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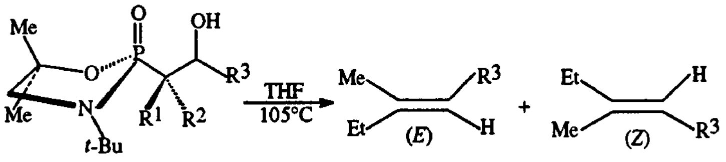
Regio- and stereoselective metal-mediated synthesis of polyfunctionalized alkenes

Alfredo Ricci[a], Errol Blart[a], Mauro Comes- Franchini[a], Gianna Reginato[b], Paolo Zani[a]

[a] Dipartimento di Chimica Organica "A. Mangini", Via Risorgimento 4, I-40136 Bologna, Italy;[b] Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni del CNR, Via G. Capponi 9, I-50124 Firenze, Italy.

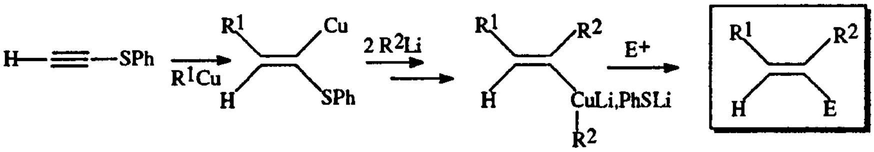
Abstract- Silyl- and stannylcupration of alkynes bearing N- or S-based functional groups takes place in a regio- and stereoselective fashion and the resulting vinyl metal species are easily quenched with a wide range of electrophiles, thereby resulting in a flexible and general route to polysubstituted silylated or stannylated olefins. For the replacement of the vinylic R_3M framework in the allylic-type systems Pd(0) catalysis is needed and through Stille-type (M=Sn) or Heck-type (M=Si) reactions, the controlling factors on the regio- and stereochemistry of the synthesis of di- and trisubstituted olefins are disclosed. Conversely displacement of the R_3Si group and functionalization with electrophiles at C-2 can be performed even in the absence of catalysts when N or S atoms are directly bound to the C=C moiety as part of enamino or vinylsulfide frameworks respectively.

The importance of stereodefined and polysubstituted carbon-carbon double bonds in organic synthesis cannot be overemphasized. In recognition of the importance of these compounds, their regio- and stereoselective preparation has been a great challenge and many ingenious and selective methods have been devised over the years. Nevertheless, there is still a need for a general and highly selective method for the synthesis of tri- and tetra-substituted alkenes. Besides the Wittig reaction for which the problems in the formation of tri- and especially of tetrasubstituted alkenes are well documented,[1] and the Peterson olefination,[2] other methods have emerged very recently. A general protocol has been developed by Denmark[3] for the highly stereoselective synthesis of trisubstituted alkenes suitable for various alkene substitution patterns by cycloelimination of β-hydroxyphosphonoimidates in THF at 105 °C.



(*u,u*)	R^1= Et	R^2= Me	R^3= n-$C_{11}H_{23}$	E/Z = 102/1
(*l,u*)	R^1=Me	R^2=Et	R3=n-$C_{11}H_{23}$	E/Z= 1/160

