C–H Activation

Enantioselective, Copper(I)-Catalyzed Three-Component Reaction for the Preparation of Propargylamines**

*Nina Gommermann, Christopher Koradin, Kurt Polborn, and Paul Knochel**

The catalytic enantioselective formation of new C–C bonds is an important class of reactions.[1] Especially attractive are multicomponent reactions which allow the formation of several bonds including new C–C bonds in a one-pot procedure.[2] For achieving optimum atom economy[3] and avoiding the production of stoichiometric amounts of metal salts as by-products, we[4] and others[5] have examined the use of an alkyne as the precursor for the nucleophilic reaction component. Alkynes of type **1** can be deprotonated catalytically in situ by means of cesium salts and reacted subsequently with aldehydes and ketones, leading to propargyl alcohols.[6] Recently, we have shown that various enamines react with terminal alkynes in the presence of copper(I) salts and quinap (**2**),[7] providing propargylamines in up to 90% *ee*.[4]

In order to avoid the generation of sensitive enamines and to extend the scope of this propargylamine synthesis to nonenolizable aldehydes (i.e. aldehydes from which enamines cannot be prepared), we have examined a new three-component reaction[8] between an alkyne **1**, an aldehyde **3**, and a secondary amine **4**. We have found that propargylamines of type **5** are formed in toluene at room temperature in the presence of CuBr (5 mol%), (*R*)-quinap ((*R*)-**2**) (5.5 mol%), and molecular sieves 4 Å in excellent yields (up to 99%) and good enantioselectivities (up to 96% *ee*; Scheme 1 and Table 1).

The reaction is usually complete within 12 to 48 h for the racemic reaction without ligand and within one to six days for the enantioselective reaction with high yields in most cases. The alkyne can bear either an aryl substituent ($R^1 = Ph$) or an alkyl substituent ($R^1 = Bu$; entries 1 and 2 in Table 1). The resulting propargylamines **5a** and **5b** were obtained in 98 and 85% yield and 86 and 82% *ee*, respectively. Branched aliphatic aldehydes like isobutyraldehyde lead to the expected propargylamines **5c** and **5d** in 60 and 99% yield and 84 and 83% *ee*, respectively (entries 3 and 4). The use of

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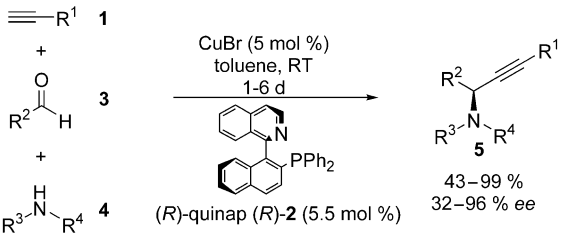
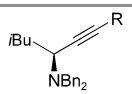
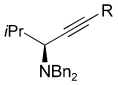
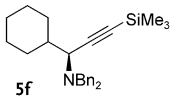
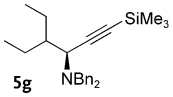
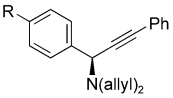
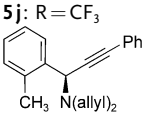
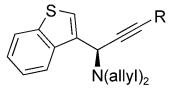
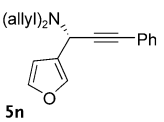


Scheme 1. Enantioselective three-component reaction for the synthesis of proparylamines. RT = room temperature.

Table 1: Enantioselective, copper(I)-catalyzed three-component synthesis of propargylamines **5**.

Entry	R^1	R^2	R^3	**5**	Yield [%][a]	Sel. [% *ee*][b]
						
1	Ph	*i*Bu	Bn	**5a**: R = Ph	98	86
2	*n*Bu	*i*Bu	Bn	**5b**: R = *n*Bu	85	82
						
3	Ph	*i*Pr	Bn	**5c**: R = Ph	60	84
4	*p*-BrC_6H_4	*i*Pr	Bn	**5d**: R = *p*-BrC_6H_4	99	83
5	$SiMe_3$	*i*Pr	Bn	**5e**: R = $SiMe_3$	87	92[c]
6	$SiMe_3$	*c*-Hex	Bn	 **5f**	99	92[c]
7	$SiMe_3$	1-ethylpropyl	Bn	 **5g**	72	96[c]
						
