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Communications

Heteroatom-Assisted Substitution of Acyclic Secondary Tosylates with Lithium Dialkylcuprates: An Expedient Route to Stereochemically Defined Deoxypropionate and Related Biosynthetic Subunits

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Summary: Secondary tosylates of a number of acyclic molecules can be easily displaced with diorganocuprates with complete inversion of configuration. The displacement reaction is greatly facilitated when a hetero atom (S or O) is proximal to the nucleofugal group and elimination is kept to a minimum.

Sir: One of the more sought after reactions in synthetic organic chemistry is the displacement of a nucleofugal group by *a carbon nucleophile with inversion of configuration.* The most popular reagents for this purpose have been the lithium diorganocuprates[1] or their more recent versatile variants.[2] Extensive studies during the past 20 years have been concerned with synthetic, mechanistic, and stereochemical aspects of the substitution reactions of the so called lower order cuprates,[3-5] as well of the higher order, mixed reagents.[6,7] In practice, halides and tosylates of simple acyclic and cyclic hydrocarbons have proved to be suitable nucleofugal groups, but not without considerable differences in reactivity patterns.[5,7,8]

In spite of their overall importance, the potential of organocopper reagents in substitution reactions at secondary carbon centers in synthetically versatile substrates has remained largely unexploited.[9] The main reasons have been ascribed to modest or unpredictable yields, compounded by the propensity for elimination and/or reduction rather than substitution.[10]

In connection with our studies on the total synthesis of ionomycin[11] and related natural products that are derived from the deoxypropionate biosynthetic pathway, we had occasion to explore the potential of organocuprates in a direct C-methylation of appropriately substituted acyclic carbon chains. We report herein the highly beneficial effect of a strategically placed heteroatom such as sulfur or oxygen, as part of the functional group array of the nucleofugal substrate in the reaction of *acyclic secondary tosylates* with lithium dialkylcuprates. A global view of the heteroatom-assisted displacement reactions is shown in Scheme I, and specific examples are listed in Tables I and II, where a number of optically pure acyclic tosylates were used as substrates. The stereochemical outcome in all cases studied was that resulting from complete inversion of configuration,[3,4] generally in excellent yields and with minimum elimination/reduction byproducts (<10%).

Although mechanistic studies are still in progress, it is clear that the heteroatom is playing a crucial role and that its location and distance from the site of nucleofugal reactivity are critical. With the (methylthio)methyl and methoxymethyl ethers, optimum conditions are reached

(1) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980 and references cited therein; *Org. React.* **1975**, *22*, 253.
(2) Lipshutz, B. H. *Synthesis*, **1987**, 325. Lipshutz, B. H.; Kozlowski, J.-A. *Tetrahedron* **1984**, *40*, 5005.
(3) For some early original contributions, see: Whitesides, G. M.; Fischer, W. F., Jr.; SanFilippo, J., Jr.; Bashe, R. W.; House, H. O. *J. Am. Chem. Soc.* **1969**, *91*, 4871. Corey, E. J.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 3911; **1968**, *90*, 5615, and references cited therein.
(4) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7783.
(5) Ashby, E. C.; DePriest, R. N.; Tuncay, A.; Srivastava, S. *Tetrahedron Lett* **1982**, *23*, 5251, and earlier papers.
(6) Lipshutz, B. H.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 4696.
(7) Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672. Lipshutz, B. H.; Wilhelm, R. S. Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928.
(8) Johnson, C. R.; Dutra, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7777.
(9) For some recent examples, see: Mori, K.; Sugai, T. *Synthesis* **1982**, 752. Itoh, Y.; Yonekawa, Y.; Sato, T.; Fujisawa, T. *Tetrahedron Lett.* **1986**, *27*, 5405. Hirama, H.; Noda, T.; Ito, S. *J. Org. Chem.* **1985**, *50*, 127.
(10) For examples in natural product synthesis, see: Still, W. C.; Galynker, I. *J. Am. Chem. Soc.* **1982**, *104*, 1774; *Tetrahedron Lett.* **1982**, *23*, 4461. Trost, B. M.; Klun, T. P. *J. Org. Chem.* **1980**, *45*, 4256; see also ref 6, 8 concerning elimination/reduction during organocuprate displacement reactions of tosylates and halides.
(11) Hanessian, S.; Murray, P. J. *Can. J. Chem.* **1986**, *64*, 2231.

