# Use of Aromatic Radical-Anions in the Absence of THF. Tandem Formation and Cyclization of Benzyllithiums Derived from the Attack of Homo- and Bishomoallyllithiums on α-Methylstyrenes: Two-Pot Synthesis of Cuparene[1]

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**Abstract:** When a homo- or bishomoallyllithium, generated by reductive lithiation of the corresponding phenyl thioether by the radical anion lithium 1-(dimethylamino)naphthalenide (LDMAN), is added to α-methylstyrene, a tandem addition/cyclization to a phenyl-substituted five- or six-membered-ring occurs. The yields are compromised by polymerization of the α-methylstyrene, a process favored by tetrahydrofuran (THF), the solvent used to generate lithium aromatic radical anions. Thus, a new method of generating LDMAN (unsuccessful for other common radical anions) in the absence of THF has been developed. The radical anion can be generated and the reductive lithiation performed in dimethyl ether at −70 °C. After the addition of diethyl ether or other solvent, and evaporation of the dimethyl ether in vacuo, the α-methylstyrene is added and the solution is warmed to −30 °C. When the unsaturated alkyllithium is primary, no adduct forms in THF due to polymerization of the α-methylstyrene, but moderate yields are attained in a solvent containing mainly hexanes. It was also found that the cyclized organolithiums, which would have become protonated in the presence of THF, can be captured by an electrophile, even at ambient temperature. A two-pot synthesis, the most efficient reported, of the sesquiterpene (±)-cuparene in 46% yield, using this technology is reported.

Since its discovery in 1978,[2] the reductive lithiation of phenyl thioethers with aromatic radical-anions in tetrahydrofuran (THF) has become recognized as one of the most general methods of organolithium production (Scheme 1).[3,4] Its great versatility has been demonstrated repeatedly. For example, it is one of the rare methods, and a particularly general one, for the production of tertiary organolithiums[5,6] and, unlike deprotonation and related methods involving electrophile removal,[7] $sp^3$ organolithiums are generated substantially more rapid than the more stable $sp^2$ organolithiums.[8,9]

A number of somewhat less versatile[10] synthetic methods also depend on reductive lithiation with aromatic radical-anions.[11] These include the reduction of organic halides,[12] sulfones,[13] sulfates,[14] nitriles,[15] selenides;[16] allylic and benzylic ethers,[17,18] sulfides,[19] amines,[19] and acetals;[20] small ring heterocycles[21] such as epoxides,[22] oxetanes,[23] and tetrahydrofurans,[18,24] and their amine and thioether analogues;[21] and carboxylic acids,[25] esters,[26] and certain ketones.[27]

One of the few weaknesses of these methods is the necessity of using THF as the solvent. No other solvent has been successful for the generation of the aromatic radical-anions with lithium counterions. We and others have often found THF to be detrimental to the optimum utilization of reductive lithiation.

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[1] Taken in part from the M.S. thesis of X. Liu, University of Pittsburgh, 1999. A preliminary report of some of this work has appeared: Liu, X.; Kulkarni, V.; Cohen, T. *Book of Abstracts*; 219th National Meeting of the American Chemical Society, San Francisco, March 26−30, 2000; American Chemical Society: Washington, DC, 2000; ORGN-630.

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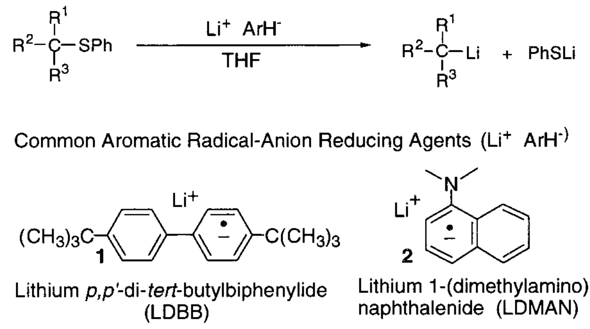
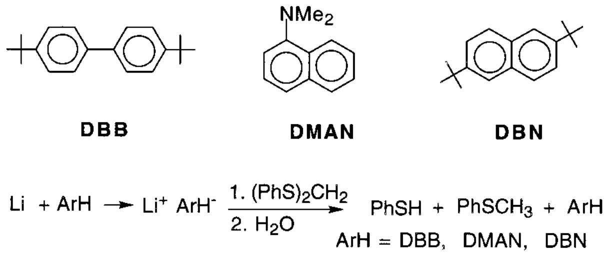
The ability of organolithiums to remove a proton from the 2-position of THF is sometimes a major problem especially for the more basic organolithiums or at temperatures above about 0 °C.[5,28–30] In other cases, as in that described below of the cyclization of benzyllithiums which were generated by attack of homo- and bishomoallyllithiums on α-methylstyrene, the presence of THF encourages an unwanted side reaction. Thus, it was deemed desirable to find an alternative solvent in which radical-anions could be generated and which could either be used for the subsequent reactions or be readily replaced by suitable solvents.