8	Ph	Ph	allyl	**5h**: R = H	91	70
9	Ph	*p*-MeO-C_6H_4	allyl	**5i**: R = OMe	76	60
10	Ph	*p*-CF_3-C_6H_4	allyl	**5j**: R = CF_3	43	63
11	Ph	*o*-CH_3-C_6H_4	allyl	 **5k**	84	32
						
12	Ph		allyl	**5l**: R = Ph	80	78
13	*c*-Hex		allyl	**5m**: R = *c*-Hex	61	74
14	Ph		allyl	 **5n**	55	64[d]

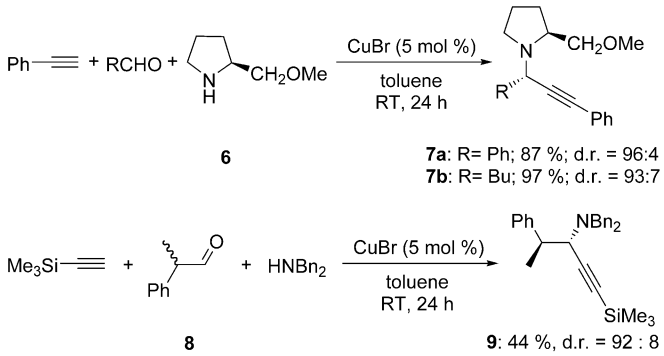
[a] Yield of analytically pure product. [b] Enantiomeric excess determined by HPLC with a Chiracel OD-H column (*n*-heptane:*i*PrOH). [c] The *ee* value was determined after desilylation. [d] The *ee* value was determined after deprotection to give the monodeallylated derivative.

trimethylsilylacetylene leads to a further increase of enantioselectivity with these branched aldehydes, affording the propargylamines **5e–g** in 72–99% yield and 92–96% *ee*. Aromatic aldehydes can also be used. The presence of either an electron-donating or an electron-withdrawing substituent in *para* position has only a moderate influence on the enantioselectivity of the reaction (entries 8–10). However, the yield of the product **5j** (R = CF_3) is strongly reduced (43%) compared to that of **5i** (R = OMe; 76%) due to a dramatic decrease in reactivity. Steric effects are more important and the presence of an *ortho* substituent in the aldehyde (2-methylbenzaldehyde) leads to a dramatic decrease of the selectivity (**5k**: 84%, 32% *ee*; cf. entries 8 and 11). Heterocyclic aldehydes like 3-formylbenzothiophene and 3-furfural are also compatible and allow the preparation of the corresponding propargylic products **5l** and **5n** in yields of 80% (78% *ee*) and 55% (64% e*e*), respectively.

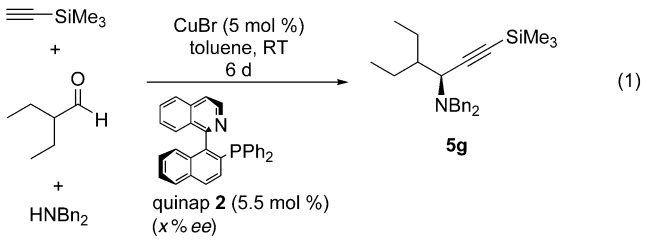
Remarkably, this reaction is highly diastereoselective if a chiral amine or aldehyde is used. Thus, the reaction of the prolinol derivative **6** with aromatic or aliphatic aldehydes and phenylacetylene produces the desired propargylamines **7a** and **7b** in yields of 87 and 97% and good diastereoselectivities of 96:4 and 93:7, respectively.[9] By using the racemic aldehyde **8**, the corresponding propargylamine **9** can also be obtained in good diastereoselectivity (92:8) (Scheme 2). The relative configuration of **9** has been determined by X-ray structure analysis.[10]

Preliminary mechanistic investigations [Eq. (1)] show that the enantioselective reaction displays a strong positive nonlinear effect (Figure 1). This suggests that a dimeric Cu/quinap complex is the catalytically active species and is in good agreement with the previously reported crystal structure of the $[CuBr\{(R)\text{-quinap}\}]_2$ complex.[11] The heterochiral complex $[Cu_2Br_2\{(R)/(S)\text{-quinap}\}]$ seems to react at a much slower rate than the corresponding homochiral complex $[Cu_2Br_2\{(R)/(R)\text{-quinap}\}]$. This explains the strong positive amplification. Thus, a ligand having an enantiomeric excess of 10% leads to the formation of the propargylamine **5g** in 68% *ee*. A lower conversion rate and product yield is observed when the ligand has lower *ee*.

