# Cupration of Organomercurials: A Mild Method for the Intramolecular Addition of Organometallics to Ester Groups†

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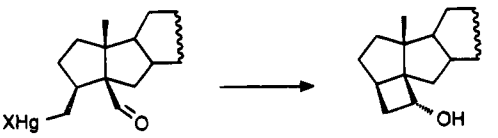
*Received December 8, 1994*

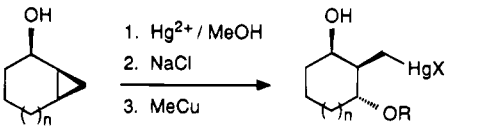
Addition of Grignard and alkyllithium reagents to carbonyl groups is one of the most widely used applications of organometallics in organic synthesis.[1] However, its intramolecular version has never been fully developed, owing to the high reactivity of the reagents required to generate the CMgX or CLi group in the molecule already containing an unprotected carbonyl function.[2] Alternatives involving less reactive organometallic species (B, Si, Sn, Zn, Cr, and Ni) are confined to allylic, benzylic, or vinylic halides and enol triflates as precursors.[3] Much more successful is the Sm(II)- and Yb(II)-mediated cyclization of halo ketones and halo esters.[4,5] We have recently shown that the intramolecular addition to an aldehyde group in **1** and **2** can be accomplished via activating the neighboring CHgX moiety by organocuprates (Scheme 1).[6,7] Similarly, intramolecular addition across an activated double bond (1,4-addition) has also been observed.[6] Herein, we describe related intramolecular additions to ester groups.

**Scheme 1**



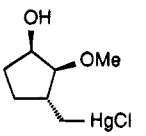

**1**, X = Br
**2**, X = $CH_3$
**3**

**Scheme 2**



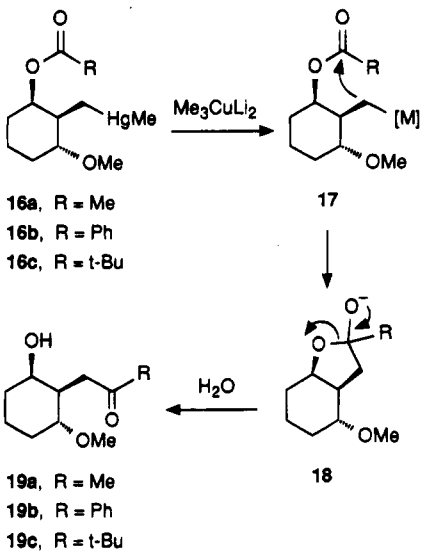

**4**, n = 1
**5**, n = 2
**6**, n = 0

**7**, X = Cl, R = Ac, n = 1
**8**, X = Cl, R = $NO_2$, n = 1
**9**, X = Cl, R = Me, n = 1
**10**, X = Me, R = Me, n = 1
**11**, X = Cl, R = Me, n = 2
**12**, X = Me, R = Me, n = 2
**13**, X = Cl, R = Me, n = 0
**14**, X = Me, R = Me, n = 0




**15**

**Scheme 3**




**16a**, R = Me
**16b**, R = Ph
**16c**, R = t-Bu

**17**

**18**

**19a**, R = Me
**19b**, R = Ph
**19c**, R = t-Bu

Whereas esters react rapidly with Grignard and alkyllithium reagents, they are essentially inert toward organocuprates.[8] However, an intramolecular reaction of this type has rarely been attempted,[2] presumably in view of the difficulties associated with generating a suitable precursor. Since the carbonyl-containing organomercurials can be prepared as stable compounds,[6,9] we reasoned that they might serve as the starting materials of choice. Furthermore, it was of interest to explore whether the species resulting from their activation by treatment with organocuprates were prone to add intramolecularly across

† Dedicated to Dr. Jiří Závada on the occasion of his 60th birthday.
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(2) (a) For examples of successful cyclization of ω-iodo-α,β-unsaturated *tert*-butyl esters by means of RLi, see: Cooke, M. P., Jr. *J. Org. Chem.* **1992**, *57*, 1495. (b) Recently, a BuLi-mediated cyclization of iodovinyl ketones has been reported: Piers, E.; Cook, C. L.; Rogers, C. *Tetrahedron Lett.* **1994**, *35*, 8573.

