Original Syntheses of Arylcycloalkanes

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Arylcycloalkanes have been prepared from acetophenone by a three-step sequence involving the synthesis of α-phenyl(ω-alkenyl)methylselenides and their reaction with butyl-lithium reagents to give an intermediate which adds across the C=C double bond to give 2-methyl-2-phenylcycloalkylmethyl-lithiums with stereocontrol; other syntheses of these compounds are also described.

Intramolecular reactions involving olefins have recently played an increasingly important role in organic synthesis.[1] Although most of the earlier examples have been concerned with the ene reaction[2] (especially the thermolysis of 1,6-dienes) and with catalysed polyolefinic cyclizations,[3] more recent results include intramolecular versions of the Diels–Alder[4] and [2 + 2] cycloaddition[5] reactions as well as ring closure involving ω-alkenyl radicals[6,7] and ω-alkenyl metal derivatives.[8] The last reaction is however the least documented one.[8—12] It often requires quite drastic experimental conditions[8—12] [ether or tetrahydrofuran (THF) reflux for several hours] and in several instances it has been carried out to gain some insight into the intimate mechanism of the halogen–metal exchange reaction,[9,10] especially for discriminating between an ionic process or a stepwise electron transfer. These reactions have not been widely used in synthesis apart from those involving allylic Grignard reagents which are believed to take place *via* an ene concerted mechanism[2] and which have found wide application in the synthesis of natural products.[12] We now report that α-phenyl(ω-alkenyl)methylselenides, readily available[13] from aromatic carbonyl compounds and ω-halogeno alkanes, cyclize very efficiently on reaction with alkyl-lithiums[13,14] or tin hydrides.[6b,7]

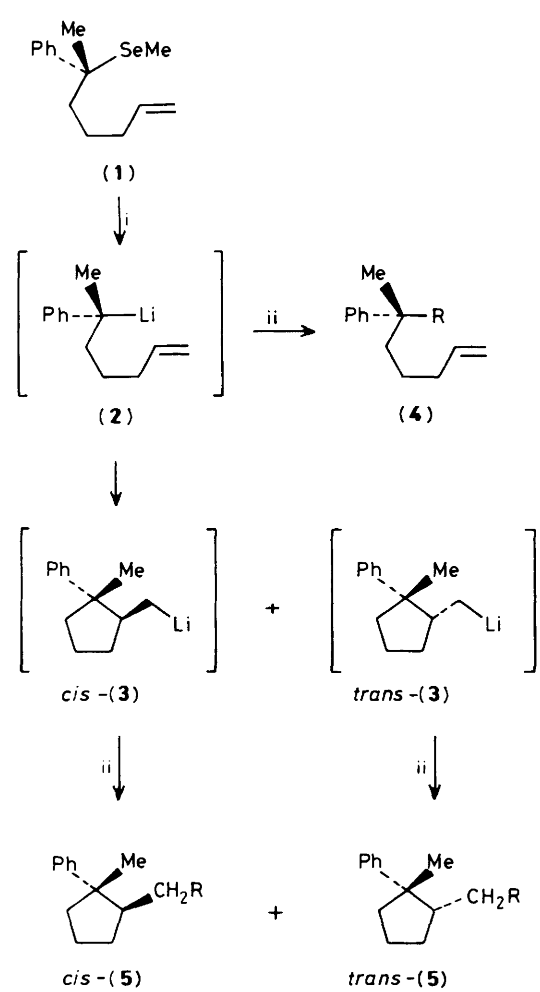
The first of these reactions, carried out at −78 °C in THF–hexane, between 6-methylseleno-6-phenylhept-1-ene (**1**) and n-butyl-lithium takes place so rapidly that the C–Se bond cleavage leading to 6-lithio-6-phenylhept-1-ene (**2**) and its cyclization to (2-methyl-2-phenyl)cyclopentylmethyl-lithium (**3**) is already complete after 0.3 h. Quenching this reaction mixture with methanol or benzaldehyde at −78 °C produces 1,2-dimethyl-1-phenylcyclopentane (**5a**, R = H) or the derived alcohol (**5b**, R = PhCHOH) in good yield (Scheme 1; Table 1, entries 1 and 2).

