(hexane) 248 nm; NMR (CCl_4) equal mixture of two stereoisomers τ 8.54 (s, 3 H), 7.56 (d, 2 H, J = 6.0 Hz), 6.68 (s, 3 H), 4.84–5.17 (m, 2 H), 3.90–4.56 (m, 1 H), 2.8–3.1 (m, 3 H), 2.2–2.45 (m, 2 H), and 2d isomer τ 8.45 (s, 3 H), 7.42 (d, 2 H, J = 6.0 Hz), 6.64 (s, 3 H), 4.84–5.17 (m, 2 H), 3.90–4.56 (m, 1 H), 2.8–3.1 (m, 3 H), 2.2–2.45 (m, 2 H); *m/e* 258 (M^+), 217, 189, 105, 104.

(11) Compound **3**: NMR (CCl_4) τ 9.92 (t, 1 H, J = 5.0 Hz), 9.10 (dd, 1 H, J = 8.0 and 5.0 Hz), 8.20 (m, 1 H), 8.38 (s, 3 H), 7.60 (d, 1 H, J = 17.5 Hz), 6.78 (dd, 1 H, J = 17.5 and 8.0 Hz), 2.61–3.10 (m, 5 H); compound **4**, see ref 6.

(12) Compound **13**: NMR (CCl_4) τ 9.58 (d, 1 H, J = 5.0 Hz), 8.95 (s, 3 H), 8.59 (d, 1 H, J = 5.0 Hz), 8.06 (s, 3 H), 7.38 (br s, 2 H), 2.5–3.0 (m, 5 H). Compound **14**: NMR (CCl_4) τ 9.80 (d, 1 H, J = 5.0 Hz), 9.38 (d, 1 H, J = 5.0 Hz), 8.74 (s, 3 H), 8.52 (s, 3 H), 7.38 (br s, 2 H), 2.5–3.0 (m, 5 H).

(13) Photolysis of 2-phenyl-3-methyl-*Z*-3-(2-butenyl)azirine also results in the exclusive formation of *endo*-azabicyclohexene **16**. These stereochemical results can now be rationalized by assuming that the collapse of the initially formed six-membered ring dipole to the thermodynamically more favored exo isomer results in a severe torsional barrier. Formation of the endo isomer (i.e., **16**), however, moves the phenyl and methyl groups further apart and is the kinetically preferred process.

(14) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1973); *ibid.*, **2**, 633 (1963); R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes", S. Patai, Ed., Interscience, New York, N.Y., 1964, pp 806–878.

(15) R. Huisgen and H. Gotthardt, *Chem. Ber.*, **101**, 1059 (1968).

(16) A. Eckell, R. Huisgen, R. Sustmann, G. Wallbillich, D. Grashey, and E. Spindler, *Chem. Ber.*, 100, 2192 (1967).

(17) It should be pointed out that the mechanism proposed here to account for the formation of the azabicyclohexenes is very similar to Firestone's stepwise diradical mechanism.[5]

(18) K. N. Houk, *Acc. Chem. Res.*, **8**, 361 (1975).

(19) From the slope and intercept of the Stern–Volmer analysis for azabicyclohexene formation in the presence of a given dipolarophile, the ratio of the external to internal rate constants for cycloaddition of the nitrile ylide can be determined. Since the rate constants for reaction of different nitrile ylides with a particular dipolarophile are almost identical,[2] the ratio slopes/intercepts of different allylazirines will give the relative rates of internal cyclization as a function of substitution about the C–C double bond.

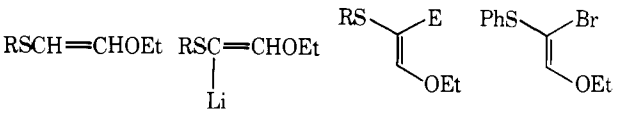
(20) W. Kirmse in "Carbene Chemistry", Academic Press, New York, N.Y., 1964.

