Preparation of Simple Chiral Allenes. Reaction of Propargylic Carbamates with Lithium Dialkylcuprates

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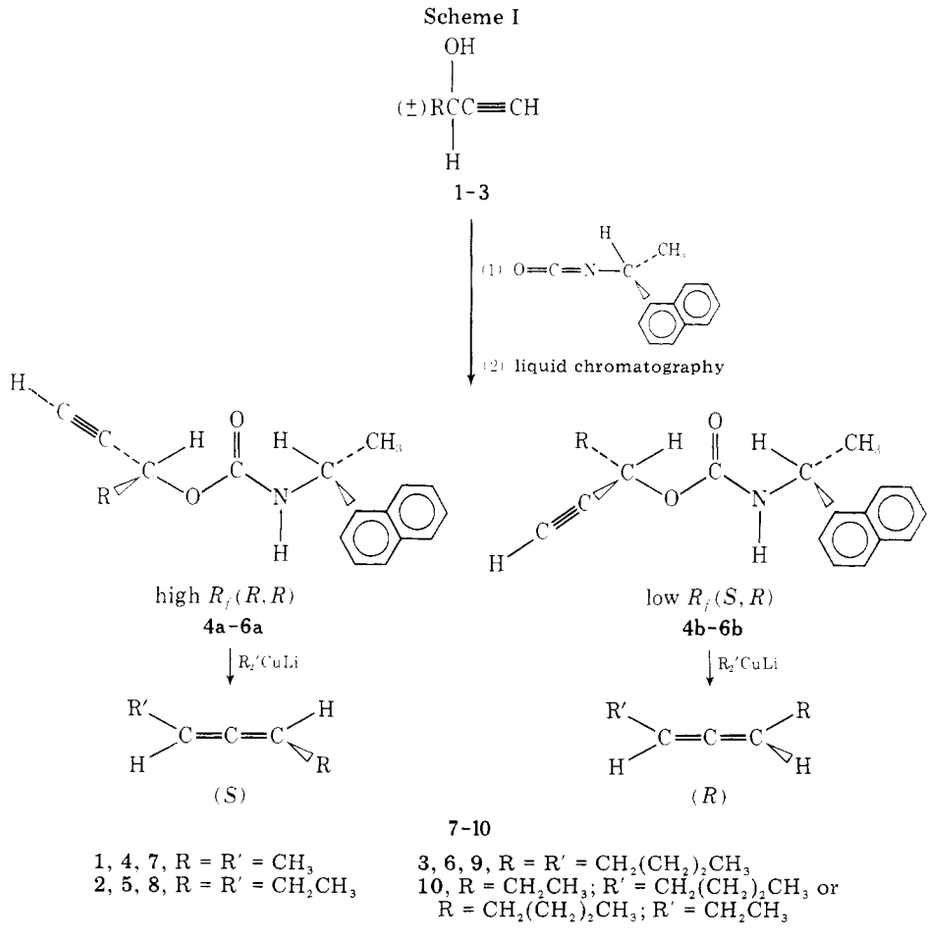
The diastereomeric carbamates derived from (*R*)-1-[1-naphthyl]ethyl isocyanate and racemic secondary propargylic alcohols such as 1-butyn-3-ol, 1-pentyn-3-ol, or 1-heptyn-3-ol are readily separable by multigram HPLC. Once separated, these diastereomers react with dialkylcuprates at low temperature to afford 1,3-dialkylallenes in high yields and with substantial enrichment (60–80% ee) in one enantiomer. Both enantiomers of the allene may be obtained; absolute configurations are predictable.

In the absence of additional functional "handles" for resolution, chiral allenes of high enantiomeric purity are not generally obtainable.[1] For example, partial hydroboration of a racemic allene with an asymmetric dialkylborane affords but modest enantiomeric enrichment of the residual allene.[2] While cycloelimination reactions leading to chiral allenes have been reported,[3,4] resolution of the chiral precursors may be tedious and the resulting allenes may be of but low enantiomeric purity.[3] Corey and Borden have prepared 1,3-di-*tert*-butylallene of high enantiomeric purity from a chiral propargyl alcohol.[5] However, this reaction, which also affords substantial amounts of an achiral acetylene, has not been shown to be generally useful as a preparative method for allenes. A preparative procedure of documented generality has been reported by Crabbé; the reaction of propargylic acetates with lithium dialkylcuprates efficiently affords a variety of allenes.[6,7] Importantly, Crabbé showed in one instance that a chiral acetate afforded an optically active allene, albeit in modest enantiomeric purity. This reaction can be considerably improved; the present report describes several such modifications that convert Crabbé's original approach to a simple and convenient method for efficiently obtaining either enantiomer of a chiral allene in relatively high enantiomeric purity.