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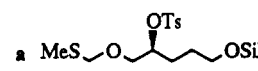
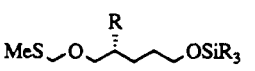
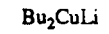
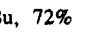
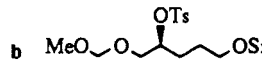
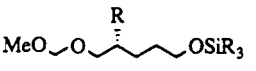
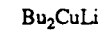
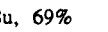
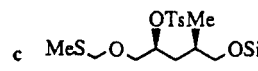
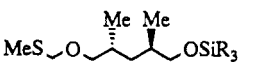
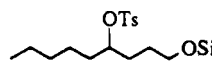
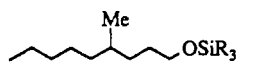
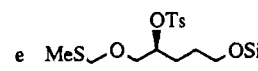
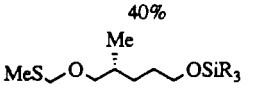
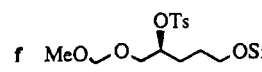
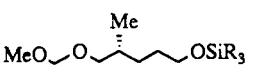
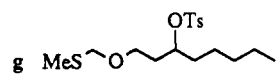
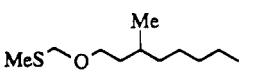
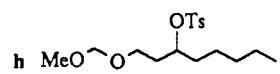
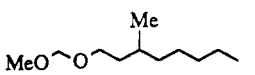
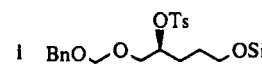
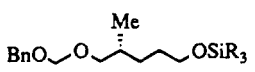
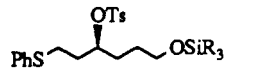
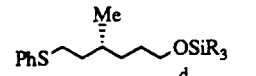
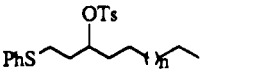
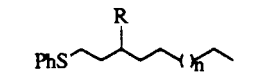
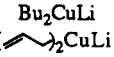
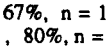
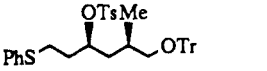
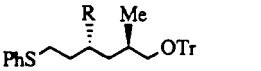
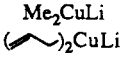
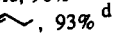
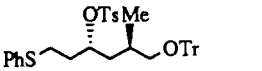
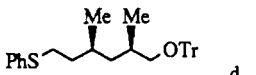
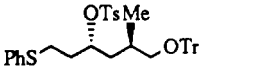
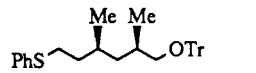
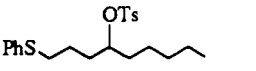
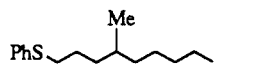
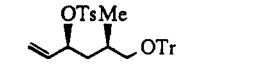
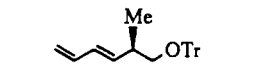
Table I. (Methylthio)methyl- and Methoxymethyl-Assisted Cuprate Displacements

entry	substrate[a]	cuprate[b]	product, %[c]
a	 1	Me_2CuLi	 2, R = Me, 83%
	R_3 = t-butyldiphenyl	Bu_2CuLi	3, R = Bu, 72%
			4, R =  , 98%
b	 5	Me_2CuLi	 6, R = Me, 65%
		Bu_2CuLi	7, R = Bu, 69%
			8, R =  , 79%
c	 9	Me_2CuLi	 10, 82%
d	 11	$Me_2CuLi - Me_2S$	 12, 25%
		Me_2CuLi	40%
e	 13	$Me_2Cu(CN)Li_2$	 14, 68%
f	 15	$Me_2Cu(CN)Li_2$	 16, 54%
g	 17	Me_2CuLi	 18, 40%
h	 19	Me_2CuLi	 20, 38%
i	 21	Me_2CuLi	 22, 45%

[a] Except for compounds 11, 17, and 19, all tosylates were prepared in optically pure form from readily available precursors. [b] Unless otherwise stated, the cuprate was in 10 M excess in ether and the reactions were done at −20 °C for 15 h (dimethylcuprates); and for 4.5 h (dibutyl and diallylcuprates). General procedures and physical constants are available in the supplementary material. [c] Yields are of isolated, chromatographically pure products.

