(15) Kobayashi, M.; Terui, Y.; Tori, K.; Tsuji, N. *Tetrahedron Lett.* **1976**, 619.

(16) Preliminary spectra obtained at intermediate temperatures show the superposition of the low- and high-temperature limiting spectra in proportions which depend on the temperature indicating that the exchange process is controlled by the occurrence of a second-order phase transition in the solid. We are currently investigating this phenomenon in more detail.

(17) $R = \sum||F_{\text{obsd}}| - |F_{\text{calcd}}||/\sum|F_{\text{obsd}}|$; $R_2 = [\sum w(|F_{\text{obsd}}|^2 - |F_{\text{calcd}}|^2)/\sum w|F_{\text{obsd}}|^2]^{1/2}$.

(18) A difference map calculated prior to the inclusion of the hydroxyl hydrogen atoms revealed a large positive peak (height 0.3 e/Å^3) greatly elongated toward the two hydroxyl oxygen atoms. Refinement of a two-hydrogen (disordered) model varying positional and thermal parameters for all atoms (isotropic for hydrogen, anisotropic for all others) gave an R of 0.049 and an R_2 of 0.078; the thermal parameters for the hydrogen atoms were reasonable. After this refinement, a difference map in the hydroxyl hydrogen region was quite smooth. Refinement of a single hydrogen model (the hydroxyl hydrogen positioned initially at the centroid of the large peak) gave an R of 0.051 and an R_2 of 0.082. However, the position of this hydrogen atom oscillated rather than converged to a definite position, the temperature factor increased to 10.9 (1.1) Å^2, and a difference map indicated considerable residual electron density.

(19) A number of other models have been tried without any improvement in the R values. A full discussion of the X-ray analysis and refinement is in preparation.

(20) See the paragraph at the end of paper regarding supplementary material.

(21) Curtin, D. Y.; Paul, I. C.; Duesler, E. N.; Lewis, T. W.; Mann, B. J.; Shaiu, W.-I *Mol. Cryst. Liq. Cryst.* **1979**, *50*, 25.

(22) (a) Sokalski, W. A.; Romanowski, H.; Jaworski, A. *Proc. Int. Symp. Specif. Interact. Mol. Ions, 3rd, 1976*, **1976**, *2*, 507. (b) Scheiner, S.; Kern, C. W. *J. Am. Chem. Soc.* **1979**, *101*, 4081.

Wen-I Shiau, Eileen N. Duesler
Iain C. Paul,* David Y. Curtin*
Department of Chemistry, University of Illinois
Urbana, Illinois 61801

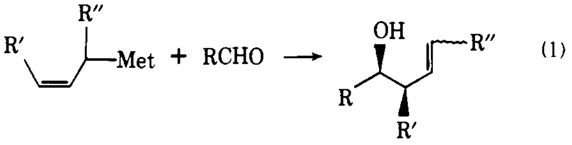
William G. Blann, Colin A. Fyfe*
Guelph-Waterloo Centre for Graduate Work in Chemistry
Geulph Campus, Deparment of Chemistry
University of Guelph, Guelph, Ontario, Canada N1G 1C1

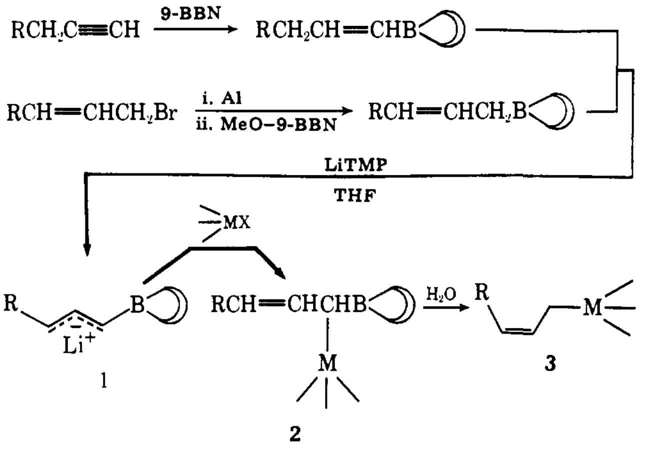
Received February 4, 1980

A New Procedure for the Stereoselective Synthesis of (*Z*)-2-Alkenylsilanes and -tins and Their Application to Erythro-Selective Synthesis of β-Alkyl Alcohol Derivatives

