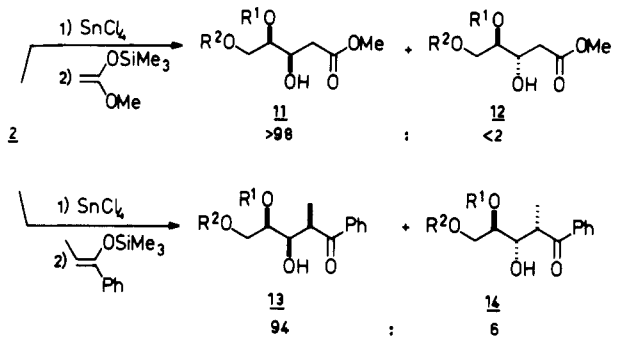
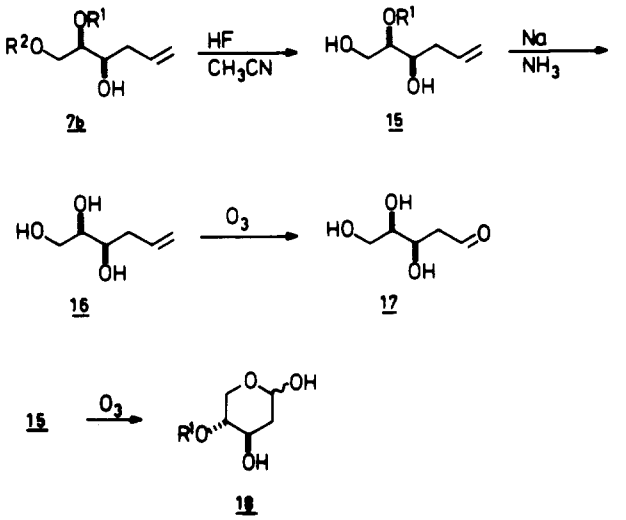


not formed. On the basis of previous work,[1] we tentatively assign the simple diastereoselectivity to be syn. In these aldol additions, $TiCl_4$ is less efficient.[5] Reversal of diastereofacial selectivity results upon using the nonchelating *Z* triisopropoxytitanium enolate of propiophenone[1b-d] in THF (−78 °C/16 h; >98% conversion), the ratio of **13**/**14** being 10:90.

The configurational assignments are based primarily on chemical correlation.[5] For example, the chelation-controlled adduct **7b** (entry 4 of Table I) was first selectively deprotected to form **15**. Debenzylation afforded the known triol **16** (identical ^{13}C NMR data),[10a] which is a precursor of 2-deoxy-D-*threo*-pentose (**17**).[10] The regiospecifically



monobenzylated derivative **18** is accessible by ozonolysis of **15**; this is an illustration of the use of **2** having two different protective groups.

In summary, **2** is a key compound for synthetically useful transformations. The main advantage relative to the classical acetonide of glyceraldehyde[2] has to do with the fact that both syn and anti adducts are accessible, depending upon the nature of the reagent. The acetonide reacts either nonselectively, or leads preferentially to the anti adducts.[2,11] Concerning the choice of organometallic reagent, weakly Lewis acidic compounds $RTi(OCHMe_2)_3$ and the related triisopropoxytitanium enolates constitute a viable method for non-chelation-controlled Grignard-type and aldol additions to α-alkoxy aldehydes,[1,6] regardless of whether additional alkoxy groups are present or not. Chelation-controlled additions to α,β-dialkoxy aldehydes such as **1** or **2** can be performed with Lewis acidic titanium reagents or sometimes $RMgX/ZnX_2$.[5] In case of methyl addition, $[CH_3Cu]MgBr_2$ works just as well or better.[4] Chelation-controlled aldol additions to **2** are best performed using $SnCl_4$/enol silanes.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Registry No. **2**, 98944-53-7; **3**, 28224-73-9; **4**, 99096-86-3; **5**, 17618-04-1; **6**, 99112-28-4; **7a**, 99096-87-4; **7b**, 99096-89-6; **7c**, 99096-93-2; **8a**, 99096-88-5; **8b**, 99096-90-9; **8c**, 99096-94-3; **11**, 99096-95-4; **12**, 99096-96-5; **13**, 99096-97-6; **14**, 99096-98-7; **15**, 99096-91-0; **16**, 99096-92-1; $PhCH_2Br$, 100-39-0; *t*-$BuMe_2SiCl$, 18162-48-6; $CH_3Ti(OCHMe_2)_3$, 18006-13-8; $CH_2{=}CHCH_2SiMe_3$, 762-72-1; Me_2Zn, 544-97-8; $CH_2{=}C(CH_3)CH_2SiMe_3$, 18292-38-1; $CH_2{=}C(OMe)OSiMe_3$, 36850-80-3; (*Z*)-$CH_3CH{=}C(Ph)OSiMe_3$, 66323-99-7; propiophenone (*Z*)-triisopropyltitanium enolate, 81643-94-9.

