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Synthesis of functionalized 4-methylenetetrahydropyrans by oxidative activation of cinnamyl or benzyl ethers

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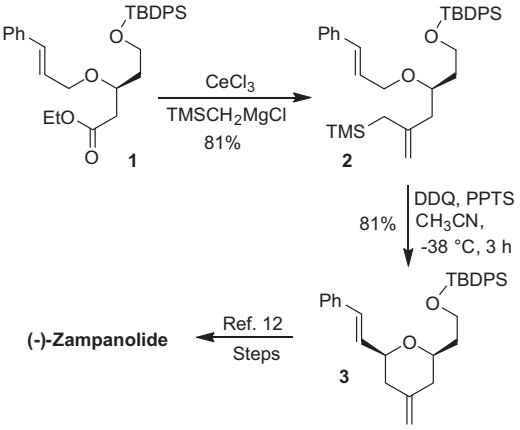
ABSTRACT

Oxidative activation of benzyl or cinnamyl ether bearing allylsilane derivatives using a catalytic amount of DDQ and 2 equiv of CAN in the presence of PPTS provided functionalized 4-methylenetetrahydropyrans in good yields and excellent diastereoselectivity. The reaction could be applied to the synthesis of a variety of substituted tetrahydropyran derivatives.

Functionalized 4-methylenetetrahydropyrans are embedded in many biologically important natural products including anticancer agents such as zampanolide, enigmazole A, and phorboxazole.[1–3] Previous construction of such substituted tetrahydropyran derivatives involved the synthesis of 4-oxotetrahydropyran followed by olefination of the ketone.[4–7] A number of asymmetric methodologies have been developed over the years that incorporated the *exo*-olefin directly. These include, a Mukaiyama Aldol-Prins cascade reaction developed by Rynchnovsky and co-workers,[8] and intramolecular Sakurai cyclizations by Marko and co-workers,[9] Keck et al.,[10] and Floreancig and co-workers.[11] Recently, in the context of our synthesis of (−)-zampanolide, we have developed a related intramolecular oxidative cyclization protocol using DDQ and a Brϕnsted acid to construct the substituted 4-methylenetetrahydropyran subunit.[12] As shown in Scheme 1, β-cinnamyloxyester **1** was efficiently converted into allylsilane **2**. Treatment of **2** with DDQ and PPTS at −38 °C in acetonitrile for 3 h afforded **3** in 81% yield as a single diastereomer. Encouraged by the observed high diastereoselectivity of the oxidative Sakurai-type cyclization process, we have now investigated the scope of this reaction with a variety of different substrates. Furthermore, we examined this reaction at a lower temperature as well as using a catalytic amount of DDQ along with other stoichiometric oxidants. Herein, we report the results of our studies in which a range of functionalized 4-methylenetetrahydropyrans were synthesized diastereoselectively using a catalytic amount of DDQ and 2 equiv of ceric ammonium nitrate (CAN).

A number of related oxidative protocols have been reported in the literature. Floreancig and co-workers reported a C–H activation protocol for the synthesis of a 4-oxo-tetrahydropyran with an alkenyl acetate as an intramolecular nucleophilic cyclization group.[13] She and co-workers recently reported a Prins type methodology and introduced bromine into the pyran ring.[14] For our studies, a model substrate **4a** with allylsilane and cinnamyl ether functional-



Scheme 1. Oxidative cyclization leading to substituted-4-methylenetetrahydro-2*H*-pyran **3**.