**Scheme 1**



**Scheme 2**



## Generation of a Lithium Aromatic Radical-Anion in the Absence of THF

In preliminary experiments, the formation of several lithium radical-anions, lithium *p,p′*-di-*tert*-butylbiphenylide (LDBB),[31] lithium 1-(dimethylamino)naphthalenide (LDMAN),[32] and lithium 2,6-di-*tert*-butylnaphthalenide (LDBN), in a variety of solvents other than THF was studied in an attempt to find such a solvent and the proper radical-anion. Bis(phenylthio)methane was used as a reductive lithiation substrate to estimate the approximate yields of radical-anions in a specified solvent by noting when during addition of the thioacetal the color of the radical-anion disappeared (Scheme 2).

Attempted generation of LDBB in other solvents, by stirring a suspension of lithium wire cuttings and DBB together in the selected solvent, was unsuccessful (Table 1). When diethyl ether was used, no radical-anion was formed even at ambient

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(10) The superior versatility of compounds containing the phenylthio group as substrates for reductive lithiation arises from their almost unique ease of construction, particularly by methods involving C–C bond formation but also by the ability of the phenylthio group to enter a molecule as a nucleophile, electrophile, or radical. In addition, the substrates are almost always able to withstand the powerful nucleophiles/bases that are present in the reductive lithiation conditions. For example, alkyl halides, sulfates, sulfonates, etc. (see below) are subject to ready nucleophilic substitution, but most seriously to base-induced elimination, thus limiting their use largely to the preparation of primary alkyllithiums unless an aryl or vinyl group is present to increase the rate of the reductive lithiation and favor it over competing processes.

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**Table 1.** Radical-Anion Formation in THF and in Diethyl Ether

| SM | radical-anion | in THF | in diethyl ether |
|---|---|---|---|
| DBB | LDBB **1** | generated at 0 °C, dark blue solution | no reaction, even at ambient temperature[a] |
| DMAN | LDMAN **2** | generated at −45 °C, dark green solution | no reaction until 0 °C at which temperature LDMAN decomposes |
| DBN | LDBN | generated at 0 °C, dark green solution | generated at 0 °C, a deep purple solution; only 20−30% yield. |

[a] LDBB was also prepared in 1,2-dimethoxyethane in less than 10% yield.

temperature. In 1,2-dimethoxyethane, the radical-anion LDBB did indeed form (the solution was dark-blue, a color indicative of a radical-anion[33]), but the yield was very low. The dark-blue color disappeared when less than 10% of 1 equiv of bis(phenylthio)methane was added.

DBN turned out to be a better radical-anion precursor. When it was treated with metallic lithium in diethyl ether at 0 °C, a deep-purple solution was obtained, but once again the yield (20−30%) was far from being practically useful.

DMAN also failed to produce radical-anion **2** in diethyl ether. A reddish solution was formed by mixing lithium and DMAN together in diethyl ether at 0 °C (below this temperature, there was no reaction as indicated by the color of the solution). The red color was completely different from the dark-green color of LDMAN formed in THF. We interpret this experiment as follows: the radical-anion LDMAN was produced at 0 °C in diethyl ether, but it was unstable at this temperature and decomposed rapidly, as found previously.[32] The decomposition product, 1-lithionaphthalene, is very probably the source of the red color.

After attempts to generate radical-anions in common solvents failed, we turned our attention to dimethyl ether which has not been widely used in synthesis. This solvent was expected to display behavior similar to that of THF since, as in THF, its oxygen atom is more exposed than that of diethyl ether and thus dimethyl ether should be more effective at solvation of the lithium ion. An added advantage of dimethyl ether was that because of its low boiling point it could be readily removed after reductive lithiation and be replaced by the desired solvent. All three aromatic compounds were tried and the results are listed below:

**Li + DBB:** There was no reaction in dimethyl ether at − 30 °C. LDBB is universally generated in THF at ambient temperature and its formation in dimethyl ether may require a higher temperature than is allowed by its boiling point, −22 °C.

