AES (auger electron spectroscopy). Before the experiment, Pd (>99.9%) was deposited by evaporation from a rod by using a commercial evaporator (Focus, EFM 3) based on electron bombardment (Pd coverage: 2.7×10^{15} cm^{-2}, sample temperature: 300 K). The evaporator flux was calibrated by a quartz microbalance prior to use. After preparation the Pd particles were stabilized by oxygen and CO exposure as discussed previously.[13, 24]

Received: March 1, 2002 [Z18807]

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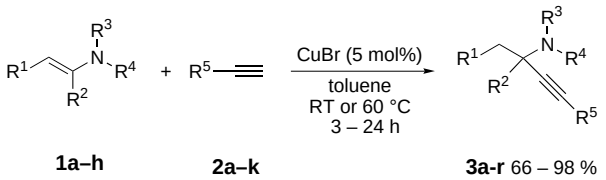
Enantioselective Synthesis of Propargylamines by Copper-Catalyzed Addition of Alkynes to Enamines**

Christopher Koradin, Kurt Polborn, and Paul Knochel*

Propargylamines are important as both synthetic intermediates for the preparation of polyfunctional amino derivatives and as biologically active compounds.[1] Their preparation in enantiomerically enriched form is therefore of great importance. Although several diastereo- and enantioselective syntheses have been developed,[2] until now no metal-catalyzed enantioselective synthesis of propargylamines is known.[3] We report herein a new copper(I)-catalyzed enantioselective addition of alkynes[4] to enamines. First, we examined the racemic synthesis of propargylamines by metal-complex catalysis. Various metal salts, including $Sc(OTf)_3$, $Zn(OTf)_2$, $Yb(OTf)_3$, and Cu^I and Cu^{II} salts,[5] were tested as catalysts. Copper(I) and copper(II) bromide proved to give the fastest conversions. We chose test enamines[6] with readily removable protecting groups such as an allyl or a benzyl group. Enamines **1a–h** (1.2–1.5 equiv) reacted readily with terminal alkynes **2a–k** in toluene in the presence of copper(I) bromide (5 mol%) to give propargylic amines of type **3** (Scheme 1, Table 1) under mild reaction conditions.



1a–h **2a–k** **3a-r** 66 – 98 %

Scheme 1. Synthesis of propargylamines by the addition of alkynes to enamines.

A range of functionalized alkynes that bear a methoxy group, a double bond, a nitrile group, a chloride, a silyloxy group, an acetal, or a silyl functionality were successfully used (Table 1, entries 1–8). In the case of nitrile **2d**, the reaction required 5 h at 60 °C for complete conversion. Disubstituted enamines tend to be more reactive than trisubstituted enamines (Table 1, entries 10/15 or entries 12/17). In the case of the cyclic enamine **1h**, which is in equilibrium with a dimeric structure,[7] the reaction was carried out for 3 h at 80 °C (Table 1, entry 18).

After this study, which showed the broad scope of the reaction, we turned our attention to the enantioselective

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[**] We thank the Deutsche Forschungsgemeinschaft (Leibniz program). C.K. thanks BASF AG (Ludwigshafen) for a fellowship. We also thank Chemetall GmbH (Frankfurt) and BASF AG (Ludwigshafen) for the generous gift of chemicals.

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  1433-7851/02/4114-2535 $ 20.00+.50/0

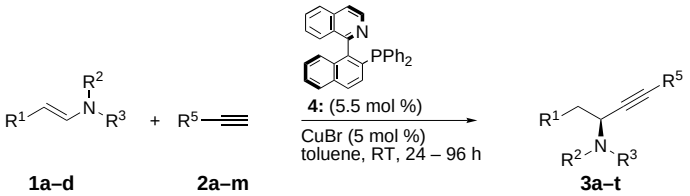
Table 1. Propargylamines of type **3** obtained by the copper(i) bromide catalyzed addition of alkynes **2** to enamines **1**.

Entry	**1**	**2**	R^5	**3**	Yield [%][a]
1	**a**	**a**	Ph	**a**	75
2	**a**	**b**	CH_2OMe	**b**	84
3	**a**	**c**	1-cyclohexenyl	**c**	77
4	**a**	**d**	$(CH_2)_3CN$	**d**	82[b]
5	**a**	**e**	$(CH_2)_3Cl$	**e**	78
6	**a**	**f**	$CH_2OTBDPS$	**f**	93
7	**a**	**g**	$CH(OEt)_2$	**g**	66
8	**a**	**h**	TMS	**h**	70
9	**b**	**a**	Ph	**i**	82
10	**b**	**i**	*n*Hex	**j**	75
11	**b**	**j**	H	**k**	69
12	**c**	**a**	Ph	**l**	98
13	**d**	**a**	Ph	**m**	94[b]
14	**d**	**k**	*p*-BrPh	**n**	90[b]
15	**e**	**i**	*n*Hex	**o**	80[b]
16	**f**	**i**	*n*Hex	**p**	82
17	**g**	**a**	Ph	**q**	75[b]
18	**h**	**a**	Ph	**r**	86[c]

[a] Yield of isolated analytically pure product. [b] The reaction was performed at 60 °C. [c] The reaction was performed at 80 °C. TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl.

addition reaction. Copper(i) bromide was used to test various chiral ligands, for example, diphosphanes, aminophosphanes, and diamines. We found that Quinap (**4**)[8] in combination with CuBr gave the best results (Scheme 2, Table 2).

