

data on nucleotides. These studies and enzymatic studies are in progress.

Acknowledgment. For support, we wish to thank the National Science Foundation (GB-25174) and the Wallace C. and Clara A. Abbott Memorial Fund of the

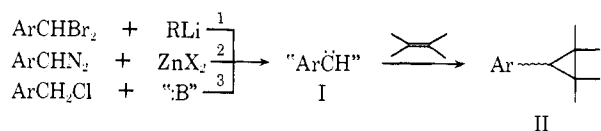
University of Chicago. We also thank the Department of Chemistry for allowing us to use their nuclear magnetic resonance spectrometers, Drs. S. Danyluk and K. Kopple for helpful comments and Dr. Ian Smith for providing copies of his papers before publication.

Communications to the Editor

A Useful Synthesis of Arylcyclopropanes

Sir:

In the best published general methods^{1,2} for the preparation of arylcyclopropanes (II) by routes involving the reaction of phenyl carbenes or carbenoids (I) with alkenes, the intermediate I is generated: (1) by treatment of the costly and often unstable benzal bromides (but not ArCHCl_2 ³) with organolithium reagents,¹ or (2) by zinc halide induced decomposition of the unstable and detonation prone aryldiazomethanes.^{2,4} A



high-yield synthesis of II from I formed (3) by reaction of a base with a benzyl chloride (usually commercially available, inexpensive) is thus attractive both economically and from a safety standpoint. Numerous past attempts to develop such a method have been unsuccessful.⁵⁻⁸ With organometallic bases, the products obtained include substances which may be visualized as derived from metal-halogen exchange reactions and from processes involving deprotonation of the alkene trap to an allyl anion. Generally, however, the base is just benzylated. Even when initial α -proton abstraction occurs, the $\text{Ar}\ddot{\text{C}}\text{HCl}$ generated does not fragment but is instead alkylated by more ArCH_2Cl . The only published exception is the reaction of

(1) G. L. Closs and R. A. Moss, *J. Amer. Chem. Soc.*, **86**, 4042 (1964).

(2) S. H. Goh, L. E. Closs, and G. L. Closs, *J. Org. Chem.*, **34**, 25 (1969).

(3) Which reacts to give $\text{Ar}\ddot{\text{C}}\text{Cl}$: R. A. Moss, *ibid.*, **27**, 2683 (1962).

(4) Simple photochemical or thermal decomposition of ArCHN_2 is a much less satisfactory source of I.^{1,2} Also: C. D. Gutsche, G. L. Bachman, and R. S. Coffey, *Tetrahedron*, **18**, 617 (1962).

(5) Bases studied include KOH, LiOMe, NaOEt, KO-*t*-Bu, HCO-NHNa in HCONH₂, LiNH₂ or NaNH₂ in NH₃, ether, THF, hydrocarbon, or (Me₂N)₃PO, MeLi, EtLi, *n*-BuLi, Na in NH₃, NaH in THF or (Me₂N)₃PO, and "active NaH" in THF. For review of material prior to 1960 see ref 6. For more recent results see ref 7 and S. Bank and M. C. Prislowski, *Chem. Commun.*, 1624 (1970); P. Caubère, *Bull. Soc. Chim. Fr.*, 1293 (1966); P. Caubère and J. Moreau, *ibid.*, 1986 (1970); *Tetrahedron*, **25**, 2469 (1969); J. F. Bunnett and J. D. Reinheimer, *J. Amer. Chem. Soc.*, **84**, 3284 (1962); P. E. Verkade, K. S. deVries, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **82**, 637 (1963). For new data see ref 8.

