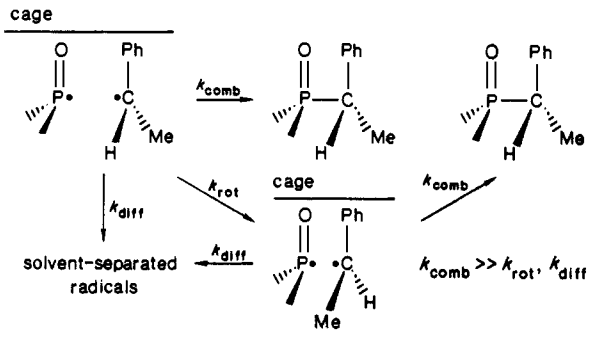
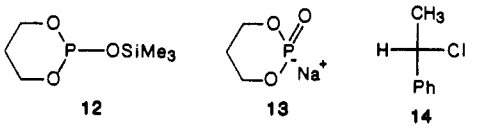
Scheme I



$\gg k_{diff}$. The enantiomeric composition of **8** was determined following stereospecific, retentive oxidation at 0 °C with $AIBN/O_2$.[6] After addition of optically pure *t*-Bu(Ph)P(S)OH,[7] a 400 MHz spectrum of **8**-oxide showed the methyls of the enantiomers of **8**-oxide as well-separated doublets of doublets (76 ± 2% ee). The enantiomeric purity of product **9** (74 ± 2% ee) was similarly assessed ($\Delta\delta$ = 13.1 Hz, $^3J_{HH}$ = 7.6 Hz, $^3J_{HP}$ = 19.1 Hz). The stereoselectivity of process **8** → **9** was thereby conservatively estimated to be >90% (C_6H_6).

The absolute stereochemistry of **8** → **9** was determined from the reactions of **12** and **13** with optically active **14**, processes of



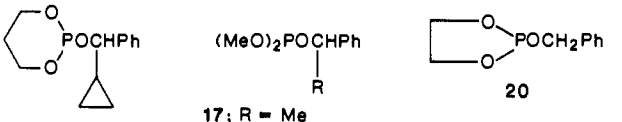
12 **13** **14**

known stereochemistry.[8] The stereoselectivity of the reaction of **12** (neat at 140–150 °C) was 95% while that of **13** (70–80 °C in DMF/C_6H_6) was about 50%. The latter reaction may involve a combination of S_N2 and S_N1 processes.

Scheme I expresses the mechanistic implications of the crossover and stereochemical results. For geminate pair **15**, *combination is decidedly more rapid than either rotation or diffusion* ($k_{comb} \gg k_{rot}, k_{diff}$).

The high stereospecificity and low percentage of diffusion products noted for the photo-Arbuzov process is similar to the findings for the thermal Stevens 1,2-rearrangement ($R_2\bar{C}$—$^+NR'_3$ → $R_2R'C$—NR'_2). Quantitative CIDNP[9] and stereochemical[10] studies led to the conclusion[9] that the major portion of the Stevens rearrangement of a series of *p*-X-C_6H_4CO-$\bar{C}H$—$^+NMe_2CH_2C_6H_4$-Y-*p* in $CHCl_3$ is either concerted or proceeds via radical pairs ($R_2\dot{C}$—NR'_2 + R'·), generated in very close proximity, which combine unusually rapidly. If the depicted P-O-CH_2Ph conformation for **5** undergoes reaction, the close proximity of the benzyl carbon to the odd electron of **1** or **15** (or the lone pair of **5**) is evident. *Alternatively*, a four-electron 1,2-sigmatropic shift with retention of configuration at both migrating carbon and phosphorus terminus is in accord with the Woodward-Hoffman rules[11] for the excited singlet of such systems. Rapid combination[12] of the singlet pair **15**, with the same stereochemical consequences, is hard to distinguish from the truly concerted process or mixture of the two. Resolution of this issue may come from work now in progress on the stereochemistry at phosphorus of the photo-Arbuzov rearrangement as well as from future investigations of rearrangements involving stereochemically restricted molecules and quantitative CIDNP studies.