The whole process is so efficient that it takes place even when a catalytic amount of n-butyl-lithium is used (0.1 equiv. Bu^{n}Li, THF, −78 °C, 0.3 h). Under these conditions 1-methyl-1-phenyl-2(methylselenomethyl)cyclopentane (**6**) is

Table 1. Cyclisation of α-phenyl(ω-alkenyl)methylselenides with alkyl-lithiums.[a]

Entry	Conditions: reactants, temperature/°C, time/h	(**4**) (Yield/%)	(**5**) (Yield/%; *cis* : *trans* ratio)
1	i, Bu^{n}Li, THF–hexane, −78, 0.5; ii, MeOH, −78	—	(**5a**) (85; 98 : 2)
2	i, Bu^{n}Li, THF–hexane, −78, 0.3; ii, PhCHO, −78	—	(**5b**) (60; 95 : 5)[b]
3	i, Bu^{t}Li, diethyl ether–hexane, −110, 0.3; ii, MeOH, −110	(**4a**) (97)[c]	(**5a**) (3; 100 : 0)[c]
4	i, Bu^{t}Li, diethyl ether–hexane, −78, 0.3; ii, MeOH, −78	(**4a**) (75)[c]	(**5a**) (25; 75 : 25)[c]
5	i, Bu^{t}Li, diethyl ether–hexane, −78, 7; ii, MeOH, −78	(**4a**) (6)[c]	(**5a**) (94; 75 : 25)[c]
6	i, Bu^{t}Li, diethyl ether–hexane, −30, 0.3; ii, MeOH, −30	—	(**5a**) (85; 2 : 98)
7	i, Bu^{t}Li, diethyl ether–hexane, −30, 0.3; ii, PhCHO, −30	—	(**5b**) (78; 5 : 95)[b]
8	i, Bu^{t}Li, diethyl ether–hexane, −78, 7; ii, −78 to −30, 0.5; iii, −30, 0.3; iv, MeOH, −30	(**4a**) (4)[c]	(**5a**) (96; 65 : 35)[c]

[a] See Scheme 1. [b] Isolated as a 60 : 40 mixture of two stereoisomers, isomeric at the benzylic alcohol carbon. [c] Yields refer to g.c. results.

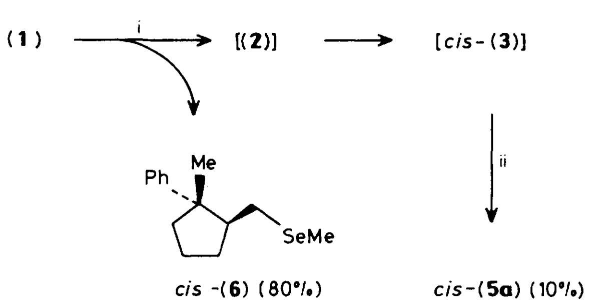


a; R = H
b; R = PhCHOH

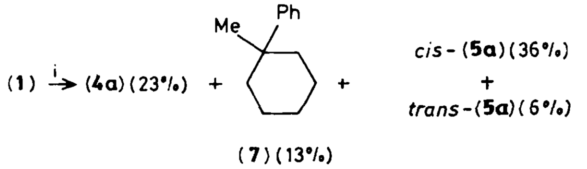
Scheme 1. *Reagents and conditions* (see Table 1): i, BuLi, THF–hexane or diethyl ether–hexane, −110 to −30 °C; ii, MeOH or PhCHO, −110 to −30 °C.

rapidly produced in very good yield (80%). Its formation has been rationalized (Scheme 2) as a chain process in which 2-methyl-2-phenylcyclopentylmethyl-lithium (**3**), initially formed, cleaves the C–Se bond of (**1**) simultaneously producing (**6**) and regenerating (**2**) which propagates the chain process.

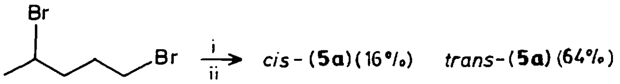
The selenide (**1**) was also treated with t-butyl-lithium in diethyl ether–hexane. Under these conditions the C–Se bond cleavage occurs at −110 °C (Table 1, entry 3) but the cyclization of the resulting benzyl-lithium does not occur to a significant extent. It takes place slowly (7 h) at −78 °C (Table 1, entries 4 and 5) but occurs rapidly at −30 °C producing, after quenching with methanol or benzaldehyde, (**5a**) and (**5b**) in 85% and 78% yields, respectively (Table 1, entries 6 and 7).



