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A Novel, Highly Enantioselective Ketone Alkynylation Reaction Mediated by Chiral Zinc Aminoalkoxides

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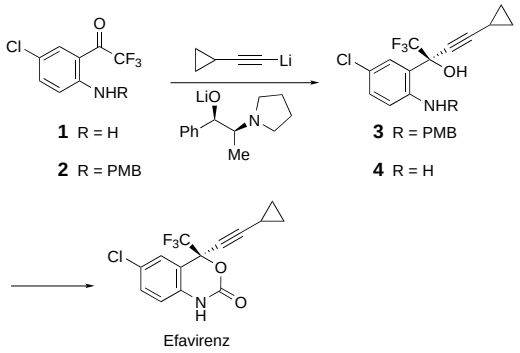
Stereocontrolled nucleophilic addition to carbonyl compounds is an important synthetic method. While the enantioselective alkylation of carbonyl compounds has been widely studied,[1] nucleophilic alkynylation has enjoyed only very limited success. A few examples of enantioselective alkynylation of aldehydes by organometallic compounds in combination with chiral modifiers have been reported.[2, 3] For example, Soai and Niwa showed that the addition of dialkynylzinc and alkylalkynylzinc reagents to benzaldehyde in the presence of amino alcohols provides propargyl alcohols with an *ee* of less than 50 %.[2c] Recently, Corey and Cimprich reported the addition of alkynylboranes to aldehydes with promotion by substoichiometric quantities of proline-derived oxazaborolidines to give propargyl alcohols with up to 97 % *ee* at low temperature.[3] We report here a novel, highly enantioselective, and practical alkynylation (up to 99.2 % *ee*) of a prochiral ketone by alkynyllithium and alkynylmagnesium reagents with mediation by chiral zinc aminoalkoxides.

Efavirenz is a potent nonnucleosidal HIV reverse transcriptase inhibitor which has just been approved by the US FDA for treatment of AIDS.[4] The importance of this compound prompted us to seek an efficient and scaleable synthesis that would allow the installation of the quaternary carbon atom with absolute stereocontrol. A recently reported asymmetric synthesis of this compound is based on a highly enantioselective addition of lithium cyclopropylacetylide to the PMB-protected ketoaniline **2** (Scheme 1).[5] The reactive



Scheme 1. Synthesis of efavirenz. PMB = *p*-methoxybenzyl.

species responsible for the strong chiral induction in this reaction was well characterized on the basis of ^{6}Li NMR data.[6] The chiral addition step, which proceeds with greater than 98 % *ee*, requires the use of 2.2 equivalents of lithium cyclopropylacetylide, 2.2 equivalents of (1*R*,2*S*)-*N*-pyrrolidinylnorephedrine alkoxide as chiral controller, and low temperatures (−60 °C). In addition, the success of the reaction relies on the protection of the aniline moiety, and this makes a protection/deprotection step necessary. The most straightforward and efficient asymmetric synthesis of efavirenz would involve the direct enantioselective alkynylation of the unprotected ketoaniline **1**[5] to afford amino alcohol **4**. Addition of lithium cyclopropylacetylide to **1** by the reported method,[5] however, suffered from low conversion and low enantioselectivity. Furthermore, the strongly basic conditions eventually led to decomposition of the product.

We reasoned that the inefficiency of the reaction between lithium cyclopropylacetylide and **1** is due to the strong basicity of the lithium reagent, which deprotonates the aniline group. It was proposed that complexation of a zinc alkoxide $Zn(OR)_2$ with the lithium acetylide would lower the basicity while maintaining the nucleophilicity of the acetylide. In addition, a chiral alkoxide could serve as a mediator for asymmetric induction. This conceptually simple approach proved to be highly effective for the asymmetric alkynylation of the unprotected ketoaniline **1**. The reaction of dimethylzinc with one equivalent of (1*R*,2*S*)-*N*-pyrrolidinylnorephedrine (**5**)[7] followed by one equivalent of methanol generated the chiral zinc alkoxide **6** (Scheme 2).[8a] The zinc reagent **6** was then treated with lithium cyclopropylacetylide, which presumably generates the zincate **7**.[8] Reaction of **7** with **1**

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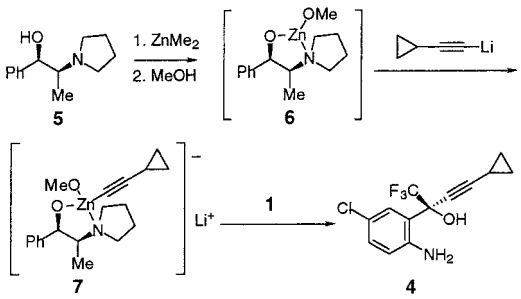
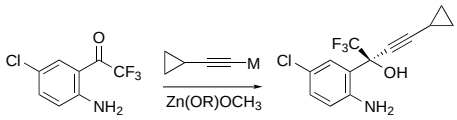


Scheme 2. Preparation of the zinc complex and its reaction with ketone **1**.

