Asymmetric Synthesis

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Diastereodivergent Synthesis of Enantiomerically Pure Homoallylic Amine Derivatives Containing Quaternary Carbon Stereocenters**

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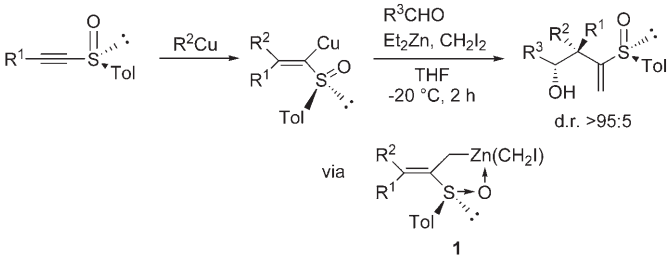
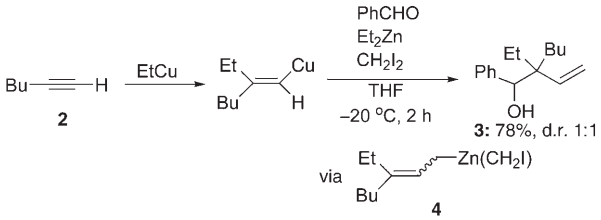
Dedicated to Professor Miguel Yus on the occasion of his 60th birthday

The design of new methods for the enantioselective construction of all-carbon quaternary stereogenic centers in acyclic systems is still a critical and challenging objective in modern chemistry.[1] Currently, the most-successful methods are asymmetric copper-catalyzed conjugate addition,[2] asymmetric Michael reactions,[3] asymmetric sigmatropic rearrangements,[4] and asymmetric electrophilic[5] and nucleophilic[6] allylic alkylation. However, the enantioselective formation of such all-carbon quaternary stereogenic centers by attack at the γ carbon atom of nucleophilic allylic substrates (that is, the reaction of 3,3-disubstituted allyl metal species with electrophiles) is much less frequent.[7] In this context, we reported an efficient multicomponent reaction for the diastereoselective formation of quaternary centers (Scheme 1).[8]

The key features of this reaction are the high degree of stereoselectivity and predictability, and the ease of execution. The reaction requires the in situ combination of a stereoselective carbometalation (introduction of the R^2 substituent), a zinc homologation (introduction of the CH_2 unit of the allyl zinc fragment),[9] and intramolecular chelation of the zinc atom by the sulfoxide, which results in the very high diastereoselectivity observed in the reaction of the allyl zinc reagent with various aldehydes.[8] The presence of the sulfoxide is essential to slow down the equilibration process of the allylic organometallic species **1** (through intramolecular chelation to the zinc atom) but also as a source of chirality and as a regiocontrol element for the carbometalation reaction. When the same reaction was performed with the nonfunctionalized 1-hexyne **2**, the expected homoallylic alcohol **3** was obtained in good yield but as a 1:1 mixture of two diastereoisomers (Scheme 2). In such cases, the homologation reaction of the vinyl copper species with the zinc carbenoid leads to an allyl zinc species, such as **4**, which is not configurationally stable,[10] and the two geometrical isomers that result from its metallotropic equilibrium react with the aldehyde.



Scheme 1. Multicomponent approach to the creation of stereogenic quaternary carbon centers in allylation reactions at carbonyl groups. Tol = *p*-tolyl.



Scheme 2. Nonstereoselective approach to the carbonyl allylation reaction.