The generality, regiospecificity, and potential usefulness of these photo-Arbuzov rearrangements are shown by the very clean formation of benzylphosphonates from **5**, **8**, and **16**–**20**.[13] By



16 **17**; R = Me **18**; R = cyclopropyl **19**; R = H **20**

contrast, secondary halides (RX, eq 1) react sluggishly with phosphites like **5**, **9**, and **18** and give several products because of the side reactions of CH_3X and EtX formed and attack by X^- at more than one carbon. Silyl phosphites such as **12**, useful in the Arbuzov reactions of secondary RX, are less easily obtained than are the corresponding $(RO)_2PCl$ precursors to the benzyl phosphites. The value of benzylphosphonates in alkene synthesis is well-known.[14]

Acknowledgment. This work was supported by grants from the National Science Foundation and Public Health Service, N.C.I. (CA 11045) which are gratefully acknowledged.

(13) For example, a 0.1 M solution of 50 mg of **8** in C_6H_6 is >95% rearranged to **9** in 2 h on irradiation through quartz.

(14) Wadsworth, W. S., Jr. *Organic Reactions*; John Wiley and Sons: New York, 1977; Vol. 25, Chapter 2.

Synthesis of (*R*)-(+)- and (*S*)-(−)-α-Damascone by Tandem Grignard Reaction–Enantioselective Protonation: Evidence for the Intermediacy of a Chiral Complex

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Received June 20, 1988

Since its discovery in 1970, (±)-α-damascone **5**[1] with its typical fruity flowery scent and exceptional odor strength has become an important perfume component, and numerous syntheses of (±)-**5** have been published.[2] The conversion of (*R*)-(+)-α-ionone into (*R*)-(+)-**5** (66% ee) by Ohloff and Uhde[1b] established the absolute configuration; however, enantiomerically pure (*R*)-(+)-**5** and (*S*)-(−)-**5** have not been prepared.[3]

We herein report the efficient synthesis of enantiomerically pure (*R*)-(+)-**5** and (*S*)-(−)-**5**[4] by regio- and diastereoselective Grignard reaction on ester enolate **2**[2a] or ketene **3**[2ac,5] followed by the highly

(6) Gajda, T. M.; Sopchik, A. E.; Bentrude, W. G. *Tetrahedron Lett.* **1981**, 4167.

(7) Harger, M. J. P. *J. Chem. Soc., Perkin Trans 2* **1980**, 1505; **1978**, 326.

(8) Vanden Berg, G. R.; Platenburg, D. H. M. J.; Benschop, H. P. *Chem. Commun.* **1971**, 606.

(9) Dolling, U. H.; Closs, G. L.; Cohen, A. H. *J. Chem. Soc., Chem. Commun.* **1975**, 545.

(10) Ollis, W. D.; Rey, M.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1975**, 543.

(11) Woodward, R. B.; Hoffman, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, 1970.

(12) (a) From studies of singlet pairs of $PhCH_3CH$·, *formed with a N_2 molecule between them* from the corresponding azo compounds, it was estimated that $k_{rot}:k_{diff}:k_{comb}$ = 15:2.4:1.0. Greene, F. D.; Berwick, M. A.; Stowell, J. C. *J. Am. Chem. Soc.* **1970**, *92*, 867. (b) Kopecky, K. R.; Gillan, T. *Can. J. Chem.* **1969**, *47*, 2371.

(1) (a) Ohloff, G. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer: Wien, 1978; Vol. 35, p 431. Demole, E.; Enggist, P.; Säuberli, U.; Stoll, M.; sz. Kovats, E. *Helv. Chim. Acta* **1970**, *53*, 541. (b) Ohloff, G.; Uhde, G. *Helv. Chim. Acta* **1970**, *53*, 531.

(2) (a) For recent syntheses, see: Fehr, C.; Galindo, J. *J. Org. Chem.* **1988**, *53*, 1828. (b) Snowden, R. L.; Linder, S. M.; Muller, B. L.; Schulte-Elte, K. H. *Helv. Chim. Acta* **1987**, *70*, 1858. Zaidlewicz, M. *Tetrahedron Lett.* **1986**, *27*, 5135. (c) Naef, F.; Decorzant, R. *Tetrahedron* **1986**, *42*, 3245. (d) Fehr, C.; Galindo, J. *Helv. Chim. Acta* **1986**, *69*, 228.