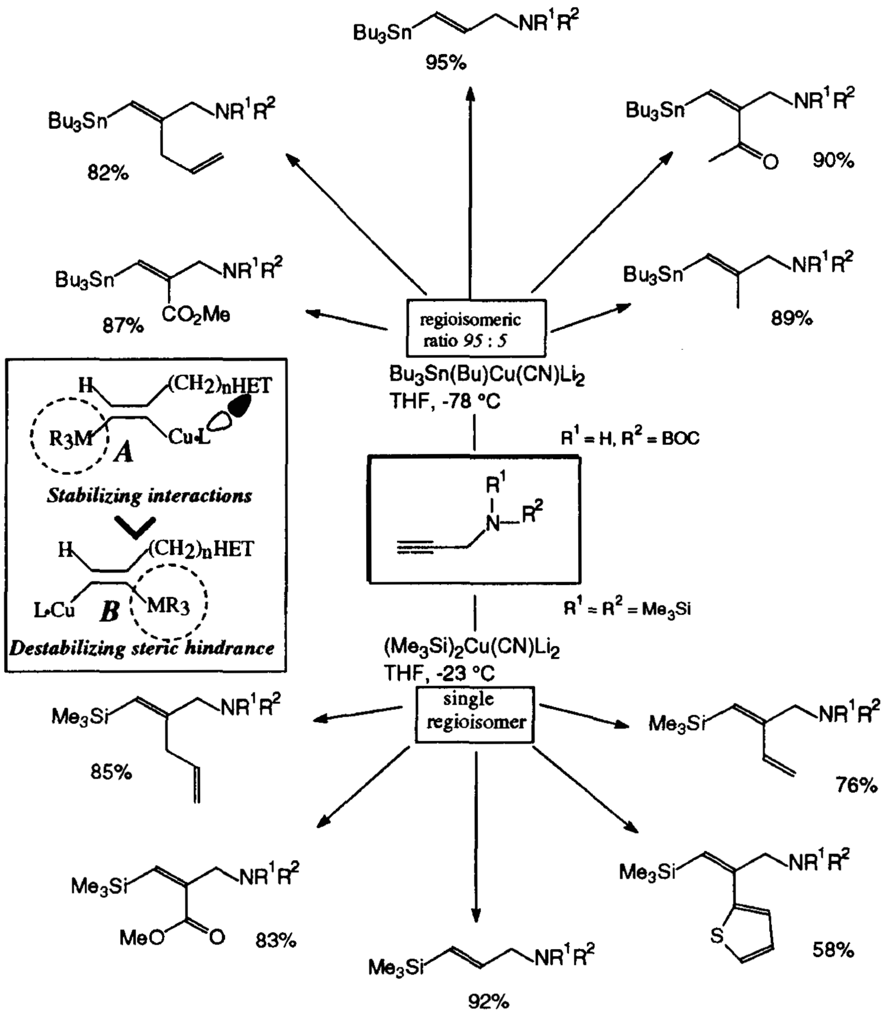
More recently, a 1,2-metal-ate rearrangement has been reported[4] by Normant and Marek through which trisubstituted alkenes can be obtained, as single isomers, in an easy and straightforward one-pot procedure.



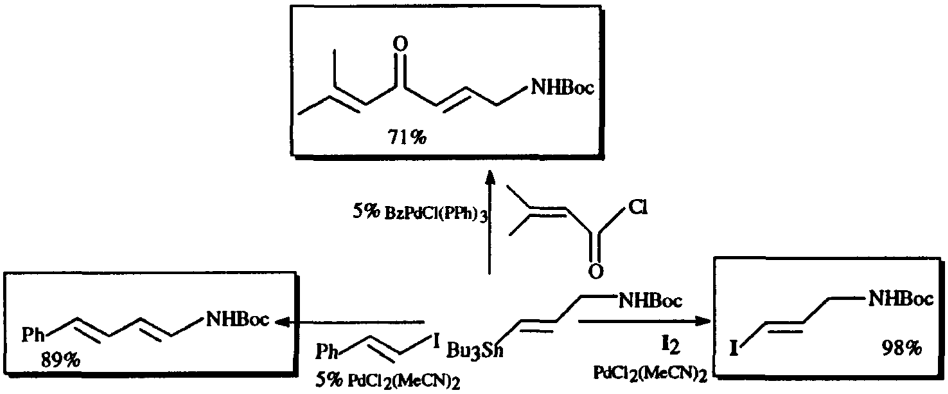
Another viable route to trisubstituted olefins is the metallo-metalation of alkynes. Terminal acetylenes react with bis-metallic reagents containing less electropositive metals such as Cu, B, Si, Zn, and Zr, in the presence of suitable catalysts (Cu^+, Pd^0, or Pd^{2+}), to give 1,2-dimetallo-1-alkenes in highly regio- and stereocontrolled reactions.[5] These can be selectively functionalized at the more reactive vinyl-metal bond to provide a monometallic alkene which upon transmetalation and further reaction with electrophiles, gives stereo- and regiodefined trisubstituted olefins.

