## CARBON-CARBON BOND FORMATION BY THE REACTION OF ORGANOLITHIUMS WITH α-LITHIATED CYCLIC ENOL ETHERS STEREOSELECTIVE SYNTHESIS OF β- AND γ-HYDROXY DI- AND TRI-SUBSTITUTED ALKENES

Thinh Nguyen and Ei-ichi Negishi

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907, USA

Summary  $\alpha$ -Lithiation of dihydrofuran, benzofuran, and dihydropyran followed by treatment with various organolithiums stereoselectively produces in good yields the corresponding ring-opened (*E*)-alkenyllithiums, i.e., (*E*)- $\beta(\text{or }\gamma)$ -hydroxy- $\omega$ -alkenyl- $\omega$ -lithioalkenes, the lithium atom of which can be readily replaced with H, D, or C groups, such as CO<sub>2</sub> and Me

In search for novel 1,2-migration reactions of organotransition metal compounds,<sup>1</sup> we prepared  $Cp_2ZrPh_2^2$  (<sup>1</sup>H NMR Cp singlet at 6.41 ppm) by treatment of  $Cp_2ZrCl_2$  with 2 equiv of PhLi at -78°C and reacted it with 2-lithuobenzofuran (1) generated *in situ* by treatment of benzofuran with 1 equiv of *n*-BuLi in Et<sub>2</sub>O at 0°C for 1 h After hydrolysis the desired product 2a was obtained in 99% yield. To ascertain the need for Zr species, we then ran the reaction of 1 with PhLi and found that it gave the same product 2a in almost 100% yield. Furthermore, quenching the reaction mixture with D<sub>2</sub>O produced 2b in 86% yield with  $\geq$ 95% D incorporation. Similarly, the reaction of 1 with *s*-BuLi and *t*-BuLi gave, after protonolysis, 3 and 4, respectively, in high yields. Generation of 1 in a discrete step may be unnecessary. Thus, for example, direct treatment of benzofuran with 2 equiv of *n*-BuLi led to the formation of 5 (80-90%), 6 (82%), and 7 (50%) in the yields indicated in parentheses, after quenching with appropriate reagents (Scheme 1)

Scheme 1



A similar organocopper reaction developed recently<sup>3</sup> has been reported to be a process requiring Cu species, although clarification of this point seems to require further investigation in view of the results presented herein Also known is the reaction of dihydropyran with 2 equiv of *n*-BuLi producing, after hydrolysis, (*E*)-4-nonen-1-ol (8) in 73% yield <sup>4</sup> This reaction was thought to involve addition of *n*-BuLi to the double bond of dihydropyran followed by  $\beta$ -elimination, providing only disubstituted alkenes rather than trisubstituted alkenes (eq 1) <sup>4</sup> We have indeed confirmed the reported experimental facts and established that, unlike the reactions shown in Scheme 1, no incorporation of D, I, or CO<sub>2</sub> occurs at the C-5 center. This reaction is therefore different from that reported here. It should also be pointed out that the Ni-catalyzed reaction of enol ethers with Grignard reagents<sup>5</sup> is a syn process, the stereochemistry of which is completely opposite to that observed in this study



A further investigation of the reaction of dihydropyran with organolithiums has revealed that the difference between the reaction reported here and that reported by Pattison and Dear<sup>4</sup> stems from the relative rates of  $\alpha$ -alkenyl proton abstraction and the presumed organolithium addition to enol ethers as in eq. 1. Thus, deprotonation of dihydropyran with 1 equiv of *t*-BuLi to produce discretely  $\alpha$ -lithiodihydropyran (9)<sup>6</sup> followed by its treatment with 2 equiv of *n*-BuLi in Et<sub>2</sub>O at 0°C for 8 h did produce a product readily convertible to 10 (60% yield, 70% D incorporation) and 11 (40% yield) (eq. 2)



Dihydrofuran reacts in a manner similar to that of benzofuran Its reaction with 2 equiv of n-BuLi has led to the formation of 12 (70-80%), 13 (65%), and 14 (55%) in the yields indicated in parentheses



In each case, the trans isomer was formed as a  $\ge 98\%$  stereoisomerically pure species. The trans geometry of the products has been established mainly on the basis of the coupling constants ( $J = ca \ 16 \ Hz$ ) and the IR bands at 965-975 cm<sup>-1</sup> for disubstituted alkenes as well as the <sup>1</sup>H NMR chemical shift values for the methyl groups bonded to the alkenyl carbon atoms, e g,  $\delta \ 163 \ ppm^7$  for 14<sup>3a</sup> Facile formation of 6, 11, and 13 via carbonation further supports the stereochemical assignment

In contrast with cyclic vinyl ethers, acyclic vinyl ethers,<sup>8</sup> such as ethyl vinyl ether, do not appear to readily undergo the same carbon-carbon bond forming reaction. Thus,  $\alpha$ -lithiovinyl ethyl ether generated *in sum* by treatment of vinyl ethyl ether with *t*-BuLi in THF (-78 to 0°C) did not react with *n*-decyllithium generated by treatment of 1-iododecane with two equiv of *t*-BuLi in ether<sup>9</sup> Removal of THF prior to the addition of *n*-decyllithium did not induce any favorable change The current practical scope of the reaction is therefore limited to the cases where cyclic ethers are used

