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Diastereo- and Enantioselective Carbolithiation of Allyl *o*-Lithioaryl Ethers. New Chiral Cyclopropane Derivatives

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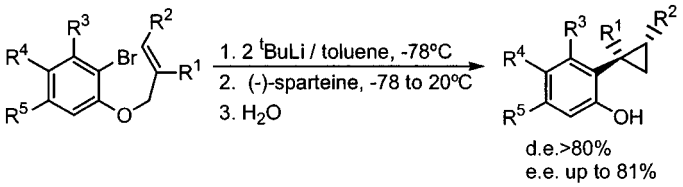
ABSTRACT



Different allyl 2-lithioaryl ethers undergo a tandem carbolithiation/γ-elimination in Et_2O/TMEDA affording *o*-cyclopropyl phenol or naphthol derivatives in a diastereoselective manner. The use of (−)-sparteine as a chiral ligand instead of TMEDA allows the synthesis of cyclopropane derivatives with up 81% ee.

The intramolecular carbolithiation of carbon−carbon double bonds is an interesting route to functionalized carbocyclic[1] and heterocyclic[2] systems that has been developed in the past years and widely used in organic synthesis. In this context, aryllithiums have been described to carbometalate double bonds allowing the preparation of indanes[3], benzofuranes,[4] indolines,[5] and isoquinolines.[6] In 1996, Bailey et al. reported the behavior of 2-(2-propenoxy)phenyllithium in the presence of TMEDA to afford 2-cyclopropylphenol in 40% isolated yield via a tandem carbolithiation/γ-elimination sequence.[7] The moderate yield of the reaction is attributed to a competitive $S_{N'}$ cleavage of the allyl moiety by the excess of *t*-BuLi used in the halogen−lithium exchange.[8] This

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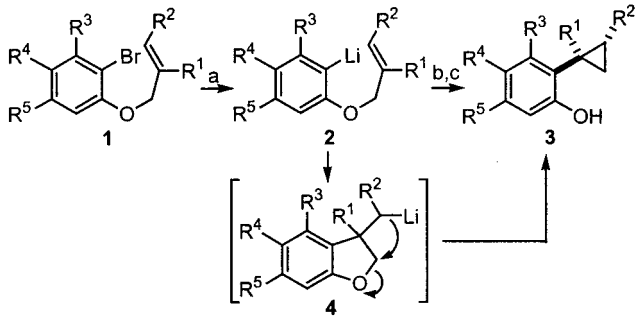
limitation could be the reason no more examples have been reported and this reaction sequence has not been generalized. Moreover, studies carried out by Hoppe,[9] Normant and Marek,[10] Bailey,[11] and Groth[12] have demonstrated that it is possible to carry out enantiofacially selective cycloisomerization of an achiral olefinic organolithium by simply conducting the carbolithiation in the presence of a bidentate chiral ligand like (−)-sparteine. On the other hand, cyclopropanes have attracted considerable interest in recent years, and although highly selective methods for the synthesis of optically active cyclopropanes have been recently developed, new approaches to enantioenriched cyclopropane derivatives are still desirable.[13] In connection with our interest in carbolithiation reactions,[14] we decided to investigate the reactivity of *o*-lithioaryl ethers and have recently reported a novel tandem anion translocation−Wittig rearrangement of these organolithiums in THF.[15] Herein we describe the stereoselective transformation of allyl *o*-lithioaryl ethers into cyclopropane derivatives in noncoordinative solvents in the presence of chelating diamines.

Treatment of allyl *o*-bromoaryl ethers **1** with *t*-BuLi (2 equiv) in diethyl ether at −78 °C led to the organolithium compounds **2**, which are stable in these reaction conditions and can be characterized through the corresponding deuterated derivatives. Addition of TMEDA (2.2 equiv) to the ethereal solution of intermediates **2** at −78 °C followed by warming to room temperature afforded, after hydrolysis, the cyclopropane derivatives **3** in good yields. NMR spectroscopic data revealed the formation of the trans diastereoisomer as the main product (Scheme 1 and Table 1).

Scheme 1[a]



[a] Reagents and conditions: (a) *t*-BuLi (2 equiv), Et_2O, −78 °C; (b) TMEDA (2.2 equiv), from −78 °C to rt; (c) H_2O.

