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A Configurationally Stable Alkoxy Allenyl Zinc Reagent, en Route to *anti-anti* Vicinal Amino Diols

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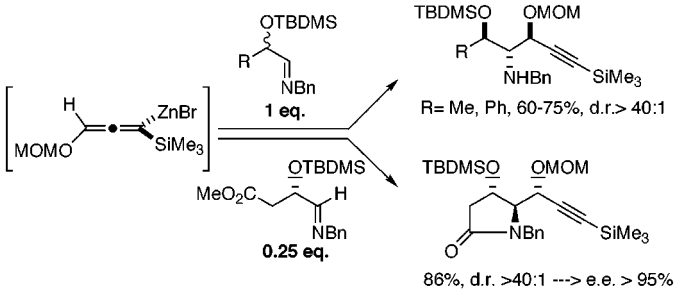
ABSTRACT

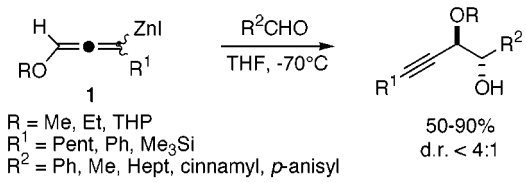


The reaction of an alkoxyallenyl zinc reagent with benzyl imines derived from lactic and mandelic acids proceeds highly diastereoselectively and leads to 2-amino-1,3-diol derivatives with an *anti-anti* pattern.

We have recently shown that allenylzinc reagents derived from lithiated 1-trimethylsilyl-1-alkynes react diastereoselectively with chiral α-alkoxy imines.[1] Those imines were used first to demonstrate the good configurational stability of the allenylzinc species at temperatures up to −10 °C[2] and second to form an enantioenriched allenyl zinc by kinetic resolution.[3] To extend the scope of this methodology, we were then interested in studying the case of allenylzinc reagents derived from propargylic ethers. These reagents have been little studied so far.

Epsztein et al. have shown that reagents **1** (Scheme 1) react with aldehydes in good yields but with low diastereoselectivities (d.r. < 4:1).[4] More recently, Yamamoto et al. have obtained analogous selectivities.[5]

Scheme 1



To our knowledge, reagents of type **1** have not yet been reacted with imines. We started up with alkoxyallenylzinc **2**. This organozinc is prepared from its lithiated analogue, which is kept at −70 °C during the Li/Zn exchange to avoid any Wittig [1,2] rearrangement (Scheme 2).[6]

As could be anticipated from our previous studies[1] (and the above-mentioned results),[4,5] the reaction of alkoxyallenylzinc **2** with a silyl-protected α-alkoxy aldehyde derived from (±)-mandelic acid led to a low diastereoselectivity: three diastereomers (48:33:19) were formed. We

(1) Poisson, J.-F.; Normant, J. F. *J. Org. Chem.* **2000**, *65*, 6553−6560.
(2) Poisson, J.-F.; Chemla, F.; Normant, J. F. *Synlett* **2001**, 305−307.
(3) Poisson, J.-F.; J. F. Normant *J. Am. Chem. Soc.* **2001**, *123*, 4639−4640.
(4) (a) Mercier, F.; Epsztein, R.; Holland, S. *Bull. Soc. Chim. Fr.* **1972**, 690−696. (b) Chwastek, H.; Epsztein, R.; Le Goff, N. *Tetrahedron* **1973**, *29*, 883−889. For an addition to a ketone, see: (c) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774−780.
(5) (a) Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem.* **1982**, *47*, 2225−2227. (b) Hiraoka, H.; Furuta, K.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2777−2780.
(6) Tomooka, K.; Yamamoto, H.; Nakai, T. *Liebigs Ann./Recueil* **1997**, 1275−1281.

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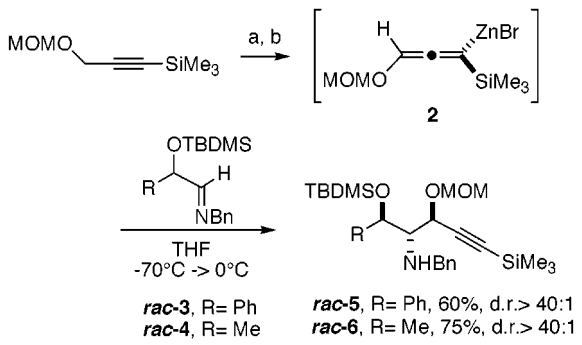
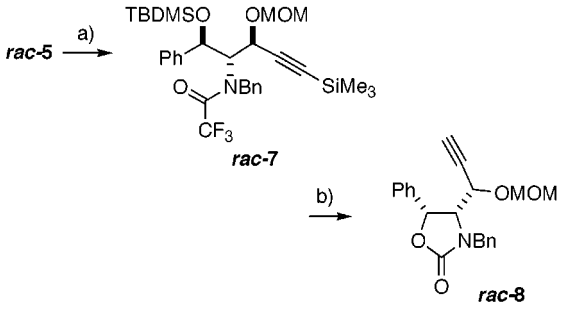
Scheme 2[a]



