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Catalytic Enantioselective Carbon-Carbon Bond Formation by Addition of Dialkylzinc Reagents to Cyclic 1,3-Diene Monoepoxides.

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Abstract. Chiral copper complexes of 2,2'-binaphthyl-based phosphorus amidites are shown to be highly effective catalysts for the conjugate addition of dialkylzinc reagents to vinyloxiranes. The corresponding allylic alcohol reaction products (S_N2'-pathway) were obtained with moderate to high regioselectivity. Both direct- (S_N2-pathway) and conjugate-opening addition (S_N2'-pathway) seem to proceed with complete *anti* stereoselectivity. The enantioselectivity of these addition reactions according to a kinetic resolution protocol turned out to be high (>90% ee) with 1,3-cyclohexadiene and 1,3-cycloheptadiene monoepoxides.

The catalytic enantioselective formation of carbon-carbon bonds is one of the more challenging areas in organic synthesis.[1] The enantioselective nucleophilic ring opening of oxiranes by the use of a chiral catalyst has become an attractive method for the preparation of optically active compounds.[2] Despite the fact that the catalyzed enantioselective ring opening of epoxides with several nucleophiles has been investigated,[3] the catalyzed enantioselective addition of organometallics to oxiranes is an almost unexplored area,[4] although this reaction may offer a powerful tool for the stereocontrolled synthesis of complex organic compounds. The S_N2' displacements of vinyloxiranes with cuprates afford synthetically useful allylic alcohols.[5] In this context, the reactions of 1,3-cycloalkadiene monoepoxides have received considerable attention.[6] The ratio of S_N2'/S_N2 products in the nucleophilic addition to cyclic vinyloxiranes turned out to be very sensitive to the reagent type and highly regio- and stereoselective additions of mixed cyanocuprates have been developed.[6] Only recently Lipshutz et al. have reported an unprecedented copper-catalyzed cross-coupling of functionalized zinc reagents with vinyloxiranes.[7] However a catalytic asymmetric version of this synthetically useful reaction has not been described to our knowledge.

In the present work we wish to report our preliminary results regarding the catalytic enantioselective addition of simple commercially available organozinc reagents to cycloaliphatic vinyloxiranes. The remarkable ligand-accelerated catalysis[8] and the high enantioselectivities previously obtained in the addition of organozinc reagents to enones,[9] prompted us to verify the possibility of using chiral copper complexes of 2,2'-binaphthyl-based phosphorus amidites, such as **1** and **2**, in the conjugate addition of organozinc reagents to vinyloxiranes (see Figure).

The reaction of Me_2Zn (1.5 eq.) with **4** (-30°C, 3h) catalyzed by $Cu(OTf)_2$ (3 mol%) afforded a complex reaction mixture containing a small amount (8 % combined yield) of a 2:1 mixture of allylic alcohols **10** (*anti*-S_N2' pathway) and **11** (*anti*-S_N2 pathway), respectively (see Scheme).

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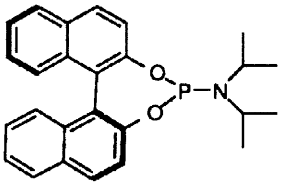
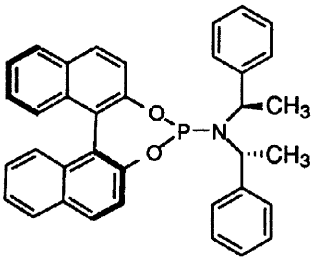
Figure



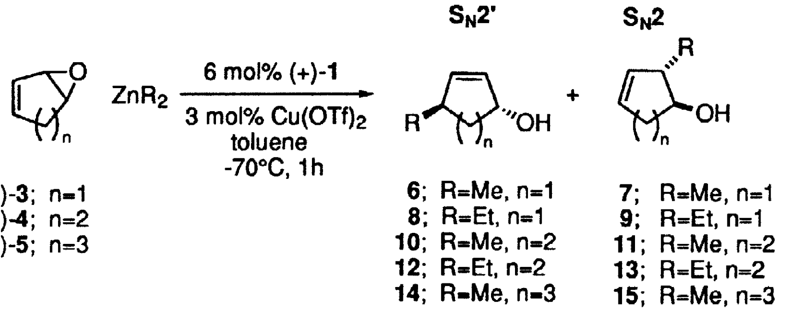
(+)-1



(+)-2

The preventive addition (see typical procedure)[10] of a catalytic amount (6 mol%) of phosphorus amidite ligand (+)-1 to the reaction mixture gave a dramatic increase in the conjugate addition pathway. In this case we obtained a 9:1 mixture of unsaturated alcohols **10** and **11**, with a substantial increase in the regioisomer **10** (55% isolated yield, data not shown in the Table). To our surprise, we found that allylic alcohol **10** showed a 60% ee despite the fact that the reaction was not performed under kinetic resolution conditions (Me_2Zn excess). The use of 0.50 eq. of Me_2Zn (-70 °C, 1h), together with the chiral ligand **1** (6 mol%) and $Cu(OTf)_2$ (3 mol%) gave practically the same enantioselectivity (entry 2, Table). This clearly indicated the prefential reactivity of one enantiomer of the racemic epoxide **4** with a high stereoselectivity factor.[11]

