-bromomalonate and K₂HPO₄ using 1 mol% [*fac*-Ir(ppy)₃] ($E_{1/2}^{\square/\square^*} = -1.73 \text{ V vs SCE}$)^[8] as photoredox catalyst. The reaction was performed in DMF under irradiation with a 1 W LEDs. To our delight, the desired product was formed in 89% isolated yield (Table 1, entry 1). The stereochemistry of **2a** was identified by 1D and 2D NMR spectra. A survey on the solvents showed that the solvent has a significant effect on the reaction efficiency (Table 1, entries 2-6). As can be seen, the

application of Ir(ppy)₂(dtb-bpy)PF₆ ($E_{1/2}^{\square/\square^*} = -0.96$ V vs SCE)^[9] led to a lower yield, and Ru(bpy)₃Cl₂ ($E_{1/2}^{\square/\square^*} = -0.81$ V vs SCE)^[10] even failed to give the desired product (Table 1, entries 7 and 8). Without K₂HPO₄, longer time was needed for the complete transformation with a slight decrease in yield (Table 1, entry 9). Notably, the product **2a** was not obtained either in the darkness or in the absence of the photoredox catalyst (Table 1, entries 10 and 11).

Table 2 Scope of photocatalytic cycloetherification of styrenes.^a

Entry	Substrates	Products	Yield (%) ^b
1	R = 4-OMe	2a	89
2	R = 2-OMe	2b	82
3	R = 4-Me	2c	81
4	R = 2-Me	2d	76
5	R = 4-OTBDPS	2e	86
6	R = 4-N,N-diMe	2f	81
7	R = 2,4-diOMe	2g	79
8	R = 2,5-diOMe	2h	74
9		2i	75
10	R ₁ = 4-OTBDPSPH, R ₂ = Me	2j	83
11	R ₁ = 4-OMePh, R ₂ = Ph	2k	81
12	R ₁ = 4-OMePh, R ₂ = 4-OMePh	2l	94
13		2m	85
14	R = Me	2n:2n' = 1:1.2	83
15	R = Ph	2o:2o' = 1:1.2	81

^aStandard conditions: styrenes **1** (0.2 mmol), diethyl 2-bromomalonate (1.2 equiv.), K₂HPO₄ (2 equiv.) and [fac-Ir(ppy)₃] (1 mol%) in DMF (1M) irradiated with blue LEDs (1W) for 3 hours; ^bIsolated yield.

With the optimized reaction conditions in hand, we investigated the scope of photocatalytic cycloetherification of styrenes, and the results were outlined in Table 2. In general, the reaction conditions worked well with a number of electron-enriched styrenes. The electron-donating substituents at *para* or *ortho* position are effective activators for styrenes (Table 2, entries 1-9); *meta*-substituted and unsubstituted styrenes are presumably

not electron-rich enough to undergo one-electron oxidation to afford the key radical cation intermediate. Trisubstituted electron-enriched styrenes were also tolerated with the reaction conditions, which enabled access to quaternary centers on the tetrahydrofuran framework (Table 2, entries 10-12).

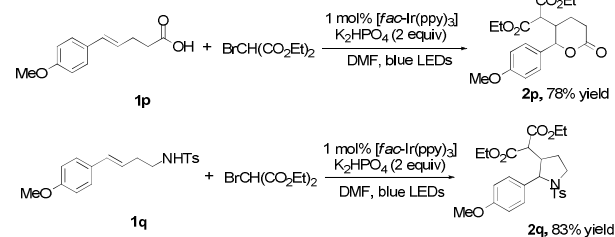
Besides the formal 5-*endo* cycloetherification mode, the alkenol with a longer chain could undergo 6-*endo* cycloetherification to furnish the anticipated substituted tetrahydropyrans (Table 2, entry 13). Particularly, this approach proceeded efficiently not only for primary alcohols but also for secondary alcohols, although the latter gave a mixture of 6-*endo* and 5-*exo* cycloetherification products, which was attributed to steric effect of more hindered secondary alcohols (Table 2, entries 14 and 15).

Table 3 Photocatalytic cycloetherification of styrene **1a** with various oxidants.^a

Oxidants:	Br-CH(CO ₂ Et) ₂	Br-C(CH ₃)(CO ₂ Et) ₂	Br-CH ₂ -CO ₂ Et	CF ₃ I
Products:	2a , R = -CH(CO ₂ Et) ₂ 89%	3a , R = -C(CH ₃)(CO ₂ Et) ₂ 81%	4a , R = -CH ₂ CO ₂ Et 84%	5a , R = -CF ₃ 85%

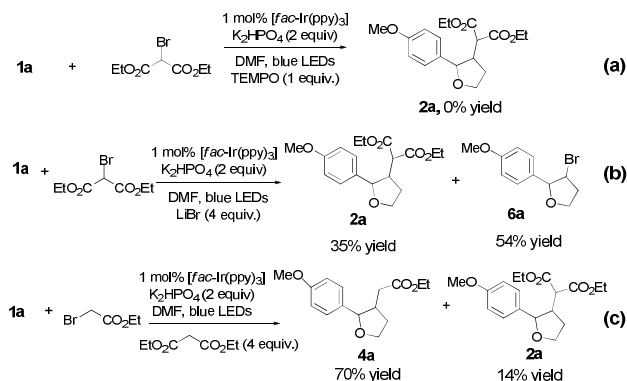
^a Standard conditions: styrenes **1** (0.2 mmol), oxidant (1.2 equiv.), K₂HPO₄ (2 equiv.) and [fac-Ir(ppy)₃] (1 mol%) in DMF (1M) irradiated with blue LEDs (1W) for 3 hours.