[a] (a) *sec*-BuLi, THF, −70 °C; (b) $ZnBr_2$ (1 M/THF), −70 °C.

thus turned to the corresponding benzylimines **3** and **4** derived from mandelic and lactic aldehydes. To our delight, a unique diastereomer is formed in good yield in each case (Scheme 2). We then checked the relative configuration of the obtained aminodiols. Aminodiol **6** was converted into trifluoroacetamide **7**, and the resulting product was treated with TBAF, leading to crystalline oxazolidinone **8** via a ring closure with liberation of fluoroform (Scheme 3).[7] The X-ray

Scheme 3[a]



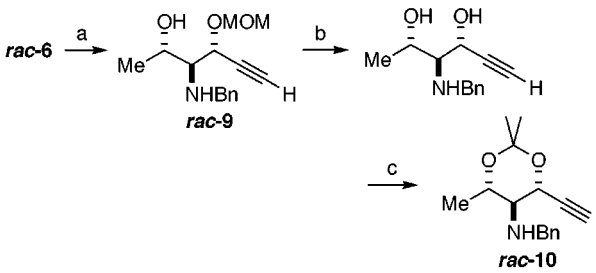
[a] (a) $(CF_3CO)_2O$, DIEA, CH_2Cl_2, 95%; (b) TBAF (1 M/THF), 80%

pattern of this oxazolidinone shows a *cis* relationship between the two substituents in the cycle (confirming the ^1H spectral data) and an *anti* relationship between the two other asymmetric centers. The relative configuration of **5** is therefore *anti-anti*.

For compound **6** our strategy relied on the formation of acetonide **10**, obtained by desilylation of **6**, followed by HCl-mediated deprotection of the MOM ether, and treatment with the dimethoxy acetal of acetone under acid catalysis (Scheme 4). The ^3J coupling constants of 9.9 Hz between the three hydrogens lying on this 1,3-dioxane showed that all substituents on the cycle occupied equatorial positions, demonstrating the *anti-anti* relationship in **6**.

(7) For reactions of CF_3 with amides see: (a) Folléas, B.; Marek, I.; Normant, J. F.; Saint-Jalmes, L. *Tetrahedron* **1998**, *39*, 2973−2976. (b) Large, S.; Roques, B.; Langlois, B. R. *J. Org. Chem.* **2000**, *65*, 8848−8856.

Scheme 4[a]



[a] (a) $HF\cdot(NEt_3)_3$, CH_3CN, rt, 70%; (b) HCl (12 N), MeOH, 90%; (c) $(MeO)_2CMe_2$, CSA.

The *anti-anti* relationship in aminodiols **5** and **6** corresponds to the general outcome already observed with non-oxygenated allenyl zinc reagents.[1] This diastereoselectivity can similarly be explained by the attack of the imine function according to the Felkin−Ahn model and by a cyclic transition state, where the imine nitrogen is chelated by the Zinc atom, leaving the substituent of the allene (OMOM) and the imine in *anti* position in order to minimize the steric interaction (Figure 1).

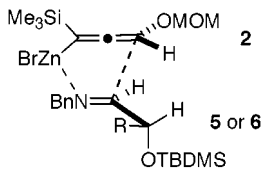


Figure 1.

We then tried to evaluate the configurational stability of reagent **1** by means of the Hoffmann test. Historically, this test was first performed on an alkoxy allenyl titanate.[8] Subsequently, Hoppe et al. studied metalated propargylic carbamates and have shown that the organotitanates are configurationally more stable than their lithio counterparts.[9]

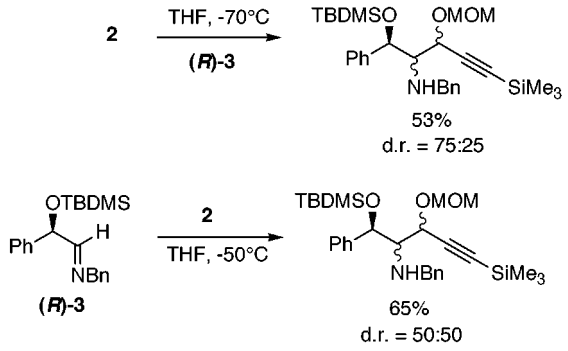
In our case, the slow addition of enantiomerically enriched imine **3** to reagent **2** in THF, at −70 °C, led to a 75:25 mixture of two diastereomers in 53% yield, accompanied by 30% of the starting material. The large proportion of unreacted product could point to a possible kinetic resolution due to the low reactivity of the mismatched pair. To avoid such a drawback, Hoffmann recommends to carry out an inverse addition, so that the organometallic is maintained in an excess of electrophile.[10] Indeed, slow addition of **2** to the imine (*R*)-**3**, at −50 °C, gives a 50:50 mixture of both isomers in 65% yield (Scheme 5).

