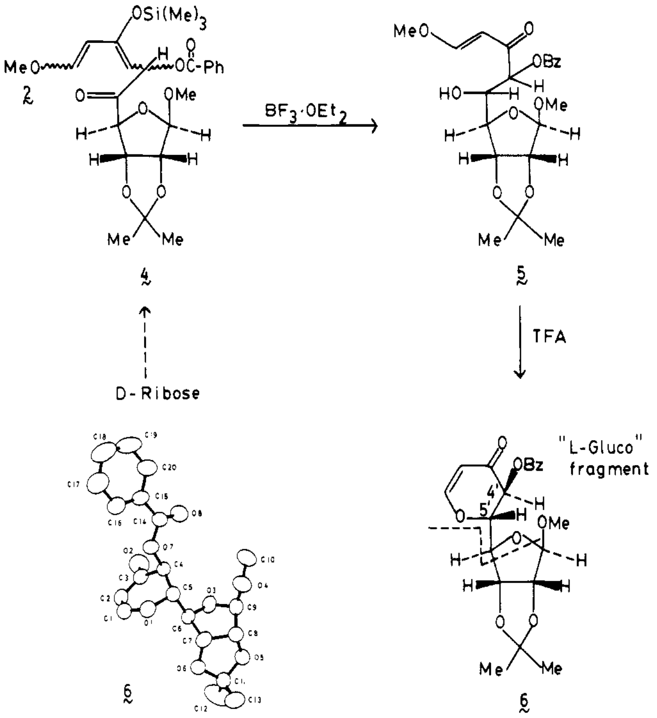
Scheme II



ganometallic reagents,[10] can be readily encompassed in this formulation.

While the reason for the facial induction is a matter for conjecture, an interesting stereochemical outcome has been achieved. The D-galactose derived aldehyde 1 has given rise to a potential L-galacto residue (see structure 3 and dotted lines) in the product. The convertibility of this type of residue to a fully substituted galactose derivative has been amply demonstrated in our previously described synthesis of lincosamine.[14]

The generality of this strict Cram–Felkin control was explored. Toward this end, the known aldehyde 4[19] derived from D-ribose was treated with diene 2 under essentially identical conditions to those employed with aldehyde 1. In this case, it was experimentally convenient to purify the major product at the stage of the β-aldol 5 by flash chromatography.[20] Subsequent cyclization with TFA afforded a cyclocondensation product, mp 184–185 °C; $[\alpha]_D$ −194.9° (c 1.22, CHCl$_3$), in 54% overall yield. The gross structure and stereochemistry of this compound were defined to be that shown in 6 by X-ray crystallographic analysis. A computer-drawn three-dimensional representation of structure 6 is provided[16] in Scheme II.

Again, the sense of the facial induction was that predicted by the Cram–Felkin rules.[17,18] It is also seen that, at least in the crystalline state, the carbon–oxygen bonds of the "pyranose" and "furanose" rings are arranged in the anti-periplanar conformation. This too is similar to the situation with compound 3. However, a *trans*-4′,5′-relationship is present in the derived dihydropyrone in product 6. *Thus, the aldehyde 1, derived from* D-*galactose, gives rise to an* L-*galacto fragment* (*vide supra*), *but the* D-*ribose derived aldehyde 4 produces a potential* L-*gluco precursor* (*see dotted lines in structure 6*).

While the facial sense of the cyclocondensation reactions is in the Cram–Felkin mode[17,18] in both cases, leading in each case to an L-sugar derivative, a seemingly subtle variation in the structure of the aldehyde has brought about a profound difference in the topological outcome. The effects of catalyst modifications as well as changes in the alkyl groups of the silyl enol ether are currently being evaluated.[21,22] Already this technology carries within it the potential for the construction of extended chiral networks.[23] The exploitation of this capability in the synthesis of several complex saccharides will be described shortly.

Acknowledgment. This research was supported by PHS Grant CA 28824. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University which was supported by NSF Chemistry Division Grant CHE7916210. A Heyl Fellowship to Clarence Maring and an NIH Postdoctoral Fellowship (Grant 1 F32 CA07586) to Michael Barbachyn are gratefully acknowledged.

