Photoinduced Electron Transfer

DOI: 10.1002/ange.201210111

Synthesis of Highly Substituted Tetrahydrofurans by Catalytic Polar-Radical-Crossover Cycloadditions of Alkenes and Alkenols**

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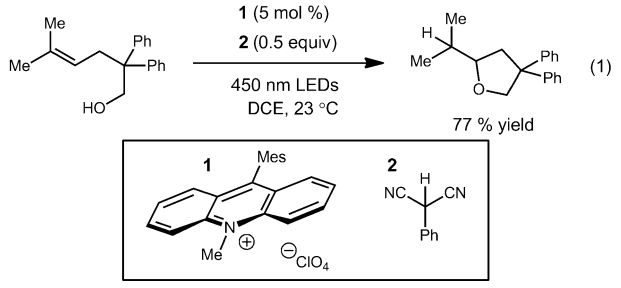
Tetrahydrofuran rings are common structural elements present in numerous biologically active naturally occurring molecules, including a number of lignans and polyether antibiotics.[1] Perhaps owing to their prevalence in natural products, there have been a number of direct catalytic synthetic methods devised to construct this motif.[1b] Common strategies include carbonyl ylide dipolar cycloadditions,[2] the Prins-Pinacol reaction,[3] the Oshima–Utimoto reaction[4] and Lewis acid catalyzed [3+2] cycloadditions of donor–acceptor cyclopropanes and aldehydes.[5] Herein, we report the development of a new organocatalytic synthetic method for the construction of tetrahydrofurans employing simple and readily available allylic alcohols and alkenes. The reaction is catalyzed by a commercially available organic single electron photooxidant coupled with a redox-active hydrogen atom donor. This catalytic method provides the direct synthesis of valuable tetrahydrofurans from common organic reagents.

We have recently established an organic photoredox catalytic system for the direct intramolecular anti-Markovnikov hydroetherification of alkenols that produces five- to seven-membered cyclic ethers with complete regiocontrol [Eq. (1); Mes = mesityl, DCE = 1,2-dichloroethane].[6] The

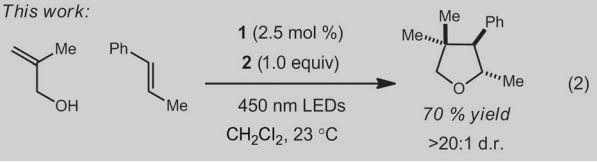
Direct anti-Markovnikov hydroetherification of alkenols



(1)

reaction proceeds via the intermediacy of a radical cation. The key innovation in this method is the ability to segregate polar and radical reaction vectors by employing a redox-active hydrogen atom donor. We realized that this unique catalytic strategy afforded the opportunity to directly synthesize highly substituted tetrahydrofurans from allylic alcohols and alkenes by a polar-radical-crossover cycloaddition (PRCC) sequence that capitalizes on the simultaneous polar and radical nature of radical cation species [Eq. (2)]. In

Polar-radical-crossover cycloaddition of alkenes and alkenols



(2)

support of this mechanistic hypothesis, Giese,[7a] Newcomb,[7b] and Crich[7c] have previously demonstrated the fundamental steps of this proposal through radical cation generation from β-(phosphatoxy)alkyl selenides and PTOC esters, respectively.

In combining successive polar and radical steps, polar-radical-crossover reactions have the potential to become a powerful strategy for the development of reactions relying on multiple bond-forming events.[8] Despite the promise held by this mechanistic approach, few practical examples of this strategy have been brought into practice.[9] In prior reports in which this mechanism is operative, superstoichiometric quantities of either an oxidant or reductant are typically needed to access the requisite reactive intermediates. To our knowledge, there are no examples of truly redox-neutral polar radical crossover reactions.

