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Regio- and Stereoselective Copper-induced Isomerization of 2-Alkenyl 2-Lithiophenyl Ethers to 2-(2-Alkenyl)phenols

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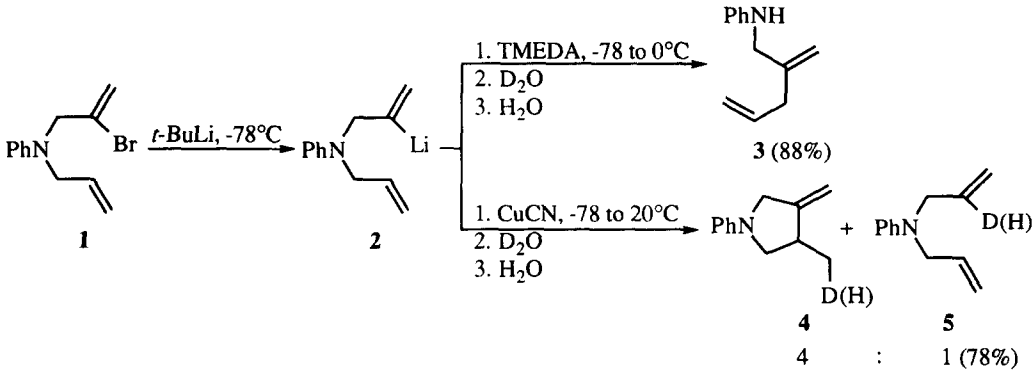
Abstract: *N*-Allyl-*N*-(2-lithioallyl)aniline undergoes intramolecular carbometallation *via* 5-*exo* addition on treatment with CuCN. 2-Alkenyl 2-bromophenyl ethers rearrange to 2-(2-alkenyl)phenols by bromine-lithium exchange and further transmetallation with CuCN. © 1997 Elsevier Science Ltd.

The 5-*exo*[1] cyclization of 5-hexenyllithium derivatives provides a convenient route to five-membered cycles,[2] including tetrahydrofurans[3] and pyrrolidines.[4] When the lithium atom is on a phenyl ring these closures afford benzofusionated cycles. So, the formation of lithiomethylindanes from 2-(3-butenyl)phenyllithium[5] and 3-lithiomethylindolines from 2-(*N*-allylamino)phenyllithium[6] have been reported. However, the anionic cyclization of 2-(2-propenoxy)phenyllithium does not provide the corresponding 2,3-dihydrobenzofuran derivative due to the easy γ-elimination process that undergoes the initially formed 3-lithiomethyl-2,3-dihydrobenzofuran.[7] On the other hand, the carbocupration of alkynes is probably the most versatile carbometallation reaction.[8] Although the carbocupration of isolated double bonds is generally not possible, some strained alkenes[9] as well as conjugated 1,2- and 1,3-dienes[10] react with several organocopper reagents. In this context, transmetallation of organolithium compounds to a less reactive organocopper species has been used in order to supress a proton-transfer in the intramolecular carbometallation of δ-allenyl alkyllithium derivatives.[11] We have recently reported the intramolecular carbolithiation of *N*-allyl-*N*-(2-lithioallyl)amines that proceeds via 5-*exo* or 6-*endo* depending on the nitrogen electron density.[12] With aromatic amines a 6-*endo* closure followed by an irreversible β-elimination process avoids the formation of pyrrolidine derivatives. In the present communication we describe the first carbocupration of an isolated alkene and the regio- and stereoselective copper promeoted isomerization of 2-alkenyl 2-lithiophenyl ethers to 2-(2-alkenyl)phenols.

Treatment of *N*-allyl-*N*-(2-bromoallyl)aniline **1** with 2 eq. of *tert*-butyllithium at -78°C afforded the vinyllithium derivative **2**. Upon addition of *N,N,N',N'*-tetramethylethylendiamine (TMEDA) a 6-*endo* intramolecular carbometallation took place giving rise to *N*-(2-methylene-4-pentenyl)aniline **3**.[12] However, the outcome of the reaction is different when 0.5 eq. of CuCN is added to the organolithium compound **2** at -78°C,

So, after removal of the cooling bath, the reaction was allowed to stand at room temperature, affording after deuteriolysis, a 4:1 mixture of 3-deuteriomethyl-4-methylenpyrrolidine **4** and *N*-allyl-*N*-(2-deuterioallyl)aniline **5**, not completely deuteriated (Scheme 1).



