~200-fold less active against avian myeloblastosis virus reverse transcriptase.

Chebulagic acid is the most potent inhibitor of mammalian DNA topoisomerase I yet reported.[21] While its molecular mechanism of topoisomerase I inhibition is uncertain at present, chebulagic acid is 10–50-fold more active than camptothecin[5] or 10-hydroxycamptothecin[6d] as an inhibitor of the overall process of DNA relaxation (cf. Figure 1). Chebulagic acid was >800-fold more potent than these camptothecins in diminishing the initial enzyme-mediated DNA nicking reaction.

(21) Both calf thymus and human colon adenocarcinoma (Colo 201) topoisomerase I were inhibited by 1.

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Silacupration of Oxabicyclic Compounds. An Interrupted Ring Opening Reaction

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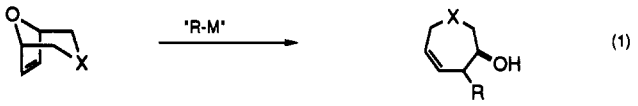
Summary: Oxabicyclo[3.2.1]octenes have been found to undergo silacupration when treated with $(PhMe_2Si)Cu\cdot LiCN$. Ring closure of the cuprate onto a remote carbonyl group at C-3 provides tricyclic compounds. Trapping experiments with a variety of other electrophiles prior to the closure reaction have also been achieved.

We have recently reported the addition/ring-opening reactions of oxabicyclo[3.2.1] and -[2.2.1] compounds with organocuprate and organolithium reagents. Complimentary stereochemistry is observed using the two classes of reagents. Organolithium reagents effect a net S_N2' reaction with retention of stereochemistry (i.e., for X = CHOR', the cis product is obtained) whereas cuprates promote an S_N2' reaction with overall inversion (the trans product is obtained for X = C=O), eq 1.[2,3] We chose to examine the

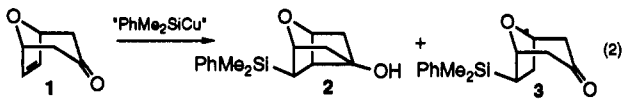


(1)

reactivity of silylcuprates and silylcopper reagents as nucleophiles to promote the ring opening due to the synthetic utility of the allylsilane which would result from ring opening.[4] We report an alternative pathway for this class of cuprates which represents a novel interrupted ring-opening process and demonstrate that silacupration of strained olefins is a facile process.

Silylcuprates and silylcopper reagents have been shown to be reactive nucleophiles toward a variety of electrophilic partners including allylic and propargylic acetates, enones, and ynones.[5] Unactivated acetylenes and allenes also undergo silacupration.[6] To our knowledge, the silacupration of simple unactivated olefins has not been reported.[7]

Treatment of 8-oxabicyclo[3.2.1]oct-6-en-3-one (1, X = C=O) with $(PhMe_2Si)Cu\cdot LiCN$ in THF at 0 °C for 1 h yields a product whose spectra are inconsistent with the expected product, eq 1, R = $PhMe_2Si$. While the product contained a phenyldimethylsilyl group, no olefinic resonances were observed, and the oxabicyclo ring was intact. Furthermore, no carbonyl stretch was observed in the infrared spectrum. We speculated that silacupration of the olefin had occurred followed by ring closure onto the ketone to generate the novel cyclobutanol **2**, eq 2. The



(2)

stereochemistry of the silicon-bearing carbon could not be conclusively determined by ^1H or ^{13}C NMR. Previous studies had established that attack from the endo face was the usual course of events in oxabicyclo[3.2.1] openings with organocuprates.[2] However, examination of molecular models indicated this product would experience severe nonbonded interactions which would disfavor the subsequent closure reaction. X-ray crystallography of the 3,4-dinitrobenzoate ester of **2** confirmed that, in fact, the silyl group had attacked from the exo face of the oxabicyclic system. Since both the stereochemistry of attack and failure to undergo ring opening were novel results in this system, an investigation of the generality of this phenomenon was undertaken.

The presence of copper is essential for controlled reactivity in this transformation since treatment of **1** with

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(2) (a) Lautens, M.; DiFelice, C.; Huboux, A. *Tetrahedron Lett.* **1989**, *30*, 6817. (b) Lautens, M.; Abd-El-Aziz, A. S.; Lough, A. *J. Org. Chem.* **1990**, *55*, 5305.

(3) For the reactions of [2.2.1] systems with cuprates or organolithium reagents, see: (a) Lautens, M.; Smith, A. C.; Abd-El-Aziz, A. S.; Huboux, A. H. *Tetrahedron Lett.* **1990**, *31*, 3253. (b) Arjona, O.; Fernandez de la Pradilla, R.; Garcia, E.; Martin-Domenech, A.; Plumet, J. *Tetrahedron Lett.* **1989**, *30*, 6437.