(3) The absolute configuration of natural **5** is unknown. For another preparation of (*R*)-(+)-**5** (17% ee), see: Shibasaki, M.; Terashima, S.; Yamada, S. *Chem. Pharm. Bull.* **1975**, *23*, 279.

(4) (*S*)-(−)-**5** is by far the more precious and powerful fragrance, see: Fehr, C.; Galindo, J. Swiss Patent application 5.2.1988. In addition, (*R*)-(+)-**5** opens a route to the diterpene (−)-forskolin, following Baraldi et al. (Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Polo, E.; Simoni, D. *J. Chem. Soc., Chem. Commun.* **1986**, 757.

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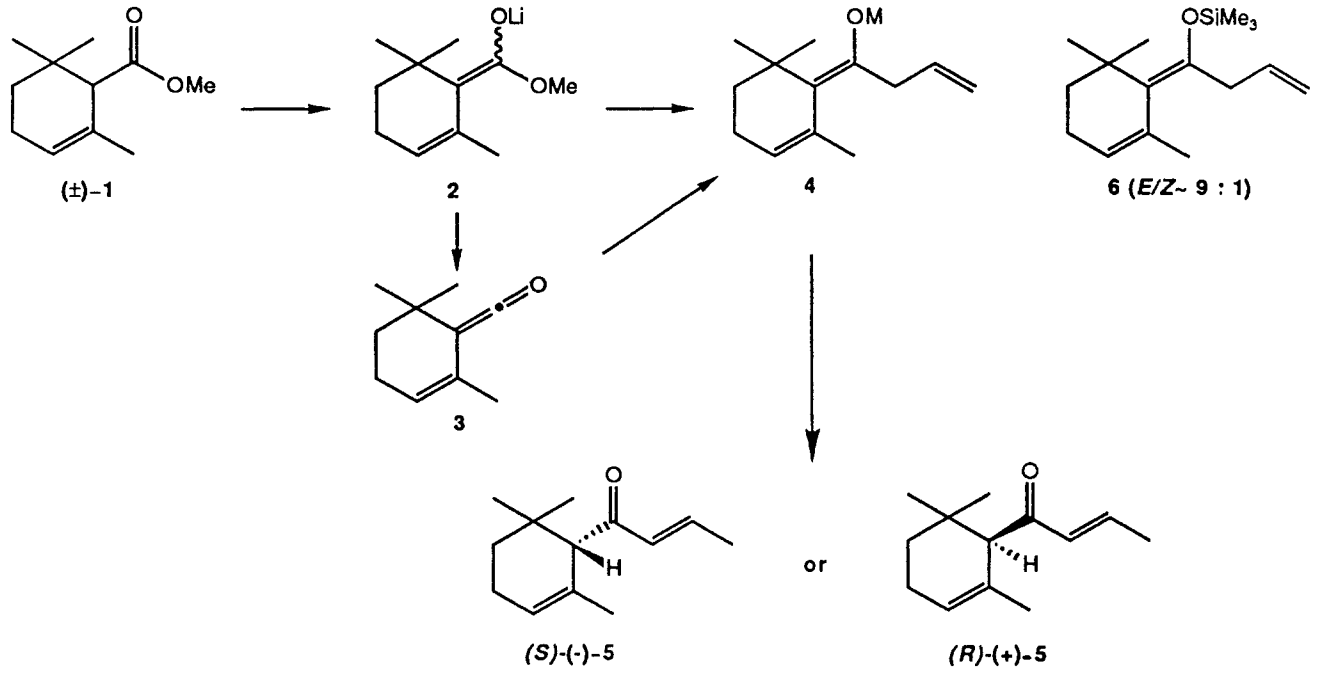
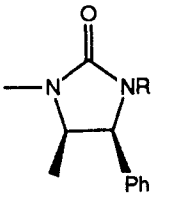
Scheme I



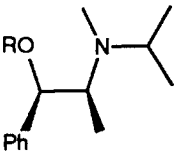
enantioselective protonation (up to 12:1) of ketone enolate **4** (Scheme I). We have found that, in addition to the choice of the chiral proton source, the success of the reaction critically depends on the formation of a mixed Li, Mg-complex between the enolate **4** and a chiral alkoxide.

