Stereoselective Synthesis

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Enantiospecific Synthesis and Allylation of All-Carbon-Substituted α-Chiral Allylic Stannanes**

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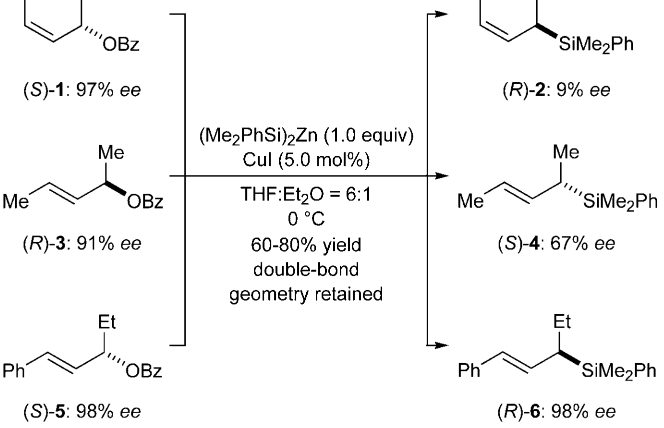
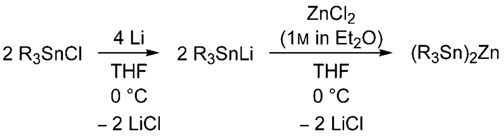
Stereodefined α-chiral allylic stannanes are well-established nucleophilic allyl-transfer reagents in reagent-controlled asymmetric synthesis.[1–3] Sufficient chemical stability is commonly secured by oxygenation at the α[4] or the γ[5] carbon atom of these secondary tin compounds, whereas allylic systems devoid of heteroatom substitution are fragile as a result of a pronounced tendency toward 1,3-tin migration or even decomposition.[1] The absence of mild methods for the synthesis of these elusive all-carbon-substituted allylic stannanes might have thwarted the development of their chemistry until now.[6] Herein, we report an exceptionally facile synthesis of α-chiral allylic stannanes through both enantiospecific and regioselective allylic substitution[7] with an undervalued tin-based zinc compound.[8,9] We also showcase the value of these new allyl-transfer reagents in enantiospecific and diastereoselective thermal[1,4] and Lewis acid promoted[1,10] carbonyl allylation.

Several years ago, we introduced manifold copper-catalyzed reactions of soft bis(triorganosilyl) zinc reagents instead of hard triorganosilyl lithium reagents for carbon–silicon bond formation.[11] The success of this chemistry hinges on a lithium-to-zinc transmetalation step, through which the nucleophilicity and basicity of the silicon atom is markedly attenuated. The otherwise essential use of stoichiometric amounts of copper is therefore unnecessary. For example, the allylic substitution of allylic benzoates proceeded cleanly in the presence of copper(I) iodide as a catalyst with $(Me_2PhSi)_2Zn$ as the source of the silicon nucleophile.[11b] Regioselectivity and the connected preservation of stereochemical integrity were highly dependent on the substitution pattern (Scheme 1):[12] Cyclic and acyclic "symmetrical" substrates were almost completely ((*S*)-**1**→(*R*)-**2**) or partially racemized ((*R*)-**3**→(*S*)-**4**), whereas acyclic "nonsymmetrical" precursors reacted regioselectively with flawless inversion of the absolute configuration at the α carbon atom ((*S*)-**5**→(*R*)-**6**). These experimental findings prompted us to also elucidate the competing reaction pathways in this catalytic process.[12]



Scheme 1. Preparation of α-chiral silanes by copper-catalyzed allylic substitution with $(Me_2PhSi)_2Zn$.[12] Bz = benzoyl.

On the basis of this enantioselective synthesis of α-chiral allylic silanes, we set out to elaborate a preparatively useful route to difficult-to-obtain, stereodefined all-carbon-substituted allylic stannanes. We synthesized the required bis(triorganostannyl) zinc compounds from the corresponding triorganostannyl chlorides through reductive metalation with elemental lithium and subsequent lithium-to-zinc transmetalation[13] (Scheme 2).[8]



$$2\,R_3SnCl \xrightarrow[\substack{THF\\0\,^\circ C\\-\,2\,LiCl}]{4\,Li} 2\,R_3SnLi \xrightarrow[\substack{THF\\0\,^\circ C\\-\,2\,LiCl}]{\substack{ZnCl_2\\(1\,\text{M in } Et_2O)}} (R_3Sn)_2Zn$$

Scheme 2. Generation of bis(triorganostannyl) zinc reagents.[8]

