lactate. The [2,3]Wittig process of **5** followed by cis hydrogenation gave oxy-Cope substrate **6**[12] in >96% ee (Mosher's assay) along with 100% *E* and *Z* and >99% erythro.[6] The oxy-Cope process of **6** afforded the erythro aldehyde **7**[13] essentially as a single product in 91% ee, which was then converted to **8**[10,14] as well as the known (3*S*,4*S*)-3,4-dimethyl-5-pentanolide:[10,15] $[\alpha]^{26}{}_D$ −45° (*c* 1.0, MeOH); lit. $[\alpha]^{22}{}_D$ −47°. The % ee of **7** was determined by HPLC analysis of the amide prepared via reaction of the preceding lactone and (*R*)-α-naphthylethylamine.[15] The most striking observation in these asymmetric oxy-Cope rearrangements is that both the absolute and relative stereochemistry of the substrate are specifically transmitted to the two new chiral centers in the product via transfer of the chiralities along the pericyclic array.

In summary, this work has convincingly demonstrated that the acyclic oxy-Cope technology, when property designed in terms of the substrate stereochemistry, provides a new, efficient method for acyclic stereocontrol. Further application of the oxy-Cope method is in progress.

Acknowledgment. We thank Professor Leo A. Paquette for helpful discussions and providing us with manuscripts prior to publication.

Supplementary Material Available: Experimental procedures and spectroscopic data for compounds **1–8**, for intermediates in Scheme III and for (3*R**,4*S**)-, (3*S**,4*S**)-, and (3*S*,4*S*)-3,4-dimethylpentanolides and ^{1}H and ^{13}C NMR spectra of compounds **2**, **4a**, **4b**, **5–7**, and (4*R*,5*S*,6*E*)-5-ethyl-6-octen-2-yn-4-ol (**13**) (26 pages). Ordering information is given on any current masthead page.

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[12] The spectral data are in accord with the assigned structure. The purities of **5** and **6** were determined by ^{1}H NMR, ^{13}C NMR, and capillary GC analyses (supplementary material).

[13] ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.70–9.85 (m, 1 H), 5.15–5.55 (m, 2 H), 2.30–2.60 (m, 1 H), 1.80–2.30 (m, 5 H), 0.98 (d, J = 6.6 Hz, 3 H), 0.97 (t, J = 7.5 Hz, 3 H), 0.90 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 203.26, 132.66, 131.39, 48.65, 41.02, 33.05, 25.69, 17.48, 16.42, 14.03; IR (neat) 1727, 973 cm^{-1}; HRMS found m/z 154.1243, calcd for $C_{10}H_{18}O$ 154.1358.

[14] Baker, R.; Billington, D. C.; Ekanayake, N. *J. Chem. Soc., Perkin Trans. I* **1983**, 1387.

[15] Mori, K.; Ueda, H. *Tetrahedron* **1982**, *38*, 1227.

Preparation and Reactions of Zinc and Copper Organometallics Bearing Acidic Hydrogens

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Summary: Organozinc and copper reagents bearing unprotected primary or secondary amines or amides or a terminal acetylenic proton were prepared and reacted with various electrophiles in good yields.

Organometallics RM (M = Li, MgX) react rapidly with acidic hydrogens, and therefore the reaction of molecules containing primary or secondary amines, amides, thiols, or alcohols with polar organometallic compounds generally requires either the protection of these functionalities or the use of excess organometallic reagent which will first abstract the acidic hydrogen.[1] Since organozinc and organocopper compounds contain a carbon-metal bond having a low ionic character (ca. 15%),[2] it may be expected that these reagents will tolerate the presence of acidic hydrogens in the reaction media. Primary amines such as *N*-ethylamine are known to react at low temperatures with $Me_2Zn(THF)_2$ affording complexes such as $Me_2Zn(H_2N\text{-}Et)_2$.[3] These complexes decompose at higher temperatures (T >−30 °C) to give zinc amides ($(EtNH)_2Zn$). Complexes of secondary amines with $Me_2Zn(THF)_2$ were found to be substantially more stable.[3] Recently, the preparation of an alkylzinc halide bearing a NH–Boc group was reported,[4] although no information concerning the integrity of the N–H bond in this reagent was given.

