

Mixed Copper, Zinc 2-Amino Benzylic Organometallics as
 Efficient Reagents for the Synthesis of Heterocycles

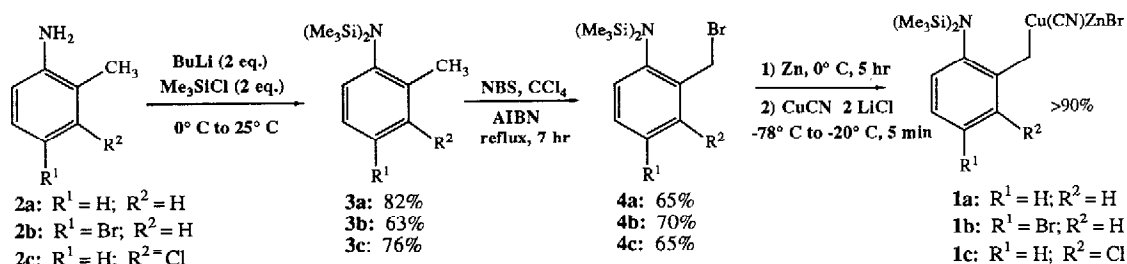
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Summary: The mixed copper, zinc benzylic organometallics **1a-1c** react efficiently with various electrophiles. By the reaction with acyl chlorides, highly functionalized 2-substituted indoles are produced. The treatment of **1a** with allylic bromides, 3-iodo-cyclohexenone and ethyl propiolate furnishes polyfunctionalized anilines. Several of them could be converted into five- or seven-membered heterocycles.

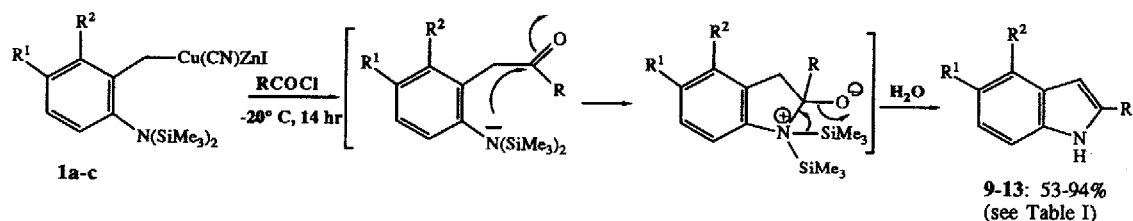
The low reactivity of the carbon-zinc bond allows the preparation of highly functionalized zinc organometallics having a broad synthetic potential^{1,2}. We recently reported a general preparation of benzylic zinc halides³ and showed that after their transmetallation with the new soluble copper salt $\text{CuCN} \cdot 2 \text{LiCl}$ ^{2a} functionalized benzylic copper compounds were obtained. They displayed a high reactivity toward a variety of organic electrophiles such as acyl chlorides, enones, allylic halides and aldehydes³. We now report the preparation and the reactivity of a new class of 2-amino benzylic copper, zinc organometallics of type **1**. The compounds were prepared from the ortho-toluidine derivatives **2**. Silylation^{4,5} of the aromatic amines **2** (BuLi , 2 eq.; Me_3SiCl , 2 eq.; 0°C to 25°C , 3 hr.) afford the bis-trimethylsilyl-anilines **3** (63-82%). Bromination of **3** with NBS (0.9 eq) in CCl_4 (cat. amount of AIBN, reflux, 7 hr.) furnishes the benzylic bromides **4** in 65-70% yield. The formation of the corresponding zinc organometallics proceeds in > 90% yield (Zn , 2 eq.; 0°C , 5 hr.; less than 10% of the Wurtz-coupling dimers were formed). The addition of a THF solution of $\text{CuCN} \cdot 2 \text{LiCl}$ ^{2a} furnishes the copper, zinc reagents **1** (-78°C to -20°C , 5 min.; see Scheme I).