(toluene/THF,25 °C, 7 h) afforded the amino alcohol **4** with 83% yield of isolated product and 83% *ee*.[9] This result prompted a systematic study of the reaction to improve the enantioselectivity and yield.

As anticipated, the chiral auxiliary has a dramatic influence on the enantioselectivity. Other chiral auxiliaries such as cinchona alkaloids, binaphthol, and tartaric acid derivatives gave very poor selectivity. The initial success with (1*R*,2*S*)-*N*-pyrrolidinylnorephedrine as chiral auxiliary led us to focus our attention on norephedrine derivatives for improving the selectivity (Table 1). (1*R*,2*S*)-Ephedrine and (1*R*,2*S*)-norephedrine gave only moderate selectivities (entries 1 and 2),

Table 1. Effect of the chiral auxiliary and the countercation on the selectivity.[a]



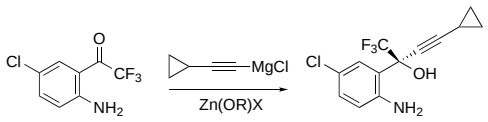
Entry	M	Ephedrine auxiliary (OR)	*ee* of **4** [%]
1	Li	(1*R*,2*S*)-ephedrine	28.2
2	Li	(1*R*,2*S*)-norephedrine	41.6
3	Li	(1*R*,2*S*)-*N*-methylephedrine	81.0
4	Li	(1*R*,2*S*)-*N*-pyrrolidinylnorephedrine	83.0
5	MgCl	(1*R*,2*S*)-*N*-pyrrolidinylnorephedrine	87.0
6	MgBr	(1*R*,2*S*)-*N*-pyrrolidinylnorephedrine	53.6
7	MgI	(1*R*,2*S*)-*N*-pyrrolidinylnorephedrine	50.6

[a] All reactions were carried out at 25 °C in THF/toluene with 1 equivalent each of chiral auxiliary, methanol, dimethylzinc, and cyclopropylacetylide, and 0.83 equivalents of **1**.

and the best results were obtained with (1*R*,2*S*)-*N*-pyrrolidinylnorephedrine and (1*R*,2*S*)-*N*-methylephedrine (entries 3 and 4). The countercation also had a significant effect on the enantioselectivity. For example, with the chloromagnesium acetylide, **4** was obtained with 87% *ee* (entry 5), but only about 50% *ee* was obtained with the bromo- and iodomagnesium acetylides.

Interestingly, variation of the achiral additive has a profound influence on the enantioselectivity of the alkynylation reaction (Table 2). At 25 °C with complexes derived from (1*R*,2*S*)-*N*-pyrrolidinylnorephedrine and chloromagnesium cyclopropylacetylide, the use of ethanol as achiral auxiliary gave **4** with 55% *ee* (entry 2), while neopentyl alcohol (entry 3) and methanol (entry 1) gave 96 and 87% *ee*, respectively. These results suggested that the achiral alcohol

Table 2. Effect of the achiral auxiliary (HX) on the selectivity.[a]



Entry	Auxiliary	*ee* of **4** [%]
1	CH_3OH	87.0
2	CH_3CH_2OH	55.0
3	$(CH_3)_3CCH_2OH$	95.6
4	$CH_2{=}CHCH_2OH$	90.0
5	$PhCH_2OH$	89.0
6	CF_3CH_2OH	95.7
7	CF_3CO_2H	89.4
8	$(CH_3)_3CCO_2H$	71.6
9	4-NO_2PhOH	89.0

[a] All reactions were carried out at 25 °C in THF/toluene with 1 equivalent each of chiral auxiliary, methanol, dimethylzinc, and cyclopropylacetylide, and 0.83 equivalents of **1**.

might exert a steric effect on the stereoselectivity. However, the increase in enantioselectivity from 55% to about 96% when 2,2,2-trifluoroethanol was used instead of ethanol indicates a possible significant inductive effect. Good enantioselectivities were also obtained with carboxylic acids and phenols as auxiliaries.

