C–H Bond Activation

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Diastereoselective Tetrahydropyrone Synthesis through Transition-Metal-Free Oxidative Carbon–Hydrogen Bond Activation**

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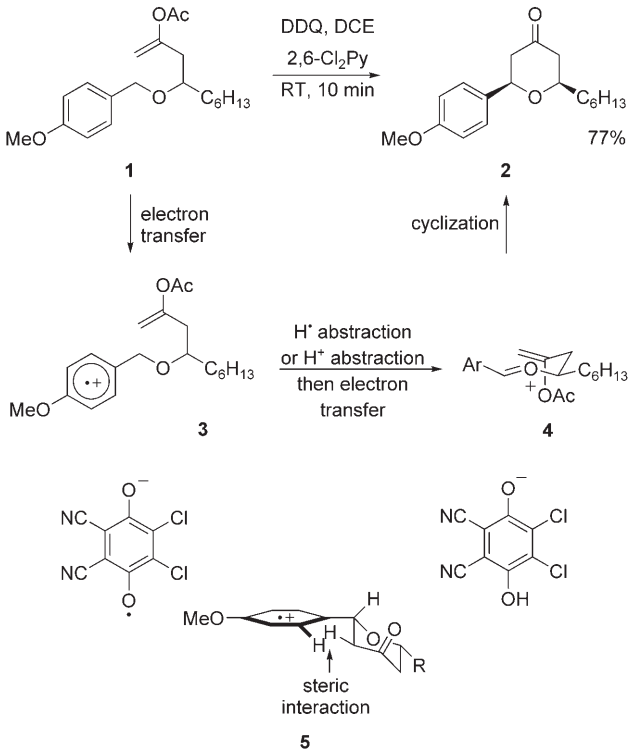
Selectively activating chemical bonds that are generally considered to be inert is an attractive strategy for introducing functionality into and enhancing the structural complexity of easily-prepared substrates, particularly when bond activation ultimately leads to carbon–carbon bond formation.[1] We have reported[2] several examples in which oxidative carbon–carbon bond activation can be used to initiate cyclization reactions through carbon–carbon bond formation. Reaction initiation through single-electron oxidation[3] alleviates chemoselectivity problems that can arise from conventional Lewis acid initiated methods for electrophile formation. To facilitate substrate synthesis and improve reaction atom economy[4] we have initiated a program that is directed toward promoting oxidative electrophile formation by carbon–hydrogen bond activation. Toward this objective we initially chose to exploit the propensity of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to form aryl-substituted oxocarbenium ions from benzylic ethers.[5] This process has been utilized for bimolecular carbon–carbon bond formation,[6] but these reactions proceed efficiently only with electron-rich arenes, and either require high temperatures with ketone nucleophiles or dicarbonyl/Lewis acid mixtures, or the addition of pregenerated nucleophiles such as enolsilanes after cation formation.[7]

Successful and broad application of DDQ-mediated carbon–hydrogen bond activation and subsequent carbon–carbon bond formation to annulation reactions requires that the nucleophiles be stable toward DDQ, that the reaction products not be subject to additional oxidation, and that a wide range of ethers serve as substrates. Herein we report that DDQ promotes the formation of stabilized carbocations by benzylic carbon–hydrogen bond activation under ambient conditions in the presence of appended nucleophilic groups and leads to diastereoselective carbon–carbon bond formation. Particularly important is the observation that, relative to bimolecular addition reactions, appending nucleophilic groups to the ether enhances the range of the benzylic groups that can serve as cation precursors. We also demonstrate that the scope of the process can be dramatically expanded by applying the protocol in an efficient approach to ring formation through allylic carbon–hydrogen bond activation. The incorporation of oxygen-containing groups into the substrates and the impact of arene or alkene substitution on the reaction rate is also discussed.

Our initial studies focused on the conversion of *para*-methoxybenzyl (PMB) ether **1** into tetrahydropyrone **2** (Scheme 1) by DDQ-mediated oxocarbenium ion formation.



Scheme 1. Cyclization through oxidative C–H activation.

This process proceeds most readily in 1,2-dichloroethane and in the presence of 2,6-dichloropyridine and powdered 4 Å molecular sieves (M.S.), which inhibit oxidative cleavage of the PMB group. Under these conditions the reaction was complete within 10 minutes at room temperature to provide **2** in 77% yield as a single diastereomer. This reaction proceeds[8] by electron transfer from **1** to DDQ to form radical-ion pair **3**. Because of the substantially weakened carbon–hydrogen bonds in alkylarene radical cations,[9] the formation of benzylic cation **4**, shown in the chair conformation that is relevant to cyclization,[10] either undergoes

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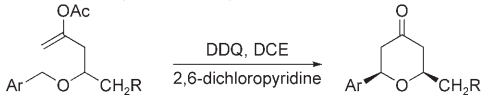
subsequent direct hydrogen atom transfer,[11] or a sequence including proton transfer and rapid benzylic radical oxidation.[8] Cyclization and acetyl group cleavage yield **2**. Although **2** is a benzylic ether, and therefore a potential oxidation substrate, overoxidation can be completely suppressed by suitable reaction monitoring. This useful result can be attributed to the steric interactions that limit access to radical-cation conformer **5** in which the benzylic hydrogen atom is aligned appropriately with the π system of the arene to effect efficient benzylic oxidation.[12]

