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Preparation and applications of a novel bis(tributylstannyl)cyclopropane: a synthetic equivalent of a cyclopropane-1,2-dianion

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Abstract—The preparation of the novel *trans*-1,2-bis-stannylcyclopropane **4** is described. Its applications in Kosugi–Migita–Stille cross-coupling and in tin–lithium exchange reactions are presented and discussed.

Cyclopropane motifs are ubiquitous in a wide diversity of naturally occurring substances.[1] *trans*-Disubstituted cyclopropane cores constitute an interesting backbone that can be found, for example, in grenadadiene **1** and constanolactone A **2** (Fig. 1).[2]

The strategic importance of the cyclopropyl moiety is clearly revealed by the wealth of contributions devoted to its preparation and subsequent functionalisation.[3] Whilst examining the structures of natural products embodying a *trans*-disubstituted cyclopropane subunit, we became interested in delineating an efficient and connective methodology for their rapid assembly. From a retrosynthetic viewpoint, the simplest approach would rely on the generation of the unusual and stereodefined cyclopropyl dianion retron **3** (Scheme 1). We thus became interested in the possibility of generating the bis-stannylcyclopropane **4** and employing it as a synthetic equivalent of dianion **3**. Surprisingly, whilst considerable attention has been devoted to the synthesis and reactivity of mono-stannylated cyclopropanes,[4] there have been few reports on the preparation of three-membered rings analogous to **4**.[5] To the best of our knowledge and despite its synthetic potential, **4** itself is hitherto an unknown compound.

In this communication, we wish to report the straightforward assembly of **4** as well as some of our preliminary

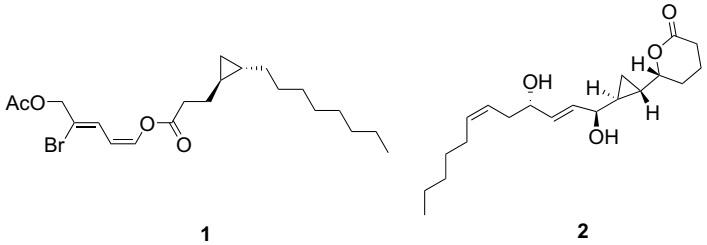

Figure 1.

Keywords: Small ring systems; Tributyltin; Cyclopropanation; Cross-coupling; Lithiation.
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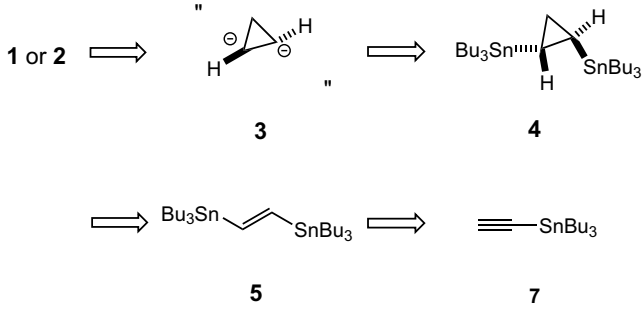


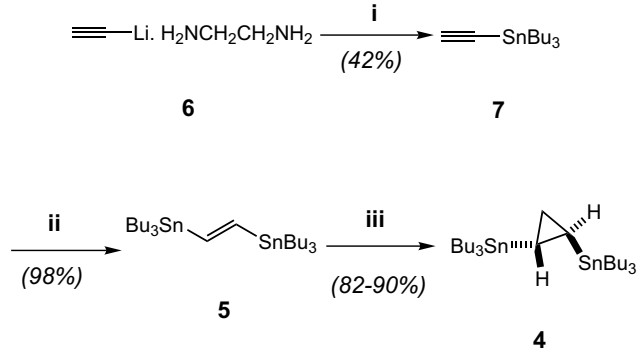
Scheme 1.

results in its subsequent functionalisation and use as a dianion building block equivalent.

