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LETTERS

A New Diastereo- and Enantioselective Copper-Catalyzed Conversion of Alkynyl Epoxides into α-Allenic Alcohols.

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Abstract. Chiral copper complexes of BINOL- and TADDOL derived phosphorus amidites proved to be highly effective catalysts for the alkylation of alkynyl epoxides with dialkylzinc reagents. The corresponding α-allenol reaction products (S_N2'-pathway) were obtained with good to excellent regio- and diastereoselectivity. The e.e. values obtained for this reaction were in the range of 26-38 %. A number of different Cu(II)-complexes were screened as possible catalysts and the results obtained indicate a complete control of the diastereoselectivity with an easy access to both enantioenriched *syn* and *anti*-α-allenols.

The development of simple, efficient procedures for the stereoselective formation of carbon-carbon bonds by the use of organometallic reagents is one of the major challenges in organic chemistry. It is known that various organometallic reagents react with chiral propargylic derivatives to form optically active allenes.[1] In the case of alkynyl epoxides, the reaction affords α-allenic alcohols,[2] which are quite interesting synthons in view of their presence in a number of natural substances, and their potential use in replacing allylic and acetylenic alcohols in pharmaceuticals.[3] Organozinc compounds represent one of the most versatile classes of organometallic reagents with the additional advantage that other reactive functionalities are tolerated.[4] In their pioneering work, Vermeer *et al.* described the Pd(0)-catalyzed alkylation of organozinc reagents with α–acetylenic epoxides.[5] The reaction worked very well with unsaturated zinc reagents, proceeding with overall *anti*-stereoselectivity. Dialkylzinc reagents were shown to be unsuitable for the alkylation reaction, as reduced allenol was the main product. Moreover, a catalytic asymmetric version of this reaction, starting from racemic propargylic derivatives and readily available organometallic reagents has not been demonstrated, to the best of our knowledge.

We recently reported a highly enantioselective alkylation of racemic cyclic vinyloxiranes by means of catalytic amounts of Cu(II) complexes with (*S*)-1,1'-2,2'-binaphthol (BINOL)-derived phosphorus amidites.[6] In this communication we report our preliminary results regarding the addition of commercially available dialkylzinc reagents to racemic alkynyloxiranes **2a-c** in accordance with a kinetic resolution protocol.[7] While the reaction of R_2Zn (-70°C to 0°C, 3h) with epoxides **2a-c** catalyzed by $Cu(OTf)_2$ (blank reactions, not reported in Table 1) did not proceed with any significant conversion (< 5%), the addition of a catalytic amount of the chiral ligand (*S, R, R*)-**1** to the reaction mixtures gave, in some cases, a remarkable increase in the corresponding tri- and tetrasubstituted *anti*-allenols reaction products **3a-c** (see Table 1). The addition reaction of Me_2Zn (-70°C to 0°C, 3h) to epoxide **2a** catalyzed by $Cu(OTf)_2$ (1.5 mol%) and (*S, R, R*)-**1** (3 mol%) afforded the corresponding alkylation product **3a** with excellent diastereoselectivity (*anti/syn* ratio) and moderate enantioselectivity (entry 1, Table 1).

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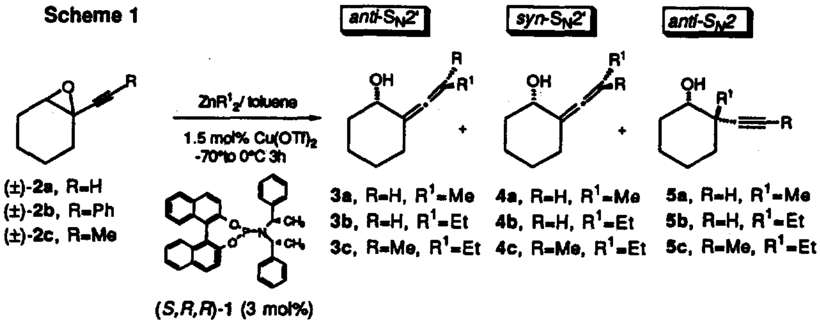
Scheme 1



The alkylation reaction of **2a** with Et_2Zn afforded a significant increase in the regioselectivity (see S_N2'/S_N2 ratio, entry 2, Table 1).[6,8] The propynyl epoxide **2c** was found to be similarly reactive with Et_2Zn in the presence of our catalytic system affording cleanly the corresponding α-allenic alcohol **3c** with moderate enantioselectivity (entry 4, Table 1). On the contrary, the alkynyl epoxide **2b** was found not to be a suitable substrate for the present alkylation protocol, affording mostly a rearrangement product (2-phenylethynylcyclohexanone) (see entry 3, Table 1). It has to be stressed that no reduction product was found in any of the reactions examined. This fact seems to indicate a mechanistic pathway which does not involve a Cu(III) intermediate, typical of stoichiometric organocopper addition reactions .[9]