Scheme I outlines the synthesis of enantiomerically enriched 1,3-dialkylallenes starting from racemic propargylic alcohols. The diastereomeric carbamates derived from racemic propargylic alcohols such as **1–3** and (*R*)-1-[1-naphthyl]ethyl isocyanate are readily separable by multigram HPLC. After separation, lithium dialkylcuprates react with these diastereomers at −78 °C to afford chiral allenes having a substantial degree of enantiomeric enrichment. Our modification simplifies the resolution of the chiral precursor, makes it unnecessary to retrieve the chiral alcohol from the resolving agent, and obviates the need to convert the alcohol to acetate. Use of reaction temperatures lower than those used by Crabbé results in enhanced enantiomeric purities.

For example, high R_f (*R*,*R*) carbamate diastereomer **6a**

Scheme I



7-10

1, **4**, **7**, R = R′ = CH_3
2, **5**, **8**, R = R′ = CH_2CH_3
3, **6**, **9**, R = R′ = $CH_2(CH_2)_2CH_3$
10, R = CH_2CH_3; R′ = $CH_2(CH_2)_2CH_3$ or R = $CH_2(CH_2)_2CH_3$; R′ = CH_2CH_3

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Table I. Synthesis of Chiral 1,3-Dialkylallenes by the Reaction of Lithium Dialkylcuprates with Propargyl Esters at −78 °C

Lithium cuprate	Registry no.	Ester	Registry no.	Allene	Registry no.	Inverse addition $[\alpha]^{25}_D$	Inverse addition % yield[a]/% ee[g]	Normal addition $[\alpha]^{25}_D$	Normal addition % yield/% ee
Di-*n*-butyl	24406-16-4	**6a**	65391-25-5	(*S*)-**9**	65253-19-2	+34.7 (5, $CHCl_3$)	78/51	+54.5 (3.6, $CHCl_3$)	76/80
		6b	65337-07-7	(*R*)-**9**	65253-20-5	−33.4 (7, $CHCl_3$)	75/49	−51.2 (5.5, $CHCl_3$)	76/75
		6b		(*R*)-**9**		−2.5 (3.3, $CHCl_3$)	77/5[b]		
		11	65252-17-0	(*S*)-**9**		+26.2 (5, $CHCl_3$)	60/39		
		12	65253-18-1	(*S*)-**9**		+30.5 (1.1, $CHCl_3$)	73/45		
		5a	65337-08-8	(*S*)-**10**	20431-70-3	+27.9 (4.6, $CHCl_3$)	74/34	+42.4 (4.2, $CHCl_3$)	77/52
		5b	65335-09-9	(*R*)-**10**	65337-12-4	−49.4 (5, $CHCl_3$)	79/61	−40.2 (4.2, $CHCl_3$)	79/50
Diethyl	38297-20-0	**5a**		(*S*)-**8**	20431-62-3	+62.8 (4, $CHCl_3$)	73/60	+33.8 (2, $CHCl_3$)	72/33
		5b		(*R*)-**8**	34862-66-3	−62.6 (5.1, $CHCl_3$)	71/60	−28.0 (1.2, $CHCl_3$)	72/27
		5b		(*R*)-**8**				−26.4 (1, $CHCl_3$)	74/26[c]
		6a		(*S*)-**10**		+53.2 (4.3, $CHCl_3$)	70/66	+21.4 (3.5, $CHCl_3$)	72/26
		6b		(*R*)-**10**		−27.7 (4.3, $CHCl_3$)	73/34	−27.4 (4.7, $CHCl_3$)	73/34
Dimethyl	15681-48-8	**4a**[d]	65337-10-2	[e]					
		6b		[e]					
		13	65337-11-3	(*R*)-**7**	20431-56-5	−29.7 (2.6, Et_2O)	30/19[d,f]		
Di-*tert*-butyl	23402-75-7	**6a**		[e,f]					
1-Pentynyl(*n*-butyl)	39697-41-1	**6a**		(*S*)-**9**					<15/-[e,f]
SPh(*n*-butyl)	53128-68-0	**6b**		(*R*)-**9**		−53.4 (1.6, $CHCl_3$)	20/82[g]		

[a] Determined by GLPC. [b] Reaction time of 3 h at −30 to −40 °C. [c] Carbamate at −78 °C when added. [d] Di-*n*-butyl ether used as solvent. [e] Recovered starting material. [f] Reaction time of 18 h. [g] Reaction time of 24 h.

