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CATIONIC [5+2] CYCLOADDITION REACTIONS PROMOTED BY TRIMETHYLSILYL TRIFLATE IN HIGHLY POLAR MEDIA

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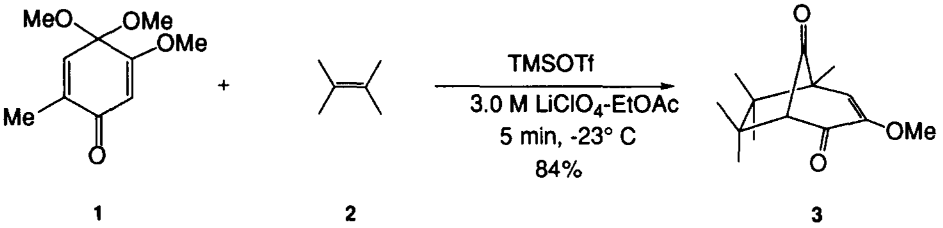
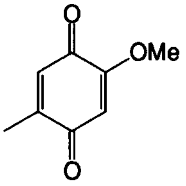
Abstract: Trimethylsilyl triflate is an effective reagent in 3.0 M lithium perchlorate-ethyl acetate for promoting cationic [5+2] cycloaddition reactions. © 1997 Elsevier Science Ltd. All rights reserved.

Following the discovery of the cationic [5+2] cycloaddition reaction by Joseph-Nathan[1] in 1965, Büchi recognized the potential of this process for natural products synthesis and successfully applied this methodology to the total syntheses of neolignans (guianin and burchellin)[2] and the sesquiterpene gymnomitrol.[3] Unfortunately, the yields associated with these transformations are modest[2-4] and as a consequence these reactions have received only scant attention. We now wish to report that yields for cationic [5+2] cycloaddition reactions can be dramatically increased by employing trimethylsilyl triflate in 3.0 M lithium perchlorate-ethyl acetate (cf **1** + **2** → **3**).



Having previously shown that medium effects can have a profound influence on both the reaction rate and diastereoselectivity of Diels-Alder reactions[5], we became intrigued with the possibility of promoting cationic [5+2] cycloaddition reactions in polar media (e.g. 5.0 M lithium perchlorate in diethyl ether). Much to our surprise, exposure of a 0.2 M solution of **1** in 5.0 M $LiClO_4$-Et_2O to 2.0 equiv of 2,3-dimethyl-2-butene at ambient temperature gave rise to none of the anticipated bicyclo[3.2.1]octenedione **3**. Use of 5.0 M lithium perchlorate in anhydrous ethyl acetate[6], which has been shown to be very effective in promoting Diels-Alder reactions, also failed to give rise to any **3**. After extensive experimentation it was found that trimethylsilyl triflate promotes cationic [5+2] cycloaddition reactions in 3.0 M lithium perchlorate-ethyl acetate.[7] The following general procedure is illustrative: to a 0.2 M solution of quinone monoketal **1**[8] (20 mg, 0.1 mmol) in 3.0 M $LiClO_4$-EtOAc (400 μL) was added 3.0 equiv of 2,3-dimethyl-2-butene (36 μL). The solution was cooled to -23 °C and 1.05 equiv of TMSOTf (20 μL) was added. After 5 min, the dark yellow reaction mixture was quenched with 500 μL of a saturated sodium bicarbonate solution. The product was isolated by extraction with ether. Flash column chromatography (2:1, hexanes: ethyl acetate) provided 19.3 mg (84%) of the known bicyclo[3.2.1] ketone **3**.[3] Use of 3.0 M $LiClO_4$-Et_2O and 3.0 M $LiClO_4$-acetone resulted in substantially reduced yields of **3**, 68% and 20% respectively.

Control experiments demonstrate that both the trimethylsilyl triflate and the polar medium (3.0 M $LiClO_4$-EtOAc) are critical for the success of this reaction. When the reaction was conducted in the absence of trimethylsilyl triflate, no reaction was observed. The importance of the polar medium was established by conducting the reaction in the absence of lithium perchlorate. Thus, treatment of a 0.2 M solution of **1** in ethyl acetate containing 3.0 equiv of **2** with 1.05 equiv of TMSOTf at -23 °C gave rise to only a 17% yield of **3** which was accompanied by substantial amounts of benzoquinone **4** (37%) and benzopyran **5** (16%).