Table II. Phenyl Thioether Assisted Cuprate Displacements

entry	substrate[a]	cuprate[b]	product, %[c]
a	 23	Me_2CuLi	 24, 90%[d]
b	 25, n=2	Me_2CuLi	 27, R = Me, 98%, n = 2
	26, n=1	Bu_2CuLi	28, R = Bu, 67%, n = 1
			29, R =  , 80%, n = 1
c	 30	Me_2CuLi	 31, R = Me, 90%[d]
			32, R =  , 93%[d]
d	 33	Me_2CuLi	 34, R = Me, 90%[d]
e	 35	$Me_2Cu(CN)Li_2$	 36, 47%
f	 37	Me_2CuLi	 38, 60%
g	 39	$Me_2Cu(CN)Li_2$	 40
h	41	Me_2CuLi	42, R = Me, 90%
		Bu_2CuLi	43, R = Bu, 50%[e]
i	44	Me_2CuLi	45, 90%[d]

[a] Compounds 23, 30, 33, 35, and 39 were optically pure (see ref 11, 14). [b] Cuprate reactions were done with 10 M excess reagent in ether at −20 °C for 15 h; except for the allyl series 2.5 h, for details see the supplementary material. [c] Yields are of isolated, chromatographically pure products. [d] Contains <10% elimination byproduct which can be separated after oxidation to the sulfone with mCPBA, −20 °C, 80%. [e] Reaction at 0 °C, 15 h.

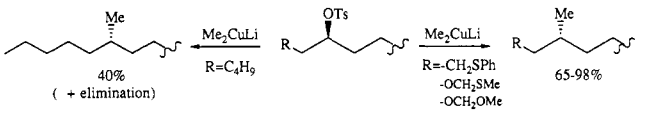
with a *vicinal* disposition to the tosyloxy group (Table I, A–C). In the case of the phenyl thioether, a separation of two methylene units is best (Table II, A–D, H, I). Beyond these limits, yields of substitution gradually decrease with increasing distance. (Table I, G, H; Table II, F). Moreover, the electron-donating ability of the sulfur atom is most important, since the reaction fails with sulfones corresponding to entries C and D in Table II. The yields of substitution products are much lower when the heteroatom is altogether absent (Table I, D) or if it is provided externally as in the case of lithium dimethylcuprate–dimethyl sulfide.[12] The allylic tosylate **39** (Table II, G) gave the diene **40** as the only product when treated with dilithio dimethylcyanocuprate. The same reagent was also less satisfactory compared to lithio dimethylcuprate (Table I; F, Table II, E). The diminished reactivity of tosylates toward higher order, mixed organocuprates compared to the lower order homocuprates is well documented.[7] In general, thioethers such as a (methylthio)-methyl ether are better than methoxymethyl ethers, and a phenyl thioether is much preferred to ordinary alkyl ethers, particularly with the less reactive lithium dimethylcuprates (Table I, A, B, I) even when the reagent was in large excess,[7] thus showing a larger affinity of the MTM group for the lower order cuprate and the preference of sulfur to oxygen as a potential coordinating site.[13]

That substitution was taking place with *inversion of configuration*[3-5] at the site of the nucleofugal group was ascertained by chemical and spectroscopic means. Thus ^1H and ^{19}F NMR spectra of the Mosher esters prepared

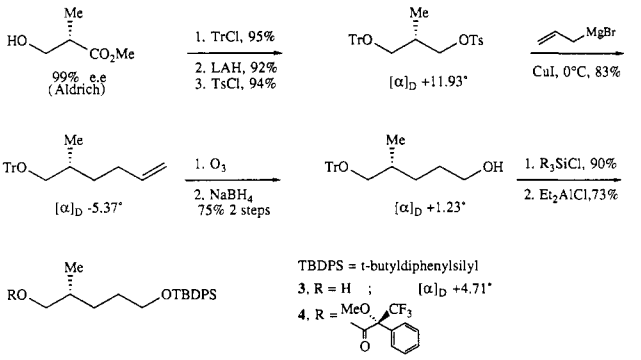
(12) For an in depth study of the reactivity of organocopper reagents in dimethyl sulfide, see: Bertz, H. S.; Dabbagh, G. *Tetrahedron* **1989**, *45*, 425. See also: House, H. O.; Lee, T. V. *J. Org. Chem.* **1978**, *43*, 4369. House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460. Hirama, H.; Noda, T.; Ito, S. *J. Org. Chem.* **1985**, *50*, 127. Kojima, Y.; Wakita, S.; Kato, N. *Tetrahedron Lett.* **1979**, 4577.

(13) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

Scheme I



Scheme II



from compounds, **3**, **8**, **10**, and **31** (where the MTM, MOM, or trityl groups were cleaved and the products esterified), showed resonance and splitting patterns expected of pure diastereomers. This was further substantiated by preparing and analyzing the Mosher ester from the racemic alcohol corresponding to **3** as a representative example. Independent chemical proof was obtained by an unambiguous synthesis starting with (*S*)-methyl 2-methyl-3-hydroxypropionate of 99% optical purity as shown in Scheme II.