Herein, we wish to report our preliminary studies showing that organozinc iodides (RZnI) can be prepared in good yields in the presence of a variety of relatively acidic hydrogens (pK_a = 18–35). Subsequent transmetalation with the THF soluble copper salt CuCN·2LiCl[5] provided the copper reagents RCu(CN)ZnI which reacted efficiently with a variety of organic electrophiles.[5,6] In order to determine the types of acidic hydrogen-bearing compounds (A–H) which are compatible with a carbon-zinc bond, a THF solution of an organic iodide (RI) and a compound (A–H) bearing an acidic hydrogen (ca. 1 M solution) was added to zinc dust, at 25 °C in the case of a primary iodide (*n*-butyl iodide) and at 5 °C in the case of a secondary iodide (cyclohexyl iodide). The reactions were performed in the presence of an internal standard (*n*-decane) and the formation of the organozinc iodide was monitored by GLC analysis of both hydrolyzed and iodolized reaction aliquots[7] (eq 1 and Table I). Primary and

$$\text{R–I} + \text{A–H} \xrightarrow{\text{Zn, THF}} \text{R–ZnI} + \text{A–H} \qquad (1)$$

secondary amines were found to be perfectly compatible with organozinc iodides and less than 5% of deprotonation was observed (entries 1–5). The presence of a primary or secondary amine (except the hindered diisopropylamine)

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[1] (a) Wardell, J. L.; Raston, C. L.; Salem, G. In *The Chemistry of the Metal-Carbon Bond*; Hartley, F., Ed.; Wiley-Interscience: New York, 1982; Vol. 4. (b) Brandsma, L.; Verkruijsse, H. In *Preparative Polar Organometallic Chemistry Vol. 1*; Springer Verlag: Berlin, 1987.

[2] Negishi, E. In *Organometallics in Organic Synthesis*; Wiley: New York, 1980.

[3] (a) Thiele, K.-H.; Bendull, M. *Z. Anorg. Allg. Chem.* **1970**, *379*, 199. (b) Thiele, K.-H., Zdunneck, P. *Organomet. Chem. Rev.* **1966**, *1*, 331. (c) Emptoz, G.; Huet, F. *J. Organomet. Chem.* **1974**, *82*, 139. (d) Inoue, S.; Furukawa, K. *J. Organomet. Chem.* **1972**, *37*, 25.

[4] (a) Jackson, R. F. W.; James, K.; Wythes, M. J.; Wood, A. *J. Chem. Soc., Chem. Commun.* **1989**, 644. (b) Jackson, R. F. W.; Wythes, M. J.; Wood, A. *Tetrahedron Lett.* **1989**, *30*, 5941. (c) Tamaru, Y.; Tanigawa, H.; Yamamoto, T.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 351.

[5] Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

[6] (a) Berk, S. C.; Knochel, P.; Yeh, M. C. P. *J. Org. Chem.* **1988**, *53*, 5789. (b) Yeh, M. C. P.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4799. (c) Chou, T.-S.; Knochel, P. *J. Org. Chem.* **1990**, *55*, 4791. (d) Retherford, C.; Yeh, M. C. P.; Schipor, I.; Chen, H. G.; Knochel, P. *J. Org. Chem.* **1989**, *54*, 5200. (e) Retherford, C.; Knochel, P. *Tetrahedron Lett.* **1991**, *32*, 441.

[7] The yield of organozinc compounds was obtained by performing first a hydrolysis of a reaction aliquot giving the percentage of unreacted iodide and then an iodolysis giving the total percentage of iodide.