A proposal that accounts for the formation of products **3** is outlined in Scheme 1 and involves an intramolecular 5-*exo* carbolithiation in the organolithium compounds **2**, favored probably by the coordination of the C=C to the lithium atom, to give the benzofuran derivatives **4**. They rapidly undergo a 1,3-elimination process[16] affording, after hydrolysis, the cyclopropane derivatives **3**. The formation of the hydrolyzed products derived from intermediates **4a** and **4k** supports this proposal. Moreover, formation of cyclopropane derivatives **3** is only observed when the starting material **1** contains a terminal alkene (R^2= H) or an allyl moiety bearing a group that can stabilize a negative charge (R^2 = TMS).[17] The important role played by the solvent is also remarkable. While the reaction carried out in THF mainly afforded anion translocation,[15] the less lithiophilic character of diethyl ether allows the coordination of the carbon−carbon double bond to the lithium atom favoring the carbolithiation step.[18] Even so, naphthyl ether **1l** afforded a 4:1 mixture of the expected

Table 1. Cyclopropyl Derivatives **3** from Ethers **1**

starting ether	R^1	R^2	R^3	R^4	R^5	product	dr[a] (trans:cis)	yield (%)[b]
1a	H	H	H	H	H	**3a**		61[c]
1b	Me	H	H	H	H	**3b**		81
1c	H	TMS	H	H	H	**3c**	90:10	76
1d	H	TMS	H	Me	H	**3d**	95:5	75[d]
1e	H	TMS	H	Cl	H	**3e**	95:5	81
1f	H	TMS	H	Br	H	**3f**	89:11	68
1g	H	TMS	H	F	H	**3g**	93:7	64[d]
1h	H	TMS	H	H	F	**3h**	90:10	70
1i	H	TMS	H	OMe	H	**3i**	84:16	73
1j	Allyl	TMS	H	H	H	**3j**	28:72	74
1k	H	H	$(CH)_4$		H	**3k**		71[e]
1l	Me	H	$(CH)_4$		H	**3l**		73[f]
1m	H	TMS	$(CH)_4$		H	**3m**	97:3	82

[a] Determined by GC, NMR, and/or HPLC. [b] Isolated yield based on the starting ether **1**. [c] Hydrolyzed compound corresponding to **4a** (∼6%) was also observed. [d] When the reactions were carried out in hexane/TMEDA, the yields increased up to 85%. [e] Hydrolyzed compound corresponding to **4k** (11%) was also isolated. [f] Alcohol **5l** (17%) was also isolated.

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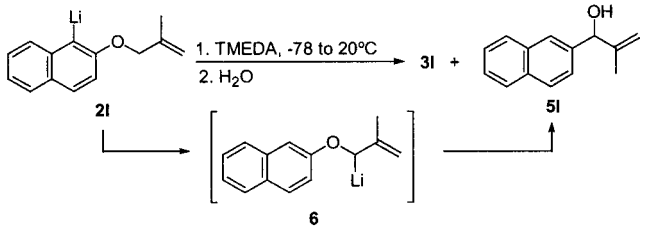
(17) It is known that a major limitation of the carbolithiation reactions is the failure of 1,2-disubstituted olefinic systems: Bailey, W. F.; Gavaskar, K. V. *Tetrahedron* **1994**, *50*, 5957−5970.

(18) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, D.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720−5727.

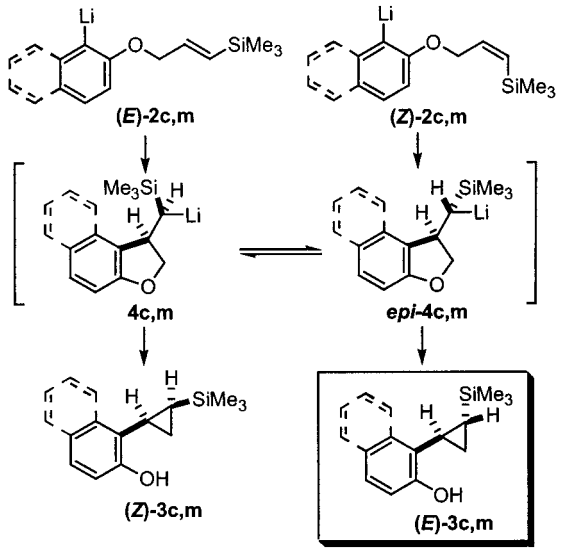
cyclopropane **3l** and rearranged alcohol **5l**. Its formation could be understood by a tandem anion translocation−Wittig rearrangement through the organolithium **6** (Scheme 2).[15]