Registry No. 1, 4933-77-1; 2, 87461-94-7; 3, 92524-95-3; 4, 33985-40-9; 5, 92524-96-4; 6, 92524-97-5.

Supplementary Material Available: Table containing the fractional coordinates, temperature parameters, bond distances, and bond angles for compounds 3 and 6 (10 pages). Ordering information is given on any current masthead page.

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[19] Arrick, R. E.; Baker, D. C.; Horton, D. *Carbohydr. Res.* **1973**, *26*, 441.

[20] In a control experiment, the crude aldol product 5 was treated with TFA and the resultant crude cyclocondensation product was carefully examined by 250-MHz ^{1}H NMR spectroscopy. The presence of major (6) and a minor cyclocondensation product in ca. a 15:1 ratio was revealed. The minor product (cf. ref 21) clearly has the cis-4′,5′ configuration, but the "absolute" stereochemistry of the newly fashioned ring is not known.

[21] For example, the Eu(hfc)$_3$-catalyzed[22] reaction of diene mixture 2 (*tert*-butyldimethylsilyl version) with aldehyde 4 (CDCl$_3$, room temperature) followed by catalytic TFA treatment afforded a ca. 12:1 mixture of two cyclocondensation products in 84% isolated yield. Examination of the 250-MHz ^{1}H NMR spectrum indicated a cis-4′,5′ relationship in both products, although the sense of facial induction was undefined. The major product obtained via lanthanide catalysis,[22] is identical with the minor cyclocondensation product[20] obtained when BF$_3$·OEt$_2$ was employed.

[22] For the use of such catalysts in cyclocondensation reactions, see: Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716.

[23] For an alternate approach to extending the chirality of carbohydrate templates, see: Fraser-Reid, B.; Magdzinski, L.; Molino, B. *J. Am. Chem. Soc.* **1984**, *106*, 731 and references therein.

Samuel J. Danishefsky,* Clarence J. Maring
Michael R. Barbachyn, Brigitte E. Segmuller
Department of Chemistry
Yale University
New Haven, Connecticut 06511

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Allenic Zinc Reagents. A Remarkably Regio- and Diastereoselective Synthesis of 2-Substituted Homopropargylic Alcohols

Summary: Allenic zinc reagents react with aldehydes in a highly regio- and diastereoselective manner to furnish *threo*-homopropargylic alcohols having 96–99% diastereomeric purities.

Sir: Recently we reported that homopropargylic alcohols are readily prepared by condensation of aldehydes with allenic alanates.[1] Although this reaction is highly regioselective, it exhibits only modest diastereoselectivity. In the course of a search of a metal which would provide greater stereocontrol, we have now found that the readily

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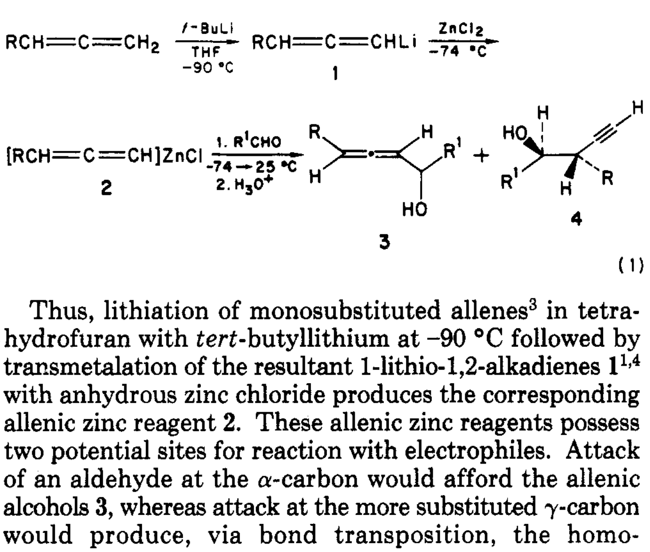
[1] Hahn, G.; Zweifel, G. *Synthesis* **1983**, 883.

