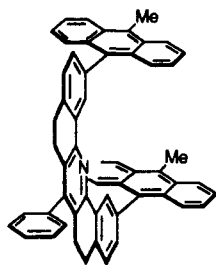


highly polarizable anthracene rings and an adenine chromophore. However, it was found that dianthryl molecular tweezer **13** shows no affinity for **4** in chloroform-*d* ($K_{\text{assoc}} < 10 \text{ M}^{-1}$).¹⁶ This striking result suggests that the benefit from π -stacking is felt only when the adenine is held proximate to the anthracenes through hydrogen bonding.¹⁷



13

(16) In other studies we have found **13** to bind π -deficient guests (e.g. 2,4,5,7-tetranitrofluorenone) as tightly as did the analogous acridine based molecular tweezers (ref 15).

Alternatively, the aromatic cleft may serve to desolvate the carboxylic acid. In either case, placing a carboxylic acid deep within an aromatic cleft markedly enhances its complexation efficiency. The flexibility of the synthesis described herein should allow the incorporation of addition hydrogen bonding functionalities resulting in receptors with even higher affinities for adenine. In a more general vein, our results suggest that the stability of hydrogen-bonded complexes can be dramatically increased by surrounding the appropriate functionality with an aromatic cleft.

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(17) In a similar system, this type of cooperativity has been attributed to a "spatio-temporal hypothesis": Sheridan, R. E.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* 1986, 108, 7120-7121.

A General Preparation of Highly Functionalized Zinc and Copper Organometallics at the α -Position to an Oxygen

Tso-Sheng Chou and Paul Knochel*

The Willard H. Dow Laboratories, Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109

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Summary: α -Bromoalkyl acetates **2**, which are readily prepared by the addition of acetyl bromide to aldehydes, insert zinc under mild conditions affording, after the addition of $\text{CuCN}\cdot 2\text{LiCl}$, polyfunctional α -acetoxy copper reagents of type **1**. Their reactivity toward various organic electrophiles is described.

Lithium organometallics at the α -position to oxygen have proven to be very useful intermediates in organic syntheses.¹ However, their high reactivity and the methods used for their preparation precludes the presence of most functional groups in these compounds. We report herein a new general preparation of highly functionalized zinc and copper organometallics of type **1**. Thus, the α -

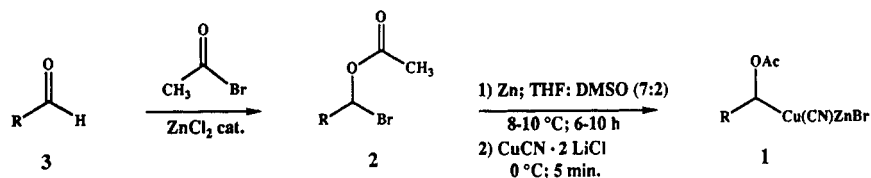
bromoalkyl acetates **2**, prepared by the addition of acetyl bromide to aldehydes **3** (CH_2COBr (1.5 equiv), ZnCl_2 catalyst, CH_2Cl_2 , 25 °C, 2 h; 85–90%)^{2,3} were found to react