**Li + DBN:** A deep-purple solution was generated at −30 °C, but the color disappeared after the addition of one drop of thioacetal solution. Again, it is conceivable that if a higher temperature were possible in dimethyl ether the radical-anion would be generated.

**Li + DMAN:** A dark-green solution was formed at −70 °C and initial experiments indicated a 60−70% yield in its formation. In the original work on LDMAN,[32] it was determined that it could be formed at −45 °C and that indeed it could not be used very much above that temperature due to decomposition to 1-lithionaphthalene. In that work, it was also found that if it was desired to use DMAN at a higher temperature, it could be successfully done by using a catalytic quantity of the aromatic and a stoichiometric amount of lithium. Presumably, under these conditions, the concentration of the putative unstable intermediate, the aromatic dianion, never becomes significant.[32]

The LDMAN case thus appeared to be promising. In a series of experiments it was found that the yield of LDMAN in dimethyl ether could reach as high as 80%. Furthermore, the subsequent reductive lithiation reaction was successful in this solvent. After reductive lithiation, if the subsequent reaction required the absence of dimethyl ether, then a desired solvent was added and a vacuum was applied to remove dimethyl ether at a very low temperature: −60 °C or lower was used to the prevent organolithiums from being protonated by dimethy ether or rearranging at higher temperatures.

The color of LDMAN in dimethyl ether is dark green. It is always contaminated by a red color that is assumed to be the color of the decomposition product 1-lithionaphthalene. A lower temperature was used in dimethyl ether (−70 °C) than in THF (−45 °C) for the generation of LDMAN to suppress the decomposition of the resulting radical-anion. Surprisingly, prolonged reaction times did not seem to be necessary: usually 5−6 h appeared to be long enough even at that low temperature. When vacuum is applied to remove dimethyl ether, great care must be taken to avoid air being sucked into the reaction system. Organolithiums in a variety of solvents could thus be generated by the following typical procedure: (1) generation of LDMAN in dimethyl ether; (2) reductive lithiation of thioethers at −78 °C; (3) addition of the desired solvent for the subsequent reaction; and (4) removal of dimethyl ether under reduced pressure.

An example of the utility of this procedure is given below. For another example, see ref 34.

## Tandem Formation and Cyclization to Five- and Six-Membered Rings of Benzyllithiums

Unlike allylic organolithiums,[30b,35] benzylic organolithium compounds have found relatively few synthetic applications. This is certainly due in part to the difficulties encountered in their preparation by the usual methods of organolithium production.[36] Krief's group has prepared benzylic organolithiums by Se−Li exchange.[37] A potentially useful method of production of benzyllithiums, because it is connective, is the addition of organolithiums to styrenes.[38] However, the anionic polymerization of styrene and its derivatives with organolithiums is a well-known process.[39] Nevertheless, there are some successful cases in which styrene and its alkenyl-substituted derivatives can undergo synthetically useful organolithium addition reactions, although it is usually necessary to optimize the choice of reaction conditions to minimize oligomerization.[40] Fraenkel found that a variety of α-methylstyrenes can undergo nearly

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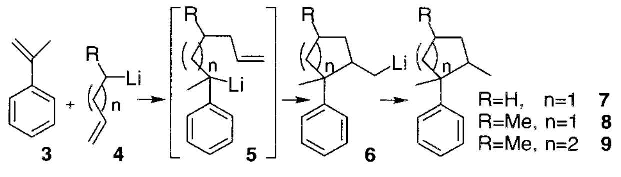
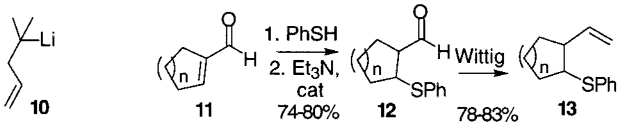
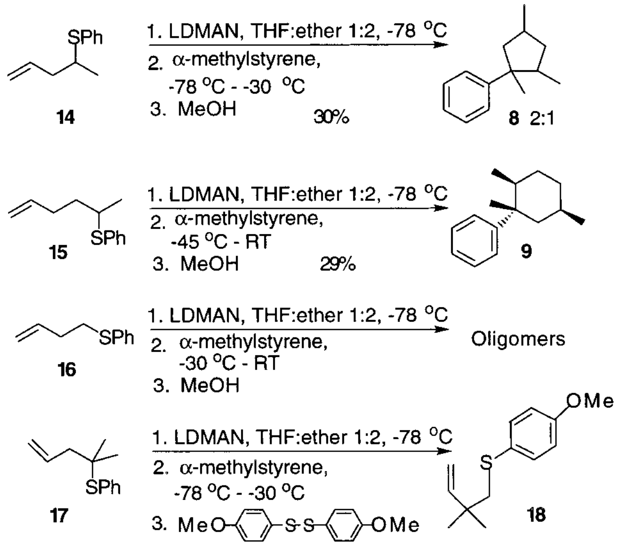
**Scheme 3**