Further optimization of this reaction was carried out with neopentyl alcohol or 2,2,2-trifluoroethanol as achiral auxiliary. We found that dimethyl- and diethylzinc were equally effective, and the chiral zinc reagent could be prepared by mixing the chiral auxiliary, the achiral auxiliary and the dialkylzinc reagent in any order without affecting the conversion and selectivity of the reaction. However, the ratio of chiral to achiral additive does affect the efficiency of the reaction. The enantioselectivity increased to 97.5% when 1.2 equivalents of (1*R*,2*S*)-*N*-pyrrolidinylnorephedrine and 0.8 equivalents of neopentyl alcohol were used to prepare the zinc alkoxide (Table 3). Further increase in the ratio of chiral to achiral auxiliary did not lead to significant improvement in stereoselectivity. For instance, the zinc alkoxide derived from two equivalents of (1*R*,2*S*)-*N*-pyrrolidinylnorephedrine gave **4** with 95.8% ee but only 50% conversion. Similar results were obtained with 2,2,2-trifluoroethanol. The enantioselectivity was only slightly dependent on the reaction temperature. Reactions with the zinc alkoxide derived from (1*R*,2*S*)-*N*-pyrrolidinylnorephedrine and 2,2,2-trifluoroethanol gave **4** with 99.2% *ee* at 0 °C and 94.0% *ee* at 40 °C.

Table 3. Effect of the amount of chiral auxiliary on the selectivity.[a]

Entry	Equiv of chiral auxiliary[b]	*ee* of **4** [%]
1	0.8	58.8
2	1	95.6
3	1.1	95.8
4	1.2	97.5
5	1.5	97.7
6	2	95.8

[a] All reactions were carried out at 25 °C in THF/toluene with neopentyl alcohol as the achiral auxiliary, (1*R*,2*S*)-*N*-pyrrolidinylnorephedrine as the chiral auxiliary, and $(CH_2)_2CHC{\equiv}CMgCl$ as the nucleophile. [b] Relative to $ZnMe_2$.

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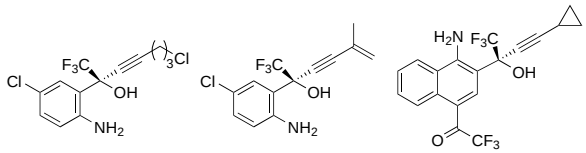
The scope of this new alkynylation reaction was briefly examined. The reaction is applicable to other acetylenes such as 5-chloropentyne and 2-methyl-1-buten-3-yne, which gave **8**[11] and **9**[12] in high yield and enantioselectivity. The presence of the unprotected amino group in the ketoaniline seems to be important for the efficiency of the reaction. Under similar conditions only 45 % *ee* was obtained with the PMB-protected ketoaniline **2**, and essentially no reaction was observed when the nitrogen center was protected with a bulky group such as trityl. Interestingly, alkynylation of 1-{1-amino-4-(2,2,2-trifluoroacetyl)naphth-2-yl}-2,2,2-trifluoroethan-1-one under the same conditions resulted in exclusive addition at the carbonyl group flanking the aniline moiety and provided **10**[13] in 91 % yield with 97 % *ee*. This result clearly demonstrates that the presence of an unprotected aniline group ajacent to the carbonyl group in the substrate is important for the reactivity (and probably selectivity).



8 (93%, 95.2% *ee*) **9** (94%, 97.0% *ee*) **10** (91%, 97.0% *ee*)

We have developed a novel, highly efficient, and practical asymmetric alkynylation of the ketoaniline **1**. The reaction has been carried out successfully and reliably on a multi-kilogram scale and is now the cornerstone of the most efficient synthesis of efavirenz[5] to date. The degreee of stereocontrol with a chiral zinc aminoalkoxide is remarkable. The reaction mechanism and extension of the method to other carbonyl compounds are currently under investigation.

