Combined Carbometalation−Zinc Homologation−Allylation Reactions as a New Approach for Alkoxyallylation of Aldehydes

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ABSTRACT
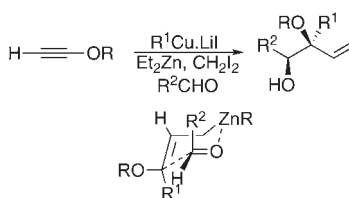
The combined carbometalation reaction of ynol ethers followed by a zinc homologation and further allylation reactions lead to an efficient preparation of allylic vicinal diols. The stereochemical outcome of the reaction shows that the substituent of the aldehyde occupies a pseudoaxial position in a Zimmerman−Traxler transition state.

Diastereoselective carbonyl allylation reaction[1] represents an important synthetic transformation that has found numerous applications in the synthesis of natural products.[2] Among all the allylation reactions, α-alkoxyallylation of aldehydes is one of the most powerful entries to stereodefined allylic vicinal diol substructures.[3] Such oxyallylorganometallic compounds are based on boron, aluminum, titanium, tin, zirconium, iridium, lithium, chromium, or zinc species,[2] and they derived generally from already constructed allyl ether derivatives[1,2] and have Z-stereochemistry as a result of intramolecular chelation.[4] Hence, access to E-configured alkoxy-substituted allylmetal reagents is still synthetically difficult.[5] Allyl complexes carrying a 3-silyl or boryl substituent may serve alternatively as alkoxyallyl surrogates.[6] One of the remaining challenges in this field is the development of strategies for the diastereoselective creation of quaternary stereocenters in acyclic systems.[1,7] Moreover, if such approaches could be performed in a single-pot operation from easily accessible or commercially available starting materials,[8] it would represent an interesting and important additional synthetic tool.

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(8) The Felkin−Anh addition to carbonyl derivatives can also be used to prepare equivalent substructures; see: Stanton, G. R.; Koz, G.; Walsh, P. J. *J. Am. Chem. Soc.* **2011**, *131*, 7969 and references cited therein.

In this context, we have developed in the past few years various approaches to prepare diastereo- and enantiomerically enriched all-carbon stereogenic centers (R^1, R^2, R^3, $R^4 \neq H$) in an acyclic system as described in Scheme 1.[9] In this letter, we report our preliminary results for the formation of stereodefined allylic vicinal diol derivatives in a single-pot operation from alkynyl ethers 1.

Simmons–Smith–Furukawa zinc carbenoid $Zn(CH_2I)_2$ 3,[16] generated *in situ* by reaction between Et_2Zn and CH_2I_2, that reacts with the vinylcopper 2 to lead to the *in situ* formation of allylzinc species 4.[17] As aldehyde is already present in the reaction mixture, a subsequent[9,17] allylation reaction gives the monoprotected 1,2-alkenyl diols 5 as described in Scheme 2.

Scheme 1. General Preparation of Diastereo- And Enantiomerically Enriched All-Carbon Stereogenic Centers in Acyclic System

Scheme 2. One-Pot Preparation of Monoprotected 1,2-Alkenyl Diols 5
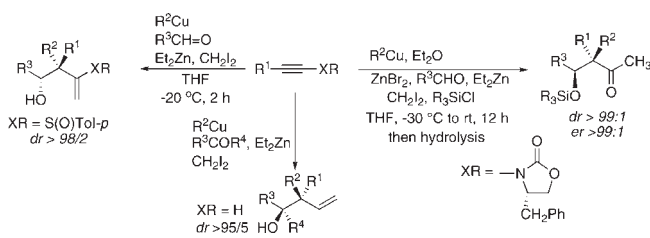
When commercially available or easily accessible[10] alkoxy-substituted acetylene 1 reacts with alkyl copper such as $R^1Cu \cdot LiI$, the isomer 2 possessing the copper atom in a β-position as regards to the heteroatom is exclusively obtained in good to excellent yields (carbocupration reaction with aryl and benzyl copper are not efficient).[11,12] The regioselectivity[13] can be rationalized by the electrostatic charge distribution in the alkynes.[14] To the vinylcopper 2 is then successively added Et_2Zn, CH_2I_2, and aldehydes at low temperature, and the expected adducts 5 are obtained in good yields and diastereoselectivities. Indeed, a domino reaction[15] proceeds by the initial formation of the