0022-3263/91/1956-5974$02.50/0

Table I. Formation of Primary and Secondary Alkylzinc Iodides in the Presence of Compounds Bearing an Acidic Hydrogen (A-H)

entry	A-H	time (h)	BuZnI formed[a] (%)	entry	A-H	time (h)	c-HexZnI formed[a,b] (%)
1	piperidine	1	89	11	1,2-diaminoethane	4	80
2	*N*-benzyl-*N*-methylamine	1	98	12	1,2-diaminobenzene	2.7	68
3	*N*,*N*-diisopropylamine	15	96	13	uracil	0.25	15
4	benzylamine	0.5	98	14	benzamide	0.25	39
5	aniline	1	98	15	imidazole	0.75	28
6	indole	4	84	16	*tert*-butyl alcohol	0.67	76
7	indole	26	47	17	*tert*-butyl alcohol	4	66
8	1-hexyne	2	91	18	dimethyl malonate	2.3	74
9	*tert*-butyl alcohol	0.15	29	19	dimethyl malonate	4.5	70
10	uracil	2	5	20	ethyl acetoacetate	0.2	31

[a] GLC yields determined by using an internal standard. [b] Reaction performed at 25–45 °C. [c] Reaction performed at 5 °C.

Scheme I

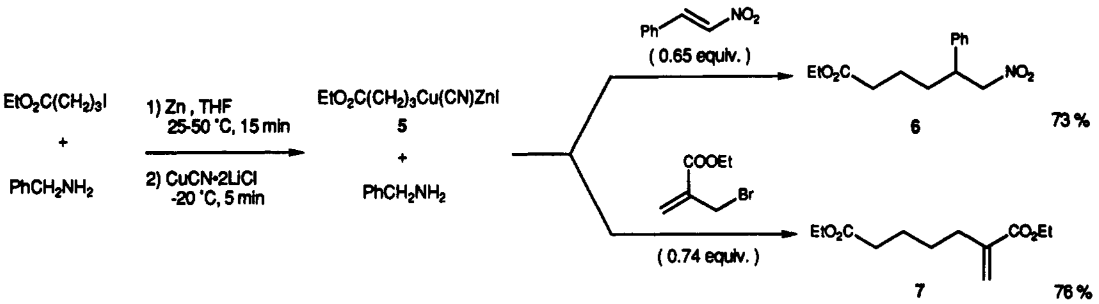
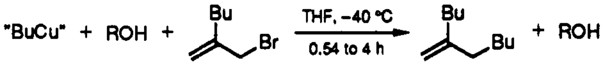


Table II. Preparation of 2-Butyl-1-heptene by the Reaction of a Butylcopper Reagent with 2-(Bromomethyl)-1-hexene at −40 °C in the Presence of Various Alcohols

entry	copper reagent	alcohol	yield[a] (%)
1	BuCu(CN)ZnI	*tert*-butyl alcohol	95
2	BuCu(CN)ZnI	cyclohexanol	86
3	BuCu(CN)ZnI	4-heptanol	93
4	BuCu(CN)ZnI	*n*-hexanol	90
5	BuCu(CN)ZnI	phenol	73
6	BuCu(CN)Li	*n*-hexanol	>95
7	$Bu_2Cu(CN)Li_2$	*n*-hexanol	>95

[a] GLC yields obtained by using dodecane as an internal standard.