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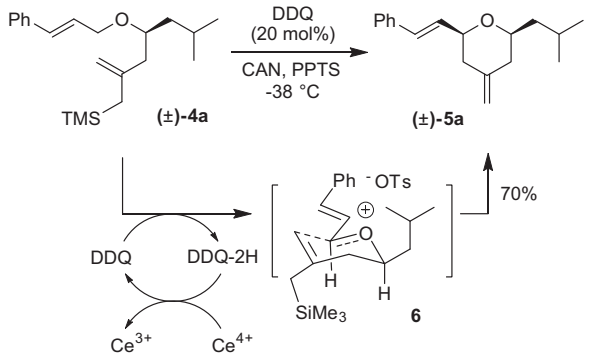
ities was prepared in gram quantities. Our choice of this model was based upon the fact that a cinnamyl ether functionality can be installed readily as described previously.[12]

The etherification substrate, the β-hydroxyester can be conveniently prepared in optically active form utilizing Noyori hydrogenation with very high enantioselectivity.[15] Also, the styrenyl side chain can be selectively differentiated from other olefins for further synthetic manipulation.[16] Allylsilane **4a** was prepared by an aldol reaction of isovaleraldehyde and ethyl acetate followed by etherification and subsequent conversion to the silane derivative as described previously for compound **2**.[12]

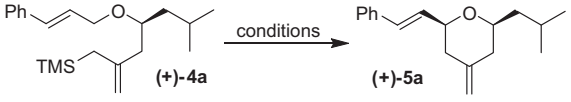
As shown in Table 1, we investigated a variety of oxidative C–H activation conditions for an effective Sakurai-type cyclization reaction. We attempted cyclization of **4a** with 1.5 equiv of DDQ and 1.5 equiv of $InCl_3$ in CH_2Cl_2 at −78 °C. These conditions, within a 3 h period resulted in 4-methylenetetrahydropyran **5a** in 40% yield (Table 1). Encouraged by this result, we then examined conditions using a catalytic amount of DDQ (20 mol %) and a stoichiometric amount of various oxidants to decrease the amount of organochloride byproducts.[17] We were also interested in using inexpensive and other readily available oxidants. In order to improve oxidant solubility, acetonitrile was used instead of CH_2Cl_2 and the reaction temperature was optimized to −38 °C. As can be seen, under these reaction conditions, oxidants $KMnO_4$, MnO_2, and $PhI(OAc)_2$ were ineffective (entries 2–4). However, the use of a catalytic amount (20 mol %) of DDQ and 2 equiv of ceric ammonium nitrate (CAN) in the presence of PPTS (2 equiv) for 16 h provided tetrahydropyran **5a** exclusively in 70% yield after chromatography (entry 5). The presence of PPTS was essential with DDQ/CAN combinations as the corresponding reaction in the absence of PPTS resulted in the decomposition of the starting material (entry 7). Our attempted optimization with pyridine however, resulted in a significantly slower reaction. Thus, PPTS is necessary for this oxidative cyclization, however, the exact role of PPTS is unclear. The assignment of *cis*-stereochemistry was established based upon extensive ^{1}H NMR NOESY experiments of **5a**. The stereochemical outcome of this oxidative cyclization can be rationalized based upon the Zimmermann–Traxler[18] transition state **6** shown in Scheme 2. As shown, the C2-cinnamyl substituent in the incipient tetrahydropyran ring assumes an equatorial position which explains the stereochemistry of the newly created asymmetric center in product **5a**.