Albert Padwa,* Per H. J. Carlsen
Department of Chemistry
State University of New York at Buffalo
Buffalo, New York 14214
Received January 12, 1976

Preparation and Reactions of 2-(Alkoxy)-1-(alkyl or arylthio)vinyllithium. Application in the Synthesis of 9-Desoxo-9-thiaprostaglandins

Sir:

The reaction of a cis–trans mixture of 2-(ethoxy)-1-(pentyl or phenylthio)ethylenes (**1a,b**)[1] with *tert*-butyllithium in THF at −70° for 1 h results in essentially quantitative formation of the 2-(ethoxy)-1-(pentyl or phenylthio)-vinyllithium (**2a,b**). Although, under similar conditions, vinyl sulfides[2] and vinyl ethers[3] are converted to the corresponding 1-vinyllithium derivatives in high yields, the lithiation of **1a,b** occurs regioselectively at C_1. Evidence for the regioselective lithiation is provided by the reactions of the anion **2** with electrophiles (E^+) to produce exclusively products such as **3**[4] (Table I). Alternatively, the anion **2a** is prepared quantitatively by treatment of 1-(bromo)-2-(ethoxy)-1-(phenylthio)ethylene (**4**)[5] with *n*-butyllithium (1 equiv) in ether[6] at −70° for 0.5 h.[7]

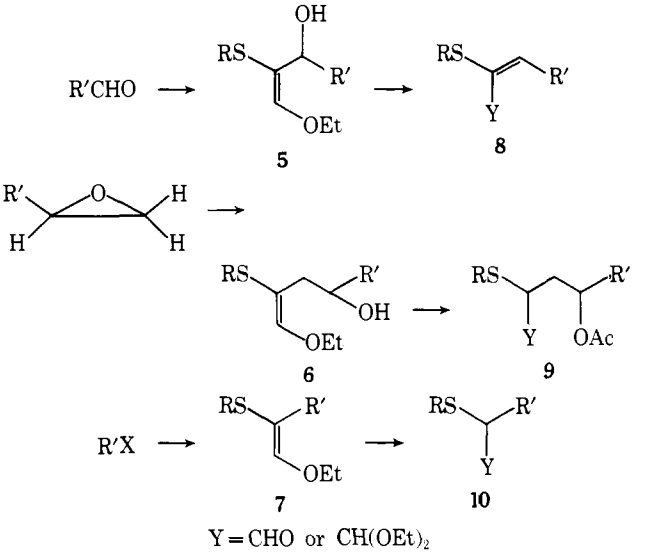


1 **2** **3** **4**

a, R = Ph b, R = n-C_5H_{11}

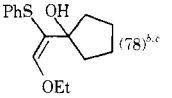
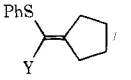
At −70°, the anion **2** reacts smoothly with aldehydes and ketones to produce the allylic alcohols **5**[8] in excellent yields (Scheme I). Under acidic (aqueous HCl, THF, 5 min, 0°) or weakly basic ($SOCl_2$–pyridine, ether–hexane, −20°) conditions, these substances undergo facile rearrangements[9] to produce α-mercapto-α,β-unsaturated aldehydes **8** (Y =

Scheme I



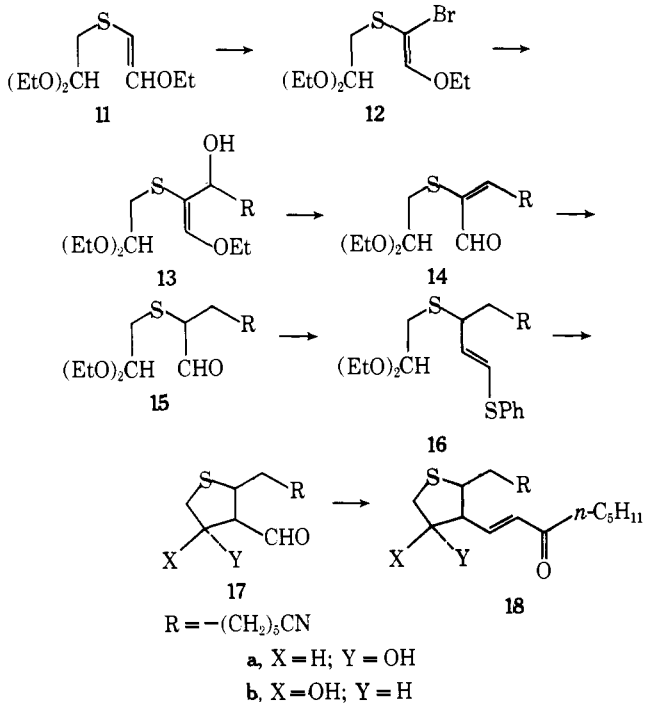
Y = CHO or $CH(OEt)_2$

Table I. Reaction of 2-(Ethoxy)-1-(pentyl or phenylthio)vinyllithium with Electrophiles