Table I. Regio- and Stereoselective Preparations of Homopropargylic Alcohols

	alcohol		yield,[a,b] %	isomeric purity,[d,e] %	threo/erythro[d] ratio
	R =	R^1 =			
4a	n-C_5H_{11}	C_2H_5	86[c]	99	96:4
4b	n-C_6H_{13}		95[c]	99	96:4
4c		*iso*-C_3H_7	86[c]	99	99:1
4d		t-C_4H_9	77	95	99:1
4e	c-C_6H_{11}	C_2H_5	80	99	98:2
4f	t-C_4H_9		69	99	99:1
9a	n-C_5H_{11}		89	98	92:8
9b		*iso*-C_3H_7	94	99	97:3
9c		t-C_4H_9	86	98	99:1
9d	n-C_3H_7	n-C_3H_7	95	99	93:7

[a] Isolated yields. [b] The IR, ^{1}H NMR, and combustion or high-resolution MS analyses were consistent with the assigned structures. [c] The alcohol contained 2–4% of the 3-substituted allenic alcohol (ref 4). [d] The isomeric purities of the alcohols 4 and 9 as well as the threo/erythro ratios were determined on a SE-54 glass capillary (J&W) column. [e] The minor isomers are the allenic alcohols resulting from addition of the aldehydes to the α-carbon of the zinc reagents 2 or 8.

available allenic zinc reagents react with a variety of aldehydes not only in a regiospecific but also in a highly diastereoselective manner to afford the *threo*-3-alkyn-1-ols **4** (eq 1).[2]

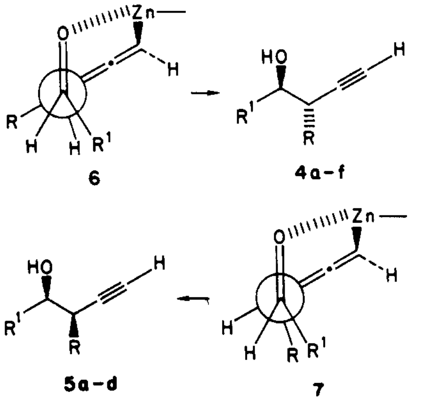


(1)

Thus, lithiation of monosubstituted allenes[3] in tetrahydrofuran with *tert*-butyllithium at −90 °C followed by transmetalation of the resultant 1-lithio-1,2-alkadienes **1**[1,4] with anhydrous zinc chloride produces the corresponding allenic zinc reagent **2**. These allenic zinc reagents possess two potential sites for reaction with electrophiles. Attack of an aldehyde at the α-carbon would afford the allenic alcohols **3**, whereas attack at the more substituted γ-carbon would produce, via bond transposition, the homopropargylic alcohols **4**.

In a study of the regioselectivities of the allenic zinc reagents–aldehyde reactions, treatment of **2** with propionaldehyde or isobutyraldehyde at −74 °C was found to furnish the 3-alkyn-1-ols of γ-attack containing only 1% of the α-condensation products.[5] This regioselectivity was independent of the nature of the alkyl group on the γ-carbon (Table I). However, a slight decrease in γ-selectivity was observed when **2** was reacted with the hindered pivalaldehyde.

The stereochemical course for carbon–carbon bond formation between the trigonal centers of the aldehyde and the allenic zinc reagent **2** can be depicted as follows. Inital coordination of the zinc with the carbonyl group could potentially lead to either or both of the activated complexes **6** and **7**.[7] However, from inspection of these models,



it is seen that **7** possesses unfavorable alkyl–alkyl interaction. Hence formation of the erythro alcohol **5** via this activated complex should not be a favorable process. Thus, it might be anticipated that the reaction of **2** with aldehydes should proceed via the more favorable complex **6** and lead, after bond transposition, to the *threo*-homopropargylic alcohol **4**. In agreement with this is the fact that the allenic zinc reagents **2** do indeed add to aldehydes producing the threo alcohols **4a–f** in 96–99% diastereomeric purities (Table I).[8,9]