The scope of the method is shown in Table 1. Remarkably, although it reacts relatively slowly, a nonsubstituted benzyl ether (Table 1, entry 1) proved to be a suitable substrate for the cyclization despite the observation that electron-donating groups are required for related bimolecular oxidative alkylation reactions.[6] The reaction rate increases as expected for the *p*-methylbenzyl ether (Table 1, entry 2), consistent with its lower oxidation potential[13] and greater capacity for stabilization of the intermediate cation. In this example, oxidation was observed only at the alkoxyalkyl group, demonstrating that the regiochemistry of carbon–hydrogen bond activation in arenes that contain multiple alkyl groups is determined by the stability of the intermediate cation or carbon–hydrogen bond strength.[14] The easily-oxidized 3,4-dimethoxybenzyl ether[15] was exceedingly reactive toward DDQ at room temperature, and efficient cyclization proceeded within minutes at −20 °C (Table 1, entry 3). The 3,5-dimethoxybenzyl ether (Table 1, entry 4), while forming the cyclized product in acceptable yield, was far less reactive than the 3,4-disubstituted isomer despite having an oxidation potential that would be expected[15] to be similar. This result is consistent with literature reports[16] in which 3,5-dimethoxybenzyl ethers undergo oxidative cleavage reactions more slowly than the corresponding 3,4-dimethoxy isomers, providing additional evidence for the importance of stability of the intermediate cation in determining the reaction rates. Furanylmethyl ethers (Table 1, entry 5) and 1-naphthylmethyl ethers (Table 1, entry 6), which are expected to have oxidation potentials that are approximately the same as **1**,[17] also served as substrates for the reaction. These results indicate that this process could be applied to the construction of a diverse set of aryl tetrahydropyrans, including biologically interesting structures related to the glycosidic antibiotics.[18] To explain the successful cyclizations of the benzylic ethers that serve as poor substrates in bimolecular reactions, we propose that oxidative carbon–hydrogen bond activation (**3**→**4** in Scheme 1), in contrast to postulates regarding electron-rich arenes,[7] is reversible when the intermediate oxocarbenium ion is not strongly stabilized by an electron-donating group on the arene. The rate enhancement derived from intramolecular nucleophilic attack on transiently-formed oxocarbenium ions promotes a successful cyclization in this system under conditions in which intermolecular nucleophilic attack is rarely observed.

Table 1: Arene and alkyl chain scope.[a]



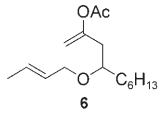
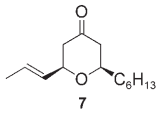
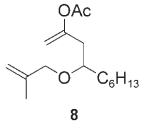
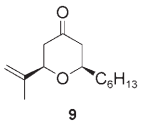
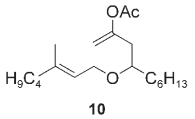
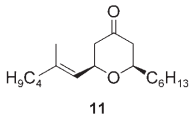
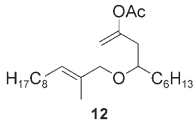
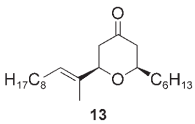
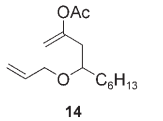
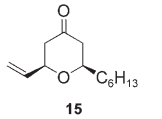
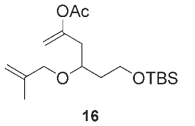
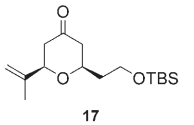
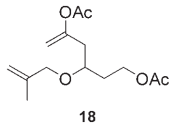
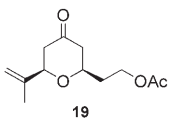
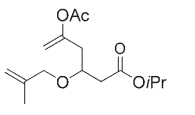
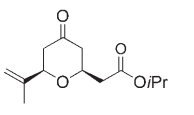
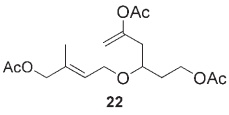
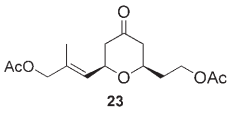
Entry	Ar	R	*t* [h]	Yield [%][b]
1	Ph	C_5H_{11}	14	63
2	4-MePh	C_5H_{11}	0.5	82
3[c]	3,4-$(MeO)_2$Ph	C_5H_{11}	0.1	83
4	3,5-$(MeO)_2$Ph	C_5H_{11}	1.5	57
5	2-furyl	C_5H_{11}	12	63
6	1-naphthyl	C_5H_{11}	4	84
7	4-MeOPh	CH_2OTBS	0.75	74
8	4-MeOPh	CH_2OAc	0.75	74
9	4-MeOPh	CO_2iPr	0.75	68

[a] Representative procedure: Substrate, 2,6-dichloropyridine (4 equiv), and 4 Å M.S. were stirred in DCE for 15-30 min. DDQ (2 equiv) was then added and the reaction mixture was stirred for the indicated time. [b] Yields are reported for isolated, purified products. [c] Reaction was conducted at −20 °C. TBS = *tert*-butyldimethylsilyl.