RSCH=CHOEt		Adduct (yield %)[a]		Rearrangement or solvolysis product[e]	
R	Electrophile	R	R'	R	R'
Ph	Benzaldehyde	5 Ph	Ph (75)[c,j]	8 Ph	Ph[f]
n-C_5H_{11}	Benzaldehyde	5 n-C_5H_{11}	Ph (80)[c,j]	8 n-C_5H_{11}	Ph[f]
Ph	Cyclopentanone	 (78)[b,c]			
Ph	Crotonaldehyde	5 Ph	$-CH=CHCH_3$ (78)[b,c]	8 Ph	$-CH=CHCH_3$[f,j]
Ph	Heptanal	5 Ph	n-C_6H_{13} (84)[c,j]	8 Ph	n-C_6H_{13}[f,g,j]
n-C_5H_{11}	Heptanal	5 n-C_5H_{11}	n-C_6H_{13} (82)[b,c]	8 n-C_5H_{11}	n-C_6H_{13}[f]
Ph	Ethylene oxide	6 Ph	H (60)[c,j]	9 Ph	H[h,i]
Ph	Propylene oxide	6 Ph	CH_3 (55)[d,j]		
Ph	1-Iodobutane	7 Ph	n-C_4H_9 (55)[d,j]		
n-C_5H_{11}	1-Bromobutane	7 n-C_5H_{11}	n-C_4H_9 (42)[d,j]	10 n-C_5H_{11}	n-C_4H_9[h]
n-C_5H_{11}	1-Iodobutane	7 n-C_5H_{11}	n-C_4H_9 (60)[d]		

[a] Unless otherwise indicated the yields were based on products isolated by preparative TLC. [b] The yields were determined by spectral data of the crude products. These adducts were subjected to rearrangement reactions without purification. [c] Reaction in THF. [d] Reaction in THF/HMPA. [e] Unless otherwise indicated, all rearrangements and solvolyses proceeded in 85–90% yields. [f] Rearrangement with 1 N aqueous HCl in THF at 0° for Y = CHO and with *p*-TsOH in ethanol at 0° for Y = $CH(OEt)_2$. [g] Rearrangement with $SOCl_2$ and pyridine in ether–hexane at −20° for Y = CHO. [h] Solvolysis with aqueous AcOH at 50° for Y = CHO and with *p*-TsOH in ethanol for Y = $CH(OEt)_2$. [i] Solvolysis proceeded in 40–50% yield. [j] Reference 17.

Scheme II



CHO). The corresponding acetals **8** (Y = $CH(OEt)_2$) are analogously prepared (*p*-TsOH, EtOH, 5 min, 0°).

We have examined the reaction of **2** with epoxides. In THF at −70°, the anion **2a** reacts smoothly with ethylene oxide to yield **6** (R = Ph R′ = H) in good yield. Under similar conditions, the alkylation of **2a** with propylene oxide is sluggish. The alkylation, however, proceeds well in the presence of HMPA and affords regioselectively the isomer **6** (R = Ph R′ = CH_3).

The alkylation of **2** with halides was also investigated. As in the case of propylene oxide, the alkylation of **2** with 1-bromo- or 1-iodobutane requires HMPA as cosolvent with THF, to provide acceptable yields of **7** (R′ = *n*-Bu). We were, however, unsuccessful in alkylating **2** with benzyl bromide or isopropyl iodide (presumably due to trans metalation).

The substituted ethylenes **6** and **7** can be further solvolized to yield α-alkyl- or arylmercaptoacetaldehydes (aqueous AcOH, 50°) or acetals (EtOH, *p*-TsOH, 25°)

A typical procedure for the generation and reaction of **2a** or **b** with electrophiles is illustrated in the preparation of 1-(ethoxy)-2-(phenylthio)-1-hexene (**7**, R = Ph, R′ = *n*-C_4H_9). To a solution of 0.9 g (5 mmol) of 1-(ethoxy)-2-(phenylthio)ethylene (**1a**)[1] in THF (20 ml) and HMPA (2 ml), 4 ml (5 mmol) of 1.23 M *t*-BuLi was added dropwise at −70° over a period of 15 min. After stirring for 1 h at −70°, 0.92 g (5 mmol) of *n*-butyl iodide in 1 ml of THF was added over a period of 1 min. The mixture was stirred at −70° for 1 h and allowed to warm up slowly to room temperature. Water was added, the mixture was extracted with ether, and the isolated crude product was subjected to preparative TLC to give 630 mg of **7** (53% yield).