Sir:

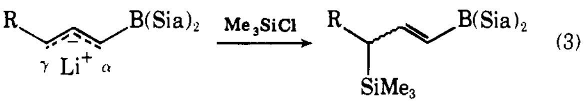
The erythro-selective synthesis of the β-methyl alcohol units of macrolide antibiotics is a problem of pressing concern in organic synthesis. The usual solution to this problem is to use the stereoselective cross-aldol condensation.[1] An alternative approach, which has not yet been studied extensively but is highly promising, is use of the erythro-selective addition of (*Z*)-2-alkenyl metal derivatives to carbonyl compounds (eq 1).[2,3] Unfortunately, however, no methodology with a wide applicability has yet been established to realize the stereoselective synthesis of such an organometallic compound.[4] We report here for the first time a convenient one-pot procedure for the synthesis of (*Z*)-2-alkenylsilanes and -tins (eq 2) and their application to erythro-selective synthesis of β-alkyl alcohol derivatives (eq 4 and 5).





M = Si or Sn (2)

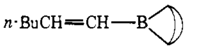
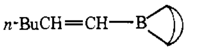
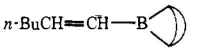
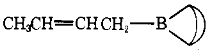
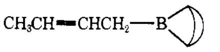
It was reported that the treatment of alkenyldisiamylborane with lithium 2,2,6,6-tetramethylpiperidine (LiTMP) generated boron-substituted allyl carbanion which reacted with trimethylsilyl chloride at the γ position owing to the steric repulsion between bulky siamyl and trimethylsilyl group[6] (eq 3).



It appeared that the regioselective reaction at the α position may be realized by replacing the siamyl group with less bulky 9-BBN. Actually, the boron-stabilized allyl carbanion (**1**), prepared from 1- or 2-alkenyl-9-BBN,[7] reacted with trialkylsilyl and -tin halides exclusively at the α position to produce **2**, which subsequently underwent protonolysis by H_2O. To our surprise, the resulting 2-alkenyl derivatives (**3**) drastically favored the *Z* configuration. The results are listed in Table I. The exclusive formation of the *Z* olefin, as well as the regiocontrol, is particularly remarkable for synthetic application.

The following procedure for the synthesis of (*Z*)-2-hexen-

Table I. Stereoselective Synthesis of (*Z*)-2-Alkenylsilanes and Tins[a]

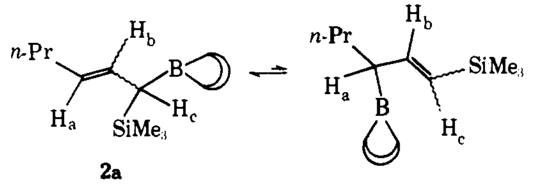
9-BBN derivative	electrophile	product[b]	yield, %[c]	isomeric purity, %[d]
 n-BuCH=CH—B	Me_3SiCl	n-PrCH=CHCH$_2$SiMe$_3$	72	~100
 n-BuCH=CH—B	n-Bu$_3$SnCl	n-PrCH=CHCH$_2$Sn(n-Bu)$_3$	76	~100
 n-BuCH=CH—B	Me_3SnBr	n-PrCH=CHCH$_2$SnMe$_3$	70	~100
 CH_3CH=CHCH$_2$—B	Me_3SiCl	CH_3CH=CHCH$_2$SiMe$_3$	40[e]	~100
 CH_3CH=CHCH$_2$—B	Me_3SnBr	CH_3CH=CHCH$_2$SnMe$_3$	(72)	70[f]

[a] All reactions were performed as described in the text. [b] All products were fully identified by spectroscopic methods and by comparison with the corresponding *E* isomers.[8] [c] Isolated yield (GLC yield). The product arising from the attack at the γ position was not detected. [d] Determined by IR spectra and by GLC with a capillary column. [e] High vapor pressure of crotyltrimethylsilane made the separation from solvents difficult, resulting in low isolated yield. [f] Crotyltin underwent facile isomerization in contrast to other derivatives; see also ref 8.

