Trans-2,5-Disubstituted Tetrahydrofurans via Addition of Carbon Nucleophiles to the Strained Bicyclic Acetal 2,7-Dioxabicyclo[2.2.1]heptane

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ABSTRACT



Addition of allyltributylstannane to 2,7-dioxabicyclo[2.2.1]heptane in the presence of TiCl₄ produces 5-allyl-2-(hydroxymethyl)tetrahydrofuran with a *trans*/cis ratio of 93:7. The *trans*-selectivity is also observed in additions of various other carbon nucleophiles.

Disubstituted tetrahydrofurans and bis(tetrahydrofurans) are prominent structural features in annonaceous acetogenins, a broad class of lipophilic natural products that includes a number of potent cytotoxins such as bullatacin, asimicin, and squamocin (Figure 1).¹ Such compounds exhibit potent



Figure 1. Tetrahydrofurans and bis(tetrahydrofurans) with a *trans*-2,5-dialkyl substitution pattern, highlighted in red in the structures above, are common among annonaceous acetogenins.

inhibition of mitochondrial complex 1 (NADH/ubiquinone oxidoreductase), an effect which has been linked with

induction of apoptosis. Recently, photoactive analogues of asimicin and squamocin have been prepared; a fluorescent analogue of squamocin lacking the butenolide portion was shown to specifically target mitochondria, implicating the tetrahydrofuran motif in a selective recognition event that may be of relevance to potential antitumor agents.² With such interest in their biological properties, tetrahydrofurans require synthetic methods for their rapid and diastereose-lective assembly.³

Key steps in the many valuable approaches to tetrahydrofurans include single or tandem cyclizations of hydroxy epoxides and haloalkanols,⁴ oxidative cyclization of alkenes or polyenes,⁵ intramolecular Prins reaction,⁶ olefin metath-

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esis,⁷ metal-catalyzed allylic substitution,⁸ radical cyclization,⁹ reductive cyclizations of carbonyl compounds,¹⁰ and a variety of [3 + 2]-annulations.¹¹

The C-glycosidic disconnection of oxacyclic compounds, i.e., addition to cyclic oxocarbenium ions (Figure 2a),¹²



Figure 2. Stereocontrol by the 5-substituent in addition of C-nucleophiles to 5-membered cyclic oxocarbenium ions.

represents a simple yet powerful strategy in which C–C bond construction and stereoselection are achieved concurrently. Thus, there have been numerous studies of the fundamental stereochemical behavior of five-membered cyclic oxocarbenium ions, notably by Reissig¹³ and Woerpel¹⁴ (Figure 2). Woerpel concluded about *trans*-2,5-disubstituted tetrahydro-furans that "controlling this array has been challenging",¹⁵ and Reissig noted that efforts to access this substitution pattern by allylsilane additions to oxocarbenium ions "seem

Woerpel, K. A. J. Am. Chem. Soc. 2005, 127, 10879–10884. (15) See page 10881 of ref 14b. to be the least predictable".¹⁶ A number of recent efforts have addressed this limitation,¹⁷ and new methods continue to warrant further development.

In developing potential solutions to the foregoing stereocontrol problem, our attention was drawn to two studies of bicyclic acetals. In 1999, Veyrieres reported a highly diastereoselective allylsilane addition reaction upon a 2,7dioxabicyclo[2.2.1]heptane ring system (Figure 3a).¹⁸ The



Figure 3. Reactivity of bicyclic acetals. (a) Reaction of an anhydropyranose with a C-nucleophile; the tetrahydropyran product is disfavored. (b) Relative rates of hydrolysis of **1** and acetaldehyde dimethyl acetal differ by a factor of 10^4 .

tetrahydrofuran product was not accompanied by the tetrahydropyran regioisomer.¹⁹ The preparation and reactivities of bicyclic acetal 1 (Figure 3b) were examined by Hall and co-workers, revealing rapid rates of acid-catalyzed hydrolysis $(k_{\rm rel} = 2.5 \times 10^4 \text{ versus acyclic acetaldehyde dimethyl})$ acetal).²⁰ Ring strain activation of the pathway to oxocarbenium ion intermediates is implied.²¹ The acetals in bicyclic ring systems depicted in Figure 3 bear an internally tethered leaving group, a feature absent from the Reissig and Woerpel precedents (Figure 2). These considerations inspired the hypothesis that C-C bond forming reactions upon the 2,7dioxabicyclo[2.2.1]heptane ring system might address the longstanding stereocontrol problem highlighted in Figure 2. We now report tests of this hypothesis, using reactions of bicyclic acetal 1 with various C-nucleophiles in the presence of Lewis acids.