Supplementary Material Available: Details of preparation of **2** and representative reactions and NMR data of **7a–b**/**8a–b** (5 pages). Ordering information is given on any current masthead page.

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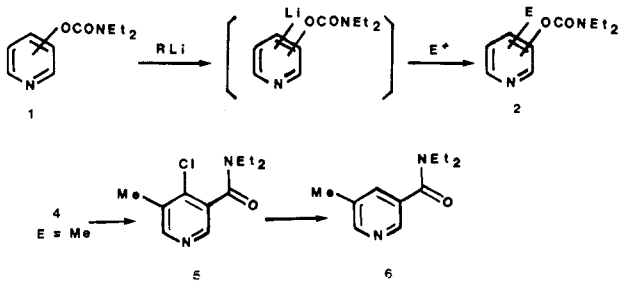
Directed Ortho Metalation of *O*-Pyridyl Carbamates. Regiospecific Entries into Polysubstituted Pyridines

Summary: Ortho-lithiated species of *O*-pyridyl carbamates **1a–c** constitute new synthetic intermediates which provide a variety of polysubstituted pyridines (Table I) by reaction with electrophiles (**2a–c**) and anionic Fries rearrangement (**3**, **4**). Further metalation (**7**), ipso carbodestannylation (**10**, E = I, COMe), and reductive elimination of the carbamate directing group (**5** → **6**) are also described.

Sir: Although a variety of polysubstituted 2- and 4-pyridones and 3-pyridinols are available by classical routes involving de novo pyridine ring-forming reactions,[1] rational methods for the synthesis of functionalized derivatives of these systems are based on the parent systems and are invariably dependent on nonregioselective electrophilic substitution reactions.[2] We report a new, general, and regiospecific method for the preparation of substituted *O*-pyridyl carbamates **2a–c** from the parent isomeric systems **1a–c** involving the powerful ortho metalation directing and 1,3 O → C migratory abilities of the carbamate functionality.[3] This constitutes a new methodology for



(10) (a) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846. (b) Concerning stereoselective allyl addition leading to the diastereomeric form, see: Hoffmann, R. W.; Endesfelder, A.; Zeiss, H.-J. *Carbohydr. Res.* **1983**, *123*, 320. (c) Harada, T.; Mukaiyama, T. *Chem. Lett.* **1981**, 1109.

(11) $PhTi(OCHMe_2)_3$ is a rare exception: Mulzer, J.; Angermann, A.; *Tetrahedron Lett.* **1983**, *24*, 2842.

(12) Dale, J. A.; Mosher, H. S.; *J. Am. Chem. Soc.* **1973**, *95*, 512.

(1) Tieckelmann, H. In "Pyridine and Its Derivatives", Suppl. Pt. 3; Abramovitch, R. A., Ed.; Wiley: New York, **1984**, p 597.

(2) For example, see ref 1, p 800 ff.