0002-7863/80/1502-4548$01.00/0

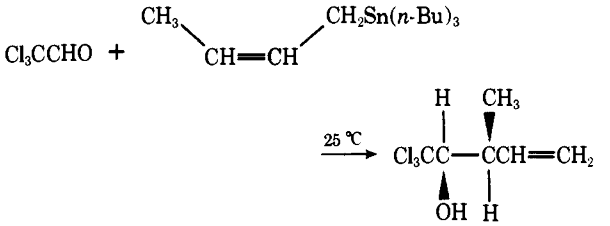
yltributyltin is representative. In a 50-mL flask, equipped with a magnetic stirrer and maintained under a static pressure of N_2, was placed 2,2,6,6-tetramethylpiperidine (5 mmol, 0.8 mL). A solution of *n*-BuLi in hexane (5 mmol, 3.5 mL) was added at 0 °C and LiTMP precipitated within a few minutes. The hexane was removed by vacuum distillation and the residue was dissolved in THF (10 mL). (*E*)-1-Hexenyl-9-BBN (5 mmol)[7] was added and the reaction mixture was stirred at room temperature for 30 min. The flask was then cooled with an ice bath and *n*-Bu_3SnCl (5 mmol, 1.63 g) was added. After the mixture was stirred for 1 h at 0 °C, water and ethanolamine (5 mmol, 0.31 mL) were added. The organic layer was extracted with petroleum ether and dried over anhydrous Na_2SO_4. Distillation via Kugelrohr gave the desired olefin in an essentially pure form: 1.41 g, 76%; bp 130-135 °C (0.5 mmHg).[9]

To help clarify the mechanism of the high stereo- and regiocontrol, the intermediate **2** was isolated by simple distillation. **2a** (R = *n*-Pr, M = $SiMe_3$): 84% isolated yield, bp 115-120 °C (0.01 mmHg). The ^1H NMR spectra at various temperatures (20-140 °C) clearly indicated that the allylic borane possessed the structure **2a** instead of **2a′**.[10] Further, the structure was confirmed by the ^1H NMR spectra of D-labeled **2a** (H_b = D);[11] the H_c proton was observed as two kinds of singlet and the H_a proton as a triplet. Accordingly, it is clear that **3** is produced by the α protonation of a mixture of (*E*)-**2** and (*Z*)-**2** or by the rapid γ protonation of its allylic isomer such as **2a′**.[12] While it is not possible at the present time to differentiate the reaction path, a novel and selective route to (*Z*)-2-alkenylsilanes and -tins is now available.

