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Comparative Study of Anionic and Radical Cyclization for the Preparation of 1,3-Dimethylindans: Highly Stereoselective Preparation of *cis*-1,3-Disubstituted Indans via Intramolecular Carbolithiation

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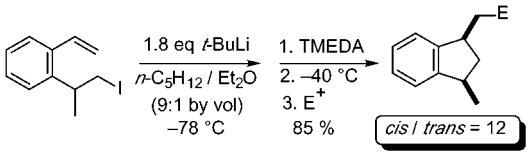
ABSTRACT



The preparation of 1,3-dimethylindans from 4-(2-bromophenyl)-1-pentene (1) and 2-(2-iodo-1-methylethyl)styrene (2) substrates via radical-mediated cyclization and intramolecular carbolithiation has been investigated. Although cyclization of the radical derived from either substrate proceeds with modest selectivity for the cis-isomer, as does cycloisomerization of the aryllithium derived from substrate 1 (cis/trans ≈ 2), intramolecular cyclization of the alkyllithium derived from substrate 2 is a highly cis-selective process (cis/trans = 12).

The 1,3-disubstituted indan skeleton is found in a variety of natural products,[1] and it was of interest to inquire whether either anionic[2,3] or radical-mediated[4] cyclization strategies might provide a useful stereoselective route to such structures. In this connection, it is of interest to note that Beckwith and Gerba reported some time ago that cyclization of the aryl radical derived from 4-(2-bromophenyl)-1-pentene (**1**) afforded an approximately 2:1 ratio of *cis*- and *trans*-1,3-dimethylindan (Scheme 1).[5]

In light of the fact that kinetically controlled cycloisomerization of an unsaturated organolithium is often more stereoselective than is the radical-mediated cyclization of a given substrate,[6] the cycloisomerization of the aryllithium generated from **1** by low-temperature bromine−lithium exchange[7] was investigated. As summarized in Scheme 1, the aryllithium cyclizes cleanly in the presence of TMEDA upon warming to room temperature for 1 h, but the

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(1) For example, the trikentrins, mutisianthol, and jungianol contain a 1,3-disubstituted indan core. See, for example: (a) Capon, R. J.; MacLeod, J. K.; Scammells, P. J. *Tetrahedron* **1986**, *42*, 6345. (b) MacLeod, J. K.; Monahan, L. C. *Aust. J. Chem.* **1990**, *43*, 329. (c) Lee, M.; Ikeda, I.; Kawabe, T.; Mori, S.; Kanematsu, K. *J. Org. Chem.* **1996**, *61*, 3406. (d) Ho, T. L.; Lee, K. Y.; Chen, C. K. *J. Org. Chem.* **1997**, *62*, 3365.

(2) For a review, see: Bailey, W. F.; Ovaska, T. V. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI Press: Greenwich, CT, 1994; Vol. 3, p 251−273.

(3) While the cycloisomerization of an unsaturated organolithium is often termed an "anionic" cyclization, it is important to note that the lithium atom is intimately involved in the process; 5-hexenyllithium is unique among the 5-hexenylalkalis in it ability to undergo facile cyclization. See: Bailey, W. F.; Punzalan, E. R. *J. Am. Chem. Soc.* **1994**, *116*, 6577.

(4) (a) Giese, B. *Radicals in Organic Synthesis*; Pergamon: New York, 1986. (b) Curran, D. P. *Synthesis* **1988**, 417 and 489. (c) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969. (d) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: New York, 1995.

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(7) Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404.