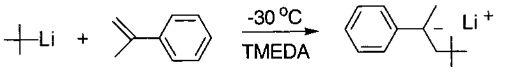
**Scheme 4**



**Scheme 5**



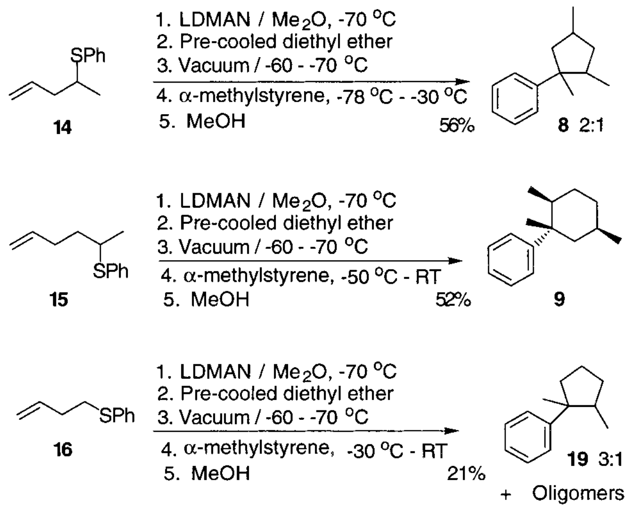
quantitative 1:1 addition with *tert*-butyllithium in isooctane–*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (eq 1).[40b]



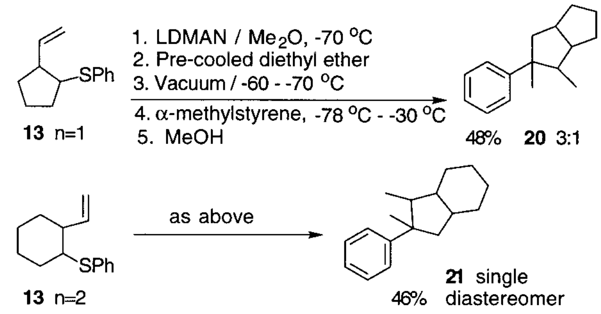
(1)

When *n*-butyllithium was added to α-methylstyrene, both 1:1 adduct and polymer were detected.[40] This result is not surprising since polymerization of the α-methylstyrene is the competing side reaction. For *n*-butyllithium, the rate of the addition step (known as the initiation step) is slower than that of the propagation step and hence formation of oligomers results along with the 1:1 adduct. Since with secondary and tertiary organolithium compounds, the initiation step is faster than propagation, under certain conditions, it is possible to obtain 1:1 adducts in high yield.[41]

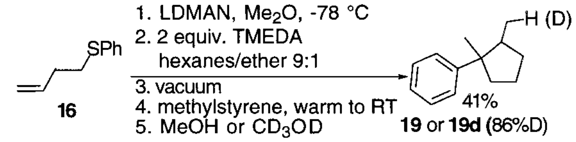
**Scheme 6**



**Scheme 7**



**Scheme 8**



In addition to the nature of organolithium substrates, solvents also play a key role in the addition of organolithiums to styrene and α-methylstyrene. When using pure hydrocarbon solvent, Fraenkel[40b] observed virtually no reaction between organolithiums and α-methylstyrene. However, when mixed solvents (isooctane–ether, isooctane–THF, isooctane–TMEDA) were used, the reaction proceeded smoothly. Taylor[40c] found that in diethyl ether at −78 to −25 °C, styrene underwent efficient addition reactions with a variety of primary, secondary, and tertiary alkyllithium reagents and the intermediate benzyllithiums could be trapped with electrophiles. In contrast, with THF as solvent, rapid polymerization was observed upon addition of the alkyllithium reagents. No reaction was observed with hexane as solvent from −78 °C to ambient temperature.