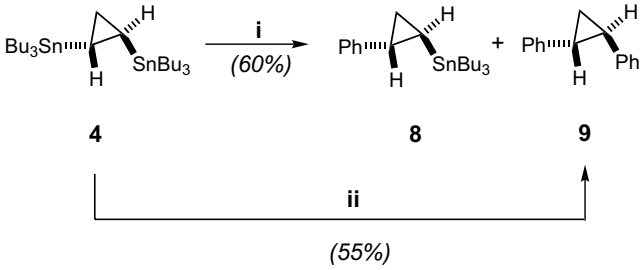
As shown in Scheme 1, our antithetic analysis of **4** revealed that the symmetric *trans*-1,2-bis(tributylstannyl)ethylene **5** would be the substrate of choice. Alkene **5** would itself derive from the readily available alkyne **7**.[6] Accordingly, we prepared *trans*-1,2-bis(tributylstannyl)ethylene **5**, following a two-step procedure reported in the literature (Scheme 2).[7] Addition of the lithium anion of acetylene (ethylene diamine complex) to tributyltin chloride furnished tri-*n*-butylethynylstannane **7** in moderate yields. Subsequent treatment of **7** with tributyltin hydride and AIBN, in a solvent-free procedure, afforded the desired alkene **5** in excellent yield.

The stage was now set for the crucial cyclopropanation step. In connection with our previous studies on the cyclopropanation of vinyl- and dienyl-boronates,[8] we treated *trans*-1,2-bis(tributylstannyl)ethylene **5** with an excess of freshly prepared diazomethane, in the presence of a catalytic amount of palladium(II) acetate.[9] To our delight, *trans*-cyclopropyl stannane **4** was obtained in 82% yield (Scheme 2). It is interesting to note that increasing the scale of this cyclopropanation reaction leads to improved yields.[10]

With a ready access to large quantities of *trans*-cyclopropyl stannane **4**, we next turned our attention to its subsequent, stereocontrolled functionalisation.



Scheme 2. Reagents and conditions: (i) 0.8 equiv Bu_3SnCl, THF, 0 °C to rt; (ii) 1.5 equiv Bu_3SnH, 5 mol% AIBN, 90 °C; (iii) ca. 5 equiv CH_2N_2, 5 mol% $Pd(OAc)_2$, Et_2O, 0 °C to rt.



Scheme 3. Reagents and conditions: (i) 5 mol% $Pd(OAc)_2$, 5 mol% CuI, 15% $AsPPh_3$, 3 equiv LiCl, 1 or 2 equiv PhI, DMF, 80 °C; (ii) 10 mol% $Pd(OAc)_2$, 10 mol% CuI, 30% $AsPPh_3$, 6 equiv LiCl, 4 equiv PhI, DMF, 80 °C.

The elegant contribution of de Meijere and co-workers in the Kosugi–Migita–Stille reaction of cyclopropyl(stannyl)amines attracted our attention, and we decided to apply their optimised conditions to the coupling of cyclopropane **4** with iodobenzene.[11]

The use of such a procedure in the case of **4**, obviously raises the important question of selectivity in the replacement of one of the two tributylstannyl substituents.

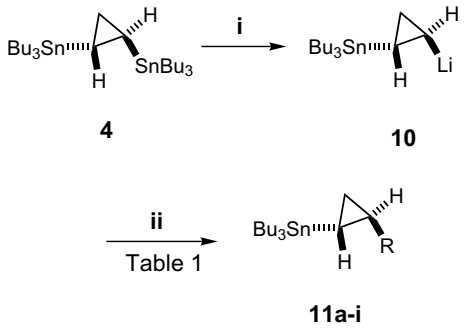
In the event, treatment of cyclopropyl bis-stannane **4** under the de Meijere conditions ($Pd(OAc)_2$, CuI, Ph_3As, LiCl), in the presence of 2 equiv of iodobenzene, led to an inseparable mixture of mono- and bis-substituted cyclopropanes **8** and **9** in 60% yield (Scheme 3). Employing an equimolar amount of iodobenzene did not obviate this problem. However, using 4 equiv of iodobenzene and doubling the catalyst loading afforded exclusively *trans*-1,2-diphenylcyclopropane **9** in 55% isolated yield.