were even found to facilitate the formation of RZnI. While the preparation of BuZnI in the absence of an amine was complete after 2 h at 25 °C (the reaction was exothermic and the temperature increased to 32 °C), the same reaction, if performed in the presence of benzylamine, was complete within 0.5 h at 25 °C (the temperature increased to 45–50 °C after mixing the reagents). Even aniline (pK_a = 27)[8a] did not undergo appreciable deprotonation. After 26 h at 25 °C, 89% of organozinc reagent was still present. However, with indole (pK_a = 17),[8b] the formation of BuZnI was complete after 4 h at 25 °C, but longer reaction times led to a slow protonation of BuZnI (entries 6 and 7). Also, a chelating diamine such as 1,2-diaminoethane was not appreciably deprotonated by this reagent, and c-HexZnI was obtained in 80% yield (0 °C, 4 h; entry 11). However, the more acidic hydrogens of 1,2-diaminobenzene slowly protonate c-HexZnI, which can be prepared in a maximum yield of 68% (entry 12); also, uracil (pK_a = 9.4)[8b] protonated BuZnI and c-HexZnI at 0 °C (entries 10 and 13). Similarly, benzamide (pK_a = ca. 17)[8c] and imidazole (pK_a = 14)[8b] were too acidic to be present during the generation of alkylzinc halides (entries 14 and 15) and only moderate yields were obtained. Interestingly, *tert*-butyl alcohol (pK_a = 19)[8c] slowly protonated BuZnI at 25 °C; however, the preparation of c-HexZnI tolerated the presence of *tert*-butyl alcohol at 0 °C (76% yield after 40 min, entries 9 and 16). Finally, reactions in the presence of acidic hydrogens attached to carbon were performed. For example, hexyne (pK_a = ca. 25)[8d] did not interfere with the preparation of BuZnI (91% after 2 h at 25 °C). Even dimethyl malonate (pK_a = 13)[8d] was not deprotonated in an appreciable amount (low kinetic acidity), and c-HexZnI was prepared in its presence in 74% yield (5 °C, 2.3 h; entries 18 and 19). However, the presence of ethyl acetoacetate (pK_a = 11)[8c] was not compatible with the preparation of organozinc reagents. It is also possible to allylate organocopper reagents at low temperature in the presence of a free hydroxyl group. The reaction of BuCu(CN)ZnI at −40 °C with 2-(bromomethyl)-1-hexene (0.85 equiv) in the presence of various alcohols (1 equiv) was examined (eq 2 and Table II). It was found that BuCu(CN)ZnI reacted faster with the allylic bromide than with the alcohol ROH, and a substantial decrease in yield was only observed with phenol (73% GC yield: entry 5; Table II). Other copper reagents such as BuCu(CN)Li and $Bu_2Cu(CN)Li_2$[9] showed the same chemoselectivity, implying that reactions of organocopper compounds that proceed rapidly at low temperatures can be performed with electrophiles bearing a free hydroxyl or amino group without the use of an excess of organocopper reagent.



(2)

Significant applications resulted from these studies. For example, 5-iodo-1-pentyne 1 was found to rapidly react with zinc dust (25–30 °C, 2 h) providing 4-pentynylzinc

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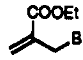
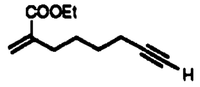
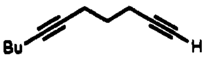
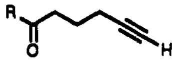
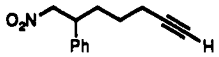
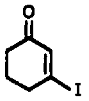
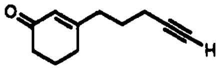
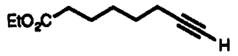
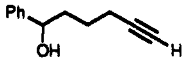
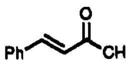
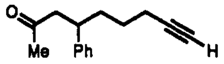
(8) (a) Wooding, N. S.; Higginson, W. C. E.; *J. Chem. Soc.* **1952**, 774. (b) Serjeant, E. P.; Dempsey, B. In *Ionisation Constants of Organic Acids in Aqueous Solutions*; Pergamon Press: New York, 1979. (c) March, J. In *Advanced Organic Chemistry*, 2nd ed.; McGraw Hill: New York, 1977; pp 227–229. (d) Streitwieser, A., Jr.; Reuben, D. M. E. *J. Am. Chem. Soc.* **1971**, *93*, 1794–5.

