product, the expected product, **14**, in which five contiguous chiral centers are present, was obtained in 95% yield.[21]

We also examined the reaction of substrates that bear no ether oxygen atom at the ε or ζ position (Scheme II).[9] Such compounds reacted much more slowly than epoxy acrylates, which bear an ether oxygen atom at the ε or ζ position (e.g., **1**, **3**, **4**, **7**, **9**, **11**, and **13**) and gave mixtures of regioisomeric products. For example, the reaction of methyl (4*R*,5*R*)-4,5-epoxy-2-heptenoate (**15**) with $(CH_3)_3Al$ required more than 6 h at −15 to −10 °C to go to completion and gave an 80:18:2 mixture of **16**, **17**, and **18**, in 85% combined yield.[9] Similarly, the reaction of ethyl 4,5-epoxy-2-pentadecenoate (**19**) (−15 to −10 °C, 6 h) gave a 78:21:1 mixture of **20**, **21**, and **22** in 79% yield. The results suggest that chelation of the aluminum reagent by the oxygen atoms of the epoxide and the ether moiety at the ε or ζ position is important for the achievement of extremely high regioselectivity, as is seen in the reactions of **1**, **3**, **4**, **7**, **9**, **11**, and **13**.[8]

The results of further studies of the methylation reaction and the application of the methodology described here to the synthesis of natural products will be reported shortly.

Acknowledgment. This work was generously supported by grants-in-Aid for Scientific Research Nos. 01540446 and 02953015.

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[21] The MPM protective group was concomitantly removed under the conditions.

On the Stereoselective Opening of Chiral Dioxane Acetals. Nucleophile Dependence

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Received July 5, 1991

Summary: The stereoselective allylation of chiral dioxane acetals **1** was found to be highly dependent on the nature of allylmetal reagent in the following order: Ph_3Si (19/1) < Me_3Si (58/1) < Ph_3Sn (90/1) < Me_3Ge (100/1) < n-Bu_3Sn (>300/1). The allylation with allyltributylstannane was significantly more selective than allyltrimethylsilane for a number of chiral dioxane acetals examined.

The Lewis acid assisted, nucleophilic opening of chiral acetals has evolved into a powerful method for the stereoselective formation of carbon-carbon bonds,[1] Scheme I. Of the many reagents capable of participating in this reaction, silicon-containing nucleophiles (allylsilanes, propargylsilanes, silylacetylenes, enol silyl ethers, ketene silyl acetals, TMS cyanide) have proven most versatile. In a recently completed study on the mechanism of reaction of dioxane acetals with allyltrimethylsilane, we demonstrated the importance of substrate structure and experimental conditions (Lewis acid, solvent, stoichiometry, concentration, temperature) on the stereochemical outcome.[2] *We report herein that the nucleophilicity of the allylating reagent also has a significant impact on the stereoselectivity of reaction.*

The optimized procedure described by Johnson[3] for the allylation of chiral acetals **1** involves the use of 8 equiv of allyltrimethylsilane and 11 equiv of a 6/5 blend of $TiCl_4/Ti(O$-i-$Pr)_4$. By following the recommended slow addition (2 h, syringe pump) of the Lewis acid we were able to reproduce the reported selectivities. Thus, using this standardized protocol for reaction with the *n*-hexyl acetal (±)-**1a** we surveyed five allylating agents bearing different metals and groups on the metal, Table I. Two important trends are apparent from these data. First, for similar R groups the trend Si < Ge < Sn is seen (compare entries 1, 3, 4 and 2, 5). Second, for a given metal, phenyl groups attenuate the selectivity compared to alkyl groups (compare 1 and 2, 4 and 5).