We next tested $(Bu_3Sn)_2Zn$ with copper(I) cyanide (5.0 mol%) in the allylic substitution of our three model substrates, (*S*)-**1**, (*R*)-**3**, and (*S*)-**5** (see Scheme 1). The desired allylic stannanes (*R*)-**7**, (*S*)-**8**, and (*R*)-**9** were formed almost quantitatively (Scheme 3). As expected, these all-carbon-substituted stannanes were stable when isolated but remarkably labile in solution (in polar solvents)[1b] and on silica gel; purification by rapid flash chromatography was feasible (see the Supporting Information for NMR spectra), whereas the determination of *ee* values by analytical HPLC or GLC failed. We therefore decided to immediately subject crude[14] (*R*)-**7**, (*S*)-**8**, and (*R*)-**9** to a thermal S_E2' reaction with an aldehyde to

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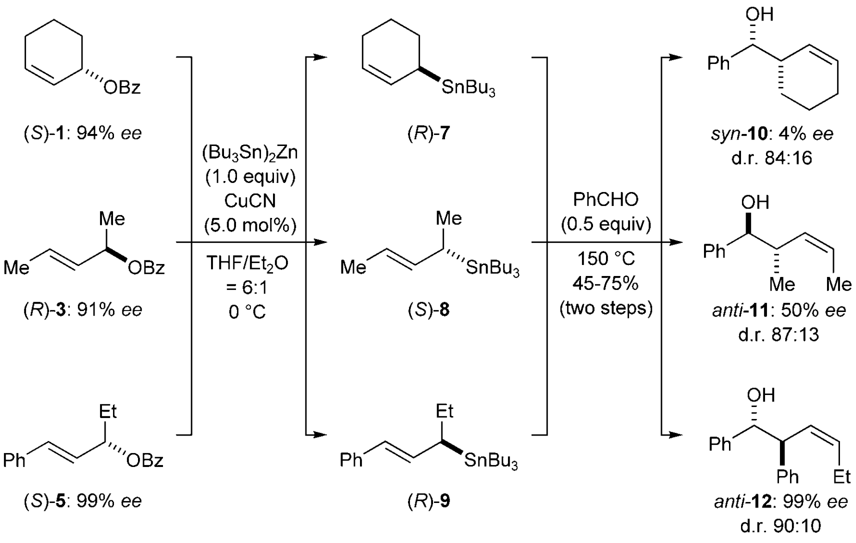
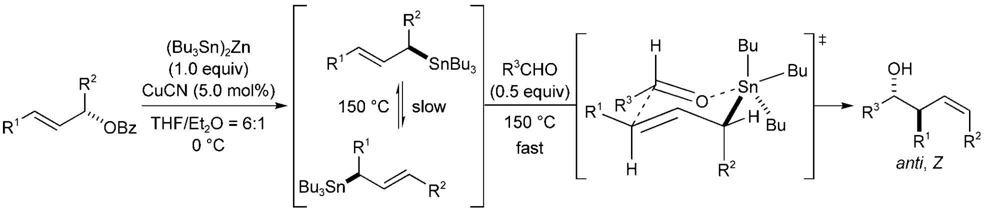


Scheme 3. Preparation of the α-chiral stannanes **7**–**9** by copper-catalyzed allylic substitution with $(Bu_3Sn)_2Zn$ and thermal S_E2' reaction with benzaldehyde.

get an indirect measure of the stereochemical course of the allylic substitution. These enantiospecific thermal carbonyl allylation reactions favor the formation of products with a *syn* relative configuration from *Z* precursors and products with an *anti* relative configuration from *E* precursors; products with a *Z* alkene geometry are formed preferentially. This outcome is rationalized by a cyclic transition state with the substituent at the α carbon atom in an axial position, an arrangement which in turn translates into a *Z* double bond in the homoallylic alcohol.[15] All three allylic stannanes of unknown enantiomeric purity reacted with benzaldehyde to afford the homoallylic alcohols *syn*-**10** (4% *ee*), *anti*-**11** (50% *ee*), and *anti*-**12** (99% *ee*). These *ee* values correlate well with the results obtained for the series of α-chiral allylic silanes (compare Schemes 1 and 3). We assume that copper-catalyzed allylic substitutions with $(R_3Si)_2Zn$ and $(R_3Sn)_2Zn$ occur by identical mechanisms.[12]

For the “nonsymmetrical” allylic benzoate (*S*)-**5**, both the regioselective allylic substitution ((*S*)-**5**→(*R*)-**9**) and the diastereoselective electrophilic substitution ((*R*)-**9**→*anti*-**12**) are enantiospecific: The product *anti*-**12** was formed with an excellent *ee* value of 99%. The chemical yield was moderate (Table 1, entry 1), as expected for a thermal S_E2' reaction.[1,4]

Table 1: Enantiospecific and highly *anti*-diastereoselective thermal S_E2' reactions of α-chiral allylic stannanes with aldehydes.



