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COMMUNICATION

Convergent diastereoselective preparation of adjacent quaternary stereocenters in an acyclic system†‡

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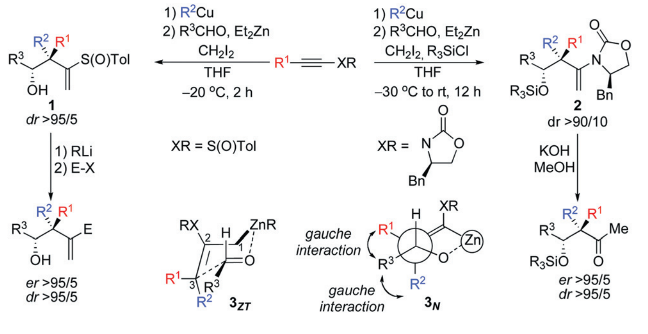
The combined carbometalation–zinc homologation–allylation reaction of the resulting stereodefined 3,3-disubstituted allylmetal species with ketones allow the preparation of allylic vicinal diol derivatives in good yields with excellent diastereomeric ratios from commercially available alkynes. Two adjacent quaternary centers are formed with the concomitant formation of three new carbon–carbon bonds in a single-pot operation in an acyclic system. The bulky substituent of the ketone occupies a pseudo-axial position in the Zimmerman–Traxler transition state.

In the last decade, the development of new strategies for the diastereo- and/or enantioselective creation of carbon atoms bonded to four different carbon substituents (all-carbon quaternary centers) have blossomed showing the contemporary interest of this field of research.[1] The creation of such centers in acyclic systems is particularly challenging (more complicated due to the number of degrees of freedom associated with these structures).[2] For the last few years, we have also been involved in this effort[3] but our approach differs from most of the other approaches (which rely on asymmetric catalysis between two components resulting in a single carbon–carbon bond formation)[2,4] as we are developing strategies that allow the synthesis of such challenging all-carbon quaternary centers through the concomitant formation of several carbon–carbon bonds in a single-pot operation from simple starting materials.[5]

Following this paradigm, we were delighted to find that acyclic homoallylic alcohols **1**[6] and aldol surrogate **2**[7] possessing the desired all-carbon quaternary stereocenter could be formed with excellent diastereo- and enantiomeric ratio from simple alkynes (alkynyl sulfoxides and ynamides respectively) in a single-pot operation (Scheme 1). The stereochemistry was rationalized through a Zimmerman–Traxler transition state ($\mathbf{3_{ZT}}$),[8] in which the bulky group of the aldehyde R^3 occupies a pseudo-equatorial position. Representing the same transition states using the Newman projection ($\mathbf{3_N}$), clearly indicate that two gauche interactions exist. The stereochemical outcome of the reactions described in Scheme 1 therefore implies that despite these two gauche interactions, the substituent of the aldehyde prefers to be pseudo-equatorial instead of being pseudo-axial to avoid the potential 1,3-diaxial interactions with the bulky substituent XR. Interestingly, we have recently shown that if we remove this possible 1,3-diaxial interaction by having a small substituent in C_2 (XR = H), 3,3-disubstituted allylzinc species,[9] easily generated by reaction of vinyl copper with zinc carbenoid,[10] reacts with aldehydes to give indeed the opposite diastereomer. The aryl- or alkyl groups of the aldehydes now occupy a pseudo-axial position in the Zimmerman–Traxler transition state ($\mathbf{4_{ZT}}$) (or Newman projection $\mathbf{4_N}$) to avoid one gauche interaction (Scheme 2, Path A).[11]

This important stereochemical outcome could be extended to the formation of stereodefined allylic vicinal diol derivatives in a single-pot operation from alkynyl ethers (Scheme 2, Path B).[12] It should be noted that a non-classical *E*-configured alkoxy-substituted allylzinc reagent is formed as an intermediate.[13]

To further extend this stereochemical concept (substituent of the carbonyl compound in a pseudo-axial position) combined with the challenge of preparing complex structural molecular fragments in a single-pot operation, we turned our attention to the reaction with ketones. Classically, tertiary alcohols are