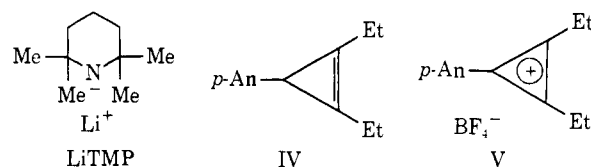
(6) G. L. Closs and L. E. Closs, *Tetrahedron Lett.*, 26 (1970).⁷

(7) But note also that the reaction of PhCH_2Cl with *n*-BuLi by a different pathway (similar conditions minus cyclohexene) is used as a quantitative assay for these RLi reagents: H. Gilman and A. H. Haubein, *J. Amer. Chem. Soc.*, **66**, 1515 (1944); D. H. Hoeg and D. I. Lusk, *ibid.*, **86**, 928 (1964); R. West and W. H. Glaze, *J. Chem. Phys.*, **34**, 685 (1961).

(8) R. A. Olofson and C. M. Dougherty, *J. Amer. Chem. Soc.*, **95**, 582 (1973).

PhCH_2Cl with *n*-BuLi in cyclohexene from which 7-phenylnorcarane (III) was isolated in a disappointing 14% yield.⁶ We have confirmed this result (13%) and have found that MeLi (<9%), PhLi (<5%), and *t*-BuLi (0%) are even less satisfactory for the production of III. In other new tests, no III was isolated with KO-*t*-Bu or with the Schlenk-Hauser base, sodium triphenylmethide,⁹ and only traces of III were obtained with lithium bistrimethylsilylamide¹⁰ or with another Hauser base, bromomagnesium diisopropylamide.¹¹ Calculated yields in these eight experiments using a radioisotope dilution assay to ensure the stability of III in the reaction media and to correct for loss during the sometimes complex isolation schemes required still were only 13, 9, 8, 2, 1-2,¹² 2, 3, and 7%, respectively. The last four reagents above have previously been recommended specifically for their excellence as very strong proton-specific bases.⁸⁻¹¹

We now report here the successful use of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) as the base¹³ in a practical synthesis of II from ArCH_2Cl . In the op-



timum experimental procedure, a rapidly stirred, concentrated solution (under N₂) of 1 equiv of ArCH_2Cl and the alkene (large excess) in ether is slowly titrated with 1 equiv of a *ca.* 1 M solution of LiTMP in ether. The reaction temperature and base addition rate are

(9) B. E. Hudson and C. R. Hauser, *ibid.*, **63**, 3156, 3163 (1941); D. F. Thompson, P. L. Bayless, and C. R. Hauser, *J. Org. Chem.*, **19**, 1490 (1954); W. Schlenk, H. Hillemann, and I. Rodloff, *Justus Liebigs Ann. Chem.*, **487**, 135 (1931).

(10) C. R. Krüger and E. G. Rochow, *J. Organometal. Chem.*, **1**, 476 (1964), and references therein; D. H. R. Barton, R. H. Hesse, G. Tarzia, and M. M. Pechet, *Chem. Commun.*, 1497 (1969); M. Tanabe and D. F. Crowe, *ibid.*, 1498 (1969); M. W. Rathke, *J. Amer. Chem. Soc.*, **92**, 3222 (1970).

(11) F. C. Frostick and C. R. Hauser, *ibid.*, **71**, 1350 (1949); C. R. Hauser and H. G. Walker, *ibid.*, **69**, 295 (1947).

(12) Depending on reaction solvent: *t*-BuOH, ether, or cyclohexene.

(13) Since 2,2,6,6-tetramethylpiperidine (HTMP) is readily prepared by reduction of 2,2,6,6-tetramethylpiperidone-4 (\equiv triacetoneamine (i)); from acetone, ammonia, and CaCl₂, it is potentially inexpensive enough for most synthetic purposes. Because of the value of the derived nitroxides as spin labeled diagnostic reagents in spectroscopy, both HTMP and i are already available from several sources. The unfortunate impurities (*ca.* 10%) in commercial samples are easily removed by distillation. Treatment of HTMP with a commercial RLi (R = Me, *n*-Bu) solution provides a convenient small scale source of LiTMP. The reaction is best performed in the addition funnel just before use.

chosen so that the exothermic process causes the alkene (or ether) to reflux gently. Representative reactions are listed in Table I. With only one exception the cyclo-