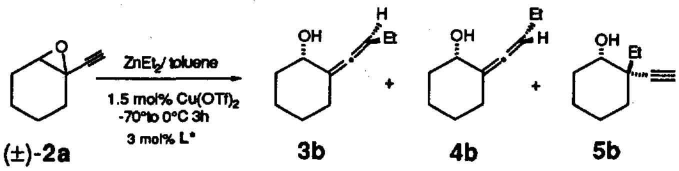
Table 1. Diastereo- and Enantioselective Addition of Dialkylzinc Reagents to Alkynyl Epoxides 2a-c Catalyzed by $Cu(OTf)_2$/ (*S*, *R*, *R*)-1.[a]

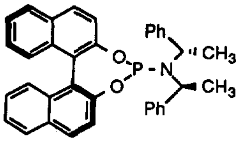
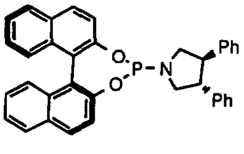
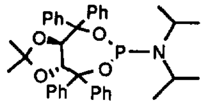
Entry	substrate	R_2Zn	*anti*/*syn*[b] 3/4	S_N2'/S_N2[c] (3+4)/5	yield (%)[d] 3	ee (%)[e]
1	2a	R=Me	97/3	55/45	42	26
2	2a	R=Et	>97/3	91/9	83	36
3	2b	R=Me or Et		rearrangement reaction		
4	2c	R=Et	>98/2	94/6	85	38

[a] All reactions were run as described in ref.8. [b] Determined by ^{13}C NMR analysis of the crude reaction mixture (see ref. 2) and by HPLC analysis of the crude benzoylated reaction mixture. [c] Determined by ^1H NMR and capillary GC analysis of the crude reaction mixture. [d] Isolated yield of pure *anti*-allenols **3a-c** based on the unreacted substrate (substrate conversion 50% ±5). [e] Determined by HPLC analysis of the corresponding benzoates using a chiral column (Daicel, Chiralcel OD-H column). Absolute configuration not determined.

Having established the ability of copper complexes of BINOL-based phosphorus amidites to catalyze the alkylation reaction of alkynyl epoxides, we tried to modify the nature of the external chiral ligand in order to obtain as high a level of stereocontrol as possible for this reaction. We therefore investigated the addition of Et_2Zn to ethynylcyclohexene oxide **2a**, taken as the model substrate. Several Cu(II)-complexes were screened using BINOL and (*R*,*R*)-α,α,α',α'-tetraphenyl-2,2'-dimethyl-1,3-dioxolane-4,5-dimethanol (TADDOL)-derived phosphorus amidites as possible catalysts for the reaction.[10] The Cu(II)-complex (1.5 mol%) with ligand **6** derived from BINOL and (*S*)-bis-phenylethylamine afforded **3b** with an increased

Table 2. Diastereo- and Enantioselective Alkylation of Ethynylcyclohexene Oxide 2a with Et_2Zn Catalyzed by $Cu(OTf)_2/L^*$.[a]



Entry	L*	anti/syn[b] 3b/4b	S_N2'/S_N2[c] (3b+4b)/5b	yield (%)[d]	ee (%)[e]
1	 *(S,S,S)*-**6**	>99/1	97/3	94 (**3b**)	2
2	 *(S,R,R)*-**7**	complex mixture[f]			
3	 *(R,R)*-**8**	>5/95	92/8	83 (**4b**)	36

[a-e] See Table 1. [f] A complex reaction mixture containing mostly (>80%) unreacted **2a** was obtained.

regio- and diastereoselectivity with respect to the diastereoisomeric (*S*, *R*, *R*)-**1**, albeit with a very low ee (entry 1, Table 2). The Cu(II)-complex with ligand **7**, derived from BINOL and (*R*, *R*)-2,3-diphenylpyrrolidine, bearing a stereogenic centre in a homologous position with respect to ligand **1** and **6**, proved to be almost ineffective for the present reaction (entry 2, Table 2). On the other hand, of the several TADDOL-derived phosphorus amidites examined, one proved to be effective: the Cu(II)-complex of ligand **8**, derived from TADDOL and diisopropylamine gave a complete reversal of the commonly observed *anti*-diastereoselectivity. In fact the corresponding *syn*-allenol **4b** (36% ee) was obtained with good regioselectivity and excellent diastereoselectivity. This high *syn* selectivity obtained is particularly remarkable when compared with literature data available for this reaction.[2,9] From the above data, it seems that both the diol and the amine counterparts of the phosphorus amidite ligand (L*) play a crucial role in directing the alkyl fragment during the S_N2' alkylation of the acetylene moiety of the alkynyloxirane.[11]

In conclusion, the present work represents the first asymmetric catalytic alkylation of racemic propargylic epoxides with organometallics. We have succeeded in using dialkylzinc reagents to perform the alkylation reaction of alkynyl oxiranes, avoiding the nonalkylated allenol commonly obtained in related organometallic additions. Moreover, it is possible to control the stereochemical outcome of the above-mentioned reactions through variation of the external chiral ligand employed. Although the enantiomeric excesses are still moderate, the stereochemical control of the reaction is of particular synthetic importance, since starting from readily available alkynyloxiranes and dialkylzinc reagents, it is possible to obtain either *syn* - or *anti* substituted allenol with high diastereoselectivities, at will. Additional studies devoted to establish scope and limitations of the reaction are currently under investigation in our laboratory.