Scheme I



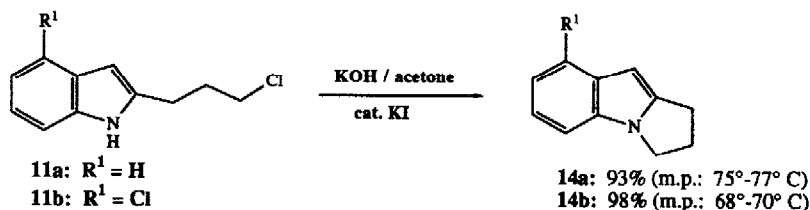
The benzylic organometallics **1a-1c** react readily with the allylic bromides **5a-5d** affording the highly functionalized anilines **6a-6d** in high yields (see entries 1-4 of Table I). The addition to 3-iodo-2-cyclohexenone **7⁶** furnishes the 3-substituted cyclohexenone **8** in almost quantitative yield (see entry 5). Various acyl chlorides⁵ react with **1a-1c** leading after aqueous work-up to the 2-substituted indoles **9-13** in 53-94% yield (see Scheme II and entries 6-12). The reaction tolerates the presence of several functional groups in the acyl chloride such as a furan ring (entry 8), a primary chloride (entries 9 and 10), a benzylic chloride (entry 11), a conjugated double bond (entry 12) and thus constitute a very mild and highly chemoselective modification of the Madelung indole synthesis⁷. The preparation of other classes of heterocycles through the cyclization of products of Table I is possible. Thus the reaction of the indoles **11a** and **11b**

Scheme II

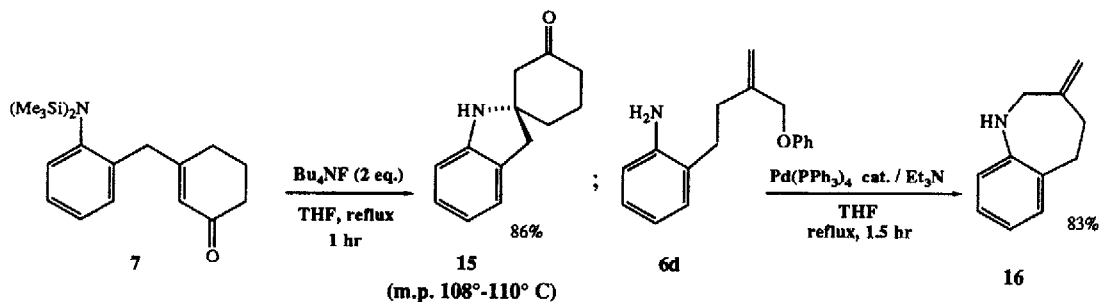


with KOH (4.0 eq., 25° C, 2 hr.) in acetone in the presence of a catalytic amount of KI provides the tricyclic derivatives **14a** (93%) and **14b** (98%) having both the mitomycin skeleton⁸ (see Scheme III). The desilylation of the silylamine **8**

Scheme III



Scheme IV



(Bu₄NF, 2 eq.; THF; reflux 1hr.) gives the spiroindoline **15** in 86% yield. The treatment of **6d** with Pd(PPh₃)₄ (0.06 eq., THF, reflux, 1.5 hr.) in the presence of triethylamine (2 eq.) leads to the benzo-hexahydroazepine **16** in 83% yield (see Scheme IV). Finally the acrylate **17** readily obtained by the carbocoupling of ethyl propiolate⁹ (0.7 eq.; -78° C, 3 hr; -30° C, 15 hr.; 85%) with **1a** could be converted into the indoline **18** in 88% yield by the addition of Bu₄NF (2 eq., THF, 25° C, 10 min.); see Scheme V.

Scheme V

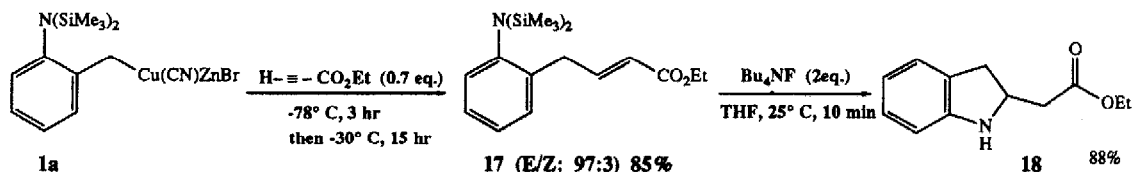


Table I. Products **6-14** Obtained by the Reaction of the 2-Amino Benzylic Organocopper Reagent **1a-1c** with Allylic Bromides, an Enone and Acyl Chlorides.