The most recent applications of metallometalation as a synthetic tool, focus on metallocupration and, in particular, on the applications of silyl-[6] and stannylcupration[7] reagents. The problems in metallometalation reactions due to the variable regioselectivity[5], can be overcome by using 1-alkynes bearing heteroatoms directly bound to the triple bond or as part of a propargylic-type system: the preferential Cu-heteroatom coordinative interaction, coupled with the decreased steric crowding should stabilize at the level of the vinylcopper adduct, type-*A* intermediates with respect to *B*, thus making these addition reactions highly regioselective. Moreover the possibility of generating polysubstituted olefins bearing heteroatom-based functionalities would result in highly reactive systems in which sites for further synthetic transformations are present or in building blocks biologically important as enzyme inhibitors.

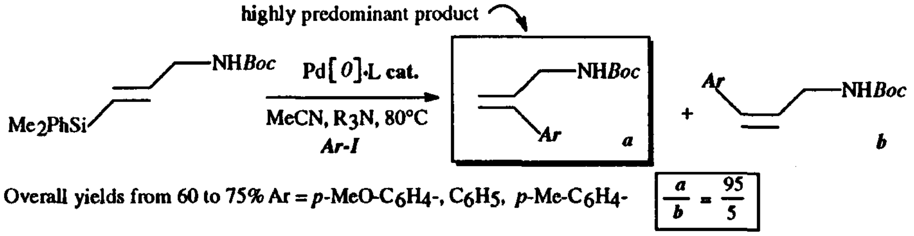
Accordingly, N-protected propargylamines upon reaction with either $(Me_3Si)_2Cu(CN)Li_2$[8] or with $Bu_3Sn(Bu)Cu(CN)Li_2$[9] afforded, after quenching with electrophiles, the corresponding 2-substituted-allylamines silylated or stannylated at position 3 in a stereoselective fashion and with the opposite regiochemistry with respect to that observed in the corresponding carbocupration reactions.



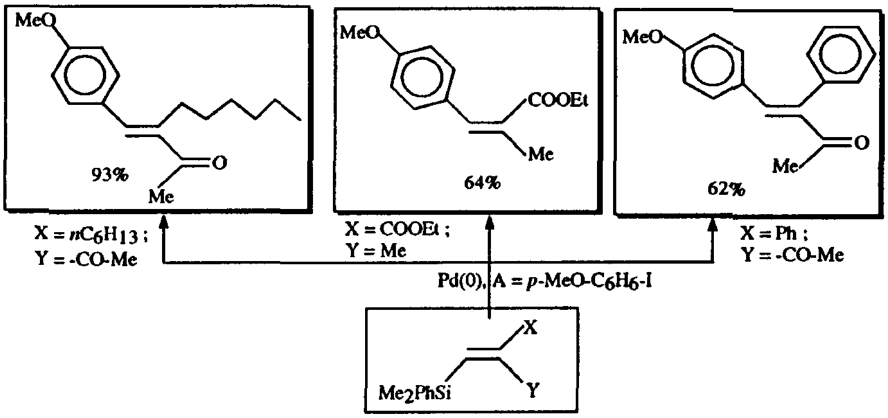
The subsequent exploitation of the reactivity of the organometallic vinylic bond in trisubstituted olefins, resulting from silylcupration and stannylcupration reactions, crucially depends upon the nature of the Group 14 element. Destannylative coupling of vinyl tin derivatives with electrophiles under Pd(0) catalysis, according to Stille's procedure,[10] turns out to be an easy process particularly attractive since it tolerates a variety of reactive substituents. When it was applied to stannylated allylic amines it led,[11] in a high regio- and stereocontrolled fashion to di- and tri-substituted olefins bearing reactive and/or heteroatom-based functional groups. Conversely, the reported cleavage methodologies of the C-Si bond in vinylsilanes based[12] on F$^-$ or strong Lewis acids are to some extent incompatible with acidic hydrogens and with heteroatom-based functions, respectively.