(8) Hoffman, R.; Lanz, J.; Metternich, R.; Tarara, G.; Hoppe, D. *Angew. Chem., Int. Ed. Eng.* **1987**, *26*, 1145−1146.

(9) Dreller, S.; Dyrbusch, M.; Hoppe, D. *Synlett* **1991**, 397−400.

(10) Hoffmann, Configurationally Stable and Configurationally Labile Chiral α-Substituted Organolithium Compounds in Stereoselective Transformation. In *Organic Synthesis via Organometallics (OSM4)*; Enders, D., Gais, H.-J., Keim, W., Eds.; Vieweg: Braunschweig, 1993; pp 79−91.

Scheme 5



The configuration of the second diastereomer has not been determined but is considered to be analogous (*anti-syn*) to those previously studied with non-oxygenated allenyl zinc reagents.[2,11] We can thus conclude that the configurational stability of **2** is important at a temperature up to −50 °C.

At this point we have shown that alkoxyallenylzinc **2** reacts diastereoselectively with racemic α-chiral imines and is configurationally stable at a temperature up to −50 °C. The addition of this organozinc to α-alkoxy imines leads to *anti-anti* 1,3-diamino-2-hydroxy derivatives, a scaffold present in many important classes of natural products, particularly when heterocycles are involved, for instance, polyhydroxylated pyrolizidines such as castanospermine, australine or casuarine, which are known glycosidase inhibitors.[12] Our approach should prove straightforward, for example, in the elaboration of the first three stereocenters of **10**, a known precursor of 1-epicastanospermine (Figure 2).[12a]

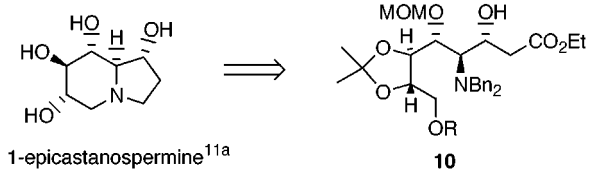
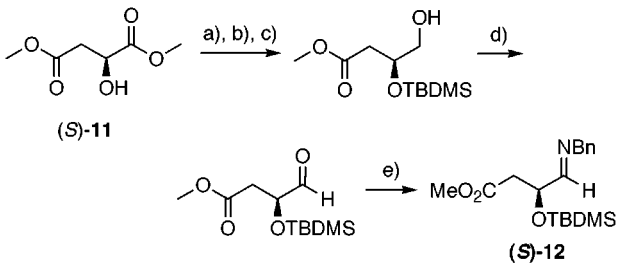


Figure 2.

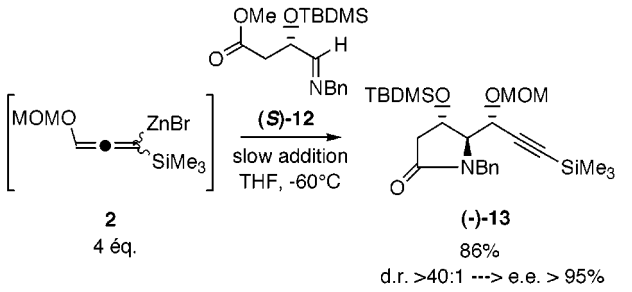
To illustrate such a strategy, we first prepared enantioenriched imine (*S*)-**12**,[13] from (*S*)-methylmalate **11**, according to Scheme 6. Knowing that organozinc reagent **2** was configurationally stable, we anticipated that the kinetic resolution would be sufficiently high, so that the slow addition of the imine (*S*)-**12**, to a slight excess of reagent **2**, would deliver a unique enantiomer of **13**. Such is the case using 4 equiv of the alkoxyallenylzinc (2 equiv of one enantiomer): **13** is obtained in an excellent 86% yield as a single diastereomer, enantiomerically enriched, with the desired O−N−O-connections (Scheme 7).

Scheme 6[a]



[a] (a) $BH_3.Me_2S$, $NaBH_4$ cat., THF, 80%; (b) TBDMSCl, imidazole, DMAP cat., DMF, quant; (c) PPTS, MeOH, 75%; (d) PCC, CH_2Cl_2, 80%; (e) $BnNH_2$, $MgSO_4$, toluene, 0 °C, quant.

Scheme 7



In summary, the configurationally stable alkoxyallenylzinc **2** displays an excellent kinetic resolution in its reaction with a non-racemic α-silyloxyimine and allows a straightforward access to 1,3-dialkoxy-2-amines, presenting an *anti-anti* pattern. Further synthetic applications of this approach are underway.

Acknowledgment. We gratefully acknowledge Rhône-Poulenc Rorer for financial support to J.-F. P.

Supporting Information Available: Spectral data for all compounds, Ortep diagram and crystallographic table of **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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