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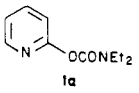
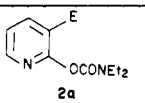
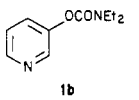
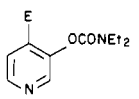
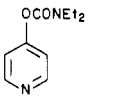
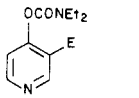
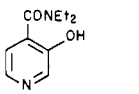
Table I. Synthesis of Substituted *O*-Pyridyl Carbamates 2a-c

substrate	E^+	product	yield,[a] %	mp (bp),[b] °C
 1a		 2a		
1a	MeOD	2a, E = D	87 (56% d_1)[c]	108-110 (0.15 mm)
1a	MeI	2a, E = Me	72	125-130 (0.2 mm)
1a	$ClCONEt_2$	2a, E = $CONEt_2$	66	155-160 (0.1 mm)
1a	Me_3SiCl	2a, E = Me_3Si	52 (62)[d]	95-100 (0.3 mm)
1a	$BrCH_2CH_2Br$	2a, E = Br	59	118-122 (0.1 mm)
1a	I_2	2a, E = I	68	134-138 (0.2 mm)
 1b		 2b		
1b	MeOD	2b, E = D	82 (51% d_1)[c]	101-104 (0.15 mm)
1b	MeI	2b, E = Me	83	98-102 (0.15 mm)
1b	$ClCONEt_2$	2b, E = $CONEt_2$	64	140-143 (0.2 mm)
1b	Me_3SiCl	2b, E = Me_3Si	69 (83)[d]	53-55 (0.04 mm)
1b	Me_3SnCl	2b, E = $SnMe_3$	82	130-134 (0.2 mm)
1b	$BrCH_2CH_2Br$	2b, E = Br	71	130-135 (0.1 mm)
 1c		 2c		
1c	MeOD	2c, E = D	75 (37% d_1)[c]	80-85 (0.15 mm)
1c	MeI	2c, E = Me	72	105-110 (0.1 mm)
1c	$ClCONEt_2$	2c, E = $CONEt_2$	69	132-135 (0.25 mm)
1c	Me_3SiCl	2c, E = Me_3Si	67	52-54[e]
1b		 3	40	oil
1c		4a, E = H	74	98-100[e]
2c		4b, E = Me_3Si	60	198-200[f]

[a] Yields correspond to isolated and purified (chromatographed or distilled) materials. [b] Boiling points are those of Kugelrohr distillation temperatures and do not necessarily reflect the true boiling points. [c] By high resolution MS. [d] Obtained using LDA/THF/−78 °C conditions. [e] Recrystallized from PhH-CH_2Cl_2. [f] Recrystallized from PhH-hexane.

the construction of diversely substituted pyridines, including nicotinamides and isonicotinamides, and further expands the utility of the directed ortho metalation strategy.[4]

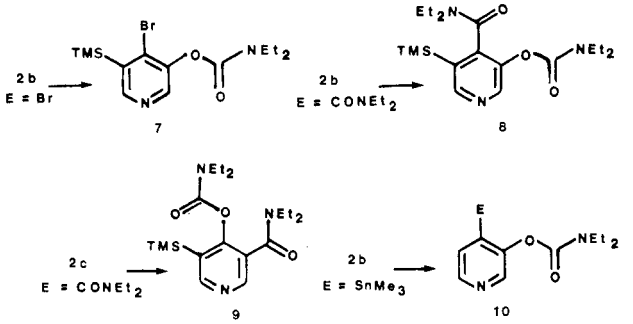
Metalation of 2-pyridyl diethylcarbamate (**1a**)[5] under standard conditions (1.1 equiv of *sec*-BuLi/TMEDA/THF/−78 °C)[3] followed by MeOD quench resulted in the formation of **2a**, E = D, in high chemical yield and 56% d_1 content.[6,7] Other electrophiles were likewise introduced to give diverse 3-substituted-2-pyridyl carbamates **2a** (Table I). Identical metalation of 3- and 4-pyridyl carbamates, **1b** and **1c**, followed by treatment with a variety of electrophiles furnished substituted products **2b** and **2c**, respectively, in moderate to excellent yields. ^1H NMR spectral identification of product substitution was corroborated by chemical means. For example, hydrolysis (NaOMe/MeOH/reflux/12–40 h) of **2a**, E = Br, and **2b**, E = Me, afforded in 80–90% yields the known 3-bromo-