Scheme I

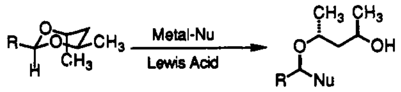
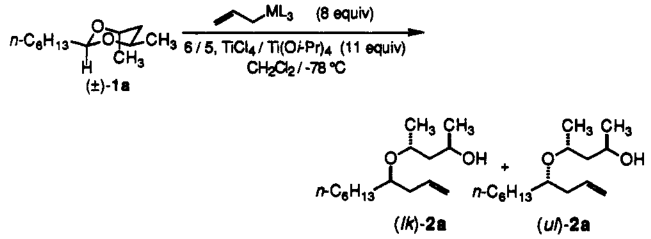


Table I. Allylation of (±)-1a: Nucleophile Dependence[a]



entry	L_3M (equiv)	time[b] (h)	yield[c] (%)	*lk*/*ul*-**2a**	$\Delta\Delta G^{\ddagger}$ [d]
1	Me_3Si (8)	3	100	58/1	1.58
2	Ph_3Si (8)	6	80	10/1	1.14
3	Me_3Ge (8)	3	100	100/1	1.79
4	n-Bu_3Sn (8)	3	100	270/1	2.17
5	Ph_3Sn (8)	3	100	90/1	1.75

[a] All reactions performed with 11 equiv of a 6/5, $TiCl_4/Ti(O$-i-$Pr)_4$ blend 0.2 M in CH_2Cl_2. [b] Total reaction time. [c] All yields and ratios based on response factors versus cyclododecane. [d] At 195 K, kcal/mol.

Table II. Allylation of (±)-1a with Allyltributylstannane: Stoichiometry Effects[a]

entry	Lewis acid[b] (equiv)	stannane (equiv)	yield[c] (%)	*lk*/*ul*-**2a**[c]	$\Delta\Delta G^{\ddagger}$ [d]
1	6/5	8	100	270/1	2.17
2	6/5	1	97	300/1	2.21
3	5/5	1	100	>300/1	>2.21
4[e]	5/5	1	93[f]	568/1	2.40
5	2.5/2.5[g]	1	32		
6	2.5/2.5[g]	2	55	>230/1	>2.11

[a] All reactions run in CH_2Cl_2 (0.1 M) at −78 °C. [b] $TiCl_4/Ti(O$-i-$Pr)_4$ (0.2 M in CH_2Cl_2) added by syringe pump over 2 h. [c] Based on response factors versus cyclododecane. [d] At 195 K (kcal/mol). [e] 2.5 mmol scale. [f] Yield of isolated, purified product. [g] Added over 1 h.

While these trends have clear mechanistic significance (vide infra), the dramatic improvement in selectivity for

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[1] Review: (a) Alexakis, A. Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477. (b) Seebach, D.; Imwinkelreid, R.; Weber, T. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer Verlag: Berlin, 1986; Vol. 4 p 125. (c) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043.

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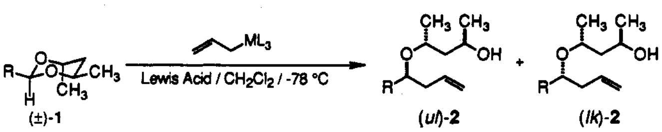
Table III. Allylation of Acetals 1b–f[a]