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⁽²¹⁾ Enhanced reactivity of **1** suggests that the range of conditions suitable for initiation of its reactions (i.e., combinations of Lewis acids and nucleophiles) might be broader than for other types of acetals.

Racemic bicyclic acetal **1** was prepared from alkene **2**,²² which was subjected to OsO_4 -catalyzed dihydroxylation to afford diol **3** (Scheme 1).²³ According to Hall's method,²⁰ a



solution of **3** in dioctyl phthalate was heated in the presence of catalytic TsOH at ca. 1 mmHg, producing first ethanol and then **1**, collected in a liquid nitrogen-cooled trap. Simple vacuum distillation through a standard short-path condenser afforded pure **1** in 40% yield.²⁴ This material was stored in the refrigerator and used over a few weeks time without significant degradation.

Using allyltrimethylsilane as the *C*-nucleophile, an initial survey of the reactivity of **1** in the presence of Lewis acids showed facile production of allyl tetrahydrofuran $4a^{25}$ (Table 1). There were sharp distinctions in the *trans/cis* diastereomer

Table 1. Survey of the Effects of Lewis Acids in Allylsilane and Allylsitannane Additions to Bicyclic Acetal 1^a

	→ M Lewis acid CH ₂ Cl ₂ , -42 °C	OH I,,,, O trans- 4a	- + cis- 4a
entry	Lewis acid	Μ	$trans/cis^{c}$
1	TMSOTf	$SiMe_3$	$50:50^{b}$
2	BF_3 ·OEt ₂	$SiMe_3$	$50:50^{b}$
3	$Cu(OTf)_2$	$SiMe_3$	50:50
4	TiCl ₄	$SiMe_3$	82:18 b
5	$AlCl_3$	$SiMe_3$	70:30
6	${ m SnCl}_4$	$SiMe_3$	77:23
7	$Zn(OTf)_2$	$SiMe_3$	65:35
8	$InCl_3$	$SiMe_3$	59:41
9	TiCl ₄	\mathbf{SnBu}_3	90:10
10	$AlCl_3$	SnBu_3	$94:6^d$
11	SnCl_4	SnBu_3	64:36
12	InCla	SnBu	$94 \cdot 6^d$

^{*a*} Conditions: 0.1 M solution of **1** (1 mmol) in CH₂Cl₂, allylmetal reagent (1.5 mmol), Lewis acid (1 mmol); workup with saturated aqueous NaHCO₃. ^{*b*} Isolated yields: entry 1, 69%; entry 2, 91%; entry 4, 72%. Conversion was complete unless otherwise noted. ^{*c*} Ratio determined by GC. ^{*d*} Reaction was incomplete.

ratio depending on the Lewis acid. In the presence of TMSOTf, BF_3 ·OEt₂, and Cu(OTf)₂ there was no selectivity (entries 1–3), congruent with precedent. On the other hand,

TiCl₄ gave a promising *trans/cis* ratio of 82:18 (entry 4), and a series of other Lewis acids were moderately effective (entries 5-8). With allyltributylstannane as the nucleophile, the selectivities generally increased (entries 9-12) with the exception of SnCl₄. In this initial screen, AlCl₃ and InCl₃ gave the highest ratios but were accompanied by incomplete conversion (entries 10 and 12). Thus, TiCl₄ was chosen for further development of this reaction.