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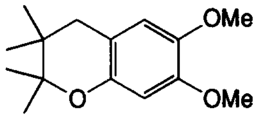

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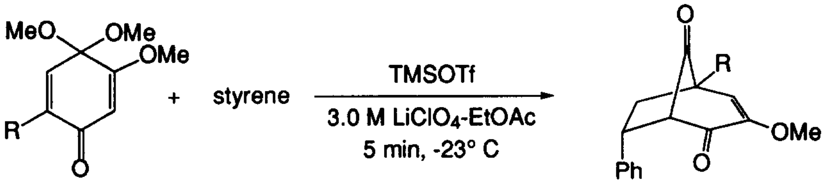
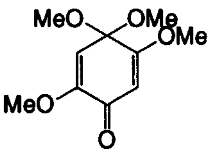
The general procedure outlined above with quinone monoketal **1** employing 3.0 M $LiClO_4$-EtOAc containing 1.05 equiv of TMSOTf has been extended to a number of olefins (Table 1). Note that all reactions are complete in 5 min at -23 °C. No reaction was observed between **1** and phenylacetylene. With respect to other quinone monoketals, one can replace the C(2) methyl group in **1** with a proton or other alkyl substituents as illustrated in Equation (1). We have observed, however, that no cycloaddition occurred between styrene and the quinone monoketals **12** and **13**.



(1)

6 (R=H)
7 (R=$CH_2CH{=}CH_2$)
8 (R=CH_2OMe)

9 (R=H) 95%
10 (R=$CH_2CH{=}CH_2$) 85%
11 (R=CH_2OMe) 74%



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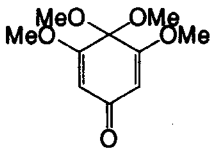

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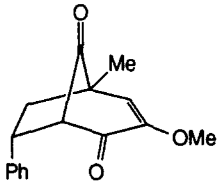
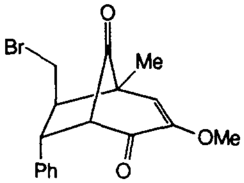
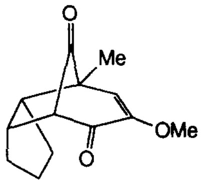
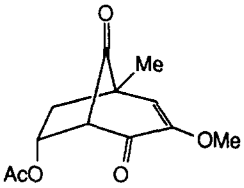
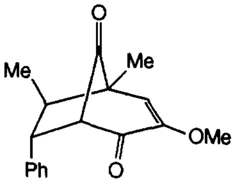
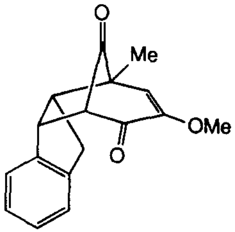
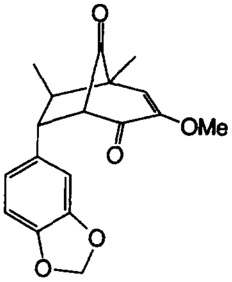
Table 1. Cationic [5+2] Cycloaddition of Quinone Monoketal 1 with a Variety of Olefins[a]

Olefin	Product	Yield (%)[b]
styrene		90
cinnamyl bromide		86
cyclopentene		48
vinyl acetate		34
β-methylstyrene		99
indene		98

[a] All reactions were conducted at -23° C employing a 0.2 M solution of 1 in 3.0 M $LiClO_4$-EtOAc containing 3.0 equiv of olefin. After addition of 1.05 equiv of TMSOTf, reactions were complete in 5 min. [b] Isolated yield.

In contrast to the results reported in Table 1 with styrene, β-methylstyrene, and cinnamyl bromide; isosafrole upon exposure (5 min, -23 °C) to **1** in 3.0 M $LiClO_4$-EtOAc containing 1.05 equiv of TMSOTf led not to the corresponding bicyclo[3.2.1]octenone **14**, but instead gave rise to tetrahydrobenzofuran **15** (89%). Under identical reaction conditions, α-methylstyrene and **1** afforded **16** in 81% yield. Similar observations have been made previously by Büchi[2] and Engler[4], however the reported yields were modest, on the order of 25%.



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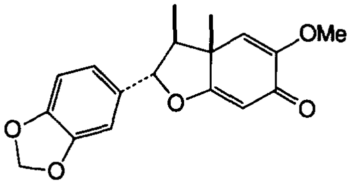

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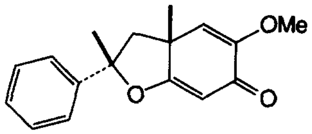

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In conclusion, we have demonstrated that TMSOTf in a highly polar medium such as 3.0 M $LiClO_4$-EtOAc functions as an effective Lewis acid for promoting the cationic [5+2] cycloaddition reaction between olefins and quinone monoketals. The mild conditions and high yields associated with the general reaction conditions make this an attractive method for the construction of bicyclo[3.2.1]octenones and hydrobenzofurans.

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7. The ethyl acetate is distilled from calcium hydride prior to use.
8. Prepared according to the procedure of Büchi: Büchi, G.; Chu, P.-S.; Hoppmann, A.; Mak, C.-P.; Pearce, A. *J. Org. Chem.* **1978**, *43*, 3983.

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