Dialkylzinc Additions to 4-Acetoxy-1,3-dioxanes: A Highly Stereoselective Route to Protected *anti*-1,3-Diols

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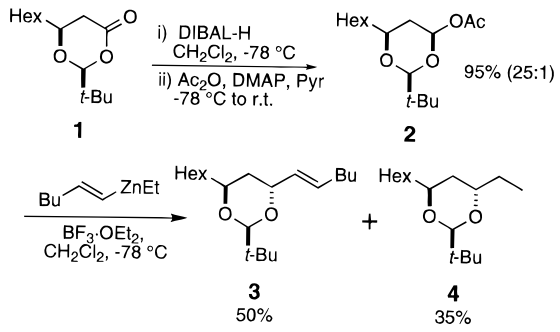
Dialkylzincs are versatile synthetic reagents that have been widely used in palladium- and copper-catalyzed coupling reactions.[1] Highly functionalized alkylzinc reagents can be prepared by direct metalation of an alkyl iodide,[2] Et_2BH hydroboration of alkenes and transmetalation with diethylzinc,[3] or nickel-catalyzed hydrozincation of alkenes using diethylzinc.[4] Complex zinc reagents have great potential in fragment coupling reactions for natural product synthesis. Unfortunately they are relatively poor nucleophiles and do not react with the most useful electrophiles, aldehydes and ketones, without added catalysts or high temperatures.[1] We recently developed a general route to 4-acetoxy-1,3-dioxanes and have begun to explore their potential in synthesis.[5−7] The 4-acetoxy-1,3-dioxanes produce oxonium ions on treatment with Lewis acids, and we report herein the mild and exquisitely selective coupling of 4-acetoxy-1,3-dioxanes with dialkylzinc reagents to generate acetal-protected *anti*-1,3-diols.

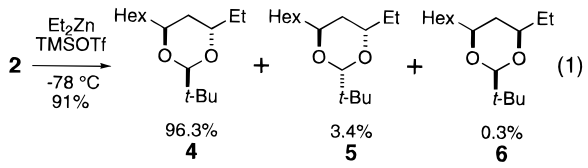
Investigation of the coupling reaction of 4-acetoxy-1,3-dioxane **2** with vinyl organometallics led to an unexpected product, Scheme 1. The 4-acetoxy-1,3-dioxane **2** was prepared by the recently reported[5] DIBAL-H reduction and in situ acetylation of 1,3-dioxan-4-ones, themselves available from 3-hydroxy carboxylic acids.[8] Coupling of **2** with the vinyl zirconium reagent generated by hydrozirconation of 1-hexyne gave only modest yields. To take advantage of the expected higher nucleophilicity of vinyl zinc reagents, the vinyl zirconium reagent was transmetalated with diethylzinc.[9] Reaction of the resulting vinyl zinc reagent with **2** in the presence of $BF_3{\cdot}OEt_2$ gave the expected olefin **3** in 50% yield accompanied by significant amounts of the ethyl adduct. We were surprised that the ethyl group transferred competitively with the vinyl group. Both the vinyl adduct **3** and the ethyl adduct **4** were isolated as single isomers. Saturated alkylzinc reagents are known to couple with glycals to produce *C*-glycosides, but the selectivities are modest, ranging from 1.5:1 to >24:1 depending on the structure of the glycal.[10] Intrigued by the high selectivity of this

Scheme 1



coupling, and by the possibility of using functionalized sp^3 alkylzinc reagents in convergent chain synthesis, we decided to investigate the scope and selectivity of the alkylzinc coupling reaction.

The addition of dialkylzinc reagents to 4-acetoxy-1,3-dioxanes showed very high anti selectivity. When 4-acetoxy-1,3-dioxane **2** was coupled with diethylzinc using TMSOTf as a promoter, the ethyl adduct **4a** was isolated as a 20:1 mixture of isomers. NOE experiments demonstrated that the major isomer had the *anti*-1,3-diol configuration shown in **4** (eq 1), but the minor isomer **5** was also an anti adduct. Only by preparing an authentic



sample could we identify any of the *syn*-1,3-diol adduct **6**. The anti:syn selectivity was ca. 300 to 1 as determined by GC analysis. Formation of the anti adduct **4** was expected based on axial addition to an intermediate oxonium ion. The dramatically higher selectivity of 1,3-dioxanes compared with glycals and glycosides can be attributed to the much higher conformational rigidity of the 1,3-dioxane system.[11] Cis alkyl substituents at the 2- and 6-positions reinforce a chairlike conformation in the dioxane so that axial addition gives the anti adduct. To maintain good orbital overlap, equatorial attack would proceed by way of the highly strained 2,5-twist boat conformation and is strongly disfavored. The minor anti isomer **5** arises from subsequent epimerization of **4** under the Lewis acidic conditions, and the ratio of **4** to **5** typically varies from 10−50:1.