Scheme 1

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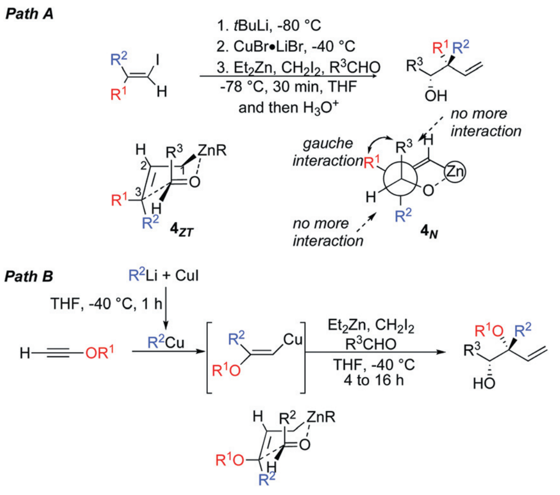
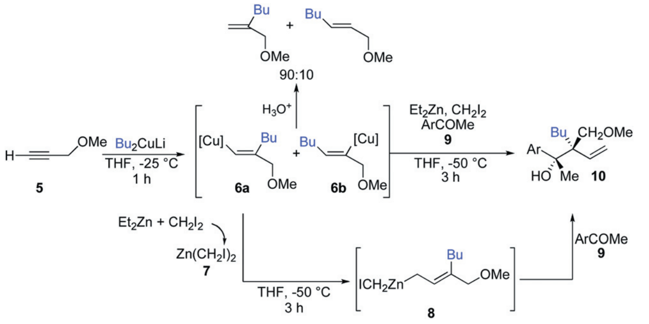
‡ Electronic supplementary information (ESI) available. CCDC 861563 and 861564. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25121c



Scheme 2

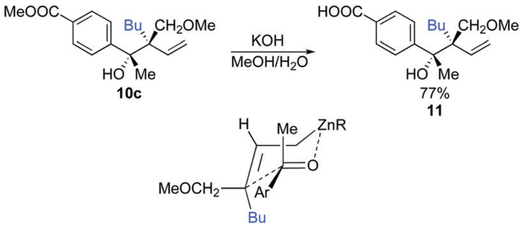


Scheme 3

Table 1 Allylation of aryl methyl ketones **9** with 3,3-disubstituted allylzinc **8**

Entry	R^1	dr[a]	Products	Yield[b] (%)
1	C_6H_5	94 : 6	**10a**	60
2	pMeC_6H_4	92 : 8	**10b**	51
3	pMeO_2CC_6H_4	95 : 5	**10c**	50
4	2-Naphthyl	86 : 14	**10d**	52

[a] Diastereomeric ratio determined by crude ^{1}H NMR and by gas chromatography analysis. [b] Yields determined after purification by column on silica gel.



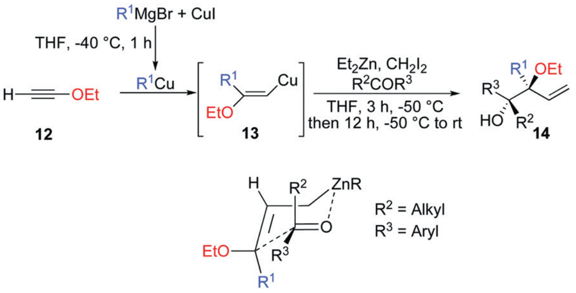
Scheme 4

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 allylation of ketones have been reported.[14] However, stereoselective construction of two contiguous tetrasubstituted stereocenters in an *acyclic system* (tertiary alcohols and all-carbon quaternary stereogenic centers) is still extremely rare and only a very limited number of strategies have been devised for directly assembling this structural unit.[15,16] 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 with a special emphasis on the stereochemistry of the reaction in the Zimmerman–Traxler transition state. Our initial focus has been directed to the transformation of commercially available propargyl ether **5** into homoallylic alcohols **10**. The addition of an organocuprate to **5** in THF proceeds with incomplete regioselectivity as two isomers **6a** and **6b** were obtained in a 90 : 10 ratio as determined by analysis of crude NMR spectra after hydrolysis of the reaction mixture.[17] Despite this ratio, the addition of various aryl methyl ketones **9**, CH_2I_2 and Et_2Zn to the vinyl copper at low temperature and stirring the reaction mixture at −50 °C for 3 h leads to a single adduct. Vinyl copper **6b** does not react with zinc carbenoid under this experimental condition and remains unchanged. Only **6a** is *in situ* transformed into the final homoallylic alcohols **10**. Indeed, neither vinylcopper **6a** nor Et_2Zn react with ketones **9** at low temperature and as the transmetalation from vinylcopper to vinylzinc is a slow process, the reaction between Et_2Zn and CH_2I_2 occurs first to leading to the *in situ* formation of the Simmons–Smith–Furukawa zinc carbenoid **7**.[18] This carbenoid species homologates the vinylcopper **6a** into the stereodefined 3,3-disubstituted allylzinc **8**,[19] which then reacts diastereoselectively with aryl methyl ketones **9** to give the expected alcohols **10** as described in Scheme 3.

First, we were pleased to see that the reaction indeed proceeds with very good diastereomeric ratio with aromatic methyl ketones as described in Table 1, entries 1 to 4 although in moderate yields. When the allylation is performed at higher temperature (*i.e.* −20 °C instead of −50 °C), yields are slightly improved but the diastereomeric ratio decreases drastically (dr 75 : 25). The relative configuration was established by X-ray crystallography[20] on the carboxylic acid **11**, obtained after hydrolysis of **10c** (Scheme 4), and the configuration of other reaction products was assigned by analogy.