To further extend our new approach to the creation of all-carbon quaternary stereocenters, we were interested in finding an alternative method, not based on intramolecular chelation of the substrate but rather on intermolecular chelation by an external ligand, to slow down the metallotropic equilibrium. We chose to focus on enantiomerically pure *R*-configured Ellman *N*-(*tert*-butylsulfinyl)imines **5** as chiral ligands.[11] We were interested in the potential of sulfinylimines, which can be used as chiral nitrogen-containing intermediates for the preparation of a wide range of chiral amines, for the intermolecular stabilization of the allyl zinc species.[12]

In our first approach (Scheme 3), the disubstituted vinyl iodides **6a–c**, which were prepared readily by the carbocupration of 1-octyne,[13] were treated with *t*BuLi in THF at −78 °C followed by CuI (1 equiv). The corresponding vinyl

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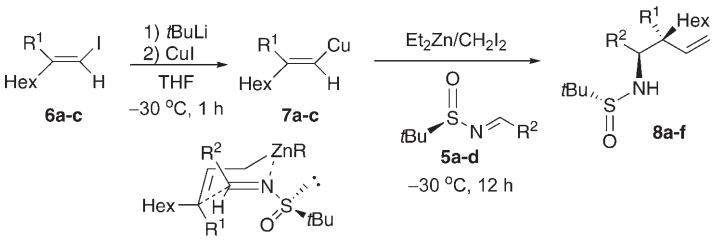


Scheme 3. Preparation of homoallylic amine derivatives from vinyl iodides. For the substituents see Table 1.

copper derivatives **7a–c** were formed at −30 °C and treated with diethylzinc, diiodomethane, and various sulfinylimines. The vinyl copper reagent underwent an homologation reaction with the zinc carbenoid[14] formed in situ from diethylzinc and diiodomethane to give the allyl zinc species,[9] which reacted diastereoselectively with the *N*-(*tert*-butylsulfinyl)imines **5a–d** to give the expected homoallylic sulfinylamines **8a–f** with very high diastereoselectivities and in good overall yields (Table 1).

Table 1: Stereoselectivity of the allylation reaction starting from vinyl iodides.

Entry	R^1	R^2	**8**	d.r.[a]	Yield [%][b]
1	Et (**6a**)	Ph (**5a**)	**8a**	>98:2	85
2	Me (**6b**)	Ph (**5a**)	**8b**	>98:2	65
3	*i*Pr (**6c**)	Ph (**5a**)	**8c**	>98:2	87
4	Et (**6a**)	*p*-BrC_6H_4 (**5b**)	**8d**	>98:2	81
5	Et (**6a**)	*p*-AcC_6H_4 (**5c**)	**8e**	>98:2	77
6	Et (**6a**)	PhCH=CH (**5d**)	**8f**	95:5	75

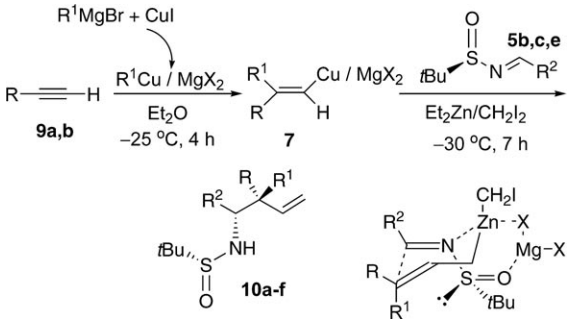
[a] The diastereomeric ratio was determined by ^{1}H and ^{13}C NMR spectroscopy of the crude product. [b] The yield was determined after purification by chromatography on silica gel.

The stereochemical course of this one-pot reaction was confirmed by X-ray analysis of **8d**, and the configurations of the other products were assigned by analogy. Sulfinylimines usually prefer to adopt a conformation in which the S=O bond and the lone pair of electrons on the nitrogen atom are antiperiplanar, mainly as a result of a significant $n_N \rightarrow S^*_{S=O}$ negative hyperconjugation interaction.[15] As such an interaction has a high rotational barrier (41.3 kJ mol^{-1}), the conformation of the sulfinylimine is conserved. The formation of the homoallylic products can be rationalized by a close transition state in which the substituent of the sulfinylinime occupies a pseudoaxial position (see Scheme 3).[16]

The alkyl group R^1 of the vinyl iodide **6** can be primary (Table 1, entries 1,2, and 4–6) or secondary (even though it occupies a pseudoaxial position in the chairlike transition state; see Table 1, entry 3 and Scheme 3). The reaction could be carried out with aromatic (Table 1, entries 1–3), functionalized aromatic (Table 1, entries 4 and 5), and conjugated sulfinylimines **5** (Table 1, entry 6). Only the use of aliphatic sulfinylimines leads to a poor diastereoisomeric ratio (d.r. 70:30; results not reported in Table 1).