The stereochemical identity of **33** was proved by comparison with a sample previously prepared via the butenolide replication strategy.[11,14] Entry H in Table II illustrates an example of the successful C-substitution of a tosylate ester assisted by a phenylthio group located on a *secondary* carbon atom. The corresponding sulfone gave mostly elimination and reduction.

Finally, the thioether-assisted displacement of a tosyloxy group can be extended to a *double C-methylation* protocol where an isoprenoid 1,5-dimethyl relationship can be efficiently created (Table II,I). As in the other examples shown in Table II, not only was elimination kept to a minimum (<10%) but no products resulting from the incorporation of methyl groups at the primary carbon atoms were observed, thus excluding the intermediacy of thietanium ions.

The conceptual basis for the heteroatom-assisted C-alkylation of tosyloxy groups reported herein[15] is the result of a rational and deductive analysis of the requirements for successful reagent and reaction design.[14] In the present case, we capitalize on the known coordinating ability of a heteroatom such as sulfur[16] or oxygen[17] to copper with the intention of enhancing the reactivity of the cuprate[18] and exploiting possible proximity effects, thus maximizing nucleofugal reactivity. Generally such functionality is often found in many intermediates for synthesis, either as O-protective groups (MTM, MOM), or as latent functionality (thioether), hence the practicality of the method for direct substitution of tosyloxy esters in acyclic systems similar to those listed in Tables I and II.[19]

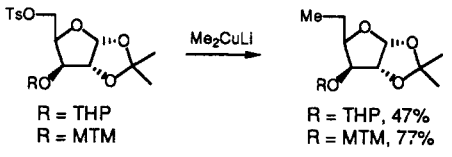
The technology we report is one of the most expedient and efficient ways for a C-substitution of a secondary alcohol via its tosylate with inversion of configuration. It should prove to be most useful in the construction of acyclic subunits comprising one or more *C*-methyl (alkyl) groups as can be found in a variety of natural products arising from the deoxypropionate, acetate, butyrate, and isoprenoid biosynthetic pathways such as ionophores,[20] macrolides,[21] and pheromones.[22,23] The extension of this methodology to other synthetically useful systems is under active study in this laboratory.

Acknowledgment. We thank NSERCC and FCAR for financial assistance and Dr. Phan Viet Tan for helping with the ^{19}F NMR measurements.

Supplementary Material Available: Selected experimental procedures; ^{1}H, ^{13}C, and ^{19}F NMR data; and physical constants of intermediates and products (62 pages). Ordering information is given on any current masthead page.

(14) Hanessian, S. *Aldrichimica Acta* **1989**, *22*, 3.

(15) Although primary tosylates are readily displaced by organocuprates,[1,8] the reactivity can be further enhanced by the presence of an MTM group in the vicinity of the nucleofugal site. Compare for example Pougny, J.-R. *Tetrahedron Lett.* **1984**, *25*, 2363, where a THP group was used with the results shown below from this work.



(16) For an example of the influence of a chelating thioether in the addition of organocopper reagents to α,β-unsaturated acetals, see: Alexakis, A.; Mangeney, P.; Ghribi, A.; Marek, S.; Sedrani, R.; Guir, C.; Normant, J. *Pure Appl. Chem.* **1988**, *60*, 49. See also: McCormick, D. B.; Griesser, R.; Siegel, H. In *Metal ions in Biological Systems*; Siegel, H., Ed.; Marcel Dekker: New York, 1974; Vol. 1, p 214. Nikles, D. E.; Andersen, A. B.; Urbach, F. L. In *Copper Coordination Chemistry: Biochemical and Inorganic Perspectives*; Karlin, K. D., Zubieta, J., Eds.; Adenine Press: New York, 1985; p 207.

(17) Larchevêque, M.; Tamagan, G.; Petit, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 31.

(18) It is conceivable that the hetero atoms in phenylthio, MTM, or MOM ethers are enhancing the reactivity of the cuprate by coordination with empty Cu_4p orbitals, see: Stewart, K. R.; Lever, J. R.; Whangbo, M.-H. *J. Org. Chem.* **1982**, *47*, 1472. See also ref 12.

(19) The reaction failed with *trans*-1-(tosyloxy)-2-((methylthio)methoxy)cyclohexane. Other cyclic systems are under investigation.

(20) Wierenga, W. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1981; Vol. 4, p 263.

(21) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489.

(22) Mori, K. *Tetrahedron* **1989**, *45*, 3233.

(23) Compound **26** is an immediate precursor of the pheromone 3-methylnonane, see ref 6 and references cited therein.