We eventually took advantage of these discoveries, adding homo- and bishomoallyllithiums directly to α-methylstyrene to obtain benzyllithium systems (Scheme 3). Krief had previously shown that such organolithiums are capable of undergoing carbanionic cyclizations.[37]

The homo- and bishomoallyllithiums were all prepared by reductive lithiation of the corresponding phenyl thioethers. The phenyl thioether precursors of **4** (R = H; *n* = 1), **4** (R = Me; *n* = 1), and **4** (R = Me; *n* = 2) as well as of **10** (Scheme 4) were prepared as in the earlier reports.[5,30a] The phenyl thioethers **13** (*n* = 1 and 2) were prepared as in Scheme 4.[5,6a]

In our initial experiments, we used our preferred reagent LDBB in THF because this generally gives the best yields of reductive lithiation product. However, it turned out that the byproduct DBB co-eluted with the product **8**. As usual in such situations, we turned to LDMAN because the byproduct DMAN is readily separable from the hydrocarbon products by a dilute acid wash.[32] The solvent was initially a mixture of THF and ether (1:2) because preliminary studies indicated that the ratio of addition/cyclization to polymerization was more favorable than in THF alone, as might be anticipated from the results in ref 40 as described above. The reactions of the unsaturated

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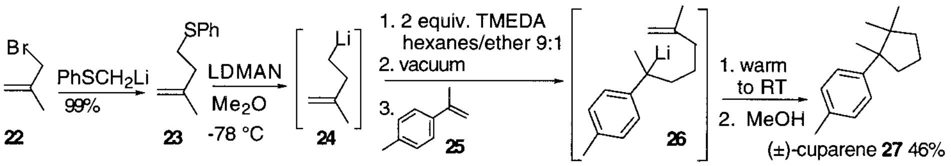
[41] Glaze, W. H.; Jones, P. C. *Chem. Commun.* **1969**, 1434–35.

**Scheme 9**



organolithiums with α-methylstyrene were performed by adding the latter as a THF solution at −78 °C very slowly, using a syringe pump, into a solution of the organolithium in THF/ether. The resulting mixture in some cases was warmed and then an electrophile, either methanol or 4,4′-dimethoxyphenyl disulfide, was added. The reaction conditions shown in Scheme 5 were the best that could be found after numerous experiments. The stereochemistry assigned to **9** was determined by the $^1$H NOESY spectrum.[42] The yields of **8** and **9** were unsatisfactory, apparently due to polymerization of the α-methylstyrene. Furthermore, in the case of the primary alkyllithium derived from **16** only oligomerization was observed. In the case of the tertiary homoallyllithium derived from **17**, it was clear that the known[5] rearrangement to a primary homoallyllithium was more rapid than addition to the α-methylstyrene; as expected, the resulting primary organolithium caused polymerization of the α-methylstyrene rather than addition.

In light of the recent reports of efficient addition of even primary organolithiums to styrene in diethyl ether, with very little concomitant oligomerization, it may be possible to carry out the tandem addition/cyclizations in higher yields by using diethyl ether as the solvent. Traditional reductive lithiation, which is the only general method to prepare homo- and bishomoallyllithiums, would not be appropriate since it involves the use of THF. However, by taking advantage of the above discovery that LDMAN can be generated in dimethyl ether, it was possible to avoid the use of THF and to replace the dimethyl ether by diethyl ether to attain a higher temperature than would be possible with dimethyl ether present. After LDMAN had been prepared in dimethyl ether at −70 °C, a solution of the reductive lithiation substrate in diethyl ether was added followed by precooled diethyl ether. The dimethyl ether was then removed at −70 °C under vacuum. As can be seen in Scheme 6, considerably improved yields are achieved in the tandem addition/cyclization reactions conducted in diethyl ether. Reaction of homoallyllithium **4** ($R = Me$; $n = 1$) derived from **14** with α-methylstyrene in diethyl ether resulted in the formation of cyclized product **8** in 56% yield, while the six-membered-ring product **9** was produced from bishomoallyllithium **4** ($R = Me$; $n = 2$), derived from **15**, in 52% yield. Even primary organolithium **4** ($R = H$; $n = 1$), derived from **16**, which failed to give any cyclized product in THF with α-methylstyrene, afforded cyclized product **19**, albeit in low yield. However, only rearrangement of **10**, the reductive lithiation product of **17**, occurred as in the experiments in which the solvent contained THF.