To directly access the tetrahydrofuran ring system, we envisioned that upon single-electron oxidation of a suitable olefinic substrate, an allylic alcohol would add to the corresponding radical cation with anti-Markovnikov selectivity (Scheme 1).[6,10] This initial polar step would afford radical **6**, which is poised to undergo a 5-*exo* radical cyclization with the pendant alkene. Finally, hydrogen-atom abstraction from $PhCH(CN)_2$ (**2**) and the loss of a proton furnishes the tetrahydrofuran adduct. In order for turnover of **1** to occur, radical **9** would have to act as a single-electron oxidant for **11**. Additionally, the phenyl malononitrile anion (**10**) can neutralize the acid generated during the reaction course and regenerate hydrogen-atom donor **2**. Importantly, this proposed mechanism would maintain overall redox neutrality by employing redox-active hydrogen-atom donor **2**.

To begin, we investigated the reaction of allyl alcohol and β-methyl styrene with acridinium perchlorate salt **1**[11] as a photoredox catalyst and phenyl malononitrile as the hydrogen-atom donor (Table 1, entry 1). We were pleased to find that irradiation of this mixture with 450 nm LEDs

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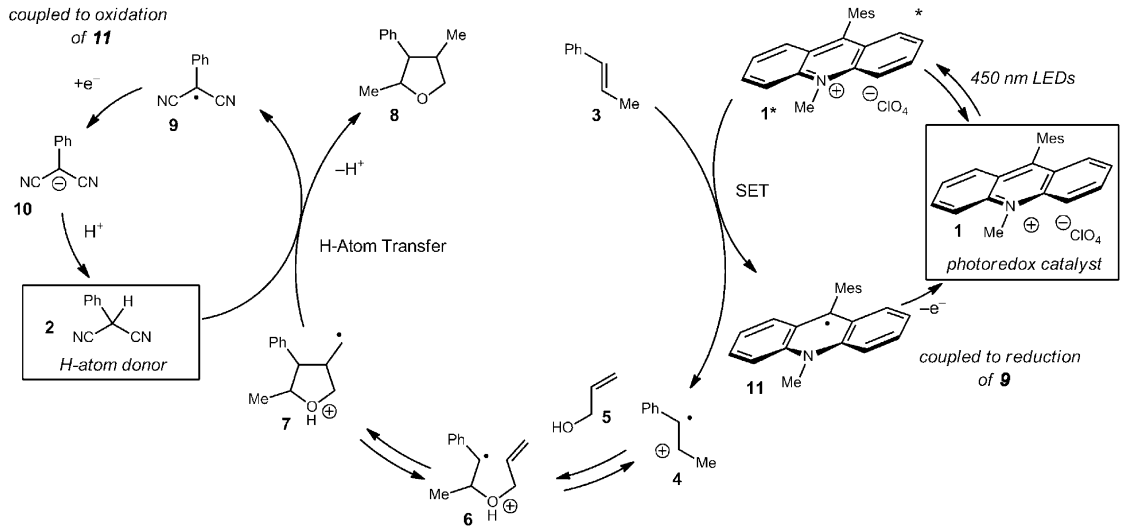
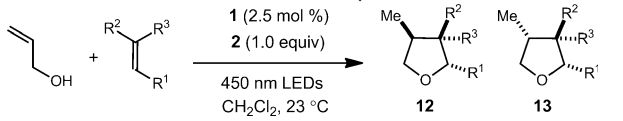
[**] This project was supported by The University of North Carolina at Chapel Hill and an Eli Lilly New Faculty Award.

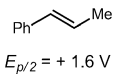
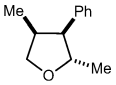
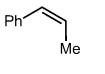
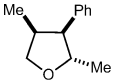
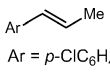
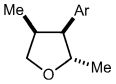
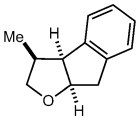
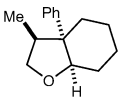
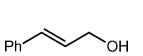
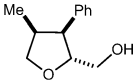
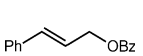
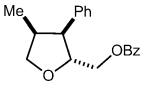
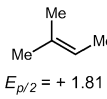
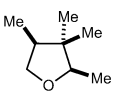
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201210111.