Scheme



The same reaction carried out with 0.50 eq. of Et_2Zn gave the corresponding allylic alcohol **12** in a low yield (18%) but with a substantial increase in both enantioselectivity and regioselectivity (entry 3, Table). The addition of Me_2Zn to 1,3-cycloheptadiene monoepoxide **5** showed similar levels of enantioselectivity and regioselectivity compared with vinyloxirane **4** (entry 4, Table). The cyclopentadiene monoepoxide **3** was found to be less reactive under these reaction conditions (-70 °C, 1h) affording the corresponding conjugate adduct **6** with a low yield and regioselectivity and a moderate enantioselectivity (entry 1, Table).

Having established the ability of phosphorus amidite **1** to strongly accelerate the rate of addition of dialkyl zinc reagents to vinyloxiranes **3-5**, we tested the chiral ligand (+)-**2**, derived from (*S*)-2,2'-binaphthol and bis-(*R*)-1-phenylethylamine (entries 5-9, Table).[9b]

While the chiral ligand **2** showed a similar level of enantioselectivity if compared to **1** in the addition of organozinc reagents to cyclopentadiene monoepoxide **3** (entries 5 and 6, Table), high enantioselectivities (>90%ee) were obtained in the cases of the six- and seven-membered analogs **4** and **5**. Once again we found an increased regioselectivity for 1,4-addition when Et_2Zn was used (entries 6 and 8, Table). The highest

Table. Enantioselective Conjugate Addition of Dialkylzinc Reagents to Vinyloxiranes 3-5 Catalyzed by $Cu(OTf)_2$/ (+)-1 and (+)-2.[a]

Entry	substrate	ligand	R_2Zn	yield (%)[b]	ee (%)[c]	S_N2'/S_N2[d]
1	**3**	**1**	R=Me	10[e]	46	4
2	**4**	**1**	R=Me	30	62 (-)	13
3	**4**	**1**	R=Et	18	86 (-)	>20
4	**5**	**1**	R=Me	32	60 (-)	10
5	**3**	**2**	R=Me	12[e]	50	3
6	**3**	**2**	R=Et	8[e]	54	12
7	**4**	**2**	R=Me	33	92(-)	13
8	**4**	**2**	R=Et	32	91(-)	59
9	**5**	**2**	R=Me	38	96(-)	16

[a] All reactions were run as described in ref.10 (0.50 eq. R_2Zn).[b] Isolated yield of allylic alcohols after chromatographic purification (SiO_2), unless otherwise stated (maximum yield 50%). [c] All ee values (compounds **6**, **8**, **10**, **12**, **14**) were determined by chiral GC (Chromopak fused silica 50 m X 0.25 mm, coated with CP-Cyclodextrin-B-236-M-19). The sign of rotation of the predominant enantiomer is indicated in parentheses. Absolute configuration not determined.[d] Composition determined by GC capillary analysis of the crude reaction mixture. [e] GC yield using 2-cyclohexen-1-ol as the internal quantitative standard.

enantioselectivity was observed for the addition of Me_2Zn to **5** (96% ee, see typical procedure).[10] In this case, the regioselectivity (S_N2'/S_N2 ratio) is even better than that obtained for the addition of MeCuCNLi to vinyloxirane **5** (entry 9, Table).[12]

In conclusion, the present work represents the first report demonstrating a successful combination of an organometallic reagent and an external chiral ligand in a kinetic resolution protocol for the nucleophilic displacement of racemic vinyloxiranes. Chiral copper complexes of 2,2'-binaphthyl-based phosphorus amidites were found to exhibit a strong ligand accelerated catalysis effect in the conjugate addition of dialkylzinc reagents to vinyloxiranes. The high selection of enantiotopic reaction sites shown by 1,3-cyclohexadiene- and 1,3-cycloheptadiene-monoepoxides **4** and **5** with organozinc reagents can allow a versatile entry for optically active 4-alkyl-2-cycloalken-1-ols of six-and seven-membered rings. Additional studies of the scope and mechanism of this process are in progress.

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(10) Typical procedure as follows (entry 9, Table): A solution of Cu(OTf)$_2$ (0.022 g, 0.06 mmol) and **2** (0.070 g, 0.12 mmol) in anhydrous toluene (6.0 ml) was stirred at rt for 40 min. The colorless solution was cooled to -70°C, and subsequently, a solution of **5** (0.220 g, 2.0 mmol) in toluene (1.0 ml) and 0.50 ml of a 2.0 M Me_2Zn in toluene, were added. The temperature was allowed to warm slowly to -30°C (1h) and 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 subjected to flash chromatography (SiO_2, 8:2 hexanes:EtOAc) to afford (-)-trans-4-methyl-2-cyclohexen-1-ol[12] (**14**) (0.094 g, 38%) as a pale yellow liquid: $[\alpha]_D$=-106.5 (*c*=0.15, CH_2Cl_2).

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