Tin-promoted Stereocontrolled Intramolecular Allylation of Carbonyl Compounds: a Facile and Stereoselective Method for Ring Construction

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The intramolecular allylation of carbonyl compounds **1** promoted by metallic tin proceeds in a stereocontrolled manner to give cyclic products **2** with high diastereoselectivity.

Allyl metal–aldehyde condensation is one of the most important methods for regio- and stereo-selective carbon–carbon bond formation. Since the resulting homoallyl alcohol can be easily converted to many important building blocks for natural product synthesis,[1] this reaction has attracted the attention of a wide range of organic chemists.[1,2] However, the high price and extreme sensitivity of many organometallic compounds lead to severe limitations and have caused many changes to this reaction involving the use of activated metals.[3]

The development of new, efficient methods for the construction of ring systems represents an important ongoing challenge for synthetic organic chemists.[4] As we know, the active metal tin has been successfully used in allylation of many aldehydes, but most of these have focused on intermolecular reactions.[5] It occurred to us that it might be possible to construct important ring systems from a molecule that incorporates both allylic halide and carbonyl group moieties, using active metal tin to promote the intramolecular reaction. Here we wish to report our recent results concerning stereoselective intramolecular allylation using tin.

Initially 2-(4′-bromobut-2′-enyl)oxybenzaldehyde (*E*-**1a**) was chosen as the substrate. The reaction of *E*-**1a** promoted by tin in solvents such as DMF, MeCN, THF *etc.* afforded only low yields of the desired cyclic product. However, when a mixture of THF and water (H_2O:THF = 1:6) was used as solvent, the cyclic product was isolated in 63% yield as a mixture of *cis* and *trans* isomers with *cis*-**2a** being the major product (entry 1 in Table 1). The configuration of the product (*cis*-**2a**) was assigned by ^{1}H NMR spectral analysis and confirmed by a proton 2D-NOESY spectrum. Attempts to optimize the reaction conditions using additives such as HMPA (hexamethylphosphoramide) or HOAc were unsuccessful (entries 2 and 3 in Table 1). In these reactions, besides the desired cyclic product, a byproduct salicylaldehyde derived from allylic carbon–oxygen bond cleavage was also isolated. It was finally found that the presence of a catalytic amount of $HgCl_2$ had a pronounced effect both on the reaction rate and the yield of the cyclic product. Thus reaction of *E*-**1a** (1.0 mmol) with active tin[6] (2.5 mmol) and $HgCl_2$ (0.18 mmol) in THF (12 ml)–H_2O (2 ml) at room temp. was complete within 16 h to give **2a** in 91% yield and high diastereoselectivity (*cis* : *trans* = 92.5 : 7.5)† (entry 4 in Table 1). No byproduct arising from cleavage of the allylic carbon–oxygen bond could be detected by TLC, possibly due to the acceleration of the intramolecular reaction by $HgCl_2$.

Yamamoto and coworkers have reported that the configuration of cyclic products depends upon the double-bond geometry of allylstannanes.[7] In our reaction, when a mixture of *E*- and *Z*-**1a** (entry 2 in Table 2) was used as the substrate, the reaction took place with similar *cis* selectivity (referring to the vinyl and hydroxy groups in the cyclic products), the stereochemical outcome being insensitive to the geometry of the carbon–carbon double bond in the starting material.

The results obtained for a variety of substrates are summarized in Table 2, fair to good yields and high stereoselectivities were obtained (Table 2). The cyclization reaction of *E*-**1b** gave a quantitative yield and only the *cis*-cyclic product was obtained (entry 3 in Table 2). In the case of cyclization of *E*-**1c**, high stereoselectivity was found, but the yield was only moderate (entry 4 in Table 2).

This reaction was also successful in the intramolecular allylation of ketones. Cyclization of ketone *E*-**1d** proceeded in good yield, but in this case, more $HgCl_2$ was needed for good results (entry 5 in Table 2).