Although we have not yet made serious efforts to clarify the mechanism of these reactions, it appears certain that  $\alpha$ -lithiated cyclic enol ethers, i.e., 1, 9, and 15, are formed as intermediates. Their reaction with organolithiums may involve an addition-elimination process similar to that suggested by Patison and Dear<sup>4</sup> Alternatively, it may involve a Li-assisted substitution via inversion at the oxygen-bearing alkenyl carbon center similar to that observed with organoboranes<sup>10</sup> In view of the previously reported results shown in eq. 1, however, the addition-elimination mechanism (eq. 3) offers an attractive feature of providing a unified mechanism for all cases observed to date. On the other hand, a reasonable assumption that such an addition-elimination process might involve a syn addition and an anti-elimination would lead to the opposite stereochemistry. Further investigation is required for clarification of such mechanistic details



The following procedure is representative To a solution of 2,3-benzofuran (10 mmol, 0 118 g, 0 11 mL) in diethyl ether (4 mL) at 0°C was added dropwise *n*-butyllithium (10 mmol, 10 mL) Lithiation to generate 1 was complete in 1 h as judged by <sup>1</sup>H NMR spectroscopy One additional equivalent of *n*-butyllithium (10 mmol) was added to 1 After 6 h at room temperature, the reaction mixture was treated with CO<sub>2</sub> at -78°C, quenched with 3N HCl, extracted with diethyl ether, dried over MgSO<sub>4</sub>, and chromatographed (silica gel, 5 1 pentane-ether) to give 0 165 g (82% yield) of 3-(*n*-butyll)-2H-benzopyran-2-one <sup>11</sup> <sup>-1</sup>H NMR (CDCl<sub>3</sub>, Me<sub>4</sub>Si)  $\delta$  0 96 (t, *J* = 7 Hz, 3H), 1 3-1 5 (m, 2H), 1 6-1 7 (m, 2H), 2 57 (t, *J* = 7 Hz, 3H), 7 2-7 5 (m, 5H), <sup>13</sup>C NMR (CDCl<sub>3</sub>, Me<sub>4</sub>Si)  $\delta$  14 09, 22 62, 30 27, 30 76, 116 56, 119 78, 124 40, 127 29, 130 21, 130 63, 138 53, 153 27, 162 05, IR (Nujol) 1726 (s), 1614 (s), 1458 (s) cm<sup>-1</sup>, MS (CI) *m/z* 203 (MH)

Acknowledgments We thank the National Science Foundation (CHE-9023728) for support of this research

## **REFERENCES AND NOTES**

- For our previous studies in this area, see (a) Negishi, E, Akiyoshi, K, O'Connor, B, Takagi, K, Wu, G J Am Chem Soc 1989, 111, 3089 (b) Takagi, K, Rousset, C J, Negishi, E J Am Chem Soc 1991, 113, 1440
- (2) Erker, G, Kropp, K J Am Chem Soc 1979, 101, 3659
- (3) (a) Kocienski, P, Wadman, S, Cooper, K J Am Chem Soc 1989, 111, 2363 (b) For a review, see Kocienski, P, Barber, C Pure Appl Chem 1990, 62, 1933 (c) For an earlier paper describing the synthesis of disubstituted (E)-alkenes, see Fujisawa, T, Kurita, Y, Kawashima, M, Sato, T Chem Lett 1982, 1641
- (4) Pattison, F L M, Dear, R E A Can J Chem 1963, 41, 2600
- (5) (a) Wenkert, E, Michelotti, E L, Swindell, C S J Am Chem Soc 1979, 101, 2246, (b) Wenkert, E, Michelotti, E L, Swindell, C S, Tingoli, M J Org Chem 1984, 49, 4894 (c) Wadman, S, Whitby, R, Yeates, C, Kocienski, P, Cooper, K J Chem Soc, Chem Commun 1987, 241 (d) Kocienski, P, Dixon, N J, Wadman, S Tetrahedron Lett 1988, 29, 2353
- (6) Boeckman, R K, Jr, Bruza, K J Tetrahedron Lett 1977, 4187
- (7) Kobayashi, M, Valente, L F, Negishi, E Synthesis 1980, 1034
- (8) (a) Schöllkopf, U, Hänssle, P Liebigs Ann Chem 1972, 763, 208 (b) Baldwin, J E, Höfle, G A, Lever, O W, Jr J Am Chem Soc 1974, 96, 7125 (c) Soderquist, J A, Hsu, G J H Organometallics 1982, 1, 830
- (9) Negishi, E., Swanson, D. R., Rousset, C. J. J. Org. Chem. 1990, 55, 5406
- (10) For a review, see Negishi, E in Comprehensive Organometallic Chemistry, Wilkinson, G T, Stone, F G A, Abel, E W, Eds, Pergamon, New York, 1982, Chap 45 8, pp 303-322
- (11) Kıtagawa, H, Iwakı, R Yakugaku Zasshu 1958, 78, 491

(Received in USA 18 July 1991)