Up to now, enantioselective protonation has met with limited success, and the rare examples which describe appreciable enantiomeric excesses (50–70%) are restricted to rigid ester enolates of defined configuration (cyclic systems or metal chelates) possessing supplementary hetero atoms and, ideally, a phenyl group at the α-C position.[6,7]

We felt that a judicious elaboration of the chiral proton source would allow wider applicability for enantioselective protonation.[8] For the rational design of an efficient and synthetically useful chiral proton source we were guided by the following criteria. The chiral reagent should be only weakly acidic (pK_A 15–20) to allow better transition-state discrimination. It should also contain electron-rich groups with coordination of chelation ability[9] which would enhance conformational rigidity in the transition state. Optimally, the transferred proton should be located in the proximity of the stereogenic center. Ideally, the chiral reagent should be readily accessible in both its enantiomeric forms and easily recoverable. These criteria are fulfilled with the ephedrine derivatives **7**(H)[10] and **8**(H):[11] imidazolidone **7**(H) has an N–H bond confined in a rigid cyclic system, and **8**(H) (also **8**(Li), **8**(MgCl)) can attain conformational rigidity through chelation.



R = H (+)-7(H)
R = Li (+)-7(Li)



R = H (-)-8(H)
R = Li (-)-8(Li)
R = MgCl (-)-8(MgCl)

In an initial experiment, ester **1** was deprotonated with *n*-BuLi, and the resultant ester enolate **2** was treated with allylmagnesium chloride to afford ketone enolate **4** (E/Z ≈9:1).[2a] Protonation of **4** with (+)-**7**(H) or (−)-**8**(H) (Table I, entries 1 and 2) and subsequent isomerization of the terminal double bond (Al_2O_3, Et_2O, 20°)[12] gave (*S*)-(−)-**5** (60%)[13] with 58% ee[14] and 70% ee,[15] respectively.[16] In contrast, protonation of **4** with 2*R*,3*R*-dipivaloyltartaric acid[6a] provided (*S*)-(−)-**5** with an ee of only 8%.

In order to better understand the influence of counterion and ligand and to avoid the use of *n*-BuLi,[13] we next investigated the reaction of allylmagnesium chloride with ketene **3**.[2a,c] The thus formed THF-solvated but otherwise ligand-free enolate **4** was either protonated directly or treated with a chelating agent prior

(5) For related works, see ref 2c and Häner et al. (Häner, R.; Laube, T.; Seebach, D. *J. Am. Chem. Soc.* **1985**, *107*, 5396). Baigrie, L. M.; Seiklay, H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 5391.

(6) (a) Duhamel, L.; Duhamel, P.; Lannay, J. C.; Plaquevent, J. C. *Bull. Soc. Chim. Fr.* **1984**, II-421. Duhamel, L.; Plaquevent, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 7415. (b) Duhamel, L.; Fouguay, S.; Plaquevent, J. C. *Tetrahedron Lett.* **1986**, *27*, 4975. Duhamel, L.; Plaquevent, J. C. *Bull. Soc. Chim. Fr.* **1982**, II-75. Duhamel, L.; Plaquevent, J. C. *Tetrahedron Lett.* **1980**, *21*, 2521. (c) Stoyanovich, F. M.; Zakharov, E. P.; Goldfarb, Y. L.; Krayushkin, M. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1986**, 1455; *Chem. Abstr.* **1987**, *106*, 49586s. Gerlach, U.; Hünig, S. *Angew. Chem.* **1987**, *99*, 1323.