A typical procedure for the preparation of **4c** is as follows. To a well-stirred solution of 1,2-nonadiene[3] (0.62 g, 5.0 mmol) in THF (12 mL) was added dropwise a 1.93 M solution of *tert*-butyllithium (5.1 mmol) in pentane while maintaining the temperature during the addition at −90 °C (methanol/liquid nitrogen bath). The resultant yellow solution was stirred at −90 to −95 °C for 1 h, warmed gradually to −74 °C (acetone/dry ice), stirred for 15 min at this temperature, and then treated with a 1.3 M solution of anhydrous zinc chloride[10] (5.5 mmol) in THF while maintaining the temperature during the addition between −74 to −65 °C. The colorless solution was stirred for 1 h at −74 °C; then the allenic zinc reagent formed was treated with isobutyraldehyde (0.48 g, 6.5 mmol). The resultant mixture was gradually warmed to 25 °C, stirred for 1 h, and then poured into ice-cold 5% HCl (20 mL). After extraction with ether the combined organic phases were washed with saturated solutions of $NaHCO_3$ and NaCl. Drying ($MgSO_4$), removal of the solvents, and distillation yielded 86% of **4c**: bp 89–93 °C (1 torr); n^{24}_D 1.4515.[11]

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(2) Only one enantiomer is shown. The stereochemical assignments of the alcohols obtained in this study have been done using the erythro–threo terminology. For a discussion of other terminologies, see: Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654.

(3) The allenes were obtained in 80–90% yields by the reaction of methyl propargyl ether with the appropriate Grignard reagent in the presence of copper(I) bromide: Moreau, J.-L.; Gaudemar, M. *J. Organomet. Chem.* **1976**, *108*, 159.

(4) Metalation of the allenes produced besides the desired 1-lithio-1,2-dienes **1**, 2–4% of the C-3 lithiated allenes. Cf. Brandsma, L.; Verkruijsse, H. D. "Synthesis of Acetylenes, Allenes and Cumulenes"; Elsevier: Amsterdam, 1981; p 7.

(5) The IR spectrum of the zinc reagent **2** (R = n-C_5H_{11}) at 25 °C exhibited a strong absorption at 1905 cm^{-1} characteristic for the allenic structure.[6] Also, treatment of **2** at 25 °C with propanal produced a 90:10 mixture of the threo and erythro alcohols **4a** and **5a**.

(6) For a review on spectral properties and reactions of allenic and propargylic anions with various electrophiles, see: Moreau, J.-L. In "The Chemistry of Ketenes, Allenes, and Related Compounds"; Patai, S., Ed.; Wiley: New York, 1980; pp 363–413.

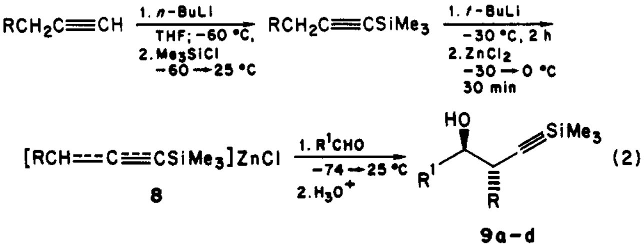
(7) Similar models have been previously proposed to explain the stereochemical course of condensations of allenic organometallics with carbonyl reagents: (a) Saniere-Karila, M.; Capmau, M. L.; Chodkiewicz, W. *Bull. Soc. Chim. Fr.* **1973**, 3371. (b) Favre, E.; Gaudemar, M. *J. Organomet. Chem.* **1975**, *92*, 17.

(8) Interestingly, the reaction of **2** (R = n-C_6H_{13}) with 2-butanone yielded a 53:47 mixture of diastereomers.

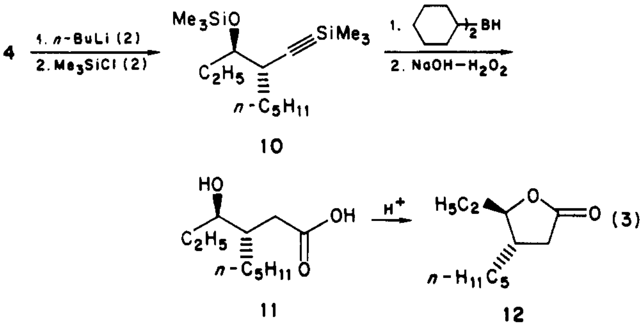
(9) It has been shown that in ^{1}H NMR the acetylenic protons of *threo*-2-alkyl-substituted 3-alkyn-1-ols appear at lower field than of corresponding erythro isomers.[6b] The same behavior was observed both with the alcohols **4** obtained directly and those obtained by desilylation of **9** with n-Bu_4NF in THF. Also, the configurations of the diastereomeric alcohols prepared in this study were correlated to those reported in ref 12.

