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Highly Diastereoselective Preparation of Homoallylic Alcohols Containing Two Contiguous Quaternary Stereocenters in Acyclic Systems from Simple Terminal Alkynes

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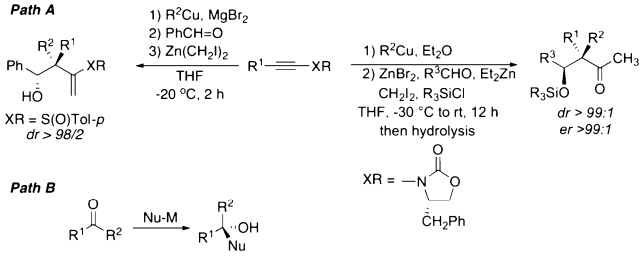
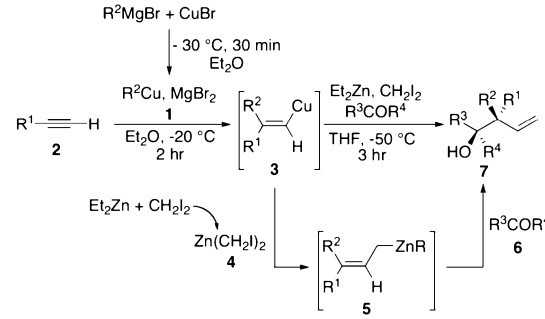
The stereoselective synthesis of quaternary stereocenters in an acyclic system is one of the major challenges in asymmetric synthesis.[1] Although many new elegant synthetic strategies were developed in the past few years, mostly through asymmetric catalysis, a single carbon−carbon bond is usually created per chemical step.[2] We have recently considered a different approach to prepare such stereocenters in an acyclic system[3] in which several carbon−carbon bonds could be formed in a single-pot operation via the use of ambiphilic zinc carbenoid species.[4] Indeed vinyl metal species, resulting from a regio- and stereoselective carbometalation reaction, react with zinc carbenoid and aldehydes to give the corresponding adducts in excellent yields and diastereoisomeric ratios as described in Scheme 1, path A. Homoallylic alcohols[3b,c−f] as well as aldol products[3a] were easily prepared in a single-pot operation from functionalized alkynes.

Scheme 1. Approaches to Stereodefined Quaternary Stereocenters



Alternatively, tertiary alcohols could be obtained from diastereoselective additions of nucleophiles to ketones, and despite the low reactivity and decreased steric discrimination of the carbonyl center, recent diastereo- and/or enantioselective alkylation,[5] alkynylation,[6] vinylation,[7] aldolization,[8] and allylation of ketones have been reported. In the latter case, organoboron,[9] titanium,[10] tin,[11] silyl,[12] and zinc species[13] were the focus of recent attention (Scheme 1, path B). However, stereoselective construction of two contiguous tetrasubstituted carbon stereocenters in an *acyclic system* is still extremely rare, and only a very limited number of strategies have been devised for directly assembling this structural unit.[14] Prominent examples only originate from sigmatropic rearrangements.[15] Herein, we report our efforts to address this challenging issue through the efficient construction of three carbon−carbon bonds in a single-pot operation from commercially available terminal alkynes. Our approach consists of the addition of organocopper reagents **1** (easily generated from the addition of 1 equiv of RMgBr with 1 equiv of CuBr in ether at −30 °C) to alkynes **2** that lead to the straightforward formation of stereodefined alkenyl copper reagents **3**.[16] Then, addition of ketones, CH_2I_2, and Et_2Zn are all added to the reaction mixture at low temperature. Neither vinylcopper **3** nor Et_2Zn reacts with ketones, and as the transmetalation from vinylcopper to vinylzinc is a slow process, the reaction between Et_2Zn and CH_2I_2 occurs first to lead to the *in situ* formation of the Simmons−Smith−Furukawa zinc carbenoid **4**.[17] This carbenoid species homologates the vinylcopper **3** into the allyl species **5**, which then react diastereoselectively with ketones **6** to give the expected homoallylic alcohols **7** as described in Scheme 2.

