Allylic Metalation of Endo- and Exo-Cyclic Alkenes: Anomalous High Reactivity of β-Pinene

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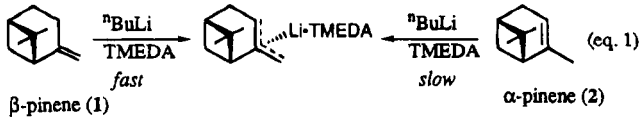
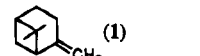
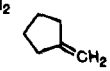
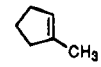
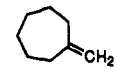
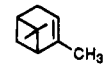
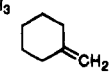
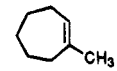
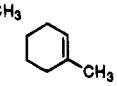
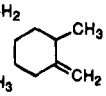
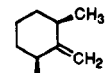
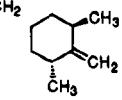
The allylic metalation of alkenes is a powerful method for the synthetic manipulation of this functionality.[1] Although metalation conditions are intolerant of many functional groups, the resulting allylmetallics can be elaborated in a wide variety of ways, including numerous carbon–carbon bond-forming reactions.[2] Direct formation of allylmetal species by deprotonation of simple alkenes requires extremely basic reagents,[1] such as *n*-BuLi·TMEDA,[3] *n*-BuLi/KO*t*-Bu,[4] or (trimethylsilyl)-potassium.[5] In the course of pursuing the preparation of new chiral auxiliaries and ligands from terpenes, we had occasion to study the metalation of α- and β-pinene. Allylic methyl groups are known[6] to be metalated more rapidly than internal allylic CH_2 positions, and on this basis one would expect that α-pinene would be more reactive than the β-isomer. Although only the metalation of α-pinene had been reported previously,[7] we found that β-pinene underwent allylic metalation far more rapidly (eq 1). This finding led us to undertake a systematic study of the relative reactivity of endo and exocyclic alkenes, and of β-pinene in particular, in an attempt to identify how structural factors influence the rate of allylic metalations.



Results

Relative Rate Studies. The most apparent difference between α- and β-pinene is in the orientation of the double bond. It is known that α-pinene is more stable than the β-isomer by 2–3 kcal/mol,[8] and β-pinene is especially reactive in cases where the double bond migrates into an endocyclic orientation[9] (e.g., ene reactions).[9a] To elucidate how double bond orientation, substitution, and ring size affect metalation, we studied the relative rates of metalation of endo and exocyclic alkenes containing five-, six- and seven-membered rings.

Table 1. Relative Rates of Metalation of Various Endo- and Exo-Cyclic Alkenes

Alkene	$k_{alkene}/k_{\beta\text{-pinene}}$[a] nBuLi·TMEDA	nBuLi/KOtBu[b]
 (1)	100	100
	76	172
	26	92
	26	48
 (2)	18	54
	16	37
	14	56
	13	36
 (3)	13	17
	12	20
	12	15
	11	15

[a] Relative rates were normalized to that of β-pinene (= 100). Values were typically reproducible to within ±10%. [b] Reaction used 0.75 M metalation reagent.

Two different metalation reagents, *n*-BuLi·TMEDA and *n*-BuLi/KO*t*-Bu, were employed. In both cases, *n*-BuLi was used as the commercially available 10 M solution in hexanes. In the reactions using TMEDA, no additional solvent was necessary; indeed, we found that dilution with solvent greatly decreased the reactivity. In the case of the *tert*-butoxide reactions, addition of a hydrocarbon solvent was necessary to suspend the solid alkoxide. For this purpose we used hexanes or (in the case of volatile alkenes) dodecane, with an overall concentration of metalation agent of 0.75 M. The relative rate studies were carried out by treating equimolar amounts of two alkenes (including a hydrocarbon internal standard) with an insufficiency of metalation reagent at room temperature. After 2–3 h, the reaction was terminated by addition of excess benzaldehyde, followed by hydrolysis and GC analysis. The amount of each unreacted alkene was determined, and the relative rate was calculated using the Ingold–Shaw equation[10] (eq 2), where [a] and

