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# Diastereoselective Synthesis of Polypropionates: Cationic Couplings of 4-Acetoxy-1,3-Dioxanes with Crotyl-Metal Reagents

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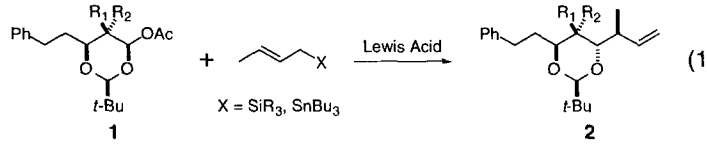
**Abstract**: Lewis acids promote the coupling of 4-acetoxy-1,3-dioxanes **1** with crotyl-metal species to generate propionate motifs such as **2**. The reactions show a marked dependence on Lewis acid, the crotyl metal species, and the presence and stereochemical disposition of a C5 methyl group. A 1,3-syn methyl relationship is favored in these additions. 

We recently described the synthesis of 4-acetoxy-1,3-dioxanes from 1,3-dioxane-4-ones,[1] by DIBAL-H reduction and *in situ* acylation.[2] These α-acetoxy ethers undergo solvolysis in the presence of Lewis acids to generate oxonium ions that can react with a variety of nucleophiles. Protected *anti*-1,3-diols have been synthesized from these precursors by coupling with allyltrimethylsilane,[3] enol silanes,[4] dialkyl zinc reagents,[5] and alkynyl alanes and stannanes.[6] Herein, we describe the coupling of 4-acetoxy-1,3-dioxanes **1** with crotyl metal species as a useful entry to polypropionate sequences.




(1)

The crotyl addition of interest is illustrated in eq 1. A stereoelectronic preference for axial attack of the organometallic nucleophile was expected and would be in line with previous observations.[5] The control of the exocyclic stereocenter should be reasonably high, based on Danishefsky's experience with the addition of crotyl silanes to glycal-derived oxonium ions.[7] Danishefsky reported that the exocyclic 1,2-*anti* selectivities ranged from 2:1 to greater than 10:1.[7] We set out to determine the stereoselectivity of crotyl metal additions to 4-acetoxy-1,3-dioxanes.

The substrates **6**, **9**, and **12** were selected for investigation. The synthesis of **6** is outlined in Scheme 1. The β-keto ester **3** was hydrogenated using a $RuCl_2$(BINAP) catalyst.[8] Saponification of the resulting hydroxy ester afforded 3-hydroxy acid **4** in 75% yield, with greater than 95% ee.[9] A $Sc(OTf)_3$ catalyzed

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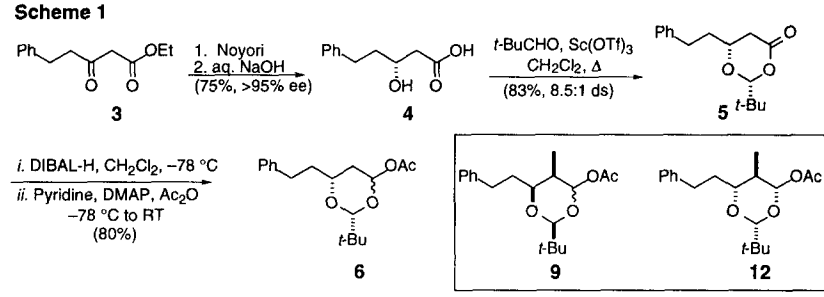
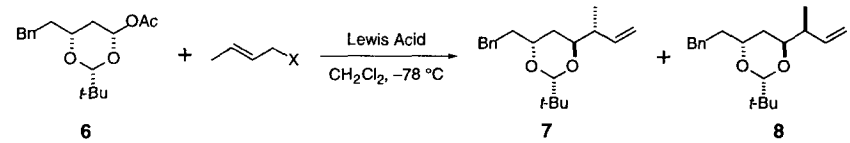
ketalization[10] generated **5** in 83% yield, as an 8.5:1 mixture of diastereomers. DIBAL-H reduction and *in situ* acylation of **5** provided **6** in 80% yield, as a mixture of diastereomers.[11] Compounds **9** and **12** were prepared in a similar fashion. The axial 5-methyl group in **9** was established in an Evans aldol reaction.[12] Heathcock's anti-aldol reaction[13] was used to introduce the anti methyl group en route to **12**.

**Scheme 1**




In initial experiments, the exocyclic selectivity in crotyl additions to **6** was low. With (*E*)-crotyl trimethylsilane and (*E*)-crotyl tributylstannane, a variety of Lewis acids afforded nearly a 1:1 mixture of the 1,2-*anti* isomer **7**, and the 1,2-*syn* isomer **8** (Scheme 2). High diastereoselectivity was achieved, however, by switching to a less reactive nucleophile, (*E*)-crotyl (dimethyl)phenylsilane.[14] In this case, coupling in the presence of $SnBr_4$ afforded a 10.8:1 mixture of separable diastereomers in 82% overall yield.