To overcome these drawbacks a new Pd-catalyzed carbodesilylation protocol was devised. Apart from the well known Hiyama reaction[13] based on the TASF(or TBAF)/Pd catalyst mediated cross-coupling of organosilanes with organic halides, the Pd-catalyzed desilylation reactions are almost completely unexplored[14]. Application of the commonly used Heck reaction conditions[15] to the reaction of vinylsilanes from silylcupration of propargylic amines with aryl iodides, resulted[16] in desilylation and formation of the products of arylation of the vinylic framework in good chemical yields and with a satisfactory regio- and stereochemical outcome.

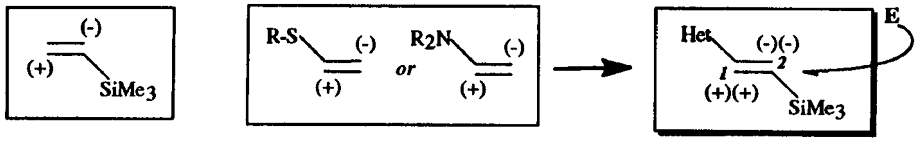


An ordinary Heck arylation at the internal carbon, followed by elimination-readdition of H-Pd-I and subsequent Pd-desilylation offers a reasonable explanation for the formation of the styrene derivatives. Support for this mechanistic proposal was provided by the deuterium scrambling recorded when a deuterated vinylsilane was employed. Extension of this methodology to the stereo- and regiocontrolled synthesis of trisubstituted olefins starting from disubstituted vinylsilanes required, according to the mechanistic hypothesis, arylation at the terminal carbon and interaction of the Pd with the internal carbon.

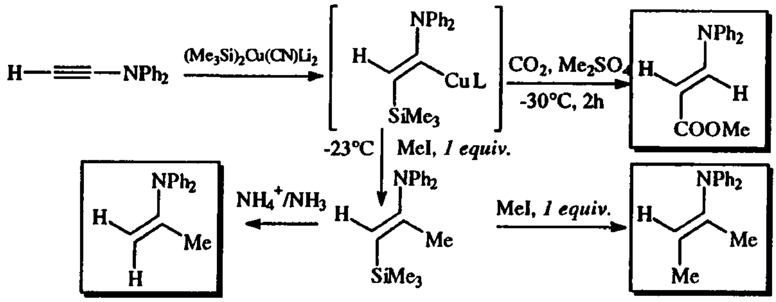


This favourable arrangement is driven by the presence of an α,β-unsaturated carbonyl framework.[17] Trisubstituted olefins, in which one the substituents was a carbonyl group, were synthesized[16] in yields ranging from 62 to 93%.

The metallocupration of terminal alkynes in which a heteroatom is directly bound to the C-C triple bond, such as ynamines and alkythioacetylenes, provides a novel entry to polysusbstituted olefins bearing vinyl sulfide or enamino moieties. A relevant feature of these reactions is again the reversal of regioselectivity as compared with that occurring in the carbocupration reactions. Furthermore, combining vinylsilane with vinyl sulfide or with enamino functional groups in the silylcupration product would account, as a consequence of their opposing polarizations, for the exceptional reactivities which allow, in most cases, for the displacement of the R_3Si group and the functionalization with electrophiles at C-2 to be performed even in the absence of catalysts.



Through the silylcupration of N-phenyl-N-ethynyl-aniline a novel and flexible entry to the not easily accessible class of mono-functionalized enamines, can thus be envisioned.[18] The bis-functionalization is achievable, as well, in the presence of excess of electrophile.



Also trimethylsilyl- or dimethylphenylsilyl-substituted thioalkenes exhibit[19] some tendency to desilylate in the absence of catalysts even though this reaction appears more difficult when additional alkyl or aryl groups are bonded at C-2. However removal of the R_3Si group can be observed under very mild acidic conditions and preliminary experiments suggest also the possibility of its replacement with reactive electrophiles. The further development and the optimization of this process would allow a viable route to polysubstituted thioalkenes to be devised.

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