Experimental Section

In a typical experiment, THF (240 mL, dried over molecular sieves), 2,2,2-trifluoroethanol[10] (19.2 g, 0.19 mol), and (1*R*,2*S*)-*N*-pyrrolidinylnorephedrine (59.1 g, 0.29 mol) were mixed under nitrogen. The mixture was cooled to 0 °C, and diethylzinc (1.1 M in toluene, 218 mL, 0.24 mol) was added slowly enough to keep the temperature below 30 °C. A solution of chloromagnesium cyclopropylacetylide was prepared by reaction of cyclopropylacetylene (15.9 g, 0.24 mol) and *n*-butylmagnesium chloride (2.0 M in THF, 120 mL, 0.24 mol) at 0 °C for 1 h. The solution was then transferred to the zinc reagent by cannula with THF (100 mL) as a wash. The mixture was cooled to 0 °C, and **1** (44.7 g, 0.20 mol) was added. The reaction mixture was quenched with 1 M citric acid (400 mL) after 15 h. The two layers were separated. The aqueous layer was saved for recovery of (1*R*,2*S*)-*N*-pyrrolidinylnorephedrine. The organic layer (assay of this solution indicated 99.2 % *ee*[9]) was washed with water (200 mL) and concentrated to about 180 mL. Toluene (100 mL) was added and the solution was again concentrated to about 180 mL to remove all THF. Heptane (240 mL) was added slowly. The mixture was cooled to 0 °C, and the solid was collected by filtration, washed with heptane (ca. 50 mL), and dried to give 55.2 g (95.3 % yield, 99.2 % *ee*) of analytically pure **4** as a white solid. M.p. 139 – 141 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.52$ (d, $J = 2.4$ Hz, 1 H), 7.12 (dd, $J = 2.4$, 8.7 Hz, 1 H), 6.61 (d, $J = 8.7$ Hz, 1 H), 4.70 (s, 1 H), 4.39 (s, 2 H), 1.39 (m, 1 H), 0.85 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta = 143.21$, 130.44, 130.04, 123.94, 123.93 (q), 121.11, 120.81, 93.51, 74.80 (q), 70.58, 8.59, – 0.85; elemental analysis calcd for $C_{13}H_{11}NOClF_3$ (%): C 53.80, H 3.77, N 4.72; found: C 53.71, H 3.75, N 4.64.

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[9] The enantiomeric excess was determined by HPLC assay on a chiralcel-AD column (hexane/isopropyl alcohol, 3/1)

[10] Trifluoroethanol is preferred to neopentyl alcohol because it gives a faster reaction.

[11] ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.53$ (d, $J = 2.4$ Hz, 1 H), 7.12 (dd, $J = 2.4$, 8.7 Hz, 1 H), 6.62 (d, $J = 8.7$ Hz, 1 H), 4.68 (br s, 3 H), 3.69 (m, 2 H), 2.57 (m, 2 H), and 2.06 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): $\delta =$ 143.18, 130.37, 130.28, 130.21, 125.60(q), 122.16, 121.09, 88.49, 76.65 (q), 74.74, 43.42, 30.62, 16.18; elemental analysis calcd for $C_{13}H_{12}NOCl_2F_3$ (%): C 47.88, H 3.71, N 4.29; found: C 48.14, H 3.39, N 4.15.

[12] ^{1}H NMR (CD_3CN, 300 MHz): $\delta = 7.47$ (d, $J = 2.4$ Hz, 1 H), 7.11 (dd, $J = 2.4$, 8.7 Hz, 1 H), 6.66 (d, $J = 8.7$ Hz, 1 H), 5.48 (m, 2 H), 5.00 (br s, 3 H), 1.95 (m, 3 H); ^{13}C NMR (CD_3CN, 75.5 MHz): $\delta = 147.19$, 131.09, 130.39, 126.32, 125.54, 125.40(q), 121.27, 120.04, 119.06, 90.75, 84.02, 75.08 (q), 22.94; elemental analysis calcd for $C_{13}H_{11}NOClF_3$ (%): C 53.80, H 3.77, N 4.72; found: C 53.67, H 3.80, N 4.67.

[13] ^{1}H NMR (CD_3CN, 400 MHz): $\delta = 9.29$ (d, $J = 9.2$ Hz, 1 H), 8.60 (br s, 1 H), 7.85 (d, $J = 8.7$ Hz, 1 H), 7.69 (dd, $J = 9.0$, 9.2 Hz, 1 H), 7.59 (dd, $J = 8.7$, 9.0 Hz, 1 H), 6.35 (br s, 2 H), 3.40 (br s, 1 H), 1.41 (m, 1 H), 0.90 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): $\delta = 179.0$ (q), 150.4, 138.9, 133.5, 130.5, 126.5, 126.4, 125.3 (q), 123.2, 122.5 (q), 120.8, 113.5, 108.3, 95.4, 76.5 (q), 70.1, 8.5, 8.4, – 0.8; elemental analysis calcd for $C_{19}H_{13}F_6NO_2$ (%): C 56.87, H 3.27, N 3.49; found: C 56.99, H 2.98, N 3.42.

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