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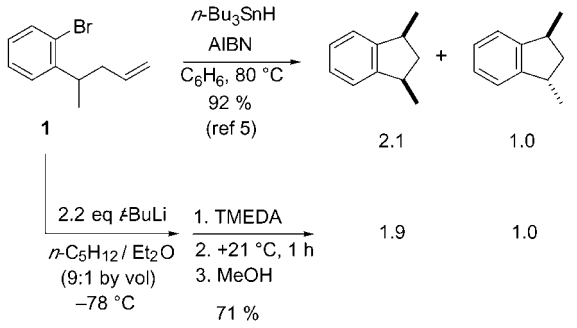
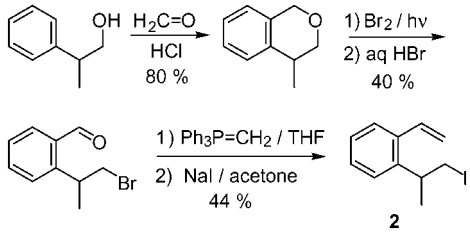
Scheme 1



isomerization is no more stereoselective than is the radical-mediated process.

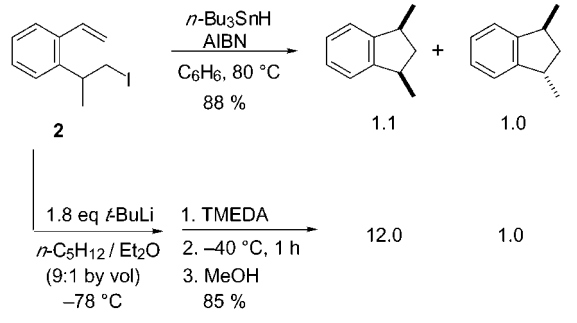
An alternative route to the 1,3-dimethylindan skeleton, involving cyclization of the styrene-tethered primary radical or alkyllithium derived from 2-(2-iodo-1-methylethyl)styrene (**2**), was also investigated. Substrate **2** was prepared in straightforward fashion, albeit in moderate overall yield, as depicted in Scheme 2.

Scheme 2



The radical-mediated cyclization of **2**, which has not been previously reported, proceeded in a 5-exo fashion, as shown in Scheme 3, to afford an approximately 1:1 mixture of *cis*-

Scheme 3



and *trans*-1,3-dimethylindan in 88% yield. The highly regioselective 5-exo closure of the primary radical generated from **2** is consistent with kinetic data demonstrating a preference for this mode of cyclization by the parent 2-(2-vinylphenyl)ethyl radical.[8] The essentially stereorandom course of the radical-mediated isomerization of **2** stands in sharp contrast to the highly cis-stereoselective cycloisomerization of the alkyllithium derived from **2**.

As illustrated in Scheme 3, 2-(2-vinylphenyl)propyllithium (**3**), generated from **2** by lithium−iodine exchange,[7] cyclizes in an exclusively 5-exo fashion at −40 °C in the presence of TMEDA to give a 12:1 mixture of *cis*- and *trans*-1,3-dimethylindan in 85% yield following quench of the organolithium product with MeOH. It might be noted that cyclization of **3** may also be effected in the absence of TMEDA with equally high selectivity for the cis-isomer (cis/trans ≈ 13), but in this case, the reaction requires warming at room temperature for 1 h to complete the isomerization. The highly stereoselective nature of this anionic approach to *cis*-1,3-disubstituted indans is unprecedented, and it raises an obvious question: what is the etiology of the substantial cis-selectivity?

In an effort to identify the factors responsible for the observed cis-selective cyclization of 2-(2-vinylphenyl)-propyllithium (**3**), the reaction was investigated computationally by ab initio methods at the B3LYP/6-311+G* level.[9] At the outset it was anticipated that the cyclization of **3** would proceed from a ground-state structure in which the lithium atom is coordinated intramolecularly to the remote vinyl group as is observed in the 5-exo closure of the parent 5-hexenyllithium.[6,10] Since the faces of the π-bond in **3** are diastereotopic, there are two Li−π coordinated structures to consider: viz., that leading to the *trans*-product (*trans*-**3** complex) and that leading to the *cis*-product (*cis*-**3** complex). The optimized B3LYP/6-311+G* structures of these intramolecularly coordinated organolithiums are depicted in Figure 1, and their energies, corrected for zero point energy and the change in enthalpy or free energy on going from 0 K (corresponding to the calculation) to room temperature, are summarized in Table 1.

