for ^{15}N increases in that *same* order for the two sulfonate X's and may also in the iodide/tosylate comparisons. This is contrary to the reactivity–selectivity principle, which states that increasing reactivity should be accompanied by *decreasing* selectivity. Similarly the implied increase in the $N{-}CH_3$ transition state bond order as CH_3X bbecomes more reactive is contrary to expectations based on the usual free energy surface models.[2] Those models assume that the barrier is "symmetric" in the sense that in the neighborhood of the transition state the barrier is an even function of the reaction coordinate about its maximum; it is that symmetry which is responsible for predictions that, as CH_3X becomes more reactive, both its selectivity and the $N{-}CH_3$ transition-state bond order should decrease.[15] Whether the variations in $N{-}CH_3$ transition state bonding reported here arise from an unsymmetric barrier, the Pross–Shaik effect,[3] or the asynchronous changes in solvation and bonding that have been proposed[16,17] to explain anomalous observations for other methyl transfers presently remains an open question.

These entering-group isotope effects confirm other evidence that the reactivity–selectivity principle and predictions based on symmetric free energy surface models are not always obeyed by nucleophilic displacements. Examples of the breakdown of the expected relationship between selectivity and reactivity in S_N2 reactions have been reviewed by Pross.[18] Arnett and Reich[17] have shown that rate ratios (nonisotopic) for quaternizations of 3- and 4-substituted pyridines are independent of the reactivity of the alkylating agent. Pross and Shaik[3] review some leaving-group isotope effects and nonisotopic substituent effects on benzyl transfers that suggest that changes in leaving groups which increase the rate also increase the nucleophile–carbon bond order in the transition state. A complementary example of the apparent effect on carbon-leaving-group bond order of changing the nucleophile is provided by Grimsrud and Taylor,[19] who observed that k_{35}/k_{37} chlorine-leaving-group isotope effects are larger for anionic sulfur nucleophiles than for the less reactive anionic oxygen nucleophiles.

For the effect on transition-state structure of changing the *leaving* group, as Pross and Shaik emphasize,[20] information concerning variation in the *nucleophile*–carbon bond order is required to distinguish between their prediction and possible predictions based on symmetric free energy surface models. *Entering*-group *isotope* effects such as those presented here provide the most direct information on that bond order. In contrast, conclusions based on the effects of nonisotopic structural changes can be challenged,[21,22] and the complementary use of leaving-group isotope effects to distinguish between predictions concerning the effect of changing the nucleophile on carbon-leaving-group bonding are more subject to ambiguities that arise from the changing desolvation free energy of the nucleophile.[19,23] Clearly, further measurements of entering-group isotope effects on these and related reactions are required in order to explore the generality of our conclusions. Such experiments are in progress.

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Registry No. 2,6-Me_2(py), 108-48-5; py, 110-86-1; 4-Me(py), 108-89-4; CH_3I, 74-88-4; CH_3OTs, 80-48-8; CH_3OTf, 333-27-7; ^{15}N, 14390-96-6.

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(12) Kurz, J. L.; Kirk, R. L., unpublished observations.

(13) Spiegel, G. W. Ph.D. Thesis, Washington University, St. Louis, MO, 1980.

(14) Lee, J. Ph.D. Thesis, Washington University, St. Louis, MO, 1981.

(15) For example: (a) Kurz, J. L. *Chem. Phys. Lett.* **1978**, *57*, 243–246. (b) Agmon, N. *J. Chem. Soc., Faraday Trans. 2* **1978**, *74*, 388–404. (c) Lewis, E. S.; Shen, C. C.; More O'Ferrall, R. A. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1084–1088.

(16) Kurz, J. L.; Lee, J.; Rhodes, S. *J. Am. Chem. Soc.* **1981**, *103*, 7651–7653.

(17) Arnett, E. M.; Reich, R. *J. Am. Chem. Soc.* **1980**, *102*, 5892–5902.

(18) Reference 1a, pp 106, 107.