entry	acetal	R	Lewis acid[b] (equiv)	L_3M (equiv)	product	yield[c] (%)	*ul*/*lk*-**2**[c,d]	$\Delta\Delta G^{\ddagger}$[e]
1	**1b**	$CH_2{=}CHCH_2CH_2$	$TiCl_4$ (4)	Me_3Si (1)	**2b**	87[f]	5.2/1[g]	0.64
2	**1b**	$CH_2{=}CHCH_2CH_2$	titanium blend (6/5)	Me_3Si (8)	**2b**	96	52/1[g]	1.53
3	**1b**	$CH_2{=}CHCH_2CH_2$	titanium blend (5/5)	*n*-Bu_3Sn (2)	**2b**	98	192/1[g]	2.04
4	**1c**	cyclohexyl	$TiCl_4$ (4)	Me_3Si (1)	**2c**	94[f]	4.0/1	0.54
5	**1c**	cyclohexyl	titanium blend (6/5)	Me_3Si (8)	**2c**	96	19/1	1.14
6	**1c**	cyclohexyl	titanium blend (5/5)	*n*-Bu_3Sn (2)	**2c**	95	133/1	1.90
7	**1d**	$C_6H_5CH_2$	$TiCl_4$ (4)	Me_3Si (1)	**2d**	94[f]	4.4/1	0.57
8	**1d**	$C_6H_5CH_2$	titanium blend (6/5)	Me_3Si (8)	**2d**	97	140/1	1.92
9	**1d**	$C_6H_5CH_2$	titanium blend (5/5)	*n*-Bu_3Sn (2)	**2d**	96	246/1	2.14
10	**1e**	C_6H_5	titanium blend (5/5)	Me_3Si (8)	**2e**	95	7.9/1	0.80
11	**1e**	C_6H_5	titanium blend (5/5)	*n*-Bu_3Sn (2)	**2e**	94[f]	62/1	1.60
12	**1f**	*n*-$C_4H_9C{\equiv}C$—	$TiCl_4$ (4)	Me_3Si (1)	**2f**	86[f]	4.0/1	0.54
13	**1f**	*n*-$C_4H_9C{\equiv}C$—	titanium blend (6/5)	Me_3Si (8)	**2f**	96	19/1	1.14
14	**1f**	*n*-$C_4H_9C{\equiv}C$—	titanium blend (5/5)	*n*-Bu_3Sn (2)	**2f**	94	1/2.0	−0.27
15	**1f**	*n*-$C_4H_9C{\equiv}C$—	titanium blend (5/5)	*n*-Bu_3Sn (8)	**2f**	93	1/2.4	−0.34

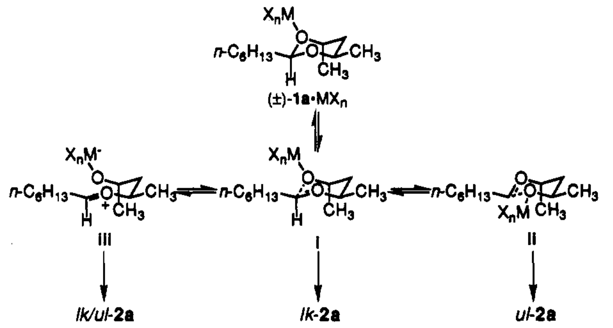
[a] All reactions run in CH_2Cl_2 (0.1 M) at −78 °C. [b] $TiCl_4/Ti(O\text{-}i\text{-}Pr)_4$ (0.2 M in CH_2Cl_2) added by syringe pump over 2 h. [c] Based on response factors versus cyclododecane. [d] Configurational assignment by analogy. [e] At 195 K (kcal/mol). [f] Yield of isolated, purified product. [g] *lk*/*ul* ratio (C-I-P priority change).

tin versus silicon reagents was also of preparative interest. Therefore, a brief optimization of reaction conditions and substrate survey was prompted. The results of changing reagent stoichiometry are combined in Table II. We were pleased to find that only 1 equiv of the stannane was sufficient for complete conversion of **1a** with no loss of diastereoselectivity. Further, the stoichiometric reagent $TiCl_2(O\text{-}i\text{-}Pr)_2$ (10 equiv) gave selectivities comparable to the 6/5 blend. Unfortunately, it was not possible to significantly reduce the amount of this Lewis acid as 5 equiv of this reagent gave only 32–55% conversion of **1a** with 1 and 2 equiv of stannane, respectively (entries 5 and 6). Larger amounts of stannane were considered preparatively disadvantageous. Indeed, the optimized procedure can be conducted without difficulty on a 2.5 mmol scale (entry 4) to afford **2a** in 93% yield with 568/1 selectivity.[4]

Allyltributylstannane reacted with a number of other simple acetals under these conditions with selectivities greater (in general) than those obtained with excess allyltrimethylsilane. The results in Table III illustrate the comparisons between the two nucleophiles for five other acetals bearing alkyl (**1b–d**), aryl (**1e**), and alkynyl (**1f**) groups. All substrates (except **1a**) were treated with allyltrimethylsilane and $TiCl_4$ to provide authentic samples of the *ul*/*lk* mixtures. These reactions are included in the table for comparison (entries 1, 4, 7, and 12).