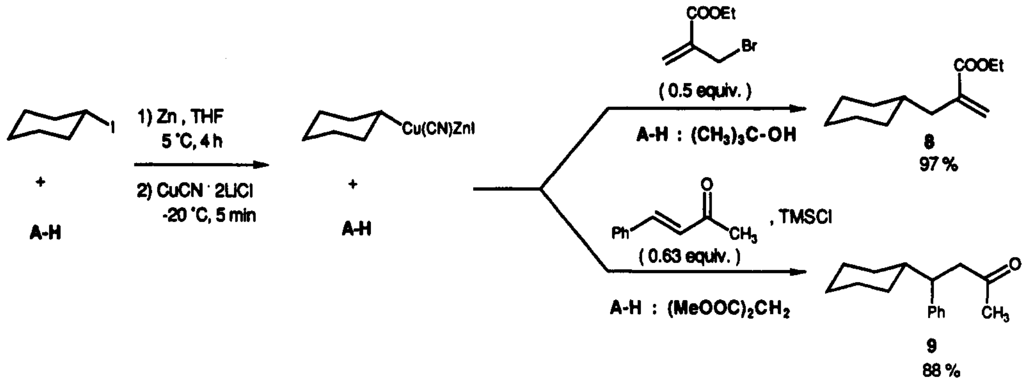
(9) (a) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. (b) Lipshutz, B. H. *Synthesis* **1987**, 325. (c) Lipshutz, B. H. *Synlett.* **1990**, 119.

Table III. Polyfunctional Alkynes 4 Obtained by the Reaction of the Copper Reagent 3 and an Electrophile[a]

electrophile	reaction conditions	product 4	yield[a] (%)
	-78 to 0 °C, 0.5 h	 **4a**	86
Bu—C≡C—I	-60 to -30 °C, 1 h	 **4b**	60
c-HexCOCl	0 °C, 1 h	 **4c**: R = c-Hex	67
PhCOCl	0 °C, 1 h	**4d**: R = Ph	68
	-78 to 0 °C, 1 h	 **4e**	78
	-30 °C, 1 h then 0 °C, 1-2 h	 **4f**	88
HC≡CCO₂Et	-60 to +30 °C, 1.5 h	 **4g**	86
PhCHO	-60 to 0 °C, 17 h	 **4h**	75[b]
	-70 to +20 °C, 8 h	 **4i**	95[c]

[a] All yields indicated refer to isolated analytically pure compounds characterized by ^1H and ^{13}C NMR, IR and HRMS. [b] This reaction was performed in the presence of $BF_3 \cdot OEt_2$ (2.0 equiv). [c] This reaction was performed in the presence of Me_3SiCl (2.0 equiv).

Scheme II



iodide 2. The iodolysis and hydrolysis of reaction aliquots indicated a yield of 90 ± 2%. After the addition of CuCN·2LiCl (1 equiv), the resulting dark red solution of the copper reagent 3 was reacted with electrophiles (0.7 equiv) such as allylic and alkynyl halides, an aldehyde, enone, nitro olefin, and acid chloride, giving polyfunctional alkynes 4 in 60–95% yield (eq 3 and Table III).[10,11] Both the

$$\underset{1}{H{-}C{\equiv}C(CH_2)_3I} \xrightarrow[\text{(2) CuCN·2LiCl, -20 °C, 5 min}]{\text{(1) Zn, THF, 25-30 °C, 2 h}} \underset{3}{H{-}C{\equiv}C(CH_2)_3\text{-}Cu(CN)ZnI} \xrightarrow[\text{60-95\%}]{E^+ \text{ (0.7 equiv)}} \underset{4}{H{-}C{\equiv}C(CH_2)_3\text{-}E} \quad (3)$$

zinc and the copper reagents 2 and 3 were stable and did not undergo self-protonation and thus, in strong contrast to the corresponding magnesium or lithium reagent, do not