(19) Grimsrud, E. P.; Taylor, J. W. *J. Am. Chem. Soc.* **1970**, *92*, 739–741.

(20) Reference 3, p 3706.

(21) Reference 17, p 5902.

(22) Thorstenson, T.; Eliason, R.; Songstad, J. *Acta Chem. Scand., Ser. A.* **1977**, *31*, 276–280.

(23) (a) Reference 1a, pp 103–107. (b) Pross, A. *J. Am. Chem. Soc.* **1976**, *98*, 776–778.

New Heterocuprates with Greatly Improved Thermal Stability[1]

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Organocopper reagents have become indispensable for organic synthesis[2] in spite of three serious shortcomings: (1) homocuprates, R_2CuLi, waste one R group in most applications; (2) heterocuprates, RCuXLi (X = ligand bonded to Cu via a heteroatom), are thermally unstable and must be used at low temperatures;[3] (3) acetylenic mixed cuprates, RCuR′Li (R′ = 1-alkynyl ligand), are much less reactive than the corresponding homocuprates.[4] House and DuBose[5] summarize the synthetic chemist's predicament most succinctly: "Thus, the reaction temperatures required to form and use $(R_2CuLi)_n$ reagents are often approximately the same as the temperatures where thermal decomposition becomes a serious competing reaction." We have invented two new classes of heterocuprates based upon phosphido and amido ligands that exhibit a remarkable degree of thermal stability and also have good reactivity in typical organocuprate reactions, thus overcoming the above problems.

Cuprates based upon diphenylphosphidocopper(I),[6] **1**, can be prepared by adding 1 equiv of Li reagent or Grignard reagent to **1** at −20 to 0 °C (method A), or by adding 1 equiv of $LiPPh_2$ to an organocopper(I) reagent (RCu) at −50 °C (method B). Exposure of **1** to O_2 yields a new complex, **2**.[7] Cuprates can also be prepared from **2** by addition of RLi at 0 °C (method C).[7] All three methods are convenient to run as one- or two-flask procedures.[8] The basic structural feature of these diphenylphosphido cuprates is suggested to be a dimeric unit consisting of two Cu atoms connected by bridging diphenylphosphides, as was revealed by X-ray crystallography in the benzene complex of diphenyl-

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(1) Presented in part at the 183rd National Meeting of the American Chemical Society, Las Vegas, March 31, 1982. Part V in the series New Copper Chemistry. Part IV: Bertz, S. H.; Dabbagh, G. *J. Chem. Soc., Chem. Commun.* **1982**, 1030. Part III: Bertz, S. H.; Dabbagh, G.; Cotte, P. *J. Org. Chem.* **1982**, *47*, 2216.

(2) Posner, G. H. "An Introduction to Synthesis Using Organocopper Reagents"; Wiley: New York, 1980.

(3) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788.

(4) Mandeville, W. H.; Whitesides, G. M. *J. Org. Chem.* **1974**, *39*, 400.

(5) House, H. O.; DuBose, J. C. *J. Org. Chem.* **1975**, *40*, 788.

(6) Issleib, K.; Fröhlich, H.-O. *Chem. Ber.* **1962**, *95*, 375. Method IIb was used starting from Ph_2PLi and $CuBr{\cdot}SMe_2$ without the aqueous workup (see ref 8). The product of method IIa (aqueous workup) is not useful for preparing cuprates.

(7) The empirical formula of **2** (determined by complete microanalysis) corresponds to $Cu(PPh_2)(O_2)$. Whitesides, G. M.; San Filippo, J., Jr.; Casey, C. P.; Panek, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 5302. Treatment of cuprates with O_2 decomposes them with coupling of the organic residue, therefore the oxygen in **2** must be very tightly bound.