(10) Russell, C. E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1983**, *105*, 943.

Recently, Yamamoto and co-workers[12] reported that condensations of 1-(trimethylsilyl)-1-propyne or 3-(trimethylsilyl)-2-propyn-1-yl 2-tetrahydropyranyl ether derived zinc reagents with cyclohexanecarbaldehyde were only moderately regioselective or only moderately stereoselective, respectively.[13] Having access to an efficient, one-pot procedure for the conversion of 1-alkynes into the zinc reagents 8[14] via treatment of the corresponding lithium reagents[15] with anhydrous zinc chloride, we briefly examined their reaction with aldehydes (eq 2). In the cases investigated, the condensations proceeded in a regio- and diastereoselective manner producing the threo alcohols **9a–d** in 92% to 99% stereoisomeric purities (Table I). Apparently the presence of a γ-alkyl group in **8** has a marked influence on both the regio- and diastereoselectivities of the reaction.



Finally, it should be noted that 3-alkyn-1-ols **4** and **9** are valuable intermediates for use in a variety of synthetic transformations. For example, conversion of **4a** into the bis-silylated derivative **10** followed by hydroboration and oxidation produces the γ-hydroxy acid **11**.[16] Lactonization stereoselectively affords the *trans*-3,4-disubstituted γ-butyrolactone **12** in 91% yield containing less than 5% of the cis isomer (eq 3).[17]



Acknowledgment. We thank the National Science Foundation (CHE 82-05954) for financial support of this investigation.

Registry No. 1 (R = $CH_3(CH_2)_4$), 80472-36-2; 1 (R = $CH_3(CH_2)_5$), 92490-11-4; 1 (R = c-C_6H_{11}), 92490-12-5; 1 (R = *t*-Bu), 81363-95-3; **2** (R = $CH_3(CH_2)_4$), 92490-13-6; **2** (R = $CH_3(CH_2)_5$), 92490-14-7; **2** (R = c-C_6H_{11}), 92490-15-8; **2** (R = *t*-Bu), 78389-91-0; **4a**, 92490-16-9; **4b**, 92490-17-0; **4c**, 92490-18-1; **4d**, 92490-19-2; **4e**, 92490-20-5; **4f**, 92490-21-6; **8** (R = $CH_3(CH_2)_4$), 92490-22-7; **8** (R = $CH_3(CH_2)_2$), 92490-23-8; **9a**, 92490-24-9; **9b**, 92490-25-0; **9c**, 92490-26-1; **9d**, 92524-59-9; **10**, 92490-27-2; **11**, 92490-28-3; **12**, 92490-29-4; $CH_3(CH_2)_4CH{=}C{=}CH_2$, 1072-19-1; $CH_3(CH_2)_5CH{=}C{=}CH_2$, 22433-33-6; c-$C_6H_{11}CH{=}C{=}CH_2$, 5664-17-5; $(CH_3)_3CCH{=}C{=}CH_2$, 26981-77-1; $CH_3(CH_2)_4CH_2C{\equiv}CH$, 629-05-0; $CH_3(CH_2)_2CH_2C{\equiv}CH$, 693-02-7; $CH_3(CH_2)_5C{\equiv}CLi$, 21433-45-4; $CH_3(CH_2)_3C{\equiv}CLi$, 17689-03-1; $CH_3(CH_2)_5C{\equiv}CSiMe_3$, 15719-55-8; $CH_3(CH_2)_3C{\equiv}CSiMe_3$, 3844-94-8; CH_3CH_2CHO, 123-38-6; $(CH_3)_2CHCHO$, 78-84-2; $(CH_3)_3CCHO$, 630-19-3; $CH_3(CH_2)_2CHO$, 123-72-8.

Supplementary Material Available: Full experimental and spectral details for compounds **4a–f**, **9a–d**, and **12** (9 pages). Ordering information is given on any current masthead page.