Transition states for the cyclization (*trans*-**3** TS and *cis*-**3** TS) were located at the B3LYP/6-311+G* level using the synchronous transit-guided quasi-Newton method of Schegel et al.[11] The optimized transition state geometries are shown in Figure 1, and their energies are listed in Table 1. The structures (Figure 1) and energies (Table 1) of the organolithium products were obtained in a similar fashion; the *trans*-product is computed to be more stable than the *cis*-product by approximately 1 kcal/mol.

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Table 1. Calculated B3LYP/6-311+G* Energies of 2-(2-Vinylphenyl)propyllithium (**3**) Depicted in Figure 1[a]

compound	energy	ZPE[b]	H_{corr}[c]	G_{corr}[c]	$S°$ [d]	$\Delta H°_{rel}$	$\Delta G°_{rel}$	$\Delta H^{‡}$	$\Delta G^{‡}$
trans-**3** complex	−434.57443	129.27	−434.35593	−434.40460	102.4	0.00	0.00		
cis-**3** complex	−434.56709	129.15	−434.34853	−434.39794	104.0	4.64	4.18		
trans-**3** TS	−434.56249	128.82	−434.34562	−434.39307	99.8	0.86	0.69	6.46	7.24
cis-**3** TS	−434.56376	128.78	−434.34699	−434.39417	99.3	0.00	0.00	0.97	2.37
trans-product	−434.59613	130.15	−434.37667	−434.42516	102.1	0.00	0.00		
cis-product	−434.59451	130.21	−434.37487	−434.42365	102.7	1.13	0.95		

[a] Total energies in hartrees (H); other energies in kcal/mol (1 H = 627.51 kcal/ mol). [b] Zero point energies in kcal/mol derived from B3LYP calculation. [c] Corrected for both ZPE and the change in enthalpy or free energy on going from 0 K (corresponding to the calculations) to 298 K. [d] Calculated entropy in cal/mol·deg.

Cursory inspection of the data summarized in Table 1 indicates that the intramolecularly coordinated ground-state structure leading to the experimentally observed *cis*-1,3-dimethylindan (*cis*-**3** complex) is considerably less stable than is the *trans*-**3** complex leading to the *trans*-product ($\Delta\Delta H$ = 4.64 kcal/mol, $\Delta\Delta G$ = 4.18 kcal/mol). The origin of this sizable energy difference appears to be largely steric. There are a number of short, nonbonded hydrogen−hydrogen and carbon−hydrogen interactions present in the *cis*-**3** complex that serve to raise its energy relative to the alternative complex; the corresponding distances in *trans*-**3** complex are somewhat longer.[12] Significantly, the repulsive steric interactions that beset the *cis*-**3** complex are largely relieved on going to the transition state depicted in Figure 1. Indeed, the *cis*-**3** TS is computed to be more stable than the *trans*-**3** TS (Table 1; $\Delta\Delta H$ = 0.86 kcal/mol, $\Delta\Delta G$ = 0.69 kcal/mol).

