Enantioselective Synthesis of Chiral α-Aminoalkyl-1,2,3-triazoles Using a Three-Component Reaction

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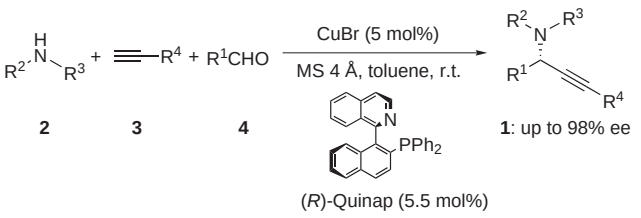
Abstract: A range of chiral α-aminoalkyl-1,2,3-triazoles have been prepared in a modular fashion in 3 steps with up to 98% ee. The key step is a CuBr/Quinap-catalyzed enantioselective asymmetric three-component synthesis of propargylamines.

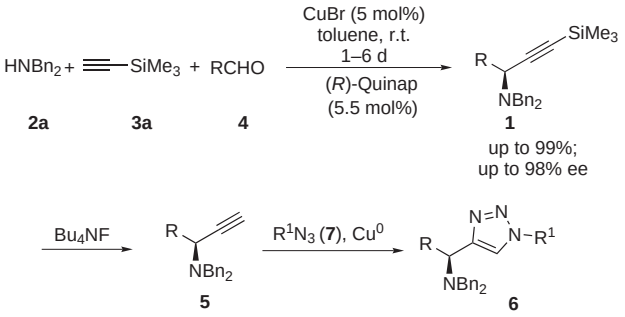
Key words: alkynes, asymmetric synthesis, C–H activation, copper catalysis, heterocycles

Heterocyclic compounds have found numerous applications as pharmaceuticals and agrochemicals. Therefore, the development of new and efficient synthesis of complex heterocycles is an active field of research. The expeditious and modular preparation of heterocyclic rings is of special importance.[1] The 1,3-dipolar cycloaddition reactions are especially useful for the preparation of 5-membered heterocycles.[2] The copper(I)-catalyzed reaction of terminal alkynes and organic azides to give 1,4-disubstituted 1,2,3-triazoles exhibits the best click reaction[3] to date. Recently, we[4] and others[5] have developed a new synthesis of chiral propargylamines of type **1** using three components: an amine **2**, a terminal alkyne **3** and an aldehyde **4** (Scheme 1). This reaction is efficiently catalyzed with CuBr (5 mol%) and (*R*)-Quinap[6] (5.5 mol%) and produces propargylamines of type **1** with high enantioselectivity (up to 98% ee) and good yields (up to 98%).



Scheme 1 Asymmetric three-component synthesis of propargylamines

Herein, we wish to report the conversion of terminal propargylamines **5** (obtained by the three-component reaction and subsequent desilylation of **1**) to chiral α-aminoalkyl-1,2,3-triazoles of type **6** by a 1,3-dipolar cycloaddition with an organic azide **7** in the presence of copper(0). Triazoles are of great interest due to their potential biological activity.[7] Our approach provides a modular synthesis of a new family of 1,2,3-triazoles **6** (Scheme 2).



Scheme 2 Formation of chiral α-aminotriazoles of type **6**

The reaction of various aldehydes **4** (RCHO) with dibenzylamine **2a** and trimethylsilylacetylene **3a** in the presence of CuBr (5 mol%) and (*R*)-Quinap (5.5 mol%) provided propargylamines **1a**–**j** in 58–98% yield and 73–98% ee. After treatment either with Bu_4NF (0.3 equiv, THF, 0 °C, 15 min) or aqueous KOH (1.2 equiv, MeOH, r.t., 12 h), the corresponding terminal alkynes **5a**–**j** were obtained in 91–99% yield (Scheme 2).

These terminal alkynes of type **5** were subsequently reacted with benzyl azide[8] (**7a**) in the presence of copper powder. The reaction was performed in *t*-BuOH–H_2O mixtures at room temperature to 60 °C. This procedure is equally well suited for aromatic and aliphatic substituted propargylamines (Table 1).