A useful synthetic application of synthons of the type **2** was the preparation of the aldehyde **15** (Scheme II), a key intermediate in one of our synthetic routes to 9-desoxo-9-thiaprostaglandins.[10] Bromination of the vinyl sulfide **11**[11,17] (1 equiv of Br_2, ether, 0°) followed by dehydrobromination without isolation of the resulting dibromide (1 equiv. of DBN, ether, 0°)[5] gave the vinyl bromide **12**[17] (75%). Lithiation without purification of **12** (1 equiv of *n*-BuLi, ether, −70°, 30 min), followed by reaction of the resulting vinyllithium with 6-cyanohexanal, gave the allylic alcohol **13**[17] (75%). Treatment of **13** with 1 equiv of thionyl chloride in the presence of 2 equiv of pyridine in ether–hexane, 1:1, at −20°, followed by addition of water, gave the unsaturated aldehyde **14**[17] (90%), which was reduced catalytically (30% Pd/C, ethanol) to give after chromatography from silica gel the desired aldehyde **15** (85%; δ 9.19 (d, CHO, *J* = 5 Hz), 4.5 (t; $CH(OEt)_2$), 2.3 (t, CH_2CN, *J* = 6 Hz).[12]

Reaction[13] of the lithium salt (*n*-BuLi, THF, −70°) of diethyl phenylthiomethylphosphonate[14] with **15** (−70° to room temperature) produced the *trans*-vinyl sulfide **16**[15] (75%; δ 6.29 (d, PhSCH=, *J* = 14 Hz), 5.72 (d of d, SCHC*H*=, *J* = 14 and 8 Hz). Compound **16** underwent a novel regioselective aldol cyclization upon treatment with an aqueous acetic–trifluoroacetic acid solution (AcOH–H_2O–CF_3COOH, 2:1:0.01; at room temperature, 48 h) to produce a 65:35 mixture of the epimeric aldehydes **17a,b**[16] (75%; ir 3420, 2245, 1715 cm^{-1}). The mixture of **17a,b** was converted (80%; $(CH_3O)_2P(O)CH_2CO$-*n*-C_5H_{11}, NaH, DME) without purification, to the known enones **18a,b**.[10]

We are presently expanding the scope of this reaction and its synthetic applications.

Acknowledgment. The authors wish to acknowledge the support and advice of Dr. H. Gschwend, the helpful discussions with Professor P. Yates, and to thank Mr. B. Korzun for thin layer chromatographies, Mr. G. Robertson for analyses, and Miss N. Cahoon, Miss R. Benke, and Mrs. B. Warren for spectra.

Supplementary Material Available: One table, listing NMR spectrum δ H values of various substituted ethylenes (1 page). Ordering information is given on any current masthead page.

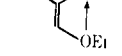
References and Notes

(1) (a) The vinyl ethers **1a,b** were prepared as a 35:65 mixture of cis–trans isomers[17] by elimination of ethanol from the corresponding mercapto acetaldehyde diethyl acetals, $RSCH_2CH(OEt)_2$ (picric acid, 150°; 65%; bp 120–125 °C (**1a**), 150–155 °C (**1b**) (15 mmHg)). (b) Alternatively, these compounds can be prepared from ethoxyacetylene and the corresponding mercaptans. See, J. F. Arens, A. G. Hermans, and J. H. Sperna Weiland, *Proc. K. Ned. Acad. Wet., Ser. B*, 58, 59 (1955).

(2) K. Oshima, K. Shimoji, H. Takashi, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **95**, 2694 (1973).

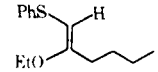
(3) J. E. Baldwin, G. A. Höfle, and O. W. Lever, Jr., *J. Am. Chem. Soc.*, **96**, 7125 (1974).

(4) Low temperature quenching of the anion **2** with D_2O or H_2O gives rise to 95% of the trans and only trace of the cis isomer **1**, indicating that the vinyllithium is the major anionic species in solution.