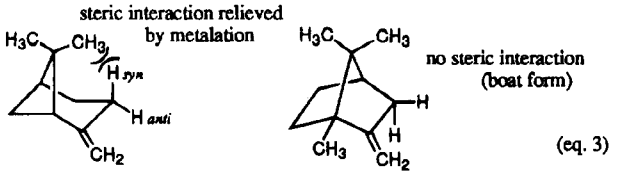
$$\frac{k_a}{k_b} = \frac{\ln[a]_i - \ln[a]_f}{\ln[b]_i - \ln[b]_f} \qquad \text{(eq 2)}$$

[b] are concentrations of alkenes being compared, and *i* and *f* denote initial and final values, respectively. With the exception of the pinenes (*vide infra*), no attempt was made to identify the reaction products, although formation of the expected number of regio- and stereoisomeric products was evident in the GC analysis. The results are summarized in Table 1.

(1) Schlosser, M. In *Organometallics in Synthesis*; John Wiley & Sons: New York, 1994; Ch. 1, pp 75–78, 116–119.
(2) Roush, W. R. In *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991; Vol. 2, p 1.
(3) Smith, W. N. *Adv. Chem. Ser.* **1974**, *130*, 23–55.
(4) Schlosser, M.; Hartman, *J. Angew. Chem.* **1973**, *85*, 544.
(5) Hartman, J.; Schlosser, M. *Helv. Chim. Acta* **1976**, *59*, 453.
(6) (a) Moret, E.; Schneider, P.; Margot, C.; Stahle, M; Schlosser, M. *Chimia* **1985**, *39*, 231. (b) Stahle, M.; Hartman, J.; Schlosser, M. *Helv. Chim. Acta* **1977**, *60*, 1730–38.
(7) (a) Andrianome, M.; Delmond, B. *J. Chem. Soc., Chem. Commun.* **1985**, 1203–04. (b) Zaidlewicz, M. *Organomet. Chem.* **1985**, *293*, 139–46. (c) Rauchschwalbe, G. Schlosser, M. *Helv. Chim. Acta* **1975**, *58*, 1094–99. (d) Brown, H. C.; Zaidlewicz, M.; Bhat, K. S. *J. Org. Chem.* **1989**, *54*, 1764–66.
(8) (a) Hawkins, J. E.; Eriksen, W. T. *J. Am. Chem. Soc.* **1954**, *76*, 2669–71. (b) Brown, C. A. *Synthesis* **1978**, 754–55.
(9) For example, see: (a) Bain, J. P. *J. Am. Chem. Soc.* **1946**, *68*, 638–41. (b) Dunne, K.; McQuillin, F. J. *J. Chem. Soc. (C)* **1970**, 2200.
(10) Ingold, C. K.; Shaw, F. R. *J. Chem. Soc.* **1927**, 2918.

0022-3263/95/1960-7051$09.00/0

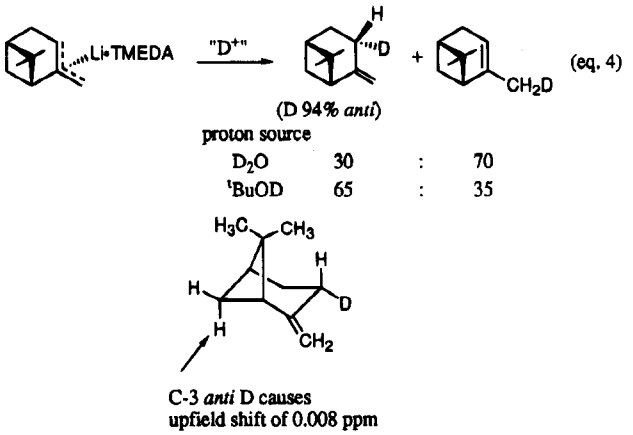
Several trends are evident: (a) The rate differences tend to be greater for n-BuLi·TMEDA than for n-BuLi/KO*t*-Bu, consistent with the greater reactivity of the latter.[4] Also, in a few cases differences in the order of reactivity are evident. (b) Five-membered ring alkenes are consistently more reactive than the corresponding cyclohexyl analogs, with the cycloheptyl compounds being of intermediate reactivity. (c) Increasing substitution of the ring in adjacent positions results in a moderate decrease in reactivity. (d) While β-pinene is much more reactive than α-pinene, comparison of 1-methylcyclohexene and methylenecyclohexane shows that this difference cannot be attributed simply to the generally increased reactivity of exocyclic double bonds. Indeed, methylenecamphor (**3**) is far less reactive than even α-pinene. These results are consistent with those of Schlosser for the difference in rates of metalation for *E* and *Z* alkenes,[6b] explained on the basis that metalations which result in a decrease in the steric crowding or overall strain within an alkene tend to proceed at faster rates. This "steric effect" can best be demonstrated by comparing the structures of β-pinene and methylenecamphor with their relative rates of metalation. In forming the allylmetallic of β-pinene, the steric interaction between the C-3 *syn* proton and the bridge methyl group is greatly diminished (eq 3). However, methylenecamphor does not benefit from the same effect, consistent with its significantly slower rate of metalation.