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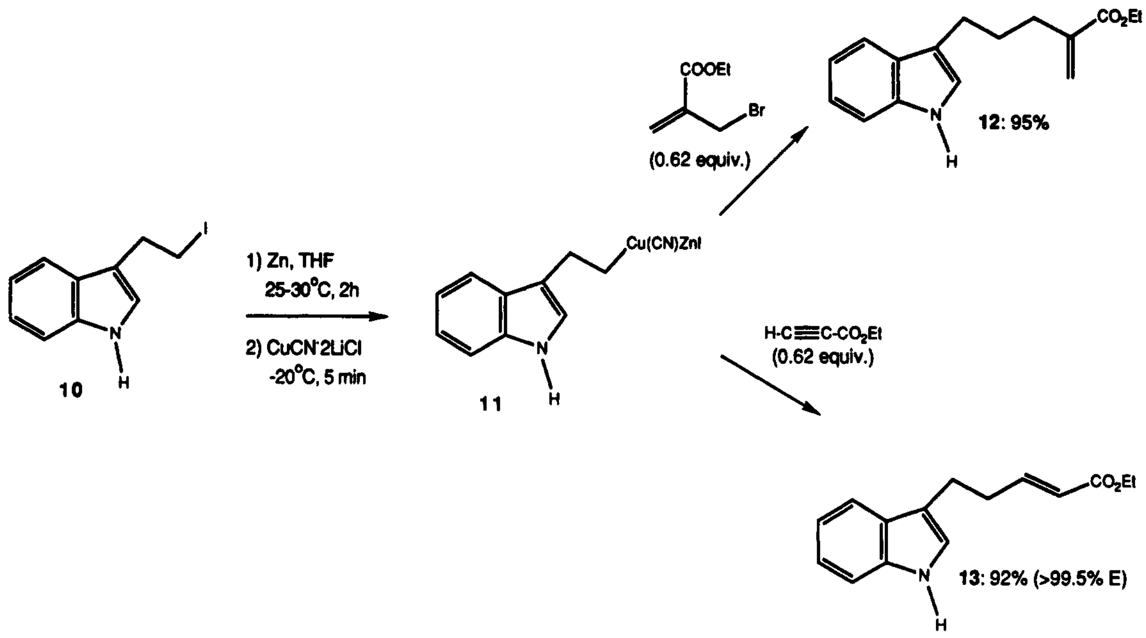
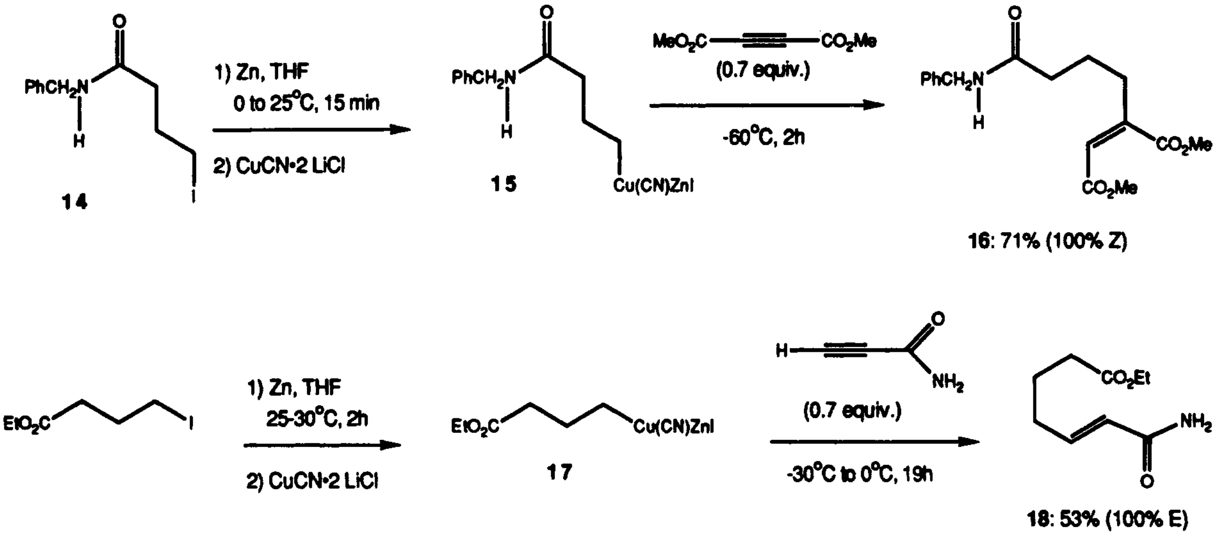
[10] Terminal acetylenic protons have to be protected during the formation of a Grignard or lithium reagent: (a) Flahaut, J.; Miginiac, P. *Helv. Chim. Acta* **1978**, *61*, 2275. (b) Hall, S. E.; Roush, W. R. *J. Org. Chem.* **1982**, *47*, 4611.

