Lewis acid mediated [3 + 2] cycloaddition of allylgermane: stereoselective synthesis of germyl substituted tetrahydrofurans

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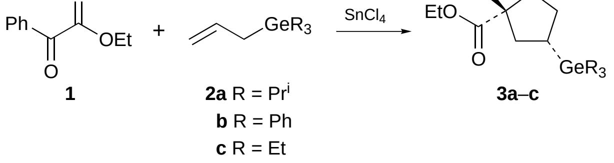
Tin(IV) chloride mediated [3 + 2] cycloaddition of allylgermanes to α-dicarbonyl compounds proceeds highly stereoselectively to give tetrahydrofurans in good yields.

Cycloadditions are one of the most useful methods for the stereoselective construction of ring compounds. Numerous cycloadditions have been developed and have been effectively employed in the total synthesis of natural products.[1] Recently Lewis acid promoted [3 + 2] and [2 + 2] cycloadditions of allylsilane with α,β-unsaturated carbonyl compounds and ketones have been extensively studied.[2] For example, allylsilanes bearing bulky silyl substituents work as 1,3-dipole equivalents and both five-membered carbocycles[3] and heterocycles[4,5] have been constructed stereoselectively. Furthermore, allylsilanes have been found to act as 1,2-dipole equivalents depending on the reaction conditions to form four-membered carbocycles[6] and heterocycles stereoselectively.[7] We have recently reported that the Lewis acid promoted [3 + 2] cycloaddition of allylsilanes bearing sterically demanding silyl substituents to α-keto esters proceeded smoothly to afford tetrahydrofurans stereoselectively.[4] Furthermore the Lewis acid mediated cycloaddition of allylstannanes has been studied.[8] In striking contrast, the Lewis acid promoted cycloaddition of allylgermane has not been reported.[9] In connection with our interest in cycloaddition in allylsilane chemistry, we studied the cycloaddition of allylgermane. Reported here is the first [3 + 2] cycloaddition of allylgermane.

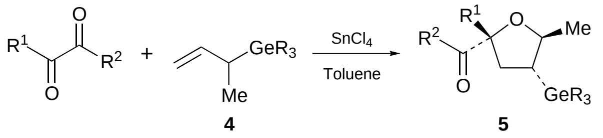
First, allyltriisopropylgermane **2a** was treated with an α-keto ester in the presence of a Lewis acid. After screening Lewis acids, we found that the use of tin(IV) chloride in toluene led to the formation of a cycloadduct **3a** as a single stereoisomer in 48% yield (Scheme 1).† Other conventional Lewis acids did not give the cycloadduct. Use of an allylgermane bearing a bulky germyl substituent is mandatory for the formation of the cycloadduct in good yield. Allylgermanes with less sterically demanding germyl substituents such as **2b** and **2c** decreased the yields of the tetrahydrofurans **3b** and **3c** to 17 and 7% yields respectively. In these cases, the normal allylation product was obtained predominantly.‡

Furthermore, introduction of a methyl group at the α-germyl position improved the yield of the tetrahydrofurans significantly and the results are shown in Table 1. Treatment of **1** with allylgermane **4** and tin(IV) chloride in toluene at −78 °C for 40 min gave rise to the cycloadduct in 53% yield (entry 1). Ethyl pyruvate and an α-diketone also afforded the cycloadducts in good yields (entries 2 and 3). The reason why use of **4** inceased the yield of the adduct is accounted for as follows: the α-germyl methyl group stabilizes the β-germyl carbocation thus facilitating the germyl migration to produce cycloadducts in better yields than with **2b**.

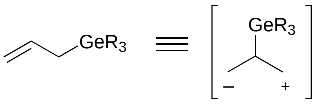


Scheme 1

Table 1 Results of the cycloaddition



Entry	R¹	R²	Conditions	Product	Yield (%)
1	Ph	OEt	−78 °C, 40 min	**5a**	53
2	Me	OEt	−40 °C, 11 min	**5b**	62
3	Me	Me	−40 °C, 12 min	**5c**	72



The present cycloadditions exhibited excellent levels of diastereoselection, producing the tetrahydrofurans with diastereoisomeric excesses (des) reaching > 96% as determined by ^{1}H and ^{13}C NMR spectroscopy. The relative stereochemistry of **3a** and **5a** was unambiguously determined by a multiple NOE study. The stereochemistries of other tetrahydrofurans were estimated by analogy.

In conclusion, we have developed a novel method for the stereoselective formation of germyl substituted tetrahydrofurans by a tin(IV) chloride promoted [3 + 2] cycloaddition of allylgermane to α-keto esters. The utility of allylgermanes bearing sterically demanding germyl substituents as 1,3-dipole equivalents has been demonstrated for the first time.

Footnotes and References

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† Compound **3a** ($R = Pr^i$) was prepared as follows: in a two-necked round bottomed flask, a mixture of **1** (41.5 mg, 0.23 mmol) and **2a** (67.2 mg, 0.28 mmol) in dry toluene (3.2 ml) was stirred at −20 °C. To this mixture tin(IV) chloride (30 μl, 0.26 mmol) was added dropwise and the stirring was continued at the same temperature for 5 min. The reaction was quenched by the addition of 1 M aqueous HCl. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. Purification of the crude mixture by preparative TLC (SiO_2, hexane–ethyl acetate, 7 : 1, v/v) gave **3a** (47.2 mg) in 48% yield.

Selected data for compound **3a**: δ_H($CDCl_3$, *J*/Hz) 1.12 (d, *J* 7.3, 18 H), 1.21 (t, *J* 7.1, 3 H), 1.38 (septet, *J* 7.3, 3 H), 1.66 (dddd, *J* 7.7, 8.2, 12.3, 12.8, 1 H), 2.60 (dd, *J* 7.7, 12.8, 1 H), 2.67 (dd, *J* 12.8, 12.8, 1 H), 4.04 (dd, *J* 8.2, 12.3, 1 H), 4.17 (q, *J* 7.1, 2 H), 4.35 (dd, *J* 8.2, 8.2, 1 H) and 7.24–7.57 (m, 5 H); δ_C($CDCl_3$) 14.06 (CH_3), 14.20 (CH × 3), 20.24 (CH_3 × 6), 23.39

(CH), 41.51 (CH_2), 61.43 (CH_2), 72.64 (CH_2), 86.41 (C), 125.56 (CH × 2), 127.44 (CH), 128.03 (CH × 2) and 141.80 (C).

‡ Compounds **2a**–**c** afforded the corresponding homoallyl alcohols in 36, 74 and 85% yield, respectively.

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