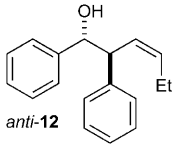
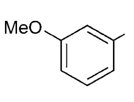
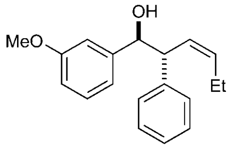
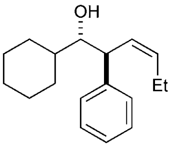
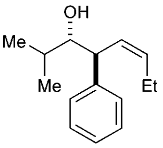
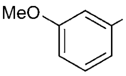
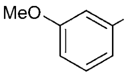
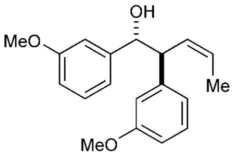
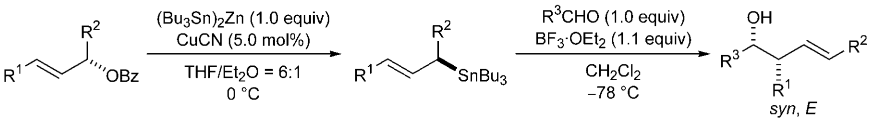
Entry		Allylic benzoate		Aldehyde		Product			
	R^1	R^2	*ee* [%][a]	R^3		Yield [%][b]	d.r.[c]	*ee* [%][a]	*ct* [%][h]
1	Ph	Et	99 (*S*)	Ph	 *anti*-**12**	76	90:10	99	100
2[d]	Ph	Et	94 (*R*)			44	91:9	91	97
3	Ph	Et	99 (*S*)	*c*-C_6H_{11}		35	>95:5	93[e]	94
4	Ph	Et	99 (*S*)	*i*Pr		32	>95:5	83[f]	84

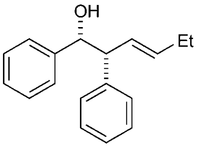
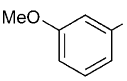
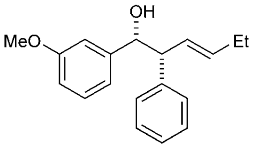
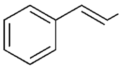
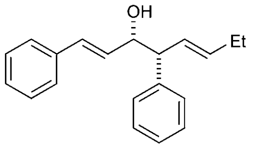
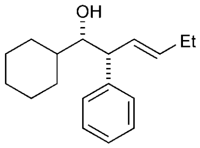
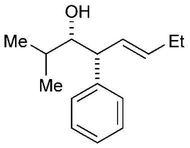
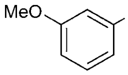
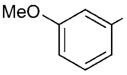
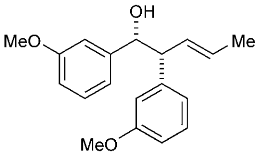
Table 1: (Continued)

Entry	Allylic benzoate			Aldehyde		Product			
	R^1	R^2	*ee* [%][a]	R^3		Yield [%][b]	d.r.[c]	*ee* [%][a]	*ct* [%][h]
5		Me	99 (*S*)			48	81:19	92[g]	93

[a] Unless otherwise noted, the *ee* value was determined by HPLC analysis by using a Daicel chiralcel or chiralpak column (baseline separation of enantiomers). [b] Yield (with respect to the aldehyde) of the analytically pure material after flash chromatography on silica gel.[15] [c] The diastereomeric ratio was determined from the ^{1}H NMR spectrum of the crude product mixture by integration of baseline-separated resonance signals of the diastereomers. The competing thermal allylic 1,3-tin shift produces the regioisomeric allylic stannane and the corresponding homoallylic alcohol (through an S$_E$2′ reaction with the aldehyde) as by-products. [d] The acetate was used instead of the benzoate. [e] Despite baseline separation of the signals for the two enantiomers, they could not be integrated accurately owing to the presence of an impurity (probably the diastereomer); the *ee* value is certainly greater than 95%. [f] The *ee* value was determined by GLC analysis by using a hydrodex β-PM column (baseline separation of enantiomers). [g] The *ee* value was determined by HPLC analysis after reductive ozonolysis (see the Supporting Information). [h] *ct* = chirality transfer.

Table 2: Enantiospecific and highly *syn*-diastereoselective BF$_3$·OEt$_2$-promoted S$_E$2′ reactions of α-chiral allylic stannanes with aldehydes.