Next, the effects of temperature and solvent were assessed for the allylstannane addition to 1 in the presence of TiCl₄ (Table 2). Inverse dependence of selectivity on temperature

Table 2. Effects of Temperature and Solvent on TiCl₄-MediatedAllyltributylstannane Additions to Bicyclic Acetal 1^a

entry	T (°C)	solvent	trans/cis ^c
1	-78	CH_2Cl_2	93:7 ^b
2	-42	$\mathrm{CH}_2\mathrm{Cl}_2$	90:10
3	ambient	$\mathrm{CH}_2\mathrm{Cl}_2$	$84:16^{b}$
4^d	ambient	$\mathrm{CH}_2\mathrm{Cl}_2$	$89:11^{b}$
5^d	ambient	benzene	75:25
6^d	ambient	toluene	77:23
7^{d}	ambient	$(CH_2Cl)_2$	89:11
8^d	-23	$(CH_2Cl)_2$	88:12

^{*a*} Conditions: see entry 9, Table 1. ^{*b*} Isolated yields: entry 1, 84%; entry 3, 76%, entry 4, 57%. Conversion was complete in all cases. ^{*c*} Ratio determined by GC. ^{*d*} 0.4 equiv of TiCl₄.

was observed, with excellent selectivity available at -78 °C (entries 1–3). Diminished TiCl₄ (0.4 equiv) was not detrimental to selectivity but lowered the yield (entries 3 and 4). At ambient temperature in benzene and toluene, the reaction exhibited lower selectivity than in dichloromethane (entries 4–6), whereas in dichloroethane there was a slight improvement (entry 7). When operation at low temperatures is undesirable, the conditions of entry 7 offer an alternative.

With conditions enabling high selectivity established, scope became of interest, so the TiCl₄-mediated reaction

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at low temperature was applied to a series of commercially available *C*-nucleophiles (Scheme 2). Excellent *trans*-

Scheme 2					
	C-nucleophiles TiCl ₄ CH ₂ Cl ₂ , –78 °C		OH I,, O 4a–4e		
C-nucleophile	product		isolated yield, dr (GC)		
SnBu ₃	OH I,,,,,O	4a	84%, dr 93:7		
OTBS OMe		e 4b	56%, dr 95:5		
OTMS OMe		e 4c	84%, dr 78:22		
OTBS Ph	OH COPh	4d	68%, dr 83:17		
TMSCN	OH I,,,,, CN	4e	60%, dr 82:18		

selectivity (dr 95:5) was observed with the silyl enol ether derivative of methyl acetate, leading to $4b^{25}$ bearing ester functionality for flexible applications in total synthesis.

From a mechanistic standpoint, if the reaction is S_N 1-like (free oxocarbenium ion **A**, Figure 4), there should be little impact of the Lewis acid on selectivity, and the results would



Figure 4. Intermediates of Suggested Relevance to Competitive Nonselective and Stereospecific Additions to Bicyclic Acetal 1.

mirror the prior observations of poor selectivity, as highlighted in Figure 2. This appears to be the case for TMSOTf, $BF_3 \cdot OEt_2$, and $Cu(OTf)_2$, which afford nonselective addition (entries 1–3 of Table 1). The other entries of Table 1 exhibit dramatic dependence of selectivity upon the identity of the Lewis acid, implying direct involvement of the Lewis acid in the configuration-determining step of the addition mechanism.

The departure from precedent in the *trans*-selective reactions of **1** may be explained by invoking a competition between **A** and intimate ion pair $\mathbf{B}^{26,27}$ (Figure 4) for the nucleophile; the latter could react stereospecifically with inversion of configuration.²⁸ Relative populations of free ion and intimate ion pair may be expected to be impacted both by intramolecular tethering of the leaving group, and by the identity of the Lewis acid. Such a scenario implies that those Lewis acids affording higher selectivities (TiCl₄, AlCl₃, and InCl₃) avoid the S_N1-like stereorandom process²⁹ by increasing the reactivity and/or proportion of ion pair **B**.

In summary, addition of *C*-nucleophiles to 2,7-dioxabicyclo[2.2.1]heptane affords access to *trans*-2,5-disubstituted tetrahydrofurans, a structural subunit common in biologically active natural products. The preparative potential of the selectivity pattern established here merits further investigation, including adaptations to enantiomerically pure substances.

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Supporting Information Available: Preparative details and characterization data for 1 and 4a–e. This material is available free of charge via the Internet at http://pubs.acs.org.

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