(8) A solution of $LiPPh_2$ in ether or THF is prepared by adding 1.0 equiv of RLi to $HPPh_2$ (Orgmet) at −50 °C and allowing the mixture to warm to room temperature. Standard syringe techniques are used with a nitrogen atmosphere. The yellow (ether)/orange (THF) solution is transferred to 1.0 equiv of $CuBr{\cdot}SMe_2$ (Aldrich) at 0 °C, and the resulting suspension is allowed to stir at room temperature for 1 h to afford **1** as a brick-red solid, which can be washed free of LiBr with fresh solvent. Removal of the supernatant and injection of 1.0 equiv (22.4 mL/mmol) of O_2 produces **2**. Unreacted O_2 is flushed out with Ar, and fresh solvent is introduced. For formation of the cuprates, 1.0 equiv of RLi or RMgBr is added to **1** at 0 °C or −20 °C, respectively, and the reaction mixture is stirred for 15 min before being cooled to −50 °C where the substrate (1.0 equiv, dissolved in solvent, also containing internal standard if desired) is added. The course of the reactions may be followed by GLC on 10 ft × 1/8 in. OV101 or Carbowax 20M (both 5% on Chromosorb W-HP) columns by using temperature programming (45–225 °C at 20 °C/min or 45–155 °C at 10 °C/min).

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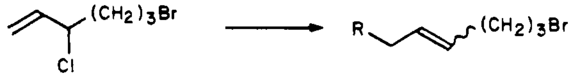
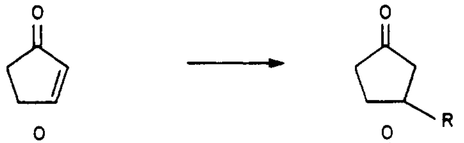
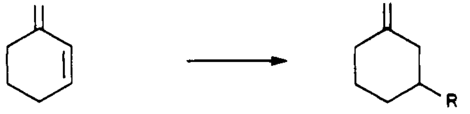
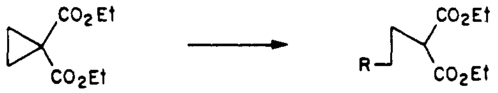
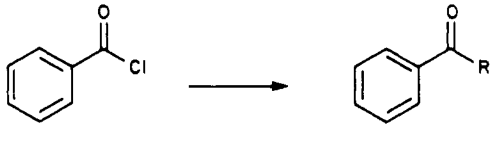
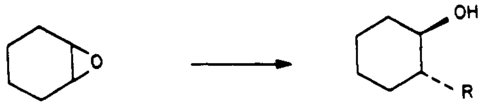
Table I. Some Reactions of the New Heterocuprates

Reaction	R[a]	Yield[b] RCu(PPh$_2$)Li Reagent (Method[c])	Yield[b] RCu(NCy$_2$)Li Reagent (Method[c])
	Heptyl	87 (A)	64 (B)
	Vinyl	68 (C)[d]	83 (A)[e]
	Bu	78 (A)[f]	92 (A)[d]
	Bu	75 (A)[d] 88 (C)[d,g]	29 (A)[d]
	Vinyl	64 (C)[d]	18 (A)[d]
	Bu	71 (B)[h]	67 (B)[h]
	Bu	100 (A)[i]	98 (A)[i]
	t-Bu	80 (C)[i]	55 (A)[i]
	Me	35 (B)[j]	46 (A)[j]
$CH_3(CH_2)_7I \longrightarrow CH_3(CH_2)_7R$	Bu	64 (C)[j]	71 (A)[j]
	Me	57 (C)[k]	84 (A)[j]

[a] Heptyl from Grignard reagent; all other entries from Li reagents. [b] Determined by GLC calibrated with authentic products and *n*-alkane internal standards; ether solvent, except in first and last reactions, run in THF. Yields are given in percent. [c] See text for descriptions of methods A–C. [d] −50 °C to 25 °C (3 h). [e] −100 °C (0.5 h). [f] 0 °C (1 h). [g] Recovered CuPPh$_2$(O$_2$) was used. [h] −50 °C (1 h). [i] Excess PhCOCl was used (from thermal stability study). [j] 25 °C (20 h). [k] 0 °C (20 h).

