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OVERRIDING NORMAL FRIEDEL-CRAFTS REGIOCHEMISTRY IN CYCLIACYLATION. REGIOSPECIFIC CARBODESILYLATION AND PARHAM CYCLIZATION ROUTES TO 7-METHOXY-1-INDANOLS

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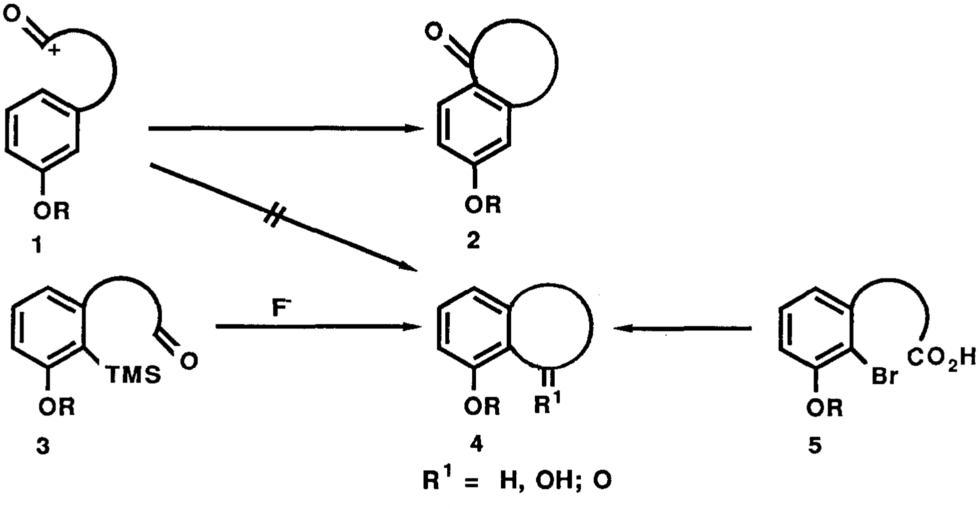
Abstract: Regiospecific syntheses of 7-methoxy-1-indanols **(11a-c)** and -indanones **(13a-c)** via fluoride-induced carbodesilylation and Parham cyclization processes respectively are reported.

The Friedel-Crafts reaction is a well-travelled route for annelation of 5-, 6-, and 7-membered ring ketones to aromatic substrates.[1] The regioselectivity of this process is dictated by the normal electrophilic substitution rules which thereby preclude the direct preparation of certain substituted systems without recourse to additional steps involving protection divergencies.[2] A textbook example, of synthetic significance, concerns the cyclization of anisole derivatives **1 (Scheme 1)** which invariably lead to para **2** rather than ortho **4** cyclized products.[1b,3] Classical preparation of systems **4** requires protection of the para site by Br and suffers from the thereby introduced deactivating effect on the desired cyclization.[2a,4]

We report on a new methodology based on the fluoride-induced ipso carbodesilylation, **3** → **4** [5] which surmounts the normal Friedel-Crafts regioselectivity. For comparison of synthetic efficacy, we also describe the complementary Parham cycliacylation process **5** → **4**. [6] To