It should be noted that these relative rates do not necessarily allow accurate prediction of how long a particular metalation might take. For example, α-pinene can be significantly metalated (~25%) within a few hours, but even very long reaction times do not result in greater than about 50% reaction. This is because the metalation rate decreases significantly with time, especially when using the *n*-BuLi·TMEDA reagent. This is unlikely to be exclusively due to metalation of TMEDA[3] and perhaps is related to changes in aggregation which occur as the reaction proceeds. Also, we have observed that β-pinene undergoes significant isomerization (~5%) to α-pinene during metalations with the *n*-BuLi/KO*t*-Bu reagent. We attribute this to the more basic character of the presumed allylpotassium relative to the allyllithium, with the former apparently able to metalate β-pinene and in the process be converted at least partially to α-pinene. Separate experiments confirmed that the pinenyl metallic formed under these conditions can catalyze the isomerization of β-pinene to α-pinene. The *n*-BuLi/KO*t*-Bu relative rates were corrected for this isomerization in β-pinene reactions. However, this isomerization was not significant for the other alkenes or in the *n*-BuLi·TMEDA metalations of β-pinene (<1% α-pinene formed).

Our findings would suggest some important differences between these two metalation agents. For the less reactive olefins, such as α-pinene, the six-membered cyclic alkenes, and those that contain highly substituted double bonds, the use of even excess *n*-BuLi·TMEDA results in incomplete metalation, and the more reactive *n*-BuLi/KO*t*-Bu reagent is superior. For the more reactive alkenes, *n*-BuLi·TMEDA is easier to use and avoids the possibility of exo-to-endo isomerization observed with β-pinene. Also, in cases where isolation of the allylmetallic is desired, the presence of alkoxides is problematic and the *n*-BuLi·TMEDA reagent is preferred.[11]

Stereochemistry of β-Pinene Metalation. Given the apparently anomalous reactivity of β-pinene, further experiments were carried out to determine the stereochemistry of metalation. β-Pinene was quantitatively metalated using *n*-BuLi·TMEDA, followed by treatment with D_2O (eq 4).[12] This resulted in a 70:30 mixture of α- and β-pinene, each of which was monodeuterated to >99% (eq 4). Proton and deuterium NMR showed that the β-pinene consisted of a 94:6 mixture of *anti*:*syn* isomers.[13] Interestingly, protonation of the pinenyllithium using *tert*-butyl alcohol-O-*d* resulted in much more β-pinene (α:β 35:65) but essentially the same stereochemistry and level of deuterium incorporation. Also, we observed that deuterium substitution in the C-3 *anti* position caused a slight (0.008 ppm) upfield shift in



