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Axial Preferences in Allylations via the Zimmerman–Traxler Transition State

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Currently, one of the most dynamic areas in organic synthesis is the asymmetric construction of molecules with quaternary carbon stereocenters, that is, carbon centers with four different alkyl substituents.[1] The state-of-the-art in this field is the asymmetric construction of these stereocenters in acyclic systems.[2] In the last few years, we have been involved in the development of synthetic strategies that have led to the formation of these desired fragments, but we have focused on the concomitant creation of several carbon–carbon bonds in a one-pot operation.[3] Our method consists of a carbometalation reaction of various α-hetero-substituted functionalized alkynes[4] followed by a zinc homologation reaction[5] through the use of a zinc carbenoid, formed in situ,[6] and then an allylation reaction of carbonyl compounds (Scheme 1).

Depending on the nature of the hetero-substituent on the alkyne, alkynyl sulfoxide (Method A) or ynamide (Method B), the formation of either homoallyl alcohol or aldol products, respectively, occurred with very high diastereo- and enantioselectivity. In both cases, the stereochemistry was rationalized through a Zimmerman–Traxler transition state,[7] in which the bulky group in the aldehyde, R^3, occupies a pseudoequatorial position. In Method A, since the S–O bond operates as an acceptor site for Lewis acids, the sulfoxide forms a metallacycle that is sterically hindered (**1** in Scheme 1). This is also the key element for the excellent diastereoselectivity observed in the transformation of yn-amides into the aldol surrogate adducts as described by transition state **2** (Scheme 1).

When sterically substantial substituents engaged in the metallacycle are present in position 2, shown as a grey circle in representations $\mathbf{I}_{ZT}$ and $\mathbf{II}_{ZT}$ in Scheme 2, the R^3 group of the aldehyde adopts a pseudoequatorial rather than pseudoaxial position to minimize potential 1,3-diaxial interactions, that is, $\mathbf{I}_{ZT}$ is favored over $\mathbf{II}_{ZT}$. However, by representing the same transition states by using Newman projections, it becomes clear that two gauche interactions exist as in $\mathbf{I}_N$, whereas in $\mathbf{II}_N$, in which the R^3 group is in a pseudoaxial position, one gauche

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and one 1,3-diaxial interaction exist (Scheme 2). The stereochemical outcome of the two reactions described in Scheme 1 implies that the combined 1,3-diaxial and gauche interactions occurring in $\mathbf{II}_{N}$ are more destabilizing since only transition state $\mathbf{I}_{N}$ (or $\mathbf{I}_{ZT}$), possessing two gauche interactions, leads to the products.

However, what would be the stereochemical outcome of a reaction if the bulky axial groups were replaced by a hydrogen atom? Are the two gauche interactions present in transition state $\mathbf{III}_{N}$ preferred to transition state $\mathbf{IV}_{N}$, in which the R^3 substituent of the aldehyde occupies a pseudoaxial position, as represented in Scheme 3?

