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Enantioselective alkynylation of a prochiral ketone catalyzed by C_2-symmetric diamino diols

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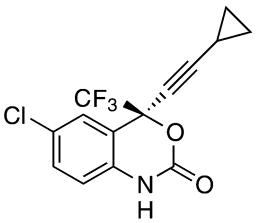
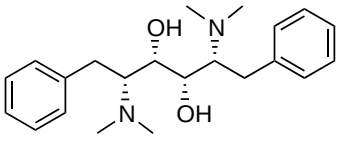
Abstract—C_2-Symmetric diamino diols were used as chiral ligands to induce the asymmetric addition of lithium acetylides to carbonyl groups. The enantiomeric excesses (up to 99% ee) depended on the structure of the acetylene.

The asymmetric nucleophilic alkynylation of carbonyl compounds is of considerable synthetic and industrial importance.[1] A new class of potent non-nucleoside reverse transcriptase inhibitors was recently reported by Merck Research Laboratories, and 1,4-dihydro-2*H*-3,1-benoxazin-2-ones (efavirenz) have been approved by the FDA for the treatment of AIDS.[2] The key asymmetric bond-forming step is the use of a lithiated ephedrine to mediate acetylide addition to a trifluoromethyl ketone.[3] Great progress has been made with the enantioselective alkynylation of aldehydes using chiral amino alcohols as ligands.[4] In contrast, enantioselective nucleophilic alkynylation of prochiral ketones has enjoyed only very limited success. To the best of our knowledge, only ephedrine derivatives have been successfully used as chiral ligands to promote enantioselection in the addition of metal alkynylides to aldehydes or ketones.



Efavirenz



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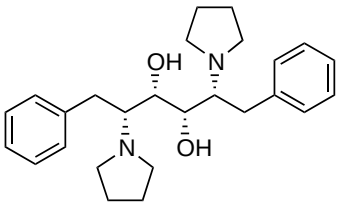

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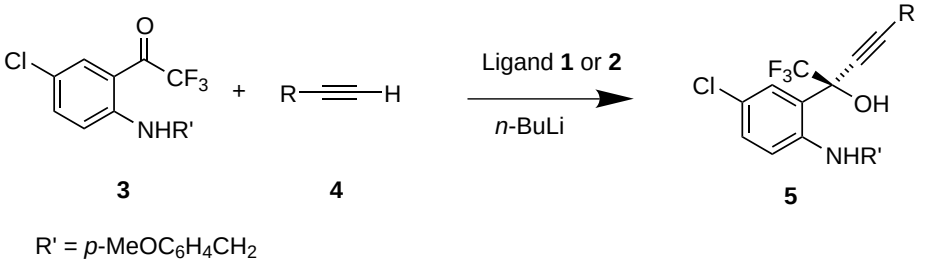

3 **4** **5**

R' = *p*-$MeOC_6H_4CH_2$

Scheme 1.

Keywords: alkynylation; enantioselective; C_2-symmetric diamino diol; ketone.

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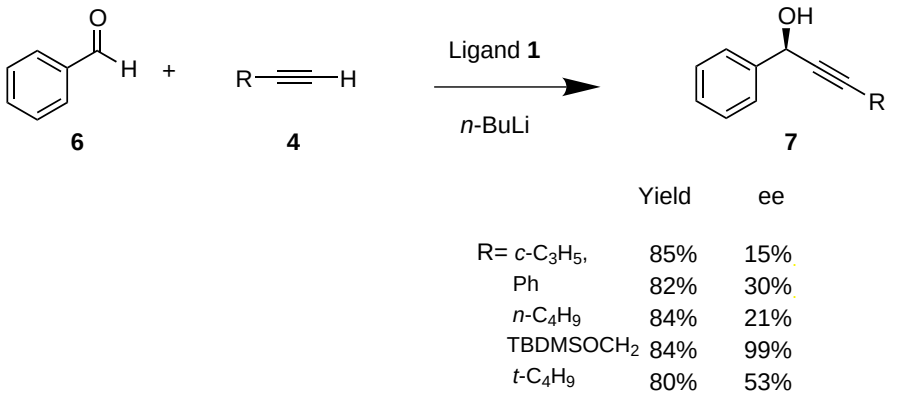
Table 1. Asymmetric addition of lithium acetylide to ketone **3**