For the C(2)-alkyl- and aryl-substituted acetals (3-butenyl **1b**, cyclohexyl **1c**, benzyl **1d**, and phenyl **1e**), reaction with allyltributylstannane was more selective than with allyltrimethylsilane. The most dramatic improvement in selectivity was observed for **1c** and **1e** (entries 5, 6, 10 and 11). Moreover, while only 2 equiv of the nucleophile were used, it is likely that only 1 equiv is needed (see Table II). Entries 10 and 11 further illustrate the advantages of allyltributylstannane. The reaction of **1e** with allyltrimethylsilane is conspicuously absent from all previous studies on asymmetric allylations. Using the allylstannane produced **2e** cleanly, in high yield and excellent diastereoselectivity.

Scheme II



The C(2)-heptynyl acetal **1f** was anomalous in that allyltrimethylsilane gave the allylation product with significantly higher selectivity (entries 13–15).[5] The weak and *inverted* selectivity observed with allyltributylstannane is difficult to explain but may reflect the enhanced reactivity of nucleophile and substrate. Further, the steric insignificance of the C(2)-alkyne may allow the Lewis acid to avoid the C(4)/C(6) methyl groups with little energy cost thus equalizing the population of the two diastereomeric reactive ion pairs.[2]

Substrates bearing C(2)-*tert*-butyl, -benzyloxymethyl, and -[(*tert*-butyldimethylsilyl)oxy]methyl groups failed to react with allyltributylstannane under these conditions. In addition, the 2-((*E*)-1-hexenyl) acetal reacted to give a complex mixture of products.

The dramatic nucleophile dependence of diastereoselectivity provides strong support for our unified mechanistic hypothesis involving the intermediacy of three distinct species each with a different stereochemical profile. Highly selective reactions proceed via an intimate ion pair i in which the Lewis acid flanks the axial C(4) methyl group. We believe the enhanced selectivities observed

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[4] In preparative-scale experiments, the rate of addition of the Lewis acid and its concentration were shown to have a significant effect on selectivity. Addition of a 0.6 M solution over 1 h gave a 161/1 selectivity on a 2.5 mmol scale.

[5] The configurational assignment of **2f**/**3f** was assured by the identity of the hydrogenation products to those from the known **2a**/**3a** mixture.

herein arise from interception of the kinetically formed Lewis acid acetal complex $(\pm)$-1·MX_n before equilibration with the diastereomeric intimate ion pair ii (Lewis acid flanking the C(6) methyl group) or the external ion pair iii can occur, Scheme II. Recent quantitative studies by Mayr on the relative nucleophilicity of allylmetals are in complete agreement with the notion that increased stereoselectivity parallels increased nucleophilicity.[6] Similar conclusions were reached in the studies by Yamamoto[7] on α-substituted chiral acetals and by Otera and Nozaki[8] with thioacetals.

In summary, we have demonstrated the extremely diastereoselective opening of chiral acetals using only one equivalent of allyltributylstannane. The high selectivities, minimal amounts of allylmetal and substrate generality combine to make this a preparatively significant reaction. Further studies with organotin-based nucleophiles are in progress.

Acknowledgment. We gratefully acknowledge financial support for this project from the National Science Foundation (NSF-CHE 881847). We are grateful to Professor Herbert Mayr (Lübeck) for a preprint of reference 6.