Thus, the reaction of phenylacetylene (**2a**) and the enamine **1a** in the presence of copper(i) bromide (5 mol %) and (*R*)-



1a–d **2a–m** **3a–t**

Scheme 2. Enantioselective synthesis of propargylamines by using copper(i) bromide and Quinap as the catalytic system.

(+)-Quinap(5.5 mol %) in toluene at room temperature (24 h) afforded the propargylamine **3a** in 78 % yield and with 83 % *ee*. Polyfunctional propargylamines that bear a chloride, an OTBDPS, or a nitrile group can be prepared with 54–72 % *ee* (Table 2, entries 4–6). The use of the β-disubstituted

Table 2. Enantioselective synthesis of propargylamines **3** by the copper(i) bromide/Quinap-catalyzed addition of alkynes **2** to enamines **1**.

Entry	**1**	**2**	R^5	**3**	Yield [%][a]	*ee* [%][b]
1	**a**	**a**	Ph	**a**	78	83
2	**a**	**b**	CH_2OMe	**b**	76	55
3	**a**	**c**	1-cyclohexenyl	**c**	84	74
4	**a**	**d**	$(CH_2)_3CN$	**d**	50	54
5	**a**	**e**	$(CH_2)_3Cl$	**e**	58	60
6	**a**	**f**	$CH_2OTBDPS$	**f**	85	72
7	**a**	**h**	TMS	**h**	73	86[c]
8	**b**	**a**	Ph	**i**	91	82[d]
9	**c**	**a**	Ph	**l**	99	77[d]
10	**d**	**a**	Ph	**m**	79	88
11	**d**	**k**	*p*-BrPh	**n**	83	90
12	**a**	**l**	3-pyridyl	**s**	57	70
13	**a**	**m**	2-pyridyl	**t**	73	70

[a] Yield of isolated analytically pure product. [b] Enantiomeric excess determined by HPLC with a Chiracel OD-H column (*n*-heptane/*i*PrOH). [c] Enantiomeric excess determined after conversion into **3a**: 1) TBAF; 2) PhI, Pd^0 (cat.), Cu^I (cat.), 77 % overall yield. [d] Enantiomeric excess determined after deprotection to the secondary amine.[11] TBAF = tetrabutylammonium fluoride.

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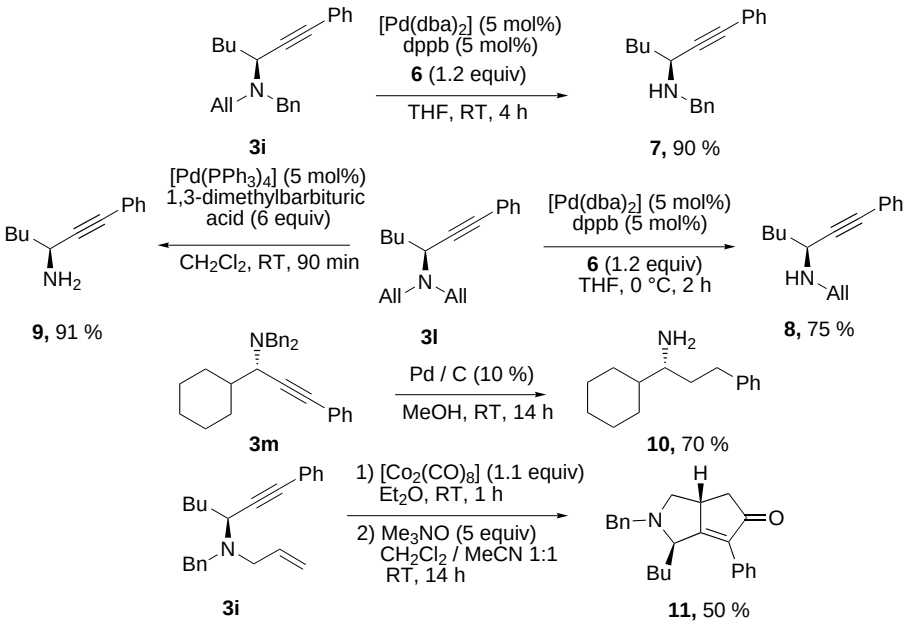
enamine **1d** and 1-bromo-4-ethynylbenzene (**2k**) furnished the corresponding propargylamine **3n** in 83% yield with the highest enantioselectivity (90% *ee*; Table 2, entry 11). The propargylamines **3s** and **3t**, which bear heterocyclic rings (Table 2, entries 12 and 13) were prepared with 70% *ee*.