Scheme 1. Postulated mechanism for the photoredox PRCC reaction between allyl alcohol and β-methyl styrene. $\pm e^- =$ redox couple, $\pm H^+ =$ proton transfer, SET = single electron transfer.

Table 1: PRCC reactions of alkenes and allyl alcohol.[a]



Entry	Alkene	Product	12/13[b]	Yield [%]
1	 $E_{p/2} = +1.6$ V		1.7:1[c]	63
2			1.7:1[c]	80
3	 Ar = *p*-ClC$_6$H$_4$		1.7:1[c]	70
4	 $E_p = +1.69$ V		2.6:1	63
5	 $E_{p/2} = +1.61$ V		1.2:1	60
6			2.1:1[c]	55
7			3.3:1	42
8	 $E_{p/2} = +1.81$ V		3:1	95[d]

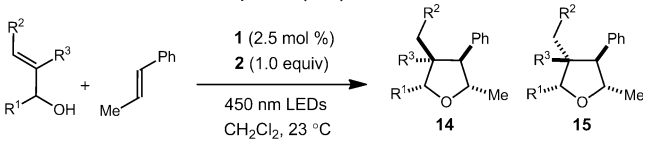
[a] Average of two experiments using alkenol (5.0 equiv) for 48–144 h. [b] Diastereomeric ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Small amounts (> 7%) of a third diastereomer were observed; see the Supporting Information for details. [d] Determined by ^{1}H NMR spectroscopy with an internal standard. Bz = benzoyl.

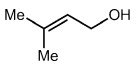
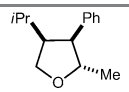
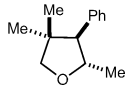
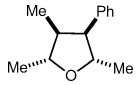
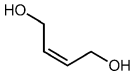
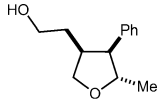
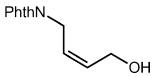
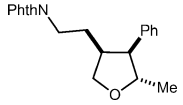
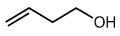
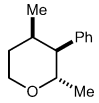
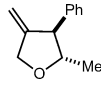
afforded the anticipated tetrahydrofuran as a single regioisomer in nearly quantitative yield in a 10:6:1 ratio of diastereomers, as determined by ^{1}H NMR spectroscopy. Somewhat lower yields of isolated product were obtained (63%), presumably owing to the volatility of the product. Attempts to increase the diastereoselectivity by employing different catalysts, or by varying reaction concentrations and solvents unfortunately failed to improve upon this preliminary result. Omission of **2** or the use of $[Ru(bpy)_3]^{2+}$ (bpy = bipyridine) as photooxidant failed to furnish even trace amounts of the desired product, likely due to the lower oxidizing power of $^*[Ru(bpy)_3]^{2+}$.[12,13]

Next, we surveyed the scope of the reaction with respect to the alkene component. Employing *cis*-β-methyl styrene gave an identical mixture of diastereomers as *trans*-β-methyl styrene (Table 1, entries 1 and 2), demonstrating the loss of alkene geometry during the course of the reaction. In probing the electronics of the reaction with respect to the alkene component, we found that 4-chloro-β-methylstyrene (entry 3) gave the corresponding tetrahydrofuran adduct in good yield, whereas 4-methoxy-β-methylstyrene was not reactive under these conditions, presumably because of the relative stability of the resultant radical cation intermediate. Cyclic alkene substrates, such as indene (entry 4) and 1-phenylcyclohexene (entry 5), were also competent reaction partners and afforded good yields of the corresponding cyclic ether adducts. Importantly, the indenyl tetrahydrofuran motif formed in entry 4 comprises the core of the *Schisandra rubriflora* isolate, rubriflordilactone B, which has documented anti-HIV activity.[14]

As demonstrated by entries 6 and 7, this catalytic method is also tolerant of free alcohols and ester functional groups. It is noteworthy that the reaction in entry 6 proceeds with complete chemoselectivity despite the presence of two different alkenols in the reaction. Aliphatic trisubstituted alkenes with higher oxidation potentials, such as 2-methylbut-2-ene, can also be employed to give highly substituted cyclic ethers