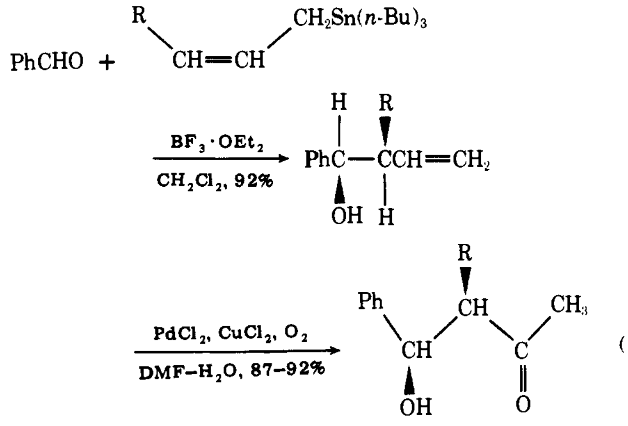


2a **2a′**

We next turned our attention to the erythro-selective addition of **3** to aldehydes. As expected, completely erythro-selective coupling was realized via the thermal[2a] or Lewis acid mediated reaction[13b] of (*Z*)-2-alkenyltins (eq 4 and 5).[14] The Wacker-type oxidation[15] of the homoallyl alcohols afforded **4** in high yields. Consequently, the above results indicate that completely *regioselective* and erythro-selective cross-aldol condensation is realized via the (*Z*)-2-alkenyl metal route.[16] This is extremely useful during elaboration of complex molecules, and further work along this line is under active investigation.[17]



(4)



(5)

4

R = *n*-Pr or Me

Acknowledgment. Financial support from the Ministry of Education, Science and Culture (Grant-in-Aid No. 484027) is gratefully acknowledged.

References and Notes

(1) (a) for review articles, see: Masamune, S. *Aldrichim. Acta* **1978,** *11*, 23. Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977,** *16*, 585. (b) For erythro-selective aldol condensations, see: Masamune, S.; Mori, D.; Horn, D. V.; Brooks, D. W. *Tetrahedron Lett.* **1979**, 1665. Hirama, M.; Masamune, S. *Ibid.* **1979,** 2225. Horn, D. V.; Masamune, S. *Ibid.* **1979,** 2229. Hirama, M.; Garvey, D. S.; Lu, L. D.-L.; Masamune, S. *Ibid.* **1979,** 3937. Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979,** *101*, 6120. Meyers, A. I.; Reider, P. J. *Ibid.* **1979,** *101*, 2501. Chan, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Tetrahedron Lett.* **1979**, 4029. Mulzer, J.; Segner, J.; Brüntrup, G. *Ibid.* **1977,** 4651. Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977,** *99*, 247. Buse, C. T.; Heathcock, C. T. *Ibid.* **1977,** *99*, 8109. Dubois, J.-E.; Fellmann, P. *Tetrahedron Lett.* **1975,** 1225. Fenzel, W.; Köster, R.; Zimmermann, H. I. *Justus Liebigs Ann. Chem.* **1975,** 2201. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974,** *96*, 7503. Jeffery, E. A.; Meisters, A.; Mole, T. *J. Organomet. Chem.* **1974,** *74*, 373. House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973,** *95*, 3310. Sugasawa, T.; Toyoda, T. *Tetrahedron Lett.* **1979,** 1423.

(2) (a) Servens, C.; Pereyre, M. *J. Organomet. Chem.* **1972,** *35*, C20. (b) Hoffmann, R. W.; Zeiss, H.-J. *Angew. Chem., Int. Ed. Engl.* **1979,** *18*, 306. (c) Hoffmann, R. W.; Landner, W. *Tetrahedron Lett.* **1979,** 4653.

(3) The double bond of the alcohols can easily be transformed into other functional groups. Further, various substituents can be introduced into R″, which is not available via cross-aldol reactions. The results will be published in due course (see also ref 2c).

(4) (*Z*)-2-Butenyl boronates were synthesized via several steps.[2b] Cf. Brown, H. C.; DeLue, N. R.; Yamamoto, Y.; Maruyama, K.; Kasahara, T.; Murahashi, S.-I.; Sonoda, A. *J. Org. Chem.* **1977**, *42*, 4089. The reaction of allylic magnesium or lithium compounds with MX (M = Si< or Sn<) or that of allylic halides with MNa and MLi gives a mixture of (*E*)- and (*Z*)-2-alkenylsilanes and -tins (see also ref 8). The cis hydrogenation of the propargyl derivatives is also promising. However, the preparation of such a compound always accompanies the formation of allenic derivatives: Lequan, M.; Guillern, G. *C. R. Acad. Sci., Ser. C* **1969,** *268*, 1001. Lequan, M.; Cadiot, P. *Bull. Soc. Chim. Fr.* **1965,** 45. Treatment of (*Z*)-2-alkenylpotassium[5] with MX may provide the desired compounds. However, it seems to us that the reaction again accompanies the isomerization observed in ref 2b and 8. We thank Professor Schlosser for his helpful discussion on this latter subject.

