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Phenylthioacetylene as a Source of Stereodefined Trisubstituted Alkenes

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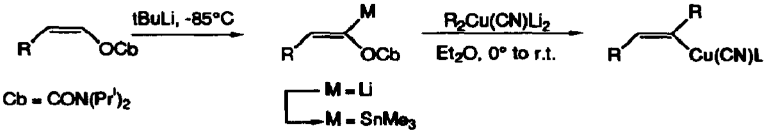
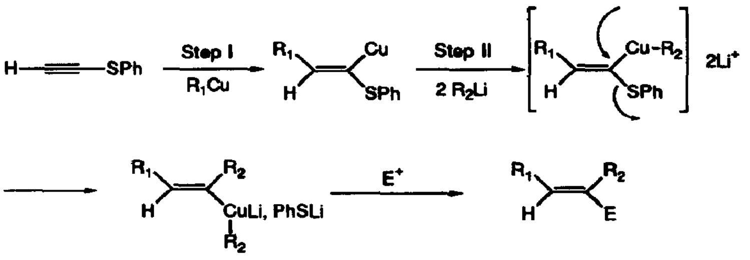
Abstract: A 1,2-metal-ate rearrangement leads to stereodefined trisubstituted alkenes, as single isomers, in an easy and straightforward one-pot procedure.

α-Haloalkenyl organometallic compounds are versatile reagents that possess ambiphilic reactivity[1], and the use of a variety of metals including Li[2], B[3], Mg[4], Al[5], Zn[6], Zr[5c,7], Cu[8] has been extensively investigated. Recently, an elegant stereoselective synthesis of functionalized alkenyl cyanocuprates by the Cu(I)-catalyzed coupling of organolithium reagents with α-lithiated cyclic enol ethers was described by Kocienski[9]. However, in acyclic systems, the Cu(I) catalyzed 1,2-alkyl migration reactions have been limited to the metallated (Z)-enol carbamates, prepared by transmetallation of the corresponding stannanes[9,10].



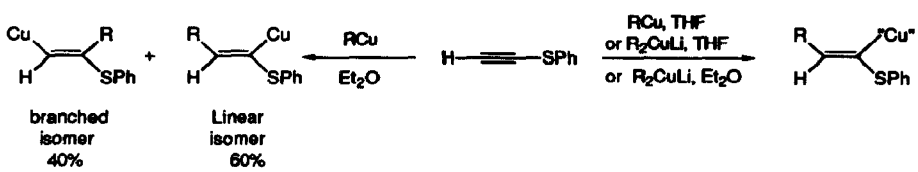
Scheme 1

Although the α-lithiated cyclic and acyclic thioethers were described to fail in this process[9a], we report our successful preliminary results obtained, under specific experimental conditions, in the stereoselective synthesis of polysubstituted alkenyl organocuprates, via a carbocupration reaction of phenylthioacetylene followed by a 1,2-metal-ate rearrangement (scheme 2).



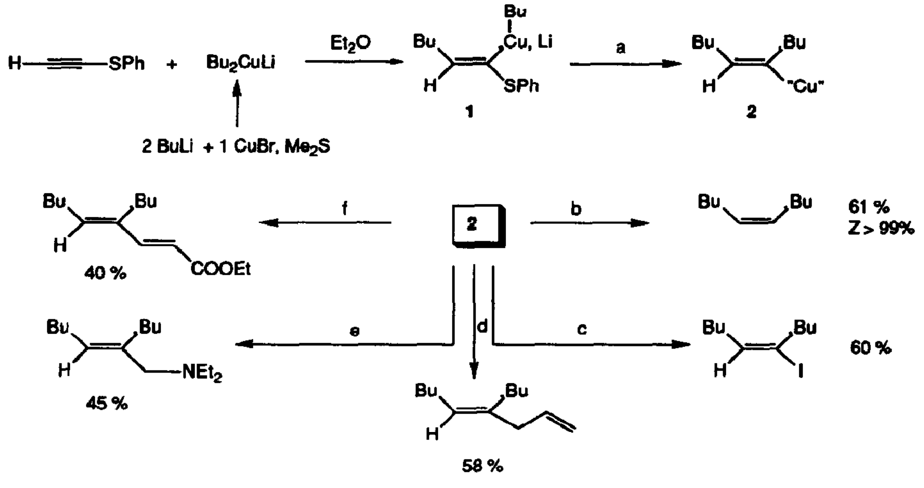
Scheme 2

The carbocupration of 1-alkynyl sulfides, the first step of this strategy, is best performed in THF. Pure regioisomers are always obtained[11], but in this solvent, the 1,2-intramolecular nucleophilic substitution (step II, scheme 2) is totally thwarted. However, in Et_2O, the requisite solvent for the subsequent metal-ate rearrangement, the regioisomer ratio is dependent on the nature of the organometallic derivatives[12] (scheme 3).