Table I. Preparation of Arylcyclopropanes from ArCH_2X , Alkenes, and LiTMP

Reactants	Yield, ^a % (syn/anti ratio)	Lit. yield, ^b %	
		A	B
$\text{PhCH}_2\text{Cl} + \text{cis-butene}$	78 (2.1)	21	70
$\text{PhCH}_2\text{Cl} + \text{trans-butene}$	50	14	
$\text{PhCH}_2\text{Cl} + \text{cyclohexene}$	53 (2.2)		90
$p\text{-MeOPhCH}_2\text{Cl} + \text{cis-butene}$	87 (~18)	55	37
$p\text{-MeOPhCH}_2\text{Cl} + \text{cyclohexene}$	82 (10)		37
$p\text{-MeOPhCH}_2\text{Cl} + \text{butadiene}$	74 ^c (2.3)		50
$p\text{-ClPhCH}_2\text{Cl} + \text{isobutene}$	65	19	
$o\text{-MePhCH}_2\text{Br} + \text{cis-butene}$	69 ^{d,e} (3.5)	<i>f</i>	<i>f</i>
$\alpha\text{-C}_{10}\text{H}_7\text{CH}_2\text{Cl} + \text{isobutene}$	69 ^{d,g}		
$p\text{-MePhCH}_2\text{Cl} + \text{H}_2\text{C}=\text{CHOEt}$	78 ^{d,h} (2.0)		
$p\text{-MeOPhCH}_2\text{Cl} + \text{H}_2\text{C}=\text{C(OMe)}_2$	87 ^{d,i}		

^a Of pure product after isolation by vacuum distillation; syn/anti ratio determined by vpc-nmr combination. ^b A, from ArCHBr_2 ; ¹ B, from $\text{ArCHN}_2 + \text{ZnX}_2$. ² ^c Of 1-*p*-anisyl-2-vinylcyclopropane. ^d New compound; satisfactory combustion analysis and corroborative spectral data have been obtained. ^e Vpc on a 5 ft \times $\frac{1}{4}$ in. 20% SE-30 on 60-80 Chromosorb W column; temperature 175°; flow rate 75 cm³/min; retention times: anti isomer, 5.4 min; syn, 6.6 min. ^f Production of the *p*-tolyl isomer in 22% yield by route A¹ and 60% yield by route B² has been reported. ^g Bp 89.5-91° (0.2 Torr). ^h Vpc on column in footnote *e*; 165°; 50 cm³/min; retention times: syn, 10.3 min; anti, 11.7 min. Isomer assignment based on comparison with vpc-nmr data for 1-MeO-2-Ph-cyclopropanes: W. Kirmse and H. Schütte, *Chem. Ber.*, **101**, 1674 (1968). The published assignment is not definitive. ⁱ Bp 92-93° (0.4 Torr).

propane yields are better—sometimes two or three times better—than published yields based on the less satisfactory ArCHBr_2 and ArCHN_2 precursors of I.

In the preparation of III from PhCH_2Cl , LiTMP, and cyclohexene, substitution of tetrahydrofuran (at 35°) for ether did not change the product yield, but with cyclohexane as solvent the yield decreased to 32%. Other evidence for the significance of ion pairing and aggregation phenomena in determining the reaction course was obtained by including 1 equiv of tetramethylethylenediamine, a complexing agent for Li⁺,¹⁴ in the ether reaction. Under these conditions, the yield was only 14%.¹⁵ In all reactions studied, the cyclopropanes were formed by stereospecific *cis* additions, and when epimer pairs were possible, the thermodynamically less stable *syn* isomer was the predominant product. The high *syn*/*anti* ratios in Table I are similar to those generally found for reactions previously characterized as carbenoid.^{1,2,16,17} The base-catalyzed isomerization normally used^{1,16,18} for the conversion of *syn*-arylcyclopropanes to the corresponding *anti* isomers is not significant under the reaction conditions: even after 3 days in 0.5 M LiTMP in ether at 25°, *syn*-1-*p*-anisyl-*cis*-2,3-dimethylcyclopropane is not appreciably contaminated by the *anti* isomer (the equilibrium mixture from reaction with KO-*t*-Bu-DMSO has a *syn*/

(14) C. Agami, *Bull. Soc. Chim. Fr. Rev.*, 1619 (1970).