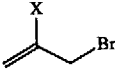
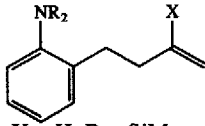
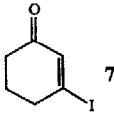
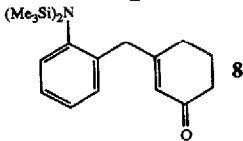
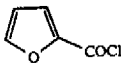
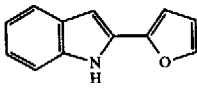

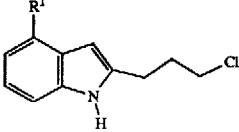
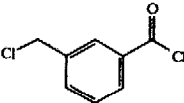
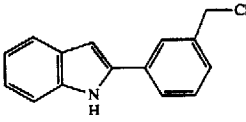
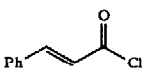
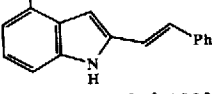
Entry	Benzylic Copper Reagents	Electrophiles	Products 6-14	Yield (%) ^a	
					
1	1a	5a: X = H	6a: X = H; R = SiMe ₃	86	
2	1a	5b: X = CO ₂ t-Bu	6b: X = CO ₂ t-Bu; R = SiMe ₃	84	
3	1a	5c: X = OCH ₂ OMe	6c: X = -OCH ₂ OMe; R = SiMe ₃	81	
4	1a	5d: X = -CH ₂ OPh	6d: X = -CH ₂ OPh; R = H	93	
5	1a			97	
6	1a	PhCOCl	9a: R ¹ = H (m.p. 172°-173° C)	94	
7	1b	PhCOCl	9b: R ¹ = Br (m.p. 175°-179° C)	75	
8	1a			10 (m.p. 123°-124° C)	78
9	1a			11a: R ¹ = H (m.p. 56°-57° C)	80
10	1c		11b: R ¹ = Cl (oil)	73	
11	1a			12 (m.p. 94°-95° C)	76
12	1c			13 (m.p. 101°-102° C)	53

Table I. (Continued)

13	1a		14 (m.p. 139°-140° C)	81

^a All indicated yields are isolated yields. Satisfactory spectral data (IR, ¹H and ¹³C-NMR, mass spectra and high resolution mass spectra) were obtained for all new compounds.

The new functionalized mixed copper and zinc organometallics **1a-1c** are useful reagents for the preparation of various five- and seven-membered heterocycles. Further applications of these and related compounds are currently studied in our laboratories.

