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The Intramolecular Alkylation of Arenes by Higher Cyclic Ethers Provides a Stereoefficient Route to Tetralins

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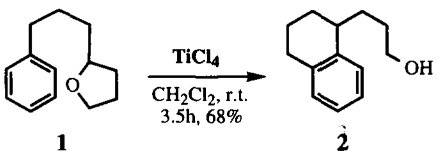
Abstract Tetrahydrofurans and tetrahydropyrans tethered to arenes through a propyl chain readily undergo cyclisation to tetralins when exposed to titanium tetrachloride. The reaction has been shown to be highly stereospecific and an S_N2 type mechanism is implicated. © 1997 Elsevier Science Ltd.

Dialkyl ethers are seldom used as electrophilic counterparts in Friedel-Crafts alkylations due to the ease with which they undergo rearrangement and elimination under the harsh conditions needed to bring about reaction. Oxiranes and oxetanes provide exceptions to this rule, allowing introduction of hydroxyethyl and hydroxypropyl side chains to arenes respectively.[1] More recently the intramolecular variant has been shown to be especially useful when applied to tetralin and related syntheses.[2] In this *Letter* we report an extension of the method to higher cyclic ethers which give the reaction in a highly stereospecific manner.[3,4]



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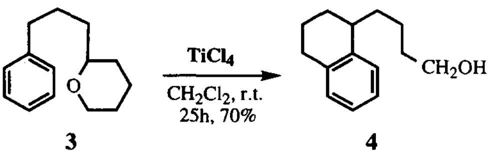

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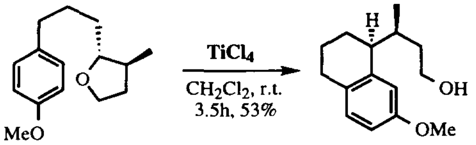
Preliminary studies focused on 2-(3-phenylprop-1-yl)-tetrahydrofuran **1**.[4c,5] Treatment of **1** with aluminium trichloride resulted in substantial decomposition, however, on exposure to a dichloromethane solution of titanium tetrachloride cyclisation proceeded smoothly giving tetralin **2** in 68% yield after 3.5 hours. Similar observations were noted for the tetrahydropyran **3**; conversion to **4** being accomplished in 70% yield on treatment with titanium tetrachloride for 25 hours.



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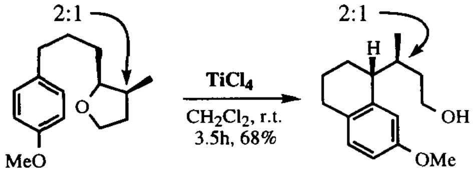

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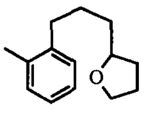
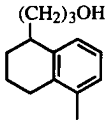
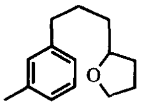
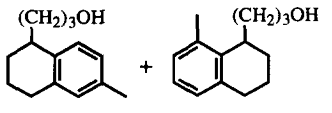
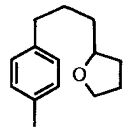
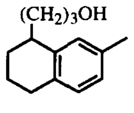
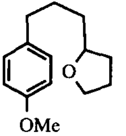
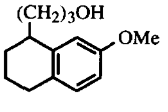
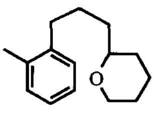
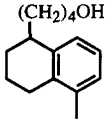
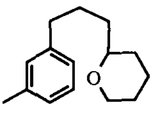
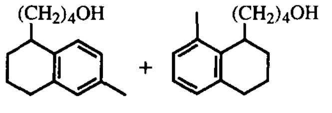
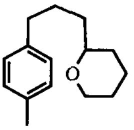
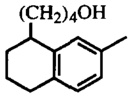
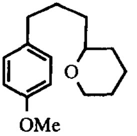
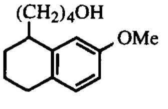
Several related cyclisations have been achieved (Table). The stereochemical course of the reaction has also been examined and an S_N2 type mechanism implicated. Cyclisation of the *trans*-disubstituted tetrahydrofuran **5** led to a single diastereoisomer of tetralin **6** while treatment of a 2:1 ratio of the *cis*- and *trans*-diastereoisomers **7** and **5** gave a 2:1 mixture of the isomeric tetralins **8** and **6**.[4]

Table: Further Examples of the Intramolecular Alkylation of Arenes by Higher Cyclic Ethers

	Substrate	Product		Substrate	Product(s)
A			**B**		
	TiCl$_4$, 3.5h, 67%			TiCl$_4$, 9h, 56%, 1:1	
C			**D**		
	TiCl$_4$, 18h, 72%			TiCl$_4$, 3.5h, 66%	
E			**F**		
	TiCl$_4$, 3h, 71%			TiCl$_4$, 3.5h, 59%, 1:1	
G			**H**		
	TiCl$_4$, 16h, 56%			TiCl$_4$, 23h, 72%	

In conclusion we have shown that intramolecular alkylations of arenes by higher cyclic ethers may be induced by titanium tetrachloride and proceed smoothly at ambient temperature in dichloromethane. The reaction is highly stereospecific and gives access to tetralins in good yield.

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4. The relative stereochemistries of **6** and **8** have yet to be rigorously established. Our assumption that cyclisation proceeds with net inversion of stereochemistry is based on the following literature precedents: **a.** Brauman, I.; Solladié-Cavallo, A. *J. Chem. Soc., Chem. Commun.*, **1968**, 1124; **b.** Segi, M.; Takebe, M.; Masuda, S.; Nakajima T.; Suga, S. *Bull. Chem. Soc. Jpn.*, **1982**, *55*, 167; **c.** Harrowven, D.C.; Dennison, S.T.; Howes, P. *Tetrahedron Lett.*, **1994**, *35*, 4243.
5. All compounds gave the expected spectral and analytical characteristics.

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