To the best of our knowledge, this is the first report of a copper-catalyzed asymmetric reaction with Quinap as the chiral ligand. We were able to isolate the complex $[BrCu(Quinap)]_2$ (**5**) as a yellow, air-stable solid, which has been characterized by X-ray crystallographic analysis (Figure 1).[9] The complex has a dimeric structure with the typical planar four-membered $Cu_2(\mu\text{-}Br)_2$ ring. The coordination spheres of both copper atoms are distorted tetrahedra, but they are not identical. The Cu1–N1 distance (2.348 Å) is much shorter than the Cu2–N2 distance (2.725 Å). In both cases, the long Cu–N distances indicate the absence of direct bonding, but they are shorter than the sum of the van der Waals radii of Cu and N. Interestingly, the P and the N atoms of the two Quinap molecules are *cis*-oriented, in contrast to monodentate P–N complexes of CuBr.[10]



Scheme 3. Selective transformations of propargylamines. dppb = Diphenylphosphanylbutane, dba = dibenzylideneacetone.

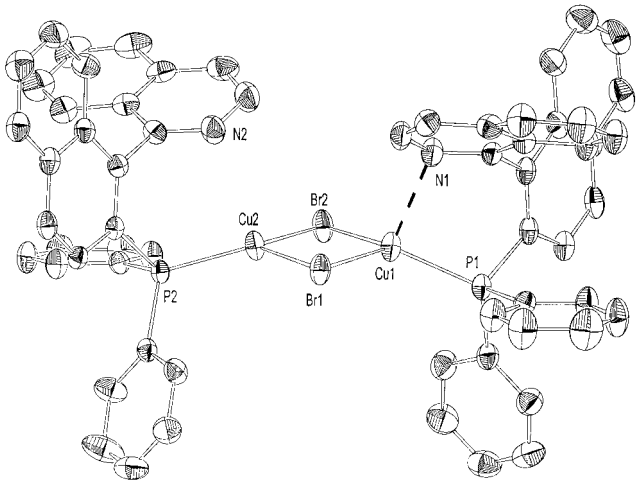
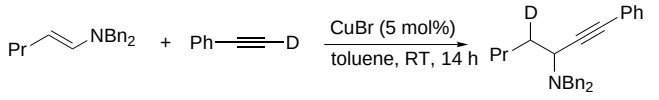


Figure 1. Structure of the complex $[BrCu(Quinap)]_2$ (**5**) in the solid state (the hydrogen atoms and crystallized solvents are omitted for clarity). Selected bond lengths [Å] and angles [°]: Cu1-Br1 2.4728(8), Cu2-Br2 2.4150(8), Cu1-P1 2.199(2), Cu2-P2 2.1827(13); P2-Cu2-Br2 129.28(4), P2-Cu2-Br1 122.75(4), Br2-Cu2-Br1 104.18(3).

The propargylamines **3** obtained can be selectively deprotected by known methods.[11, 12] Treatment of the mixed allyl benzyl propargylamine **3i** with thiosalicylic acid (**6**) in the presence of a palladium(0) catalyst ($[Pd(dba)_2]$ (5 mol%) and dppb (5 mol%)) leads to the monobenzylated propargylamine **7** in 90% yield (Scheme 3). The monoallylated amine **8** can be obtained from **3l** in 75% yield by using the same catalyst. Furthermore, the absolute configuration of the propargylamine **3l** was determined by its transformation into the amine **9** by using the method of Guibé and co-workers,[12] and comparison of its optical rotation with literature data.[2e, 13] Primary amines can be obtained by hydrogenation of the propargylamines **3** in good yields. For example, the amine **3m** is hydrogenated to the amine **10** in 70% yield. To demonstrate further synthetic applications, the allyl-protected amine **3i** was used in a Pauson–Khand reaction.[14] Treatment with $[Co_2(CO)_8]$ (1.1 equiv), followed by oxidation with Me_3NO (5 equiv) afforded the bicyclic compound **11** as a single diastereoisomer in 50% yield.[15]

Preliminary mechanistic studies showed that the acetylenic deuterium atom of [D]phenylacetylene (**2n**) is transferred to the β position of the enamine **1a** (> 90% deuterium incorporated), leading to **12** in 91% yield (Scheme 4).



Scheme 4. Deuterium incorporation in propargylic amines.

