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Practical highly enantioselective synthesis of terminal propargylamines. An expeditious synthesis of (*S*)-(+)-coniine†

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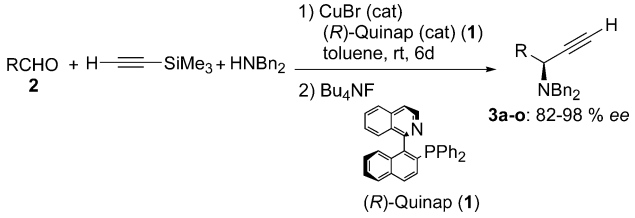
Received (in Cambridge, UK) 2nd July 2004, Accepted 23rd July 2004
First published as an Advance Article on the web 7th September 2004

The one-pot three-component addition reaction of trimethylsilylacetylene, aldehydes and dibenzylamine provides in the presence of CuBr/Quinap as catalyst, various enantiomerically enriched propargylamines in good yields (up to 99%) and excellent enantiomeric excess (up to 98% *ee*) which can be used as a key intermediate in the synthesis of the alkaloid (*S*)-(+)-coniine.

Fifty years ago, Reppe demonstrated that ethynylcopper catalyzes the addition of various terminal alkynes to aldehydes.[1] This reaction is a model of atom economy[2] since it allows the formation of a new carbon–carbon bond *via* a catalytic C–H bond activation[3] of the terminal alkyne. Recently, we reported a related three-component copper-catalyzed reaction of a terminal alkyne, an aldehyde and a secondary amine leading to propargylamines.[4,5] The reaction was performed in the presence of the chiral ligand (*R*)-Quinap[6] **1** (5 mol%) providing chiral propargylamines with enantioselectivities ranging from 32–96% *ee*. The enantioselectivity was found to be highly dependent on the structure of the alkyne. This optical purity dispersion of the products is detrimental for a practical use of the reaction. Thus, we have decided to investigate the stereoselectivity of the three-component reaction using trimethylsilylacetylene as the alkyne component since the triple bond can be readily functionalized after desilylation. Also, we have kept the amine-component invariable and have used dibenzylamine, since the benzyl groups have the appropriate steric hindrance for achieving high enantioselectivities and can be readily removed by hydrogenation.

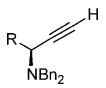
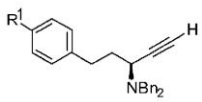
We wish now to report that under these reaction conditions, a broad range of aldehydes of type **2** participate in the three-component reaction in the presence of CuBr (5 mol%) and (*R*)-Quinap (5.5 mol%) as the catalytic system in toluene affording propargylamines of type **3** after desilylation. Remarkably, uniformly high enantioselectivities (82–98% *ee*) and overall yields (72–97%) are obtained (Scheme 1 and Table 1). Various unbranched aldehydes **2** (R = *n*-Pr, *n*-Bu, *n*-Pent) provide the expected propargylamines **3a–c** in 88–90% *ee* as determined by HPLC analysis[7] (entries 1–3 in Table 1). Branched aldehydes lead to the corresponding propargylamines **3d–g** with an improved enantioselectivity (94–98% *ee*, entries 4–7). Aldehydes bearing a cyclic substituent like cyclopropyl-, cyclopentyl- and cyclohexylcarbaldehyde afford the desired propargylamines **3h–j** in 92–97% yield and 92–96% *ee* (entries 8–10, Table 1). Aldehydes containing aromatic rings could be also used in this reaction (see Table 1 entries 11–15).[8] It is interesting to notice that both dihydrocinnamaldehydes (entries 13–15, 87–88% *ee*) as well as cinnamaldehydes (entries 11 and 12, 82–84% *ee*) are excellent substrates. Functional groups like a bromine or an ester group are also tolerated without significant loss of stereoselectivity (entries 14 and 15).



Scheme 1 Enantioselective preparation of propargylamines of type **3**.

To improve the synthetic utility of our method, we have recovered the expensive Quinap-derived catalyst and used it in several reaction cycles. The catalyst is not soluble in pentane and can be recovered by filtration from the crude reaction mixture. The results obtained with the recovered catalyst are summarized in Table 2. Up to three runs can be performed with the same catalyst without significant loss in enantioselectivity and with only a slight drop in yield. Furthermore, it is not necessary to use the same reactants with the recycled catalyst. Its use in the synthesis of amine **3c** and afterwards in the synthesis of **3g** furnished the same enantiomeric excess (**3g**: 98% *ee*). Several of the amines **3** were

Table 1 Enantioselective copper(I)-catalyzed synthesis of propargylamines of type **3**

Entry	RCHO	Product of type **3**	Yield (%)[a]/ time (days)	% *ee*[b]
				
1	*n*-Pr	**3a**: R = *n*-Pr	88/5	90
2	*n*-Bu	**3b**: R = *n*-Bu	75/5	90
3	*n*-Pent	**3c**: R = *n*-Pent	95/3	88
4	*i*-Bu	**3d**: R = *i*-Bu	84/6	94
5	*neo*-Pent	**3e**: R = *neo*-Pent	93/6	94
6	*i*-Pr	**3f**: R = *i*-Pr	84/3	96
7	*s*-Pent	**3g**: R = *s*-Pent	97/6	98
8	*c*-Pr	**3h**: R = *c*-Pr	97/6	92
9	*c*-Pent	**3i**: R = *c*-Pent	97/6	96
10	*c*-Hex	**3j**: R = *c*-Hex	92/4	92
11	(C_6H_5) CH=CH	**3k**: R = (C_6H_5) CH=CH	93/3	82
12	$(C_6H_5)_2$ C=CH	**3l**: R = $(C_6H_5)_2$ C=CH	80/3	84
				
13	$C_6H_5(CH_2)_2$	**3m**: R^1 = H	76/3	88
14	4-Br-$C_6H_4(CH_2)_2$	**3n**: R^1 = Br	72/2	88
15	4-CO_2Et-$C_6H_4(CH_2)_2$	**3o**: R^1 = CO_2Et	83/2	87

[a] Isolated yield of analytically pure product. [b] Enantiomeric excess determined by HPLC using Chiracel OD-H column (*n*-heptane : *i*-PrOH).