(4) The utility of allyl silanes in organic synthesis is well documented, see: (a) Fleming, I. *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds.; Pergamon Press: New York, 1979. (b) Colvin, E. *Silicon in Organic Synthesis*; Butterworths: London, 1981. (c) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: New York, 1983. (d) Larson, G. L. *The Chemistry of Organic Silicon Compounds*; Patai, S., Ed.; Wiley Interscience: Toronto, 1989; Part 1, Chapter 11. (e) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57.

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(6) (a) Fleming, I.; Roessler, F. *J. Chem. Soc., Chem. Commun.* **1980**, 276. (b) Fleming, I.; Newton, T. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1805. (c) Fleming, I.; Rowley, M.; Cuadrado, P.; Gonzalez-Nogal, A. M.; Pulido, F. J. *Tetrahedron* **1989**, *45*, 413. (d) Fleming, I.; Landais, Y.; Raithby, P. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 715.

(7) Silylzirconation and silylsilylation of olefins have been reported, see: (a) Arnold, J.; Engeler, M. P.; Elsner, F. H.; Heyn, R. H.; Tilley, T. D. *Organometallics* **1989**, *8*, 2284. (b) Hayashi, T.; Kawamoto, A. M.; Kobayashi, T.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1990**, 563.

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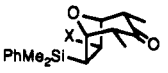
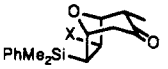
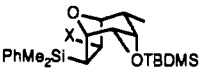
Table I. Silacupration of Oxabicyclic Compounds

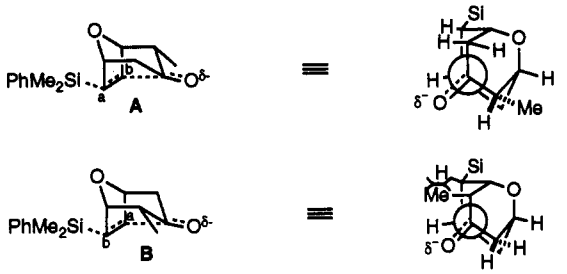
no.	substrate	time[a] (h)	adduct	yield[b] (%)
1		0.5		
	4		**5a** X = H	quant
			b = OH	quant
			c = Me	quant
2	**4**	3		
			6	59
3		0.25		
	7		**8a** X = H	98[c]
			b = OH	78[d]
4	**7**	1		
			9	53%[c]
5		1		
	10		**11a** X = H	quant
			b = OH	31[f]
			c = I	10[g]
			d = $SnBu_3$	65
			e = $SnMe_3$	82

[a] 1.1 equiv of $(PhMe_2Si)Cu{\cdot}LiCN$ in THF. [b] Isolated yields of analytically pure material. [c] A 6:1 mixture of regioisomers. [d] A 4:1 mixture of regioisomers. [e] A 24:1 mixture of regioisomers. [f] Accompanied by 11a (60%). [g] This compound rapidly reconverted to 10 upon standing.

phenyldimethylsilyl lithium gives a complex mixture of products. We find that whereas both $(PhMe_2Si)Cu{\cdot}LiCN$ and $(PhMe_2Si)_2CuCNLi_2$ undergo rapid silacupration with all the compounds examined, their tendency to attack the remote carbonyl group is quite different. Thus, a 2.2:1 mixture of **2**:**3** is isolated in 95% combined yield upon treatment of **1** with $(PhMe_2Si)_2CuCNLi_2$ whereas only **2** is isolated following treatment with $(PhMe_2Si)Cu{\cdot}LiCN$. The substituents on the cyclohexane ring have a significant impact on the rate of the cyclization reaction as well, Table I, entry 1. The dimethyl derivative **4** undergoes rapid silacupration with $(PhMe_2Si)Cu{\cdot}LiCN$ or $(PhMe_2Si)_2CuCNLi_2$, but almost no ring closure was observed under the latter conditions. Instead, **5a** was isolated in quantitative yield. The ring closed compound **6** was formed after extended reaction (3 h) in the presence of the silylcopper reagent, entry 2. The sluggishness of the ring closure provided an opportunity to trap the intermediate with an electrophile such as methyl iodide which furnished **5c** in quantitative yield, entry 1.[8]

An interesting and, to our knowledge, unprecedented trapping reaction occurs upon adding the intermediate from silacupration of **4** onto dry silica gel. β-Hydroxy silane **5b** was isolated in quantitative yield.[9] Attempts to trap the reactive intermediate with gaseous oxygen in situ did not produce appreciable quantities of the alcohol. The silica gel surface clearly plays an important role in mediating this process.[10] The hydroxysilane instantaneously undergoes a base-catalyzed Peterson elimination when treated with KH in DMF, reverting quantitatively back to **4** thus confirming the syn orientation of the $PhMe_2Si$ and OH groups on the ring.[11]