[11] Typical procedure. Preparation of 3-(4-pentynyl)cyclohexen-1-one 4f (Table III). A dry, three-necked 100-mL flask was charged with zinc dust (3.27 g, 50 mmol) and flushed with argon. After zinc activation with 1,2-dibromoethane and Me_3SiCl as reported previously[5] a THF solution of 4-pentynyl iodide 1 (4.46 g, 23 mmol) in 8 mL of THF was slowly added. The temperature was maintained below 40 °C during the addition. After 0.5–1 h of stirring at 25 °C, the reaction was complete as indicated by GLC analysis. After the addition of 10 mL of dry THF, the excess of zinc was allowed to settle for 1 h. One-half of this solution (ca. 10 mmol) was transferred via syringe to a solution of CuCN (0.90 g, 10 mmol) and LiCl (0.84 g, 20 mmol, dried 1 h under vacuum at 140 °C) in 10 mL of THF at -20 °C. A dark red solution of 3 was immediately formed. The reaction mixture was cooled to -60 °C after 5 min of stirring, and 3-iodo-2-cyclohexen-1-one (1.55 g, 7 mmol (0.7 equiv)) was added. The reaction mixture was stirred 1 h at -30 °C and then was slowly warmed to 0 °C (1–2 h) and worked up under the usual conditions. The resulting crude oil was purified by flash chromatography (CH_2Cl_2/ether/hexane (1:1 to 5:90)), affording 1.0 g (88% yield) of analytically pure produce 4f.

Scheme III



Scheme IV



require the protection of the terminal alkyne group.[10] Functionalized zinc and copper reagents FG–RCu(CN)ZnI could also be generated in the presence of a primary amine. Thus, the addition of an equimolar mixture of ethyl 4-iodobutanoate and benzylamine as a THF solution to zinc dust at 25 °C leads to an exothermic reaction, which was complete within 15 min (95% yield by GLC analysis). The THF solution of (3-carbethoxypropyl)zinc iodide was added at −20 °C to a THF solution of CuCN·2LiCl leading to the copper reagent 5. The addition of nitrostyrene (0.65 equiv; −20 to 0 °C, 0.5 h) or ethyl α-(bromomethyl)acrylate[12] (0.74 equiv; −50 to 0 °C, 50 min) to the organocopper reagent 5 gave the desired adducts 6 and 7 in 73 and 76% yields, respectively (Scheme I). These satisfactory yields show the compatibility of a free amine with an organocopper or organozinc functionality. Similarly, the addition of an equimolar mixture of cyclohexyl iodide and *tert*-butyl alcohol or dimethyl malonate to zinc dust (3 equiv, 5 °C, 4 h) leads to the formation of cyclohexylzinc iodide in 66% and 70% yields, respectively. Addition of the former solution to a THF solution of CuCN·2LiCl (−20 °C, 5 min) followed by ethyl α-(bromomethyl)acrylate (0.5 equiv, −78 to 0 °C, 45 min) gave 8 in 97% yield. Similar treatment of the latter solution with CuCN·2LiCl followed by benzylideneacetone (0.63 equiv; TMSCl (2 equiv), −78 to +25 °C, 15 h) gave the 1,4-adduct 9 in 88% yield (Scheme II). Organozinc and copper compounds bearing a secondary amino or amide group were also prepared. Thus, the treatment of 3-(2-iodoethyl)indole[13] 10 with zinc dust (3 equiv; 25–30 °C, 2 h) afforded the desired zinc reagent in ca. 90% yield. After its addition to CuCN·2LiCl (0.2 M THF solution), the resulting copper compound 11 reacted smoothly with ethyl α-(bromomethyl)acrylate (0.62 equiv; −70 to −20 °C, within 1 h) and ethyl propiolate (0.62 equiv; −70 to +25 °C, −60 °C, 2 h, then warm to 25 °C) providing the acrylates 12 and 13 (>99.5% *E* isomer) in excellent yields (95% and 92% yields, respectively, Scheme III). The *N*-benzyl iodoamide 14 was converted to the zinc–copper reagent 15 as usual (Zn (2 equiv), THF, 0 to 25 °C,