(7) Benzoin, obtained from the corresponding potassium dienolate via enantioselective enol–ketone tautomerization (80% ee), falls into the same structural category. For a related enantioselective photodeconjugation of α,β-unsaturated esters (max. 70% ee), see: Piva, O.; Henin, F.; Muzart, J.; Pete, J. P. *Tetrahedron Lett.* **1987**, *28*, 4825.

(8) Typically, a chiral proton source used for the "deracemization" of amino acid derivatives by enantioselective protonation of the corresponding anions was 2*R*,3*R*-dipivaloyltartaric acid.[6a,b] A priori, it seemed attractive to take into account the *enolate* structural requirements for the design of the proton source.

(9) For the influence of chiral or achiral ligands (R_1R_2NH), see ref 6b. The presence of a phenyl group was also expected to be beneficial. For stacking interactions, see: Rebek, J., Jr.; Nemeth, D.; Ballester, P.; Lin, F. T. *J. Am. Chem. Soc.* **1987**, *109*, 3474.

(10) Prepared from (−)- or (+)-ephedrine and urea: Helmchen, G.; Peters, E. M.; Peters, K.; Schnering, H. G. *Angew. Chem.* **1984**, *96*, 895. Close, W. J. *J. Org. Chem.* **1950**, *15*, 1131.

(11) Prepared from (−)- or (+)-ephedrine, acetone, and a reducing agent in analogy to the following: Saavedra, J. E. *J. Org. Chem.* **1985**, *50*, 2271. Adamski, R. J.; Numajiri, S. U.S. Patent 3860651 (application 23.10.1969); *Chem. Abstr.* **1975**, *82*, 170330t: $[\alpha]_D^{20}$ ($CHCl_3$, *c* 6) −2.1° or +2.1°; bp 90 °C/0.05 Torr.

(12) Reetz, M. T.; Wenderoth, B.; Urz, R. *Chem. Ber.* **1985**, *118*, 348.

(13) To ensure complete deprotonation of **1**, a 20% excess of *n*-BuLi was employed; however, under these conditions, the formation of undesired 2,6,6-trimethyl-2-cyclohexen-1-yl-1-pentanone (~10%) could not be completely avoided.

(14) Crystalline (+)-**7**(H) is recovered by filtration.

(15) Amine (−)-**8**(H) is recovered by extractive acid–base treatment.

(16) Taking into account the diastereomeric excess of enolate **4** (80–85% de) the measured (NMR with Eu(HFBC)$_3$) enantiomeric excesses of **5** are excellent.

Table I. Enantioselective Protonation of Enolate 4

entry	substrate	reaction cond (equiv; °C; min)	% ee 5	% dist yield 5
1	1	(1) *n*-BuLi (1,2; −78 → 15; 30) (2) C_3H_5MgCl (1.3; 15 → 35; 20) (3) (+)-7(H) (2.0; −50 → −10; 60)	58(*S*)	60[a]
2		(3)[b] (−)-8(H) (2.0; −50 → −10; 60)	70(*S*)	60[a]
3	3	(1) C_3H_5MgCl (1.2; −78 → 35; 30) (2) (−)-8(H) (1.5; −50 → −10; 60)	16(*R*)	*c*
4		(2)[b] MeOLi (1.0; 35; 30) (3) (−)-8(H) (2.0; −50 → −10; 60)	70(*S*)	75
5		(2)[b] (−)-8(Li) (1.0; 20; 30)	84(*S*)[e]	73[e]
		(3) (−)-8(H) (2.0; −50 → −10; 60)[d]	>98(*S*)[f]	48[f]
6		(2)[b] (+)-8(Li) (1.0; 20; 30)	84(*R*)[g]	73[g]
		(3) (+)-8(H) (2.0; −50 → −10; 60)	>98(*R*)[g]	48[g]
7		(2)[b] (−)-8(Li) (1.0; 20; 30) (3) (+)-8(H) (2.0; −50 → −10; 60)	63(*R*)	*c*
8		(2)[b] (−)-8(Li) (1.0; 20; 30) (3) *t*-BuOH (2.0; −78 → 0; 60)	62(*S*)	70