Table 2: PRCC reaction of β-methyl styrene and unsaturated alcohols.[a]



Entry	Alkenol	Product	14/15[b]	Yield [%]
1			1.1:1[c]	79
2			>20:1	70
3			1.2:1	58
4[d]			2.6:1	78
5			2.2:1[c]	71
6[d]			2.6:1[c]	32
7			10:1	60

[a] Average of two experiments using alkenol (5.0 equiv) for 12–120 h. [b] Diastereomeric ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Small amounts (>7%) of a third diastereomer were observed; see the Supporting Information for details. [d] Nitromethane solvent. PhthN = phthalimide.

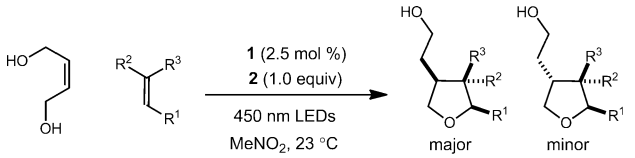
(entry 8). However, prolonged reaction times (1–6 days) are often required for high reaction conversion.

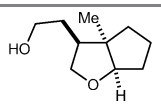
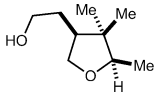
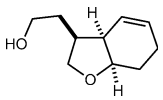
Next, a variety of unsaturated alcohols were examined in reactions with β-methylstyrene (Table 2). Prenol afforded good yields of the expected tetrahydrofuran adduct, albeit in a 1.1:1 ratio of diastereomers (entry 1). We were pleased to find that the use of methallyl alcohol furnished essentially a single diastereomer (>20:1 d.r.) of product (entry 2). To probe the effect of resident stereochemistry on the reaction, 2-methallyl alcohol was employed (entry 3) and furnished only 2 out of 8 possible diastereomeric tetrasubstituted tetrahydrofurans. Finally, further evidence demonstrating the functional group compatibility of this reaction is indicated in entries 4 and 5 of Table 2. Indeed, alkenols bearing free alcohols (entry 4) or protected amines (entry 5) furnished the intended cycloadducts in good yields, leaving the functional groups unperturbed.

In addition to the synthesis of tetrahydrofuran adducts, we attempted the formation of tetrahydropyran ring systems by using homoallyl alcohol (entry 6). A modest yield (32%, 1.2:1 d.r.) of the desired six-membered ring was obtained with the remainder of the mass balance attributed to the non-cyclized anti-Markovnikov hydroalkoxylation adduct. Attempts to increase the yield of the tetrahydropyran adduct by lowering the amount of **2** were unsuccessful. Current efforts are underway to design more effective hydrogen-atom donors for this reaction. Lastly, we were pleased to find that propargyl alcohol afforded a 4-*exo*-methylene tetrahydrofuran in good yield and with excellent levels of diastereoselectivity (60% yield, 10:1 d.r., entry 7), thus providing additional opportunities to expand the synthetic potential of this catalytic sequence.[15]

Non-styrenyl substrates also undergo the PRCC reaction, and a subset of these alkenes and dienes were tested with *cis*-butene-1,4-diol (Table 3). Methylcyclopentene afforded the

Table 3: PRCC reaction of *cis*-butene-1,4-diol and non-styrenyl alkenes and dienes.[a]

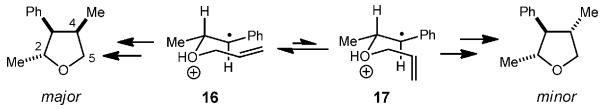


Entry	Alkene	Product	d.r.[b]	Yield [%]
1	 $E_{p/2}$ = + 1.82 V		1.6:1	43
2	 $E_{p/2}$ = + 1.81 V		3:1	54
3	 $E_{p/2}$ = + 1.81 V		5:1	57

[a] Average of two experiments using alkenol (5.0 equiv) for 96–120 h. [b] Diastereomeric ratio determined by ^{1}H NMR analysis of the crude reaction mixture.

corresponding bicyclic ether adduct in moderate yield to afford the corresponding bicyclic ether as a single regioisomer (entry 1). Similarly, 2-methylbut-2-ene gave the expected tetrasubstituted cycloadduct bearing a pendant alcohol (entry 2). The reaction of *cis*-butene-1,4-diol with cyclohexadiene furnished the intended cycloadduct in 57% yield with an intact olefin for further possible synthetic manipulations, a result which further demonstrates both the functional group tolerance and the chemoselectivity of this method.