Regioselective addition of Si–Cu to the olefin was observed when the unsymmetrical oxabicyclic compound **7**, bearing a single methyl group, was reacted with $(PhMe_2Si)Cu{\cdot}LiCN$.[12] Protonation immediately following cuprate addition afforded a 6:1 mixture of **8a** and its regioisomer. By allowing the reaction to proceed for an extended period, ring closure afforded cyclobutanol **9** with higher selectivity (24:1). Examinations of molecular models and Newman projections looking along the incipient C–C bond shows an evolving steric interaction between the methyl group and a pseudoaxial hydrogen in structure B which is absent in A. Molecular mechanics calculations indicate that A is more stable than B by 1.5 kcal. If the silacupration is reversible, it is possible to rationalize the improved selectivity of the cyclobutanol compared to the ketone if the ring closure occurs faster for isomer A.



We have previously noted that a ketone at C-3 was essential for *organo*cuprate openings of oxabicyclic systems, and we were interested in determining the reactivity of a silylcuprate with silylether **10**.[2a] In the event, reaction occurred smoothly and furnished the addition product **11a**. The rate of addition to the olefin is somewhat slower than for the substrates bearing a carbonyl group. In contrast to **4**, the trapping reaction of **10** with O_2 on silica gel gives **11b** in 31% yield along with **11a**, the product from simple protonation. However, several other electrophiles were found to be reactive including NIS, methyl iodide, and trimethyl- or tributylstannyl chloride, entry 5. These latter two products are 1,2-dimetalated compounds resulting from a net syn silylstannylation of an olefin.[13]

Silacupration of the alkoxide, prepared by deprotonation of **12** with *n*-BuLi, was carried out at −40 °C due to competing side reactions of intermediate **13**. Reaction of **13** with water gave the protonated alcohol whereas addition of NIS to **13** gave an iodide which quickly underwent intramolecular displacement by the hydroxyl group. Compound **14** was isolated in 85% yield in one pot from **12**, eq 3. This sequence is a net exo–endo difunctionalization of the olefin.

The failure of the silacuprate to induce ring opening is intriguing. The stereochemistry of the incoming silyl nucleophile is opposite to that observed in other [3.2.1] re-

(8) The question as to whether the ring closure was reversible under the reaction conditions was probed by attempting to trap the intermediate *following* the closure process with an electrophile other than a proton. However, addition of methyl iodide after a 3-h period (by which time the closure was judged by TLC to have occurred) gave **6** with none of **5c**.

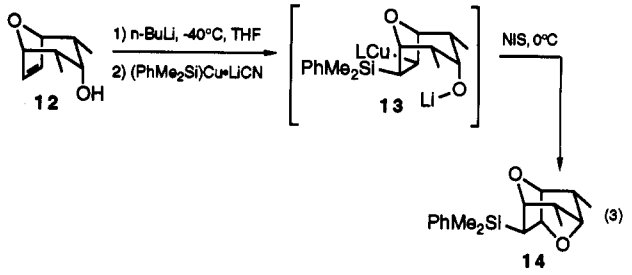
(9) The usual course of events in organocuprates is an oxygen promoted oxidative coupling, see: (a) Whitesides, G. M.; SanFilippo, J.; Casey, C. P.; Panek, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 5302. (b) Camus, A.; Marsich, N. *J. Organomet. Chem.* **1972**, *46*, 385.

(10) The effect of adsorbents has been reviewed, see: (a) Posner, G. H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 487. (b) McKillop, A.; Young, D. W. *Synthesis* **1979**, 401, 481.

(11) Ager, D. J. *Org. React.* **1990**, *38*, 1.

(12) Treatment with $(PhMe_2Si)_2CuCNLi_2$ was much less selective (1.3:1 ratio of regioisomers).

(13) For studies on the palladium-catalyzed bis-silylation of an olefin or acetylene, see: (a) Murakami, M.; Andersson, P. G.; Suginome, M.; Ito, Y. *J. Am. Chem. Soc.* **1991**, *113*, 3987. (b) Yamashita, H.; Catellani, M.; Tanaka, M. *Chem. Lett.* **1991**, 241. (c) Ito, Y.; Suginome, M.; Murakami, M. *J. Org. Chem.* **1991**, *56*, 1948.



actions with organocuprates. Anti attack of an organocuprate, relative to the bridging oxygen, may be required for a successful ring opening in [3.2.1] systems.[13] In this mode of attack, as bond formation occurs, steric compression created by the incoming nucleophile may provide a driving force for the opening. The successful silacupration of **10** and **12** suggests that the reactivity arises from the release of strain in the olefin rather than any special features associated with the oxygen bridge or the ketone.[14]

(14) This supposition was proven correct by the successful silacupration of 2,4-dimethylbicyclo[3.2.1]oct-5-en-3-one with $(PhMe_2Si)$-Cu·LiCN or $(PhMe_2Si)_2CuCNLi_2$. The behavior of this compound was nearly identical to the oxabicyclic analogue. Similarly, treatment of a bicyclo[2.2.1] system with $(PhMe_2Si)$Cu·LiCN gave the product from silacupration in 87% yield. Thus the reaction appears to be general for strained olefins.