For instance, when the carbocupration of commercially available ethoxyacetylene 1a was performed with BuCu•LiI followed by the zinc homologation and reaction with benzaldehyde at −40 °C, the corresponding monoprotected 1,2-alkenyl diol 5a was obtained in good isolated yield and diastereoselectivity (Table 1, entry 1, dr 91/9). Surprisingly, when the same reaction was initially performed with an organocopper reagent resulting from an alkylmagnesium halide, BuCu•MgX₂, the diastereoselelectivity of the reaction is lower (dr 80:20 instead of 91:9, not indicated in Table 1). The reaction proceeds well using classical organocopper reagents and aromatic aldehydes (Table 1, entries 1−10). The reaction of benzyloxyacetylene 1b provides benzyl-*O*-protected 1,2-alkenyl diols (Table 1, entries 8−10) that can be easily deprotected to afford the corresponding diols. To our delight the reaction is not only limited to aromatic aldehydes but also proceeds with aliphatic aldehydes in equally good yield, albeit with slightly lower diastereoisomeric ratios (Table 1, entries 13−17) that may be explained by the allylation reaction proceeding at a slightly higher temperature. The relative configuration was established by X-ray crystallography on 5d (see experimental procedure),[18] and the configuration of other reaction products was assigned by analogy. Interestingly, a lower diastereomeric ratio was obtained when the aryl group has a substituent in

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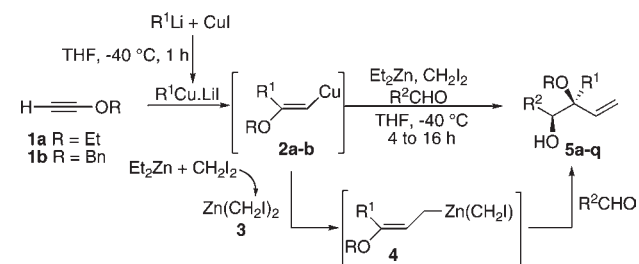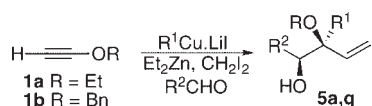
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(18) The following crystal structure has been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 817588.

Table 1. Combined Carbometalation−Zinc Homologation−Allylation Reactions of Alkynyl Ethers **1a,b**

$$\text{H}-\!\!\equiv\!\!-\text{OR} \xrightarrow[\substack{\text{Et}_2\text{Zn, CH}_2\text{I}_2 \\ \text{R}^2\text{CHO}}]{\text{R}^1\text{Cu.LiI}} \begin{array}{c}\text{RO}\quad\text{R}^1 \\ \text{R}^2 \overbrace{} \\ \text{HO}\quad\text{5a,q}\end{array}$$

1a R = Et
1b R = Bn

| entry	R	R^1	R^2	pdts	dr[a]	yield (%)[b]
1[c]	Et	Bu	C_6H_5	5a	91:9	75
2[c]	Et	Bu	$p\text{-BrC}_6H_4$	5b	90:10	65
3[c]	Et	Bu	$p\text{-ClC}_6H_4$	5c	90:10	71
4[c]	Et	Bu	$p\text{-CF}_3C_6H_4$	5d	86:14	65
5[c]	Et	Et	C_6H_5	5e	86:14	76
6[c]	Et	Et	$p\text{-BrC}_6H_4$	5f	86:14	72
7[c]	Et	Et	$p\text{-ClC}_6H_4$	5g	90:10	64
8[c]	Bn	Bu	$p\text{-BrC}_6H_4$	5h	92:8	78
9[c]	Bn	Et	C_6H_5	5i	83:17	63
10[c]	Bn	Me	$p\text{-ClC}_6H_4$	5j	80:20	71
11[c]	Et	Bu	$o\text{-ClC}_6H_4$	5k	67:33	62
12[c]	Et	Et	$p\text{-MeC}_6H_4$	5l	67:33	71
13[d]	Et	Bu	Et	5m	83:17	64
14[d]	Et	Bu	$i\text{-Pr}$	5n	88:12	67
15[d]	Et	Bu	Bu	5o	80:20	58
16[d]	Et	Bu	$PhCH_2CH_2$	5p	80:20	64
17[d]	Et	Et	Bu	5q	88:12	70

[a] Diastereomeric ratio determined by ^{1}H NMR spectroscopy of the crude mixture. [b] Isolated yields after purification by column chromatography. [c] Allylation reaction proceeds at −40 °C in 4 h. [d] Allylation reaction proceeds by slowly warming the reaction mixture from −40 °C to rt in 12 h.

the ortho-position or has an electron-donating group (Table 1, entries 11 and 12 respectively, see discussion later).