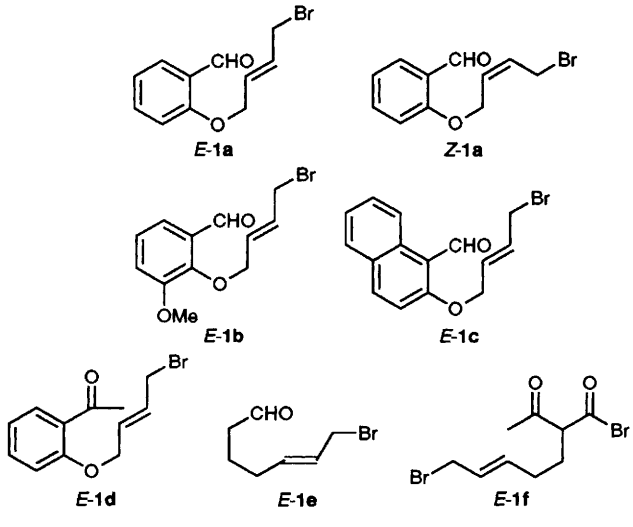
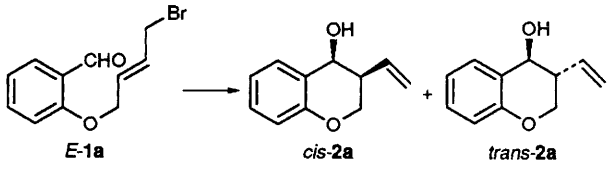


Table 1 Cyclization reaction of *E*-**1a** promoted by tin under different conditions[a]



Entry	Additive	*T*/C	*t*/h	Yield of 2a (%) (*cis* : *trans*)[b,c]
1	—	Room temp.	28	63(91.3 : 8.7)
2	HMPA (1 ml)	40	28	63(83.8 : 17.2)
3	HOAc (1 ml)	Room temp.	24	68(91.8 : 8.2)
4	$HgCl_2$[d]	Room temp.	16	91(92.5 : 7.5)

[a] Sn (2.5 equiv.), THF (12 ml)–H_2O (2 ml). [b] Refers to vinyl and hydroxy groups in **2a**. [c] Determined by HPLC and ^{1}H NMR spectroscopy. [d] 18 mol% of $HgCl_2$ added.

Table 2 Tin-promoted intramolecular allylation

Entry	Substrate	*t*/h	Yield (%)[a]	(*cis* : *trans*)[b]
1	*E*-**1a**	16	91	(91.5 : 8.7)
2	*Z*-**1a** + *E*-**1a**[c]	16	91	(92.0 : 8.0)
3	*E*-**1b**	12	98	(>97.0 : <3.0)
4	*E*-**1c**	24	65	(>97.0 : <3.0)
5	*E*-**1d**[d]	30	79	(82.0 : 18.0)
6	*E*-**1e**	18	81	(53.0 : 47.0)
7	*E*-**1f**	24	53[e]	

[a] Isolated yield. [b] Determined by 300 MHz ^{1}H NMR spectroscopy. [c] *Z*-**1a** : *E*-**1a** = 33 : 67. [d] 35 mol% of $HgCl_2$ added. [e] The stereochemistry of the product was not determined.

For synthesis of carbon-ring compounds, an allylic carbon–oxygen bond should be absent from the substrate. The starting material 7-bromohept-5-en-1-al (*E*-**1e**) reacted with tin in the absence of $HgCl_2$, affording a functionalized cyclopentane in good yield, but with low diastereoselectivity. Cyclization of an acyclic ketone substrate *E*-**1f** proceeded only in low yield.

The stereoselectivity and the fact that the diastereoselectivity was not dependent upon the double-bond geometry of substrates implies that our reaction proceeds through a transition state in which there is no interaction between the oxygen atom of the carbonyl group and the tin atom,[8] which may be due to the presence of the phenyl group. Where no phenyl group was present, as in *E*-**1e** and *E*-**1f**, low selectivity was observed.

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Footnote

† *Spectroscopic data* for *cis*-**2a**: IR: ν_{max}/cm^{-1} (neat) 3350, 3050, 1630, 1605, 1580, 1450, 1220, 1040. ^1H NMR δ_H ($CDCl_3$, 300 MHz, $SiMe_4$) δ 7.39 (d, 1H, *J* = 7.4 Hz), 7.20 (t, 1H, *J* = 7.4 Hz), 6.94 (t, 1H, *J* = 7.4 Hz), 6.83 (d, 1H, *J* = 7.4 Hz), 5.79–5.67 (m, 1H), 5.32–5.21 (m, 2H), 4.61 (d, 1H, *J* = 6.17 Hz), 4.30 (dd, 1H, *J* = 11.2, 4.3 Hz), 4.08 (dd, 1H, *J* = 11.2, 7.53 Hz), 2.65 (m, 1H), 1.98 (br, 1H); MS: *m/z* (%): 177 ($M^+ + 1$), 176 (M^+), 159, 131, 121(100), 104, 93, 77, 65.

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