The relative configuration of **11**, assuming that the allylzinc retains its configuration,[21] led us to hypothesize that the stereochemistry of the major isomer results from a transition state where the alkyl group of the ketone occupies a pseudo-axial position (therefore the aryl group occupies the pseudo-equatorial position).

Although the reaction proceeds as expected to give the two adjacent quaternary centers in an acyclic system, the moderate yield of this transformation, due to the uncompleted carbocupration reaction of propargyl ether **5**, led us to consider a different alkyne as starting material giving a single regioisomer in the carbometalation reaction. The formation of polysubstituted diol derivatives through alkoxyallylation of ketones and to investigate its stereochemical outcome would be particularly interesting. For this purpose, commercially available ethoxyacetylene **12** was carbometalated with organocopper reagents to give the corresponding vinyl copper species **13**. All reactants were added to

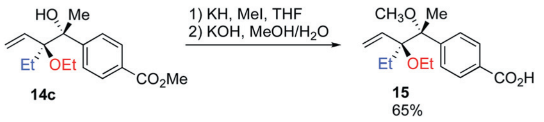


Scheme 5

Table 2 Allylation of ketones with 3,3-disubstituted alkoxyallylzinc

Entry	R^1	R^2	R^3	dr^a	Products	Yield^b (%)
1	Et	Me	C_6H_5	98 : 2	**14a**	71
2	Et	Et	C_6H_5	94 : 6	**14b**	70
3	Et	Me	$p\mathrm{CF_3C_6H_4}$	98 : 2	**14c**	58
4	Et	Me	$p\mathrm{BrC_6H_4}$	98 : 2	**14d**	54
5	Et	Me	$p\mathrm{MeOOCCC_6H_4}$	98 : 2	**14e**	68
6	Bu	Me	C_6H_5	90 : 10	**14f**	68
7	Bu	Et	C_6H_5	95 : 5	**14g**	57
8	Me	Me	C_6H_5	98 : 2	**14h**	61
9	Me	Me	$p\mathrm{BrC_6H_4}$	98 : 2	**14i**	57

^{a} Diastereomeric ratio determined by crude ^{1}H NMR. ^{b} Yields determined after purification by column on silica gel.



Scheme 6

the latter at low temperature and the corresponding diol derivatives **14** were obtained in good yields with excellent diastereoselectivities as shown in Scheme 5 and Table 2.

For instance, when EtCu is added to ethoxyacetylene **12**, the vinylcopper **13a** is quantitatively formed. Addition of Et_2Zn, CH_2I_2 and acetophenone led to the diol derivative **14a** in 71% isolated yield with an outstanding diastereomeric ratio of 98 : 2 (Table 2, entry 1). The relative configuration was established by X-ray crystallography[22] on the carboxylic acid **15**, obtained after methylation of the alcohol and hydrolysis of **14e** (Scheme 6). The configuration of other reaction products was assigned by analogy. Here again, the stereochemistry of **15** led us to assume that the substituent alkyl occupies the pseudo-axial position in the Zimmerman–Traxler transition state.[23] When the size of the alkyl substituent increases (R^2 = Et, namely addition of phenyl ethyl ketone, Table 2, entry 2), diastereomeric ratio and yields are very similar. So the bulky substituent occupies a pseudo-axial position to avoid the gauche interaction. Various functionalized aryl ketones were also engaged in this reaction and in all cases, excellent ratios were obtained although in lower yields in some cases (Table 2, entries 3–5).

It should be noted that the allylation reaction proceeds only on the carbonyl group of the ketone without any traces of the reaction on the ester moiety (Table 2, entry 5). Obviously, the reaction is not restricted to the addition of EtCu and various different organocopper reagents can be added including the less reactive MeCu (Table 2, entries 6–9). Although, the alkoxyallylation of dialkylketone (*i.e.* 2-hexanone) proceeds, yields are lower (40%) and the two diastereomers were logically obtained in equal amount showing the limitation of our approach (not indicated in Table 2). In this case, we could not generate any differentiation in the position of the alkyl groups of the ketone in the Zimmerman–Traxler transition state.

In conclusion, the combined carbometalation–zinc homologation–allylation reactions of ketones allow the preparation of various diol derivatives in good yields with excellent diastereomeric ratio from very simple and commercially available starting materials. In these reactions, two adjacent quaternary centers are formed with the concomitant formation of three new carbon–carbon bonds in a single-pot operation in an acyclic system and represents a powerful method for the stereodefined synthesis of allylic vicinal diol substructures.

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22 The crystal structure of **15** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 861564‡.

23 Although the A-value (numerical values used in the determination of the most stable orientation of atoms in a molecule) is 1.7 for a methyl group and 3 for an aryl group, it is important to note that these A-values do not predict the physical size of a molecule. As the phenyl ring is planar, it may adopt a position leading to less steric interaction than a non-planar methyl group.