(5) The vinyl bromide **4**[17] is the only isomer produced (75%; bp 105–108 °C (0.1 mmHg)) by bromination of **1b** (1 equiv of Br_2, ether, 0°) to give the unstable dibromide, PhSCHBrCHBrOEt, followed by dehydrobromination of the latter (1 equiv of diazabicyclononane, ether, 0°).

(6) The choice of ether as the solvent in this metalation reaction is critical. When, for example, THF is used instead, the product



is produced in 40% yield. The synthetic significance of this finding is presently being investigated.

(7) For an analogous to **2** but substantially less stable organolithium species, see J. Ficini and J. C. Depezay, *Tetrahedron Lett.*, 937 (1968).

(8) These substances can also be prepared by addition of alkyl or arylmercaptans to the corresponding ethoxyacetylenes. See J. F. Sperna Weiland and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **75**, 1358 (1956).

(9) We feel that allylic rearrangement, rather than hydrolysis to the aldol and dehydration, is the appropriate characterization of the conversion of **5** → **8**, considering the rate of this transformation and the conditions under which it occurs.

(10) I. Vlattas and L. DellaVecchia, *Tetrahedron Lett.*, 4264, 4459 (1974).

(11) Prepared[1b] from ethoxyacetylene and mercaptoacetaldehyde diethyl acetal (bp 144–148 °C/15 mmHg).

(12) Alternatively, this compound was synthesized as follows:

$(EtO)_2CHCH_2SCH_2COOEt \rightarrow (EtO)_2CHCH_2SCH(COOEt)(CH_2)_6CN \rightarrow$ **15**

(13) E. J. Corey and J. I. Shulman, *J. Am. Chem. Soc.*, **92**, 5522 (1970).
(14) Prepared $((EtO)_2P(O)CH_2SPh$, bp 145–150 °C (0.1 mmHg)) from triethyl phosphite and chloromethyl phenyl sulfide (Arbusow reaction). For a recent preparation of chloromethyl phenyl sulfide, see B. M. Trost and R. A. Kunz, *J. Org. Chem.*, **39**, 2648 (1974).
(15) A 2:3 mixture of *cis*- and *trans*-vinyl sulfides **16** was obtained when the aldehyde **15** was treated with triphenylphosphinephenylmercaptomethylene in Me_2SO at 25°.
(16) The yield, as well as the ratio of the epimeric aldehydes **17a,b** was not affected when a cis–trans mixture of the sulfide **16**[15] was subjected to the cyclization reaction.
(17) For NMR spectrum δ H values of this compound, see Table in Supplementary material.

Isidoros Vlattas,* Laurence DellaVecchia, Avelina Ong Lee
Research Department, Pharmaceuticals Division
CIBA-GEIGY Corporation
Summit, New Jersey 07901
Received August 22, 1975

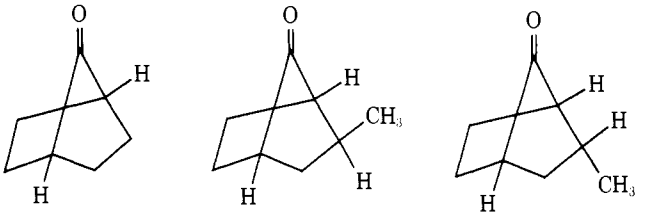
Evidence against Product Development Control as an Important Factor in the Reduction of Ketones by Simple and Complex Metal Hydrides

Sir:

All mechanisms concerning the stereoselective addition or reduction of ketones assume that the entering group approaches the carbonyl carbon on a line perpendicular to the plane of the carbonyl group so that maximum orbital overlap is achieved in the transition state. Dauben and co-workers[1] coined the terms "steric approach control" and "product development control" and suggested that these factors are important in determining the stereochemistry of $LiAlH_4$ reduction of cyclohexanones. Steric approach control implies an early, reactant-like transition state in which the entering group approaches the least-hindered side of the ketone. Product development control implies a late, product-like transition state in which the observed isomer ratio reflects the stability of the product.