phosphido(bis-1,2-diphenylphosphinoethane)copper(I).[9] The (dicyclohexylamido)cuprates are prepared at 0 °C by adding a Li or Mg reagent to (dicyclohexylamido)copper(I), **3** (prepared in situ from Li dicyclohexylamide[10] and CuBr·SMe$_2$, **4**, at 0 °C) in analogy to method A above. Alternatively, they can be prepared by adding lithium dicyclohexylamide to RCu at −50 °C (method B). Since LiPPh$_2$ and LiNCy$_2$ can be prepared with inexpensive lithium reagents such as MeLi or BuLi, cuprates based on **1**–**3** require but 1 equiv of potentially valuable Li or Mg reagent.

For the purpose of comparing thermal stability, the butyl organic residue (R) was chosen, as it was the one studied by Whitesides et al.[11] The various cuprates prepared in diethyl ether or THF were aged at 0 and 25 °C, and samples taken after 30 min at each temperature were quenched with excess PhCOCl. The yields of PhCOBu were (respectively) 99% and 95% for BuCu(PPh$_2$)Li, 97% and 89% for BuCu(PCy$_2$)Li, 98% and 89% for BuCu(NCy$_2$)Li, 100% and 87% for BuCu(N-*i*-Pr$_2$)Li, 98% and 73% for BuCu(NEt$_2$)Li, and 19% and 0% for BuCu(SPh)Li, all in ether. (The yields after 30 min at −50 and −25 °C for BuCu(SPh)Li were 100% and 97%). Thus, the new heterocuprates based upon phosphido and amido ligands are vastly more stable than previous ones, of which those with X = SPh were reported to be the most stable and those with X = NEt$_2$, the least stable.[3] As far as the mixed homocuprates are concerned, the corresponding yields for BuCu(C≡C-*t*-Bu)Li[12] were 92% and 89%; and those for Johnson's and Dhanoa's[13] new BuCu(CH$_2$SO$_2$Ph)Li were 86% and 38% in ether (99% and 91% in THF). Lipshutz et al.[14] have recently introduced lithium dialkyl(cyano)cuprates

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(9) Greiser, T.; Weiss, E. *Chem. Ber.* **1978**, *111*, 516. Koten, G. van; Noltes, J. G.; Spek, A. L. *J. Organomet. Chem.* **1978**, *159*, 441.

(10) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 582.

(11) Whitesides, G. M.; Stedronsky, E. R.; Casey, C. P.; San Filippo, J., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 1426.

(12) House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 3893.

(13) Johnson, C. R.; Dhanoa, D. S. *J. Chem. Soc., Chem. Commun.* **1982**, 358.

(14) (a) Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672. (b) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *Ibid.* **1982**, *104*, 2305. (c) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. *Tetrahedron Lett.* **1982**, *23*, 3755.

J. Am. Chem. Soc. 1982, 104, 5826-5828

as reagents with improved thermal stability. For comparison, the corresponding yields for $Bu_2Cu(CN)Li_2$ were 95% and 84% in ether.

With their thermal stability established[15] the reactivity and economy of cuprates based on **1**–**3** are illustrated by the examples in Table I. In the first, 6-bromo-3-chloro-1-hexene was added to the reagent prepared with **1** (from **4** and $LiPPh_2$, prepared in situ[8] from $HPPh_2$ and BuLi) and 1.0 equiv of *n*-heptylmagnesium bromide in THF at −20 °C to obtain 87% of an *E*–*Z* mixture (6:4) of 1-bromo-4-tridecenes (**5**) and 11% of 1-bromo-4-vinylundecane (**6**). So that a comparable total yield (97% **5**, <1% **6**) could be obtained, 1.8 equiv of the corresponding homocuprate (prepared from 3.6 equiv of Grignard reagent and 1.8 equiv of **4**) was required. The yield of **5** based upon heptyl in this case is only 27%. In a related example, Macdonald and co-workers[16] treated 9-bromo-3-chloro-1-nonene with 1.0 equiv of the cuprate prepared from 2.0 equiv of *n*-propylmagnesium bromide and 1.0 equiv of **4** to obtain 80% of 1-bromo-7-dodecene (40% based on propyl). Besides the requirement of less Grignard reagent for complete action, the higher reactivity of our reagent is indicated by the presence of **6** from the direct displacement of Cl at a secondary center,[14a] not observed with the homocuprate.