The obvious limitations of this procedure in terms of chemoselectivity prompted us to examine tin–lithium exchange reactions. Such exchange reactions are well-known in the cyclopropane context and overwhelming precedents[4] in the literature point towards retention of stereochemistry in the subsequent capture of the lithium species.[12] Nevertheless, to the best of our knowledge, no report has been published on exchange reactions using di-stannylated substrates such as **4**.

In the event, treatment of **4** with 1.3 equiv of *n*-butyllithium, in anhydrous THF, at −78 °C, gave rise to a deep orange solution of mono-lithiated species **10**. Gratifyingly, anion **10** reacted smoothly with a range of electrophiles (Scheme 4). Some selected examples are displayed in Table 1.

It can be seen from Table 1 that a wide variety of functionalised tributylstannyl cyclopropanes can be prepared by this method in good to excellent yields. In all cases except **11a** (entry 1), the *trans*-disubstituted cyclopropane is obtained exclusively.[13]

Interestingly, only mono-substitution of one of the two tributyltin substituents is observed. The stereocontrolled



Scheme 4. Reagents and conditions: (i) 1.3 equiv *n*-BuLi, THF, −78 °C; (ii) 3–20 equiv electrophile, THF, −78 °C to rt.

formation of new C–C bonds proceeds smoothly and generally in high yields, as exemplified by entries 2, 5, 7 and 9.

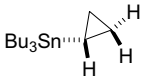
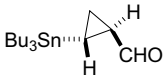
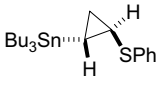
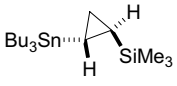
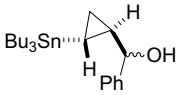
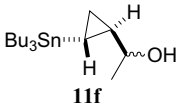
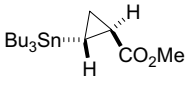
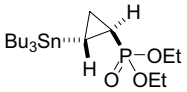
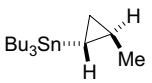
Whilst coupling of anion **10** with benzaldehyde provides the desired adduct **11e** in excellent yield, only a complex mixture of products is obtained when acetaldehyde is employed, probably owing to the basicity of **10** (compare entries 5 and 6).

The stereoselective replacement of one of the two tin residues by a silicon group proceeds quantitatively, affording the interesting cyclopropane **11d** (entry 4).

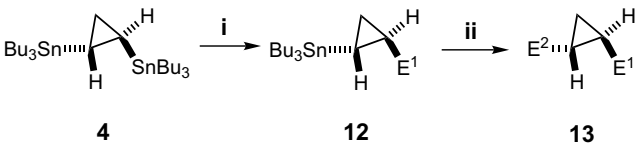
In contrast, only moderate yields of adduct **11c**, bearing a sulfur substituent, have been obtained for the moment (entry 3). No reaction is observed with a phosphorus-containing electrophile (entry 8).

It is interesting to note that the preparation of most of the compounds listed in Table 1 would either be difficult or impossible by direct cyclopropanation of the corresponding alkene or would require a lengthy sequence

Table 1.

Entry	Electrophile	–R	Compound	Yield[a] (%)
1	NH_4Cl aq	–H	 **11a**	>99
2	DMF	–CHO	 **11b**	82
3	$PhSSO_2Ph$	–SPh	 **11c**	37
4	Me_3SiCl	$–SiMe_3$	 **11d**	>99
5	PhCHO	–CH(OH)Ph	 **11e**	81
6	CH_3CHO	$–CH(OH)CH_3$	 **11f**	—[b]
7	$ClCO_2Me$	$–CO_2Me$	 **11g**	64
8	$ClP(O)(OEt)_2$	$–P(O)(OEt)_2$	 **11h**	—[c]
9	CH_3I	$–CH_3$	 **11i**	95

[a] All yields are for pure, isolated products.
[b] A complex mixture of products was obtained.
[c] Compound **11a** was obtained in 75% yield.