(15) Because this complex is not very soluble in ether, the reaction conditions are not strictly comparable. An alternate yield reducing mechanism involves alkylation of the tertiary amine by the PhCH_2Cl .

(16) R. A. Moss, *J. Org. Chem.*, **30**, 3261 (1965).

(17) G. L. Closs, R. A. Moss, and J. J. Coyle, *J. Amer. Chem. Soc.*, **84**, 4985 (1962).

(18) F. R. Jensen and D. B. Patterson, *Tetrahedron Lett.*, 3837 (1966).

anti ratio of <0.1). The variation of III yield with LiNR_2 structure is discussed in the accompanying paper.⁸

Of special note in Table I is the fact that no methyl insertion product was found using *o*-MePhCH₂Br as the reaction substrate (expected carbenoid selectivity) and the discovery (especially in view of the data in the following communication⁸) that benzyne formation was not a competitive process in the *p*-ClPhCH₂Cl reaction when 1 equiv LiTMP was used as the base. An attempt to extend the cyclopropane synthesis to secondary benzylic halides (e.g., α -chloroethylbenzene) failed; only styrene derived (β elimination) products were found. However, Traylor and Brown¹⁹ have recently obtained *cis*-1,2-ethylenedioxy-3-phenylcyclopropane from 1,4-dioxene, PhCH_2Cl , and LiTMP, and we have similarly isolated a monooxygen functionalized cyclopropane using commercial $\text{H}_2\text{C}=\text{CHOEt}$ as the alkene component (78%, Table I). The further elaboration of this discovery to a superior preparation of arylcyclopropanone acetals from ketene acetals has also been achieved. The previously favored route to this interesting class of compounds—reductive dehalogenation of the Cl-substituted derivative (from an $\text{Ar}\ddot{\text{C}}\text{Cl}$ or $\text{Cl}\ddot{\text{C}}\text{Cl}$ reaction)²⁰—failed when the three-membered ring was substituted by hydrogen.²⁰ The 87% yield in the example in Table I signifies the removal of this restriction.

By use of nonterminal acetylenes in place of the alkene substrates, 3-arylcyclopropenes are also available by the present method. An example is the isolation of 1,2-diethyl-3-*p*-anisylcyclopropene (IV, 60%; bp 87-88.5° (0.4 Torr); ν 5.32 μ ²¹) after addition of LiTMP to a 3-hexyne-ether solution of *p*-MeOPhCH₂Cl. As part of the structure proof for IV, it was converted (81%) to V (mp 72-72.5°, $pK_{\text{R}^+} = 6.8$ ²¹) by treatment with trityl fluoroborate in CH_2Cl_2 . This last reaction also illustrates the utility of the overall scheme as a source of cyclopropenium cations.

Acknowledgment. We are grateful to the National Science Foundation (GP-10834) and the donors of the Petroleum Research Fund, administered by the American Chemical Society (3992-A), for grants which provided the primary support for this research.

(19) We thank Dr. R. S. Brown and Professor T. G. Traylor for permission to quote this result. Other methods (*vide supra*) involving phenyl carbenoid intermediates failed completely.

(20) S. M. McElvain and P. L. Weyna, *J. Amer. Chem. Soc.*, **81**, 2579 (1959).

(21) For comparison data see: R. Breslow, H. Höver, and H. W. Chang, *ibid.*, **84**, 3168 (1962).

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Received July 26, 1972

Lithium 2,2,6,6-Tetramethylpiperidide and Related, Strong, Proton-Specific Bases. Evaluation in Synthesis

Sir:

The immense utility in synthesis and rarity of bases which selectively abstract protons from substrates containing intrinsically more reactive sites toward nucleophilic attack is recognized in the fact that superior rea-