This important stereochemical question can only be solved by control of the constitutional stability of η^1-allylmetal compounds, that is, if the haptotropic rearrangement (metalotropic equilibrium) is slower than the reaction with the aldehyde.[8] After extensive experimentation, we found that the successive treatment of vinyl iodides **3**, prepared by carbometalation of alkynes[4] with *t*BuLi followed by the addition of a soluble solution of copper salt led to the formation of vinyl copper **5**. Then, at −80°C, the addition of aldehydes, Et_2Zn, and CH_2I_2 to this vinyl copper compound gave the expected homoallylic alcohols **7** through the formation of 3,3-disubstituted allylzinc species **6** (Scheme 4). As shown previously,[3] neither vinyl copper nor Et_2Zn reacts with aldehydes at low temperature and as the transmetalation from vinyl copper to vinyl zinc is also a slow process at these temperatures, the reaction between Et_2Zn and CH_2I_2 occurs first to give in situ formation of the zinc carbenoid.[9] This carbenoid then readily homologates vinyl copper **5** into the allyl species **6**,[5] which reacts diastereoselectively with aldehydes to give homoallylic alcohols **7** in very high diastereoselectivities (Scheme 4 and Table 1). As shown for **7a** (R^1=Hex, R^2=Et; Table 1, entry 1) and **b** (R^1=Et, R^2= Hex; Table 1, entry 2) with aromatic aldehydes, but also for **7j** and **k** with an aliphatic aldehyde, permutation of the alkyl groups at the vinyl iodide allows the independent formation of the two diastereoisomers at the quaternary carbon center. This implies that 1) the haptotropic rearrangement is slower than the reaction of allyl zinc with aldehydes[8] and 2) the reaction does not proceed through an open transition state, but rather occurs via a cyclic transition state. Several different alkyl groups were easily introduced at the all-carbon stereogenic center, which shows the flexibility of the described method. Functionalized aldehydes can also be used in this allylation reaction, such as 4-bromo-benzaldehyde (Table 1, entries 1–5), 4-carbomethoxybenzaldehyde (Table 1, entry 9), and even 4-acetylbenzaldehyde (Table 1, entry 8). In all cases, the reaction proceeds chemo-selectively with respect to the aldehyde. The reaction is not restricted to aromatic aldehydes, since aliphatic aldehydes also lead to the homoallylic alcohols with decent stereoselectivities (Table 1, entries 10–13). The stereochemistry observed in this one-pot reaction was confirmed by comparison with an authentic sample of **7g** previously prepared in our research group and analyzed by X-ray crystallographic analysis.[3f] The configurations of other reaction products were assigned by analogy.

Importantly, the relative configuration of all homoallylic alcohols **7** implies that the R^3 group of the aldehyde now occupies a pseudoaxial position in a chair-like transition state when it reacts with 3,3-disubstituted allylzinc species, as shown in $\mathbf{IV}_{ZT}$ (Scheme 3).[10]

To have a better stereochemical understanding of the reaction of 3,3-disubstituted allylzinc compounds with carbonyl compounds, we have performed theoretical calculations on a model system (Figure 1).[11] We initially investigated the reaction of an allylzinc species possessing a sulfoxide group at C2 with benzaldehyde (as described in **1**, Scheme 1). The reaction proceeds via the chair-like transition states shown in $\mathbf{TS_I}$ and $\mathbf{TS_{II}}$ (Figure 1). We also tried to locate possible boat-like transition states, but these could not be found as stationary points. As expected, $\mathbf{TS_I}$, in which the aryl group occupies the pseudoequatorial position, is 4.9 $kcalmol^{-1}$ more stable than $\mathbf{TS_{II}}$, in which the aryl group occupies the

pseudoaxial position (the carbon of the aldehyde is circled).[12] However, if the sulfoxide on C2 of the allylzinc is replaced by a hydrogen atom, the reaction still proceeds through a similar chair-like Zimmerman–Traxler transition state, but the stereochemical outcome is reversed since the aryl group of the aldehyde in a equatorial position (**TS_{III}**) is now higher in energy (by 2.2 kcalmol^{-1}) than if the same aryl group is in the axial position (**TS_{IV}**).

These computational results show that two gauche interactions lead to a transition state of higher energy and, to avoid this configuration, the system prefers to have the substituent of the aldehyde in an axial position.[13] Finally, we also checked the case of an aliphatic aldehyde, such as *i*PrCHO, as the electrophilic partner by computational methods. Again, having the alkyl substituent in the equatorial position is much higher in energy (**TS_V**) than if the substituent is in an axial position (**TS_{VI}**).

To further probe experimentally the stereochemical outcome resulting from the Zimmerman–Traxler transition state, a 2,3,3-trialkyl-substituted allylzinc compound was prepared and tested in our reaction. In this particular case, the alkyl group at C2 is less sterically demanding than the metallacycle containing the sulfoxide or oxazolidinone moieties and a mixture of diastereoisomers is expected. To check this hypothesis, vinyl iodide **8**, easily prepared by zirconium-promoted ethylzination of 2-butyne,[14] was treated under the conditions described in Scheme 4 with 4-carbomethoxybenzaldehyde as the electrophilic partner and homoallyl alcohol **9** was obtained in 53% yield with a diastereoisomeric ratio of 7:3 (Scheme 5). The configuration of the major diastereoisomer was determined by X-ray crystallographic analysis and found to result from a reaction in which the aromatic group of the aldehyde still occupies the pseudoaxial position. However, the formation of the two isomers shows the limitations of the system.