On the other hand, a variety of oxidants were examined in the photocatalytic cycloetherification of styrene **1a** (Table 3). Apart from diethyl 2-bromomalonate, other α -bromo esters also enabled access to disubstituted tetrahydrofurans in good yields (**3a** and **4a**). Notably, when CF₃I was chosen as the oxidant, β -CF₃ substituted tetrahydrofuran was obtained in 85% isolated yield (Table 3, **5a**).



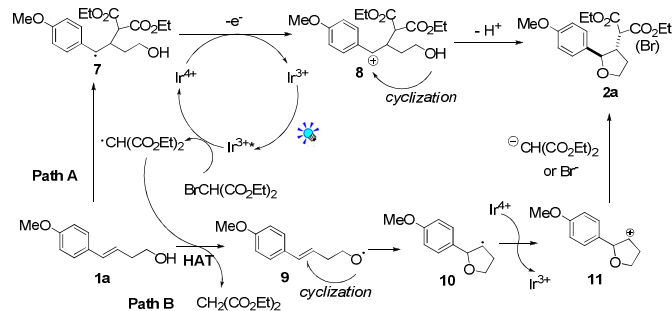
Scheme 2 Photocatalytic lactonization and aminocyclization

To further investigate the applicability of this protocol in organic synthesis, we envisioned a scenario, when the hydroxyl group is replaced by another nucleophilic group, such as a carboxyl or an amino group, then would the cyclization still work out? Hence, we treated pentenoic acid **1p** and N-tosyl butenyl amide **1q** with diethyl 2-bromomalonate under the standard conditions. Fortunately, substituted lactone **2p** and pyrrolidine **2q** were obtained in 78% and 83% yield respectively (Scheme 2). Therefore, this protocol could also be applied to lactonization and aminocyclization reactions.



Scheme 3 Preliminary mechanistic investigations.

A preliminary investigation of the reaction mechanism suggested that the reaction involves a diethyl malonate radical. Under the optimized reaction conditions, **1a** did not produce a diethyl malonate-substituted tetrahydrofuran **2a** in the presence of TEMPO (Scheme 3, a). Furthermore, when 4 equivalents of LiBr was added to the reaction of **1a** with diethyl 2-bromomalonate, malonate-substituted product **2a** was formed in 35% yield along with the bromo-product **6a** in 54% yield (Scheme 3, b). Meanwhile, the reaction of **1a** with ethyl bromoacetate in the presence of additional diethyl malonate under the optimized reaction conditions afforded acetate-substituted product **4a** in 70% yield as well as the malonate-substituted product **2a** in 14% yield (Scheme 3, c). The above two experimental results revealed that both the carbon radical and carbon cation were involved in the reaction, and the main pathway depends on the conditions and reactants applied.



Scheme 4 Proposed mechanism for photocatalytic cyclization of styrenes

Accordingly, a tentative mechanism for this photocatalytic cyclization of styrenes is proposed in Scheme 4. Oxidative quenching of the visible light-induced excited state Ir^{3+*} by diethyl 2-bromomalonate generates a radical $\cdot\text{CH}(\text{CO}_2\text{Et})_2$ along with the Ir^{4+} complex. In path A, the radical $\cdot\text{CH}(\text{CO}_2\text{Et})_2$ adds to alkene **1a** to afford intermediate **7** which can undergo oxidation by Ir^{4+} to generate a benzylic carbocation **8** and a further cyclization leads to the final product **2a**. Based upon the results of control experiments (Scheme 3, b and c), the path B also could not be excluded. Hydrogen atom transfer (HAT) generated oxygen radical **9**, which can be efficiently trapped by alkene to form the tetrahydrofuran ring radical **10**. A further oxidation by Ir^{4+} affords the carbocation **11**, which combines diethyl malonate carbon anion or Br^- to provide the

final product.

In conclusion, we have developed a visible light-induced difunctionalization of electron-rich styrenes using photoredox catalyst $[\text{fac-Ir}(\text{ppy})_3]$. This highly efficient and regioselective cycloaddition of styrenes provided a mild and environment-friendly approach toward the synthesis of substituted tetrahydrofurans and tetrahydropyrans.

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† Electronic supplementary information (ESI) available: Full experimental details, product characterization and NMR spectral data. See DOI: 10.1039/c000000x/

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