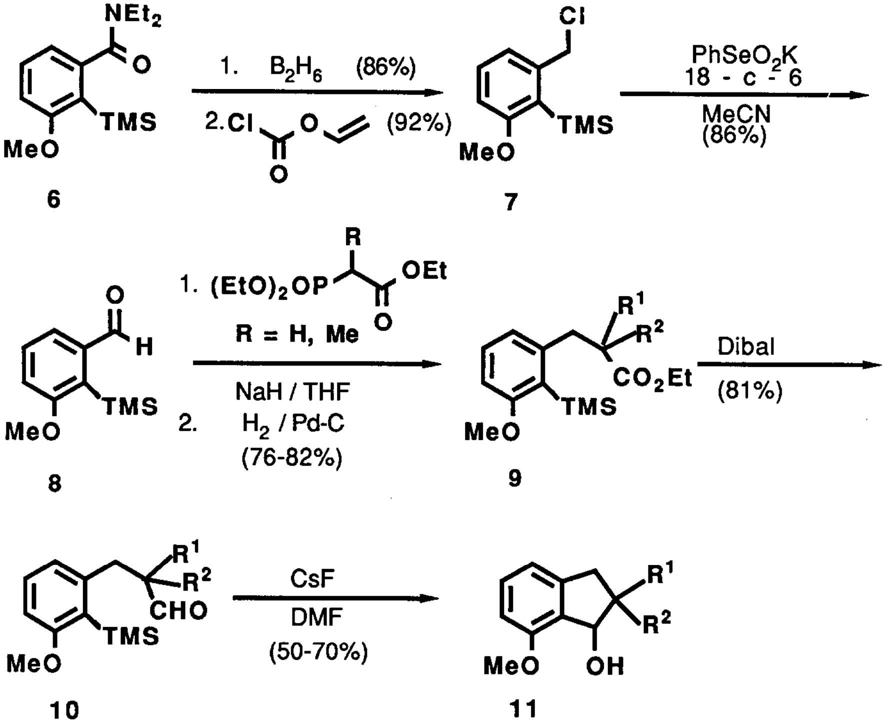
SCHEME 1

demonstrate these methods, the prototype transformations of **10a-c** and **12a-c** into the synthetically useful[3,7] 7-methoxy-1-indanols **11a-c** and -indanones **13a-c** have been investigated. In view of the convenient access of the precursors **10** and **12** via the directed ortho metalation strategy[8] and a regiospecific ipso bromodesilylation adjunct, **9** → **12**, these methods may have general implications for the construction of unusually substituted carboannelated aromatics.

The preparation of the key aldehyde intermediates **10a-c** **(Scheme 2)** incorporates an efficient amide **6** into aldehyde **8** conversion which also enhances the scope of benzamide metalation chemistry. Diborane reduction of the silylated m-anisamide **6** [9] followed by treatment with vinyl chloroformate[10] afforded the benzyl chloride **7** which upon oxidation with potassium phenyl selenite (18-crown-6/MeCN)[11] smoothly gave the benzaldehyde **8.** Wadsworth-Emmons-Horner reaction of **8** with appropriate phosphonate synthons followed by hydrogenation led to the substituted phenylpropionic esters **9a-b.** Dibal reduction provided the somewhat unstable silylated phenylpropionaldehydes **10a-b.** The α,α-dimethyl derivative **10c** was prepared by LICA-mediated condensation of **7** with ethyl isobutyrate[12] followed by dibal reduction. When **10a-c** were subjected to reaction with anhydrous CsF in DMF at 110°C, the 7-methoxy-1-indanols **11a-c** were obtained in 55-75% yields.[13] The lack of substantial improvement in the yields of 10b-c compared to **10a** suggests that these reactions are not significantly compromised by fluoridecatalyzed intermolecular aldolizations.[14]

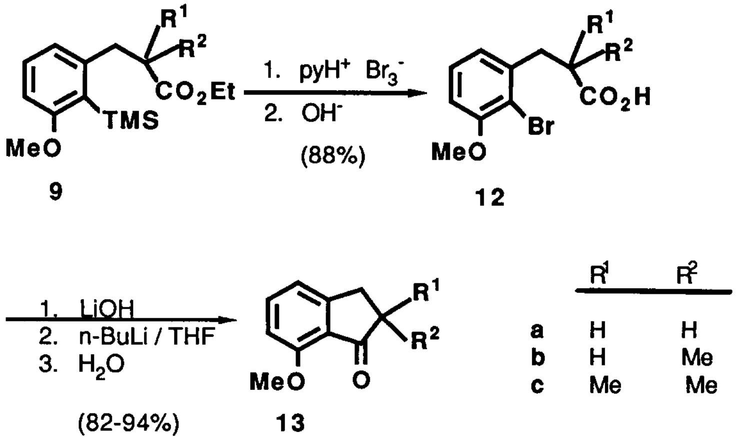
Precursors **12a-c** **(Scheme 3)** for the Parham cycliacylations were obtained in high yield from the pivotal esters **9a-c** by successive ipso bromodesilylation[9] and base-catalyzed hydrolysis. Two sets of experimental conditions were used for the transformation of **12a-c** into the 1-indanones **13a-c.** Following the Parham procedure,[15] bromo acids **12a-c** were treated with n-BuLi (THF/-100°C → room temp) to give compounds **13a-c** [16] in 60-70% yields. Using the Whitlock recipe,[17] **12a-c** were first converted into their lithio salts (LiOH) which were thoroughly dried and allowed to react with n-BuLi (THF/-78°C/2h/-40°C/3h) to provide **13a-c** in 82-94% yields.

The fluoride-induced intramolecular carbodesilylation and Parham cycliacylation methods are complementary approaches to 7-methoxy-1-indanol derivatives and constitute prototype methods for overcoming Friedel-Crafts regioselectivity in methoxy-substituted aromatics. Although somewhat less efficient, the silicon-directed method has the advantage of mild neutral conditions. The extension of this reaction to systems bearing other directed metalation groups may lead also to new heteroannelation procedures.[18,19]



a: $R^1 = R^2 = H$; b: $R^1 = H$, $R^2 = Me$; c: $R^1 = R^2 = Me$

SCHEME 2



	R^1	R^2
a	H	H
b	H	Me
c	Me	Me

SCHEME 3

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18. All new compounds show analytical and spectral (IR, NMR, MS) data in full agreement with the assigned structures.

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