This method also provided a strategy for the formation of annulated hydrocarbon systems (Scheme 7). Reaction of α-methylstyrene with the cyclic homoallyllithium derived from **13** ($n = 1$) resulted in formation of **20** as a mixture of two diastereomers. The cyclic homoallyllithium, produced by reductive lithiation of **13** ($n = 2$), reacted with α-methylstyrene to provide the fused ring hydrocarbon **21** as a single diastereomer of undetermined configuration.

While attaining any tandem addition/cyclization product in the case of the primary organolithium from **16** was gratifying, the poor yield of **19** did not bode well for the use of this technology in a planned highly efficient synthesis of the sesquiterpene (±)-cuparene (see below) which also requires the use of a primary organolithium. However, we were gratified to discover that the organolithium from **16** could be used in a still less polar solvent consisting mainly of hydrocarbon, but containing TMEDA, with the result of doubling the yield of product **19** (Scheme 8) as a mixture of two diastereomers. As indicated above, even primary alkyllithiums do not survive in THF. However, in the solvent used in this experiment, the precursor of **19** does survive as indicated by the deuteriation experiment shown. Thus, it is highly likely that the new method of generating and using the aromatic radical-anion LDMAN will be very useful in preventing unwanted side reactions caused by the presence of THF.

Finally, the new technology was applied to the total synthesis of the sesquiterpene (±)-cuparene **27**, a frequent target in the development of synthetic methodology, in part because of the presence of the two adjacent quarternary carbon atoms. It has already been shown by Krief and Barbeaux,[29] in the seminal study of this type of cyclization, that **26**, which was prepared by an apparent four-step route from commercially available materials, cyclizes to cuparene in good yield. Since **26** is readily produced from commercially available **22**[43] and **25** by the methodology revealed in the present work, Scheme 9 constitutes a two-pot synthesis of the racemic natural product and the most efficient of those reported.[44] The mass and NMR spectra of **27** were identical with those reported (see Supporting Information).

In conclusion, for the first time, a method of generation of lithium aromatic radical-anions in a solvent devoid of THF has been developed. This finding should considerably enhance the utility of the widely used reductive lithiation for the preparation of organolithium compounds. Using this technology, a tandem addition of homoallyl- and bishomoallyllithiums to α-methylstyrenes and cyclization of the resultant benzyllithiums has been developed as an effective way to build certain five- and six-membered rings, including annulated systems, containing a pendant aryl ring. Limitations due to polymerization of the

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(42) The spectrum exhibited strong NOE values between the protons on methyl-1 and those of methyls-2 and -5. The proximity of methyls-1 and -5 is due to their expected diaxial orientation.

(43) **23** would also be conveniently produced in one pot by reaction of thiophenol in base on commercial 4-bromo-2-methyl-1-butene.

(44) (a) Other total syntheses of (±)-cuparene in addition to the one by Krief:[29] Mandelt, K.; Fitjer, L. *Synthesis* **1998**, *10*, 1523−26. Bailey, W. F.; Khanolkar, A. D. *Tetrahedron* **1991**, *47*, 7727−38. Nakatani, H.; So, T. S.; Ishibashi, H.; Ikeda, M. *Chem. Pharm. Bull.* **1990**, *38*, 1233−37. Kametani, T.; Kawamura, K.; Tsubuki, M.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 193−200. Ishibashi, H.; So, T. S.; Nakatani, H.; Minami, K.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1988**, *12*, 827−8. Bovicelli, P.; Mincione, E. *Synth. Commun.* **1988**, *18*, 2037−50. Kametani, T.; Kawamura, K.; Tsubuki, M.; Honda, T. *J. Chem. Soc., Chem, Commun.* **1985**, *19*, 1324−5. Reetz, M. T.; Westermann, J.; Kyung, S.-H. *Chem. Ber.* **1985**, *118*, 1050−7. Posner, G. H.; Kogan, T. P. *J. Chem. Soc., Chem. Commun.* **1983**, *24*, 1481−2. Wu, C.-L.; Liu, S. *Tetrahedron* **1983**, *39*, 2657−61. (b) Enantiomeric syntheses of (+)-cuparene: Fuganti, C.; Serra, S. *J. Org. Chem.* **1999**, *64*, 8728−30. Abad, A.; Agullo, C.; Arno, M.; Cunat, A. C.; Garcia, M. T.; Zaragoza, R. *J. Org. Chem.* **1996**, *61*, 5916−19 and citations therein.

α-methylstyrenes and protonation of the cyclized organolithium by the medium have been largely overcome.

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**Supporting Information Available:** Experimental procedures and compound characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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