Eliel and co-workers[2-5] have cast doubt on the importance of product development control by studying competitive rate experiments involving $LiAlH_4$ and 3,3,5-trimethylcyclohexanone. They have shown that an axial methyl group in the 3 and/or 5 position retards the rate of axial attack compared to 4-*tert*-butycyclohexanone, whereas the rate of equatorial attack remains essentially the same. This observation is not consistent with that predicted by product development control in which an axial methyl substituent would be expected to retard equatorial attack. However, in cyclohexanones other influential factors can be involved, such as torsional strain,[6] compression effect,[7] and conformational changes.[8] We would like to report reduction studies of a model ketone system in which the above mentioned effects are nonexistent so that steric approach control and product development control can be evaluated independently of these other effects.

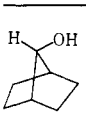
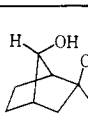
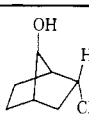
The ketone, 7-norbornanone (I), exhibits bridgehead hydrogen atoms in the 1 and 4 positions which eclipse the carbonyl group in the 7 position. This unique feature, unlike that of the 2,6-diequatorial hydrogens in cyclohexanone which lie 4–5° below the plane of the carbonyl group, eliminates torsional strain or compression effect as a complicating factor in evaluating stereochemical data obtained from this system. The fact that I is a rigid bicyclic system further eliminates conformational changes in the substrate as a further complicating factor. It is clear then the validity of the concept of product development control involving the reaction of $LiAlH_4$ with ketones can be more rigorously tested using this system.



I II III

The reaction of $LiAlH_4$ with I should produce the corresponding alcohol at twice the rate that $LiAlH_4$ reacts with II to produce the syn-alcohol, provided that product development control is not important in this reaction. If product development control is important, then of course, the rate of attack on II to produce the syn-alcohol should be decreased due to the effect of the 2-*exo*-methyl group on the developing transition state (product development control). Whether or not the 2-*exo*-methyl group is sufficiently bulky to exert a valid test for product development control can of course be evaluated by comparing the syn-anti alcohol ratio when $LiAlH_4$ is allowed to react with II. If the 2-*exo*-methyl group exerts a significant steric effect in this system then significally less anti-alcohol should be produced compared

Table I. Reaction of $LiAlH_4$ and AlH_3 with Ketones I, II, and III in Ether and Tetrahydrofuran[a]

Run	Reducing agent	Solvent	Ratio[b] hydride:ketone I	II	III	Recovered Ketone (%)[c] I	II	III	Products (%)[d] 			Mass Bllance
1	$LiAlH_4$	Et_2O	6	–	–	0	–	–	95.0	–	–	95.0
2	$LiAlH_4$	Et_2O	–	6	–	–	0	–	–	93.7	–	93.7
3	$LiAlH_4$	Et_2O	–	–	6	–	–	0	–	–	92.2	92.2
4	$LiAlH_4$	Et_2O	0.25	0.25	–	60.6	80.4	–	27.5	13.9	–	91.2
5	$LiAlH_4$	Et_2O	0.25	–	0.25	70.8	–	71.8	20.1	–	20.8	91.8
6	$LiAlH_4$	Et_2O	–	0.25	0.25	–	74.3	59.0	–	14.2	28.9	88.2
7	$LiAlH_4$	Et_2O	0.11	0.11	0.11	69.3	81.7	71.8	20.6	11.2	19.7	91.4
8	$LiAlH_4$	THF	–	6	–	–	–	–	–	94.3	–	94.3
9	$LiAlH_4$	THF	–	0.25	0.25	–	78.6	61.7	–	14.9	29.1	92.0
10	$LiAlH_4$	Et_2O	–	0.22	0.11	–	168.8	72.6	–	21.3	22.0	94.9
11	$LiAlH_4$	Et_2O	–	0.16	0.04	–	325.5	81.7	–	31.2	15.8	90.8
12	$LiAlH_4$	Et_2O	–	0.04	0.16	–	89.3	321.7	–	4.1	35.7	90.2
13	AlH_3	THF	–	6	–	–	–	–	–	96.3	–	96.3
14	AlH_3	THF	–	0.25	0.25	–	70.9	62.7	–	15.8	30.4	90.0

[a] The hydride was added to 0.032 mmol of ketone at 25° for 2 h. [b] Hydride:ketone = 6 is equivalent to $LiAlH_4$:ketone mole ratio of 1.5:1. [c] Percent of each ketone recovered based on 100% relative to the hydride added. [d] Percent of each product based on 100% relative to the amount of hydride added.