Scheme 2. Diastereoselective Formation of Homoallylic Alcohols Possessing Two Contiguous Quaternary Stereogenic Centers



In this strategy, the stereochemistry of the allylzinc species **5** results from the *syn*-controlled carbocupration reaction of simple alkynes **2** but the reaction of **5** with ketones **6** should be faster than any metallotropic equilibrium and diastereoselective.[3c] We were pleased to see that when the zinc homologation−allylation reaction was performed at low temperature, the stereochemistry of the allylzinc species was preserved as the reaction proceeds diastereoselectively with ketones as described in Table 1. For instance, when the carbocupration of 1-hexyne was performed with EtCu followed by the zinc homologation and reaction with acetophenone at −50 °C, the corresponding homoallylic alcohol **7a** was obtained in good isolated yield with an excellent diastereoselectivity of 98/2 (Table 1, entry 1). Permutation of the alkyl group of the alkyne R^1 and of the organocopper reagent R^2 allows the formation of the opposite diastereoisomer at the quaternary stereocenter with the same level of diastereoselectivity (97/3) excluding an open transition state mechanism (Table 1, entry 2). As quoted before, the metallotropic equilibrium competes with the allylation reaction, and if the same combined carbocupration−zinc homologation−allylation reaction of **2a** was performed at −40 or −20 °C instead of −50 °C, the homoallylic alcohol **7a** was also obtained but with a lower diastereoselectivity (91/9 and 60/40 respectively). At a lower temperature than −50 °C, the reaction becomes extremely sluggish and yields are lower.

When propiophenone was used (instead of acetophenone), the diastereoisomeric ratio of **7c** is slightly lower (Table 1, entry 3).

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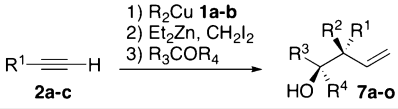
Table 1. Diastereoselective 3,3′-Disubstituted Allylzincation of Ketones



entry	R^1	R^2	R^3	R^4	pdts	Yield[a] %	dr[b]
1	C_4H_9 (**2a**)	C_2H_5 (**1a**)	C_6H_5	CH_3	**7a**	70	98/2
2	C_2H_5 (**2b**)	C_4H_9 (**1b**)	C_6H_5	CH_3	**7b**	72	97/3
3	C_2H_5 (**2b**)	C_4H_9 (**1b**)	C_6H_5	C_2H_5	**7c**	60	91/9
4	CH_3 (**2c**)	C_2H_5 (**1a**)	C_6H_5	CH_3	**7d**	60	99/1
5	CH_3 (**2c**)	C_2H_5 (**1a**)	C_6H_5	C_2H_5	**7e**	50	91/9
6	C_4H_9 (**2a**)	C_2H_5 (**1a**)	$pCH_3O_2CC_6H_4$	CH_3	**7f**	72	99/1
7	C_2H_5 (**2b**)	C_4H_9 (**1a**)	$pCH_3O_2CC_6H_4$	CH_3	**7g**	70	99/1
8	C_4H_9 (**2a**)	C_2H_5 (**1a**)	p-$CH_3C_6H_4$	CH_3	**7h**	60	98/2
9	CH_3 (**2c**)	C_2H_5 (**1a**)	p-BrC_6H_4	CH_3	**7i**	62	98/2
10	C_4H_9 (**2a**)	C_2H_5 (**1a**)	p-BrC_6H_4	CH_3	**7j**	60	97/3
11	CH_3 (**2c**)	C_2H_5 (**1a**)	p-$MeOC_6H_4$	CH_3	**7k**	55	97/3
12	CH_3 (**2c**)	C_2H_5 (**1a**)	2-naphthyl	CH_3	**7l**	65	98/2
13	C_4H_9 (**2a**)	C_2H_5 (**1a**)	PhCH=CH	CH_3	**7m**	40	98/2
14	C_4H_9 (**2a**)	C_2H_5 (**1a**)	2-thiophenyl	CH_3	**7n**	55	90/10
15	C_2H_5 (**2b**)	C_4H_9 (**1b**)	2-thiophenyl	CH_3	**7o**	57	90/10

[a] Isolated yields. [b] Diastereoisomeric ratios determined by ^1H, ^{13}C NMR and gas chromatography analysis of the crude reaction mixture.

The same trend was also observed when EtCu was added to propyne and reacted, after zinc homologation, with these two ketones (Table 1, entries 4 and 5 respectively). Several functionalized ketones were successfully used, and in all cases, excellent diastereoisomeric ratios were observed (Table 1, entries 6−11 and 14−15). When ester and ketone functionalities are present in the same electrophilic partner, only the carbonyl group of the ketone reacts to give functionalized adducts (Table 1, entries 6 and 7). The relative configuration was established by X-ray crystallography on the carboxylic acid **8f** resulting from the saponification of **7f** (see experimental procedure), and the configurations of other reaction products were assigned by analogy. An enone such as cinnamyl ketone reacts also with excellent diastereoselectivity albeit in lower yield (Table 1, entry 13). The diastereoselectivity of the reaction might be rationalized by a chairlike transition state in which the aryl group of the ketone occupies a pseudoequatorial position.

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Supporting Information Available: Experimental procedures with a description of ^1H and ^{13}C NMR data and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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