(3) B and Si: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1. Sn: (b) Marshall, J. A.; Crooks, S. L.; DeHoff, B. S. *J. Org. Chem.* **1988**, *53*, 1616. (c) Marshall, J. A.; Gung, W. Y. *Tetrahedron Lett.* **1988**, *29*, 1657. (d) Trost, B. M.; Sato, T. *J. Am. Chem. Soc.* **1985**, *107*, 719. Zn: (e) Semmelhack, M. F.; Wu, E. S. C. *J. Am. Chem. Soc.* **1976**, *98*, 3384. (f) Semmelhack, M. F.; Yamashita, A.; Tomesch, J. C.; Hirotsu, K. *J. Am. Chem. Soc.* **1978**, *100*, 5565. (g) Knochel, P. Reference 3a; Vol. 1, p 211. Cr: (h) Still, W. C.; Mobilio, D. *J. Org. Chem.* **1983**, *48*, 4785. (i) Drewes, S. E.; Hoole, R. F. A. *Synth. Commun.* **1985**, *15*, 1068. (j) Okuda, Y.; Nakatsuka, S.; Oshima, K.; Nozaki, H. *Chem. Lett.* **1985**, 481. (k) Shibuya, H.; Ohashi, K.; Hori, K.; Murakami, N.; Kitagawa, I. *Chem. Lett.* **1986**, 85. (l) Kato, N.; Tanaka, S.; Takeshita, H. *Chem. Lett.* **1986**, 1989. (m) Ledoussal, B.; Gorgues, A.; Le Coq, A. *J. Chem. Soc., Chem. Commun.* **1986**, 171; *Tetrahedron* **1987**, *43*, 5841. (n) Saccomano, N. A. Reference 3a; Vol. 1, p 173. Ni: Reference 3e.

(4) (a) Molander, G. A.; Etter, J. B. *Synth. Commun.* **1987**, *17*, 901. (b) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1986**, *51*, 1778. (c) Sugibome, H.; Yamada, S. *Tetrahedron Lett.* **1987**, *28*, 3963. (d) Sosnowski, J. J.; Danaher, E. B.; Murray, R. K., Jr. *J. Org. Chem.* **1985**, *50*, 2759. (e) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132. (f) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1993**, *58*, 7216. (g) Molander, G. A. Reference 3a; Vol. 1, p 107. (h) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

(5) Although C=O is not particularly prone to radical addition, successful cyclizations producing 5- and 6-membered rings have been described: (a) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, *108*, 2116 and 8102. (b) Tsang, R.; Dickson, J. K.; Pak, H.; Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987**, *109*, 3484. (c) Zhang, W.; Dowd, P. *Tetrahedron Lett.* **1992**, *33*, 3285. For rare 4-membered ring formations, see: (d) Jung, M.; Trifunovich, I. D.; Lensen, N. *Tetrahedron Lett.* **1992**, *33*, 6719 and references cited therein. (e) Mori, M.; Isono, N.; Kaneta, N.; Shibasaki, M. *J. Org. Chem.* **1993**, *58*, 2972.

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(7) We have ruled out a radical mechanism.[6b]

(8) Organocuprates react with aldehydes at −78 °C in minutes; ketones require much higher temperature, whereas esters are practically inert even at rt: (a) Posner, G. H.; Whitten, C. F.; McFarland, P. E. *J. Am. Chem. Soc.* **1972**, *94*, 5106. For recent overviews of organocuprates, see: (b) Lipshutz, B. H. Reference 3a; Vol. 1, p 107. (c) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (d) Lipshutz, B. H. In *Organometallics in Synthesis*; Schlosser, M., Ed.; J. Wiley & Sons; Chichester, 1994; p 283.

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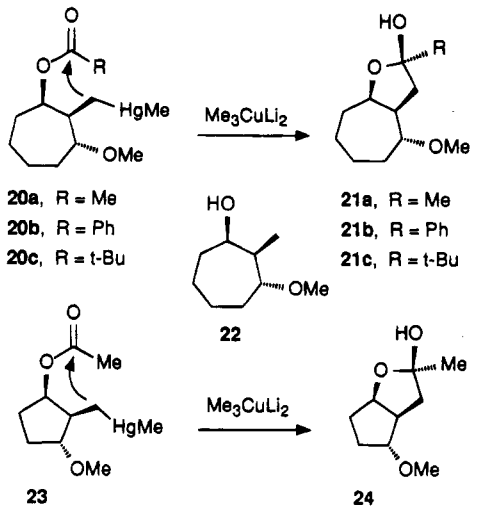
**Scheme 4**




the ester carbonyl as they are in the case of aldehydes (e.g., **1** and **2**).[6]

The model organomercurials were prepared by mercury(II)-mediated ring opening of cyclopropyl alcohols **4**–**6**, which, in turn, were obtained via the stereoselective Simmons–Smith cyclopropanation of the corresponding allylic alcohols.[10] As expected, the reaction rate of the ring-opening is dependent on the nature of the mercury(II) salt. Of the three reagents used, $(AcO)_2Hg$, $(CF_3CO_2)_2Hg$, and $Hg(NO_3)_2$, acetate is least electrophilic and reacts relatively slowly; nitrate is the fastest. When the reaction was run in methanol, $(AcO)_2Hg$ gave acetate **7**[10] (after NaCl workup), whereas treatment with $Hg(NO_3)_2$ resulted in the formation of nitrate **8**.[10] Hence, even $NO_3^-$ is sufficiently nucleophilic to compete with the solvent in capturing the electrophilic intermediate. On the other hand, $(CF_3CO_2)_2Hg$/MeOH afforded methoxy derivative **9** (86%),[11] reflecting the very weak nucleophilicity of $CF_3CO_2^-$.[12] In order to avoid complications associated with the presence of potentially reactive AcO– or $O_2NO$– groups, we have concentrated our attention on the methoxy series. Methylation[6] of **9** with MeCu furnished the methylmercurio derivative **10** (88%), required for further study.