(3) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935.
(4) For use of directed metalation reaction on pyridines, see, $CONR_2$: (a) Watanabe, M.; Snieckus, V. *J. Am. Chem. Soc.* **1980**, *102*, 1457. (b) Epsztajn, J.; Bieniek, A.; Brzezinski, J. Z.; Jozwiak, A. *Tetrahedron Lett.* **1983**, *24*, 4735. (c) Iwao, M.; Kuraishi, T. *Tetrahedron Lett.* **1983**, *24*, 2649. See, however: (d) El Din, M. G.; Knaus, E. E.; Giam, C. S. *Can. J. Chem.* **1982**, *60*, 1821. CONR: (e) Katritzky, A. R.; Rahimi-Rastgoo, S.; Ponkshe, N. K. *Synthesis* **1981**, 127. Kelly, T. R.; Echavarren, A.; Chandrakumar, N. S.; Koksai, Y. *Tetrahedron Lett.* **1984**, *25*, 2127. 2-Oxazolino: (f) Meyers, A. I.; Gabel, R. A. *J. Org. Chem.* **1982**, *47*, 2633. SO_2NR_2: (g) Breant, P.; Marsais, F.; Quéguiner, G. *Synthesis* **1983**, 822. OR: (h) Marsais, F.; Le Nard, G.; Quéguiner, G. *Synthesis* **1982**, 235. (i) Wade, A.; Kanatomo, S.; Nagai, S. *Chem. Pharm. Bull. Jpn.* **1984**, *33*, 1022. NCO_2t-Bu: (j) Tamura, Y.; Chen, L. C.; Fujita, M.; Kita, Y. *Chem. Pharm. Bull. Jpn.* **1982**, *30*, 1257. (k) Gungor, T.; Marsais, F.; Quéguiner, G. *Synthesis* **1982**, 499. (l) Turner, J. A. *J. Org. Chem.* **1983**, *48*, 3401. Cl: (m) Marsais, F.; Breant, F.; Guiguene, A.; Quéguiner, G. *J. Organomet. Chem.* **1981**, *216*, 139. Br: (n) Marsais, F.; Laperdrix, B.; Gungor, T.; Mallet, M.; Quéguiner, G. *J. Chem. Res., Synop.* **1982**, 278. (o) Mallet, M.; Quéguiner, G. *Tetrahedron* **1982**, *38*, 3035. (p) Corey, E. J.; Pyne, S. G.; Schafer, A. I. *Tetrahedron Lett.* **1983**, *24*, 3291. F: (q) Marsais, F.; Granger, P.; Quéguiner, G. *J. Org. Chem.* **1981**, *46*, 4494. (r) Gungor, T.; Marsais, F.; Quéguiner, G. *J. Organomet. Chem.* **1981**, *215*, 139. (s) Marsais, F.; Quéguiner, G. *Tetrahedron* **1983**, *39*, 2009.

(5) Prepared according to standard procedures: 1a: bp 98–100 °C (0.1 mm); 1b: bp 89–91 °C (0.05 mm); lit. bp 91–93 °C (3.5 mm) (Millner, O. E., Jr.; Stanley, J. W.; Purcell, W. P. *J. Med. Chem.* **1974**, *17*, 13); 1c: bp 95–98 °C (0.25 mm).
(6) Although we are unable to explain the low d_1 incorporation into 1a-c vs. the high yield of products with less reactive electrophiles, we note that similar results have been observed by others, see ref 4b.
(7) Position of metalation and therefore electrophile introduction was readily ascertained by examination of the pyridine ring proton region of the NMR spectra of the carbamate products.