[a] See footnote 13. [b] (1) (and (2)) as above. [c] Yield not determined. [d] Use of 1.3 equiv of (−)-8(H) gave 78% ee. [e] Procedure (entry 5): ketene 3 (10 g, 66.6 mmol) in THF (200 mL) was sequentially treated with C_3H_5MgCl (in THF), (−)-8(Li) (from (−)-8(H) + *n*-BuLi (1.0 equiv) in THF), and (−)-8(H) (for equiv; °C; min, see Table I). The reaction mixture was poured into aqueous NH_4Cl/ice and extracted (Et_2O), and the organic phase was treated with 5% aqueous HCl. The combined aqueous phases were washed (Et_2O), basified (20% aqueous KOH), and extracted (Et_2O) to afford (−)-8(H) (98% distilled yield). The ketone mixture obtained from the organic extracts was distilled (bulb-to-bulb, 70 °C (oven), 0.5 Torr; 9.7 g) and isomerized (Al_2O_3, Et_2O, 20 °C, 1 h;[12] or *p*-TsOH/toluene, 20 °C, 15 h) to afford (*S*)-(−)-5 (9.3 g, 73%) containing ~5% of isomeric butenones ($[\alpha]^{20}_D$ ($CHCl_3$, *c* 4.0) −396°). [f] Enantiomerically pure (*S*)-(−)-5 [(6.13 g, 48%), $[\alpha]^{20}_D$ ($CHCl_3$, *c* 4.0) −488°; mp 27.5–28 °C] was obtained by repeated crystallization (pentane). [g] Same procedure as above, see *e* and *f*; (*R*)-(+)-5: $[\alpha]^{20}_D$ ($CHCl_3$, *c* 3.6) +487°; mp 27.5–28 °C.

to protonation. Much to our surprise, protonation of the ligand- and lithium-free enolate 4 (M = MgCl) afforded (*R*)-(+)-5 (16% ee) as the major enantiomer (Table I, entry 3). On the other hand, addition of 1 equiv of MeOLi prior to protonation (Table I, entry 4), thus restoring the conditions present when starting from ester 1 (Table I, entry 2), furnished (*S*)-(−)-5 with 70% ee. Next, enolate 4 (M = MgCl, from ketene 3) was treated with (−)-8(Li) and protonated with (−)-8(H) to afford (*S*)-(−)-5 with 84% ee (>98% ee after crystallization[4]) (Table I, entry 5). These results represent the highest ee yet reported for enantioselective enolate protonation and can be considered as the result of a double stereodifferentiation.[16] Interestingly, protonation of the same species with (+)-8(H) (Table I, entry 7) gave (*R*)-(+)-5 (63% ee), whereas protonation with an achiral proton source (*tert*-butyl alcohol) gave (*S*)-(−)-5 with 62% ee (Table I, entry 8). In addition, the use of (+)-8(Li) and (+)-8(H) (Table I, entry 6) allowed the synthesis of (*R*)-(+)-5 (84% ee;[16] >98% ee after crystallization[4]).

Although enolates are known to form aggregates,[17] deaggregation and chelation[6b,17bc] should also be considered for the understanding of enolate chemistry. In particular, the dichotomy observed when apparently the same enolate 4 (with or without lithium alkoxide) is protonated with (−)-8(H) (Table I, entries 3, 4, and 5) leads us to the conclusion that the formation of a mixed lithium–magnesium 1:1 complex between 4 and an alkoxide is a prerequisite for high enantioselectivity.[18] Moreover, the protonation with *tert*-butyl alcohol (Table I, entry 8) constitutes the first example of substantial chirality induction via an in situ formed chiral enolate–alkoxide complex.[19] At present, it is premature to present a detailed mechanistic rationale for the observed enantioselectivity; nevertheless, it is evident that the protonating species does not undergo fast proton exchange with the chelated alkoxide: otherwise the experiment with (−)-8 (Li) as ligand and (+)-8(H) as proton source (Table I, entry 7) would have given essentially racemic 5 (ee ≤33%). On the other hand, exchange processes between Li and Mg are rapid: indeed, in a crossover experiment, the lithium enolate 4 (M = Li; from 6 + MeLi in THF) was treated with the magnesium alkoxide (−)-8(MgCl) (from (−)-8(H) + C_3H_5MgCl) and subsequently protonated with (−)-8(H) to afford (*S*)-(−)-5 with 84% ee. Thus, the same mixed lithium–magnesium complex is obtained, independent of the origin of Li and Mg. The analogous magnesium-free–lithium complex shows lower enantiofacial discrimination (65% ee), and the lithium-free–magnesium complex is ineffective (10% ee).