Registry No. **1a**, 136315-79-2; **1b**, 136315-80-5; **1c**, 97996-52-6; **1d**, 136315-81-6; **1e**, 130693-67-3; **1f**, 136237-96-2; **2a**, 136237-97-3; **2b** (isomer 1), 136315-82-7; **2b** (isomer 2), 136315-83-8; **2c** (isomer 1), 136315-84-9; **2c** (isomer 2), 136315-85-0; **2d** (isomer 1), 136237-98-4; **2d** (isomer 2), 136315-86-1; **2e** (isomer 1), 136237-99-5; **2e** (isomer 2), 136315-87-2; **2f** (isomer 1), 136262-84-5; **2f** (isomer 2), 136374-59-9; 4-pentenal, 2100-17-6; 2,4-pentanediol, 1825-14-5; cyclohexanecarboxaldehyde, 2043-61-0; phenylacetaldehyde, 122-78-1; 2-hexynal, 27593-24-4; allyltrimethylsilane, 762-72-1; allyltriphenylsilane, 18752-21-1; allyltrimethylgermane, 762-66-3; allyltributylstannane, 24850-33-7; allyltriphenylstannane, 76-63-1; titanium chloride, 7550-45-0; titanium isopropoxide, 546-68-9.

Supplementary Material Available: General procedures for the preparation of acetals and for their reaction with allyltributylstannane along with full characterization of **1b–d**, **1f**, and **2a–f** (10 pages). Ordering information is given on any current masthead page.

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[7] Yamamoto, Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116.

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Palladium-Catalyzed Polycyclization of Dienynes: Surprisingly Facile Formation of Tetracyclic Systems Containing a Three-Membered Ring

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Received May 29, 1991

Summary: Substituted dienynes **9** undergo a palladium-catalyzed 4-fold cyclization process to give tetracycles **12** as sole products.

The formation of carbon–carbon bonds by way of the Heck reaction has found widespread applications in organic synthesis.[1] In the past few years, the palladium-catalyzed construction of oligocyclic systems from open-chain precursors in one step has emerged as a new potent synthetic strategy.[2] So far, this methodology has mainly been used for biscyclization reactions and relatively little attention has yet been paid to the possible one-step construction of tri- and tetracyclic compounds.[3] We now wish to report an unprecedented palladium-catalyzed domino cyclization leading to a new type of tetracyclic skeleton.

In pursuing a concept for the novel construction of tricyclic systems like **7**, initiated by biscyclization under Heck coupling conditions[4] of a suitable dienyne followed by electrocyclization, we treated 2-bromo-4-oxa dienyne **1**[5,6] with 5 mol % $Pd(OAc)_2$, 20 mol % PPh_3, and 2 equiv of K_2CO_3 in refluxing acetonitrile. Instead of the expected tricyclic diene **7**, the cross-conjugated triene **4** was isolated in 60% yield. Apparently, the reaction initially proceeded as expected by oxidative addition of the carbon–bromine bond to palladium (0), followed by a 6-*exo-dig*[7] and subsequently a 5-*exo-trig* ring closure to give the alkylpalladium species **2**. But under these conditions, the conjugated triene intermediate **5**, when formed from **2** by β-hydride elimination, completely isomerizes to **4**. With 1 equiv of silver nitrate added to the reaction mixture,[8] this isomerization is suppressed and **7**, formed by electrocyclic rearrangement of **5**, is isolated in 52% yield.

Under both types of conditions, the interesting tetracyclic byproduct **8** is formed in 5 and 10% yield, respectively. This can be rationalized in terms of a relatively slow β-hydride elimination in **2**, so that this alkylpalladium species can undergo another 5-*exo-trig* ring closure to the

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[1] (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) Heck, R. F. *Pure Appl. Chem.* **1978**, 50. (c) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 41.

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[5] All compounds reported herein were fully characterized by IR and ^1H and ^{13}C NMR spectroscopy. Satisfactory molecular mass and/or combustion analysis were obtained for new compounds. Stereochemical assignments are based on 2D-NOESY and COLOC studies.

[6] Dienyne **1** was readily assembled by alkylation of non-8-en-3-yn-1-ol with 2,3-dibromopropene under phase-transfer conditions in 79% yield.

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[8] (a) Andersson, C. M.; Hallberg, A.; Anderson, C. *J. Org. Chem.* **1985**, *50*, 3891. (b) Abelman, M. M.; Oh, T.; Overman, L. E. *Ibid.* **1985**, *52*, 4130.

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