(5) Rauchschwalbe, G.; Schlosser, M. *Helv. Chim. Acta* **1975,** *58*, 1094. Schlosser, M.; Hartmann, J. *J. Am. Chem. Soc.* **1976,** *98*, 4674. Schlosser, M.; Rauchschwalbe, G. *Ibid.* **1978,** *100*, 3258.

(6) Kow, R.; Rathke, M. W. *J. Am. Chem. Soc.* **1973,** *95*, 2715.

(7) (a) For the synthesis of 1-alkenyl-9-BBN, see Brown, H. C.; Scouten, C. G.; Liotta, R. *J. Am. Chem. Soc.* **1979,** *101*, 96. (b) For 2-alkenyl-9-BBN, see Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1977**, *132*, 9.

(8) Verdone, J. A.; Mangravite, J. A.; Scarpa, N. M.; Kuivila, H. G. *J. Am. Chem. Soc.* **1975,** *97*, 843.

(9) Normally (*Z*)-2-alkenylsilanes and -tins, except crotyltin, are configurationally stable at reasonably high temperature. Filtration through the column of silica gel induces isomerization and decomposition, though the compounds can be purified by using the short column of alumina.

(10) The interconversion between *cis*-**2a** and *trans*-**2a** must proceed via **2a′**. Chemical shifts at the olefinic and allylic region of **2a** were as follows: δ (CCl_4) 5.58 (b, dd, *J* = 12, 14 Hz), 5.00 (b, td, *J* = 14, 6 Hz), 2.58 (d, *J* = 12 Hz), 2.46 (d, *J* = 12 Hz). The two signals at the allylic region, which coalesced at 120 °C, were assigned to those of *E* and *Z* isomer of **2a**. Although it seems that the *J* value (14 Hz) of the olefinic protons does not show evidence for *cis*-vinyl protons, this is because of the close chemical shifts and broadening of trans H_b and cis H_b. ^{13}C NMR spectra clearly indicate the presence of two stereoisomers of **2a,** that is, four kinds of olefinic signals: δ ($CDCl_3$, Me_4Si as an internal standard) 128.594, 127.962, 125.771, and 124.407.

(11) The material was easily prepared by using D-9-BBN.

(12) This is quite an interesting observation, since protonation of allylic boranes is believed to occur at the γ position via a cyclic transition state.[7b] Moreover, the exclusive formation of *Z* isomer suggests intervention of an anionic intermediate in the protonation stage.[5]

(13) For a general allylation of carbonyl compounds via Si and Sn derivatives, see the following. (a) Si: Abel, E. W.; Rowley, R. J. *J. Organomet. Chem.* **1975,** *84*, 199. Hosomi, A; Sakurai, H. *Tetrahedron Lett.* **1976,** 1295. Deleris, G.; Dunogues, J.; Calas, R. *Ibid.* **1976,** 2449. Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976,** 941. Ojima, I.; Miyazawa, Y.; Kumagai, M. *J. Chem. Soc., Chem. Commun.* **1976,** 927. Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977,** *99*, 1673. Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1978,** 2589. Hosomi, A.; Shirahata, A.; Sakurai, H. *Chem. Lett.* **1978,** 901. (b) Sn: Maruyama, K.; Naruta, Y. *J. Org. Chem.* **1978,** *43*, 3796. Maruyama, K.; Naruta, Y. *Chem. Lett.* **1978,** 431. Naruta, Y.; Maruyama, K. *Ibid.* **1979,** 881. Naruta, Y.; Maruyama, K. *Ibid.* **1979,** 885. Naruta, Y.;

Ushida, S.; Maruyama, K. *Ibid.* **1979,** 917. Naruta, Y. *J. Am. Chem. Soc.*, in press. (c) The reaction of allylic boron ate complexes with carbonyl compounds is highly interesting in respect of the stereoselection: Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1978,** *100*, 6282. The results will be published soon.