Scheme 2



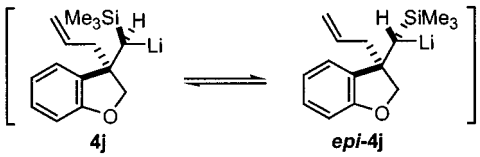
It is also interesting to note the high diastereoselectivity found in the transformation of organolithium compounds **2** (R^2 = TMS), being the corresponding *trans*-1-aryl-2-trimethylsilylcyclopropane derivatives **3** the major products. In addition, we have observed that the results are the same independently of the configuration of the allylic double bond. So, both organolithium compounds (*E*)-**2c** and (*Z*)-**2c** led to the same *trans*-1,2-disubstituted cyclopropane **3c**. Also, the corresponding naphthyl organolithiums (*E*)-**2m** and (*Z*)-**2m** led to the same *trans*-cyclopropane **3m**. From the stereochemical standpoint these results can be interpreted by accepting that organolithium compounds (*E*)-**2c**,**m** and (*Z*)-**2c**,**m** undergo a 5-*exo*-*trig* carbolithiation through a *syn* addition affording intermediates **4c**,**m** and *epi*-**4c**,**m** respectively. A rapid epimerization[19] of organolithium intermediates **4c**,**m** to *epi*-**4c**,**m** prior to the 1,3-elimination and assuming that the ring closure takes place with retention of the configuration of the metallic carbon would favor the formation of the *trans*-**3c**,**m** instead of *cis*-**3c**,**m** (Scheme 3). The steric hindrance between the $SiMe_3$ and aryl groups in the fixed conformation needed for the elimination also favors the epimerization step.[20]

Scheme 3



Moreover, the formation of the *Z*-isomer of **3j** as the major product from organolithium compound **2j** presumably could be due to steric hindrance between the allyl or aryl groups and the silyl moiety as in **4j** and *epi*-**4j**, in this case favoring to the former (Scheme 4).

Scheme 4



Encouraged by the good yields and diastereoselectivities obtained with trimethylsilyl-substituted ethers **1** and taking into account the possibility of carrying out this reaction in an enantioselective manner,[11,12] we next turned our attention to this task. Our first experiment was performed with ether **1c**: after the addition of 2 equiv of *t*-BuLi to an ethereal solution of **1c** at −78 °C, 2.2 equiv of dry (−)-sparteine were added at low temperature and the resulting mixture was allowed to warm to 20 °C prior to quenching with water. The expected cyclopropane derivative **3c** was obtained in 80% yield but with only 20% ee (Table 2, entry 1). In an attempt to improve the enantioselectivity of the process we performed the reaction at lower temperatures. Thus, **3c** was formed in 34% ee when the reaction was carried out at −20 °C and 39% ee at −30 °C (Table 2, entries 2 and 3). Although a slight increase in the ee was obtained, the yields were lower and variable amounts of the corresponding

Table 2. Influence of the Solvent and Temperature in the Asymmetric Cyclization of **2c** to **3c** Using (−)-Sparteine

entry	solvent	conditions	ee (%)[a]	yield (%)[b]
1	Et_2O	−78 to 20 °C	20	80
2	Et_2O	−20 °C (15 h), then to 20 °C	34	55
3	Et_2O	−30 °C (15 h), then to 20 °C	39	42
4	toluene	−78 to 20 °C	73	70
5	toluene	−20 °C (15 h)	78	38
6	toluene	−20 °C (15 h), then to 20 °C	78	52
7	hexane	−78 to 20 °C	77	84

[a] The ee values were assayed by HPLC using mixtures of hexane/2-propanol. [b] Isolated yield based on the starting ether **1c**.