Scheme 1

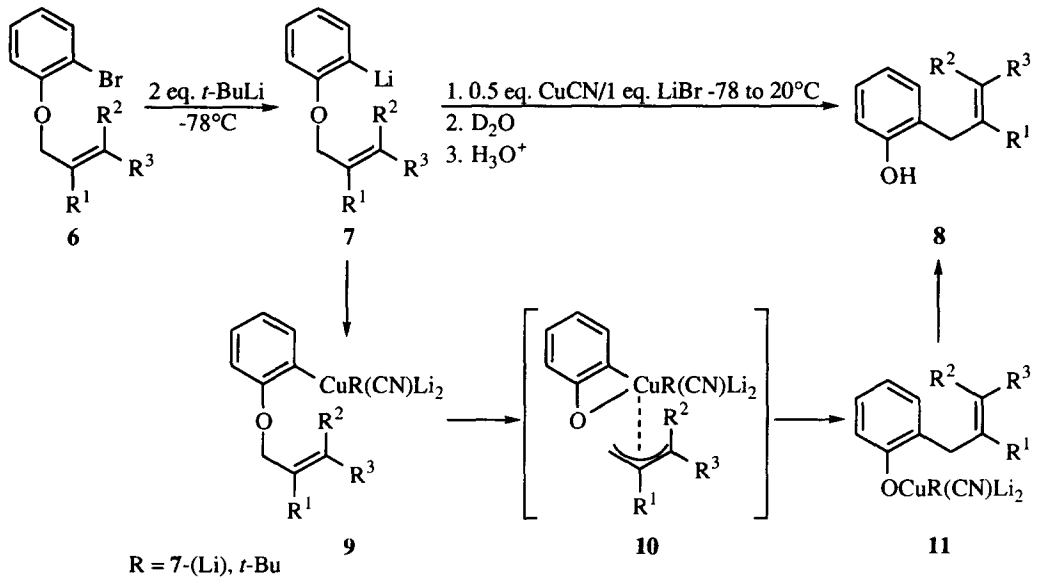
Due to the lower basicity of organocopper compounds the 6-*endo* closure is not favored and pyrrolidine formation could be achieved. Since higher temperatures (0-20°C) are needed for the carbocupration reaction, a partial decomposition of the cuprate[13] could take place prior to the deuteriolysis.

In light of the different outcome of this carbocupration process, we were prompted to investigate the possibility of preparing 2,3-dihydrobenzofurans by cyclization of 2-(2-alkenoxy)phenyl-copper derivatives. The direct formation of these systems by carbolithiation is not possible because of the elimination process in the previously generated γ-oxygenated organolithium compound. Solutions of aryllithiums **7** were prepared at -78°C in ether by treatment of the corresponding 2-bromophenylether **6**[14] with 2 eq. of *t*-BuLi. After addition of 0.5 eq. of CuCN and 1 eq. of LiBr[15] at -78°C, the temperature was allowed to rise to 20°C. Deuteriolysis and further hydrolysis of the reaction mixture allowed the formation of 2-(2-alkenyl)phenols **8** in good yields (Scheme 2 and Table 1).

It is interesting to note that the process is completely regio- and stereospecific and the substituents of the double bond in the phenol **8** are at the same position and with the same stereochemistry that in the ether **6**. The overall transformation constitutes a unique Claisen rearrangement without migration to the *para* position and with the opposite regiochemistry in the allyl substituents. The rate of the formation of phenols depends on the degree of substitution of the double bond, so while the reaction of **6a-c** and **6f** proceeds in two hours at room temperature, the complete transformation of more substituted systems (**6d,e** and **6g**) needs four to six hours.

The formation of phenols **8** could be understood by assuming a homo higher-order cuprate intermediates **9** (R=**7**-(Li)), which undergo an oxidative addition generating the π-allyl complexes **10**. Reductive elimination afford 2-substituted phenolates **11** which give, after hydrolysis, phenols **8**. The second equivalent of *t*-BuLi seems to play an important role in order to regenerate an active cuprate of type **9** (R=*t*-Bu) by transmetallation with **11** and complete the transformation. In this way, the addition of only 1 eq. of *t*-BuLi in the metallation

step gives an equimolecular mixture of the rearranged phenol and the phenylether resulting from hydrolysis of organolithium intermediate **7**. On the other hand, addition of 1 eq. of CuCN instead 0.5 eq. results in a different reaction and a mixture of phenols **8**, hydrolyzed compounds corresponding to lithiophenylethers **7**, and addition products of *t*-BuLi to the double bond were obtained. The fact that the reaction does not work in the case of benzyl 2-bromophenyl ether supports the possible formation of a π-allyl complex **10**.



6 **7** **8** **9** **10** **11**

Scheme 2

Table 1. Isomerization of allyl 2-bromophenyl ethers **6** into 2-allylphenols **8**.

Starting ether	R^1	R^2	R^3	Product[a]	Yield (%)[b]
6a	H	H	H	**8a**	70
6b	H	Ph	H	**8b**	77
6c	H	Me	H	**8c**	72
6d	H	Me	Me	**8d**	67
6e	H	$(CH_2)_2CH{=}CMe_2$	Me	**8e**	71
6f	Me	H	H	**8f**	70
6g	$(CH_2)_4$		H	**8g**	69

[a]All products were fully characterized by spectroscopic methods (IR, HRMS, ^1H and ^{13}C NMR). [b]Isolated yield based on the starting ether **6**.

In conclusion we have described the first carbocupration of an isolated alkene and the transformation of 2-(2-alkenoxy)phenyllithium compounds to the lithium salt of 2-(2-alkenyl)phenols in a regioselective way. This transformation represents a Claisen rearrangement with retention of the regiochemistry of the allyl fragment and without migration to the *para* position; moreover it procceeds under mild conditions in good yields.

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