(14) Examination of the ^{1}H NMR spectra of the homoallyl alcohols clearly indicated that the threo isomers were not involved over 1%.

(15) Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett.*, **1976,** 2975.

(16) Despite numerous efforts in the chemistry of enolates, it still remains difficult to control regiochemistry: (a) d'Angelo, J. *Tetrahedron* **1976,** *32*, 2979. (b) Jackman, L. M.; Lange, B. C. *Ibid.* **1977**, *33*, 2737.

(17) NOTE ADDED IN PROOF. (*Z*)-2-Alkenylsilanes and -tins can be regio- and stereoselectively obtained through allyl-type organopotassium compounds: private communication from Professor Schlosser.

Hidetaka Yatagai, Yoshinori Yamamoto,* Kazuhiro Maruyama
Department of Chemistry, Faculty of Science
Kyoto University, Kyoto 606, Japan

Received December 28, 1979

β′-Lithiation of α,β-Unsaturated Secondary Amides

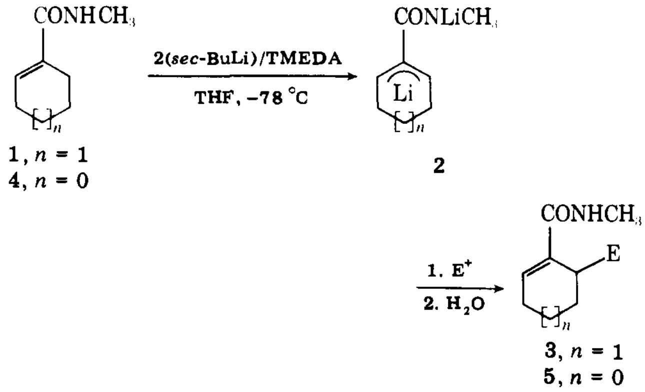
Sir:

Although "ortho" metalations of aromatic systems have been known for some time, directed metalations of nonaromatic systems have been much less studied.[1] The potential value of regiospecifically metalated functionally substituted molecules is high and investigations in this area could provide both new and useful results.

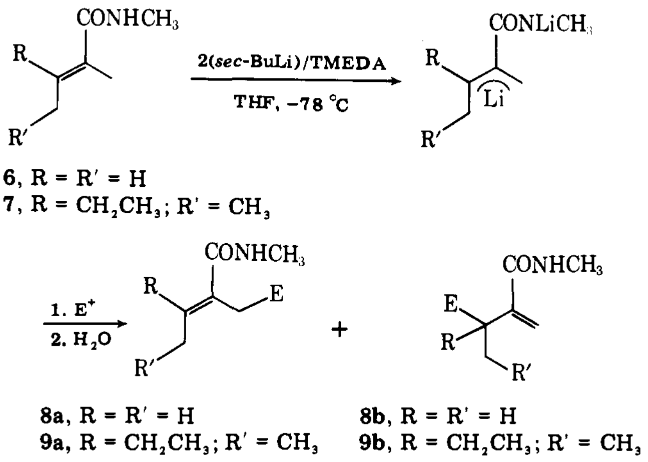
Consideration of the functional groups which might be generally effective for directed metalations of nonaromatics suggests that dilithiation of secondary amides would be of interest for at least three reasons: initial proton removal from nitrogen would deactivate the carbonyl group toward both nucleophilic addition and enolate anion formation; the secondary amide is one of the strongest directors of "ortho" metalation; and the amide group can be readily converted into other functions.[1-4]

We now report that in the dilithiation of α,β-unsaturated secondary amides the second metalation occurs at the β′ position. This result is unprecedented for an α,β-unsaturated carbonyl system which has potentially acidic γ and β protons.