The vinyl cuprate prepared from **3** and vinyllithium reacts with 2-cyclopentenone to afford 83% of 3-vinylcyclopentanone. The yield reported for the (phenylthio)cuprate was 30%.[3] The vinylcuprate prepared from **2** and vinyllithium adds 1,4 to isophorone in 64% yield, compared with 52–58% for acetylenic mixed cuprates.[12,17] While the yields of 3-vinyl adduct from isophorone and 2 equiv of divinylcopper(I) lithium[18] or divinyl(cyano)copper(I) dilithium[14c] are higher based on isophorone (85% and 88%, respectively), the yields based on vinyllithium are significantly lower (21–22%). The conjugate addition of vinyl copper(I) reagents is important because of its relevance to certain prostaglandin syntheses, where the optically active vinyllithium reagent from which the cuprate is made can be more valuable than the cyclopentenone substrate.[19] In such cases it is more valid to calculate yields based on the Li reagent.

Considering the 92% yield from 2-cyclohexenone and $BuCu(NCy_2)Li$, the low yields of isophorone conjugate addition products using cuprates based on **3** (see Table I) are due to steric inhibition of the reaction. In line with this view, the smaller $BuCu(NEt_2)Li$ affords a 60% yield of 3-butyl-3,5,5-trimethylcyclohexanone. This result suggests the possibility of tailoring heterocuprate reactivity by choosing the appropriate amido ligand.

Examples of reactions where thermal stability and reactivity are crucial are the opening of epoxides and the displacement of primary iodides. Cyclohexene oxide yields 62% of *trans*-2-methylcyclohexanol when treated with 5 equiv of Me_2CuLi.[20] (The yield based on Me is but 6%.) With cuprates prepared from **1** and **3**, the yields based on Me (or on cyclohexene oxide) are 35% and 46%, respectively. With use of $MeCu(CN)Li$ to effect this transformation, the yield is 29%;[21] the yield we obtain using 1.0 equiv of Lipshutz's[14b] $Me_2Cu(CN)Li_2$ is 53% (27% per Me). A 97% yield of nonane from octyl iodide and 3 equiv of Me_2CuLi has been reported.[22] On the basis of Me the yield is 16%, compared with 57% from the methyl derivative of **2** and 84% from that of **3**.

As a final example of the high reactivity of these new heterocuprates, $BuCu(PPh_2)Li$ and $BuCu(NCy_2)Li$ are able to open a 1,1-diactivated cyclopropane with the kind of yield (70%) that often requires 2 equiv of R_2CuLi.[23]

We believe that the high thermal stability and reactivity of the new cuprates introduced here will make them valuable reagents for the synthesis of complex molecules.

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[15] For a more detailed discussion of the factors influencing thermal stability, see Part IV of our series (ref 1).

[16] Macdonald, T. L.; Narayanan, B. A.; O'Dell, D. E. *J. Org. Chem.* **1981**, *46*, 1504.

[17] Ledlie, D. B.; Miller, G. *J. Org. Chem.* **1979**, *44*, 1006.

[18] Hooz, J.; Layton, R. B. *Can. J. Chem.* **1970**, *48*, 1626.

[19] Patterson, J. W., Jr.; Fried, J. H. *J. Org. Chem.* **1974**, *39*, 2506. Sih, C. J.; Heather, J. B.; Peruzzotti, G. P.; Price, P.; Sood, R.; Lee, L.-F. H. *J. Am. Chem. Soc.* **1973**, *95*, 1676.