Nonbonding interactions contributed by substrate substituents may provide the dominant stereochemical control element. In many cases, the preassociation of a metal with polar functional groups in the vicinity of the reaction center has been reported to influence the stereochemical outcome of the process and even to lead to the opposite stereochemical outcome to that expected in the absence of such an interaction.[17] As the S=O bond can act as an acceptor site for Lewis acids,[18] the conformation of the sulfinylimine moiety in the transition state could be influenced by intramolecular chelation[19] with metal salts.[20]

Under this assumption, we performed the reaction in the presence of MgX_2. Although MgX_2 could be added to the vinyl copper species **7a–c**, direct carbocupration of the alkyne with RCu/$MgBr_2$ (readily prepared from 1 equivalent each of the alkyl magnesium halide and CuI)[13] was a more attractive and efficient route (Scheme 4). Et_2Zn, CH_2I_2, and an *R*-configured *N*-(*tert*-butylsulfinyl)imine were then added to the vinyl copper reagent **7** at −30 °C, and the corresponding homoallylic amines **10** were obtained within a few hours with excellent diastereoselectivity (Table 2).[21]



Scheme 4. Preparation of homoallylic amine derivatives from alkynes. For the substituents see Table 2.

Table 2: Stereoselectivity of the allylation reaction starting from alkynes.

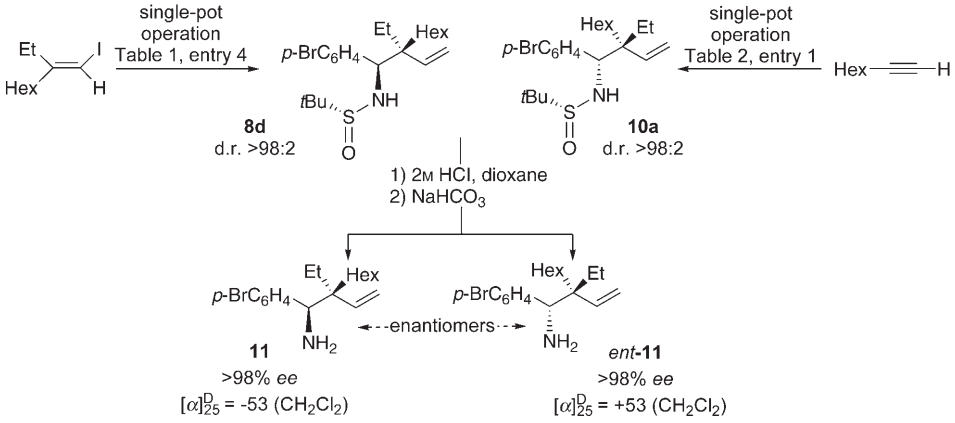
Entry	R	R^1	R^2	**10**	d.r. [%][a]	Yield [%][b]
1	Hex (**9a**)	Et	*p*-BrC_6H_4 (**5b**)	**10a**	>98:2	75
2	Hex (**9a**)	Et	*p*-AcC_6H_4 (**5c**)	**10b**	>98:2	67
3	Hex (**9a**)	Et	Bu (**5e**)	**10c**	>98:2	67
4	Hex (**9a**)	*i*Pr	*p*-BrC_6H_4 (**5b**)	**10d**	>98:2	62
5	Hex (**9a**)	Bu	*p*-BrC_6H_4 (**5b**)	**10e**	97:3	70
6	Bu (**9b**)	Hex	*p*-BrC_6H_4 (**5b**)	**10f**	96:4	60

[a] The diastereomeric ratio was determined by ^{1}H and ^{13}C NMR spectroscopy of the crude product. [b] The yield was determined after purification by chromatography on silica gel.