Scheme 3

Thus, in order to get a regioselective carbocupration step in ether, it will be necessary to use an organocuprate. The second step, the intramolecular rearrangement, can be easily performed by adding to the resultant vinyl-alkyl cuprate, an organolithium derivative, which yields, after the 1,2-metal-ate rearrangement the organocuprate **2**. The organometallic copper species is now trans to the alkyl group, the opposite stereochemistry of the one obtained after the carbocupration step, and of the vinyl cyanocuprate obtained from (Z)-enol carbamates (scheme 1). After recooling to -40°C, the indicated electrophiles are added to give the corresponding polysubstituted alkenes (scheme 4).

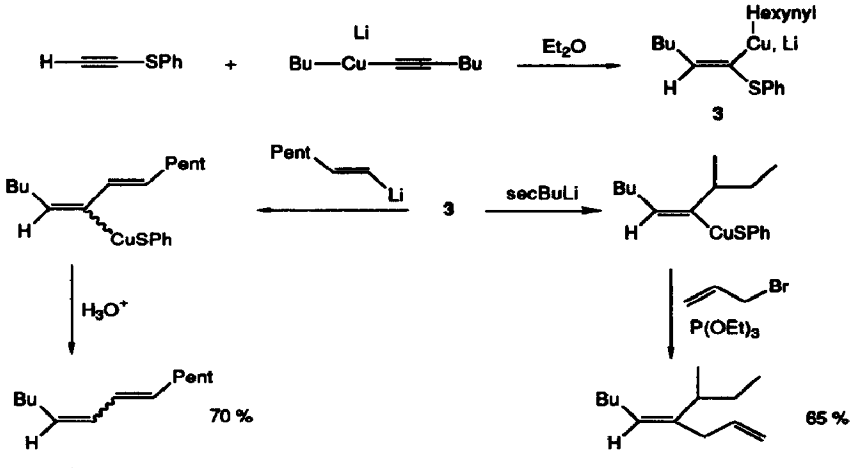


Reaction conditions : a). 2 eq BuLi (-40°C) ; MeSMe (10 eq) 26-28°C, 30 min b). NH_3/NH_4Cl c). $ZnBr_2$ (1 eq) -40°C, 30 min to 0°C ; I_2 (1 eq) -60°C, 2h. d).$P(OEt)_3$, 1 eq.,-40°C and freshly distilled allyl bromide, 1 eq, -40°C, 2h e). diethylaminomethylbutylether, 1 eq, -40°C to r.t. f). ethyl propiolate, 1 eq, -40°C, 3h.

Scheme 4

In every cases examined, the stereochemistry of the formed polysubstituted alkenes corresponds to > 99% stereoselectivity[13]. The kinetic of the intramolecular nucleophilic substitution is dependent on the reaction mixture temperature. If the temperature is too low (e.g., -10°C) rearrangement does not take place; At 0°C, the rearrangement occurs but a 60%-70% yield is obtained after a long period of time (48h). However, at 26°C-

28°C, the *cis* vinyl alkyl cuprate is transformed into the *trans* vinyl alkyl cuprate in 30 min. Thus, in order to increase the stability of the vinyl organometallic towards the temperature, MeSMe was introduced before the rearrangement step. Using an acetylenic group as a non-transferable or "dummy ligand"^{14} in the organocopper reagents, allows the selective transfer of two different alkyl groups according to the following scheme^{15}.The transfer of a vinyllithium is also possible, but the dienyl organocuprate generated is isolated as a mixture of 2 isomers.



Scheme 5

Although the chemical yield is modest, this strategy leads to stereodefined trisubstituted alkenes^{11,16} via stereoselective creation of three C-C bonds, as single isomers (except for the dienyl cuprate), in an easy and straightforward one-pot procedure^{17}, starting from a common starting material^{18}. We are currently exploring the scope of this methodology and the extension to the synthesis of tetrasubstituted alkenes.

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