In most cases, the reaction proceeded already at room temperature, but with sometimes longer reaction times. For propargylamines **5a**–**h**, derived from aliphatic aldehydes, the 1,3-dipolar cycloaddition reaction with benzyl azide (**7a**) proceeded with general high yield (up to 98%, entries 1–8). Propargylamines bearing cyclic substituents like cyclopropyl, cyclopentyl or cyclohexyl groups **5f**–**h** afforded longer reaction times. This could be overcome by heating the reaction mixture to 40–60 °C leading to the corresponding triazoles **6f**–**h** in high yield (74–96%). Propargylamines **5i**–**j**, derived from heteroaromatic aldehydes, could be reacted likewise, giving triazoles **6i**–**j** in moderate to good yield (76–98%, entries 9, 10). For these propargylamines, the reaction was carried out at 40 °C. No racemization was observed during the addition reaction as was proven by analysis of the starting material

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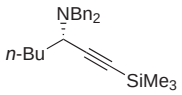
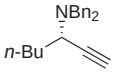
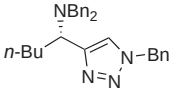
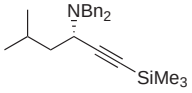
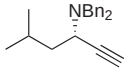
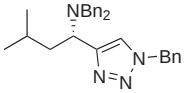
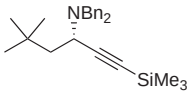
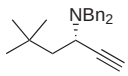
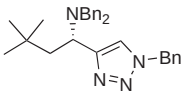
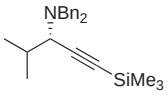
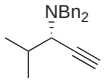
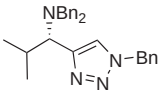
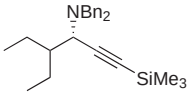
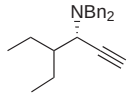
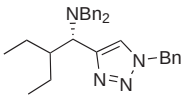
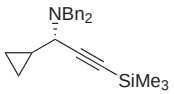
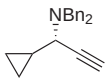
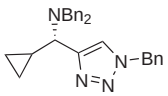
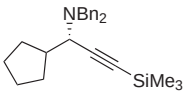
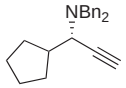
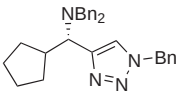
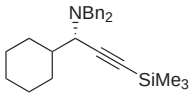
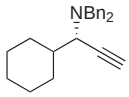
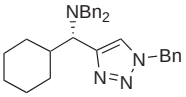
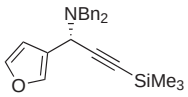
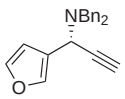
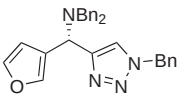
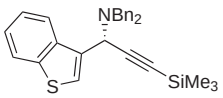
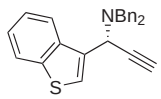
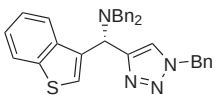
Table 1 Triazoles of Type **6** Prepared from Chiral Propargylamines **1**

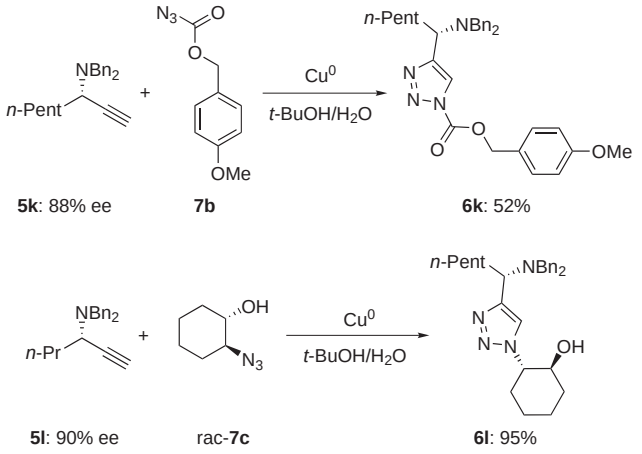
Entry	Propargylamine **1**	Yield (%)	ee (%)	Propargylamine **5**	Yield (%)	Triazole **6**	Conditions	Yield (%)
1	 **1a**	82	90	 **5a**	92	 **6a**	r.t., 8 d	98
2	 **1b**	85	94	 **5b**	94	 **6b**	r.t., 3 d	85
3	 **1c**	94	94	 **5c**	94	 **6c**	r.t., 4 d	97
4	 **1d**	87	96	 **5d**	91	 **6d**	r.t., 2 d	73
5	 **1e**	95	98	 **5e**	98	 **6e**	r.t., 4 d	89
6	 **1f**	98	92	 **5f**	99	 **6f**	40 °C, 1 d	95
7	 **1g**	98	96	 **5g**	99	 **6g**	r.t., 8 d	74
8	 **1h**	86	97	 **5h**	95	 **6h**	60 °C, 2.5 d	92
9	 **1i**	58	73	 **5i**	99	 **6i**	40 °C, 1 d	98
10	 **1j**	92	82	 **5j**	93	 **6j**	40 °C, 8 d	76