After optimization of the reaction conditions, we examined the scope of this catalytic process with a variety of allylsilane/benzyl/cinnamyl ether substrates. The results are shown in Table 2. As can be seen, an electron rich 4-methoxy cinnamyl substrate provided **5b** in very good yield (entry 1). A furyl allyl substrate under the above catalytic conditions provided significant decomposition of product **5c**. Therefore, this cyclization was carried out using 1.5 equiv of DDQ to provide **5c** within 30 min in 61% isolated yield. We have also examined a 4-methoxy benzyl derivative which provided **5d** in 81% yield (entry 3). The scope of the reaction was investigated with a benzyl ether side chain and an alcohol side chain. As shown, the side chain benzyl ether was stable during the cyclization reaction and product **5e** was obtained in 79% yield (entry 4). Also, the cyclization proceeded smoothly in the presence of a primary alcohol (entry 5). Substrates **4g** and **4h** containing vinyl and chlorine substituents provided very clean cyclization products **5g** and **5h**, respectively (entries 6 and 7). The presence of a bulky *t*-butyl side chain did not diminish the reactivity and the resulting tetrahydropyran derivative **5i** was obtained in very good yield (entry 8). A PMB type substrate **4j** also gave rise to the cyclized product **5j** in good yield and selectivity (entry 9). The oxidative cyclization also proceeded in a manner of annulation to provide the bicyclic derivative **5k** (entry 10). The reaction with an (*E*)-(3-alkoxybut-1-enyl)benzene substrate afforded tetrahydropyran **5l** with a quaternary center in 63% yield as a mixture (*dr* = 4.7:1) of diastereomers. The mixture was separated by silica gel chromatography and **5l** with *i-trans* Bu and Me groups was the major isomer. After the exploration of cyclization substrate scope, we carried out the cyclization reaction in gram scale using optically active material. Substrate **2** (Scheme 1) was prepared in 97% ee as described previously.[12] Subsequent oxidative cyclization was carried out in 1.8 g scale by treating **2** with DDQ/CAN/PPTS in acetonitrile at −38 °C to yield the 4-methylenetetrahydropyran derivative **3** in 71% yield and 97% ee.[19] This tetrahydropyran derivative was previously converted into (−)-zampanolide.[12]



Scheme 2. Possible reaction pathway with a catalytic amount of DDQ.

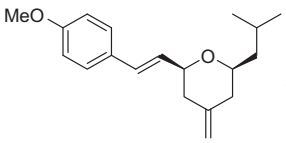
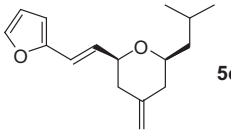
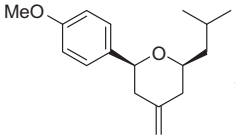
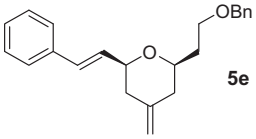
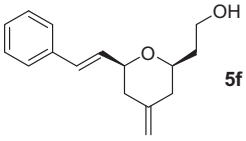
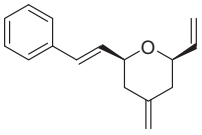
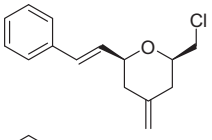
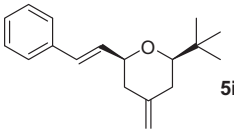
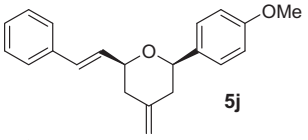
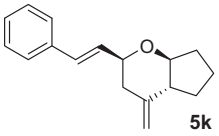
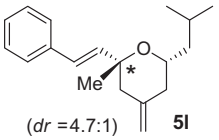
Table 1
The screening of cyclization conditions[a]



Entry	Condition	Time (h)	Yield (%)
1	DDQ (1.5 equiv), $InCl_3$ (1.5 equiv), CH_2Cl_2, −78 °C	3	40[b]
2	DDQ (20 mol %), $KMnO_4$ (1.5 equiv), PPTS (1.5 equiv) in MeCN, −38 °C	24	<10[c]
3	DDQ (20 mol %), MnO_2 (1.5 equiv), PPTS (1.5 equiv) in MeCN, −38 °C	24	<10[c]
4	DDQ (20 mol %), $PhI(OAc)_2$ (1.5 equiv), PPTS (1.5 equiv) in MeCN, −38 °C	24	<10[c]
5	DDQ (20 mol %), CAN (2 equiv), PPTS (2 equiv) in MeCN, −38 °C	16	70[b]
6	CAN (2 equiv), PPTS (2 equiv) in MeCN, −38 °C	24	NR[d]
7	DDQ (20 mol %), CAN (2 equiv) in MeCN, −38 °C	0.5	Decomp

[a] All the reactions were carried out in the presence of 4 Å MS.
[b] Yield after chromatography.
[c] Conversion yield by ^{1}H NMR.
[d] NR, no reaction.