George Zweifel,* Gregory Hahn

Department of Chemistry
University of California, Davis
Davis, California 95616

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[11] Spectral data for **4c**: IR (neat) 3460 (OH), 3335 (≡CH), 2110 (C≡C), 630 (≡CH); ^{1}H NMR (CCl_4, 360 MHz) δ 3.11 (dt, J = 3.7, 7.1 Hz, 1 H, H_a), 2.58 (m, 1 H, H_b), 2.12 (d, J = 2.4 Hz, 1 H, H_c), 1.84 (sextet, J = 7.1 Hz, 1 H), 1.64 (m, 1 H), 1.57 (s, 1 H), 1.53 (m, 1 H), 1.38–1.26 (m, 8 H), 1.03 (d, J = 7.1 Hz, 3 H), 0.94 (d, J = 7.1 Hz, 3 H), 0.89 (t, J = 6.5 Hz, 3 H); exact mass, *m/e* 196.1796 (calcd for $C_{13}H_{24}O$, 196.1828).

[12] Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem.* **1982**, *47*, 2225.

[13] For additional examples of condensations of aldehydes with 1-(trimethylsilyl)-1-alkyne derived organometallics, see: (a) Daniels, R. G.; Paquette, L. A. *Tetrahedron Lett.* **1981**, *22*, 1579 and references cited therein. (b) Yamakado, Y.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 5568. (c) Corey, E. J.; Rücker, C. *Tetrahedron Lett.* **1982**, *23*, 719. (d) Wang, K. K.; Nikam, S. S.; Ho, C. D. *J. Org. Chem.* **1983**, *48*, 5376 and references cited therein.

[14] The zinc reagent **8** (R = *n*-C_5H_{11}) at 25 °C showed a strong IR absorption at 1890 cm^{-1} characteristic for the allenic structure.[5,12]

[15] Rajagopalan, S.; Zweifel, G. *Synthesis* **1984**, 111.

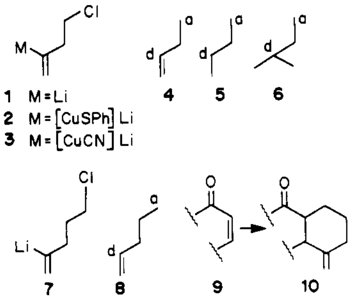
[16] Zweifel, G.; Backlund, S. J. *J. Am. Chem. Soc.* **1977**, *99*, 3184.

[17] The precursor **10** for the lactone **12** may also be prepared by treatment of **8** (R = *n*-C_5H_{11}) with propanal followed by addition of chlorotrimethylsilane at 25 °C.

5-Chloro-2-lithio-1-pentene and Related Reagents. Efficient Methylenecyclohexane Annulation Sequences

Summary: 5-Chloro-2-lithio-1-pentene (**7**), obtained by transmetalation of the (trimethylstannyl)alkene **11**, can be converted into the corresponding Grignard and organocopper reagents. Conjugate addition of the latter species to the enones **13–19**, followed by ring closure of the resultant adducts **20–26**, provides the methylenecyclohexane annulation products **27–37**.

Sir: A recent report[1a] from this laboratory described, inter alia, the preparation of the unusual donor–acceptor reagent 4-chloro-2-lithio-1-butene (**1**). Subsequently, it was shown[1b] that the cuprate reagents **2** and **3**, derived from **1**, could serve as pivotal species in the development of a new five-membered-ring annulation method. Furthermore, application of the latter operation to the synthesis of the structurally interesting sesquiterpenoids (±)-$\Delta^{9(12)}$-capnellene[1c] and (±)-pentalenene[1d] has demonstrated clearly the utility of the process. In fact, in these syntheses, reagents derived from **1** served as efficient synthetic equivalent to the three donor–acceptor synthons **4–6**.



A potentially important extension to the methodology summarized above involved the possibility of preparing

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[1] Piers, E.; Karunaratne, V. (a) *J. Org. Chem.* **1983**, *48*, 1774; (b) *J. Chem. Soc., Chem. Commun.* **1983**, 935; (c) *Can. J. Chem.* **1984**, *62*, 629; (d) *J. Chem. Soc., Chem. Commun.* **1984**, 959.