References and Notes.

(1) For a review, see: Pasto, D.J. *Tetrahedron* **1984**, *40*, 2805-2827.

(2) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J.F. *Tetrahedron* **1991**, *47*, 1677-1696 and references therein.

(3) See for example: Gooding, O.W.; Beard, C.C.; Jackson, D.Y.; Wren, D.L.; Cooper, G.F. *J. Org. Chem.* **1991**, *56*, 1083-1088.

(4) For a recent review of organozinc-mediated reactions see: Knochel, P.; Almena Perea, J.J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275-8319.

(5) Kleijn, H.; Meijer, J.; Overbeek, G.C.; Vermeer, P. *Rec. Trav. Chim. Pays-Bas* **1982**, *101*, 97-101.

(6) Badalassi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Arnold, A.; Feringa, B.L. *Tetrahedron Lett.* **1998**, *39*, 7795-7798.

(7) For a discussion of kinetic resolution see Kagan, H.B.; Fiaud, J.C. *Top. Stereochem.* **1988**, *18*, 249. Racemic alkynyloxiranes **2a-c** were prepared in accordance with ref. 2. Racemic *anti* allenols **3a-c** and *syn* allenols **4a-c** were also prepared in accordance with ref. 2. The relative stereochemistry (*syn*/*anti*) was established by ^{13}C NMR and the data obtained were in agreement with those reported for the same compounds by Alexakis *et al* (see ref. 2).

(8) Typical procedure as follows (entry 2, Table 1): A solution of $Cu(OTf)_2$ (5.5 mg, 0.015 mmol) and **1** (17.5 mg, 0.03 mmol) in anhydrous toluene (3.0 ml) was stirred at rt for 40 min. The colorless solution was cooled to -70 °C, and subsequently, a solution of **2a** (122 mg, 1.0 mmol) in toluene (1.0 ml) and 0.46 ml of a 1.1 M Et_2Zn in toluene, were added. The solution was allowed to warm slowly to 0 °C (1.5h) and then stirred at this temperature for an additional 1.5 h. The mixture was quenched with saturated aqueous NH_4Cl (3.0 ml). Extraction with Et_2O and evaporation of the dried ($MgSO_4$) organic phase gave a crude product which was purified by flash chromatography (SiO_2, 85:15 hexanes:EtOAc) to afford (+)-(S*,S*)-2-butenylidene-1-cyclohexanol[2] (**3b**) (61 mg, 41%) as a colorless liquid: $[\alpha]_D^{20}=+21$ (c=1.0, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (t, 3H, J=7.5 Hz), 1.20-2.12 (m, 10H), 2.30-2.48 (m, 1H), 3.90-4.05 (m, 1H), 5.40-5.51 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.5, 22.5, 23.7, 26.6, 30.0, 35.9, 68.8, 97.6, 108.4, 194.3.

(9) a) Elsevier, C.J.; Meijer, J.; Westmijze, H.; Vermeer, P.; Van Dijk, L.A. *J. Chem. Soc. Chem. Comm.* **1982**, 84-85. b) Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* **1984**, *25*, 3059-3062 and 3063-3066. c) Dollat, J.M.; Luche, J.-L.; Crabbè, P. *J. Chem. Soc. Chem. Comm.* **1977**, 761-762. For a review see: Krause, N.; Gerold, A. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 186-204.

(10) a) Keller, E.; Maurer, J.; Naasz, R.; Schader, T.; Meetsma, A.; Feringa, B.L. *Tetrahedron Asymm.* **1998**, *9*, 2409-2413. b) Alexakis, A.; Vastra, J.; Burton, J.; Benhaim, C.; Mangeney, P. *Tetrahedron Lett.* **1998**, *39*, 7869-7872.

(11) The actual chiral catalyst is probably a copper (I) species which is formed by *in situ* reduction of the copper (II) complex. See: (a) de Vries, A.H.M.; Meetsma, A.; Feringa, B.L. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2374-2376. (b) Feringa, B.L.; Pineschi, M.; Arnold, L.A.; Imbos, R.; de Vries, A.H.M. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2620-2623. c) Krause, N. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 283-285.

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