The couplings of functionalized dialkylzinc reagents with 4-acetoxy-1,3-dioxane **2** are summarized in Table 1. The stereoselectivity in each case resembles that of the ethyl addition in eq 1 with a 10:1 to >100:1 selectivity for the major anti adduct over the minor anti adduct. The syn isomers were not observed by ^1H NMR and could not be assigned in the GC analysis.[12] The dialkylzinc reagents used in the coupling reaction were either purchased or prepared from the corresponding primary iodides or alkenes.[2−4] Diethylzinc coupled efficiently with **2** in the presence of TMSOTf in a variety of common solvents at −78 °C (entry a). $BF_3{\cdot}OEt_2$ also acts as a

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(12) The small peaks in a GC trace that might correspond to the syn isomer were each present in <0.5%.

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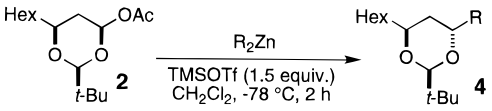
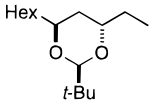
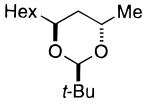
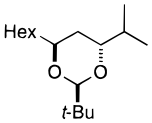
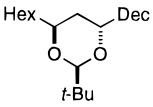
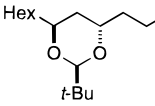
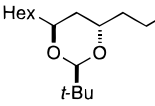
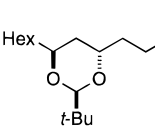
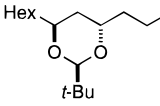
Table 1. Coupling of Dialkylzinc Reagents with 2

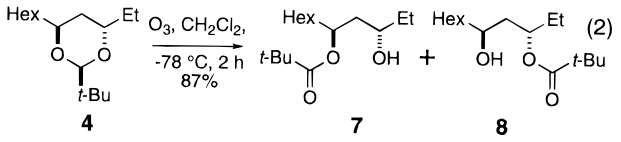


Entry	R	Equiv. R_2Zn	Product	Yield of **4** (Acetal Ratio)
a	Et	2		91% (51:1) 75% (6:1)[a] 100% (1:0)[b] 83% (21:1)[c] 91% (15:1)[d]
b	Et	0.6		90% (1:0)
c	Me	2		90 % (1:0)
d	*i*-Pr	2		90 % (1:0)
e	Dec[e]	2		69 % (1:0)
f	$Cl(CH_2)_4$[f]	2		82 % (1:0)
g	$EtO_2C(CH_2)_3$[f]	2		77 % (1:0)
h	$PhCO_2(CH_2)_3$[e]	2		55 % (18:1)
i	$TBSO(CH_2)_3$[e]	2		83 % (13:1)

[a] $BF_3{\cdot}OEt_2$ used as Lewis acid, and mixture was warmed to 20 °C.
[b] Et_2O was used as the solvent.
[c] THF was used as the solvent.
[d] Toluene was used as the solvent.
[e] Prepared by boron zinc transmetalation from olefin.
[f] Prepared by iodide-zinc exchange from primary iodide.

promoter, but only when the reaction mixture was allowed to warm to 20 °C. In most cases 2 equiv of the dialkylzinc reagent were used, although 0.6 equiv of Et_2Zn still gave the product in 90% yield, showing that both alkyl groups on the zinc are transferred efficiently (entry b). Secondary dialkylzinc reagents also coupled efficiently (entry d), suggesting that configurationally stable secondary dialkylzinc reagents[13] might couple selectively with these electrophiles.[14] Many functional groups are compatible with these coupling reactions including halogens, esters, and silyl ethers (entries f−i). The mild conditions, high yields, and extremely high stereoselectivities of these coupling reactions will make them valuable for coupling segments in natural products synthesis.

In order for a 4-acetoxy-1,3-dioxane−dialkylzinc coupling reaction to be a practical synthetic tool, one must be able to deprotect the product. Cyclic acetals are relatively difficult to hydrolyze.[15] For nonlabile adducts, simply treating the acetal with CSA in 1,3-propanediol at 65 °C leads to a nearly quantitative yield of the *anti*-1,3-diol adduct. Among the less obvious deprotection strategies is treatment with ozone, eq 2.[16] On treatment with ozone at −78 °C the ethyl adduct **4** was converted



into a 3:1 mixture of monopivalate esters **7** and **8** in 87% yield. Although clearly not applicable to unsaturated substrates, this deprotection should be compatible with highly oxygenated substrates and would not affect acetonide protecting groups.

We have described an efficient and highly anti-selective coupling reaction between 4-acetoxy-1,3-dioxanes and dialkylzinc reagents. Although substrate **2** was used as a racemate, optically pure 4-acetoxy-1,3-dioxanes can be prepared from the readily available enantiopure 3-hydroxy acids.[17] The reaction is compatible with many functional groups and will be useful in the convergent synthesis of highly oxygenated natural products. We are actively developing the chemistry of these 1,3-diol synthons.

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Supporting Information Available: Experimental details and characterization data for the coupling of dialkylzinc reagents to form acetals **4a**−**i**, as well as synthesis and characterization of the syn acetal standard **6** (12 pages).

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