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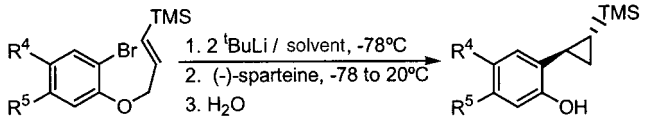
(20) Results in which the carbolithiation reaction is stereospecific in the formation of the new carbon−carbon bond and nonstereospecific in the formation of the new carbon−lithium bond have been reported. (a) Hoffmann, R. W.; Koberstein, R.; Remacle, B.; Krief, A. *Chem. Commun.* **1997**, 2189−2190. (b) Hoffmann, R. W.; Koberstein, R.; Harms K. *J. Chem. Soc., Perkin Trans. 2* **1999**, 183−191.

hydrolyzed products derived from **2c** and **4c** were also generated. The effect of the solvent on the enantioselectivity was also studied. Thus, the use of toluene as a solvent led to a considerable increase in the ee (73%) (Table 2, entry 4). To rigorously check the effect of the temperature on the enantioselectivity, we first determined the temperature at which the carbolithiation step took place (about −20 °C). When the reaction was carried out at this temperature, the ee slightly increases up to 78% (Table 2, entries 5 and 6). If the reaction is not warmed to room temperature before the hydrolysis, the yield of **3c** is lower, as the 1,3-elimination has not completely occurred (Table 2, entry 5). However, if the mixture is allowed to reach room temperature (Table 2, entry 6) the ee obtained was the same but the chemical yield improved up to 52%. In both cases, variable amounts of the hydrolysis product derived from **4c** are observed. These facts seem to indicate that longer times at lower temperatures (−20 °C) lead to the formation of the hydrolysis product derived from **4c** by abstraction of a proton from the reaction media. Finally, when hexane was used as a solvent, the yield was slightly higher than it was when obtained in toluene, whereas the ee was similar (Table 2, entry 7).

To test the enantioselectivity of this process on other substrates, we performed the reaction with substituted starting ethers **1d**−**i**. The experiments were carried out in toluene or hexane as solvents at temperatures ranging between −78 and 20 °C and using (−)-sparteine as a chiral ligand (see Table 3). Moderate to good and consistent enantioselectivities were observed for all the substrates. However, lower enantioselectivities were obtained from the 5-F- and the 4-MeO-substituted ethers **1h** and **1i** (Table 3, entries 7−9). Although we do not have an explanation for this fact, it seems that the distribution of the electronic density on the aromatic ring plays a role on the selectivity of the process. On the other hand, chemical yields are again slightly better in hexane and the lower yields obtained with ether **1h** could be attributed to a competitive metalation of the 6-position adjacent to the oxygen and fluorine atoms.

Disappointingly, when we tried to extend this sequence to the naphthyl ether **1m**, we found that, in the same reaction conditions, the expected cyclopropane derivative **3m** was isolated in 70% yield but the ee was less than 5% in diethyl ether. Only a modest 14% ee could be obtained when the carbolithiation reaction was carried out in toluene.

Table 3. Asymmetric Transformation of **1** into Cyclopropane Derivatives **3** Using (−)-Sparteine



entry	starting ether	solvent	product	ee (%)[a]	yield (%)[b]
1	**1d**	toluene	**3d**	78	61
2	**1d**	hexane	**3d**	74	71
3	**1e**	toluene	**3e**	77	74
4	**1e**	hexane	**3e**	76	80
5	**1g**	toluene	**3g**	81	69
6	**1g**	hexane	**3g**	79	76
7	**1h**	toluene	**3h**	56	58
8	**1h**	hexane	**3h**	60	57
9	**1i**	hexane	**3i**	64	78

[a] The ee values were assayed by HPLC using mixtures of hexane/2-propanol. The absolute configuration of the major enantiomers was not determined. [b] Isolated yield based on the starting ethers **1**.

In summary, we have described an intramolecular carbolithiation of *o*-lithioaryl ethers that affords cyclopropane derivatives in a diastereoselective manner. When the reaction was carried out in the presence of (−)-sparteine, moderate to good enantioselectivities were obtained, expanding the use of this chiral ligand in cyclizations of achiral olefinic organolithiums.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via Internet at http://pubs.acs.org

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