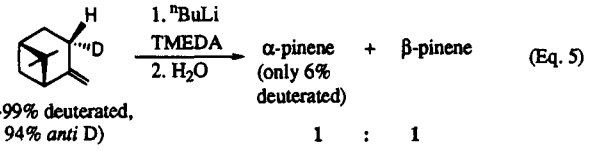
the C-7 *anti* proton, which appears as a doublet at 1.41 ppm.[13] This proton in the C-3 *syn* deuterated isomer is not shifted relative to unlabeled β-pinene (1.42 ppm). This long-range anisotropy, which had not been reported previously, confirmed the assigned stereochemistry. Integration of these doublets proved to be the most accurate way to quantify the stereochemistry of deuterium incorporation. The deuterated α- and β-pinenes were separated by either preparative GC or (preferably) by radial chromatography on silver nitrate-impregnated silica.[14] Subjection of the β-pinene obtained in this manner to the *n*-BuLi·TMEDA metalation conditions, followed by quenching with H_2O, yielded a 50:50 mixture of α:β pinenes in which the α-pinene was only 6% deuterated (eq 5). Thus, the metalation of β-pinene occurs with essentially complete selectivity for the C-3 *anti* position.

(11) We have isolated pinenyllithium·TMEDA from these solutions and obtained an X-ray structure (Shiner, C. S.; Garner, C. M.; Haltiwanger, R. C., unpublished results). The structure exhibits an essentially symmetrical η^3 allyllithium and, interestingly, was that of racemic material. The structural details will be published elsewhere.

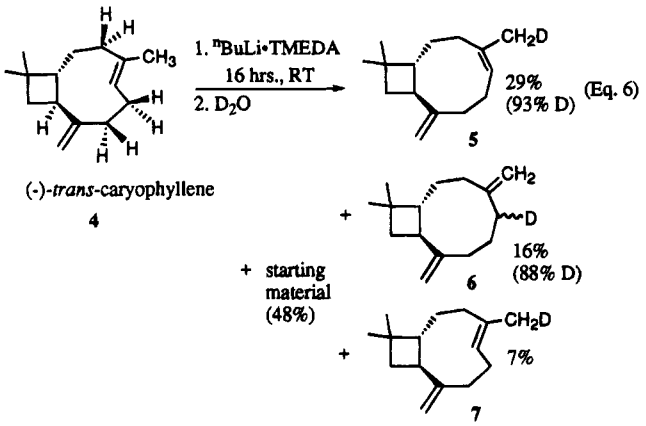
(12) Other routes to deuterated β-pinene: (a) Zaidlewicz, M.; Panda, C. S. *Synthesis* **1987**, 645. (b) Hori, T.; Singer, S. P.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 1456.

(13) The NMR assignments for the C-3 protons in β-pinene have recently been revised (Smith, W. B. *Magn. Reson. Chem.* **1994**, *32*, 316), correcting certain earlier reports (Laihia, K.; Kolehmainen, E.; Malkavaara, P.; Korvola, J.; Manttari, P.; Kauppinen, R. *Magn. Reson. Chem.* **1992**, *30*, 754; and B.-H. Ahmed, A. Y.; Meklati, B. Y.; Watson, H.; Pham, Q. T. *Magn. Reson. Chem.* **1992**, *30*, 807).

(14) Instrumentation and procedures for silver nitrate radial chromatography were obtained from Harrison Research, Palo Alto, CA.



The relative rates presented in Table 1 suggest that selective allylic metalations of appropriate substrates should be possible. However, we have observed that factors other than ring size and substitution can sometimes play an important role. For example, *trans*-caryophyllene presents five different potentially reactive allylic sites. Treatment with an equimolar amount of *n*-BuLi·TMEDA (25 °C, 16 h) resulted in approximately 50% metalation (eq 6). Separate reactions of the resulting allyllithium with benzaldehyde and with D_2O, followed by extensive GC, NMR, and MS analyses, revealed that metalation had occurred exclusively at the allylic methyl group. We attribute this high selectivity to the strained *trans* double bond.



Experimental Section

General. Except as noted, all reagents were used as received. (−)-β-Pinene and (+)-α-pinene were Aldrich products of approximately 92% ee. Methylenecycloheptane, methylenecamphor, *cis*- and *trans*-2,6-dimethyl-1-methylenecyclohexane, and 2-methyl-1-methylenecyclohexane were prepared from the corresponding ketones according to a literature procedure.[15] Isomerically pure 1-methylcycloheptene was prepared by addition of methyllithium to cycloheptanone followed by dehydration of the resulting tertiary alcohol with iodine. In all cases, *n*-BuLi used as a 10 M solution in hexanes. It was periodically titrated[16] to establish its exact concentration. TMEDA was distilled from CaH_2 under argon. Benzaldehyde was purified by washing with a 10% solution of sodium carbonate followed by distillation under reduced pressure. Deuterium oxide was the 99.8 atom % D grade. All glassware was carefully oven-dried, and air-sensitive materials were handled under Ar or N_2, according to standard procedures.