Treatment of *N*-methyl-1-cyclohexenecarboxamide (**1**) with 2.1 equiv of *sec*-butyllithium–tetramethylethylenediamine in tetrahydrofuran at −78 °C followed by addition of methanol-*O-d*, *n*-hexyl bromide, tri-*n*-butyltin chloride, carbon dioxide, acetone, or benzophenone gives the *N*-methyl-6-substituted 1-cyclohexenecarboxamides **3** in useful yields as shown in Table I. Similar results are obtained for the conversion of *N*-methyl-1-cyclopentenecarboxamide (**4**) into the β′-substituted products **5**, also shown in Table I. The dilithiated species **2** is the proposed intermediate in these reactions.



Acyclic cases behave similarly. Thus, (*E*)-*N*-methyl-2-methyl-2-butenamide (**6**) and *N*-methyl-3-ethyl-2-methyl-2-pentenamide (**7**) on treatment with 2.1 equiv of *sec*-butyllithium–tetramethylethylenediamine in tetrahydrofuran at −78 °C for 15–45 min, followed by reaction with an added electrophile, provide the products **8** and **9** in the yields indicated in Table I. The formation of isomers **8a**–**8b** and **9a**–**9b**, which were separated and characterized in each case, does show the lack of regiospecificity often found with allylic organometallics. The reaction of **7** is particularly interesting as it demonstrates regiospecific metalation even in the presence of a γ proton which is cis to the amide group.



These results suggest a new direct approach to the synthesis of a variety of α,β-unsaturated carbonyl derivatives. For example, the lactones **10** and **11** are produced in 52 and 33%

Table I. Lithiation and Electrophilic Substitution of **1**, **4**, **6**, and **7**

amide	equiv of *s*-BuLi/TMEDA	electrophile	product	yield,^{a} %
1	2.1/2.1	CH_3OD	**3**, E = D	81 (79 d_1)
1	2.1/2.1	$CH_3(CH_2)_5Br$	**3**, E = $(CH_2)_5CH_3$	58
1	2.1/2.1	$(n\text{-}C_4H_9)_3SnCl$	**3**, E = $Sn(n\text{-}C_4H_9)_3$	49
1	2.7/2.3	CO_2	**3**, E = CO_2H	42
1	2.1/2.1	$(CH_3)_2CO$	**3**, E = $COH(CH_3)_2$	62
1	4.5/4.2	$(C_6H_5)_2CO$	**3**, E = $COH(C_6H_5)_2$	59
4	3.3/6.3	CH_3OD	**5**, E = D	44 (98 d_1)
4	2.1/2.1	$CH_3(CH_2)_5Br$	**5**, E = $(CH_2)_5CH_3$	30^b
4	3.3/8.0	$(C_6H_5)_2CO$	**5**, E = $COH(C_6H_5)_2$	53
6	2.1/2.1	CH_3OD	**8a**, **8b**, E = D	77 (96 d_1)^c
6	2.1/2.1	$CH_3(CH_2)_5Br$	**8a**, **8b**, E = $(CH_2)_5CH_3$	78^d
7^e	2.1/2.1	CH_3OD	**9a**, **9b**, E = D	84 (67 d_1)^f
7^e	2.1/2.1	$(CH_3)_2CO$	**9a**, **9b**, E = $COH(CH_3)_2$	55^{g,h}
7^e	2.1/2.1	$CH_3(CH_2)_5Br$	**9a**, **9b**, E = $(CH_2)_5CH_3$	56^{b,i,j}

[a] Analytically pure material. [b] The spectral properties for **5** and **9a** (E = *n*-hexyl) are satisfactory but analytical samples have not been obtained. [c] 89:11 **8a:8b.** [d] 43:57 **8a:8b.** [e] The amide **7** contains 10% *N*-methyl-3-ethyl-2-methyl-3-pentenamide. [f] 93:7 **9a:9b.** [g] 95:5 **9a:9b.** [h] Contains ~25% **11.** [i] In addition, 10% *N*-hexyl-*N*-methyl-amides corresponding to **9a** and **9b** are obtained. [j] 23:77 **9a:9b.**

0002-7863/80/1502-4550$01.00/0