Entry	R in **4**	Ligand	Yield of **5** (%)[a]	ee (%)[b]	$[\alpha]_D^{20}$
1	*c*-C_3H_5	1	80	99	+8.3
2	*c*-C_3H_5	2	78	42	–
3	Ph	1	82	75	+22.4
4	*n*-C_4H_9	1	78	53	+4.5
5	$TBDMSOCH_2$	1	75	49	+40.3
6	*t*-Butyl	1	75	11	+0.6

[a] Isolated yield.
[b] Determined by Chiral HPLC on Chiralpak AD column eluted with hexane:isopropanol 7:3.



Scheme 2.

In the course of our studies in the field of asymmetric synthesis, we have developed a new family of C_2-symmetric diamino diols **1** and **2** which have proved to be good ligands in the enantioselective nucleophilic addition of diethylzinc to aldehydes[5] and in asymmetric allylic substitution.[6] To probe further the potential of this family in asymmetric reactions, we report here the asymmetric alkynylation of aryl trifluoromethyl ketones with lithium acetylides in the presence of C_2-symmetric diamino diols (Scheme 1).

A preliminary study of the reaction was aimed at determining the capacity for enantioselective alkynylation using **1** and **2** as chiral promoters. We found that when the nucleophilic addition of lithium cyclopropylacetylide (2 equiv.) to trifluoromethyl ketone **3** was carried out in toluene in the presence of ligand **1** (1 equiv.), the acetylene **5** was obtained in an excellent enantiomeric excess (99%) (Table 1, entry 1) and in high chemical yield, while the use of **2** as a ligand gave poor enantioselectivity (42% ee) (Table 1, entry 2).[7] The results with various lithium acetylides in the asymmetric addition are summarized in Table 1. The results show that the enantiomeric excess of the reaction depends on the structure of the acetylene: lithium phenylacetylide gave a product of 75% ee (Table 1, entry 3), while lithium *n*-butyl acetylide, lithium *t*-butyldimethylsilyloxymethyl acetylide and lithium *t*-butyl acetylide gave the corresponding propargylic alcohols with low enantioselectivity (Table 1, entries 4–6).

Extension of this reaction to the nucleophilic addition of lithium acetylides to benzaldehyde gave the opposite results (Scheme 2). When nucleophilic addition was carried out by reacting lithium cyclopropylacetylide with benzaldehyde in the presence of ligand **1**, the product was isolated with poor enantioselectivity (15% ee). On the other hand, when the bulky lithium *t*-butyldimethylsilyloxymethyl acetylide was used, high enantioselectivity was obtained (99% ee).

In summary, we have demonstrated the utility of C_2-symmetric diamino diol **1** as a chiral ligand for the asymmetric addition of lithium acetylides to aryl trifluoromethyl ketone and benzaldehyde. The enantioselectivity of the alkynylation catalyzed by the C_2-symmetric diamino diol **1** depends on the structure of the acetylene. Up to 99% ee was obtained in the nucleophilic addition of lithium cyclopropylacetylide with trifluoromethyl ketones.

Acknowledgements

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7. **All of the compounds gave satisfactory spectroscopic data: Representative experimental procedure:** Under argon, to a solution of compound **1** (178 mg, 0.5 mmol) in THF (2 mL) was added cyclopropylacetylene (0.09 mL, 1 mmol) at −20°C, and this was followed by the addition of a solution of *n*-BuLi in hexanes (2.5 M, 0.8 mL, 2 mmol). The mixture was then warmed to 0°C and then cooled to −70°C. A solution of trifluoromethyl aryl ketone **3** (172 mg, 0.5 mmol) in THF (10 mL) was added. The resulting red solution was stirred for 2 h and then quenched by the addition of 2N HCl (5 mL). The reaction mixture was extracted with ethyl acetate (3×20 mL). The combined extracts were washed with brine and dried with sodium sulfate. After the solvent was removed in vacuo, the residue was purified by flash chromatography (eluent:hexane:ethyl acetate = 8:1, $R_f = 0.6$) to give **5** as a yellow solid (120 mg, 80% yield). The product was shown to have 99% ee by chiral HPLC (Chiralpak AD column eluted with hexane:isopropanol 7:3).