In summary, the stereochemical outcome of the allylation reaction of 3,3-disubstituted allylzinc species with aldehydes shows that the aryl or alkyl group on the electrophilic carbonyl reactant occupies a pseudoaxial position in the Zimmerman–Traxler transition state to avoid gauche interactions. However, if bulky substituents are present at the C2 center of the allylzinc species, the additional 1,3-diaxial interaction counterbalances the two gauche interactions. We are currently expanding the scope of this new stereochemical feature to other systems. It has become clear from these considerations that the size of the metal and associated ligands in the Zimmerman–Traxler transition state of the 3,3-disubstituted allylmetal[15] should also influence the stereochemistry. This is currently being investigated in our laboratory.

Experimental Section

General procedure for the reaction of vinyl iodides 3

*t*BuLi (2.2 equiv, 2.2 mmol) was added to a solution of vinyl iodide **3** (1 mmol) in THF (10 mL) at −78°C. The resulting mixture was stirred at this temperature for 10 min. The reaction mixture was then warmed to −40°C and a solution of CuBr·LiBr (1.1 equiv, 1.1 mmol) in THF (2 mL) was added. The mixture was stirred for an additional 40 min. After cooling the reaction mixture to −78°C, a solution of the aldehyde (1 equiv, 1 mmol) in THF (1 mL) was added and the mixture was stirred for 10 min. CH_2I_2 (6 mmol) and Et_2Zn (3 mmol) were then added and the reaction mixture was stirred at −78°C for a further 30 min (for aliphatic aldehydes, the reaction mixture was stirred at −40°C for 4 h). The hydrolysis was performed with an aqueous solution of NH_4Cl/NH_3 (2:1). After a standard workup, the crude product was purified by column chromatography on alumina to give pure homoallylic alcohol **7**.