In conclusion, we note that in contrast to the displacement reactions of other electrophiles with alkyl- vs silylcuprates, significant differences exist between silylcuprates and organocuprates in addition reactions with oxabicyclo[3.2.1] compounds. The stereochemistry of attack is exo, with no more than 5% endo adduct observed in any case. While ring opening follows the addition for organocuprate nucleophiles, silylcuprates add to these substrates without subsequent ring opening. Substituted oxabicyclic compounds undergo silacupration and ring closure but at significantly slower rates. The decrease in rate of ring closure provides an opportunity to trap the intermediate with a variety of electrophiles so as to doubly functionalize the olefin. The use of silica gel to oxygenate the cuprate is a particularly novel process which is currently under investigation.

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Supplementary Material Available: General and specific procedures and characterization for the compounds reported (5 pages). Ordering information is given on any current masthead page.

Remote Directed Metalation of Biaryl *o*-Carbamates. Ring to Ring Carbamoyl Transfer Route to Biaryls, Dibenzo[*b*,*d*]pyranones, and the Natural Fluorenone Dengibsin

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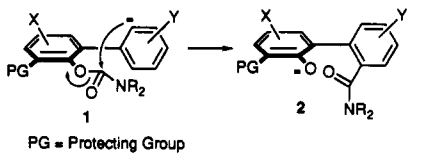
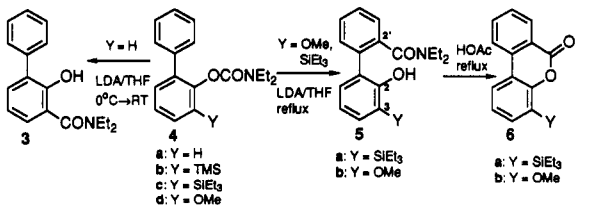
Summary: A new remote metalation, carbamoyl transfer process (Scheme I), is demonstrated and elaborated for the regiospecific synthesis of highly hindered biaryls, dibenzo[*b*,*d*]pyranones (Table I), and the naturally occurring fluorenone dengibsin (**15**).

We wish to report on a new carbanion-induced ring to ring carbamoyl transfer reaction **1** → **2** (Scheme I), formally a remote anionic Fries rearrangement,[1] which provides general regioselective entries into sterically encumbered biaryls and substituted and condensed dibenzo[*b*,*d*]pyranones and fluorenones, including the natural product dengibsin (**15**). The discovery of this reaction was based on the logic that, by prior protection of the normal site of metalation in **1**, alternate ring remote deprotonation is thermodynamically favored[2] by a complex induced proximity effect (CIPE),[3] a useful mechanistic concept[4] which posits that acid–base coordination may identify

Scheme I



Scheme II



weakly acidic remote C–H sites for potential deprotonation. Subsequent carbamoyl transfer, driven by departure of phenolate ion, a good leaving group, then leads to the 2,2′-substituted product **2**. Since this new carbanionic transformation may be closely linked to the versatile directed ortho metalation[5] and aryl boronic acid–aryl X (X = Br, OTf)[6] cross-coupling regimens, it has promising

(1) For the ortho equivalent, see: Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935. For a carbamoyl transfer from a benzylic alcohol induced by metal–halogen exchange, see: Lamas, C.; Castedo, L.; Dominguez, D. *Tetrahedron Lett.* **1990**, *31*, 6247.

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(3) The synthetic advantage of this tenet has been previously provided in regiospecific routes to 9-phenanthrols and fluorenones: (a) Fu, J.-m.; Sharp, M. J.; Snieckus, V. *Tetrahedron Lett.* **1988**, *29*, 5459. (b) Fu, J.-m.; Zhao, B.-p.; Sharp, M. J.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 1683.

(4) For 2,2′-dideprotonation of biphenyl driven by double lithium bridging stabilization, see: Ashe, A. J., III; Kampf, J. W.; Salva, P. M. *J. Org. Chem.* **1990**, *55*, 5558 and references cited therein.

(5) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(6) Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405 and references cited therein. Fu, J.-m.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1665 and references cited therein.

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