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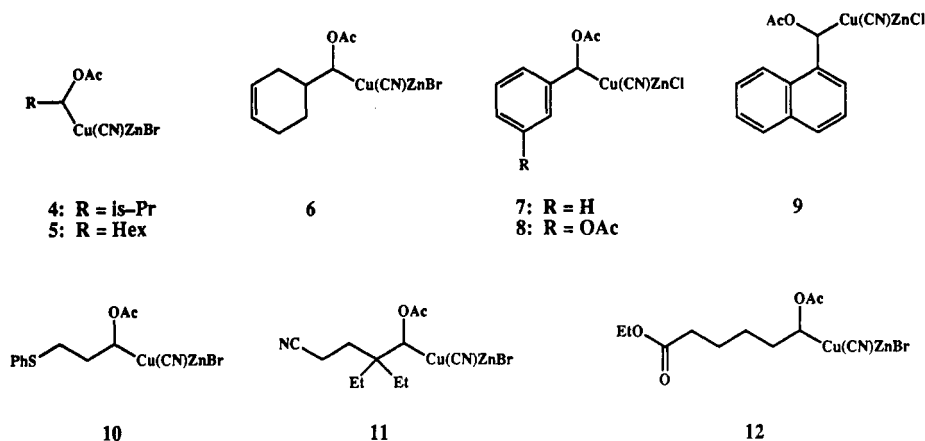
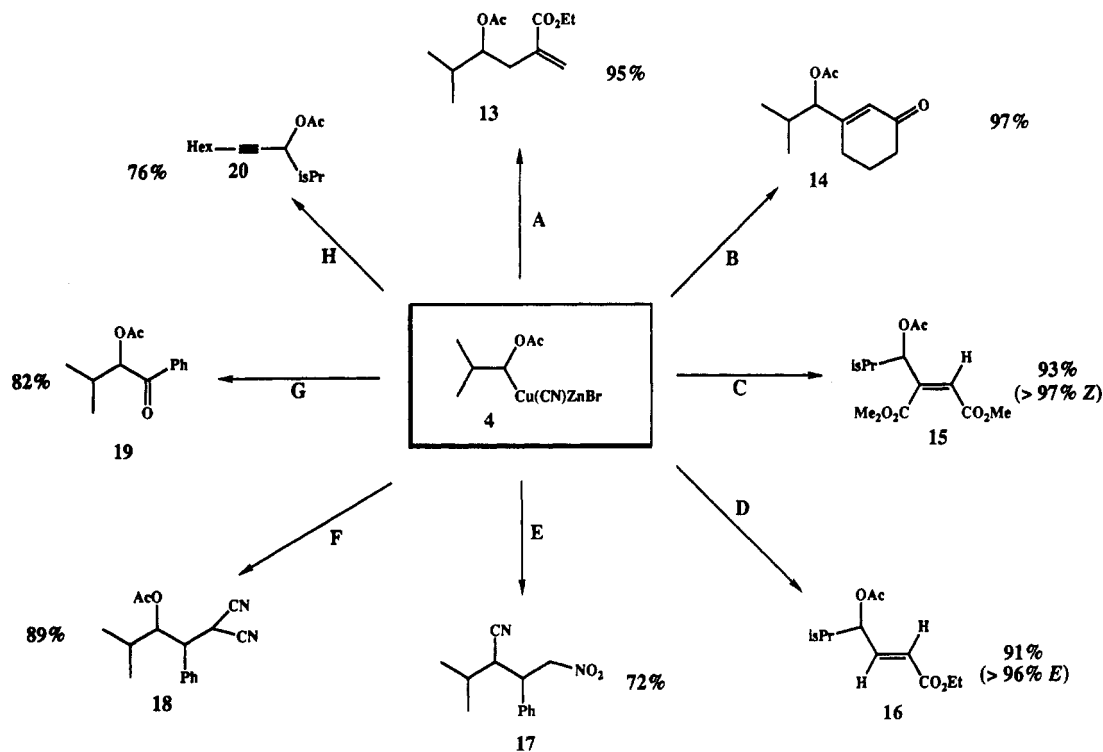
(3) Typical procedure: preparation of an organozinc reagent derived from an α -(bromoalkyl) acetate and its reaction with an allylic bromide; (a) **Preparation of (1-Acetoxy-2-methylpropyl)zinc Bromide.** A three-necked, 25-mL flask equipped with an argon inlet, a stirring bar, a low-temperature thermometer, and an addition funnel was charged under argon with zinc dust (Aldrich, 325 mesh; 1 g, 15 mmol), 2 mL of dry DMSO, and 2 mL of dry THF. The mixture was cooled to 0 °C, and 1-bromo-2-methylpropyl acetate (**2**; R = *i*-Pr, 1.95 g, 10 mmol) in 5 mL of THF prepared as described above was added dropwise within 10 min. The reaction mixture was warmed to 8–10 °C and stirred at this temperature overnight (10 h) leading to an almost quantitative formation of the corresponding zinc organometallic as indicated by GLC analysis of a hydrolyzed reaction aliquot. (b) **Preparation of Ethyl 4-Acetoxy-5-methyl-2-methylhexanoate (13).** The THF solution of (1-acetoxy-2-methylpropyl)zinc bromide (10 mmol) prepared as described above was added via syringe at –78 °C to a suspension of LiCl (0.7 g, 16 mmol) and CuCN (0.72 g, 8 mmol) in 3 mL of THF. A solution of ethyl α -(bromo-methyl)acrylate (0.97 g, 5 mmol) in 3 mL of THF was added, and the reaction mixture was warmed to 0 °C. The reaction was completed after 0.5 h as shown by GLC analysis. The reaction mixture was then diluted with 50 mL of ether and poured in 25 mL of a saturated NH_4Cl solution. The organic and aqueous layers were separated, and the aqueous layer was extracted twice with 25 mL of ether. The combined organic phase was successively washed with H_2O (2 \times 20 mL) and brine (10 mL). After drying over MgSO_4 and filtration, the solvent was evaporated and the crude oil was purified by flash chromatography (solvent: hexane/ether 20–10:1), yielding 1.08 g (95%) of the analytically pure product **13** (purity >99% by GLC analysis).