(17) (a) Seebach, D. *Proc. R. A. Welch Foundation Conf.* **1984**, *27*, 93. (b) Polt, R.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1930. Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373. Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622. Strazewski, P.; Tamm, C. *Helv. Chim. Acta* **1986**, *69*, 1041. (c) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539.

(18) Ongoing work confirms the importance of alkoxide ligands: replacement of MeOLi (see Table I, entry 4) by *t*-BuOLi affords 5 with 79% ee.

(19) The asymmetric induction reported by protonation of an aminoester enolate–chiral amine (R_1*R_2NH) complex with an achiral proton source is rather poor (6–24%): ref 6b. See, also: Wasmuth, D.; Seebach, D. *Angew. Chem.* **1981**, *93*, 1007. Hogeveen, H.; Menge, W. M. P. B. *Tetrahedron Lett.* **1986**, *27*, 2767 and references cited therein.

Allylic Radicals in Cyclization Reactions

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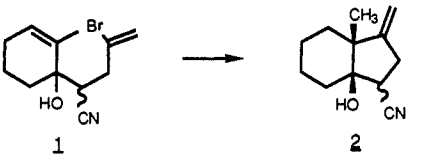
One important attribute of the vinyl radical cyclization (e.g., 1 → 2)[1] is that the vinyl functionality is retained in the resulting



1 2

ring and allows for varied subsequent chemical transformations. Another extension of the synthetic usefulness of radical cyclization reactions would result if allylic radicals could be involved in cyclization processes. It is this possibility that we address here.

We now show that allylic radicals, although clearly less reactive than their saturated or vinylic counterparts,[2,3] can provide a route complementary to a number of recently described organometallic[4] and Lewis acid[5] processes, to vinyl cyclopentane systems.

For instance, under the standard cyclization conditions (0.005 M benzene solution of 1.1 equiv of tributylstannane and 0.1 equiv of AIBN, reflux 1–2 h) the allylic bromide 3 as well as its isomer 4[6] cyclized readily (80% yield) to give a mixture of 5, 6, and 7

(1) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321.

(2) The allyl delocalization energy has recently been estimated to be 14.0–14.5 kcal/mol (Korth, H.-G.; Trill, H.; Sustmann, R. *J. Am. Chem. Soc.* **1981**, *103*, 4483).

(3) For isolated examples of cyclizations which involve allylic radicals produced by intramolecular hydrogen transfer to an alkoxy or a vinyl radical, see: Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81. Johns, A.; Murphy, J. A. *Tetrahedron Lett.* **1988**, *29*, 837.

(4) (a) Felkin, H.; Umpleby, J. D.; Hagaman, E.; Wenkert, E. *Tetrahedron Lett.* **1972**, *13*, 2285. (b) Lennon, P.; Rosenblum, M. *J. Am. Chem. Soc.* **1983**, *105*, 1233. (c) Oppolzer, W.; Jacobsen, E. J. *Tetrahedron Lett.* **1986**, *27*, 1141.

(5) (a) Majetich, G.; Defauw, J.; Hull, K.; Shawe, T. *Tetrahedron Lett.* **1985**, *26*, 4711. (b) Schinzer, D.; Solyom, S.; Becker, M. *Tetrahedron Lett.* **1985**, *26*, 1831. (c) Schinzer, D.; Allagiannis, C.; Wichmann, S. *Tetrahedron* **1988**, *44*, 3851.

(6) The dialkyl malonates 3, 4, and 8 were prepared by malonic ester alkylation (NaH, THF, 0 °C) with the appropriate allylic or propargylic substrates.

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