Scheme 5. Reagents: (i) (a) *n*-BuLi, THF; (b) E^1–X; (ii) (a) *n*-BuLi, THF; (b) E^2–X.

of synthetic operations.[3,14] The readily available compounds **11a**–**e**,**g** and **11i** clearly constitute highly valuable building blocks in the context of the total synthesis of cyclopropane-containing natural products. For example, the cyclopropyl aldehyde **11b**, which can be 'conventionally' elaborated by directed-cyclopropanation of a suitably functionalised allylic alcohol, followed by oxidation, has been employed by Itoh et al. as an advanced intermediate towards the synthesis of dictyopterene A, an odoriferous marine natural product.[15]

In summary, we have prepared a novel cyclopropyl bisstannane **4** through palladium-catalysed cyclopropanation of the readily available alkene **5**.[16] The synthetic potential of **4** was evaluated, initially by submitting it to a Kosugi–Migita–Stille coupling and subsequently by performing a selective tin–lithium exchange, followed by an electrophilic quench. Whilst the former approach met with limited success, the latter proved to be a fairly general procedure for the preparation of functionalised, *trans*-disubstituted tributylstannyl cyclopropanes. The subsequent replacement of the tributyltin substituent, present in adducts **11**, by various electrophiles has been well described in the literature.[12] The ready availability of cyclopropane **4** provides us, for the first time, with the exciting possibility of generating a range of functionalised *trans*-disubstituted cyclopropanes **13** by the sequential, stereocontrolled substitution of both tin residues (Scheme 5). Further applications of compounds **4** and **11**, including their use as building blocks in the total synthesis of relevant natural products, are currently being pursued in this laboratory. The results of these investigations will be reported in due course.

Acknowledgements

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16. *Typical experimental procedure*: *Preparation of cyclopropane* **4**. To a suspension of *N*-methyl-*N*-nitrosourea (6.3 g, 61.2 mmol, 12 equiv) in dry ether (45 mL), was added 12.3 mL (21.6 equiv) of 50% aq KOH dropwise at 0 °C. After 15 min stirring at this temperature, the yellow organic phase was transferred to a solution of *trans*-1,2-bis(tributylstannyl)ethylene **5** (3.0 g, 5.1 mmol, 1 equiv) and $Pd(OAc)_2$ (57 mg, 0.25 mmol, 5 mol%) in 22.5 mL of dry ether. The resulting dark suspension was stirred at 0 °C for 30 min before being filtered through a pad of Celite. The solvents were evaporated under reduced pressure to

afford the crude product, which was further purified by chromatography (silica gel, petroleum ether) to afford 2.8 g (90%) of cyclopropyl bis-stannane **4**. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = -0.32$ (t, $J = 7.5$ Hz, 1H), 0.56 (t, $J = 7.5$ Hz, 1H), 0.68–0.85 (m, 32H), 1.18–1.30 (m, 14H), 1.37–1.47 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -3.65$, 5.38, 8.68, 13.80, 27.50, 29.32.

Preparation of aldehyde **11b**. In a 25 mL flame-dried round-bottomed flask were introduced 421 mg of cyclopropyl bis-stannane **4** (0.7 mmol, 1 equiv) and 4 mL of dry THF. After cooling to −78 °C, 0.56 mL (0.9 mmol, 1.3 equiv) of *n*-BuLi (1.6 M in hexanes) was added dropwise. The resulting orange suspension was stirred at −78 °C for an additional hour, then 0.5 mL (7.0 mmol, 10 equiv) of DMF was added at once. The resulting clear-yellow solution was stirred for a further 2 h at −78 °C. The reaction was quenched by the addition of 3 mL of H_2O. The organic layer was repeatedly extracted with ether, dried over $MgSO_4$ and the solvents were removed under reduced pressure. The crude aldehyde was purified by chromatography (silica gel, petroleum ether) to afford 205 mg (82%) of pure aldehyde **11b**. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.54$–0.65 (m, 1H), 0.78–0.92 (m, 16H), 0.98–1.1 (m, 1H), 1.22–1.60 (m, 12H), 1.68–1.76 (m, 1H), 8.53 (d, 1H, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 1.87$, 8.86, 11.21, 13.72, 26.92, 27.33, 29.13, 201.24.