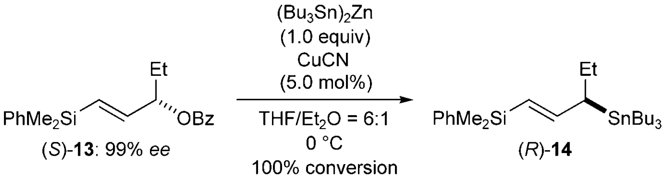
Entry	Allylic benzoate			Aldehyde		Product			
	R^1	R^2	*ee* [%][a]	R^3		Yield [%][b]	d.r.[c]	*ee* [%][a]	*ct* [%]
1	Ph	Et	99 (*S*)	Ph		56	> 95:5	99	100
2	Ph	Et	99 (*S*)			49	92:8	92[d]	93
3	Ph	Et	99 (*S*)			63	92:8	94[d]	95
4	Ph	Et	99 (*S*)	*c*-C$_6$H$_{11}$		62	> 95:5	99	100
5	Ph	Et	99 (*S*)	*i*Pr		46	> 95:5	98	99
6[e]		Me	99 (*S*)			50	93:7	99	100

[a] The *ee* value was determined by HPLC analysis by using a Daicel chiralcel or chiralpak column (baseline separation of enantiomers). [b] Yield (based on the initial amount of the allylic benzoate) of the analytically pure material after flash chromatography on silica gel. [c] See [c] in Table 1. [d] See [e] in Table 1. [e] The depicted homoallylic alcohol was not isolated; remaining 3-anisaldehyde reacted with the expected product to give an isochroman (for full details, see the Supporting Information).

In a separate experiment, we heated stannane ((R)-**9** for several hours at 150 °C and thereby proved that allylic transposition of the tin moiety occurs at a slow rate: An isomeric ratio of approximately 75:25 in favor of (R)-**9** was detected after 36 h. Encouraged by these promising results, we tested representative aldehydes in the S_E2' reaction with (R)-**9**. Except when *i*PrCHO was used as the electrophile, the *anti*-configured homoallylic alcohols[16] were produced in essentially enantiomerically pure form (Table 1, entries 1–4). As *meta*-methoxy-substituted arenes can be viewed as masked β-ketoesters,[17] we also prepared the appropriately substituted allylic stannane and treated it with 3-anisaldehyde (Table 1, entry 5).

Lewis acid promoted carbonyl allylation reactions, for example, with $BF_3{\cdot}OEt_2$ as the Lewis acid,[1,2,10] are far more widespread than thermal S_E2' reactions. They proceed via acyclic transition states, the precise conformation of which (that is, antiperiplanar or synclinal) is still under debate.[18] However, the stereochemical outcome is *syn*. When an equimolar mixture of the enantiomerically pure all-carbon-substituted stannane (R)-**9** and an aldehyde was treated with $BF_3{\cdot}OEt_2$, *syn*-configured,[17] highly enantiomerically enriched homoallylic alcohols were formed in good yields; the diastereoselectivity was reasonably high in all cases (Table 2, entries 1–5). The methoxy-functionalized system performed equally well but afforded the desired homoallylic alcohol only as an intermediate (Table 2, entry 6), which reacted with remaining aldehyde to form a hemiacetal and eventually an isochroman (for a mechanistic outline, see the Supporting Information).

In an attempt to further expand the scope of the reaction, we identified the silicon-containing benzoate (S)-**13** as an enantioselective entry into the attractive chemistry of tin- and silicon-functionalized allylic building blocks.[19,20] Copper-catalyzed carbon–tin bond formation did give the enantiomerically enriched bifunctional building block (R)-**14** (Scheme 4); however, this stannane was too unstable for subsequent steps. Control experiments verified that $BF_3{\cdot}OEt_2$ alone decomposes (R)-**14** quantitatively within minutes, whereas (R)-**9** is reasonably stable towards Lewis acids. Thus, the application of (R)-**14** remains a challenge.



Scheme 4. Synthesis of an α-chiral bifunctional allylic building block.

Our copper-catalyzed allylic substitution with a bis(triorganostannyl) zinc reagent fills a gap in enantioselective allylation chemistry. Enantiospecific and diastereoselective thermal and Lewis acid promoted carbonyl allylation reactions demonstrated the synthetic potential of this formerly elusive class of α-chiral allylic stannanes. We are currently testing glyoxalates as electrophiles and will then address the demanding chemistry of tin- and silicon-substituted bifunctional allylic systems.

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Keywords: allylation · allylic substitution · enantiospecificity · stannanes · stereoselective synthesis

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[13] Although triorganostannyl lithium compounds are already relatively soft, in contrast to the related hard triorganosilyl lithium reagents, it is necessary to form the corresponding zinc compounds to enable the allylic substitution of benzoates and acetates without deacylation.

[14] Reductive metalation and lithium-to-zinc transmetalation release substantial amounts of lithium chloride and zinc chloride. Removal of these Lewis acids by repeated extraction with H_2O might be advantageous (see the Supporting Information).

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