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Four-Component Reactions for a New Diastereoselective Synthesis of Chiral Quaternary Centers

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One of the major challenges in synthesis nowadays is to approach the ideal synthesis in which a given target molecule would be assembled from readily available starting materials in a one-step synthesis and in a simple, safe, and straightforward manner. Of exceptional importance is the goal of step economy, which can be achieved only through the use of reactions that allow a great increase in complexity or through operations that incorporate many steps that collectively achieve the same high-complexity increase. In this communication, we describe a unique diastereoselective four-component condensation reaction for the preparation of homoallylic alcohols with the creation of chiral quaternary centers. The enantioselective addition of allylmetal reagents to aldehydes is a powerful method for stereoselective carbon−carbon bond formation[1] and often-employed in the total synthesis of polypropionate-derived natural products.[1a] The overwhelming majority of examples which proceed with excellent diastereo- and enantioselectivity lead to the creation of chiral tertiary carbon centers[1,2] in allylic position. On the contrary, only very few general methods are available for the stereoselective construction of chiral quaternary carbon centers.[3] With the major problem being the control of the metallotropic equilibrium, most of the efforts were directed toward the preparation of stereochemically pure 3,3-disubstituted allylsilanes, stannanes, or boranes.[1] However, these few methods either required several chemical steps for the preparation of geometrically pure 3,3-disubstituted allylmetal reagents,[3b−c] or when prepared in a single-pot operation, the control of the asymmetric induction with chiral auxiliaries was achieved only for symmetrically 3,3-disubstituted allylmetal.[3a] Herein, we report the first two direct entries into enantiomerically pure quaternary centers[4] in a single-pot operation from very common starting materials. Our first approach was based on the successive reaction of the readily available racemic or chiral alkynyl sulfoxides **1a**−**d**,[5] with organocopper reagents **2**, aldehydes or imines **3a**−**c**, and bis(iodomethyl)zinc carbenoid **4**. Chiral 1-alkynyl-*p*-tolyl-(S)-sulfoxide **1a**,**d** are easily prepared by sulfinylation of alkynylmagnesium bromide with (−)-menthyl-(*S*)-*p*-toluenesulfinate.[6]

First, the regio- and stereospecific carbocupration reaction of alkynyl sulfoxide **1a**,**b** with organocoppers **2a**−**c**, easily prepared from alkylmagnesium halide and CuBr, provides the corresponding metalated β,β-dialkylated α,β-ethylenic sulfoxide **5** in quantitative yield.[7] The reaction mixture is then treated with aldehydes or imines **3a**−**c** followed by the bis(iodomethyl)zinc carbenoid **4** (Scheme 1).[8] The vinylic copper reagent **5** as well as the zinc carbenoid **4** is not reactive enough to add to the aldehyde or imine **3a**−**c** derivatives; however, **5** is readily homologated by a methylene unit with the carbenoid **4**, affording in situ a highly reactive allylic zinc and copper species **6**[9] that reacts diastereoselectively with the electrophiles, giving after hydrolysis the corresponding adducts in good overall yields with a very high diastereoselectivity (Scheme 1 and Table 1). The zinc carbenoid homologation followed by the allylation reaction occur in less than 5 min at −15 °C. The formation of mainly one diastereomer is in strong contrast with the addition of substituted allyl zinc halide to aldehydes, which usually occurs without diastereoselectivity.[10]

Scheme 1

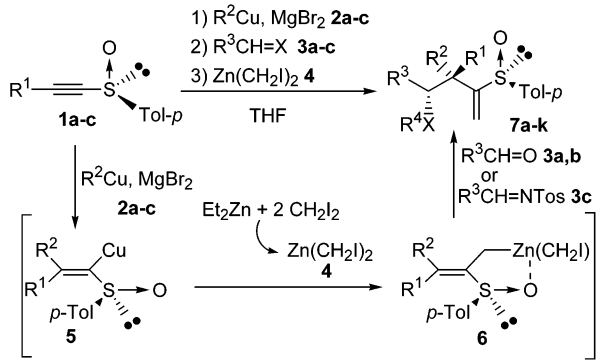

Table 1. Stereocontrol in the Allylation Reaction

entry	R^1	R^2	R^3	pdts	dr[a]	yield, %[b]
1	Bu **1a**	Et **2a**	Ph **3a**	**7a**	>99/1	78
2	Bu **1a**	Et **2a**	Bu **3b**	**7b**	30/1	60
3	Et **1b**	Bu **2b**	Ph **3a**	**7c**	>99/1	68
4	Bu **1a**	CH_3 **2c**	Ph **3a**	**7d**	>99/1	66
5	Et **1b**	CH_3 **2c**	Ph **3a**	**7e**	>99/1	66
6	Et **1b**	CH_3 **2c**	Bu **3b**	**7f**	30/1	58
7	Bu **1a**	Et **2a**	Ph **3c**	**7g**	>99/1	72
8	Bu **1a**	CH_3 **2c**	Ph **3c**	**7h**	28/1	75
9	Et **1b**	Bu **2b**	Ph **3c**	**7i**	>99/1	70
10	H **1c**	Et **2a**	Ph **3a**	**7j**	80/20	78
11[c,d]	Bu **1a**	Et **2a**	Ph **3a**	**7a**	20/1	75
12[c]	Bu **1a**	CH_3 **2c**	Ph **3a**	**7d**	20/1	88
13[c]	CD_3 **1d**	CH_3 **2c**	Ph **3a**	**7k**	25/1	82

[a] Determined on the crude ^{1}H and ^{13}C NMR. [b] Isolated yield after purification by chromatography on silica gel. [c] Cu-catalyzed reaction with R_2Zn. [d] Cu-catalyzed reaction with RZnBr.