(relative and therefore absolute configurations assigned by NMR differences between **6a** and **6b**[8]) reacts with lithium di-*n*-butylcuprate at −78 °C to afford (*S*)-(+)-1,3-di-*n*-butylallene whereas (*S,R*) diastereomer **6b** similarly affords (*R*)-(−)-1,3-di-*n*-butylallene. Enantiomeric purities of 75–80% have been attained. Table I summarizes the yields and estimated enantiomeric purities[9] for allenes prepared in the course of this study.

An important and unanticipated finding is that the optical yield of the reaction depends upon the order in which reagents are mixed and that the optimum mixing order is not the same for all cuprates. This "mixing order" effect[12] on allene enantiomeric purity is greater in magnitude than the small but real variations in enantiomeric purity encountered between two diastereomers using a given mixing order.[13] The difference in stereospecificity between a pair of diastereomers was most pronounced during the "crossing" experiments that led to 3,4-nonadiene. That such differences may occur is clear in principle. However, we presently have no insight into the actual origin of these differences. Indeed, there is little detailed understanding of the mechanism of this multistep allene-forming reaction.[6]

It is evident from data in Table I that the nature of the leaving group also influences the enantiomeric yield of the reaction. Using similar conditions, the enantiomeric purities of the allenes derived from inverse addition of lithium di-*n*-butylcuprate to the tosylate (**11**), acetate, (**12**), and carbamate(s) (**6a** (or **6b**)), respectively of resolved 1-heptyn-3-ol, were observed to increase in the order 39, 45, and 51% (or 49%). It would appear that poorer leaving groups afford higher enantiomeric yields. Similarly, less reactive cuprates may also afford higher enantiomeric yields.[14] For example, the mixed lithium thiophenoxy(*n*-butyl)cuprate did react with carbamate **6b** to afford 1,3-di-*n*-butylallene of greater enantiomeric purity (82% ee) than that obtained using optimal conditions with di-*n*-butylcuprate (76% ee). However, the yield of allene was much reduced (20%) and most of the starting carbamate was recovered. Lithium dimethylcuprate was also found to be unreactive toward propargyl carbamate **4a.** However, this reagent does react with the tosylate (**13**) of (*S*)-1-butyn-3-ol to afford (*R*)-(−)-1,3-dimethylallene albeit in low yield and enantiomeric purity.

In summary, racemic secondary propargylic alcohols can be readily resolved as diastereomeric carbamates by multigram HPLC. These carbamates react with lithium dialkylcuprates at −78 °C to afford chiral allenes of high enantiomeric purity and in high yield. This reaction sequence represents a simple and convenient two-step synthesis of chiral allenes from readily available starting materials.

Experimental Section

Cuprous iodide was purified by a method previously described.[15] Ethyllithium was prepared in diethyl ether in a manner analogous to Gilman's preparation of *n*-butyllithium.[16] *n*-Butyllithium in hexane was obtained from Ventron Corp. Racemic propargylic alcohols were either prepared by the addition of the appropriate aldehyde to ethynylmagnesium bromide[17] or were purchased from Farchan Acetylenes. Lithium dialkylcuprates were prepared as previously described: dimethyl,[18] diethyl,[18] di-*n*-butyl,[18] di-*tert*-butyl,[19] thio-

phenoxy (*n*-butyl),[19] and 1-pentynyl (*n*-butyl).[20] Alcohols (*S*)-**1** and (*R*)-**3** were prepared from **4b** and **6a** respectively by trichlorosilane cleavage.[21]

Carbamates 4–6. These diastereomers were prepared and separated as previously described.[8] Chromatographic separation of the propargylic carbamate diastereomers is general and facile, increasing in ease for higher members of the series.