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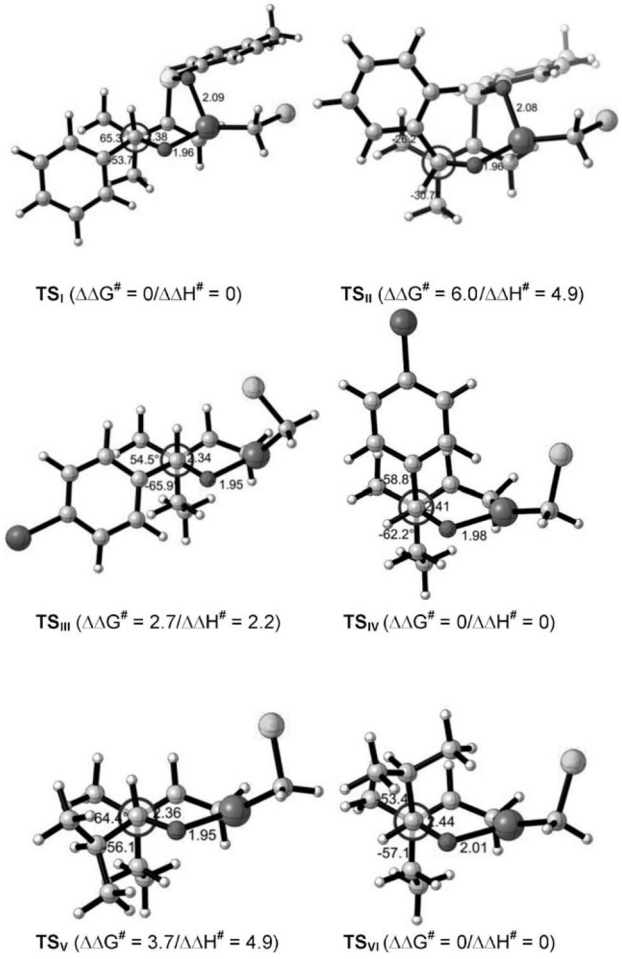
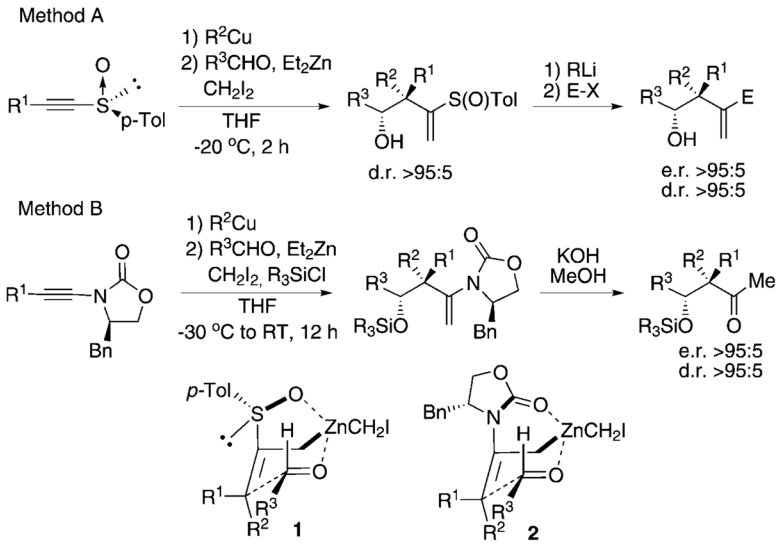
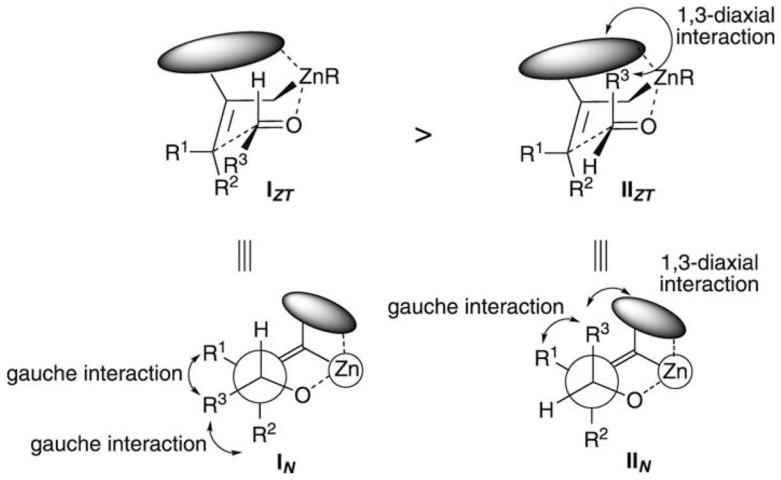


Figure 1.
MO5-2x/6-31G(d) optimized structures for all transition states (**TS**).



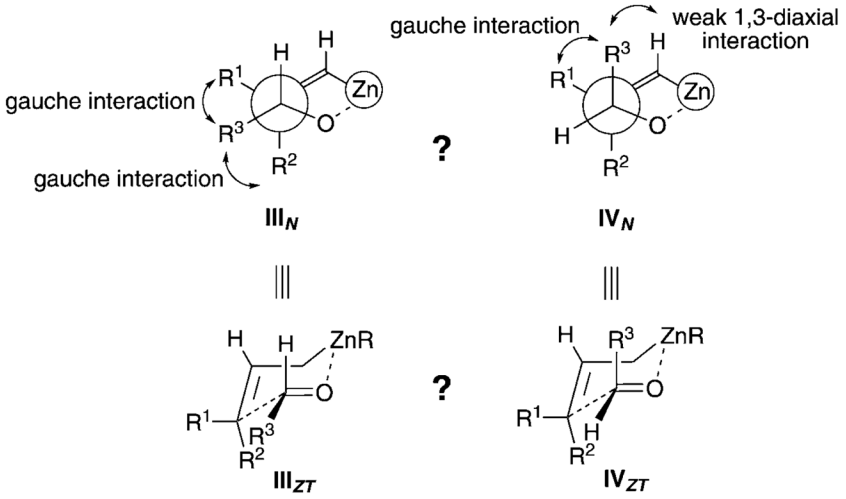
Scheme 1.

Combined carbometalation–zinc homologation and allylation reactions en route to the formation of quaternary stereocenters.