The reaction can be performed on a larger scale with similar results (Table 1, entry 1 on 5 mmol scale of **1a** leads to **5a** in 68% yield with a diastereomeric ratio of 90/10). It should be noted that the metalotropic equilibrium may compete with the allylation reaction, and if the same combined carbocupration−zinc homologation−allylation reaction of **1a** was performed at −20 °C instead of −40 °C, the monoprotected alkenyl 1,2-diol **5a** was obtained with the same chemical yield but with a lower diastereoselectivity (dr 66:33 instead of 91:9). However, when the reaction is performed at lower temperature (−60 °C), the zinc homologation becomes extremely slow and the yield drops dramatically (conversion of 10−20%). The best compromise we found was to perform the reaction at −40 °C; the *in situ* generated allylzinc species react with the aldehyde already present in the reaction mixture, to give the product with minimum stereochemical erosion. Interestingly, if one assumes that the stereochemistry of the major product results from a reaction where the allylzinc species retains its configuration, (1) a nonclassical *E*-configured alkoxy-substituted allylmetal reagent **4** is formed[5] and (2) the substituent of the aldehyde occupies a pseudoaxial position in a Zimmerman−Traxler transition state as depicted

in **II$_{ZT}$**. This counterintuitive stereochemical outcome results from a transition state where only one gauche interaction is present (see Newmann projection **II$_N$**) when the substituent is pseudoaxial whereas two gauche interactions would be generated if the substituent would occupy a pseudoequatorial position (**I$_N$** and **I$_{ZT}$**, Scheme 3).[19] When an aromatic group has a substituent in the ortho-position, a lower diastereomeric ratio is then obtained as 1,3-diaxial interactions increase (Table 1, entry 11).

Scheme 3. Transition States for the Allylation Reaction
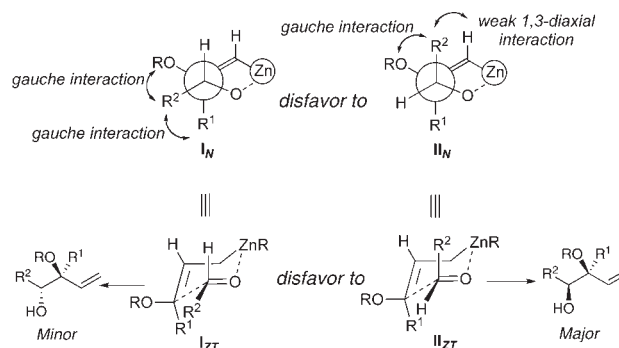
The stereochemistry of the major isomer **5** could also be rationalized by the reaction of the fully isomerized species **4Z** (thermodynamically more stable due to intramolecular chelation) with an aldehyde in which the substituent would now occupy a pseudoequatorial position in a boat transition state (Scheme 4). However, as the zinc homologation proceeds in the presence of the aldehyde and that the highest diastereoselectivity is observed at low temperature (−40 °C, dr 90:10 whereas at −20 °C, dr 66:33), the outcome of the reaction must be kinetically controlled and, therefore, the allylation reaction is faster than any haptotropic equilibrium.[20]

Scheme 4. Alternative Transition State
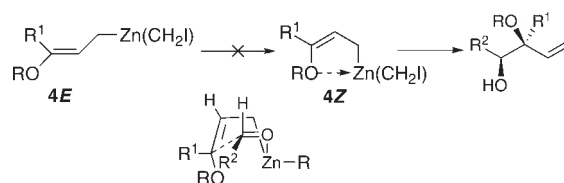
In summary, the combined carbocupration of ynol ether followed by a zinc homologation in the presence of aldehydes leads, in a single-pot operation, to stereodefined allylic vicinal diol substructures in good isolated yields and stereoselectivities. The stereochemistry of the final adducts suggests that the reaction proceeds through a chairlike

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transition state in which the substituent of the aldehyde preferentially occupies a pseudoaxial position to avoid gauche interactions with an *E*-configurated alkoxy-substituted allylmetal species.

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