Gas chromatographic analyses used a 0.25 mm × 25 m SE-54 capillary column with flame ionization detection. All NMR analyses were done on a 360 MHz instrument using $CDCl_3$ as solvent unless otherwise noted. ^1H NMR spectra were referenced to TMS ($\delta = 0$); ^2H and ^{13}C NMR spectra were referenced to $CDCl_3$ ($\delta = 7.25$ and 77.0), respectively. MS analyses were done on a high resolution magnetic sector instrument.

General Procedure for the Relative Rate Studies. Two different alkenes of roughly similar reactivity from Table 1 were mixed in a 1:1 molar ratio with 5% of a hydrocarbon internal standard (octane or nonane). Several 5 μL aliquots were removed for GC analysis to confirm the initial amounts of both alkenes. The appropriate solvent and metalation reagent (0.5 equiv relative to the combined number of millimoles for both alkenes) was added. For the metalation reactions involving *n*-BuLi·TMEDA, the TMEDA was added prior to the dropwise addition of an equimolar amount of *n*-BuLi. For reactions involving *n*-BuLi/KO*t*-Bu, it was more convenient to add the potassium *tert*-butoxide to the reaction vessel (in a glove bag under argon) before adding the alkenes and internal standard. The solid residue was then suspended in anhydrous dodecane (~0.75 M in metalation reagent) followed by addition of *n*-BuLi. After 3 h of vigorous stirring under inert atmosphere, the reaction was quenched by slow addition of a slight excess of benzaldehyde at 0 °C. The resulting deep red suspension was hydrolyzed and analyzed by GC to determine the final amounts of both alkenes present in the mixture. Equation 2 was used to calculate the relative rate constants for the two alkenes. In order to obtain reproducible values (generally within ±10%), typically three different combinations were studied for any given alkene. In the *n*-BuLi/KO*t*-Bu reactions involving β-pinene, the relative rates were corrected for approximately 5% isomerization to α-pinene. For ease of comparison, relative rates were normalized relative to that of β-pinene (= 100).

Determination of the Stereospecificity of the Metalation of β-Pinene Using Deuterium Labeling: β-Pinene-3-*d*. β-pinene (2.5 mL, 16 mmol) was quantitatively metalated by addition of excess TMEDA (3.0 mL, 20 mmol) followed by *n*-BuLi (2.0 mL, 20 mmol) at 0 °C. The yellow suspension was allowed to warm to room temperature, and adequate stirring was continued for 6 h. Ether (5 mL) was added to the resulting deep orange allyllithium immediately before cooling the reaction vessel to −78 °C (dry ice/acetone bath). To the viscous suspension was added D_2O (99.8% D, 0.5 mL, 28 mmol) in a dropwise fashion. The heterogeneous mixture was allowed to warm to ambient temperatures over a period of 1 h. It was noted that its deep orange color did not dissipate until the temperature of the bath had reached −25 °C. The white residue was made homogeneous by addition of 5 mL each of water and hexanes. The two phases were separated, and the aqueous phase was reextracted with 5 mL of hexanes. The combined organic phases were washed with 5 mL each of water, 10% $CuSO_4$, and brine. They were dried over Na_2SO_4, and concentrated to a yellow oil. The ratio of α- to β-isomer in the product mixture was 70:30 as indicated by GC. The two deuterated pinenes were separated from more polar impurities by passing the sample through silica gel using hexanes. They were then separated using radial chromatography by employing a 4 mm plate coated with $AgNO_3$-impregnated silica.[14] Most of the endocyclic α-isomer was eluted by hexanes followed by a steep gradient elution of hexanes–EtOAc (98:2) to pure EtOAc to elute the much more strongly retained exocyclic β-isomer in a minimum amount of solvent. The resulting β-pinene-3-*d* (0.4 g, 18%) was 98% pure by GC. GC-MS indicated that it was >99% deuterated. Based on relative integrations from both ^1H and ^2H NMR spectra, the regioisomeric distribution of deuterium was found to be 94% *anti* and 6% *syn*.[13]