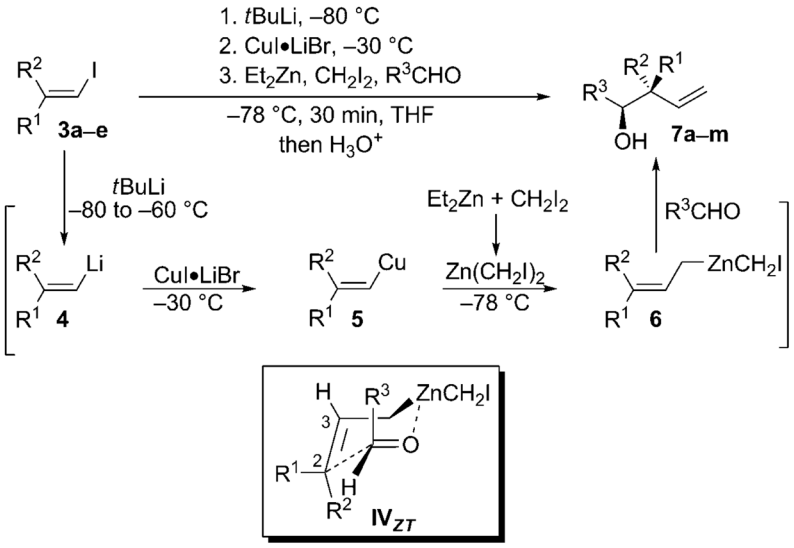


Scheme 2.

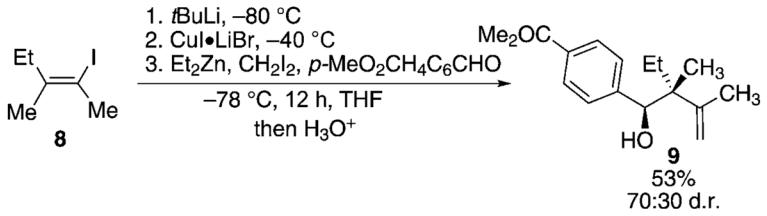
Zimmerman–Traxler transition states for the allylation reaction of 2,3,3-trisubstituted allylzinc species. Both “chair” and Newman projections are shown.



Scheme 3.
Transition states for the allylation reaction of 3,3-disubstituted allylzinc species.



Scheme 4.
Diastereoselective allylation reactions of 3,3-disubstituted allylzinc species.



Scheme 5.
Diastereoselective allylation reactions of 2,3,3-trialkyl-substituted allylzinc species.

Table 1

Allylation reactions of 3,3-disubstitued allylzinc species with various aldehydes.[a]

	Starting material	R^1	R^2	R^3	Product	Yield [%][b]	d.r.[c]
1	**3a**	Hex	Et	*p*-BrH_4C_6	**7a**	71	97:3
2	**3b**	Et	Hex	*p*-BrH_4C_6	**7b**	55	90:10
3	**3c**	Hex	Bu	*p*-BrH_4C_6	**7c**	60	98:2
4	**3d**	Bu	Et	*p*-BrH_4C_6	**7d**	70	92:8
5	**3e**	Me	Et	*p*-BrH_4C_6	**7e**	52	90:10
6	**3a**	Hex	Et	*p*-MeH_4C_6	**7 f**	60	98:2
7	**3d**	Bu	Et	H_5C_6	**7g**	70	98:2
8	**3d**	Bu	Et	*p*-$OAcH_4C_6$	**7h**	63	88:12
9	**3d**	Bu	Et	*p*-$MeO_2CH_4C_6$	**7i**	65	88:12
10[d]	**3b**	Hex	Et	*n*Bu	**7j**	70	96:4
11[d]	**3a**	Et	Hex	*n*Bu	**7k**	66	91:9
12[d]	**3d**	Bu	Et	$Ph(CH_2)_2$	**7l**	62	83:17
13[d]	**3d**	Bu	Et	*i*Pr	**7m**	41	80:20

[a] Hex=hexyl.

[b] Determined after purification by column chromatography on alumina.

[c] Determined by analysis of the crude product by ^{1}H NMR spectroscopy and gas chromatography.

[d] For aliphatic aldehydes, the allylation reaction proceeds at −40°C and the increased temperature can explain the lower diastereoselectivity.

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