To determine whether the process is tolerant of functional groups, we prepared substrates that bear oxygen-containing substituents in the alkyl side chain. Silyl ethers are tolerated and do not lead to undesired acetal formation (Table 1, entry 7). Electrophilic groups such as acetate (Table 1, entry 8) and isopropyl ester (Table 1, entry 9) groups are also tolerated, highlighting the capacity of oxidative cleavage reactions in creating unique and useful chemoselectivity patterns in functionalized molecules. Notably, the yields of cyclizations that employ functionalized alkyl chains are comparable to those that employ unfunctionalized alkyl chains and, though oxidations produce oxocarbenium ions in which the adility of the oxygen atom to stabilize the cation is diminished by the electron-withdrawing substituents, the reaction rates drop only slightly.

To expand the scope of potential substrates with the objective of preparing products that do not contain an aromatic ring, we turned our attention to allylic ethers. Whereas Yadav et al. has shown[19] that primary, but not secondary, allyl ethers slowly undergo DDQ-mediated oxidative cleavage in the presence of water, we found only a single precedent for carbon–carbon bond-forming reactions[2d] from allylic ethers. Inspired by the successful cyclization of the unsubstituted benzyl ether, we subjected a series of allylic ethers to a modification of the reaction conditions in which a catalytic amount of $LiClO_4$ was added to inhibit overoxidation (Table 2).[20] Reactivity in this series again followed expected trends based on the substrate oxidation potentials[21] and the stability of the intermediate cations. (*E*)-1,2-Disubstituted allylic ether **6** reacted smoothly to form **7**. When mixtures of **6** and its corresponding *Z* isomer were subjected to the reaction conditions the *E* isomer was consumed much more rapidly because of the heightened steric interactions that destabilize the oxocarbenium ion of the *Z* isomer.[22] 1,1-Disubstituted allylic ether **8** reacted more slowly than **6** because the vinyl methyl group does not directly stabilize the intermediate cation. Trisubstituted alkenes **10** and **12** reacted quite quickly,[23] with cyclizations being complete within 1 hour at or below room temperature. No alkene isomerization was noted in the formation of **11** and **13**. While reacting slowly and requiring slightly elevated temperatures, unsubstituted allyl ether **14** provides **15** in good yield

Table 2: Cyclization through vinyl-substituted oxocarbenium ions.[a]

Entry	Substrate	Product	*t* [h]	Yield [%]
1	 **6**	 **7**	2	81
2	 **8**	 **9**	17	77
3[b]	 **10**	 **11**	1	82
4[b]	 **12**	 **13**	1	85
5[c]	 **14**	 **15**	48	80
6	 **16**	 **17**	24	75
7	 **18**	 **19**	30	73
8[c]	 **20**	 **21**	12	77
9	 **22**	 **23**	5.5	80

[a] Reactions were conducted according to the procedure given in Table 1 with the addition of $LiClO_4$ (0.1 equiv). [b] Reaction was conducted at 10 °C. [c] Reaction was conducted at 45 °C.

with no loss of stereocontrol. This result could prove to be quite useful for complex molecule synthesis in consideration of the numerous processes that utilize terminal alkenes in bond forming processes.

As demonstrated in entries 6–9 in Table 2, cyclization reactions of allylic ether substrates are also tolerant of oxygen-containing groups. For entries 6–8 in Table 2, we deliberately selected the relatively unreactive isobutenyl ether group to determine the impact of inductive deactiviation in a challenging system. Whereas these reactions proceeded somewhat more slowly than the parent reaction, yields were comparable and stereocontrol remained high. Although incorporating an electron-withdrawing group into the unsaturated fragment of ether **22** (Table 2, entry 9) slows the reaction to a greater extent than incorporating an electron-withdrawing group on the aliphatic fragment, the reaction still proceeds efficiently and stereoselectively. The efficient cyclization of a substrate in which both chains in the ether contain functional groups indicates that the method should be applicable to complex molecule synthesis.

We have demonstrated that a range of benzylic and allylic ethers, which contain enol acetate nucleophiles, serve as substrates for DDQ-mediated oxidative cyclization reactions. These processes proceed through efficient carbon–hydrogen bond activation and result in diastereoselective tetrahydropyrone formation. Appending a nucleophilic group to the ether allows the use of arenes and alkenes with a wide assortment of substitution patterns and oxidation potentials. The method is tolerant of commonly encountered functional groups on either side of the ether linkage, making it applicable to structurally complex substrates. Strategically, the use of allylic and benzylic ether formation as a facile method for fragment coupling, and the capacity of ether groups to serve as effective hydroxy-protecting groups prior to oxidative cyclization coupled with the unique chemoselectivity patterns that can be accessed by oxidative processes make this an attractive method for ring formation. Studies directed toward expanding the scope of the nucleophile and elucidating the mechanistic nuances of the process are in progress and will be reported in due course.

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