Protonation of the Allyllithium from β-Pinene-3-*d*. The allyllithium of β-pinene-3-*d* (150 mg, 1.1 mmol) was generated according to the same procedure used for the metalation of β-pinene. After adding ether (2 mL) to the orange allyllithium suspension and cooling to 0 °C, it was quenched by dropwise addition of water (0.2 mL, 11 mmol). The resulting mixture was worked up in the same manner as for β-pinene-3-*d*, with the exception that the α- and β-isomers (50:50 mixture by GC) were not separated. GC-MS indicated that the α-pinene formed in the protonation was 6% deuterated, and its ^1H NMR vinyl resonance ($\delta = 5.2$) was integrated to 91% of its normal value.

Metalation of (−)-*trans*-Caryophyllene (4). A mixture of (−)-*trans*-caryophyllene (0.50 mL, 2.2 mmol), nonane (25 μL), and TMEDA (0.33 mL, 2.2 mmol) at 0 °C under argon was treated with 10 M *n*-BuLi (0.23 mL, 2.3 mmol), allowed to warm to room temperature and stir for 16 h. A 10 μL aliquot was quenched with excess benzaldehyde, and GC analysis revealed that the reaction was 50% complete. The remainder of the reaction was cooled to −78 °C, diluted with ether (2 mL), treated with excess D_2O (0.1 mL, 5.6 mmol), and allowed to warm slowly to room temperature. Then water (2 mL) was added, and the products were extracted with hexanes. GC and GC-MS analysis versus nonane showed the presence of caryophyllene (1.21 mmol, 21% deuterated), isocaryophyllene (**5**, 0.66 mmol, 93% deuter-

(15) Fitjer, L.; Quabeck, U. *Synth. Commun.* **1985**, *15*, 855.
(16) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

ated), and the exocyclic isomer **6** (0.38 mmol, 88% deuterated). Identities of the products were determined by comparison to authentic materials[17] and/or by NMR analysis (^1H, ^2H, ^{13}C) of the mixture.

Isocaryophyllene-*d* (5): ^1H NMR (partial) 4.76 (m, 1H); 5.23–5.33 (m, 2H); ^{13}C NMR 22.9 (1:1:1 t, J = 19), 23.0, 25.6, 28.4, 28.7, 29.9, 33.0, 35.5, 40.0, 40.4, 51.8, 110.3, 124.9, 136.1, 156.5; $^2H\{^1H\}$ NMR 1.70 (s, C-13 allylic methyl); MS 206 (10.4%), 205 (100%), 204 (7.4%).

Exocyclic isomer 6: ^1H NMR (partial) 4.75 (br s); 4.78 (br s); ^{13}C NMR 22.0, 22.7, 26.7, 29.7, 31.1, 33.3, 34.1 (1:1:1 t, J = 19), 37.1, 37.4, 45.1, 54.2, 108.9, 119.9, 153.6, 156.5; $^2H\{^1H\}$ NMR 2.19 (s, allylic methylene); MS 205 (100%), 204 (14%).

Caryophyllene (4:1 mixture of 4:7): ^1H NMR (partial) 4.82 (br s, 1H); 4.94 (br s, 1H); 5.23–5.33 (m, 1H); ^{13}C NMR 16.3 (1:1:1 t, J = 19), 22.6, 28.4, 29.4, 30.1, 33.0, 34.8, 40.0, 40.3, 48.5, 53.5, 111.7, 124.3, 135.4, 154.6; $^2H\{^1H\}$ NMR: 1.64 (s, allylic methyl); MS 206 (0.6%); 205 (40%); 204 (100%).

(17) Authentic isocaryophyllene was prepared by isomerization of caryophyllene with sulfur: Kitchens, G. C., Ger. Patent 2 044 018, 1971; *Chem. Abstr.* **1971**, *75*, 49364j.

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