To our delight, amines **10** formed by this procedure were the opposite diastereoisomers to amines **8** obtained from vinyl iodides by the procedure illustrated in Scheme 3. This discrepancy can be rationalized by a cyclic transition state with MgX_2 coordinated to the oxygen atom of the sulfinyl group and to the zinc atom (as opposed to the antiperiplanar arrangement described in Scheme 3 with respect to the S=O bond and the lone pair of electrons on the nitrogen atom).

Presumably, the high level of preorganization contributes to the very high selectivity for attack opposite to the large *t*Bu group. The scope of the reaction is broad, as excellent diastereoselectivities were observed with both functionalized aromatic sulfinylimines (Table 2, entries 1, 2, and 4–6) and aliphatic sulfinylimines (Table 2, entry 3). By exchanging the alkyl groups on the alkyne and the organocopper reagent it is possible to prepare independently both isomers of a given homoallylic amine with respect to the configuration at the quaternary carbon center (Table 2, entry 5 versus entry 6).

Finally, the sulfinyl group can be cleaved readily under mild acidic conditions to provide in quantitative yield the free amine derivatives **11** as acyclic systems with an all-carbon quaternary stereogenic center (Scheme 5).



Scheme 5. Cleavage of the sulfinyl group to give free homoallylic amines containing enantiomerically pure quaternary stereogenic centers.

In conclusion, free homoallylic amines **11** containing quaternary carbon centers can be prepared readily by a strategy involving zinc homologation of a vinyl copper species followed by treatment in situ with various sulfinylimine derivatives. Both enantiomers can be obtained at will from common vinyl copper intermediates formed from either a vinyl iodide or an alkyne. This spectacular enantiofacial discrimination is due to the presence of different metal salts (MgX_2 or LiI). Moreover, permutation of the alkyl groups of the alkyne and the organocopper reagent enables the independent synthesis of two diastereomers with the opposite configuration at the quaternary carbon center.

Experimental Section

General procedure (from vinyl iodides): *t*BuLi (2.2 equiv, 2.2 mmol) was added to a solution of the vinyl iodide **6** (1 mmol) in THF (5 mL) at −80 °C, and the resulting mixture was stirred at this temperature for 10 min. The reaction mixture was then warmed to −30 °C, CuI (1.2 equiv, 1.2 mmol) was added, and the mixture was stirred for additional 30 min. CH_2I_2 (6 mmol), a solution of the sulfinylimine **5** (1.3 mmol) in THF (2 mL), and Et_2Zn (3 mmol) were added, and the reaction mixture was stirred at −30 °C for 6–12 h, then hydrolyzed with an basic aqueous NH_4Cl/NH_3 (2:1) solution. After a standard workup, the crude product was purified on silica gel to give the pure homoallylic sulfinylamine **8**.

General procedure (from alkynes): A solution of R^1MgBr (1.8 mmol) in Et_2O was added to a suspension of CuI (344.7 mg, 1.8 mmol) in Et_2O (12 mL) at −30 °C, and the resulting mixture was stirred at this temperature for 30 min. The alkyne (1 mmol) was then added, and the reaction mixture was warmed slowly to −25 °C. Upon the completion of the carbocupration reaction, which was monitored by GC and generally complete within 4 h, the reaction mixture was cooled to −30 °C. CH_2I_2 (6 mmol), a solution of the sulfinylimine (1.3 mmol) in THF (2 mL), and Et_2Zn (3 mmol) were added, and the mixture was stirred for an additional 6 h at −30 °C, then hydrolyzed with a basic aqueous NH_4Cl/NH_3 (2:1) solution. After a standard workup, the crude product was purified on silica gel to give the pure homoallylic sulfinylamine **10**.

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