**Scheme 2**




| Entry | X = | Lewis Acid | Overall Yield (**7**:**8**) |
|---|---|---|---|
| 1 | $-SiMe_3$ | $SnBr_4$ | 73% (1.4:1) |
| 2 | $-SnBu_3$ | $TiCl_2(OPr^i)_2$ | 82% (1.4:1) |
| 3 | **$-SiMe_2Ph$** | **$SnBr_4$** | **82% (10.8:1)** |

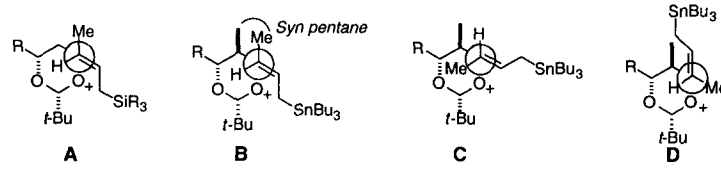
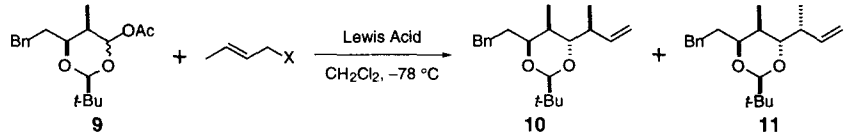



Figure 1. Models for addition of crotyl organometallics to cyclic oxonium ions.

The stereoselectivity is consistent with the model introduced by Danishefsky (Model A, Fig. 1): synclinical approach of the crotyl silane with the crotyl methyl group pointed away from the ring predicts the 1,2-anti selectivity observed.

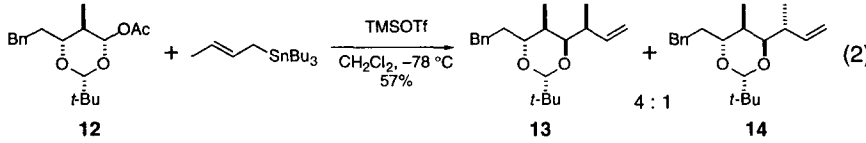
Couplings with compound **9**, which bears an axial methyl group, showed a similar pattern of selectivity. Treatment of **9** with (*E*)-crotyl (dimethyl)phenylsilane in the presence of $SnBr_4$ afforded a 10:1 mixture of **10** and **11** in 56% yield.

**Scheme 3**



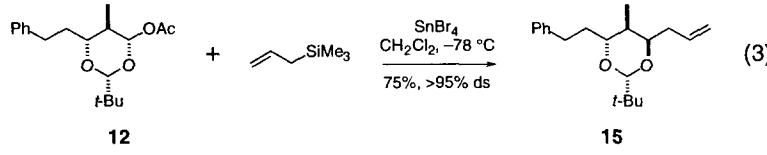

| Entry | X = | Lewis Acid | Overall Yield (10:11) |
|---|---|---|---|
| 1 | $-SiMe_3$ | $SnBr_4$ | 81% (4.7:1) |
| 2 | $-SiMe_3$ | $BF_3{\cdot}OEt_2$ | 45% (1.3:1) |
| 3 | $-SnBu_3$ (1:1 E/Z) | TMSOTf | 95% (1:1) |
| **4** | **$-SiMe_2Ph$** | **$SnBr_4$** | **56% (10:1)** |

Dramatic changes in reactivity and selectivity were observed in couplings of 4-acetoxy-1,3-dioxane **12**, which bears an equatorial methyl group at the C5-position. The best conditions for addition to **6** or **9** gave little or no crotyl addition when applied to **12** and instead returned epimerized starting material. However, treatment of **12** with the more reactive (*E*)-crotyl tributylstannane[15] in the presence of TMSOTf afforded a 4:1 mixture of diastereomers **13** and **14** favoring the 1,2-*syn* isomer **13** (eq 2).




The turnover in exocyclic selectivity can be attributed to a developing *syn*-pentane interaction shown in model B in Fig. 1. The major isomer, **13**, would arise from either the synclinical model C or the antiperiplanar model D. Either one of the models leading to **13** has unfavorable steric interactions that could be alleviated by increasing the dihedral angle between the plane of the oxonium ion and the plane of the alkene.

In contrast to crotyl nucleophiles, allyl nucleophiles efficiently couple with **12**. For example, treatment of **12** with allyltrimethylsilane in the presence of $SnBr_4$ affords **15** as a single diastereomer in 75% yield (eq 3).




The Lewis acid promoted coupling of 4-acetoxy-1,3-dioxanes with crotyl metal reagents represents an interesting approach to polypropionate synthesis. The 1,3-syn relationship between methyl groups favored in these reactions complements the 1,3-anti configuration normally produced in aldol and crotyl metal additions to aldehydes.[16] Crotyl additions to 4-acetoxy-1,3-dioxanes should prove useful in the convergent synthesis of natural products.

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