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Regio- and Stereoselective Synthesis of Novel (*E*)-1-Alkenyl Carbamate via Carbocupration Reaction

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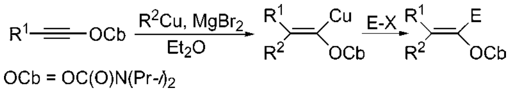
ABSTRACT



The stereoselective carbocupration and copper-catalyzed carbomagnesiation reactions of alkynyl carbamates are described as a new and straightforward method for the preparation of (*E*)-alkenyl enol carbamates.

We have recently reported that heterosubstituted alkenes such as enol ether,[1] silyl enol ether,[2] vinyl (alkyl)arylsulfides, vinyl sulfoxides, and even vinyl sulfones[3] were excellent candidates for the stereospecific preparation of alkenyl and conjugated dienyl[4] organometallic derivatives.[5] With the goal of extending the scope of this powerful new reaction as well as gaining better insight into the stereochemical outcome, we were interested in studying the transformation of vinylic carbamates into organometallic derivatives.

Vinyl carbamates, or enol carbamates, are well-known species and were originally shown to be very useful intermediates for the access to agricultural chemicals, pharmaceutical product intermediates, or precursors of transparent polymers.[6] General methods leading to unsaturated carbamates have been described and generally used either the dehydrohalogenation of α-halogeno-[7] or β-halogenoalkyl carbamates[8] or the addition of amines to the vinyl chloroformates[9] resulting from dehydrohalogenation[10] or from enolmercury(II) derivatives.[11] In all cases, only unsubstituted enol carbamate derivatives were prepared. The catalytic addition of terminal alkynes to ammonium carbamates, generated in situ from the secondary amines and CO_2, led selectively in the presence of ruthenium catalyst to vinylic carbamates.[12] However, both (*E*)- and (*Z*)-isomers were obtained with the (*Z*)-isomer as the major product (typically with a *Z*:*E* ratio of 85:15). More recently, the stereoselective preparation of the (*Z*)-isomer of 1-vinyl carbamate through the isomerization of 2-alkenyl carbamate,[13] via Hoppe's homoaldolization methodology,[14] was reported (Scheme 1,

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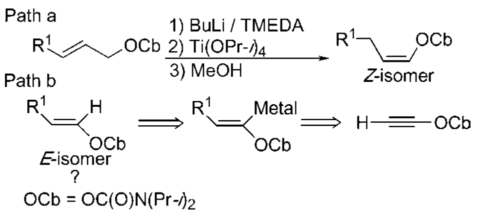
10.1021/ol036154b CCC: $25.00

Scheme 1

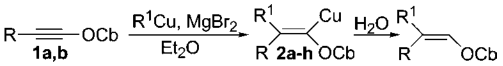


path a) and led to outstanding new applications in organic synthesis.[14,15] Surprisingly, no stereoselective preparation of the (*E*)-isomer was described in the literature. As quoted before, as we needed an easy and straightforward access for our study to either the (*E*)- or the (*Z*)-isomer of vinylic carbamate derivatives, we decided to develop a new stereoselective preparation of the (*E*)-isomer. The retrosynthetic analysis of the (*E*)-isomer shows that it should be easily prepared by a regiospecific syn addition of susbtituent R^1 and H across an alkyne. Obviously, the proton addition can be derived from the hydrolysis of a carbon−metal bond (Scheme 1, path b).

According to the retrosynthetic analysis described in Scheme 1, a regio- and stereospecific carbometalation reaction of ethynyl carbamate should be the key reaction for the preparation of (*E*)-enol carbamate. Among all the possible candidates for the carbometalation reactions,[16] we were interested in using the carbocupration reaction since organocopper derivatives are known for their high stereo- and chemoselectivity, which enables them to add smoothly to the triple bond of various alkynes[17] even in the presence of other functionalities.[18] When organocopper reagents are added to heterosubstituted acetylenes, pure regioisomers are usually obtained; however, the directing effect of oxygen and nitrogen leads to the branched product (copper in a β position to the heteroatom), while those of sulfur and phosphorus lead to the linear one (copper is geminated to the heteroatom).[19] Although the ethynyl carbamate is an oxy-substituted acetylene and therefore should lead to the branched product, we thought that the electron-withdrawing group properties of the carbamoyl group combined with its strong ability to coordinate organometallic derivatives should have a major directing effect and thus favor the linear isomer.