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Scheme I



Scheme II

Scheme III^a

under mild conditions with zinc dust⁴ (Zn (2.0 equiv), THF-DMSO (7:2), 8–10 °C, 6–10 h; >85% yield)³ to afford

(4) The exact structure of the reagents 1 is not known and the formula $\text{RCu}(\text{CN})\text{ZnI}$ reflects its stoichiometry. (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390. (b) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1988**, *29*, 2395. (c) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 5069. (d) Yeh, M. C. P.; Knochel, P.; Santa, L. E. *Tetrahedron Lett.* **1988**, *29*, 3887. (e) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4799. (f) Retherford, C.; Yeh, M. C. P.; Schipor, I.; Chen, H. G.; Knochel, P. *J. Org. Chem.* **1989**, *54*, 5200.

the corresponding zinc derivatives, which were transmetalated to the copper compounds 1 by the addition of the soluble copper salt⁴ $\text{CuCN} \cdot 2\text{LiCl}$ (0 °C, 5 min) (Scheme I). This preparation proved to be very general, and a broad range of new highly functionalized copper and zinc compounds 1 bearing primary or secondary alkyl substituents, such as 4–6, or phenyl and naphthyl substituents, such as 7–9, can be obtained in high yields (>85%). Remarkably the benzylic derivatives can be prepared without

significant amounts of Wurtz coupling products (<5%).⁵ Important functional groups like esters, nitriles, or thioethers are tolerated in these reagents (10–12; Scheme II), allowing the first general preparation of polyfunctional organometallic compounds at the α -position to oxygen. All of the copper–zinc reagents 4–12 could be allylated by allylic bromides in 70–90% yield.³ Several other classes of electrophiles⁴ react with the derivatives of type 1 in good to excellent yields as indicated in Scheme III. Thus, the allylation of 4 with ethyl α -(bromomethyl)acrylate⁶ affords the acetoxy acrylate 13 in 95% yield. The addition of 4 to 3-iodocyclohexenone⁷ gives the γ -acetoxy enone 14 in quantitative yield. Interestingly, dimethyl acetylenedicarboxylate undergoes a clean carbocupration reaction giving stereospecifically the *Z* adduct 15 (93%; >97% *Z*) no reduction product resulting from one-electron transfer reactions was observed.⁸ Similarly, the addition of 4 to ethyl propiolate furnishes the (*E*)- γ -acetoxy acrylate 16 (91%; >96% *E*). The Michael addition of 4 to nitrostyrene

affords the γ -cyano nitroalkane 17 (72%). The formation of 17 may be rationalized by the intramolecular displacement of the acetoxy group by the intermediate zinc–copper nitronate followed by a CuCN ring opening assisted by zinc salts. Such an intramolecular displacement is not possible in the case of benzyldenemalononitrile, and the expected γ -acetoxy dinitrile 18 is isolated in 89% yield. Reaction with benzoyl chloride readily converts 4 to the γ -acetoxy ketone 19 (82%) while the coupling reaction with 1-bromooctyne gives the propargylic acetate 20 (76%).

In conclusion, we have developed a new general preparation of *highly functionalized* zinc and copper organometallics 1 at the α -position to oxygen. These reagents react efficiently with several classes of electrophiles, affording a broad range of polyfunctional molecules. Further extensions of this methodology are currently underway in our laboratories.

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Supplementary Material Available: Typical procedures and spectral data for new compounds (11 pages). Ordering information is given on any current masthead page.

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