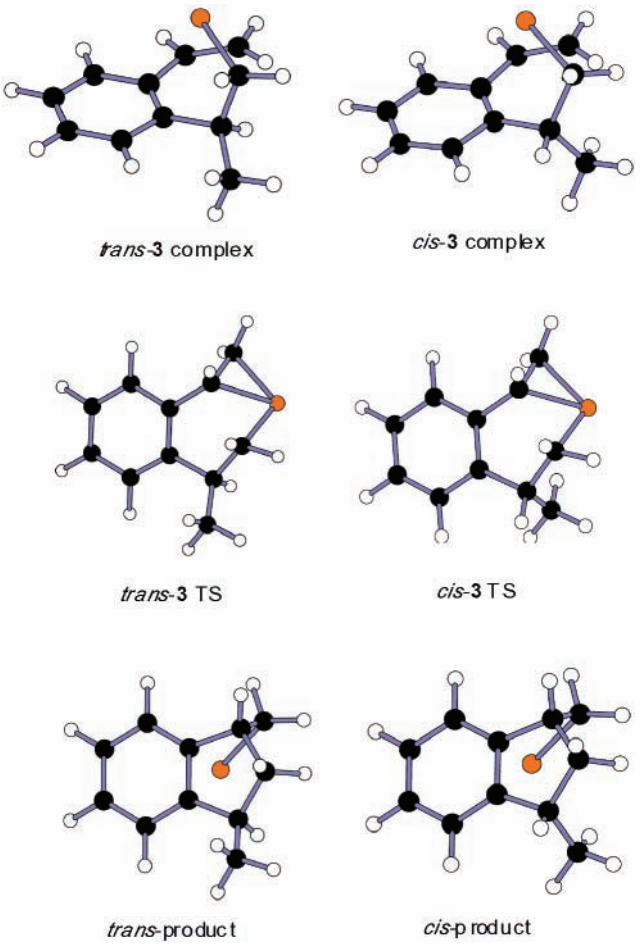
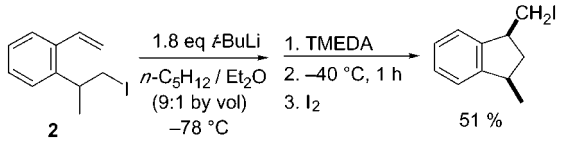


Figure 1. B3LYP/6-311+G* structures of the ground states, transition states, and products for cyclization of 2-(2-vinylphenyl)-propyllithium (**3**).

The results of this computational analysis of the cyclization of **3** provide a compelling rationale for the highly cis-selective nature of the process. The computed activation free energy for cyclization from the lower energy *trans*-**3** complex to give the *trans*-product (Table 1, $\Delta G^{‡}$ = 7.24 kcal/mol) is considerably higher than is the activation energy required to deliver the *cis*-product. The *cis*-**3** complex, which lies some 4.18 kcal/mol higher in free energy than the *trans*-**3** complex, is calculated to require an activation free energy of only 2.37 kcal/mol for cyclization to the *cis*-product. On the reasonable assumption that the *trans*-**3** complex and the *cis*-**3** complex are in equilibrium, the $\Delta G^{‡}$ for cyclization from the lower energy intramolecularly coordinated ground state (*trans*-**3** complex) to deliver the *cis*-product via the *cis*-**3** TS would require 6.55 kcal/mol (i.e., 4.18 + 2.37 kcal/mol). Given the fact that the cycloisomerization of **3** is modeled in the computational study by gas-phase species, the computed $\Delta\Delta G^{‡}$ of 0.69 kcal/mol favoring formation of a *cis*-1,3-dimethylindan is fully in accord with the high cis-selectivity observed experimentally.[13]

It should be noted that, although MeOH was used to quench reaction mixtures in the exploratory phase of this study (Scheme 3), the product organolithium may be trapped with any of a variety of electrophiles. For example, as illustrated in Scheme 4, isomerically pure *cis*-1-iodomethyl-3-methylindan may be prepared in 51% isolated yield by trapping the cyclization product with iodine.

Scheme 4



In summary, although radical-mediated cyclization of either 4-(2-bromophenyl)-1-pentene (**1**) or 2-(2-iodo-1-methylethyl)styrene (**2**) proceeds with, at best, modest cis-selectivity, intramolecular carbolithiation of the alkyllithium (**3**) derived from **2** provides an experimentally convenient and highly stereoselective route to the *cis*-1,3-disubstituted indan skeleton.

(12) The calculated atomic coordinates for the structures depicted in Figure 1 are given in Table S1 of Supporting Information.

(13) It might be noted that the computed $\Delta\Delta G^{\ddagger}$ of 0.69 kcal/mol is equivalent at −40 °C to a product ratio of approximately 5:1 favoring the *cis*-isomer.

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Supporting Information Available: Detailed experimental procedures and calculated atomic coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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