Indeed, when alkynyl carbamates **1a**,**b**, easily prepared from 2,2,2-tribromoethyl carbamate with excess LDA at low temperature as reported by D. Hoppe,[20] are added to organocopper derivatives RCu and $MgBr_2$ in Et_2O at −78 °C for only 90 min, the expected linear carbometalated products **2a**−**h** are obtained as a single (*E*)-isomer after hydrolysis as described in Table 1. The reaction is extremely rapid (90 min at −78 °C), and primary as well as secondary alkylcopper (entries 1−3) leads cleanly to the pure (*E*)-isomer after hydrolysis. It is interesting to note that although phenyl and methyl groups are known to be very sluggish in the carbocupration reactions,[19a] the carbamate moiety allows the reaction to proceed in excellent and moderate yields, respectively (Table 1, entries 4 and 5). A substituted alkynyl derivative such as propynyl carbamate **1b** also reacts easily with organocopper to afford stereospecifically the trisubstituted enol carbamate as a single isomer (Table 1, entries 6−8). Et_2O is the solvent of choice for this reaction since THF leads to the branched product as the major product (branched/linear = 80/20, Scheme 2). From this experiment, we can deduce that the coordinating effect of the carbamate to the organocopper plays a major role; carbocupration in

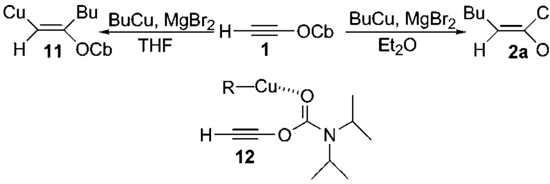
Table 1. Carbocupration Reaction of Alkynyl Carbamate



entry	starting material	R	R^1	products	yield[a] (%)
1	**1a**	H	n-C_4H_9	3	81
2	**1a**	H	c-C_6H_{11}	4	72
3	**1a**	H	C_2H_5	5	65
4	**1a**	H	C_6H_5	6	86
5	**1a**	H	CH_3	7	40
6	**1b**	CH_3	n-C_4H_9	8	80
7	**1b**	CH_3	c-C_6H_{11}	9	71
8	**1b**	CH_3	C_6H_5	10	60

[a] Yield of isolated pure products after purification on silica gel.

Scheme 2



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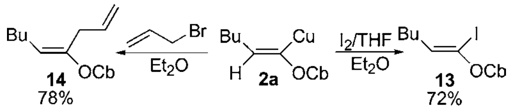
THF furnishes the "normal" (branched) product **11**, whereas in Et_2O, the product results from a directed reaction. A carbamate−organocopper complex **12** is therefore proposed to be the intermediate in the latter case.[21]

The formation of a new functionalized organometallic was checked by reaction of **2a** with iodine or by reaction with allyl bromide to give **13** and **14** in 72 and 78% yields, respectively, as described in Scheme 3.

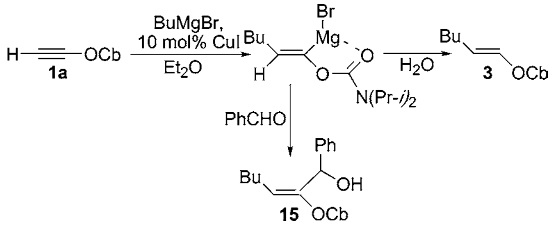
Scheme 3



To increase the efficiency of this reaction, we were also interested in developing the copper-catalyzed carbomagnesiation reaction. Therefore, ethynyl carbamate **1a** was added to a stoichiometric amount of alkylmagnesium halide in Et_2O in the presence of 10 mol % CuI. The carbometalated pure (*E*)-isomer is obtained after hydrolysis in 70% isolated yield. The addition of a typical electrophile of vinylmagnesium halide such as classical aldehyde is, therefore, now possible (Scheme 4); **15** is formed in 69% isolated yield.

Interestingly, this copper-catalyzed carbomagnesiation reaction proceeds at slightly higher temperatures than the stoichiometric process described in Table 1 (−40 instead of −78 °C), which can be attributed to a slow copper to magnesium transmetalation step, probably due to a strong intramolecular chelation of the sp^2 organometallic derivative by the carbamate moiety (Scheme 4).

Scheme 4



In conclusion, pure di- and trisubstituted (*E*)-alkenyl carbamates are easily prepared by a carbocupration reaction. Solvent plays a detrimental role in the regioselectivity of the reaction, and only Et_2O leads to the linear isomer, due to a precomplexation of the organocopper with the carbamate moiety. Finally, typical electrophiles of organocopper or organomagnesium chemistry can be added to the corresponding α-metalated enol carbamates.

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Supporting Information Available: Detailed experimental procedures and compounds data. This material is available free of charge via the Internet at http://pubs.acs.org.

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