[20] Johnson, C. R.; Herr, R. W.; Wieland, D. M. *J. Org. Chem.* **1973**, *38*, 4263.

[21] Acker, R.-D. *Tetrahedron Lett.* **1977**, 3407.

[22] Whitesides, G. M.; Fischer, W. F., Jr.; San Filippo, J., Jr.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871.

[23] Yates, P.; Stevens, K. E. *Tetrahedron* **1981**, *37*, 4401 (for R = Me). Alexakis, A.; Cahiez, G.; Normant, J. F. *Ibid.* **1980**, *36*, 1961 (for R = (*Z*)-1-butenyl. In the former a 75% yield was obtained by using 2 equiv of cuprate (19% per Me), and in the latter a 92% yield was reported by using 1 equiv (46% per butenyl). The substrates were 2,8-dicarbomethoxy-4,4-dimethyltricyclo$[3.2.1.0^{2,8}]$octan-3-one and dimethyl cyclopropane-1,1-dicarboxylate, respectively.

Cavitands: Synthetic Molecular Vessels[1]

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In host–guest complexation, the concave surface of a host complements the convex surface of a guest.[2] Similarly, the receptor sites of enzymes frequently contain rigid cavities whose internal surfaces complement the convex surfaces of substrates or inhibitors.[3] To imitate nature's complexes, hosts that contain enforced concave surfaces of substantial dimensions must be designed and synthesized. We propose the class name *cavitand* for synthetic organic compounds that contain *enforced cavities* large enough to accommodate simple molecules or ions.

The spherands,[4] exemplified by **1** (Chart I) are a specific type of cavitand. Unlike the chorands (crowns) or cryptands, they contain rigid cavities formed during their syntheses rather than during their complexation. The spherands's preorganization resulted in the highest binding and selectivity yet observed for the alkali metal ions.[5] Cyclotriveratrylene (**2**), which at 25 °C possesses a rigid saucer shape, is another type of cavitand.[6] Collet et al. have recently reported the elegant synthesis of a cavitand composed of two cyclotriveratrylene units connected by three dimethylene bridges (**3**).[7] Gutsche et al. has recently rigidified calixarene **4** by trimethylsilylation to give a cone-shaped cavitand.[8] We describe here the four new cavitands **7**–**10**, prepared from the conformationally mobile resorcinol–acetaldehyde condensation

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[1] We thank the National Science Foundation for Grant NSF CHE 81-09532 and the U.S. Public Health Service for Grant GM 12640, which supported this research.

[2] (a) Kyba, E. P.; Helgeson, R. C.; Madan, K.; Gokel, G.; Tarnowski, T. L.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 2564–2571. (b) Cram, D. J.; Trueblood, K. N. *Top. Curr. Chem.* **1981**, *98*, 43–106. (c) Cram, D. J. *Science* (*Washington, D.C.*), in press.

[3] Dickerson, R. E.; Geis, I. "The Structure and Action of Proteins"; Harper and Row: New York, 1969; pp 67–97.

[4] Cram, D. J.; Kaneda, T.; Helgeson, R. C.; Lein, G. M. *J. Am. Chem. Soc.* **1979**, *101*, 6752–6754.

[5] (a) Cram, D. J.; Lein, G. M.; Kaneda, T.; Helgeson, R. C.; Knobler, C. B.; Maverick, E.; Trueblood, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 6228–6232. (b) Lein, G. M.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1982**, 301–304.

[6] (a) Lindsey, A. S. *J. Chem. Soc.* **1965**, 1685–1692. (b) Lüttringhaus, A.; Peters, K. C. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 593–594.

[7] Gabard, J.; Collet, A. *J. Chem. Soc., Chem. Commun.* **1981**, 1137–1139.

[8] Gutsche, C. D.; Levine, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 3782–3783.

0002-7863/82/1504-5826$01.25/0