(*R*)-1-Heptynyl 3-Acetate (12). To a cold (0 °C) stirred solution of (*R*)-**3** (4 mmol) in diethyl ether (10 mL) was added *n*-butyllithium in hexane (4 mmol). After stirring for 10 min, acetyl chloride (4.2 mmol) was added dropwise and the mixture was stirred for 2 h. The reaction mixture was extracted with 10% $NaHCO_3$ (2 × 10 mL) and dried ($MgSO_4$) and the ether was removed under reduced pressure to afford **12** (95%) as a colorless liquid: NMR (CCl_4) δ 0.9 (triplet, 3, CH_3), 1.4 (multiplet, 4, $CH_2CH_2CH_2CH_3$), 1.7 (multiplet, 2, $HOCHCH_2$), 2.0 (singlet, 3, CO_2CH_3), 2.27 (doublet, 1, C≡CH), 5.2 (dt, 1, HOCH).

Allenes. All allenes were prepared by either (or both) of the procedures described below for the preparation of 1,3-di-*n*-butylallene.

A. Normal Addition. Carbamate **6a,** 1.04 g (3.5 mmol), in diethyl ether (25 mL) was added dropwise over a 10-min period to a stirred solution of di-*n*-butylcuprate (3.5 mmol) in diethyl ether (15 mL) cooled with acetone–dry ice. After being stirred for an additional 7 h at −78 °C, the cooling bath was removed and the reaction mixture was allowed to come to 0 °C, quenched with saturated aqueous NH_4Cl (20 mL), and stirred for 15 min to allow the copper salts to precipitate. The mixture was filtered and the organic layer was separated, washed with saturated aqueous NH_4Cl (20 mL), dried ($MgSO_4$), and concentrated at reduced pressure. Molecular distillation of the residue afforded 0.4 g (76%) of (*S*)-(+)-1,3-di-*n*-butylallene: $[\alpha]^{25}_D$ +54.5° (3.6, $CHCl_3$); IR (film) 1945 cm^{-1} (allene); NMR)ccl$_4$) δ 0.9 (triplet, 6, CH_3), 1.3 (multiplet, 8, $CH_2CH_2CH_2CH_3$), 1.95 (multiplet, 4, C=CCH_2), 4.95 (quintet, 2, HC=C).

B. Inverse Addition. Lithium di-*n*-butylcuprate (3.5 mmol) in diethyl ether (15 mL) cooled to −78 °C was added portionwise over 5 min to cold (−78 °C) stirred solution of carbamate **6a,** 1.08 g (3.5 mmol). The reaction mixture was stirred for 7 h at −78 °C and allene was isolated by a workup identical to that above. (*S*)-(+)-1,3-Di-*n*-butylallene, 0.39 g (74%), $[\alpha]^{25}_D$ +34.7° (5, $CHCl_3$), was obtained.

1,3-Dimethylallene (7). This allene was prepared from **13** as described in Table I. The allene was identical to authentic material by GLPC and gave the same methoxymercuration adduct.[2]

1,3-Diethylallene (8). This allene was prepared in various yields and enantiomeric purities as shown in Table I: IR (film) 1945 cm^{-1} (allene); NMR (CCl_4) δ 1.0 (triplet, 6, CH_3), 2.0 (multiplet, 4, CH_2CH_3), 5.1 (quintet, 2, HC=C).

3,4-Nonadiene (10). This allene was prepared in various yields and enantiomeric purities as shown in Table I: IR (film) 1955 cm^{-1} (allene); NMR (CCl_4) δ 0.97 (triplet, 6, CH_3), 1.32 (multiplet, 4, $CH_2CH_2CH_2CH_3$), 1.9 (multiplet, 4, C=CCH_2), 4.8 (quintet, 2, HC=C).

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Registry No.—(±)-**1,** 65337-13-5; (±)-**2,** 65253-21-6; (±)-**3,** 51586-58-4; (*R*)-**3,** 51703-65-2; (*R*)-1-[1-naphthyl]ethyl isocyanate, 42340-98-7.