2-pyridone[8a] and 4-methyl-3-hydroxypyridine,[8b] respectively. The regiospecific formation of monobromo- and monoiodopyridones and hydroxypyridines underscores the advantage and complimentarity of this methodology vis-à-vis the electrophilic halogenation approach.[9]

By analogy to the *O*-aryl carbamates,[3] the metalated pyridyl carbamates **1b**, **1c**, and **2c** underwent the anionic Fries rearrangement (−78 °C → room temperature/8 h) to give the isonicotinamide **3** and nicotinamides **4a** and **4b**, respectively (see Table I). In view of the well-known facile reductive conversion of hydroxypyridines to the corresponding pyridines via their chloro derivatives,[10] **2a–c** and **3**, **4** systems are, in principle, prototype precursors to diversified pyridines. As an illustrated of such a sequence, the substituted 4-pyridone **4**, E = Me, prepared by anionic Fries rearrangement of **2c**, E = Me (2.1 equiv *sec*-BuLi/TMEDA/THF/−78 °C → room temperature/8 h), was transformed into the 4-chloropyridine **5** ($POCl_3$/reflux/10 min) and hydrogenolyzed (H_2/Pd–$BaSO_4$/EtOH/16 h)[10] to afford the 5-methylnicotinamide **6** in 40% unoptimized yield.



As initial tests of further directed metalation possibilities on the derived *O*-pyridyl carbamates, metalation and Me_3SiCl quench sequences were carried out on **2b**, E = Br,[11] **2b**, E = $CONEt_2$, and **2c**, E = $CONEt_2$. The isolated products, **7** (65%), **8** (66%), and **9** (68%), respectively, indicate that metalation occurs at the 5-position irrespective of the directing group.[12,13] The propensity of pyridine tin derivatives to undergo electrophile-induced ipso destannylation,[14] invited iodination and acylation experiments on **2b**, E = $SnMe_3$. In the event, treatment with I_2 ($CHCl_3$/room temperature/4 h) and MeCOCl (PhH/reflux/40 h) afforded the ipso-substituted products **10a** (90%) and **10b** (57%), respectively, thus offering an additional connecting link between the directed metalation tactic and electrophilic substitution chemistry.

The directed ortho metalation chemistry of *O*-pyridyl carbamates **1a–c** described herein provides efficient and short avenues to new diversely functionalized pyridines which should be useful in heterocyclic and natural product synthesis.[15,16]

Registry No. **1a**, 98976-68-2; **1b**, 51581-40-9; **1c**, 98976-69-3; **2a** (E = D), 98976-70-6; **2a** (E = Me), 98976-71-7; **2a** (E = $CONEt_2$), 98976-72-8; **2a** (E = Me_3Si), 98976-73-9; **2a** (E = Br), 98976-74-0; **2a** (E = I), 98976-75-1; **2b** (E = D), 98976-76-2; **2b** (E = Me), 98976-77-3; **2b** (E = $CONEt_2$), 98976-78-4; **2b** (E = Me_3Si), 98976-79-5; **2b** (E = Me_3Sn), 98976-80-8; **2b** (E = Br), 98976-81-9; **2c** (E = D), 98976-82-0; **2c** (E = Me), 98976-83-1; **2c** (E = $CONEt_2$), 98976-84-2; **2c** (E = Me_3Si), 98976-85-3; **3**, 98976-87-5; **4a**, 98976-88-6; **4b**, 98976-89-7; **5**, 98990-26-2; **6**, 98976-90-0; **7**, 98976-91-1; **8**, 98976-92-2; **9**, 98976-93-3; **10a**, 98976-94-4; **10b**, 98990-27-3; 3-bromo-2-pyridone, 98976-86-4; 4-methyl-3-hydroxypyridine, 1121-19-3.

(8) (a) mp 175–179 °C, lit. mp 181–187 °C, see ref 1, p 844. (b) mp 114–115 °C, lit. mp 117–119 °C, see ref 1, p 981.

(9) Monohalogenation of these systems is difficult to achieve, see: Katritzky, A. R.; Khan, G. R.; Leahy, D. E.; DeRosa, M. *J. Org. Chem.* **1984**, *49*, 4784 and ref 1, p 800.

(10) See, for example: Stevens, J. R.; Beutel, R. H.; Chamberlain, E. *J. Am. Chem. Soc.* **1942**, *64*, 1093.

(11) Metalation was carried out according to the conditions (LDA/THF/−78 °C) described for 3-bromopyridine by Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137.