5h and the product **6h** (98% ee) by chiral HPLC. In each case, both the non-racemic and the racemic product were analyzed.

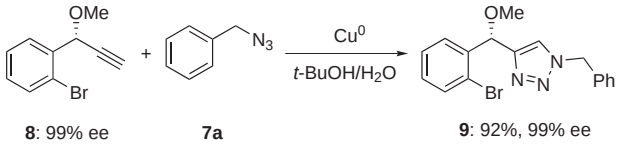
Besides benzyl azide (**7a**), other functionalized azides were used in the cycloaddition reaction. 4-Methoxy-benzyloxycarbonyl azide (**7b**) was reacted with propargylamine **5k** under standard conditions, furnishing the cycloaddition product **6k** in 52% yield (Scheme 3). Likewise, 2-azidocyclohexanol[9] (**7c**) was reacted with propargylamine **5l** leading to product **6l** in 95% yield (Scheme 3).

Furthermore, this methodology was successfully applied to the synthesis of α-alkoxy-1,2,3-triazoles. Thus, chiral propargyl ether **8** was successfully reacted with benzyl azide (**7a**) in the presence of copper powder leading to the desired triazole **9** in 92% yield and 99% ee (Scheme 4).

In summary, we have developed a short and highly modular synthesis of chiral α-aminotriazoles of type **6** using a copper-catalyzed asymmetric three-component reaction for the preparation of propargylamines and subsequent 1,3-dipolar cycloaddition reaction with organic azides. The obtained products display a high synthetic potential.



Scheme 3 Formation of functionalized chiral α-aminotriazoles **6k–l**



Scheme 4 Synthesis of α-alkoxytriazole **9**

Further applications of this methodology towards the preparation of natural products and biologically active compounds are currently underway in our laboratories.

Preparation of (–)-*N*,*N*-Dibenzyl-1-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2-ethylbutan-1-amine (6e)

Propargylamine (–)-**5e** (306 mg, 1.0 mmol)[4b] was dissolved in *t*-BuOH–H_2O (2:1, 3 mL) at r.t. Benzyl azide **7a** (200 mg, 1.5 mmol) was added, followed by copper(0) powder (1.0 g). The reaction mixture was stirred at r.t. for 4 d, diluted with CH_2Cl_2 and filtered over a pad of Celite. The filtrate was concentrated and the crude product was purified by column chromatography (SiO_2, pentane–Et_2O 4:1) leading to triazole (–)-**6e** (389 mg, 0.9 mmol, 89%) as a colorless solid.

$[\alpha]_D^{25}$ –88 (*c* 0.56, $CHCl_3$); mp 91–93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.11 (m, 16 H), 5.31 (d, *J* = 2.9 Hz, 2 H), 3.81–3.73 (m, 3 H), 3.11 (d, *J* = 13.8 Hz, 2 H), 2.14–2.01 (m, 1 H), 1.91–1.76 (m, 1 H), 1.64–1.43 (m, 2 H), 1.06–0.91 (m, 1 H), 0.90–0.73 (m, 1 H), 0.63 (t, *J* = 7.5 Hz, 3 H), 0.51 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.3, 140.3, 135.6, 129.5, 129.4, 129.0, 128.6, 128.1, 127.1, 122.9, 56.8, 54.7, 54.4, 40.4, 22.1, 20.4, 10.5, 9.5. IR (KBr): 2963, 2936, 1495, 1454, 747, 727, 699 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 438 (<1) [M^+], 368 (24), 367 (100), 91 (63). HRMS (EI, 70 eV): *m/z* calcd for $C_{29}H_{34}N_4$: 438.2783; found: 438.2788.

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