References and Notes

(1) For a review of synthetic approaches to chiral allenes, see R. Rossi and P. Diversi, *Synthesis*, 25 (1973).
(2) W. L. Waters, W. S. Linn, and M. C. Caserio, *J. Am. Chem. Soc.*, **90,** 6741 (1968); W. R. Moore, H. W. Anderson, and S. D. Clark, *ibid.*, **95,** 835 (1973).
(3) J. M. Walbrick, J. W. Wilson, and W. M. Jones, *J. Am. Chem. Soc.*, **90,** 2895 (1968).
(4) R. J. Convers, PhD Thesis, University of Illinois, Urbana, Ill., 1974.
(5) W. T. Borden and E. J. Corey, *Tetrahedron Lett.*, 313 (1969).
(6) J. L. Luche, E. Barreiro, J. M. Dollat, and P. Crabbé, *Tetrahedron Lett.*, 4615 (1975).
(7) It has been recently reported [M. M. Midland, *J. Org. Chem.*, **42,** 2650 (1977)] that trialkylboranes act upon acetylide ions derived from propargylic acetates to efficiently afford allenes. The stereochemistry of this reaction has not yet been reported.
(8) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **42,** 1839 (1977).
(9) Some of the estimations of enantiomeric purity are based upon the assumption that all simple chiral allenes should have approximately the same maximum molecular rotation. This assumption seems reasonable on the basis of Brewster's model of optical activity.[10] Brewster's calculation of the maximum specific rotation to be expected for 1,3-dimethylallene ($[\alpha]_D$ +174°) receives considerable support from our recent experimental determination ($[\alpha]_D$ ±157°) of this rotation.[11] Experimentally determined maximum molecular rotations for 1,3-dimethylallene and 1,3-diethylallene are 107 and 100°, respectively.[11] For the purpose of this paper, we have used ±100° as the molecular rotation expected for an enantiomerically pure 1,3-di-*n*-alkylallene.
(10) J. H. Brewster, "Topics in Stereochemistry", Vol. 2, Wiley, New York, N.Y., 1967.
(11) W. H. Pirkle and C. W. Boeder, *J. Org. Chem.*, **42,** 3697 (1977).
(12) While the origin of this effect cannot be stated with certainty, it may reflect different solution structures for the cuprates.
(13) This small difference between allene enantiomeric purities suggests that structural variation of the chiral amine portion of the carbamate could lead to allenes having still greater enantiomeric purities.
(14) Since the degree of stereospecificity shown by a reaction is a consequence of the energy difference between the diastereomeric transition states, very low activation energies preclude large energy differences between the alternate pathways. When both activation energies are large, the difference between the pathways may be, but is not necessarily, large enough to afford significant stereoselectivity.
(15) G. B. Kauffman and L. A. Teter, *Inorg. Synth.*, **7,** 9 (1963).
(16) H. Gilman, "Organic Reactions", Vol. 8, Wiley, New York, N.Y., 1954, p 285.
(17) L. Skattebøl, E. R. H. Jones, and M. C. Whiting, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1967, p 792.
(18) C. R. Johnson and G. A. Dutra, *J. Am. Chem. Soc.*, **95,** 7777 (1973).
(19) G. H. Posner, C. E. Whitten, and J. J. Sterling, *J. Am. Chem. Soc.*, **95,** 7788 (1973).
(20) J. P. Marino and D. M. Floyd, *J. Am. Chem. Soc.*, **96,** 7138 (1974).
(21) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **42,** 2781 (1977).

Preparation of *exo*-Tricyclo[3.3.2.0^{2,4}]decan-9-one and Related Compounds

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Synthesis of *exo*-tricyclo[3.3.2.0^{2,4}]decan-9-one (**5**) through efficient (92%) Simmons–Smith reaction of olefinic ketal **4** is described. Efforts to extend this work to ketals **16** and **17** led unexpectedly to selective cyclopropanation anti to the ketal function and formation of **27** and **28,** respectively. Improvements in the preparation of various known intermediates are reported, including a doubling of the yield (to 50%) in oxidation of cycloheptatriene to tropone.

As part of a study of the photochemistry of tricyclic ketones we required *exo*-tricyclo[3.3.2.0^{2,4}]decan-9-one (**5**). In this report we describe convenient preparation of this substance along with other related synthetic transformations. Many of the compounds involved have been recorded previously, but we were able to make material improvements in some earlier preparations, provide two stereochemical assignments, and also uncover two examples of the Simmons–Smith reaction that specifically furnish an unexpected stereoisomer. There have been recent publications in related

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