Scheme 2. *Reagents and conditions:* i, Bu^{n}Li (0.1 equiv.), THF–hexane, −78 °C, 0.3 h; ii, MeOH, −78 °C.



Scheme 3. *Reagents and conditions:* i, Bu$_3$SnH (1 equiv.), AIBN (0.2 equiv.) in benzene [0.006 M in (**1**)]. Use of a more concentrated solution (0.25 M) gave (**4a**) as the sole product (85%).



Scheme 4. *Reagents and conditions:* i, MeC(SeMe)(Li)Ph, THF–hexane, −78 °C, 0.5 h; ii, Bu^{n}Li THF–hexane, −78 to −30 °C, 0.5 h. Overall yield 80%, *cis* : *trans* ratio 20 : 80.

The most exciting observation is that complete control of the stereochemistry between the substituents of the cyclopentane derivatives† can be achieved by proper choice of the experimental conditions. Thus whereas compound (**5a**) bearing two methyl groups in the *cis* position is exclusively produced [diastereoisomeric excess (d.e.) 96%] when the reaction is performed at −78 °C in THF–hexane (Table 1, entry 1), its stereoisomer is stereoselectively (d.e. 96%) formed when the reaction is carried out in diethyl ether–hexane at −30 °C (Table 1, entry 6). We found that in diethyl ether, the ratio between the two stereoisomers is highly dependent upon the reaction temperature (Table 1, entries 3,4, and 6). In this solvent the reaction seems to be kinetically controlled since the *cis* : *trans* ratio for (**5a**) remains almost identical when the reaction mixture is quenched at −78 °C after 0.3 or 7 h (entries 4 and 5) (*cis* : *trans* ratio 75 : 25) or when (entry 8) it is allowed to reach −30 °C and then maintained at this temperature for 0.3 h prior to quenching (*cis* : *trans* ratio 65 : 35). These results clearly differ from those obtained in the same solvent for the same time at −30 °C throughout (entry 6), which produces the two stereoisomers of (**5a**) in a completely different ratio (*cis* : *trans* ratio 2 : 98).

Little is known about the stereochemical outcome and control of such reactions. Kinetic/thermodynamic control has been achieved[8b] in an allylic Grignard ene reaction by altering the reaction temperature but such control could not be extended[8a] to the Grignard reagent derived from 6-chlorohept-1-ene which exclusively produced *trans* 1,2-dimethylcyclopentane whatever the conditions used.

In the course of this work we have also prepared 1,2-dimethylcyclopentane by other routes but none of them proved as versatile as the one reported. For example, (**1**) was cyclized [tributyltin hydride (1 equiv.), azobisisobutyronitrile (AIBN) (0.006 M), benzene] (Scheme 3) to an intractable

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† The ^{1}H n.m.r. spectrum of *cis*-(**5a**) exhibits *inter alia* peaks at δ 0.82, (d, *J* 7 Hz, 3H, CHMe), 1,16 (s, 3 H, PhCMe); *trans*-(**5a**) presents peaks at δ 0.53 (d, *J* 7 Hz, 3H, CHMe), 1.26 (s, 3H, PhCMe). These structures have been established on the basis of COSY and 2D n.m.r. experiments.

mixture of 1-methyl-1-phenylcyclohexane (**7**) and (**5a**) (*cis* : *trans* ratio 85 : 15) whereas sequential treatment of 1,4-dibromopentane in THF–hexane with 1-lithio-1-methyl-1-phenyl-selenoethane then with n-butyl-lithium (1 equiv. each) at −78 °C provided (**5a**) (*cis* : *trans* ratio 20 : 80) in 80% overall yield (Scheme 4).‡ 6-Methylseleno-6-phenylhex-1-ene and 7-methylseleno-7-phenyloct-1-ene also react with Bu^nLi in THF–hexane. The cyclization takes place at −30 °C instead of −78 °C and produces, after methanolysis at −30 °C, 1-methyl-2-phenylcyclopentane and 1,2-dimethyl-1-phenylcyclohexane (**5a**) in 70% and 80% yield, respectively.§

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‡ Addition of 1,4-dibromopentane to 1-lithio-1-methyl-1-phenylselenoethane changes the course of the reaction, giving 2,7-(dimethylseleno)-2,7-diphenyl-3-methyloctane (78% based on the dibromide used).

§ The stereochemical outcome of these reactions has not yet been established.