Table 2
Substrate scope of oxidative cyclization[a]

Entry	Product	Time (h)	Yield (%)
1	 **5b**	16	75
2	 **5c**	0.5	61[b]
3	 **5d**	14	81
4	 **5e**	16	79
5	 **5f**	20	73
6	 **5g**	12	79
7	 **5h**	16	82
8	 **5i**	20	79
9	 **5j**	16	73
10	 **5k**	10	79
11	 (*dr* = 4.7:1) **5l**	3	63[b]

[a] DDQ (20 mol %), CAN (2 equiv), PPTS (2 equiv), 4 Å MS, MeCN, −38 °C.
[b] DDQ (1.5 equiv), PPTS (1.5 equiv), 4 Å MS, MeCN, −38 °C.

In summary, we have developed a useful oxidative protocol for a Sakurai-type cyclization using a catalytic amount of DDQ and 2 equiv of CAN and PPTS as a promoter. The protocol provides access to a variety of functionalized 4-methylenetetrahydropyrans in very good yield and excellent diastereoselectivity.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.041.

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19. All new compounds gave satisfactory spectroscopic and analytical results (for more details, please see Supplementary data).
Representative example: 4-Methylenetetrahydropyran **3**: To a suspension of DDQ (147 mg, 20 mol %), PPTS (1.63 g, 6.48 mmol), CAN (3.51 g, 6.48 mmol), and 4 Å MS (3.6 g) in MeCN (120 mL) was added a solution of **2** (1.8 g, 3.24 mmol). The suspension was stirred at −38 °C for 16 h and quenched with Et_3N (1 mL). The mixture was filtered through a silica gel column with hexanes/ethyl acetate (v/v = 95:5) as the eluent. The concentrated product was purified by silica gel chromatography with hexanes/ethyl acetate (v/v = 95:5) as eluent to give 4-methylenetetrahydropyran **3** as an oil (1.17 g, 71%). The analysis data comply with the reported value.[12]
4-Methylenetetrahydropyran **5a**: To a suspension of **4a** (33 mg, 0.1 mmol) and 4 Å MS (100 mg) in MeCN (4 mL) was added DDQ (4.5 mg, 20 mol %), PPTS (50.4 mg, 0.2 mmol) and CAN (110 mg, 0.2 mmol) at −38 °C. Then the mixture was stirred at −38 °C until TLC showed full conversion. Et_3N (0.2 mL) was added. The mixture was filtered through a short silica gel pad with hexanes/ethyl acetate (v/v = 97:3) as eluent to give crude product that was purified by silica gel chromatography with hexanes/ethyl ether = 97:3 as eluent to give **5a** as colorless oil (17.9 mg, 70%).
^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.21 (m, 5H), 6.62 (d, J = 16 Hz, 1H), 6.26 (dd, J = 5.9, 16.0 Hz, 1H), 4.77 (s, 2H), 3.97–3.93 (m, 1H), 3.46–3.40 (m, 1H), 2.35 (d, J = 13.2 Hz, 1H), 2.23 (d, J = 13.2 Hz, 1H), 2.15 (t, J = 13.2 Hz, 1H), 1.97 (t, J = 12.7 Hz, 1H), 1.91–1.83 (m, 1H), 1.64–1.57 (m, 1H), 1.33–1.26 (m, 1H), 0.93 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 136.8, 130.1, 128.4, 127.4, 126.4, 108.6, 78.6, 45.3, 41.0, 40.9, 24.3, 23.0, 22.5.
IR (thin film, cm^{-1}) 2954, 1732, 1652, 1500, 1315, 1133, 1079, 965, 890, 745, 692. R_f = 0.35, hexanes/ethyl ether = 98:2 UV. MS (EI) m/z 256 (M^+).