A tentative reaction mechanism is described in Scheme 3. The dimeric[11] chiral copper complex **10** complexes the alkyne **1,** leading to the side-on complex **11**. The complexation of **11** with the intermediate aminal **12** (obtained by the reaction of the amine **4** with the aldehyde **3**) provides the complex **13**. Deprotonation of the



Scheme 2. Diastereoselective three-component reactions.



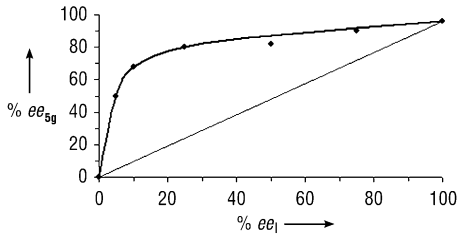
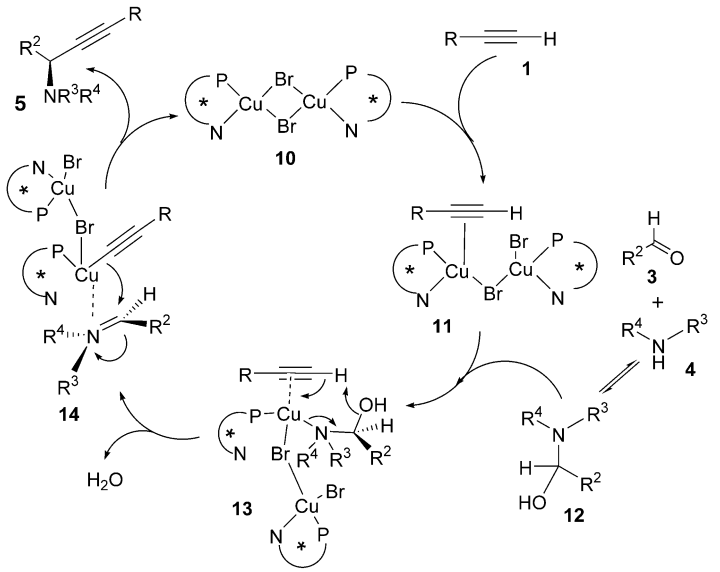


Figure 1. Nonlinear effects in the three-component reaction leading to **5g** [Eq. (1)]. $\%ee_l$: enatiomeric excess of the ligand, $\%ee_{5g}$: enantiomeric excess of the product.



Scheme 3. Tentative mechanism of the three-component reaction.

coordinated alkyne and the elimination of H_2O gives complex **14**, an end-on copper acetylide with a coordinated iminium ion. The addition of the acetylide to the iminium salt in the coordination sphere of the chiral copper(I) complex leads to the chiral propargylamine **5** and regenerates the catalyst **10**.

In summary, we have shown that a wide range of chiral propargylamines can be prepared in a one-pot three-component reaction in good yield and good enantioselectivity. Further applications in natural-product synthesis and mechanistic studies of this reaction are currently underway in our laboratories.

Experimental Section

(−)-**5a**: A dry and argon-flushed 10-mL flask equipped with a magnetic stirrer and a septum was charged with copper(I) bromide (3.6 mg, 0.0250 mmol) and (*R*)-quinap (12.1 mg, 0.0275 mmol). Anhydrous toluene (2 mL) was added, the mixture was stirred at room temperature for 30 min. Molecular sieves (4 Å, 0.3 g) and *n*-decane (30 mg, as internal standard) were added, followed by phenylacteylene (51 mg, 0.5 mmol), 3-methylbutanal (43 mg, 0.5 mmol), and dibenzylamine (99 mg, 0.5 mmol). The reaction mixture was stirred for 70 h at room temperature. The molecular sieves were removed by filtration and washed with diethyl ether. The crude product was concentrated in vacuo and purified by chromatography on silica gel (pentane:diethyl ether = 98:2) yielding the propargylamine ((−)-**5a**) as a colorless oil (180 mg, 98 %, 86 % *ee*).

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[9] The absolute configuration was determined by comparison to a known compound (see the Supporting Information).

[10] The crystal structure is shown in the Supporting Information. CCDC 216200 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[11] An X-ray analysis of quinap–CuBr shows that the complex is dimeric (see ref. [4]).