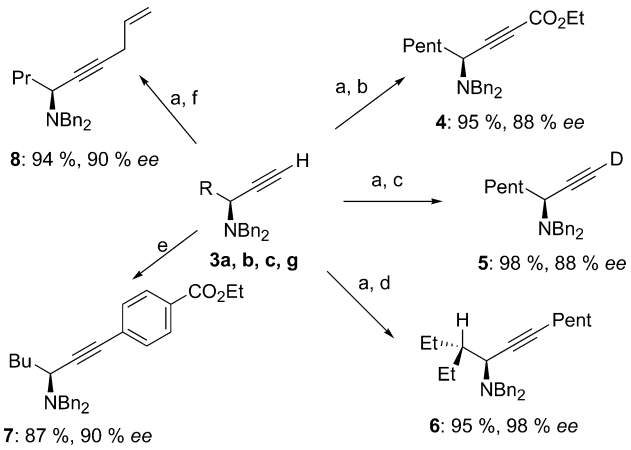
† Electronic supplementary information (ESI) available: full experimental procedures and analytical data. See http://www.rsc.org/suppdata/cc/b4/b409951f/

DOI: 10.1039/b409951f

Table 2 Catalyst recycling in the preparation of propargylamine **3g**

Run	Yield (%)[a]	*ee* (%)[b]
1	99	98
2	87	97
3	89	98

[a] Isolated yield of analytically pure product. [b] Enantiomeric excess determined by HPLC using Chiracel OD-H column (*n*-heptane : *i*-PrOH).

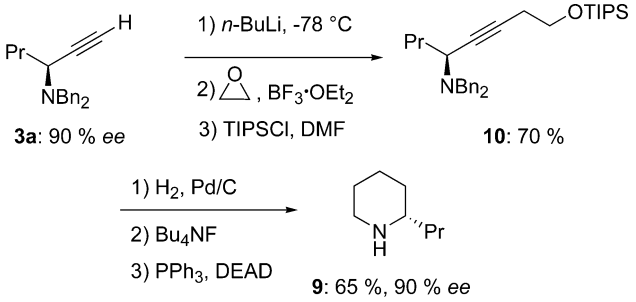


Scheme 2 Transformations of propargylamines of type **3**: a) *n*-BuLi, −78 °C, 0.5 h; b) $ClCO_2Et$, −78 °C to 25 °C; c) D_2O (excess), −78 °C, 0.5 h; d) Pent-I, 50 °C, 20 h; e) 4-$IC_6H_4CO_2Et$ (1.1 equiv.), $PdCl_2(PPh_3)_2$ (2 mol%), CuI (2 mol%), Et_3N, THF, 25 °C, 15 h; f) allyl iodide, 25 °C, 12 h.

further functionalized to demonstrate that this method can give an access to a range of polyfunctionalized propargylamines **4**–**8** with high enantioselectivities.

Thus, the reaction of the alkynyllithium derived from **3c** with ethyl chloroformate provided the chiral alkynyl ester **4** in 95% yield and 88% *ee*. The deuteration of **3c** with D_2O provided the mono-deuterated alkyne **5** in 98% yield and > 95% deuterium incorporation. The alkylation of the lithium derivative of **3g** with pentyl iodide furnished after 20 h at 50 °C the chiral propargylamine **6** in 95% yield and 98% *ee*. Similarly, the Sonogashira cross-coupling[9] of **3b** with ethyl 4-iodobenzoate in the presence of $PdCl_2(PPh_3)_2$ (2 mol%) and CuI (2 mol%) led to the functionalized phenylacetylene derivative **7** in 87% yield and 90% *ee*. Finally, the allylation of **3a** with allyl iodide (25 °C, 12 h) gave the enyne **8** in 94% yield and 90% *ee* (Scheme 2). To demonstrate the synthetic utility of our approach, we have developed a short enantioselective synthesis of (*S*)-(+)-coniine **9**.[10] Coniine is an highly toxic alkaloid inducing curare type paralysis. The chiral propargylamine **3a** obtained in 90% *ee via* the three-component reaction was alkylated with ethylene oxide after deprotonation with *n*-BuLi in the presence of $BF_3{\cdot}OEt_2$ under mild conditions (−78 °C, 2 h)[11] leading after silylation with TIPSCl in the presence of imidazole to the TIPS-protected derivative **10** in 70% overall yield. The hydrogenolysis of the benzyl groups and the reduction of the triple bond are readily achieved by hydrogenation of **10** in methanol (Pd/C, H_2 (1 atm), 3 d) leading to an intermediate primary amine which was desilylated with Bu_4NF and submitted to an intramolecular Mitsunobu reaction[12] affording (*S*)-(+)-coniine **9** in 5 steps with 41% overall yield (Scheme 3).

In summary, we have developed a general enantioselective



Scheme 3 Enantioselective synthesis of (*S*)-(+)-coniine **9**.

synthesis of terminal propargylamines with consistently high enantioselectivities > 82% *ee*. Further applications of this method are currently underway in our laboratories.

We thank the Fonds der Chemischen Industrie for financial support. We thank the DFG (SPP 1118 "Sekundäre Wechselwirkungen als Steuerungsprinzip zur gerichteten Funktionalisierung reaktionsträger Substrate") for a fellowship for N. G.

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