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[12] Villieras, J.; Rambaud, M. *Synthesis* 1982, 924.

[13] Prepared from the commercially available alcohol; see: Neumeyer, J. L.; Moyer, U. V.; Leonard, J. E. *J. Med. Chem.* 1969, *12*, 450.

15 min, $CuCN\cdot 2LiCl$ (1.0 equiv), -20 °C). Addition of dimethyl acetylenedicarboxylate (0.7 equiv, -60 °C, 2 h) gave the pure syn-carbometalation adduct **16** in 71% yield. The addition of the functionalized copper-zinc reagent **17** to propiolamide[14] (0.7 equiv; -30 to 0 °C, 19 h) provided the unsaturated amide **18** (100% *E*) in 53% yield (Scheme IV).

In conclusion, we have demonstrated that organozinc halides RZnX and the copper reagents RCu(CN)ZnI are perfectly compatible with primary or secondary amines and terminal alkynes. Under appropriate reaction conditions, the presence of amides and hydroxy groups was also possible, although synthetic applications may be more limited. Several new types of organometallic reagents such as **3**, **11**, and **15** were prepared and subsequently reacted with a broad range of electrophiles. This remarkable functional group tolerance avoids using protecting groups and should find numerous synthetic applications. Extensions of these studies are currently underway in our laboratories.

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Supplementary Material Available: Typical experimental procedures and full characterization data for all new compounds (7 pages). Ordering information is given on any current masthead page.

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[14] Vogt, R. B. U.S. Patent No. 4,128,644, Dec 5, 1978.

Use of the Magnesium Cation in Aldol Additions. A Convenient Method for Achieving Anti-Aldol Selectivity

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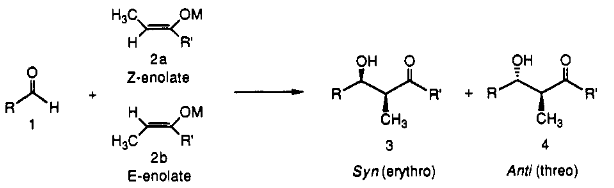
Summary: A practical and convenient procedure for achieving anti selectivity in aldol reactions which utilizes Mg(II) aldolate (or enolate) equilibrations is reported.

The aldol addition of an aldehyde (**1**) with the enolate of an ethyl ketone (**2**) gives two diastereomeric aldol products: syn (**3**) and anti (**4**) (Scheme I).[1] Over the last 20 years, this simple reaction has commanded considerable attention, resulting in its evolution from a method of limited utility to an invaluable tool in synthetic chemistry.[2] Both the geometry of the enolate and the nature of its counter cation[2,3] play important roles in controlling the diastereoselectivity of the aldol reactions. In addition, the use of enantiomeric auxiliaries[4] or enantiomeric bases[5] have permitted enantiofacial selective attacks on aldehydes to favor one diastereomer over the other three possibilities.

Scheme I



In general, under kinetically controlled conditions, group I, II, and III metal *Z* enolates (**2a**) usually give the syn aldol products with a high degree of diastereoselection while their *E* enolates (**2b**) favor the anti product but with poorer selectivity.[2,3a,6] Recently, several research groups reported kinetically controlled procedures which result in improved anti aldol selectivity.[8] All of these results can be rationalized using some embodiment of the well-known Zimmerman/Traxler six-membered chair transition-state

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[5] For example, see: Imasawa, N.; Mukaiyama, T. *Chem. Lett.* **1982**, 1441.

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