(12) The reluctance to even partial 2-metalation in **1b**, **2b** (E = Br, $CONEt_2$, Me_3Si), and **2c** (E = $CONEt_2$) is somewhat surprising in view of the recent result on metalation (*n*-BuLi/*t*-BuOK/THF/−105 °C) of pyridine which show kinetic acidity ratios of 6:1:6 for the (2 + 6):(3 + 5):4 positions: Verbeek, J.; George, A. V. E.; de Jong, R. L. P.; Brandsma, L. *J. Chem. Soc., Chem. Commun.* **1984**, 257.

(13) In the *O*-aryl carbamate series, inter- and intramolecular competition experiments have shown that the $OCONEt_2$ is a somewhat more powerful directed ortho metalation group than the $CONEt_2$: Miah, M. A. J.; Snieckus, V., unpublished results.

(14) Yamamoto, Y.; Yanagi, A. *Chem. Pharm. Bull. Jpn.* **1982**, *30*, 1731. Yamamoto, Y.; Yanagi, A. *Heterocycles* **1982**, *19*, 168.

(15) All new compounds show analytical and spectral (IR, ^1H NMR, MS) data in full agreement with the assigned structures.

(16) We are grateful to NSERC Canada and Merck Frosst Canada for financial support of our programs. M.A.J.M. is indebted to the University of Waterloo for a scholarship and Rajashahi University, Bangladesh, for a study leave. We thank Reilly Tar and Chemical Co. for providing generous samples of pyridine derivatives.

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Concerted 1,2-Carbonyl Migrations in Organic Synthesis. A Practical Synthesis of Spiro Cyclic 1,3-Diketones

Summary: A general method for the synthesis of α,β-unsaturated cyclic enones is described that involves the α-thioalkylation of cyclic silyl enol ethers in tandem with a low-temperature metaperiodate oxidative dehydrosulfenylation of a β-keto sulfoxide. The facile Lewis acid catalyzed acyl migration of a series of α,β-epoxy ketones affords a practical synthesis of cyclic spiro 1,3-diketones.

Sir: The methodology for the elaboration of quaternary carbon centers has become increasingly sophisticated.[1] When the molecular architecture includes a spiro carbon center, the synthetic challenge is particularly demanding.[2] A systematic study demonstrating the synthetic utility of 1,2-acyl migrations in α,β-epoxy ketones has not appeared, although there have been sporadic reports on this Lewis acid catalyzed rearrangement.[3] Acyl migration has yet to be established as an effective transformation in organic synthesis since the unusual migratory aptitude of the carbonyl group has not been generally recognized. Mechanistic studies have established that 1,2-carbonyl

(1) Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(2) (a) Krapcho, A. P. *Synthesis* **1976**, 425. (b) Trost, B. M.; Adams, B. R. *J. Am. Chem. Soc.* **1983**, *105*, 4849 and references therein.

(3) (a) Williams, J. R.; Sarkisian, G. M.; Quigley, J.; Hasiuk, A; VanderVernen, R. *J. Org. Chem.* **1974**, *39*, 1028. (b) Hawkins, E.; Large, R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2169. (c) Hartman, B. C.; Richborn, B. *J. Org. Chem.* **1972**, *37*, 943. (d) Watanabe, H.; Katsuhara, J.; Yamamoto, N. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1328. (e) Hart, H. *Acc. Chem. Res.* **1971**, 337. (f) Nojima, M.; Hinove, K.; Tokura, N. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 827. (g) Reusch, W.; Anderson, D. F.; Johnson, C. K. *J. Am. Chem. Soc.* **1968**, *90*, 4988. (h) House, H. O.; Ryerson, G. D. *J. Am. Chem. Soc.* **1961**, *83*, 979 and references therein. (i) Shapiro, E. L.; Steinberg, M.; Gould, D.; Gentles, M. J.; Herzog, H. L.; Gilmore, M.; Charney, W.; Hershberg, E. B.; Mandell, L. *J. Am. Chem. Soc.* **1959**, *81*, 6483. (j) Collins, D. J. *J. Chem. Soc.* **1959**, 3919.

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