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References

- (a) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 5559; (b) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955; (c) Nakamura, E.; Sekiya, K.; Kuwajima, I. *Tetrahedron Lett.* **1987**, *28*, 337; (d) El Alami, N.; Belaud, C.; Villieras, J. *J. Organomet. Chem.* **1987**, *319*, 303; (e) Comins, D.L.; O'Connor, S. *Tetrahedron Lett.* **1987**, *28*, 1843; (f) Comins, D.L.; Foley, M.A. *Tetrahedron Lett.* **1988**, *29*, 6711; (g) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Angew. Chem.* **1987**, *99*, 1193; *ibid*, *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1157.
- (a) Knochel, P.; Yeh, M.C.P.; Berk, S.C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390; Yeh, M.C.P.; Knochel, P. *Tetrahedron Lett.* **1988**, *29*, 2395; (c) Yeh, M.C.P.; Knochel, P.; Santa, L.E. *Tetrahedron Lett.* **1988**, *29*, 3887; (d) Yeh, M.C.P.; Knochel, P.; Butler, W.M.; Berk, S.C. *Tetrahedron Lett.* **1988**, *29*, 6693.
- Berk, S.C.; Knochel, P.; Yeh, M.C.P. *J. Org. Chem.* **1988**, *53*, 5791.
- Schumann-Ruidish, I.; Kalk, W.; Brüning, R. *Z. Naturforsch* **1968**, *23b*, 307.
- Typical procedure. (a) **N,N-bis-trimethylsilyl-ortho-toluidine 3a**. To a solution of 5.0 g (46.6 mmol) of o-toluidine in 60 mL of THF was added at 0° C 61.2 mL of a solution of n-BuLi in hexanes (98.0 mmol, 1.6 N solution). The white suspension was stirred for 3 hr. at 0° C, then 11.6 g (107.3 mmol) was slowly added. The reaction mixture was stirred 3 hr. at 25° C; 30 mL of hexane was added and the (Me₃SiCl) white solid was filtered. After evaporation of the solvents and distillation of the residue, 9.65 g (82.5%) of **3a** (b.p. 121°-124° C/30 mm Hg) was obtained as a colorless oil.
(b) **2-Bromomethyl-N,N-bis-trimethylsilylaniline 4a**: A mixture of 2.0 g (7.96 mmol) of **3a** (over 98% pure by GC analysis), 1.28 g (7.2 mmol) of N-Bromosuccinimide and 10 mg of AIBN was heated to reflux for 5-7 hrs. in freshly distilled CCl₄ (20 mL). The succinimide was filtered and the deep red residue obtained after evaporation of the solvents was distilled in vacuum to give 1.71 g (65% yield) of the benzylic bromide **4a** as a light yellow oil (b.p. 90°-92° C/0.05 mm Hg).
(c) **2-Phenylindole 9a**. A solution of 1.0 g (3.0 mmol) of the benzylic bromide **4a** in 5 mL of THF was slowly added (1 drop each 5s) at 0° C to 0.4 g (6.0 mmol) of cut zinc foil (99.99% purity) activated with dibromoethane^{2a} or of zinc dust (325 mesh, Aldrich). The reaction was stirred 5 hr. at this temperature and added to a cold (-78° C) slurry of 0.26 g (6 mmol) of LiCl (dried at 140° C/0.05 mm Hg for 1 hr.) and 0.27 g (3 mmol) of CuCN in 5 mL of THF. The mixture was warmed up to -15° C and cooled after 5 min. back to -78° C. Then 338 mg (2.4 mmol, 0.8 eq.) of benzoyl chloride in 0.5 mL of THF was added and the reaction mixture was warmed up to -20° C and stirred at this temperature for 14 hr. The reaction was poured into a solution of saturated NH₄Cl and worked up as usual. After a flash chromatography of the crude material (solvent: hexane/ether = 3:1 with a few drops of NH₄OH), 328 mg (94% yield) of white crystals (m.p. 175°-179° C) was obtained.
- Piers, E.; Nagakura, I. *Synth. Comm.* **1975**, *5*, 193.
- (a) Brown, R.K. in *Indoles*, ed. Houlihan, W.J., Wiley Interscience, **1972**, *25*, part I; (b) Fuhrer, W.; Gschwend, H.W. *J. Org. Chem.* **1979**, *44*, 1133; (c) Houlihan, W.J.; Parrino, V.A.; Uike, Y. *J. Org. Chem.* **1981**, *46*, 4511; (d) Smith, III, A.B.; Visnick, M. *Tetrahedron Lett.* **1985**, *26*, 3757; (e) Smith, A.B.; Visnick, M.; Haseltine, J.N.; Sprengeler, P.A. *Tetrahedron* **1986**, *42*, 2957; (f) Li, J.P.; Newlander, K.A.; Yellin, T.O. *Synthesis* **1988**, *73*; (g) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Todesco, P.E. *J. Chem. Soc., Chem. Commun.* **1988**, 807.
- (a) Wender, P.A.; Cooper, C.B. *Tetrahedron* **1986**, *42*, 2985; (b) Wender, P.A.; Cooper, C.B. *Tetrahedron Lett.* **1987**, *28*, 6125.
- See the accompanying publication.

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