The stereochemistry observed in this one-pot four-component reaction was confirmed by X-ray analysis of **7a**, **7d**, and **7h**, and the configurations of other reaction products were assigned by analogy. Whatever the electrophiles used (aromatic **3a** or aliphatic aldehydes **3b** as well as *N*-sulfonyl aldimines **3c**[11]), excellent diastereomeric ratios were obtained in good overall yields as described in Table 1, entries 1, 2, and 7, respectively. As shown with **7a** (R^1 = Bu, R^2 = Et, entry 1) and **7c** (R^1 = Et, R^2 = Bu, entry 3), permutation of the alkyl groups of the alkyne and the organocopper reagent allows the independent formation of the two isomers at the quaternary carbon center, respectively.[12] Even the methyl copper, known to be a sluggish group in the carbocupration reaction,[13] adds cleanly to the alkynyl sulfoxide and gives after the homologation−allylation reactions, the expected homoallylic alcohol as mainly one isomer (see Table 1, entries 4−6 and 8).

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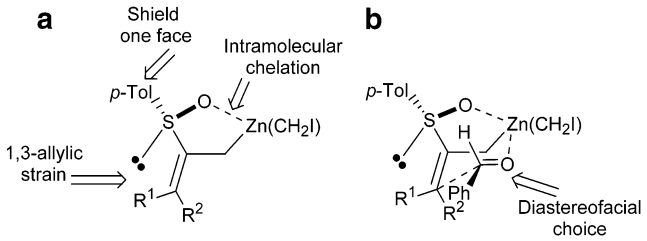
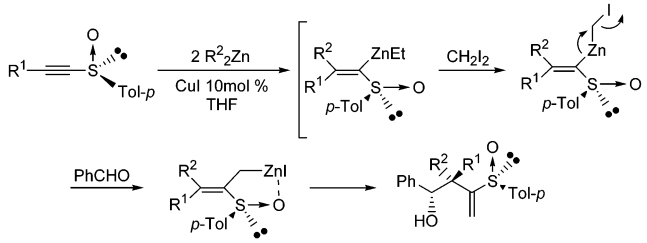


Figure 1.

Scheme 2



Interestingly, when the same one-pot sequence was applied to **1c** for the preparation of tertiary carbon centers (R^1 = H, Table 1, entry 10), two syn isomers (related to the sulfur stereogenic center) were obtained in 80/20 ratio.[14] Since the S−O bond operates as an acceptor site for Lewis acids, the conformation of the sulfoxide is strongly influenced by complexation of the zinc atom and also by the *Z*-substitution of the carbon−carbon double bond (compare entries 1−9 and 10). It seems likely that the additional R^1-substituent causes severe 1,3-allylic strain,[15] and the most stable conformer is the one having the lone pair of the sulfoxide eclipsing the double bond. Thus, the combination of this intramolecular chelation with the related allylic strain[16] leads probably to a unique conformation of the allyl zinc derivatives as described in Figure 1a. Moreover, simple diastereoselection in the reaction of allylic zinc derivatives with aldehydes is usually critically dependent on the configurational stability of the reagent.[17] As a general rule, most substituted allylic zinc reagents are sensitive to sequential 1,3-metal shifts (1,3-metallotropic rearrangement)[18] that result in *E*- to *Z*-olefin isomerization. In this particular case, no isomerization of the primary allyl zinc derivative **6** is observed since the aldehyde, present in the reaction mixture, reacts instantaneously with **6**. Therefore, aldehyde or imine moieties **3a**−**c** reacts with 3,3-disubstituted allyl zinc **6** with the bulky substituent at the pseudoequatorial position. In this conformation, one face of the allyl group is shielded by the *p*-tolyl residue at the sulfur. Thus, this level of stereoselectivity is rationalized by the combination of all these parameters in the Zimmerman−Traxler chairlike transition state (Figure 1b).

To further increase the efficiency of this new approach, we found an unprecedented catalytic assembly from these four simple precursors: alkynes, dialkylzinc, aldehyde, and diiodomethane (Scheme 2, Table 1, entries 11−13).

This copper-catalyzed carbozincation of alkynyl sulfoxides[19] proceeds quantitatively either with dialkylzinc or alkylZnBr (Table 1, entry 11). Then, the aldehyde **3a** and the diiodomethane **8** were successively added to give the homoallylic alcohol after hydrolysis in excellent yield with a diastereoisomeric ratio of 20/1 (Table 1, entries 11−13). In this case, the zinc carbenoid is generated[20] in situ. By using this improved procedure, the smallest possible difference for the creation of chiral quaternary center was achieved (Table 1, entry 13) in which a CH_3 and a CD_3 groups on the same carbon center were diastereoselectively fixed. In conclusion, this new multicomponent condensation leads to the creation of three new carbon−carbon bonds and two new chiral centers, including a quaternary one, from a very simple starting material in a single-pot reaction. By using this promising new strategy, even a chiral CH_3/CD_3 center was easily prepared. Further studies are currently underway to extend the scope of this reaction.

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Supporting Information Available: Experimental procedures, spectra data of all compounds as well as X-ray analyses of selected compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org

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