In analogy to the above series, cycloheptane derivative **5**[10] was regioselectively opened to give, after NaCl workup, chloromercurio derivative **11** (90%), methylation of which with MeCu afforded the desired methylmercurio derivative **12** (80%). Cleavage of the cyclopentane analogue **6** turned out to be less regioselective, producing a mixture of **13** and **15** in *ca.* 2:1 ratio (82%), which was directly methylated with MeCu. The desired methylmercurio derivative **14** was then obtained by chromatographic separation.

The six-membered ring acetate **16a**, obtained by acetylation of **10** ($Ac_2O$, DMAP; 94%), was treated with an excess of $Me_2CuLi$ in $Et_2O$, but no reaction was observed. On the other hand, when $Me_3CuLi_2$ was used as the reagent, a fast conversion into the hydroxy ketone **19a** took place (−78 °C, 10 min; 70% isolated yield).[11,13,14] The reaction turned out to be very clean; only traces of unidentified byproducts were detected. Since MeLi itself gives a complex mixture of products, it is obvious that Cu plays a crucial role in the reaction, so that the reactivity must originate from $Me_3CuLi_2$ (or a similar species) rather than from free MeLi.

The acyl migration can be rationalized as follows: the organometallic species **17**, generated from **16a**, reacted via attack on the neighboring ester group and the corresponding intermediate **18** subsequently collapsed to **19a** on aqueous workup. The benzoate **16b** and pivalate **16c**[15] exhibited the same behavior, producing **19b** (60%) and **19c** (55%).

The reaction of the seven-membered ring acetate **20a** with $Me_3CuLi_2$ gave rise to a mixture of acetal **21a**[16] (37%) and the hydrolysis product **22** (23%).[17] On the other hand, the corresponding benzoate **20b**[15] and pivalate **20c**[15] gave the acetals **21b** (65%) and **21c** (59%), respectively, in good yields as the sole products.

With the 5-membered ring analogue **23**, the reaction was again successful: on treatment with $Me_3CuLi_2$, **23** afforded the expected acetal **24** (57%) as a single product.

Two mechanisms of the intramolecular addition can be envisaged: (a) second methylation of $MeHg-CH_2R$ to generate $[Me_2Hg-CH_2R]^-$ and (b) transmetalation[19] or formation of a cluster [Me,Cu,Li,Hg]R[19] as the reactive intermediate. More experiments will be needed to resolve this issue.

In summary, on treatment with $Me_3CuLi_2$, organomercurials containing a suitably located ester group (**16**, **20** and **23**) give the corresponding acetal species (**18**, **21**, and **24**, respectively). This unique transformation represents a novel, mild way for *intramolecular* addition of organometallics across a carbonyl group.

**Acknowledgment.** We thank EPSRC and Glaxo for a CASE award to J.M.G. and Dr. Jiří Šrogl for stimulating discussions.

**Supplementary Material Available:** Experimental procedures and spectral and analytical data for the new compounds (9 pages).

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(11) All yields refer to isolated (preparative) yields of the often volatile compounds. The genuine yields (e.g., the "GC yields") were, in most cases, much higher.

(12) For nucleophilicity, see: (a) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; p 369. (b) Reference 1; p 348.

(13) All new compounds were characterized by spectral and analytical methods.

(14) Reinvestigation of the reaction of **2** with $Me_2CuLi$ revealed that a large excess of the reagent has to be used;[6] with only 1 equiv of $Me_2CuLi$ (prepared from 1 equiv of CuI and 2 equiv of a freshly titrated MeLi) no reaction occurs. By contrast, 1.1 equiv of $Me_3CuLi_2$ induced an essentially quantitative conversion of **2** into **3** at −78 °C in 10 min.

(15) Prepared from the parent alcohol by acylation with $(PhCO)_2O$/$Et_2O$ (rt) or *t*-BuCOCl/THF (reflux), respectively, in the presence of 4-(*N*,*N*-dimethylamino)pyridine.

(16) The configuration at the anomeric center has not been experimentally established. However, MM2 calculations suggest that the anomers with *endo*-OH (i.e., **21**) are more stable.

(17) (a) Lithium methyl(α-thiophenyl)cuprate gave a similar mixture of **21a** (41%) and **22** (22%), whereas MeCuCNLi effected simple deacetylation. No reaction was observed with $Me_2CuMgCl$ at low temperature (−78 °C), while a complex mixture resulted on heating to 0 °C. Finally, the reagent generated from $(Bu_3P)CuI$ and MeLi turned out to be inert. (b) Another possible approach would be the activation of the carbonyl by a strong Lewis acid, such as $MoCl_5$ or $AlCl_3$.[6,18] However, treatment of **20a** with $MoCl_5$ resulted only in the demethylation and chlorination: $RCH_2HgMe \rightarrow RCH_2HgCl$ (14%) + $RCH_2Cl$ (60%).

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(19) (a) For the transmetalation $RHgX \rightarrow RCu$, see: Bergbreiter, D. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1974**, *96*, 4937. (b) For a review on transmetalations in organocopper chemistry, see: Wipf, P. *Synthesis* **1993**, 537.