We suggest the tentative mechanism described in Scheme 5. The dimeric copper complex **5** dissociates to afford the monomeric copper species **13**, which after successive complexation of alkyne **2** and enamine **1** results in the zwitterionic intermediate **14**. After intramolecular transfer of the alkyne moiety to the immonium ion, the copper-complexed product **15** is formed. Decomplexation produces the free propargylamine **3** and regenerates the catalyst **13**.

In summary, we have reported the first copper(I)/Quinap-catalyzed addition of functionalized alkynes to enamines in

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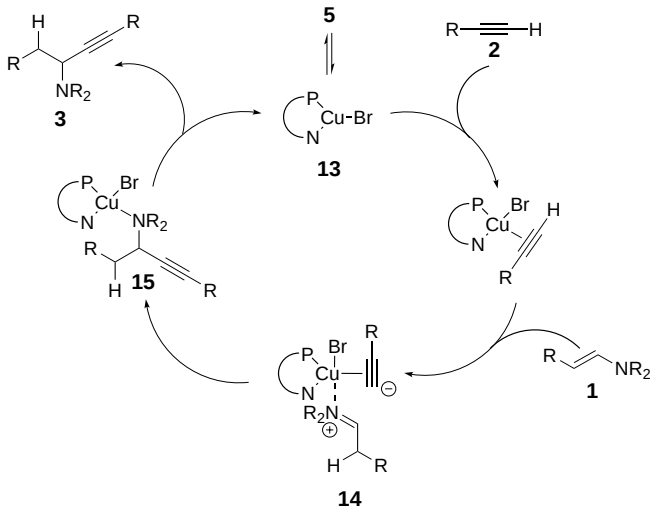

Scheme 5. Proposed mechanism.

high yields with up to 90% *ee*. The mild reaction conditions, the broad scope of the reaction, and the selective deprotection of the propargylamine products show the potential synthetic utility of this method. Further synthetic and mechanistic investigations of this new asymmetric reaction are currently underway.

Experimental Section

Typical procedures:

a) **3m**: CuBr (22 mg, 0.15 mmol, 5 mol%) was suspended in toluene (3 mL) in a 25-mL Schlenk tube under argon. A solution of **1d** (1.049 g, 3.60 mmol, 1.2 equiv), **2a** (0.306 g, 3.00 mmol, 1.0 equiv), and *n*-decane (0.300 g, 2.11 mmol) as internal standard in toluene (3 mL) was added at room temperature. The reaction mixture was stirred for 24 h at room temperature and then for 3 h at 60 °C. Standard workup and purification by column chromatography (SiO_2, pentane/Et_2O 98:2) afforded the desired product as a white solid (1.115 g, 2.83 mmol, 94%).

b) (−)-**3a**: CuBr (3.6 mg, 0.025 mmol, 5 mol%) and (*R*)-(+)-Quinap (12.1 mg, 0.0275 mmol, 5.5 mol%) were suspended in toluene (2 mL) in a 10-mL Schlenk tube under argon. After 30 min, a solution of **1a** (0.173 g, 0.65 mmol, 1.3 equiv), **2a** (0.051 g, 0.50 mmol, 1.0 equiv) and *n*-decane (0.050 g, 0.35 mmol) as internal standard in toluene (2 mL) was added at room temperature. After stirring for 24 h, standard workup and purification by column chromatography (SiO_2, pentane/Et_2O 98:2) yielded **3a** as a colorless oil (0.144 g, 0.39 mmol, 78%).

Received: March 28, 2002 [Z19004]

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[9] Crystal data for **5**: $M_r = 1287.82$, orthorhombic, space group $C2_{221}$, $a = 15.549(3)$, $b = 16.989(2)$, $c = 42.706(7)$ Å, $V = 11281(3)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.516$ Mg m^{-3}, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), $\mu = 2.366$ mm^{-1}. Data were collected on a NONIUS MACH3 system at 295 K. The structure was solved by direct methods and refined on F_0^2 by full-matrix least-squares methods (SHELXS-86, SHELXL-93). All non-hydrogen atoms were refined anisotropically. $R1 = 0.0374$, $\omega R2 = 0.0834$ for all data with $I > 2\sigma(I)$. CCDC-182716 contains the supplementary crystallographic data (excluding structure factors) 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 CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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Hydrolytic Activation of C–F Bonds in the Gas Phase by Intrinsically Unreactive Chromium Cations**

Ulf Mazurek, Detlef Schröder, and Helmut Schwarz*

To the best of our knowledge, hydrolytic activation of C–F bonds in the gas phase has hitherto been unknown.[1] Moreover, considering the facts that 1) thermalized chromium cations are generally unreactive in the gas phase,[2–6] 2) C–F bonds show a bond-dissociation energy of 105–110 kcal mol^{-1} [7, 8] thus being more stable than any other C–X bond, and 3) hexafluoroacetone is commercially available in the forms of sesqui- and trihydrates, which means it is

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.