Control of the relative stereochemistry at C2 and C3 is high in all cases (>15:1), however, as is often the case with neutral open-shell cyclizations, this transformation proceeds with lower diastereoselectivity in the radical cyclization. Analysis by ^{1}H NMR and NOESY experiments, as well as literature precedent,[16] indicates that the major diastereomer produced has a *cis* relationship between the C3 and C4 groups. A Beckwith-type model can be invoked to rationalize this observation (Scheme 2).[17] Envelope-like conformer **16** is presumed to be the lowest energy conformer and leads to the major stereoisomer. A third diastereomer that is occasionally observed in some reactions (Table 1, entries 1–3 and 6; Table 2, entries 5 and 6) is presumed to be the fully saturated furan in which all of the substituents have a *cis* relationship.



Scheme 2. Proposed Beckwith transition state.

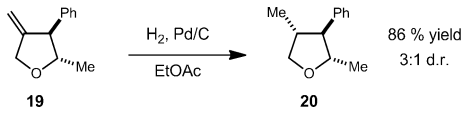
We hypothesize that this stereoisomer arises by rapid equilibration between the two alkene radical cation geometrical isomers.

We considered that diastereoselective hydrogenation of the *exo*-methylene adducts formed from reactions with propargyl alcohol might provide a means to circumvent the lower levels of diastereoselectivity observed in the radical cyclization step. We were pleased to find that reaction of dihydronaphthalene and propargyl alcohol under the organocatalytic conditions followed by diastereoselective hydrogenation of the derived *exo*-methylene intermediate, afforded tetrahydrofuran **18** in 14:1 d.r. and 40% overall yield [Eq. (3)]. We attribute the high levels of diastereocontrol to

(3)

the highly selective hydrogenation from the convex face of the tricyclic structure to afford the major stereochemical triad typically observed in the allyl alcohol reactions in Table 1.

Conversely, hydrogenation of methylene tetrahydrofuran **19** furnished saturated furan **20** in 86% yield as a 3:1 ratio of diastereomers [Eq. (4)]. This is typically the minor diastereomer observed in the PRCC reactions of olefins and alkenols and represents a viable alternative to easily access the minor stereoisomer in the PRCC reactions.



(4)

In summary, we have demonstrated a new PRCC reaction catalyzed by an organic photoredox system to synthesize highly substituted tetrahydrofurans from readily available allylic alcohols and oxidizable alkenes. This is a simple synthetic disconnection that provides valuable cyclic ether scaffolds. The method demonstrates a broad range of functional group compatibility and could find unique applications in complex molecule synthesis. The expansion of this method to allow the construction of additional classes of heterocyclic compounds is currently underway.

Experimental Section

Typical procedure for the PRCC reaction: Phenylmalononitrile (120 mg, 0.85 mmol, 1.0 equiv) and the acridinium catalyst (8.7 mg, 0.0033 mmol, 0.025 equiv) were added to a four-dram vial containing a magnetic stir bar. The vial containing the solids was then brought into a glove box where solvent (1.5 mL) was added. The alkenol (4.2 mmol, 5.0 equiv) and alkene (0.85 mmol, 1.0 equiv) were then introduced via syringe. The vial was fitted with a septum cap, transferred from the glove box, and placed on a magnetic stirring plate in front of a blue-light flood lamp (450 nm). The course of the reaction was monitored by TLC and, upon completion, the solvent was removed and the crude reaction mixture purified by silica gel chromatography.

Received: December 18, 2012
Published online: February 25, 2013

Keywords: organocatalysis · photoredox catalysis · radicals · tetrahydrofuran

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